The development of a safe and effective method of providing analgesia to patients with a broken hip

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Abstract

This PhD project developed the femoral 3-in-1 nerve block to provide safe, effective regional analgesia to the 60,000 patients admitted annually to UK hospitals with a fractured neck of femur. The hospital mortality for patients with a fractured hip in a large UK study was 14.3% with cardiac aetiologies predominating in the first 2 days (Bottle & Aylin 2006). In contrast to the marked improvements in mortality for elective surgery, the overall mortality from emergency surgery and in particular surgery for fractured neck of femur patients has remained unchanged (Roberts & Goldacre 2003). Development of the femoral 3-in-1 nerve block for fractured neck of femur patients will provide analgesia but may also improve outcome. A relationship between effective pain analgesia and improved cardiac morbidity and reduced mortality in patients with a fractured neck of femur was demonstrated by Matot et al using epidural analgesia in 2001 but this is not the current clinical standard in the UK (Matot et al. 2003). The femoral 3-in-1 nerve block (also called the fascia iliacus block or anterior psoas compartment block) offered a viable solution to provide analgesia to patients with a fractured neck of femur prior to surgical fixation. The femoral 3-in-1 nerve block is technically undemanding and requires a minimum of extra training and resources. In contrast to epidural analgesia which requires extensive training of practitioners and continuous cardio-respiratory monitoring of patients and an increased level of nursing care, ultrasound guided nerve blocks have been associated with an increased success rate, need less local anaesthetic and have shorter onset times than traditional techniques (Marhofer et al. 1997;Marhofer et al. 1998). Ultrasound guidance may increase the nerve block success rate and lower complication rates but it is associated with the extra cost of the ultrasound machine, disposables and staff training. In contrast, needle guidance using loss of resistance for a femoral 3-in-1 block is technically simple and cheap but is potentially inaccurate and, as a result, may be less effective. Anaesthetists currently utilise the femoral 3-in-1 nerve block to provide effective pain after surgical fixation of the femur but these techniques use large doses of local anaesthetic. Further information on dosing based on efficacy and duration of action will allow a reduction in dose and hence an improvement in safety of the femoral 3-in-1 nerve block.

The information needed to develop the femoral 3-in-1 nerve block to provide analgesia for patients with a fractured neck of femur was provided by undertaking one prospective observer-blinded muticentre randomised controlled study, a clinical trial of an investigational medicinal product and a cadaveric dissection study. A multicentre randomised controlled study compared the efficacy of using ultrasound, nerve stimulator and loss of resistance techniques to guide the needle for a femoral 3-in-1 nerve block in elective primary total hip arthroplasty patients. This initial study recruited patients scheduled for a similar operation to fracture neck of femur patients (elective primary total hip arthroplasty) as it was impossible to recruit and assess a large number (>100) elderly, frail emergency patients. The use of the nerve stimulator is the current gold standard for elective femoral 3-in-1 nerve blocks but if used on patients with a fractured neck of femur it will cause unnecessary discomfort in a limb with an unfixed fracture. In order to determine the comparative efficacy of ultrasound, nerve stimulator and loss of resistance techniques, we performed femoral 3-in-1 nerve blocks on 180 patients scheduled for elective primary total hip arthroplasty. The efficacy of these three techniques was measured by assessing femoral nerve sensory and motor response at 30 minutes after the femoral 3-in-1 nerve block. The use of ultrasound and nerve stimulator (US+NS) for the femoral 3-in-1 femoral nerve block for elective total hip replacement was statistically significantly more effective than loss of resistance (LOR-59.5%, US+NS-80.3%, $p=0.0159$ ($p\leq0.025$)) with a number needed to treat of 5. There was no statistically significant difference in the effectiveness of using the nerve stimulator(NS) and ultrasound(US) to guide the insertion of a femoral 3-in-1 nerve block (NS-77.5, US-83.1%, $p=0.527$ ($p\leq0.025$). Since the use of nerve stimulator would result in significant unnecessary discomfort in patients with an unfixed fracture it was concluded that ultrasound was the optimal technique to guide femoral 3-in-1 nerve blocks for analgesia in patients with a fractured neck of femur.

The dosing and safety of the femoral 3-in-1 nerve block was determined in patients with a fractured neck of femur. Levobupivacaine dosing was estimated by a Dixon's up/down sequential methodology. Femoral 3-in-1 nerve blocks were performed and the concentration of levobupivacaine was increased or decreased (using a fixed volume) for an ineffective or effective nerve block

respectively, as a result the concentration tended towards the EC_{50} (effective concentration in 50% of patients). The EC_{50} and the EC_{95} (effective concentration in 95% of patients) for 30 ml of levobupivacaine was estimated using a binary probit regression model; in which the probability of an effective nerve block was modelled against the concentration of levobupivacaine.

The second part of this clinical trial assessed the pharmacokinetics (to ensure that serum levels were within the safe range) and pharmacodynamics (to assess duration of analgesia). The estimated EC_{95} concentration of levobupivacaine for the femoral 3-in-1 nerve block was 30mls of 0.036% with 95% confidence interval of 0.0332% to 0.0383%. The EC_{95} concentration of levobupivacaine gave a mean duration of analgesia of 166 minutes with a standard error of the mean of 35 minutes and peak median plasma level of 52 ng/ml 30 minutes after the femoral 3-in-1 nerve block. The measured plasma levobupivacaine concentrations were below the threshold (2100ng/ml) associated with toxicity.

The clinical anatomy of the femoral 3-in-1 nerve block was determined by dissection. We investigated the distribution of 30 ml of black 10% latex injected lateral to the femoral nerve under the fascia iliacus membrane in two unembalmed adult cadavers. In all four dissections the lateral cutaneous and femoral nerves were stained at the inguinal ligament and the latex travelled distally in the adductor canal into the popliteal fossa to stain the sciatic nerve and its terminal branches.

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Author's Declaration

I declare that I am the sole author of this thesis and the work presented here is entirely my own, except where acknowledged to others. This thesis does not include work that has been submitted for consideration for another degree in this or any other university.

The following presentation to a learned society was based on the work in this thesis:

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List of abbreviations

DALYs	disability adjusted life years
QALYs	quality adjusted life years
CI	confidence interval
SIGN	Scottish Intercollegiate Guideline Network
pain VAS	pain visual analogue scale
RR	risk ratio (or relative risk)
NS	nerve stimulator
LOR	loss of resistance
US	ultrasound
NNT	number needed to treat
ECG	electrocardiogram
SVS	simplified verbal scale
SaO_2	arterial oxygen saturation
pain NRS	pain numerical rating scale
EC_{50}	effective concentration in 50% of patients
EC_{95}	effective concentration in 95% of patients
S_mPC	summary of product characteristics
ASA	American Association of Anethesiologists
AMT score	acute metal test score
%	concentration of local anaesthetic expressed in grams per 100ml (i.e. 10mg/1ml=1% solution)
δ	stepping value, change in concentration between patients in sequential up/down study
σ	standard deviation
μ	mean
mins.	Minutes
ml	Millilitre
mm	Millimetre
G	Guage
ICH-GCP	Medicines for human use (clinical trails) regulations 2004 number 1031. 2004 with amendment 2006/1928
Ln	$\log_e$ (log base e)
ROC	receiver operator curve
IMP	investigation and medicinal product
GMP	good manufacturing practice
LC-MS/MS	specific Liquid chromatography tandem mass spectrometry
SE	standard error
Kpa	kilopascals
mmol/l	millimoles per litre
μmol/L	micromoles per litre
U/l	units per litre
g/l	grams per litre
INR	international normalised ratio
MAC	minimum alveolar concentration
NHS GGC health board	National Health Service Greater Glasgow and Clyde Health Board
CRFs	case report forms
ß-blocker	beta-blocker
$ά_2$ blocker	alpha 2 blocker
NSAIDS	non steroidal anti-inflammatory drugs
CHF	congestive heart failure
PA	programmed activity
MHRA	Medicines and Healthcare Regulatory Agency
NICE	National Institute for health and clinical excellence

Chapter 1

1 The development of a safe and effective method of providing analgesia to patients with a broken hip

1.1 Introduction

This chapter will outline the disease burden represented by patients with a fractured neck of femur, discuss the aetiology of the mortality associated with this disease and briefly look at the potential for improving the outcome. The clinical evidence for improved outcomes associated with the use of regional analgesia in patient groups other than those with a fractured neck of femur will also be discussed. The term fractured neck of femur will be used inclusively throughout this thesis to include all types of proximal femoral fracture, ((extracapsular).subtrochnetric, intratrochentric fractures and intracapsular (fractured surgical neck of femur fracture).

1.1.1 Burden of disease caused by fractured neck of femur

Fractured neck of femur or proximal femoral fracture is a significant cause of morbidity and mortality in the developed world. Johnell et al calculated that hip fracture was associated with 1.75 million disability adjusted life years (DALYS) which represented 1.4% of the total disease burden calculated in DALYS for women in established market economies in 1990 (Johnell & Kanis 2004). Disability adjusted life years (DALYS) are a sum of years lost due to premature mortality and disability directly related to hip fracture for the number of years that patient survives multiplied by a disability factor between 0 (no disability) to 1 (death). The disability weight has been estimated for hip fracture by expert panels at 0.272 for each year of illness (Murray & Lopez 1997). Fractured neck of femur represents a greater burden of disease in established market economies for women than cirrhosis of the liver (1.1%), stomach cancer (0.9%) or ovarian cancer (0.9%) (Johnell & Kanis 2004). Fractured neck of femur was found to be significantly more common in the women, with a male to female ratio of 1 to 2.71 worldwide with a ratio of 1 to 4 in the established market economies of

Western Europe, North America, Japan and Australia (Gullberg, Johnell, & Kanis 1997). Gullberg et al estimated that worldwide the total number of hip fractures in men and women in 1990 was 338,000 and 917,000 respectively, a total of 1.26 million (Gullberg, Johnell, & Kanis 1997). Gullberg also estimated the incidence of hip fractures will double to 2.6 million by the year 2025, and 4.5 million by the year 2050 with a 95% confidence interval of between 7.3 and 21.3 million if we assume no change in the age and sex specific incidence.

1.1.2 Prognosis, historical perspective and operative/ non-operative management

The prognosis for patients with a fractured neck of femur in the UK is poor with an overall 1 year mortality of approximately 25% (Heikkinen, Parker, & Jalovaara 2001) and a hospital mortality of 14.3% for patients admitted from home (Bottle & Aylin 2006). The one year mortality improved significantly since Beals reported a 50% 1 year mortality in a surgically managed cohort of patients recruited between 1956 and 1961 (Beals 1972). Subsequently, Roberts et al retrospectively analysed the mortality rates for 32590 English patients with a fractured neck of femur between 1968 and 1998 (Roberts & Goldacre 2003) and concluded that although mortality rates had reduced between 1968 and 1983, no significant fall in mortality was observed in the next 15 years.

Holmberg found that while following up 3002 patients with a intracapsular femoral neck fracture admitted during a 3-year period in the Stockholm area that those admitted from institutional care had a 3 to 4 times higher long-term mortality than those admitted from home (Holmberg et al. 1986). After 6 years, 54% of the patients admitted from home were alive compared with only 16% of those admitted from institutions. Several other studies have concluded that prognosis was and is associated with the age, morbidity and preoperative functional status of the patient and no single surgical, medical or anaesthetic intervention has yet impacted significantly on the overall morality of these patients (Bannister et al. 1990;Holmberg et al. 1986;Jensen, Johansen, & Morch 1977). This may be due to the multifactorial nature of the patients' co-morbidities and the single factorial nature of many clinical trials looking for

improved outcomes. In 2005 Foss et al suggested that only 25%-60% of the mortality observed in an unselected population may be susceptible to intervention (Foss & Kehlet 2005).

In a review of 50235 fractured neck of femur patients over 7 years in Ontario Canada non-operative management of fractured neck of femur was associated with significantly higher 30 day mortality (18%) compared to operative management (11%) (Jain, Basinski, & Kreder 2003) . In this study by Jain et al 89.4% of all patients were treated operatively and the odds ratio for 30 day mortality when non-operative management was compared with operative management was 1.7, with a 95% confidence interval (CI): 1.6 to 1.8. Jain et al also examined a series of 62 elderly patients within their 5235 patient cohort with severe co-morbidity treated non-operatively, 41 had bed rest and traction, while 21 were mobilised early. They found no statistically significant difference in mortality between operatively treated patients (29%) and patients treated non-operatively with immediate mobilization (19%) but they found that non-operative treatment and bed rest was 2.5 times more likely to be associated with mortality compared to operative treatment with early mobilisation (95% CI: 1.1 to 5.5) (Jain, Basinski, & Kreder 2003). These results should be interpreted with caution due the possibility of bias from the small cohort of non-operatively treated patients analysed but it does suggest that early mobilisation may improve outcome even in patients with severe co-morbidity.

1.1.3 Prognosis and delay in definitive surgical management

Delayed mobilisation caused by delays in definitive surgical fracture fixation was also associated with an increased risk of mortality. Bottle et al examined a retrospective cohort of 129522 patients from 151 Trusts in England and Wales between April 2001 and March 2004 and found an independent association between delayed operative treatment and an increased risk of death in hospital (Bottle & Aylin 2006). For all deaths in hospital, the odds ratio for more than one days delay relative to one day or less was 1.27 (95% CI: 1.23 to 1.32) after adjustment for co morbidity. It is interesting to note that if the death rates in patients with at most one days delay had been repeated throughout all 151

trusts in this study, there would have been an average of 581 (95% CI: 478 to 683) fewer deaths per year (9.4% of the total deaths per year). The association between delay in surgical treatment and increased mortality was also shown by Moran et al (Moran et al. 2005). Moran et al conducted a prospective observational study examining the mortality rates for 2660 patients in Nottingham, UK and concluded that if patients who were fit for surgery were delayed more than four days it was associated with a significant increase in mortality at 30 days (risk ratio=2.4; $p<0.001$) and 1 year (risk ratio 2.25; $p<0.001$).

1.1.4 Prognosis and aetiology for fractured neck of femur patients

The aetiology of this poor prognosis is multifactorial; a review of multiple post mortem studies suggested that the principal cause of death was bronchopneumonia in 46% of patients, cardiac failure and myocardial infarction in 23% of patients and pulmonary embolism in 14% of patients (Perez et al. 1995). Mortality from bronchopneumonia and pulmonary embolism were significantly reduced but cardiac failure was not altered in those patients who had surgical fixation of the fracture within 24 hours (Perez et al. 1995). Todd et al and Jain et al found an association between the use of thromboprophylaxis and reduced death from fatal pulmonary embolism (Jain, Basinski, & Kreder 2003;Todd et al. 1995). The positive impact of early mobilisation on outcome may be as a result of reduced infectious and thromboembolic respiratory complications. Currently, best practice aims to minimise the delay to surgical fixation of proximal neck of femur fractures and encourage early mobilisation (Scottish Intercollegiate Guidelines Network (SIGN)-Guideline 111).

1.1.5 Could improved analgesia from regional analgesia and anaesthesia result in better outcomes for patients?

The SIGN guidelines on proximal hip fractures have been widely implemented but the outcome for fractured neck of femur patients remains poor (Scottish Intercollegiate Guidelines Network (SIGN)-Guideline 111). The possibility that

regional analgesia could improve the poor outcome associated with fracture neck of femur may be considered. The trials which deal with regional anaesthesia and analgesia and outcome in patients with a fractured neck of femur and these will be discussed in Chapter 2. The remainder of this chapter will deal with the impact on outcome associated with regional anaesthesia and analgesia in the general surgery and cardiac patient populations.

The Cochrane review by Nishimori used meta-analysis to assess the risks and benefits of postoperative epidural analgesia compared with postoperative systemic opioid based pain relief for adult patients scheduled for elective abdominal aortic surgery (Nishimori, Ballantyne, & Low 2006). Nishimori et al looked at published trial data on OVID MEDLINE between 1966 to July 2004 and on EMBASE between 1980 and June 2004. They found 13 studies which met their quality control criteria which had recruited a total of 1224 patients; 597 patients received epidural analgesia and 627 received systemic opiate based analgesia. The epidural analgesia group showed significantly lower pain visual analogue scale (VAS) scores on movement for up to three days postoperatively; on postoperative day one, weighted mean difference was -1.78 (95% CI: -2.32 to -1.25), day two weighted mean difference was -1.63 (95% CI: -2.16 to -1.10), and day three weighted mean difference was -1.37 (95% CI: -2.24 to -0.51). The duration of postoperative tracheal intubation and mechanical ventilation was also reduced by 48% in patients receiving epidural analgesia Risk ratio (RR)=0.52 (95% CI: 0.41-0.72), $p<0.048$). The statistically significant results of the Cochrane review by Nishimori are shown in Table 1-1. The Cochrane review showed that epidural analgesia was associated with a reduction in all cardiovascular complications, including acute myocardial infraction. Epidural analgesia was also associated with reduced respiratory, gastrointestinal and renal complications in the 2008 Cochrane review.

Table 1-1: Summary of statistically significant results from the 2008 Cochrane review of epidural analgesia compared with opiate based analgesia

	RR (95% CI)	NNT (95% CI)
All Cardiovascular complications	0.74 (0.56-0.97)	14 (7-100)
Myocardial infarctions	0.52 (0.29-0.93)	25 (14-100)
Acute respiratory complications	0.63 (0.51-0.79)	9 (6-17)
Gastrointestinal complications	0.37 (0.15-0.92)	50 (20-∞)
Renal insufficiency	0.64 (0.46-0.90)	14 (8-50)

RR-Risk ratio, NNT-number needed to treat, CI-confidence interval

Nishimori did not find any evidence regarding the effect of postoperative epidural analgesia on mortality (Peto odds ratio: 0.86, 95% CI: 0.48-1.55).

In contrast, Yeager et al found an improved mortality in those patients assigned to receive epidural analgesia compared with those who received opiate based analgesia in a mixed population of high risk patients (Yeager et al. 1987). Yeager recorded 16% mortality in the control group which received opiate based analgesia postoperatively and 0% mortality in the epidural analgesia group. This study was stopped after recruiting only 53 patients; 28 patients received standard anaesthetic and epidural analgesia and 25 patients received standard anaesthetic and analgesic techniques based on opiates without epidural anaesthesia. The study has been widely criticised due to the small number of patients recruited and the early termination. However, surgical "risk" was evaluated preoperatively and found to be comparable in both groups. When compared to control patients, patients who received epidural analgesia had a reduction in the overall postoperative complication rates (p= 0.002) and in the incidence of both cardiovascular failure (p= 0.007) and major infectious complications (p= 0.007). Urinary cortisol excretion, a marker of the stress response, was significantly diminished during the first 24 postoperative hours in the group receiving epidural analgesia and anaesthesia (p= 0.025). The significant survival benefits observed therefore were consistent with the other endpoints measured.

The MASTER trial was the largest prospective clinical trial conducted comparing postoperative epidural analgesia and systemic opiate based postoperative analgesia (Rigg et al. 2002). The MASTER trial did not find a statistically significant difference in 30 day mortality between those patients assigned to receive postoperative epidural analgesia and those assigned to receive systemic opiate analysed on an intention to treat basis. The MASTER trial was conducted over 6 years in 6 counties and 25 hospitals and recruited a total of 955 patients. The MASTER trial recruited patients undergoing major abdominal, non laparoscopic surgery with significant comorbidity and an estimated baseline 30 day mortality of 5%. It was calculated that a minimum of 814 patients were required for the MASTER trial to have a power of 80% to find a 10% relative risk reduction in the primary outcome (30 day mortality), with a two sided alpha error=0.05. Compliance with the protocol was a significant issue, with protocol violations in 42.5% (192 of 447 patients) of those assigned to the epidural analgesia group. In the epidural group 190 patients had their epidural catheters removed at less than 72 hours, in 26 patients the epidural catheter was accidentally removed in theatre and in 43 patients the catheter was removed due to inadequate analgesia and in the remaining 121 patients the catheter was removed without reason less than 72 hours after surgery. Therefore, it is arguable that the intention to treat analysis was not appropriate as 42.5% of patients allocated to receive epidural analgesia did not receive 72 hours of epidural analgesia. The MASTER trial did show a reduction in the incidence of respiratory failure in the postoperative period requiring prolonged ventilation (p=0.02, NNT=15). Rigg et al did note a non significant decrease of 3.6% in the incidence of death or major complication in the group of patients treated with epidural analgesia. It is worth considering that if the true 30 day morality benefit was a 3.6% reduction in relative risk then to adequately power this trial 6000 patients would be needed. The possibility that the MASTER trial represents a false negative must be considered.

In contrast, the meta analysis of Rodgers et al included 141 trials with a total of 9559 patients on or before 1 January 1997 found overall mortality was reduced by about a third in patients allocated to intraoperative neuraxial blockade with or without concomitant use of general anaesthesia compared to only general anaesthesia (103 deaths/4871 patients versus 144/4688 patients, odds ratio =

0.70 [95% CI: 0.54 to 0.90, p=0.006]) (Rodgers *et al*. 2000). Neuraxial blockade reduced the odds of deep vein thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression by 59% (all p<0.001). There were also reductions in myocardial infarction and renal failure but this result was less reliable as the number of patients in this subgroup was small. These effects appeared consistent with different types of surgical patients; however, only the orthopaedic subgroup of patients had enough patients to be able to show a positive mortality benefit. Rodgers et al concluded that the size of the effect of neuraxial block would be 1 less death per 100 patients treated. This very small effect may be the reason that previous studies examining mortality effects of neuraxial blockade have failed to find any mortality benefit.

Beattie et al performed a meta analysis to determine whether postoperative epidural analgesia continued for more than 24 hours after surgery reduced postoperative myocardial infarction or in hospital death in high risk cardiac patients (Beattie, Badner, & Choi 2001). A total of 11 trials and 1173 patients were included in the meta analysis and patients had aortic surgery (in five trials), peripheral vascular surgery (in two trials), mixed vascular surgery (in one trial) abdominal surgery (in two trials) or mixed high risk surgery (in one trial). Postoperative epidural analgesia resulted in better analgesia for the first 24 hours after surgery and this effect was statistically significant in three out of the four studies. The pain scores were lower in the epidural group in the fourth study but the effect was not statistically significant. The frequency of in-hospital death was 3.3%, with no statistically significant difference between epidural and non epidural groups but a lower death rate in the epidural group (event rate difference:-1.3% [95% CI: -3.8% to 1.2%, p=0.091]). The rate of postoperative myocardial infarction was 6.3%, with lower event rates in the epidural group (event rate difference: -3.8% [95% CI: -7.4% to -0.2%, p=0.049). Subgroup analysis of postoperative thoracic epidural analgesia showed a significant reduction in postoperative myocardial infarction in the epidural group (event rate difference:-5.3% [95% CI: -9.9% to -0.7%, p=0.04]). Three trials reported the incidence of postoperative ischemia which was monitored using Holter monitoring; the incidence was reduced in the group receiving 24 hours of epidural analgesia but did not reach statistical significance (event rate

difference: -7.5%; p=0.19). Two studies found an improvement in coagulation variables in the group receiving epidural analgesia. In summary, this meta analysis was conducted by using both the fixed effects and random effects model, calculating both an odds ratio and a rate difference and the analysis did show a consistent reduction in postoperative myocardial infarction rate despite the analytical method used with the subset analysis suggesting that thoracic epidural analgesia was significantly more beneficial than lumbar epidural analgesia.

A recent publication which addressed the impact of epidural analgesia and anaesthesia on outcome was a retrospective cohort study of 259037 patients, aged 40 years or older, who underwent selected elective intermediate-to-high risk non-cardiac surgical procedures between April 1 1994, and March 31 2004, in Ontario, Canada (Wijeysundera *et al*. 2008). A propensity-score method was used to construct a matched-pairs cohort that reduced important baseline differences between patients who received epidural anaesthesia or analgesia and those that did not to determine the association of epidural anaesthesia and analgesia with 30-day mortality within these matched-pairs. A total of 259037 patients were included in the data base, 56556 (22%) received epidural anaesthesia, 44094 patients that received an epidural were matched with 44094 patients who did not receive an epidural analgesia and anaesthesia was associated with a small reduction in 30-day mortality (1·7% vs 2·0%; relative risk 0·89 [95% CI: 0·81–0·98, p=0·02]). Epidural anaesthesia and analgesia was associated with a small improvement in 30-day survival, but this effect should be interpreted cautiously as the estimate had borderline significance and it corresponded to a number needed to treat of 477. This study did not provide compelling evidence that epidural anaesthesia and analgesia improved postoperative survival but it did support the safety of perioperative epidural anaesthesia when used for indications other than improving survival such as improved postoperative pain relief and preventing postoperative pulmonary and cardiac complications. The evidence suggests that major postoperative pulmonary and respiratory complications are reduced by providing epidural anaesthesia and it would seem logical to review the evidence of improved outcome in cardiac surgery as this patients group should see a particularly large

benefit as cardiac and respiratory comorbidity are almost universal in this patient group and the surgical insult is significant.

1.1.6 The use of regional analgesia to improve outcomes in cardiac surgery

The evidence for a positive outcome for the use of regional analgesia in the form of thoracic epidural analgesia in cardiac surgery is currently limited to a single randomised controlled trial (Scott et al. 2001). Scott et al 2001 showed outcome benefits in 420 cardiac surgery patients. It is notable that in this cohort of 420 patients anaesthesia was maintained using a target controlled infusion of propofol and alfentanil and that they continued the epidural infusion of bupivacaine and clonidine for four days postoperatively. The improvements in outcome noted by this study were substantial and the reduction in the incidence of lower respiratory infections was particularly striking. The incidence of lower respiratory tract infection was 31 in 206 patients (15.3%) in those patients receiving thoracic epidural analgesia compared with 59 of 202 patients (29%) in the general anaesthesia patient group (p=0.0007), odds ratio 2.33 (1.43-3.79), which after adjustment for baseline covariates was 2.06 (1.22-3.47) (p=0.0065). Patients were extubated significantly earlier using standardised extubation criteria in the thoracic epidural analgesia group, with only 11 of 202 patients in the general anaesthesia group compared with 51 of 206 in the thoracic epidural analgesia group extubated within the first four hours postoperatively. The incidence of new supraventricular arrhythmias that required treatment in patients receiving thoracic epidural analgesia was significantly reduced compared with those receiving general anaesthesia (45 of 202 [22.3%] vs 21 of 206 [10.2%], p=0.0012, odds ratio 2.53 [1.44-4.42], which after adjustment for baseline covariates was 2.56 [1.41-4.66], p=0.002). There was no difference in the incidence of bradycardia, ventricular arrhythmia, conduction defects, or myocardial infarction between the two groups. Myocardial infarction occurred in eight patients in the general anaesthesia group and six patients in the thoracic epidural analgesia group, and the overall incidence in the study was 4%. There was a significant reduction in the incidence of acute renal failure in patients receiving thoracic epidural analgesia (general anaesthesia = 14 of 202, thoracic epidural analgesia = 4 of 206; p=0.016) and also in the incidence of postoperative confusion (general anaesthesia = 11 of 202, thoracic epidural

analgesia = 3 of 206; p=0.031). The incidence of cerebrovascular accidents was less in patients receiving thoracic epidural analgesia (general anaesthesia = 6 of 202, thoracic epidural analgesia = 2 of 206), however the overall number was small and the difference was not statistically significant (p=0.17).

Liu conducted a meta analysis on thoracic epidural analgesia (Liu, Block, & Wu 2004) in cardiac surgery which analysed the results of 15 trials which recruited a total of 1178 patients (Table 1-2). The meta-analysis did show significant benefits of thoracic epidural compared to opiate based analgesia. Liu estimated that 30000 patients would be needed to detect a difference in mortality in cardiac patients with thoracic epidural analgesia.

Table 1-2: The benefits of thoracic epidural analgesia in cardiac patients

	Peto odds ratio	95% confidence interval	p value
Reduction in arrhythmias	0.52	0.29 to 0.93	0.03
Reduced pulmonary complications (pneumonia and atelecasis)	0.41	0.27 to 0.60	<0.00001
Pain scores at rest	-7.8	-15 to -0.6	0.03
Pain scores during activity	-11.6	-19.7 to -3.5	0.005
Opiate requirements	-11	-15 to -7	<0.00001

Fillinger et al did not see any benefits of thoracic epidural anaesthesia in cardiac surgery but the study included a total of 60 patients (Fillinger *et al*. 2002). Thiopentone was used for induction and propofol was used for maintenance of anaesthesia, normothermic cardiopulmonary bypass was used and patients were not cooled to 28 degrees as in the study by Scott et al. The thoracic epidural was sited at the T3-T10 interspaces in contrast to Scott et al who used the T3-T5 interspaces. Fentanyl not clonidine was used in combination with bupivacaine in the epidural catheters infusion. Fillinger did also not record any differences in pain scores and it is therefore possible to conclude that the epidurals were not providing any analgesic or sympatholyic effect.

Hansdottir et al conducted a trial of epidural thoracic analgesia in cardiac patients examining length of stay and quality of analgesia (Hansdottir *et al*. 2006). They found no difference between the quality of analgesia but they only

randomised a total of 97 patients. A non-statistically significant reduction in the number of episodes of confusion (p=0.1) and lower respiratory tract infections (p=0.086) but no reduction in arrhythmias was observed. This may be due to the use of β-blockers intra-operatively and in the immediate postoperative period. They concluded that epidural analgesia may have a role in those patients with significant morbidity (unstable angina and obesity) at high risk of adverse cardio respiratory problems.

1.2 Summary of Chapter 1

Fractured neck of femur is a significant cause of morbidity and mortality in the developed world, the aetiology of these deaths is mainly cardiac and respiratory complications. The patients suffer high rates of morbidity and mortality and despite many studies the current most effective treatments are rapid mobilisation by surgical fixation of the fracture or early mobilisation in association with non operative management. The use of regional anaesthetic techniques in all types of surgical patient has shown benefit; however, the impact on mortality has diminished as improvements in surgical and anaesthetic techniques resulted in a significant reduction in the overall mortality. The mortality from high risk elective surgery is now less than 5%; therefore, it is very difficult to show a reduction in mortality as the study would need to recruit thousands of patients. To quantify benefit, secondary outcome measures (i.e. lower respiratory tract infection, the need for ventilation and renal support) have been used to assess the effect of regional analgesia. In contrast to the marked improvements in the previous 30 years in elective surgery, the overall mortality from emergency surgery and in particular surgery for fractured neck of femur patients has remained unchanged. Regional analgesia and anaesthesia offers the potential of reduced complications in patient populations with significant cardiac and respiratory co-morbidity. It is therefore possible that effective regional analgesia could improve morbidity and mortality in patients with a fractured neck of femur and may impact positively on their morbidity and mortality

2 Review of analgesia for patients with a fractured neck of femur

2.1 Introduction

This chapter will examine the analgesic regimes that have been used in patients with a fractured neck of femur and the evidence for their effectiveness. Three analgesic regimes have been commonly used in this population, parenteral opiates, lumbar epidural analgesia and femoral 3-in-1 nerve block. In order to avoid confusion it should be noted that the femoral 3-in-1 nerve block has also been called the femoral nerve block, anterior psoas compartment block and the fascia iliacus block depending on the method of guiding the needle and the chosen end point. It is the opinion of this worker that these are the same nerve block as all the descriptions result in local anaesthetic being injected below the fascia iliacus membrane close to the femoral nerve, therefore the term femoral 3-in-1 nerve block will be use throughout this thesis.

2.1.1 Parenteral opiate based analgesia for fractured neck of femur patients

Evidence from a prospective observational study by Morrison et al suggested that the beneficial effects of improved analgesia may also be observed in fractured neck of femur patients receiving opiate based analgesia (Morrison et al. 2003). Four hundred and eleven consecutive cognitively intact patients admitted with a diagnosis of fractured neck of femur to four hospitals in New York were enrolled in a prospective cohort study. Patients were interviewed daily using standardised pain assessments. Morrison et al used multiple logistic regression and ordinary least squares linear regression to examine the association of post-operative pain on immediate post-operative outcomes (duration of stay, physical therapy sessions missed or shortened, ambulation following surgery, and post-operative complications) and outcomes six months following fracture (locomotion, mortality, return to the community, residual pain). The study found that patients with higher pain scores at rest had a statistically significantly increased length of hospital stay ($p=0.03$), were more likely to have physical therapy sessions missed or shortened ($p=0.002$), were less likely to be ambulating by post-operative day three ($p=0.001$), took longer to ambulate past

a bedside chair (p=0.01), and had lower locomotion scores at six months (p=0.02). Pain at rest was not significantly associated with post-operative complications, nursing home placement, survival at six months, or residual pain at six months.

A further prospective observational study by Morrison et al found an association between inadequate analgesia and the development of delirium in patients with a fractured neck of femur (Morrison et al. 2003). This study enrolled 541 patients at four hospitals in New York with a diagnosis of traumatic hip fracture without delirium. Delirium was identified prospectively by patient interview supplemented by medical record review. Multiple logistic regression techniques were used to identify risk factors. Eighty-seven of 541 patients (16%) became delirious. Among all subjects, risk factors for delirium were cognitive impairment (relative risk [RR], 3.6, [95% CI: 1.8 to 7.2]), abnormal blood pressure (RR=2.3, [95% CI: 1.2 to 4.7]), and heart failure (RR=2.9, [95% CI: 1.6 to 5.3]). Patients who received less than 10 mg of parenteral morphine sulphate equivalents per day were more likely to develop delirium than patients who received more analgesia (RR=5.4, [95% CI: 2.4 to 12.3]). Patients who received meperidine were at increased risk of developing delirium as compared with patients who received other opioid analgesics (RR=2.4, [95% CI: 1.3 to 4.5]). In cognitively intact patients, severe pain significantly increased the risk of delirium (RR=9.0, [95% CI: 1.8 to 45.2). Cognitively intact patients with under treated pain were nine times more likely to develop delirium than patients whose pain was adequately treated. Under treated pain and inadequate analgesia appear to be risk factors for delirium in frail older adults. The use of opiate based analgesia is recommended (in SIGN guideline 111) as part of the early management of patients with a fractured neck of femur. The work of Morrison et al demonstrated that the use of adequate amounts of opiate analgesia was associated with improved cognitive function but it did not demonstrate any reduction in other cardio-respiratory outcomes or mortality.

2.1.2 Lumbar epidural analgesia for a fractured neck of femur patients

In 2000 Scheinin et al published a prospective clinical trial comparing epidural and parental opiate based analgesia in 77 patients scheduled for surgical repair

of a traumatic hip fracture (Scheini *et al*. 2000). Patients were randomised to conventional analgesic regimen of intramuscular oxycodone (opiate group) or continuous epidural infusion of bupivacaine and fentanyl (epidural group). The analgesic regimens were started preoperatively. The patient's hip fractured was fixed under spinal anaesthesia and the analgesic regimes were continued three days postoperatively. The electro cardiogram (ECG) was continuously recorded using Holter monitors. Ischaemic episodes were defined as an ST segment depression of ≥0.1 mV or elevation of ≥0.2 mV lasting ≥1 minute. Nocturnal arterial oxygen saturation (SaO_2) was recorded perioperatively, and pain was assessed every morning using a pain visual analogue scale (VAS) scores. Fifty-nine patients (30 in the opiate group and 29 in the epidural group) of the total 77 patients were evaluated by Holter monitors. Thirteen patients (43%) in the opiate group and 12 patients (41%) in the epidural group had ischaemic episodes (p=1.0). However, significantly more patients in the opiate group had ischaemic episodes during the surgery (8 vs 0 patients in the epidural group, p=0.005). The median (interquartile range) total ischaemic burden (i.e. integral of ST-change vs. time) in patients with ischaemic episodes was ten times larger in the opiate group (340 [342] mm·min) compared with the epidural group (30 [36] mm·min) (p=0.002). The vast majority of the total ischaemic time was postoperatively with almost 80% of the total ischaemic burden during this time period. There were no significant differences between the groups in average heart rates or in heart rates at the start of ischaemic episodes or in maximal heart rates during the attacks. Average nocturnal SaO_2 was similar in the two groups and there were no differences in the number of hypoxaemic (SaO_2<90%) episodes. Preoperatively there were no differences in pain VAS scores, but postoperative and average perioperative pain VAS scores for pain were almost 40% lower in the epidural group (p=0.006). The reduced pain scores observed postoperatively may have resulted in reduced sympathetic activation and produced fewer imbalances between coronary artery oxygen supply and myocardial oxygen demand. However it is not possible to explain the reduction in ischaemic episodes in the epidural group intra-operatively based on differential sympathetic activation. Spinal anaesthesia was used intra-operatively for all patients in this study and no patients required conversion to general anaesthesia or supplemental regional analgesia intra-operatively and therefore all patients had a dense sympathetic block. Preoperative epidural infusion of bupivacaine

and fentanyl may have resulted in myocardial preconditioning that prevented ischaemic episode in the epidural group. The tentative conclusion from this small study was that continuous epidural bupivacaine and fentanyl analgesic regimen, started preoperatively, reduced the amount of myocardial ischaemia in elderly patients with hip fracture. This study was well conducted and although the number of patients recruited was small it appears methodologically sound. However ischaemic episodes were not verified by measuring the cardiac enzyme profile.

In 2003 Matot et al also published a study which randomised patients with a fractured neck of femur to conventional intramuscular opiate based analgesia or epidural analgesia using both local anaesthetic and opiate in the infusion (Matot et al. 2003). The effect of early administration of epidural analgesia during the pre-surgical period, on preoperative cardiac events was evaluated in a prospective randomised study in 68 patients with hip fractures who either had known coronary artery disease or were at high risk for coronary artery disease. On admission to the emergency room, patients were assigned to receive either a standard analgesic regimen (intramuscular meperidine, control group, n=34) or continuous epidural infusion of local anaesthetic and opioid (epidural group, n=34). Matot et al found that preoperative adverse cardiac events were significantly more prevalent in the control group compared with the epidural group (7 of 34 vs. 0 of 34; p=0.01). The adverse cardiac events recorded included fatal myocardial infarction in three patients, fatal congestive heart failure in one patient, nonfatal congestive heart failure in one patient, and new onset atrial fibrillation in two patients. The incidence of intra-operative and postoperative adverse cardiac events was similar for the two groups. The data from this study indicated that compared with standard opiate based analgesia, early administration of continuous epidural analgesia was associated with a lower incidence of preoperative adverse cardiac events in elderly patients with hip fracture who have, or are at risk of, coronary artery disease. It is interesting to note that this effect does not appear to be related to a reduction in resting pain scores as the control groups also received adequate analgesia based on the pain scores at rest preoperatively. The results of this study should be treated with caution as the significant difference in the incidence of preoperative cardiac events prompted termination of the study after the planned interim

analysis. The possibility of bias in the study was increased by the unblinded methodology utilised; however, the cardiac end points chosen were objective in nature. It is notable that at one hour after analgesia and before surgery, the pain scores on movement were statistically significantly lower ($p<0.05$) in the patients with lumbar epidural analgesia.

The previous two studies using lumbar epidural analgesia studies were published in 2000 and 2003; however, the majority of UK hospitals do not use lumbar epidurals to provide analgesia patients with a fractured neck of femur despite the compelling evidence in these studies. The reason for this lack of implementation is likely to be financial. In 2003, the average hospital cost for a patient over 60 years of age undergoing surgery for a hip fracture was retrospectively estimated at £12163. There were 6369 hip fracture patients in 2008 in Scotland the estimated annual hospital cost for NHS Scotland was around £77 million in 2008. The extra cost of implementing lumbar epidural analgesia (increased medical and nursing staff and mandatory constant cardiorespiratory monitoring) for the commonest orthopaedic emergency would be prohibitive.

2.1.3 Femoral 3-in-1 nerve blocks for analgesia of fractured neck of femur patients

The femoral 3-in-1 nerve block can provide effective analgesia to fractured neck of femur patients prior to definitive surgical fixation. The remainder of this chapter will present the clinical anatomy, sonoanatomy, history, methods of insertion, adverse events and benefits associated with the femoral 3-in-1 nerve block. This chapter will also discuss the clinical evidence for and against the utilisation of this nerve block.

2.2 Summary of clinical anatomy

The lumbar plexus is formed from the anterior primary rami of lumbar nerve roots L1-L4 in the body of the psoas muscle approximately one centimetre deep to the transverse processes of the respective lumbar vertebra. The branches emerge from the medial (obturator nerve), anterior surface (gentitofemoral nerve) and the lateral border (ilioinguinal, iliohypogastric, lateral cutaneous nerve of thigh and the femoral nerve from above downwards) of the psoas

muscle to supply the skin of the groin, upper leg and the muscles of the hip and knee joint (see Figure 2-1).

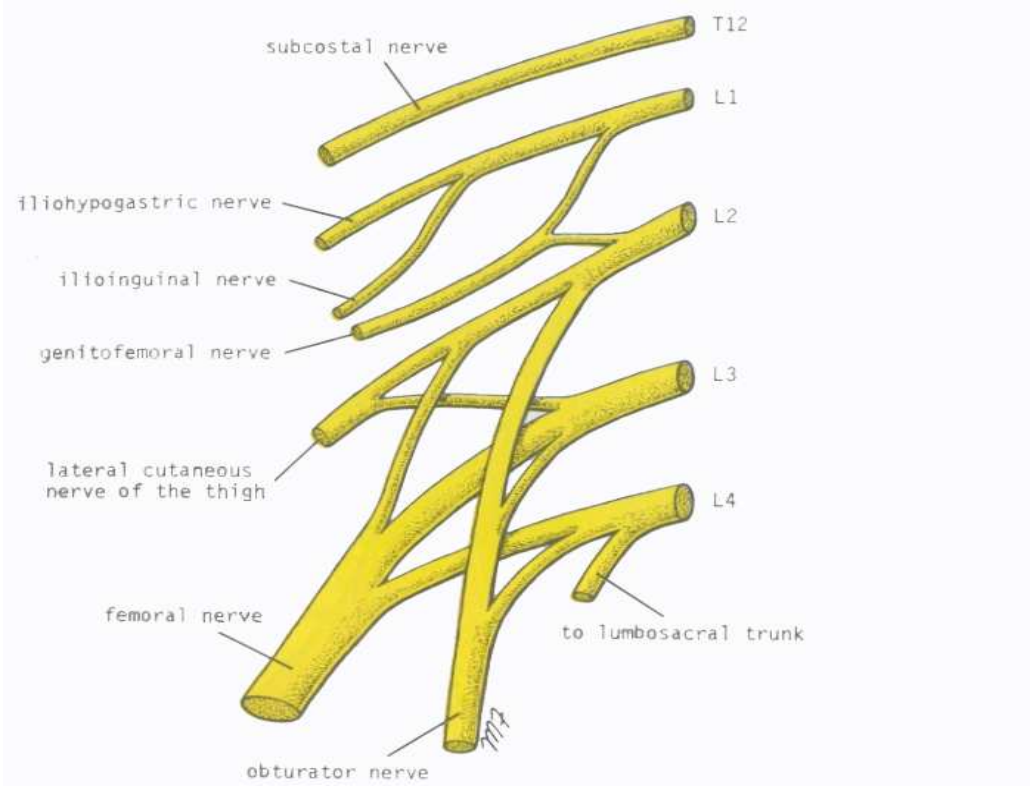
The femoral nerve is formed in the body of the psoas muscle from the posterior divisions of the anterior primary rami of L2-4. Inferiorly it lies on the surface of a groove between iliacus muscle laterally and psoas muscle medially. It is covered by the iliacus facia which also covers the lateral cutaneous nerve of the thigh and separates both nerves from the femoral artery and vein (see Figure 2-2). The femoral nerve passes under the inguinal ligament and divides into an anterior and posterior division and its terminal branches. The anterior division supplies muscular branches to the sartorius and pectineus muscles and cutaneous branches to the intermediate and medial cutaneous nerves of the thigh. The posterior division supplies the quadriceps muscles and forms the saphenous nerve which supplies the skin on the medial side of the foot and leg.

The lateral cutaneous nerve of the thigh is formed from the anterior primary rami of L2 and L3 travel inferiorly and laterally on the body of the iliacus muscle covered by the iliacus fascia to lie on top of the sartorius muscle. It then pierces the lateral end of the inguinal ligament and divides into anterior and posterior divisions to supply an extensive area of skin on the lateral aspect of the leg from the lower lateral quadrant of the buttock to the lateral aspect of the hip and knee joints.

The obturator nerve is formed from the anterior primary rami of L2, L3 and L4. It emerges from the medial border of the psoas muscle and travels inferiorly to cross the pelvic brim and lie anterior to the sacroiliac joint and posterior to the common iliac vessels. It leaves the pelvis and passes into the thigh by passing through the obturator foramen and dividing into anterior and posterior divisions. The anterior division emerges over the top of the obturator externus muscle and passes between the obturator longus muscle anteriorly and the adductor brevis muscle posteriorly to supply both these muscles and the gracilis muscle. It gives an articular branch to the hip joint and supplies a variable branch to the skin overlying the subsartorial canal (see Figure 2-3). The posterior division passes through the obturator externus muscle supplying it and passes between the

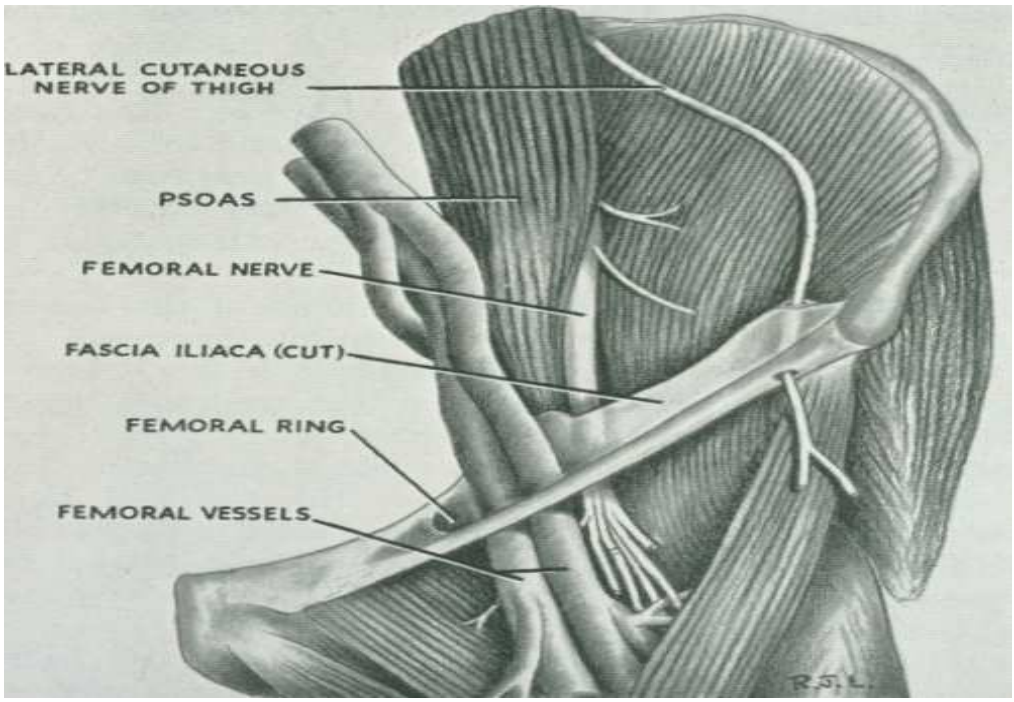
adductor brevis muscle and adductor magnus muscle supplying the adductor part of adductor magus and terminates with articular branches to the knee joint.

Figure 2-1: The Lumbar plexus



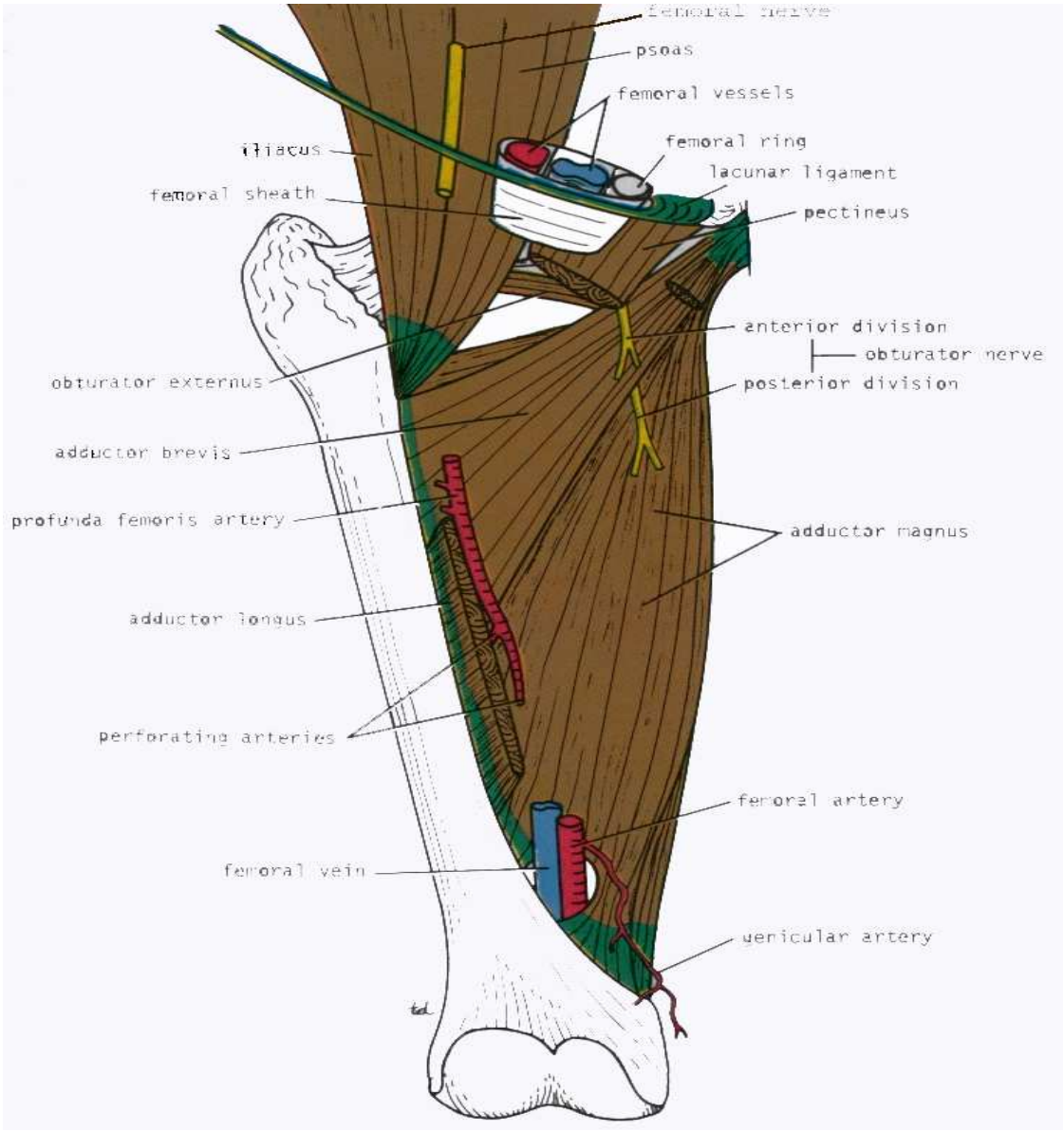
The Lumbar plexus Adapted from Snell Clinical Anatomy For Medical Students, 3rd edition by Little, Brown and Company publishing, page 263.

Figure 2-2:.The femoral vein artery and nerve and the lateral cutaneous nerve with superficial structure removed.



Adapted from Last's Anatomy Regional And Applied, 4th edition Churchill publishing page 193

Figure2-3: The obturator nerve in the anterior thigh:



Adapted from Snell Clinical Anatomy For Medical Students, 3rd edition by Little Brown and company publishing page 585.

2.2.1 The sonoanatomy of 3-in-1 femoral nerve block

The ultrasound probe should be positioned parallel to the inguinal ligament at that level or just below it and moved medially and lateral until the common femoral artery is imaged in cross section proximal to the profunda femoris branch. The position of the ultrasound probe and the ultrasound image of the femoral nerve, artery and vein are shown in Figure 2-4 and Figure 2-5 respectively.

Figure 2-4: The position of the ultrasound probe to generate the image below of the femoral artery vein and nerve.

Image from personal collection of Dr Malcolm Watson

Figure 2-5: The femoral nerve is usually seen lateral to the femoral artery as a triangular speckled structure.

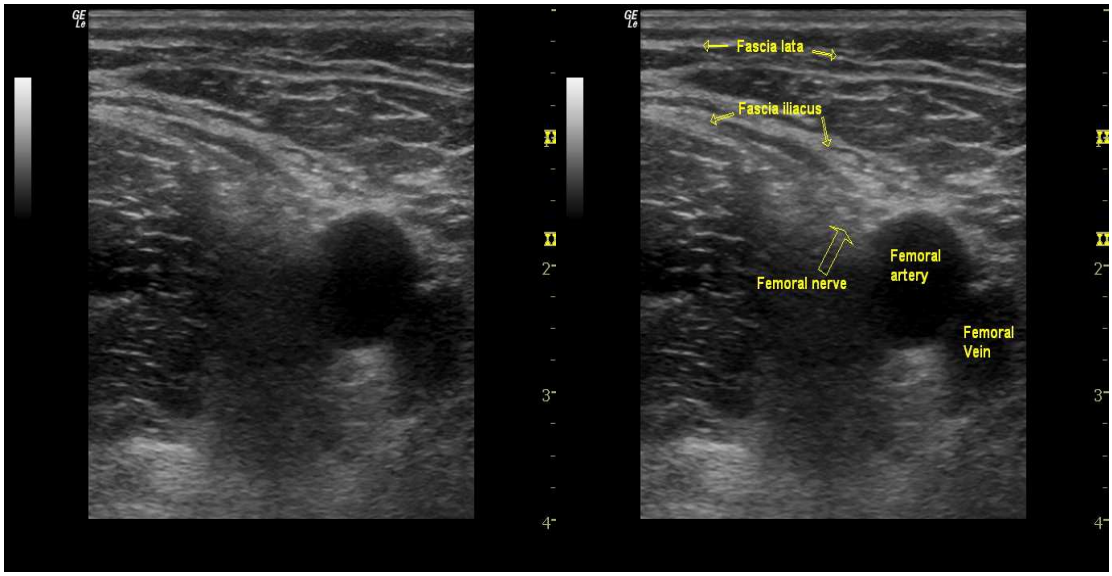


Image from personal collection of Dr Malcolm Watson

2.2.2 History

Winnie et al first described the femoral 3-in-1 block in 1973 in a paper which was entitled the 'inguinal perivascular technique for lumbar plexus anaesthesia, the "3-in-1 Block"(Winnie, Ramamurthy, & Durrani 1973). In this paper, Winnie et al described the anatomy of the femoral 3-in-1 nerve block, and claimed that a single injection would consistently block the femoral, obturator and lateral cutaneous nerves due to the presence of a fascia sheath enveloping all three nerves and rostral spread of local anaesthetic. The existence of the fascia sheath and the ability to block all three nerves, consistently, with a single injection has been widely disputed. The omission of the obturator nerve block has been demonstrated by a number of investigators. The first clinical trial to demonstrate this was published by Parkinson et al in 1989 (Parkinson et al. 1989). Two case reports pre-dated this by Sharrock (Sharrock 1980) and Lonsdale (Lonsdale 1988) in which they descried inadvertent femoral nerve block with no motor (adductors muscle weakness) evidence of an obturator nerve block while attempting to block the lateral cutaneous nerve in 1980 and 1988 respectively. The most widely quoted evidence for 'obturator escape' was provided by Lang et al in 1993. Lang et al demonstrated that sensation in the medial part of the upper thigh was supplied by the femoral nerve in a majority of cases, and that determination of obturator nerve block could only be done by measuring adductor power (Lang et al. 1993). Bouaziz et al confirmed this finding by selectively blocking the obturator nerve and then performing a femoral 3-in-1 nerve block using a nerve stimulator (Bouaziz et al. 2002). Bouaziz et al found that in 57% of patients the obturator nerve had no cutaneous sensory innervation and in the remaining 23% had an area of hypoesthesia (partial innervation) on the inferior medial aspect of the thigh and that only 20% of patients had a cutaneous sensory distribution.

2.3 Methods used to site the femoral 3-in-1 nerve block

2.3.1 The use of nerve stimulators for femoral 3-in-1 nerve blocks

Greenblatt et al 1962 produced the first description of the percutaneous use of a nerve stimulator in a method which would be recognisable to anaesthetists today (Greenblatt & Denson 1962). However the technique and principles of nerve localisation using electrical stimulation were first described by Pearson in 1955 (Pearson 1955) and Sarnoff in 1951 (Sarnoff & Sarnoff 1951).

Nerve stimulator is the current gold standard in regional anaesthesia to detect proximity of the needle tip to the nerve. Fanelli et al conducted a prospective multicentre observational study in Italy of 3996 patients of which 2175 had combined femoral and sciatic nerve blocks guided with a nerve stimulator for a lower limb surgery (Fanelli et al. 1999). Fanelli reported a failure rate of only 153 (7%), which was defined as the use of general anaesthesia to complete the surgical procedure. It is interesting to note that 635 (29%) of these patients when questioned afterwards would refuse the same anaesthetic technique if they were scheduled to have further similar surgery. Fanelli et al thought that this was the result of the transient discomfort during the block placement due the combined effects of nerve stimulation and multiple needle advancements. It is interesting to postulate that it could have been due to the discomfort of an incomplete nerve block during surgery which would have been treated initially with wound infiltration and supplementary block by the surgeon. The observational design of this study could have allowed observer bias. It is therefore reasonable to conclude that the true block failure rate for combined sciatic and femoral nerve blocks using a nerve stimulator was likely to have been higher than the 7% reported by Fanelli et al. A study by Marhofer et al estimated the success rate of a nerve stimulator guided femoral 3-in-1 nerve block as 85% (Marhofer et al. 1997).

2.3.2 Loss of resistance for femoral 3-in-1 nerve blocks

The loss of resistance technique was a development of the inguinal perivascualar technique of Winnie's original description. It utilised the presence of a loss of resistance to the advancement of a blunt tipped needle to the fascia lata and

fascia iliacus membranous layers (covering the branches of the lumbar plexus anteriorly). The first description of this technique in the literature was by Khoo et al in 1983 (Khoo & Brown 1983) but this method was first used in a clinical trial published in 1989 by Dalens et al (Dalens, Vanneuville, & Tanguy 1989). Dalens et al claimed a 90% success rate with a loss of resistance technique in the first published series using quality of analgesia as the primary end point in a paediatric patient population. The technique utilised by Dalens did not require a nerve stimulator or special needles and used a blunt 'Tuohy' tipped needle to detect loss of resistance to advancement. Dalens et al also claimed to consistently block the obturator, femoral and lateral nerves using this technique. Capedvila et al was the first to use the loss of resistance technique in an adult population (Capdevila et al. 1998). In contrast to Dalens, but in common with the studies using the femoral 3-in-1 technique of Winnie (Lang 1998), Capdevila et al was unable to demonstrate consistent motor blockade of the obturator nerve but was able to demonstrate reliable blockade of the femoral and lateral cutaneous nerves. Morau et al concluded that the loss of resistance technique was at least as effective in providing post operative analgesia in a cohort of 44 adults scheduled for elective anterior cruciate repair or femoral osteotomy as the femoral 3-in-1 nerve block guided by a nerve stimulator and was quicker cheaper and required less equipment.

The simplicity and effectiveness of the loss of resistance technique has lead to it being used successfully in the pre-hospital trauma setting for fractured shaft of femur (Lopez et al. 2003) and in accident and emergency departments to provide pain relief for fractured neck of femur patients (Monzon, Iserson, & Vazquez 2007).

2.3.3 The use of ultrasound for the femoral 3-in-1 nerve block

Thirty years ago, Winnie and colleagues succeeded in blocking the femoral, obturator and lateral cutaneous femoral nerves with a single inguinal perivascular injection. This approach came to be known as the 'femoral 3-in-1 nerve block'. Despite the use of nerve stimulation and the loss of resistance the femoral 3-in-1 nerve block has a failure rate of approximately to 20% (Tierney *et al*. 1987). It is possible that the use of ultrasound could reduce the failure rate of the femoral 3-in-1 nerve block.

The femoral 3-in-1 nerve block is ideally suited to the use of ultrasound guidance with a high frequency (10 MHz or more) linear probe because of the relatively superficial position of the femoral nerve distal to the inguinal ligament, lateral to the femoral artery, and below the fascia iliacus membrane. The Vienna group demonstrated that ultrasound guidance significantly improved the puncture-to-onset interval and the quality of sensory block in all three nerves while avoiding complications such as arterial puncture (Marhofer et al. 1997). The use of ultrasound monitoring has allowed repositioning of the needle in the event of misdistribution of local anaesthetic above the fascia iliacus membrane. The work of Marhofer et al also demonstrated that less local anaesthetic was required for a femoral 3-in-1 nerve block with ultrasound guidance in comparison to the use of a nerve stimulation (Marhofer et al. 1998).

2.3.4 Adverse events related to femoral 3-in-1 nerve block

The largest study of the complications associated with regional anaesthesia was a survey of 158083 regional anaesthetic procedures performed by 487 anaesthesiologists over a 10 month period in France (Auroy et al. 2002). 10309 femoral 3-in-1 nerve blocks were performed during this study; no deaths, cardiac arrests, episodes of respiratory failure or seizures were reported and only three peripheral neuropathies were reported all of which had completely recovered by three weeks. The study estimated that the true incidence of deaths, cardiac arrests, episodes of respiratory failure or seizures associated with the femoral nerve block using loss of resistance and nerve stimulation was a 95% CI: 0 - 2.9/10000 nerve blocks. The recorded incidence of transient neurological complications was 2.9/10000 (95% CI: 0 to 7.8/10000 nerve blocks. Fanelli et al reported a 2% incidence (45 nerve blocks) of transient neurological complications in his observational study of 2175 combined femoral 3-in-1 and sciatic nerve blocks in Italy and all but one of these complications had resolved completely by the 12 week follow up (Fanelli et al. 1999). The very high incidence of neurological complication in Fanelli's study may be partly explained by the use of a multiple injection technique, high tourniquet pressures (>400 mmHg) and the combined reporting of adverse events from both the sciatic nerve block and the femoral nerve blocks. In the study by Auroy (Auroy et al. 2002) the popliteal approach to the sciatic nerve was associated with a neurological complication

incidence of 31/10000 (95% CI: 0 to 84.0/10000 nerve blocks), however Fanelli et al used the classic subgulteal approach of Labat which was associated with very low neurological complication incidence of 3/10000 (95% CI: 0 to 8.2/10000 nerve blocks).

Neurological complications are the category of adverse events most frequently attributed to a peripheral nerve blockade but several factors have been highlighted in the development of neurological complications. These factors include neurotoxicity of local anaesthetics and malpostioning during surgery, tourniquet inflation pressure (Fanelli et al. 1999)and Blumenthal et al (Blumenthal *et al*. 2006) suggested that pre-existing subclinical polyneuropathy may be a risk factor for the development of neurological complications.

The aggregate incidence of transient neurological adverse events associated with a femoral 3-in-1 nerve block in meta-analysis of 4 trials by Brull et al was 34/10000 (95% CI: 0.04 to 2.81%) (Brull et al. 2007). The femoral 3-in-1 nerve blocks were inserted using various techniques (nerve stimulator, loss of resistance and elicitation of paraesthesia). Brull reported only one incidence of permanent neurological injury associated with a femoral nerve block after 13378 (incidence 7.5/100000) femoral 3-in-1 nerve blocks. The vast majority of neurological complications reported have been transient but Cuvillon et al reported one femoral paraesthesia without motor weakness which had only partially resolved at one year follow up in 211 patients who had femoral nerve block using a nerve stimulator and catheter insertion (Cuvillon *et al*. 2001).

In comparison, in the meta analysis by Brull the incidence of neurological complications caused by brachial plexus block using the interscalene approach (2.84/100 [95% CI: 1.33 to 5.98]) and the axillary approach (1.48/100 [95% CI: 0.52 to 4.11]) and the sciatic nerve (0.41/100 (95% CI: 0.02 to 9.96]) was in excess of the cumulative incidence in the femoral nerve group (0.34/100 [95% CI: 0.04 to 2.81]) (Brull et al. 2007). In summary, several studies have confirmed that femoral nerve block has one of the lowest incidences of adverse events both in terms of cardiac and respiratory complications and peripheral neuropathies.

2.3.5 The use of ultrasound to increase success rate and decreased adverse events

The systematic review by Abrahams et al did find that ultrasound guided blocks were associated with fewer vascular punctures (RR(risk ratio)=0.16 [95% CI: 0.05 to 0.47]) compared to those blocks performed with a nerve stimulator they did not find any statistically significant difference in paraesthesia during block or persistent neurological symptoms after the block's resolution (Abrahams et al. 2009). However, the total number of patients included in the meta analysis was only 946. Four studies containing a total of 240 patients reported vascular puncture and only two studies reporting neurological symptoms and these studies contained a total of 206 patients. The systematic review may be criticised on the basis that one of the studies included by Sauter et al (Sauter *et al*. 2008) contained a worryingly high rate of vascular punctures in the nerve stimulator treatment group (i.e. 13 vascular punctures in 40 patients and therefore provided 56.4% of the weighting of the final result). However, all the studies included favoured the use of ultrasound over nerve stimulator to reduce vascular puncture. If the incidence of serious neurological symptoms following the resolution of the block is assumed to be 1/10000 (averaging the values found by Auroy et al for the supraclavicular (0/10000 [95% CI: 0.0 to 15.9]) block and axillary block (1.8/10000, [95% CI: 0.0 to 6.3]) then it is unlikely that any conclusion could be drawn from this meta analysis for neurological complications as they where only reported in two of the studies containing a total of 206 patients.

2.3.6 Comparison of methods; ultrasound, nerve stimulator, loss of resistance

The success of a peripheral nerve block can be measured in many different ways, loss of sensory and motor function, postoperative pain scores, analgesia consumption postoperatively or by the need for supplementary regional or general anaesthesia to complete the scheduled surgical procedure. In 1997, Marhofer et al used sensory and motor testing to define success and published a series of patients with a 95% success rate using sensory testing as the primary end point in patients with a fractured neck of femur and 85% success rate using a nerve stimulator guided technique (Marhofer et al. 1997). The 1997 Marhofer

et al study recruited forty patients American Association of Anesthesiologists (ASA) physical status II or III) undergoing hip fixation or replacement hemiarthroplasty after suffering a fractured neck of femur. Patients were randomised to receive 20 ml bupivacaine 0.5% administered using ultrasound (US) guidance or with nerve stimulator (NS) guidance. The quality and the onset of the sensory block was assessed by using the pinprick test in the central sensory region of each of the three nerves and compared with the same area on the contra lateral leg every 10 minutes for one hour. The rating was performed using a scale from 100% (uncompromised sensation) to 0% (no sensory sensation). The onset of sensory blockade was significantly quicker in the US Group compared with NS Group (US 16 ± 14 min, NS 27 ± 16 min; $P<0.05$). The quality of the sensory block after injection of the local anaesthetic was also significantly better in US Group compared with NS Group (US 15% ± 10% of initial value, NS 27% ± 14% of initial value; $P<0.05$). A successful femoral nerve block was achieved in 95% of the patients in the US group and in 85% of the patients in the NS group. In the US group, visualisation of the cannula tip, the femoral nerve, the major vessels, and the local anaesthetic spread was possible in 85% of patients. Incidental arterial puncture (n=3) was observed only in the NS group. Marhofer et al concluded that a US guided approach for femoral 3-in-1 nerve block reduced the onset time, improved the quality of the sensory block and minimised the risks associated with this regional anaesthetic technique. Although this study included a small number of patients it did show an improved sensory block and a reduced onset of block time associated with the use of ultrasound. The use of nerve stimulators in patients with an unfixed proximal femoral fracture would be unlikely to gain ethical approval if repeated today but otherwise the study appeared to be methodologically sound.

Marhofer published a further study in 1998 which supported his original conclusions that ultrasound guidance improved sensory blockade, increased the success rate and could also allow reduction in local anaesthetic dosing (Marhofer et al. 1998). Sixty patients with a fractured neck of femur were recruited and randomly assigned to three groups of 20. Group A received a femoral nerve block with ultrasound and 20 ml of 0.5% bupivacaine, group B and group C received a femoral nerve block using a nerve stimulator with 20 and 30 ml of bupivacaine respectively. The overall success of the blocks defined by sensory

testing as in the previous study was 95% in the ultrasound group and 80% in the two nerve stimulator groups ($p>0.01$). The onset time for group A was 13mins ± 6mins, group B was 27±12mins and group C was 26±13mins. The onset of the femoral 3-in-1 nerve block was significantly shorter ($p<.01$) when group A (which used ultrasound) was compared to both to groups B and C (which both used nerve stimulator) to guide the femoral 3-in-1 nerve block.

Dalens et al published a 90% success rate with femoral 3-in-1 nerve block using the loss of resistance technique in but the majority of workers have achieved a lower rate of success. (Dalens, Vanneuville, & Tanguy 1989). However Morau et al claimed a 100% success rate in two small groups of patients; 22 patients in the 3-in-1 group using a nerve stimulator and 22 patients in the loss of resistance group (Morau *et al*. 2003). The results of a study by Dolan et al suggested that the femoral 3-in-1 nerve block was significantly less successful if loss of resistance was used to guide the needle placement in comparison with ultrasound guidance (47% success with loss of resistance in comparison to 85% with ultrasound)(Dolan et al. 2008).

A systematic review and meta-analysis by Abrahams et al showed that the use of ultrasound in comparison with using nerve stimulators to guide the needle was associated with fewer block failures (risk ratio=0.41 [95% CI: 0.26 to 0.66; $p<0.001$]) (Abrahams et al. 2009). Abrahams et al defined block failure as necessitating the use of additional general or spinal anaesthesia to complete the planned surgical procedure as all the blocks were used to provide surgical anaesthesia. The systematic review and meta analysis by Abrahams does suggest that the use of ultrasound is superior to the use of a nerve stimulator. It should also be noted that of the nine studies included in this part of this meta analysis only one used a combined femoral nerve and only sciatic nerve block for lower limb surgery. The strength of this conclusion is further weakened by the fact that the largest study recruited only 126 patients with 4 out of nine studies recruiting less than 40 patients.

2.3.7 The use of the femoral nerve block and hip fracture to reduce pain scores and morphine consumption

In 1995 Haddad et al randomised 50 patients with a fractured neck of femur to opiate analgesia or femoral 3-in-1 nerve block using a controlled prospective unblinded methodology (Haddad & Williams 1995). Paraesthesia was elicited by a needle inserted perpendicular to the skin one centimetre lateral to the femoral artery and 0.3 ml/Kg of 0.25% bupivacaine was injected. The pain visual analogue scores (VAS) were then recorded at 15 minutes, two hours and eight hours and complication rate and systemic analgesia required during the subsequent 24 hours were recorded. A statistically significant reduction in mean pain VAS score, was noted between the group of 24 patients with a femoral 3-in-1 nerve block and the 21 patients in the control group at 15 minutes (4.8 mm, range 1-8 mm; 6.8 mm, range 3-10 mm, $p<0.05$) and two hours (3.7 mm, range 1-8 mm; 5.7 mm range 2-9 mm $p<0.05$) respectively post femoral 3-in-1 nerve blockade. A reduction in respiratory complications in femoral 3-in-1 nerve block group (two incidences versus nine incidences) was recorded. However Haddad et al failed to define the nature or severity of the respiratory complications or the number of the affected patients. No difference was noted in the incidence of urinary tract, wound infection, skin break down, cardiac complications or proven deep vein thrombosis. A statistically significant reduction in the number of doses of parental opiate given in the first 24 hours after the femoral nerve block was also recorded (35 doses versus 12 doses; $p<0.05$). However Haddad et al provided no details of the doses of analgesia given, nature of the opiate analgesia or the prescribing procedures used. Five patients were recruited to this study but their results are not included in the final analysis as this accounts for 10% of the total population of the study their removal from the study could confound the results and conclusions of this study. This study was open to bias as many of the end points used were subjective. The failure to define the outcome adequately further weakens this study and limits its usefulness.

In 1988 Finlayson et al recruited thirty-six patients with traumatic femoral neck fractures attending the accident department during a three month period who received femoral 3-in-1 nerve blocks from one of the two authors (Finlayson & Underhill 1988). The effect of the block was assessed both subjectively and objectively. Thirty patients reported a ‘worthwhile reduction in pain’ following

the procedure and this was supported by objective sensory testing in 29 patients. In all six patients who reported no benefit, the block had also failed on objective sensory testing.

In 2003 the femoral 3-in-1 nerve block guided by loss of resistance was used in a pre-hospital setting to provide analgesia for 27 patients with a femoral shaft fracture to allow transport to hospital and hip radiography (Lopez et al. 2003a). The block produced a significant reduction in pain ($p<0.05$ in comparison to the pre-block pain score although a simplified verbal scale (SVS) from 0 (no pain) to 4 (severe pain) was used to assess pain. The use of a non standard pain score detracted from the impact of this study.

In 2007 Monzon et al published a prospective, interventional, and uncontrolled study of the utility of the femoral 3-in-1 nerve block in patients with a traumatic fractured neck of femur (Monzon, Iserson, & Vazquez 2007). Sixty three sequential adult patients were recruited with traumatic fractured neck of femur. A loss of resistance technique was used to guide needle placement and 0.3 ml/kg of 0.25% bupivacaine was injected under the fascia iliacus membrane. The physician tested the block's efficacy by assessing cutaneous sensory loss. Pain assessments were done using a 10-point Likert Visual Analogue Scale (VAS) before, and at 15 minutes, two hours, and eight hours after the block. Post femoral 3-in-1 nerve block pain was reduced in all patients, but not completely abolished in any patient. Pre femoral 3-in-1 nerve block, the pain ranged from 2 to 10 points (average 8.5) using the pain VAS; at 15 minutes post-injection, it ranged from 1 to 7 points (average 2.9); at two hours post-injection, it ranged from 2 to 6 points (average 2.3); at eight hours post-injection, it ranged from 4 to 7 points (average 4.4). Analgesic requests in the first 24 h after admission averaged 1.2 doses (range 1 to 4 doses) of diclofenac 75 mg. There were no systemic complications and only two local haematomas. The confounding variables in this study were the inclusion of patients who became confused during the study period which could have invalidated the pain VAS assessment in these patients, the administration of unrecorded and uncontrolled oral analgesia during the study period and the use of different volumes of local anaesthetic in patients of different weight. The study results suggest that a marked reduction

in pain VAS score may be possible 15 minutes after the injection of a relatively low volume and dose of local anaesthetic.

A Cochrane meta-analysis by Parker et al in 2002 examined the effects of nerve blocks (inserted pre-operatively,intra-operatively or post-operatively) as part of the treatment for a hip fracture (Parker, Griffiths, & Appadu 2002). Parker et al analysed eight randomised or quasi-randomised trials involving 328 patients and was published in 2002. He concluded that nerve blocks resulted in a reduction of the quantity of parenteral or oral analgesia administered to control pain from the fracture or during surgery and a reduction in reported pain levels. It was not; however, possible to demonstrate any other outcome benefits. This may have been due, in part, to the heterogeneity of methodology of the studies included and the relatively small number of patients recruited to the studies.

2.4 Summary of Chapter 2

The femoral 3-in-1 nerve block, (femoral nerve, fascia iliacus, or anterior psoas compartment block) appears to be a viable solution to provide analgesia to patients with a fractured neck of femur prior to definitive surgical fixation. It blocks the majority of the five nerves innervating the hip and since the acetabulum is normally undamaged by surgery or trauma it may block the three most important nerves (femoral, obturator and lateral cutaneous nerve). The femoral 3-in-1 nerve block is technically simple in contrast to epidural anaesthesia and requires little extra monitoring and nursing care. Ultrasound offers the potential of an increased success rate with fewer complications but it is associated with the cost of the ultrasound machine and extra of staff training. In contrast, the loss of resistance technique is technically simple and cheap but potentially inaccurate and associated with a higher complication rates.

Chapter 3

3 The development of study protocols designed to answer the research questions for the project

3.1 Background

This project will answer research questions which will allow the development a protocol to provide safe, effective regional analgesia to the 60000 to 70000 patients admitted annually to UK hospitals with a fractured neck of femur (Bottle & Aylin 2006). The hospital mortality for patients with a fractured neck of femur in a large UK study was 14.3% with cardiac aetiologies predominating in the first 2 days (Bottle & Aylin 2006). A study has suggested a link with effective pain relief and improved cardiac morbidity and reduced mortality in patients with a traumatic fractured neck of femur (Matot et al. 2003). Anaesthetists currently utilise the femoral 3-in-1 nerve block to provide effective pain relief postoperatively but these techniques use large, potentially toxic doses of local anaesthetic. Ultrasound guided nerve blocks have been associated with an increased success rate, lower local anaesthetic doses and shorter onset times than traditional techniques (Marhofer et al. 1998). This will reduce the pain experienced by patients with a fractured neck of femur but may also result in reduced mortality and morbidity.

3.2 Research questions

In order to develop a method of providing pain relief to patients with a fractured neck of femur we need to answer the questions below:

1. Which method do we use to site the local anaesthetic?
2. Which local anaesthetic should we use?
3. What is the effective dose of levobupivacaine for a femoral 3-in-1 nerve block
4. What is the duration of analgesia from the EC_{95} dose of levobupivacaine?
5. What is the pharmacokinetic profile of levobupivacaine in the population of patients with a fractured neck of femur?
6. What is the clinical anatomy of the femoral 3-in-1 nerve block?

3.2.2 Research question 1: Which method should we use to site local anaesthetic for the femoral 3-in-1 nerve block?

There are currently three methods available to guide the injection of local anaesthetic around the femoral nerve; loss of resistance, nerve stimulation and ultrasound. The use of nerve stimulators is the current standard but their use on patients with a fractured neck of femur will potentially cause significant discomfort. No clinical study has compared all three techniques for a femoral 3-in-1 nerve block. Utilising the data from previous studies we calculated that 180 patients would need to be recruited to a study to have 80% power to discriminate between all three methods (see Chapter six section 6.4.7 for the sample size calculation). The efficacy of a nerve block was determined by assessment of the sensory and motor changes associated with the local anaesthetic action on nerve fibres. Indirect measures of success such as postoperative pain scores, reduced morphine consumption and the need to convert to general anaesthesia have multiple confounding factors. Primary total hip arthroplasty patients were chosen as the patient population for this study due to the subjective nature of sensory testing, the inability to use the current standard method (nerve stimulator) on unfixed fractures, the large number of patients needed (180) and the inability to conduct motor testing on a limb with a fracture.

3.2.1.1 Summary of methodology

We recruited 180 competent patients scheduled for elective primary total hip arthroplasty on three hospitals in Glasgow, Scotland. A femoral 3-in-1 nerve block was performed preoperatively using either ultrasound, loss of resistance or nerve stimulator to guide the positioning of the needle tip. Sensory and motor function in the upper leg was assessed to determine the effectiveness of the nerve block at 10 minute intervals for 30 minutes. Spinal anaesthesia was used in the vast majority of cases however if the spinal block was considered inadequate or the spinal was technically difficult general anaesthesia was used at the discretion of the attending consultant anaesthetist. A primary total hip arthroplasty was performed using standard surgical procedures. Postoperatively, all patients received regular paracetamol, patient controlled morphine and

titrated doses of morphine as required to provide a pain NRS (numerical rating scale) scores <30/100 (mild pain). At six hours and 24 hours postoperatively the acute mental test score, total morphine usage and patient satisfaction scores were recorded. We also recorded the day and time the patient was first mobilised by physiotherapy and the hospital mortality. Please see chapter six for a description and full discussion of this study.

3.2.3 Research question 2: Which local anaesthetic should we use?

The choice of local anaesthetic was dictated by two factors namely, duration of action and toxicity. bupivacaine and its stereoisomer levobupivacaine have the longest duration of action of any commercially available local anaesthetic agent in the UK, with 90% hepatic metabolism and a metabolic half life of 3.5 hours in adults (Rossi S 2006). A single injection of bupivacaine or levobupivacaine will provide pain relief (measured by time to first dose of analgesia) for a median of approximately 16.5 hours (Urbanek et al. 2003). Levobupivacaine is the S (-) stereoisomer of the racaemic mixture of bupivacaine. There is convincing evidence from in-vitro studies on sodium channels of guinea pig myocytes (Valenzuela *et al*. 1995), from in-vivo animal studies on anaesthetised sheep (Chang et al. 2000;Huang et al. 1998) and from human volunteer studies (Bardsley et al. 1998) that the probability of an adverse event (Bardsley et al. 1998) related to the cardiac and CNS toxicity of local anaesthetics can be reduced when levobupivacaine is used instead of bupivacaine.

The vast majority of local anaesthetic dosing is based on administering the maximum safe dose were it to be accidentally given intravenously. This dose is 2 mg/kg for both levobupivacaine and bupivacaine (Mulroy 2002). We currently have no information from studies that would allow dosing based on the analgesic effectiveness of levobupivacaine for the femoral 3-in-1 nerve block. Sequential plasma measurements of levobupivacaine after femoral 3-in-1 nerve block in children showed that the concentration increased rapidly from baseline to peak after 10 to 45 minutes (Paut et al. 2004). It is necessary to determine the effective dose in patients with a fractured neck of femur as they are usually elderly and they are therefore at theoretically greater risk of local anaesthetic

toxicity due to reduced plasma clearance (Knudsen et al. 1997;Paut et al. 2004). In contrast, the efficacy of local anaesthetics is greater in peripheral (Paqueron et al. 2002) and neuraxial blocks (Bromage 1969;Paqueron et al. 2002;Simon et al. 2004) in elderly patients. The Summary of Product Characteristics updated on the eMC: 26/08/2009 for levobupivacaine states in Section 4.4 Special warnings and precautions for use 'The lowest dosage of local anaesthetic that results in effective anaesthesia should be used to avoid high plasma levels and serious adverse effects.'

3.2.4 Research question 3: What is the effective dose of levobupivacaine for a femoral 3-in-1 femoral nerve block?

Several studies have attempted to determine the effective concentration but each had methodologically issues which limit the interpretation of the results. The currently accepted method is to determine the effective concentration (with a fixed volume of local anaesthetic) in 50% of patients (EC_{50}) using a binary regression modelling and estimate the EC_{95} and the 95% confidence intervals for both the EC_{50} and EC_{95}. This is done by testing the effectiveness of various concentrations while the volume remains constant. The only variable should be the concentration of local anaesthetic and hence dose of local anaesthetic administered. Casati et al increased and decreased the volume of local anaesthetic for the femoral 3-in-1 nerve block and kept the concentration the same. Therefore the total drug dose and the volume were both altered by each change in volume (Casati *et al*. 2007). A study by Taboada et al used identical methodology to determine the volume of 1.5% mepivacaine for the subgluteal and popliteal approach to the sciatic nerve (Taboada *et al*. 2006) and two further studies by Gupta et al and Duggan et al used the same methodology to calculate the median effective volume for the supraclavicular block (Duggan et al. 2009;Gupta & Hopkins 2008). In all studies no details on the quality control for both the volume and concentration of local anaesthetic was given, no clear study end point or justification of sample size was given and no justification of the value by which the concentration or the volume was changed (stepping value) was given. The current information available is not adequate to

recommend an effective dose of local anaesthetic for peripheral regional anaesthesia.

3.2.3.1 Summary of methodology

To determine the effective dose of levobupivacaine, patients with a traumatic femoral neck of femur fracture were recruited prior to surgical fixation. All patients recruited to the clinical trial received standard anaesthesia and surgical fixation of their femoral neck fracture. Prior to operative fixation of the fractured neck of femur an ultrasound guided femoral 3-in-1 nerve block was used to anaesthetise the nerves supplying the proximal femur. At 10 minute intervals the sensation to pin prick and cold in the upper leg and pain numerical rating scale (NRS) scores were recorded for a total of 30 minutes. A successful femoral 3-in-1 nerve block was defined as ≥20/100 decease in the pain NRS score at 30 minutes with a sensory change (to cold or pin prick) in skin supplied by the femoral nerve. The concentration of levobupivacaine was increased or decreased if the femoral 3-in-1 nerve block was ineffective or effective respectively. The concentration of levobupivacaine tended towards a concentration which was successful in 50% of patients (EC_{50}). Please see chapter four for details of this clinical trial.

3.2.5 Research question 4: What is the duration of analgesia from the EC95 dose of levobupivacaine?

In the study by Urbank et al the mean duration of analgesia (measured by time to first dose of analgesia) for the femoral 3-in-1 nerve block with 20 mls of 0.5% levobupivacaine sited using a nerve stimulator in various procedures was a mean of 16 hours 41minutes with 95% confidence intervals of (14 hours 4 minutes to 19 hours 18 minutes) (Urbanek et al. 2003). The vast majority of patients should have surgical fixation of the fractured neck of femur within 24 hours of admission within day time working hours (Scottish Intercollegiate Guidelines Network (SIGN)-Guideline 111), therefore if the duration of analgesia is longer than 24 hours it will prevent early mobilisation of the patient. In the past, delayed surgical management and therefore delayed mobilisation has been associated with increased mortality as discussed in chapter one. Jain et al

examined a series of 62 elderly patients within their cohort with severe co-morbidity treated non-operatively (Jain, Basinski, & Kreder 2003). They found that non-operative treatment with bed rest was 3.8 times more likely to be associated with mortality compared to non-operative treatment and operative treatment with early mobilisation (95% CI 1.1 to 14). However, If the duration of analgesia provided by the femoral 3-in-1 nerve block is too short it may also ameliorate any benefit.

3.2.4.1 Summary of methodology

Once the effective concentration to provide analgesia in 95% of patients (EC_{95}) had been determined the duration of analgesia by a single 30ml dose of the EC_{95} of levobupivacaine was determined. Patients with a traumatic proximal femoral fracture were recruited prior to surgical fixation. Prior to operative fixation of the fractured proximal femur an ultrasound guided femoral 3-in-1 nerve block was used to anaesthetise the nerves supplying the proximal femur. At 10 minute intervals the sensation to pin prick and cold in the upper leg and pain verbal analogue scores (VAS) were recorded for a total of 30 minutes. A successful femoral nerve block was defined as ≥20/100 decease in the pain NRS score after 30 minutes associated with a sensory change (to pin prick and cold) in skin supplied by the femoral nerve. If the nerve block was defined as being successful then the duration of analgesia was recorded hourly until the pain score returned to the starting value. Please see chapter five for details of this clinical trial.

3.2.6 Research question 5: What is the pharmacokinetic profile of levobupivacaine in the population of patients with a fractured neck of femur?

The population of patients that suffer a fractured neck of femur often have multiple co-morbidities as shown by the study of Bottle et al (Bottle & Aylin 2006). Bottle et al noted that only 29.2% of those patients operated on within 24 hours of admission had no recorded significant co-morbidity, and this decreased to 19.2% in those patients delayed greater than two days. The femoral 3-in-1 nerve block has been associated with rapid absorption which

raises the possibility of systemic toxicity (Paut et al. 2004). The Summary of Product Characteristics (SmPC) last updated on the eMC: 26/08/2009 for levobupivacaine states in Section 4.2 Physiology and method of administration that 'Debilitated, elderly or acutely ill patients should be given reduced doses of levobupivacaine commensurate with their physical status.' (Abbott Laboratories Limited 2010). The SmPC also states that levobupivacaine should be used in reduced dose in those patients with liver impairment or cardiac problems (Abbott Laboratories Limited 2010). It is therefore prudent to characterise the pharmokinetic profile of the EC_{95} concentration of levobupivacaine before conducting a large multicentre study by non-anaesthetists outside the operating theatre environment.

3.2.5.1 Summary of methodology

The blood samples to answer this question were collected using the protocol outlined in this section, The concentration of levobupivacaine used was the EC_{95} which was determined from the Up/Down Dixon's method (Dixon 1965) to determine the effective dose of local anaesthetic. A blood sample was taken before the insertion of the EC_{95} dose of levobupivacaine and at 5, 10, 20, 30 and 60 minutes post insertion of femoral 3-in-1 nerve block from a cannula. The levobupivacaine blood samples were centrifuged and frozen to -20^0C 1 hour after the first sample was collected for delayed batch analysis. Please see chapter five for details of this clinical trial.

3.2.7 Research question 6: What is the clinical anatomy of the femoral 3-in-1 block?

The femoral 3-in-1 nerve block is a misnomer as the majority of investigators have been unable to consistently anaesthetise the femoral, obturator and lateral cutaneous nerves with a single injection (Capdevila et al. 1998;Lang et al. 1993;Parkinson et al. 1989;Ritter 1995). A recently published study by Dolan et al reignited this debate by demonstrating a motor block of the obturator nerve in 44% of cases and a loss of sensation in the medial aspect of the upper thigh in 60% of ultrasound guided femoral 3-in-1 nerve blocks (Dolan et al. 2008). We undertook pilot research work to determine the maximal spread of 30 ml of

black latex dye injected lateral to the femoral nerve under the fascia iliacus membrane. It was hypothesised that the black latex dye may include the obturator nerve or its branches as a result of proximal spread or spread across the muscular planes in the upper thigh.

3.2.7.1 Summary of methodology

In the Anatomy department of Glasgow University two adult female cadavers who had donated their bodies to medical science where dissected for this study. The two unfixed cadavers had bilateral ultrasound guided femoral 3-in-1 nerve blocks with 30 ml of black latex. They were then fixed and 3 months later dissected to determine the maximal extent of the spread of black latex dye. The results of this pilot study are discussed in chapter seven.

3.3 Summary of protocols used in this project

An initial randomised multicentre trial compared the efficacy of using ultrasound, nerve stimulator and loss of resistance techniques to guide the needle for femoral 3-in-1 nerve block in patients scheduled for an elective primary total hip arthroplasty. Sensation and movement in the upper leg was assessed to determine the effectiveness of the method of guiding the femoral 3-in-1 nerve block at 10 minutes intervals for 30 minutes.

The dosing and safety of utilising levobupivacaine to provide femoral 3-in-1 nerve block was determined in the fractured neck of femur patient population. Levobupivacaine dosing was determined using a sequential Dixon's up/down methodology. Femoral 3-in-1 nerve blocks were performed and the concentration of levobupivacaine was increased or decreased for an ineffective or effective nerve block respectively until the concentration of levobupivacaine was effective in 50% of patients (EC_{50}). A final clinical trial assessed levobupivacaine pharmacokinetics (to ensure that serum levels were within safe limits for the estimated EC_{95} dose of levobupivacaine) and the pharmacodynamics (to assess duration of analgesia) using serial blood sampling and by monitoring pain NRS scores respectively. A final pilot dissection study was conducted to determine the extent of the spread of a 30 ml volume in the space underneath the fascia iliacus membrane and lateral to the femoral nerve.

Chapter 4

4 A dose finding clinical trial for analgesia of a broken hip

4.1 Aim

To determine the effective concentration of 30 ml of levobupivacaine required to produce a reduction in pain numerical rating scale (NRS) score of ≥20 points on a 100 point scale in 50% of patients (EC_{50}) and 95% of patients (EC_{95}) with a fractured neck of femur using an ultrasound guided femoral 3-in-1 nerve block.

4.2 Study design

The EC_{50} and EC_{95} for levobupivacaine with an ultrasound guided femoral 3-in-1 nerve block were determined using the sequential up down (Dixon) methodology (Dixon 1965).

4.3 Study Population

We recruited competent patients with a fractured neck of femur.

4.3.1 All patients recruited to this trial were required to meet the following inclusion criteria

- Patients with a fractured neck of femur
- American Society of Anesthesiology (ASA) grading ≤4/5 (Little 1995)
- Able to give informed consent
- Resting pain numerical rating scale (NRS) score of greater than 50 on a 100 scale before recruitment (moderate pain).
- Able to cooperate with sensory testing of lower limb function

4.3.2 The following exclusion criteria were applied to patients recruited to this trial

- Acute mental test score of ≤7/10 at any time preoperatively
- Allergy to local anaesthetic
- Contra-indication to levobupivacaine administration

- Signs, symptoms or laboratory evidence of:
    - local infection (at intended site of needle insertion)
    - systemic sepsis which would normally preclude regional analgesia
- Pre-existing known neurological deficit (sensory or motor) affecting the lower limb
- Patient with lower limb amputations or other condition affecting sensation in the lower limbs

4.3.3 Criteria for withdrawal of patient from the trial

- Patient initiated withdrawal. Patients could withdraw from the clinical trial at any time.
- Administration of regional anaesthesia or analgesia not in the protocol
- Failure of rescue analgesia 'top-up' with a 20 ml injection of 0.25% levobupivacaine through the catheter sited after the initial injection of 30 ml of levobupivacaine.
- A protocol violation leading to a patient safety issue or a quality issue
- An urgent safety issue with the clinical trial protocol

4.4 Methodology

All patients were recruited preoperatively and were scheduled for fixation of the fractured neck of femur. Consented patients were transferred to the operating theatre suite and initial sensory function testing and a pain NRS score was performed on arrival in theatre. In order to be eligible for recruitment the patient had to have a pre-block resting pain NRS score of ≥50/100. Femoral 3-in-1 nerve blocks were inserted preoperatively using ultrasound needle guidance and 30 ml of levobupivacaine the concentration of which was determined by the response of the previous patient. Needle placement for the femoral 3-in-1 nerve block was guided by ultrasound. Ultrasound images of the common femoral artery, femoral vein and nerve in the short axis were obtained and a 100 mm or 50 mm 18G Contiplex Tuohy tipped needle (supplied by B-Braun Ltd.) was advanced in plane until the tip of the needle was under the fascia iliacus membrane immediately lateral to the femoral nerve. After a 'negative'

aspiration to detect accidental intravascular placement, the local anaesthetic dose was injected. Real time ultrasound images were used to ensure that the injected local anaesthetic (30 ml of levobupivacaine) spread around the femoral nerve with associated 'tenting' of the fascia iliacus membrane. After injection of 30 ml of levobupivacaine a catheter was threaded through the 100 mm or 50 mm 18G Contiplex Tuohy tipped needle and its position confirmed by visualising movement of the catheter under the fascia iliacus membrane. The concentration of levobupivacaine was 0.10% for the first patient recruited. Subsequent concentrations were increased or decreased by 0.025% (the stepping value (δ)) dependant on whether the dose provided ineffective or effective analgesia respectively. At 10, 20 and 30 minutes after the injection of levobupivacaine pain numerical rating scale (NRS) scores and sensory testing on the upper thigh was preformed.

Effective regional analgesia was defined as a ≥20 point reduction in pain NRS score on a 100 point scale with evidence of a sensory impairment in the upper anterior thigh (effective regional analgesia) then the concentration of levobupivacaine was decreased by 0.025% for the next patient recruited. Conversely, if no reduction in sensory impairment was detected on testing in the upper anterior thigh and the pain score decreased by less than 20 points on a 100 scale (ineffective regional analgesia) then the concentration of levobupivacaine for the next patient recruited was increased by 0.025%. If the sensory response in the anterior upper thigh and the pain NRS score were at odds the response was defined as equivocal and the concentration was repeated. If the 30 ml dose of levobupivacaine failed to provide analgesia at 30 minutes post insertion, a further 20 ml of 0.25% levobupivacaine was administered through the femoral nerve catheter to provide rescue analgesia. If, following the injection of 20 ml of 0.25% levobupivacaine, the pain NRS score was not ≤30/100 after a further 30 minutes ineffective regional analgesia was attributed to a failure of placement of the initial 30 ml dose of levobupivacaine.

4.4.1 Interim analysis

An interim analysis was performed after 16 patients had been recruited to estimate the optimal stepping value (δ). The concentration stepping value (δ)

was reduced from 0.025% to 0.005% to increase the accuracy of the final estimation of the EC_{50} and the EC_{95}.

4.4.2 Assessment of pain scores

A pain score measures a patient's pain intensity or other features. Pain scores are based on self-report, observational (behavioural), or physiological data. A self-reported score such as the Numeric Rating Score provides the most accurate data. It may be used for adults and children over 10 years old or older. Pain scores were assessed on a 100 point Numerical Rating Scale (NRS) scoring system. The following verbal descriptions were used to guide patients; 0-29 no to mild pain, 30-69 moderate pain and 70-100 severe pain. Pain NRS scores were used throughout all clinical studies in this thesis as the pain visual analogue scale (VAS) scoring was found to be very difficult to use in patients with a fractured neck of femur. The pain NRS scores were used throughout this project.

4.4.3 Assessment of sensory function

The primary sensory response was based on the sensory response of the middle third of upper thigh. The patient's sensory function was assessed by the intensity of a pin prick sensation and cold sensation produced by melting ice. Pin prick sensation was measured using a blunted 25G orange needle. The patient was asked to grade the intensity of the sensory response to the 'orange' needle by verbalising or marking a line from 0 (no sensation) to 100. 100 was defined as the same intensity of sensation as the contra lateral upper middle third of the thigh. Melting ice was also used as a stimulus and the patient was asked if the cold sensation was reduced on the side on which the femoral 3-in-1 nerve block was performed compared with the contra lateral (unblocked side) on the medial (M), anterior(A) and lateral region(L) of the upper thigh (Figure 4-1). The change in sensation associated with effective regional analgesia was defined as a reduction in sensation to blunted 25G needle in the anterior aspect of the upper thigh (area marked as A in diagram 1) of ≤30/100 or a reduction in cold sensation to melting ice in comparison with the contra lateral area of the thigh in the upper anterior aspect of the thigh.

Figure 4-1: The surface anatomy of the upper thigh: The anterior (A), lateral (L) and medial (M) aspects of the upper thigh are shown in the diagram below.

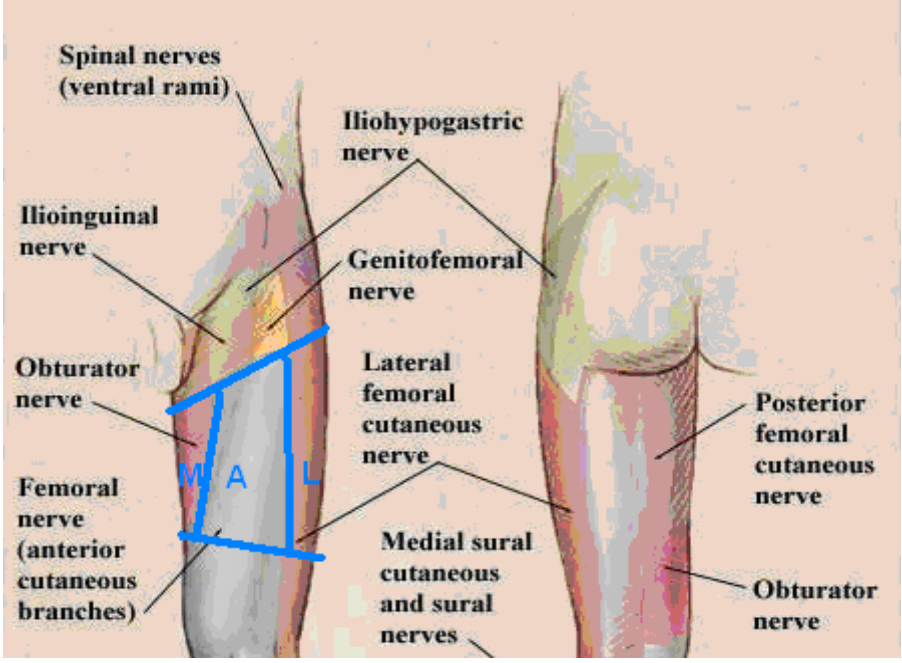


Image from personal collection of Dr Malcolm Watson

4.4.4 Summary of an effective or ineffective block

Effective, ineffective or equivocal femoral 3-in-1 nerve blocks were defined by the answers to questions 1 and 2 below and summarised in table 4.1.

Question 1

Has there been a reduction in pain NRS score by ≥20 points from pre block pain NRS score at 30 minutes post block? (Yes/No)

Question 2

Has there been a sensory change in anterior (A) aspect of thigh at 30 minutes post block? (please see section 4.4.3 'Assessment of sensory function') (Yes/No)

Table 4-1: Summary of outcome: effective, ineffective and equivocal regional analgesia

Outcome of block	Next concentration	Answers to questions1 and 2
Ineffective regional analgesia	Increased	(1-No/2-No)
Effective regional analgesia	Decreased	(1-Yes/2-Yes)
Equivocal regional analgesia	Repeat concentration	(1-Yes/2-No or 1-No/2-Yes)

4.4.5 Secondary end points

- Regression analysis of sensory scores against pain NRS scores at 10, 20 and 30 minutes
- Sensory function of the upper middle third of the thigh (femoral nerve) was tested at 0 minutes (before insertion of levobupivacaine) and at 10 and 20 minutes post insertion of 30 ml of levobupivacaine.

4.4.6 Standards

This clinical trial was conducted to ICH–GCP (2004), it was audited by Greater Glasgow and Clyde Heath board (please see report included in appendix 1) with only minor findings, all Investigational and Medicinal Products were produced by an accredited pharmacy production unit, the data was recorded and processed to comply with ISO 9001:2008 and the statistical analysis has been supervised by Dr Alex McConnachie, senior statistician at the Robertson centre, Glasgow University.

4.4.7 Sample size calculation

Sample size calculation has never been adequately discussed in any published study using the sequential up/down Dixon methodology (Pace & Stylianou 2007). A full discussion of the initial sample size calculation is included in Appendix two; however, in summary, it depends on two variables, the stepping value and the difference between the starting value and the actual value of EC_{50} of levobupivacaine. If the stepping value is large then it will require fewer patients to reach the EC_{50} value but the precision and accuracy with which the probability model will be able to estimate the levobupivacaine EC_{50} will be reduced. In contrast, a small stepping value will increase the precision and accuracy with the EC_{50} can be estimated but will also increase the number of patients that need to be recruited. To minimise this effect a low starting concentration of levobupivacaine and a large stepping value was initially chosen and the steeping value was optimised using the information from an interim analysis. To estimate the optimal stepping value a probability model was constructed with the data (for the first 16 patients) for concentration of levobupivacaine against probability of an effective femoral 3-in-1 nerve block using probit logistic regression analysis. The optimum stepping value which

needed the minimum number of patients for the greatest accuracy and precision is fulfilled when the steeping value (δ) is 2/3 to 3/2 of the standard deviation (σ) of the probit logistic regression model.

4.5 Results

4.5.1 Demographics

A total of 40 patients with traumatic proximal femoral fractures were prospectively recruited from 1 February 2010 to 17 November 2010. The average age of the 40 patients recruited was 78.9 years with an interquartile range of 71.4 to 83.5 years. The median time taken to insert a femoral 3-in-1 nerve block was 62 seconds with an interquartile range of 48 to 94 seconds. The mean (median) number of skin punctures and needle advancements was 1.025(1) and 1.25(1) respectively with a standard deviation (interquartile range) of ± 0.16 (1 to 1) and ± 0.6 (1 to 1), respectively.

4.5.2 Adverse event reported during the clinical trial

The following adverse events listed in Table 4-2 were reported during the study to the MHRA and the ethics committee.

Table 4-2: Adverse event log

Patient randomisation number	Adverse event
13	Patient of died of metastatic breast cancer complicated by chronic obstructive airways disease, morbid obesity, congestive heart failure, renal failure and type II diabetes mellitus.
27	Pulmonary tuberculosis

4.5.3 Physiological observations

The physiological observations of the patients pre-block and at 10, 20 and 30 minutes after the femoral 3-in-1 nerve block are shown in Table 4-3.

Table 4-3: Physiological observations pre-block and at 10, 20 and 30 minutes after the femoral 3-in-1 femoral nerve block

	Pre-block	10 minutes post block	20 minutes post block	30 minutes post block
Systolic BP median (interquartile range)	143 (126-155)	142 (124-162)	141 (123-157)	138 (122-170)
Diastolic BP median (interquartile range)	75 (68-80)	69 (62-78)	72 (61-78)	70 (61-80)
O_2 saturation median (interquartile range)	94 (93-96)	95 (94-97)	95 (94-97)	96 (93-97)
Number of litres of supplementary O_2 median (interquartile range)	0 (0-1)	0 (0-2)	0 (0-2)	2 (0-2)
Respiratory rate median (interquartile range)	14 (12-16)	14 (12-16)	15 (12-18)	16 (12-16)
Pulse rate median (interquartile range)	79 (70-92)	81 (71-92)	81 (71-96)	76 (69-91)

No statistically significant changes in physiological observations were found (all interquartile ranges for all the parameters measured overlapped) during the period of observation.

4.5.4 Summary of results of sequential up/down Dixon's methodology

One patient did not respond to a 'rescue top up' (an injection of 20 ml of 0.25% levobupivacaine through the femoral nerve catheter sited after the initial injection of 30 ml of levobupivacaine) with a reduction in pain NRS score to ≤30/100 after 30minutes. Therefore, 39 patients had technically successful femoral 3-in-1 nerve blocks. A further three patients had conflicting pain NRS scores and the sensory assessments and were therefore deemed to have equivocal results and were excluded from the final and interim EC_{50} and EC_{95} analysis. The data for 36 patients was used for primary analysis to estimate the

EC_{50} and EC_{95} of 30 ml levobupivacaine required to provide effective analgesia, a summary of this data in shown below in table 4-4.

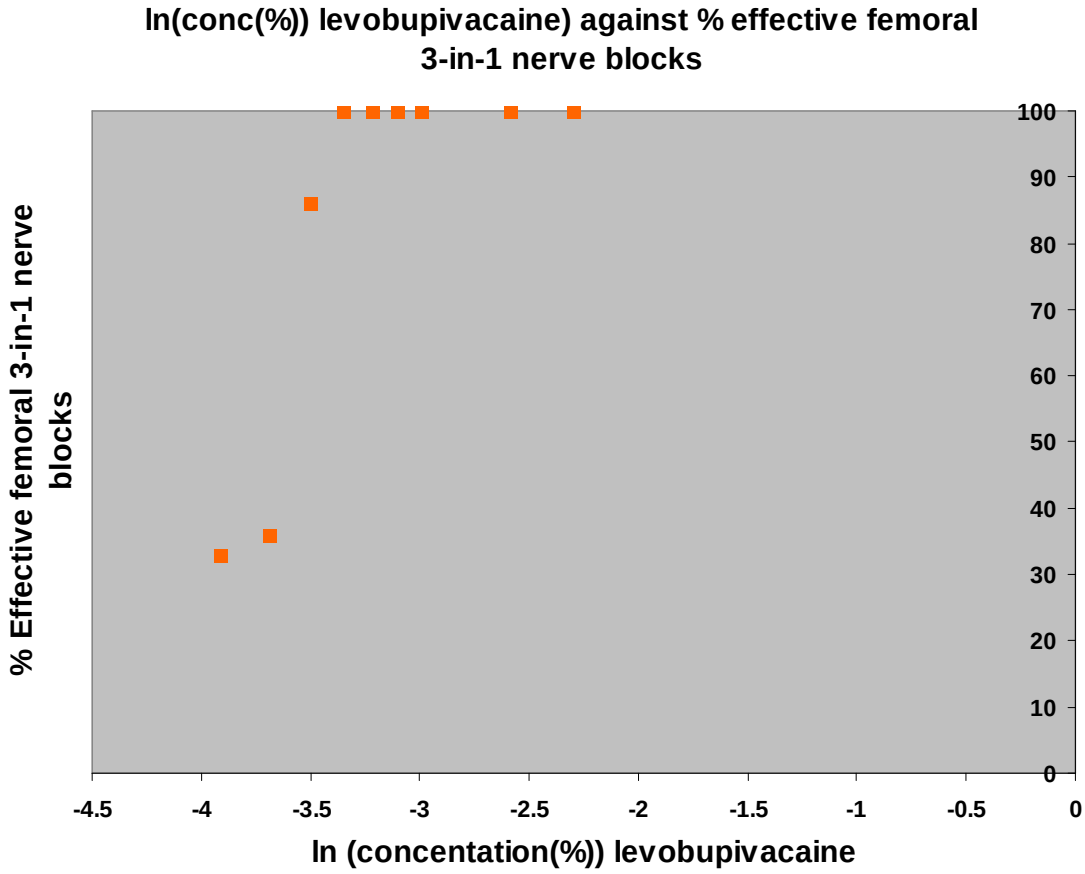
Table 4-4: Summary of data for EC50 and EC95 estimate

Concentration of levobupivacaine (%)	Effective analgesia	Ineffective analgesia	Equivocal /technical failure	% Effective anaesthesia	Number patients analysed
0.1	1	0	0	**100**	1
0.075	1	0	0	**100**	1
0.05	5	0	0	**100**	5
0.045	1	0	0	**100**	1
0.04	1	0	0	**100**	1
0.035	2	0	0	**100**	2
0.03	6	1	1	**86**	7
0.025	5	9	3	**36**	14
0.02	1	2	0	**33**	3
0.015	0	1	0	**0**	1
Total patients	**23**	**13**	**4**		**36**

4.6 Results Part 1 Calculation of ED_{50} and ED_{95}

The aim of this trial was to estimate the levobupivacaine EC_{50} and EC_{95} concentrations from the logistic regression model of the $\log_e$ natural (ln) concentration-response relationship.

Figure 4-2: Graph of natural $\log_e$ (concentration) of levobupivacaine against percentage of effective femoral 3-in-1 nerve blocks



In order to estimate the EC_{50} and EC_{95} of levobupivacaine with logistic regression analysis it was assumed that for a given log natural (log_e) concentration, x, the probability, P(x), that the concentration will be effective was:

$$P(x) = \Phi\left(\frac{x - \mu}{\sigma}\right)$$

Where Φ was defined as the cumulative density function of a standard Normal distribution, μ was the concentration at which 50% of the population would achieve pain relief, or EC_{50} and σ was the standard deviation of the Normal distribution.

Since $P(\mu) = \Phi(0) = 0.5$.

The regression model that was used to analyse the binary response data in this clinical trial, was the probit model. This model assumed that for a given concentration, x, the probability, P(x), that the concentration will be effective was:

$$\Phi^{-1}\{P(x)\} = \beta_0 + \beta_1 x$$

(Where β_0 is the y-intersect and $\beta 1$ is the gradient of the best fit line)

which is equivalent to the standard linear regression model. Minitab 15 software was used to estimate β_0 and β_1 and obtain standard errors of these estimates.

The EC_{50} or μ can be written as:

$$\Phi^{-1}\{P(\mu)\} = \beta_0 + \beta_1 \mu$$

$$\Phi^{-1}\{0.5\} = \beta_0 + \beta_1 \mu$$ (Since the probability of μ is 50% then $\{P(\mu)\} = 0.5$)

$$0 = \beta_0 + \beta_1 \mu$$ (Φ is the cumulative normal distribution function, so $\Phi^{-1}\{0.5\} = 0$)

$$\mu = -\beta_0 / \beta_1$$

Under the probit model the EC_{95} is given by:

$$\Phi^{-1}\{0.95\} = \beta_0 + \beta_1 EC_{95}$$

$$1.644854 = \beta_0 + \beta_1 EC_{95}$$

$$EC_{95} = (1.644854 - \beta_0) / \beta_1$$

4.6.1 Calculation of the 95% confidence interval (CI) for the EC_{95} and the EC_{50}

The 95% Confidence Interval (CI) for the EC_{95} and EC_{50} of levobupivacaine required the use of a mathematical technique (the delta technique) utilising matrices as any change in either β_0 or β_1 altered the both parameters. A change in the gradient of the best fit line (β_1) affected the Y-axis intersection (β_0). The delta method was used to give an estimate of the combined errors by transformation of the parameters β_0, β_1 and their variance-covariance matrix.

4.6.1.1 Estimated values for EC_{95} and EC_{50}

The estimate of EC_{95} and EC_{50} depended the whether those patients defined as a technical failure and equivocal regional analgesia are included in the final analysis.

Definition one If all patients are included in the analysis and those with equivocal regional analgesia and the technical failure are included as ineffective regional analgesia then

EC_{50}=0.0266% with 95% CI 0.0240% to 0.0295%

EC_{95}=0.0381% with 95% CI 0.0345% to 0.0417%

Definition two If patients with equivocal regional analgesia were included as unsuccessful regional analgesia blocks but the technical failure was excluded then

EC_{50}=0.0264% with 95% CI of 0.0237% to 0.0294%

EC_{95}=0.0381% with 95% CI of 0.0342% to 0.0415%

Definition three If patients with equivocal regional analgesia and the technical failure were excluded then

EC_{50}=0.0255% with 95% CI of 0.0229% to 0.0284%

EC_{95}=0.0357% with 95% CI of 0.0332% to 0.0383%

In summary, the influence of the technical failure and equivocal blocks was minimal and it is possible to argue that the equivocal regional analgesia and or the technical failures should be included to maximise the amount of data used in the calculation. The final result for the EC_{50} and EC_{95} was given by method three as defined in the protocol.

4.7 Results: Part 2: Calculation to determine the concentration stepping value (δ)

The most accurate estimate of EC_{50} and EC_{95} will be given using probit logistic regression analysis if the stepping value (δ) was the region of σ (3/2σ to 3/2σ). Initially, the stepping value (δ) was set at 0.025; this was revised based on the results of a planned interim analysis after the first 16 patients had been recruited. The optimal stepping value (δ) was then changed to be as close to σ as possible (please see Appendix three for the interim analysis results).

4.7.1 Interim analysis Optimum stepping value (δ) (16 patients)

The probit logistic regression model gave the parameter estimates in table 4-5:

Table 4-5: Effective and ineffective regional analgesia versus concentration (16 patients)

Predictor	Coefficient	SE Coefficient	Z	P
Constant(β_0)	-5.982	615.746	-0.010	0.992
Concentration(β_1)	233.706	24629.804	0.009	0.992

β_0=-5.982

β_1=233.706

The estimated value of the standard deviation (σ) was 0.00428%

The stepping value of 0.025% was outside the optimal range of stepping value (3/2σ to 3/2σ). The concentration stepping value (δ) was therefore reduced to 0.005%.

4.7.2 Final analysis Optimum stepping value (δ) (40 patients)

Probit logistic regression analysis model gave the parameter estimates in table 4-6:

Table 4.6: Effective and ineffective regional analgesia versus concentration (40 patients)

Predictor	Coefficient	SE Coefficient	Z	P
Constant(β_0)	-5.04224	2.11487	-2.38	0.017
Concentration(β_1)	196.100	80.6845	2.43	0.015

β_0=-5.04224

β_1=196.1

The estimated value of the standard deviation (σ) was 0.0051

This was between 2/3 and 3/2 of the concentration stepping value of 0.005%.

4.8 Results Part 3 Regression analyses of sensory scores against pain NRS scores.

A placebo analgesic effect may be difficult to separate from true analgesia due to the subjective nature of pain. Sensory testing was included in the protocol to confirm that any analgesic effects recorded were associated with a sensory change and therefore were a result of the pharmacologic effects of levobupivacaine. Two modes of sensory response were tested; cold sensation in response to ice, and prick response to a blunt 25G needle as very little published data was available on which to base the protocol. The contra lateral (unblocked) leg was used as the control. The work of Marhofer et al had suggested that the analgesic response was correlated to a ≤30/100 sensory score to 25G blunted needle and the protocol was based on this information (Marhofer et al. 1997). We found that the relationship between pin prick sensation rated 0-100 at 30 minutes after the injection of levobupivacaine and a ≥20/100 reduction in pain NRS scores was not as described by Marhofer et al (Marhofer et al. 1997). In contrast, the reduction in cold sensation was frequently associated with a ≥20/100 reduction in pain NRS score.

In this section of the results we determined whether a relationship existed between sensory pin prick response and analgesia and the temporal nature of any relationship (please see figures 4-3, 4-4, 4-5 and tables 4-7, 4-8 and 4-9). A receiver operator curve was used to determine the characteristics of the relationship between sensory pin prick response and analgesia at 30 minutes after 3-in-1 femoral nerve block(please see figure 4-6). The data from 39 patients was analysed (1 patient was excluded due to technical failure, i.e. failure of the femoral catheter to show an analgesic response to top-up with 20 ml of 0.25% levobupivacaine).

4.8.1 Pain reduction against sensation to blunted needle at 30 minutes

- Pain NRS score reduction at 30 minutes = The reduction in pain score rated 0-100 at 30 minutes after the injection of 30 ml of levobupivacaine

- Sensation to blunt needle at 30 minutes = Sensation to blunted 25G needle on the anterior thigh rated 0-100 at 30 minutes after the injection of 30 ml of levobupivacaine

The calculated regression equation was (please see figure 4-3)

(*Pain NRS score reduction at 30 minutes*)=61.1-0.478(*Sensation to blunt needle at 30 minutes*)

Figure 4-3: The best fit regression equation is shown below

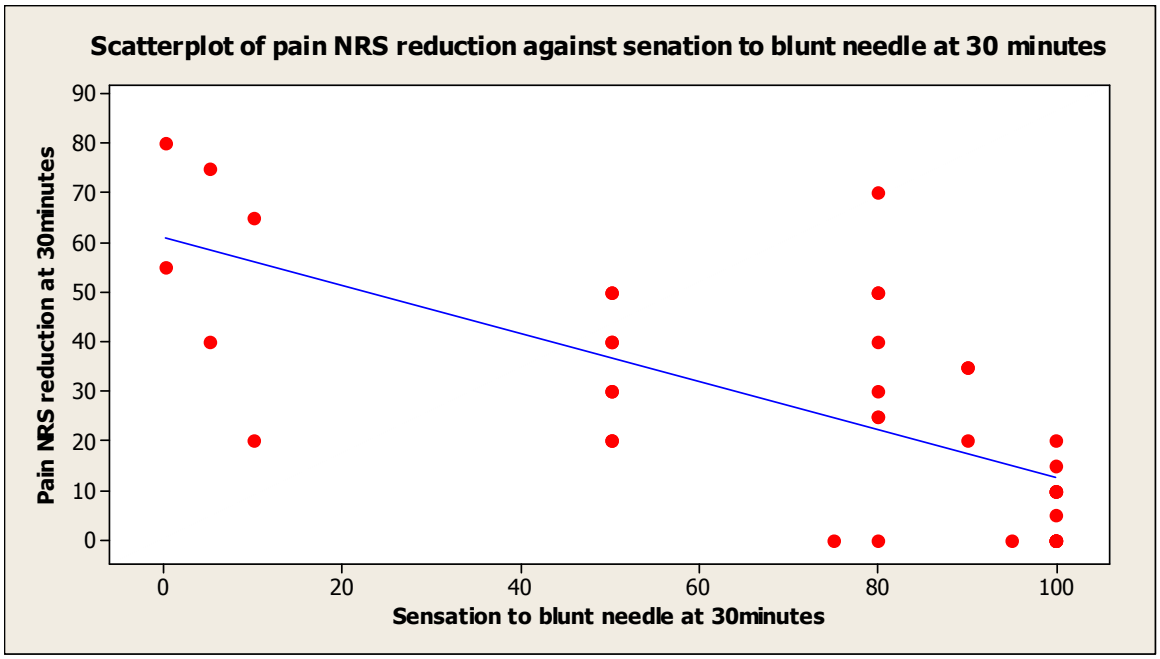


Table 4-7: Pain reduction against sensation to blunted needle at 30 minutes

Predictor	SE	Coef	T	P
Constant	61.055	6.201	9.85	<0.001
Sensation to blunt needle at 30mins	-0.47844	0.08006	-5.98	<0.001

S=16.5820 R-Sq = **49.1%** R-Sq(adj)=47.7%

Giving a correlation coefficient of r=√(49.1/1000.69)=**0.70** (please see table 4-7)

4.8.2 Pain reduction against sensation to blunted needle at 20 minutes

- Pain NRS score reduction at 20 minutes = The reduction in pain score rated 0-100 at 20 minutes after the injection of 30 ml of levobupivacaine
- Sensation to blunt needle at 20 minutes = Sensation to blunted 25G needle on the anterior thigh rated 0-100 at 20 minutes after the injection of 30 ml of levobupivacaine

The calculated regression equation was (please see figure 4-4)

(*Pain NRS score reduction at 20 minutes*)=56.5-0.431(*Sensation to blunt needle at 20 minutes*)

Figure 4-4: The best fit regression equation is shown below

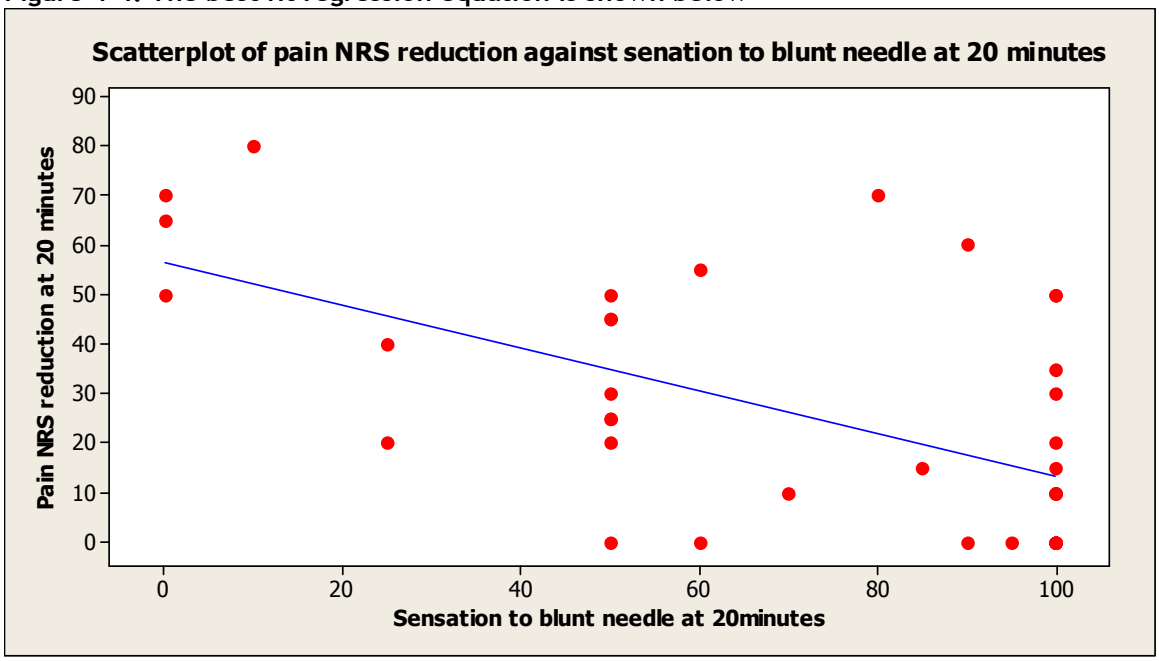


Table 4-8: Pain reduction against sensation to blunted needle at 20 minutes

Predictor	SE	Coef	T	P
Constant	56.534	7.636	7.40	<0.001
Sensation to blunt needle at 20mins	-0.43126	0.09615	-4.49	<0.001

S=20.0522 R-Sq = **34.6%** R-Sq(adj) = 32.9%

Giving a correlation coefficient of r=√(34.6/1000.69)=**0.59** (please see table 4-8)

4.8.3 Pain reduction against sensation to blunted needle at 10 minutes

- Pain NRS score reduction at 10 minutes = The reduction in pain score rated 0-100 at 10 minutes after the injection of 30 ml of levobupivacaine
- Sensation to blunt needle at 10 minutes = Sensation to blunted 25G needle on the anterior thigh rated 0-100 at 10 minutes after the injection of 30 ml of levobupivacaine

The calculated regression equation was (please see figure 4-5)

(*Pain NRS score reduction at 10 minutes*)=28.8-0.110(*Sensation to blunt needle at 10 minutes*)

Figure 4-5: The best fit regression equation is shown below

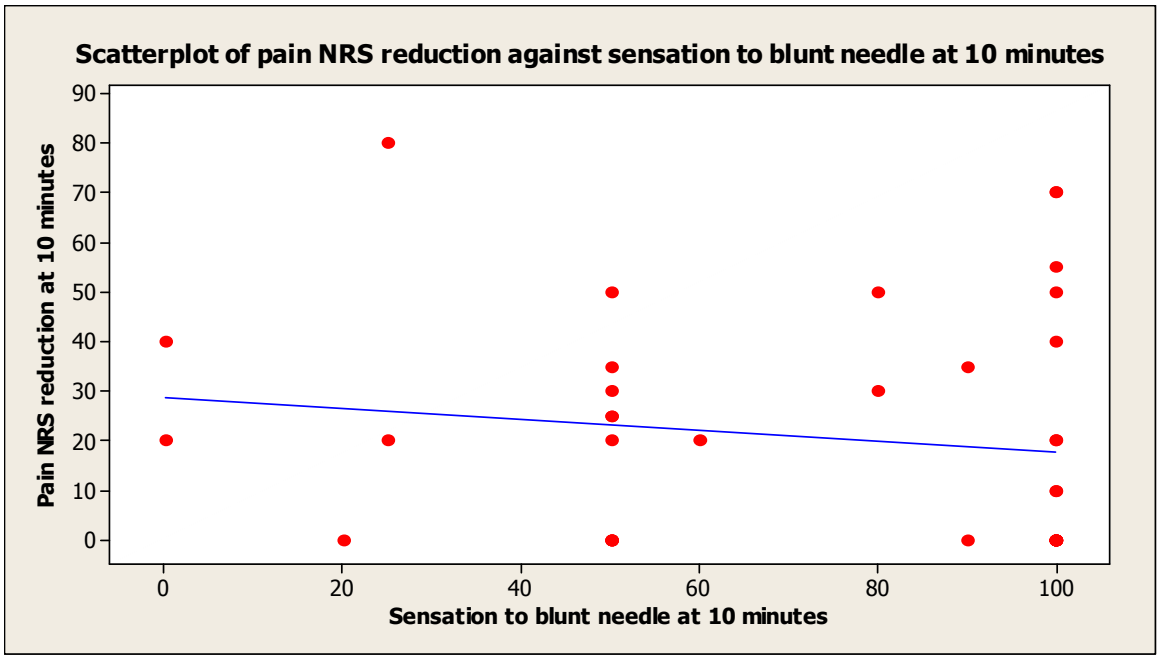


Table 4-9: Pain reduction against sensation to blunted needle at 10 minutes

Predictor	SE	Coef	T	P
Constant	28.785	9.511	3.03	0.004
Sensation to blunt needle at 10mins	-0.1099	0.1181	-0.93	0.358

S=23.2501 R-Sq = **2.2%** R-Sq(adj) = 0.0%

Giving a correlation coefficient of r=√(2.2/1000.69)=**0.14** (please see table 4-9)

Linear regression techniques resulted in a statistically significant correlation ($p<0.001$) between sensory testing with a pin prick to a blunt 25G needle and pain NRS score reduction at 20 and 30 minutes after injection of the 30 ml dose of levobupivacaine response using linear regression techniques. No correlation ($p=0.358$) was seen at 10 minutes between sensation and pain NRS scores.

Sensory testing with a blunt 25G needle at 30 minutes was associated with reduction in pain response. If the defined analgesic response (reduction in pain NRS score of ≥20/100) is the standard, we can calculate the specificity and sensitivity of different sensory scores. A receiver operator curve (ROC) was used to calculate the change in pin prick sensory score with a blunted 25G needle that was associated with the highest sensitivity and specificity at 30 minutes after a femoral 3-in-1 nerve block (please see figure 4-6 and table 4-10).

Standard Definitions:
True positive =pain reduction>=20 points on 100 point scale
True negative=pain reduction<20 points on 100 point scale

Specificity= true negatives / (true negatives + false positives)

Sensitivity= true Positives / (true positives + false negatives)

Therefore:

If sensory score is set to <=**80/100** then true negatives =14
False positives=4

Therefore specificity= 13/13+1=93.3%

True positives=25
False negatives=1

Therefore sensitivity= 21/21+4=84%

If sensory score is set to <=**90/100** then true negatives =14
False positives=1

Therefore specificity= 13/13+1=93.3%

True positives=25

False negatives=1

Therefore sensitivity= 24/24+1=96.1%

If sensory score is set **to <=30** then

True negatives =14

False positives=19

Therefore specificity= 14/14+0=100%

True positives=25

False negatives=0

Therefore sensitivity= 14/14+19=56%

If we use cold sensation as an indicator of pain reduction instead of a blunt needle

True negatives =14

False positives=1

Therefore specificity= 14/14+1=93.3%

True positives=25

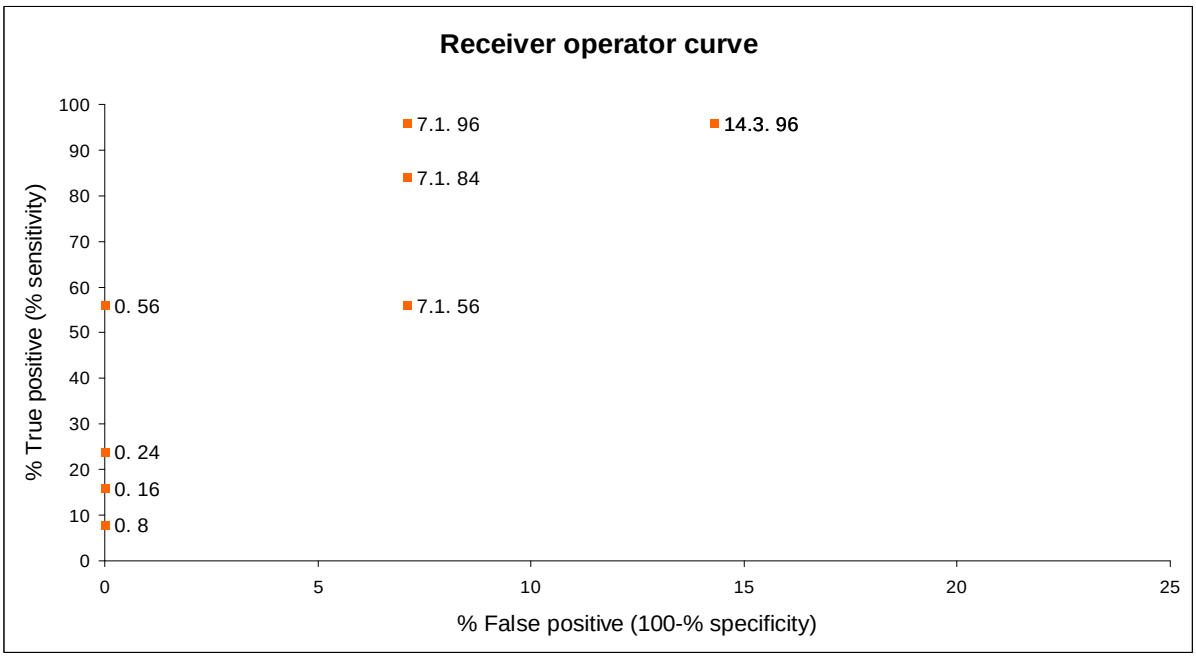
False negatives=2

Therefore sensitivity= 25/25+2=92.6%

Table 4-10: True positives against false positive (data for receiver operator curve)

Sensation in anterior Sensory score (upper anterior thigh)	True positive (% sensitivity)	False positive rate (100-% specificity)
0	8	0
5	16	0
10	24	0
50	56	0
75	56	7.1
80	84	7.1
90	96	7.1
95	96	14.3
100	96	14.3

Figure 4-6: Receiver operator curve for sensory scores against analgesia



Therefore, the pin prick sensation to a blunt 25G needle that was associated with a 20 point/100 or greater reduction in pain NRS score with the highest specificity and sensitivity was a sensory score of ≤90/100.

4.9 Part 4: Trends in pain scores over time

All pain scores decreased or remained the same at 10 minutes after the injection of 30 ml of levobupivacaine. However, at 20 minutes and 30 minutes after injection some pain scores increased. The pain experienced by the patients recruited to this study with a fractured hip was not of a constant intensity; therefore, the trends in pain NRS scores observed between 0 and 10 minutes are anomalous. The analgesia observed at 10 minutes has a much weaker relationship to pin prick sensation to a 25G needle than the analgesia seen at 20 and 30 minutes. Pain NRS scores for each patient were plotted against time, for concentration below the EC_{50} and above the EC_{50} and separated for effective and ineffective regional analgesia to determine if the anomalous pain NRS score trends between 0 and 10 minute were related to these factors

Figure 4-7: Change in pain NRS scores over time

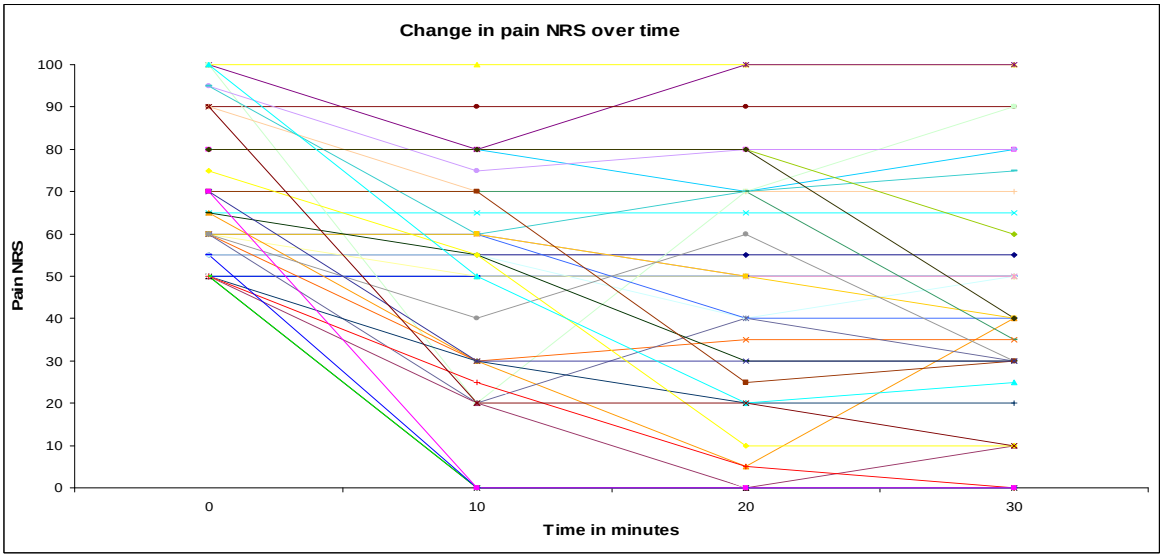


Table 4-11: Summary of changes in pain NRS scores over time

	0-10 minutes	10-20 minutes	20-30 minutes
Decrease in pain NRS score	23	15	8
No change in pain NRS score	17	18	24
Increase in pain NRS score	0	7	8
Total patients	40	40	40

Figure 4-8: Changes of pain NRS scores over time for concentrations at or below the calculated ED50

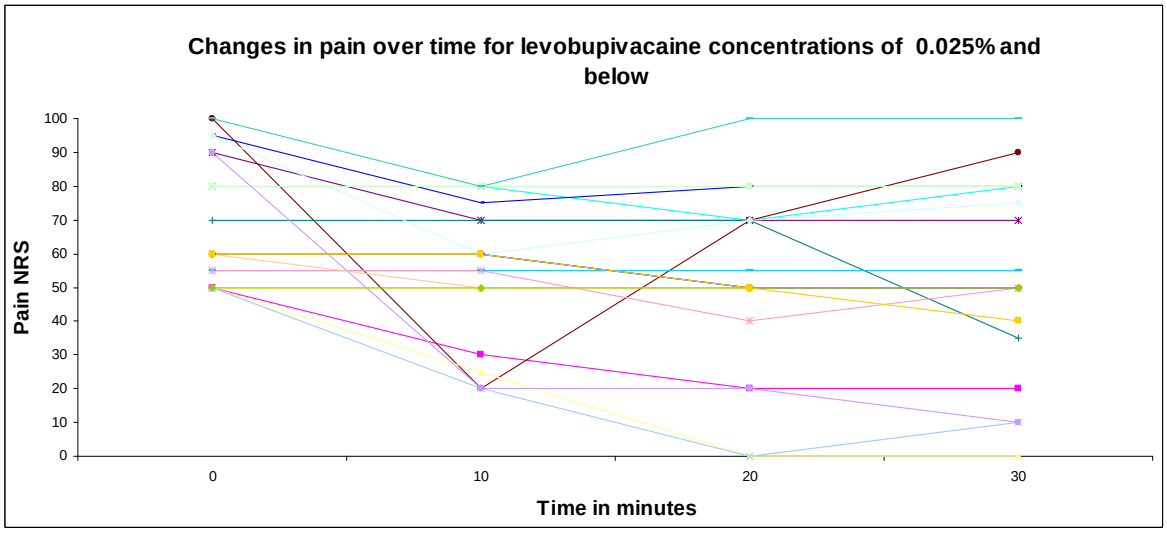


Figure 4-9: Changes of pain NRS scores over time for concentration above the calculated ED_{50}

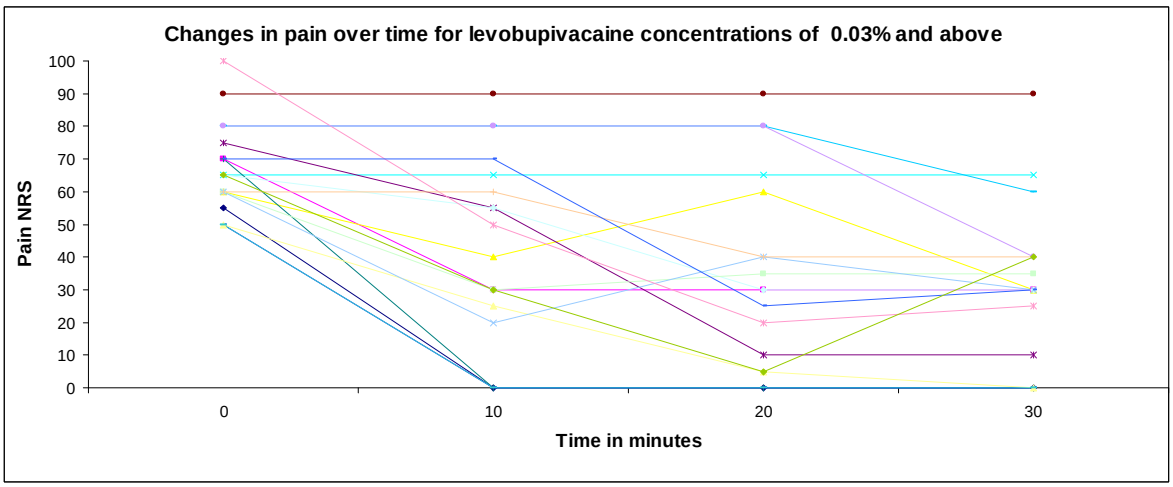


Figure 4-10: Changes of pain NRS scores over time for patients with ineffective regional analgesia

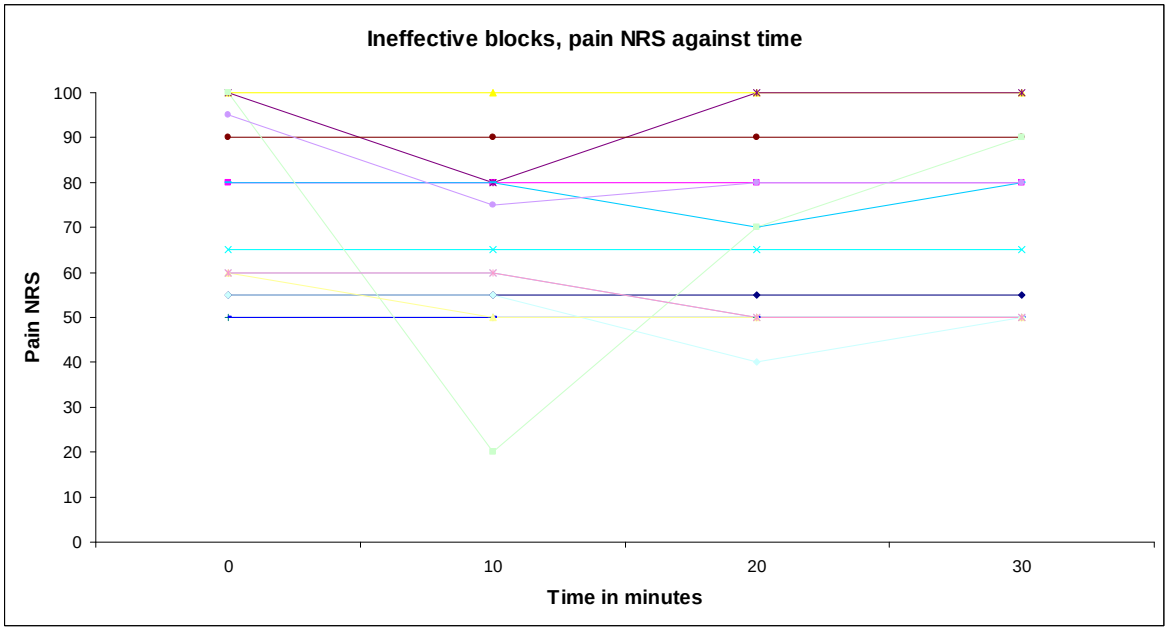


Figure 4-11: Changes of pain NRS scores over time for patients with effective regional analgesia

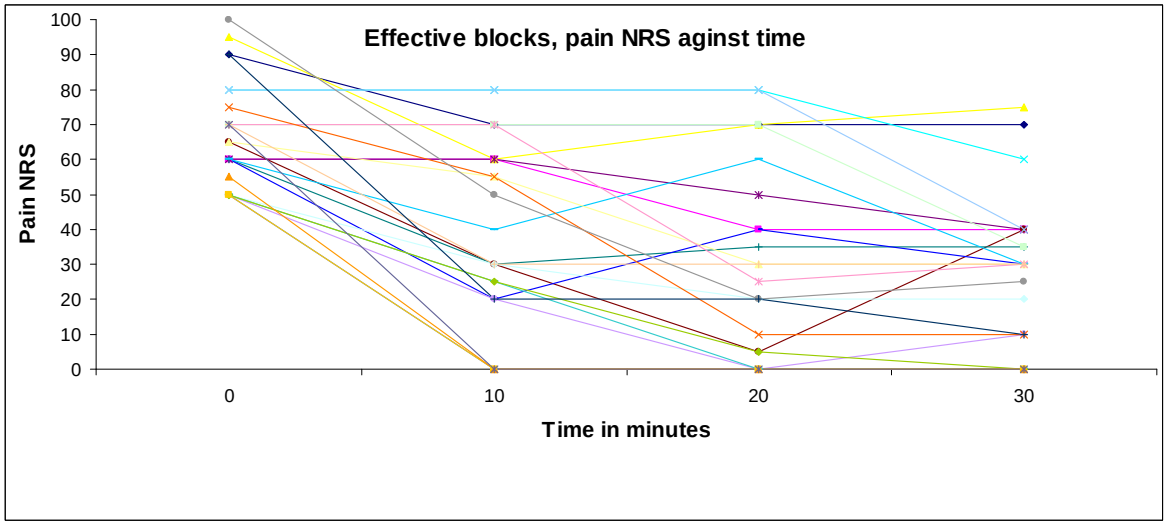


Table 4-12: Summary of the number of patients with increased and decreased pain NRS scores for concentrations of levobupivacaine above (Graph 4-8) and below (Graph 4-9) the EC_{50}

Time interval (minutes)	0-10			10-20			20-30		
Pain NRS scores	Increase	Decease	Same	Increase	Decease	Same	Increase	Decease	Same
Concentrations at 0.025% and below	0	10	11	5	8	8	5	3	13
Concentrations at 0.030% and above	0	13	6	3	7	9	4	5	10

Table 4-13: Summary of the number of patients with increased and decreased pain NRS scores for effective(Graph 4-10) and ineffective (Graph 4-11) analgesia

Time interval (minutes)	0-10			10-20			20-30		
Pain NRS scores	Increase	Decease	Same	Increase	Decease	Same	Increase	Decease	Same
Ineffective	0	4	11	3	4	8	3	0	12
Effective	0	19	6	4	11	10	5	8	12

No trends were noted over time in the pain NRS scores (Figure 4-7) or in association with the concentration used (Figure 4-8 and 4-9) or ineffective or effective regional analgesia (Figure 4-10 and 4-11).

4.10 Discussion

In all published literature available at the start of this clinical trial both the total dose and volume of local anaesthetic delivered were changed with each stepping value (δ) which is at odds with the primary tenant of the Dixon methodology in which only one variable should be altered (Dixon 1965). Therefore no information was available on which to base the initial stepping value (δ) and range of concentrations to be used in the trial protocol. As a result the protocol included an interim analysis to recalculate the concentration stepping value (δ), after the first 16 patients had been recruited. A relatively large concentration stepping value (δ) was chosen initially, which allowed the concentration to rapidly trend towards and oscillate around the ED_{50} concentration. We then calculated the optimal concentration stepping value (δ) for accuracy using information for the first 16 patients. A large range was also initially chosen (0.1%-0.025%) but 0.025% was close to the estimate final ED_{50} concentration.

If the log concentration against effective analgesia 'Figure 4-2: Graph of natural $\log_e$ (concentration) of levobupivacaine against percentage of effective femoral 3-in-1 nerve blocks' is viewed then levobupivacaine 0.02% appears to have a higher success rate than would be expected; however, this estimate is based on relatively few patients. This arose because the lowest value for the initial range

of concentrations of levobupivacaine was 0.025% therefore an effective block at 0.025% resulted in a repeat of this concentration and only the last seven patients were recruited with a lower minimal concentration due to the difficultly of obtaining approval to amend the protocol of a clinical trial (see Appendix 4). The probit logistic regression model used to analyse the data to estimate the ED_{50} and ED_{95} for levobupivacaine appropriately weighted the small number of patients recruited to 0.02% levobupivacaine group.

The most significant omission from the initial protocol was the threading of a catheter through the needle used to inject the 30 ml dose of levobupivacaine (IMP). A catheter was sited for every patient as part of their normal care. The pain NRS score response to the 'top up' of the catheter provided prolonged analgesia for the patients recruited to the study and added to the scientific value of the study by providing further clinical information and confirmation that the levobupivacaine was delivered to the correct site.

4.10.1 Quantifiable error in final concentration and volume of IMP

The error associated with the manufacture of a specific volume and concentration of levobupivacaine was estimated. The IMP (levobupivacaine) was manufactured to good manufacturing practice (GMP) standards in an accredited pharmacy facility.

The stock drug (levobupivacaine 0.75% manufactured by Abbot Ltd.) was diluted with saline 0.9% to produce the 30 ml of the test concentration of levobupivacaine which was stored for a maximum of 28 days before administration (Jappinen *et al*. 2003). We obtained the accurate concentration assay preformed by Abbot Ltd on each batch of 0.75% levobupivacaine used in the clinical trial (Appendix 5). The actual concentration of levobupivacaine 0.75% used was between ± (0.2% to 1.4%) of the marked value. If the average of these errors is taken:

(0.4%+0.2%+1.2%+1.4%+0.5%)/5=0.74% was the average error in the concentration

The estimated error during manufacture arose from two sources, the estimated weight of the saline bag used to dilute the stock levobupivacaine 0.75% (max error=0.88% of final concentration) and the volume of the two syringes used to measure stock 0.75% levobupivacaine concentration and to store and administer the levobupivacaine which was 3.5% per syringe using data from BD Ltd (Appendix 6 for BD data sheet). Therefore the maximal error in the concentration of the IMP and hence the EC_{95} is ± (1.4%+0.88%+3.5%+3.5%) ± 9.3%. This assumption is likely to be grossly in excess of the true error as it assumes that all the errors were maximal and that they all changed the concentration in the same direction.

A more reasonable calculation is to sum the squares of the error and take the square root of the result. This assumes that some of the errors will cancel each other out (Taylor 1982).

Therefore Final error=$\surd(0.74)^2+(0.88)^2+(3.5)^2+(3.5)^2$

$=\surd(0.5476)+(0.7744)+(12.25)+(12.25)$

$=\surd(25.822)$

$=5.1\%$

EC95%= 0.0357% maximal error (±9.3% of the marked concentration)i.e. ±0.003%

or sum of squares(±5.1% of the marked concentration)i.e. ±0.0018%

4.10.2 Combined biological variation and pharmacological errors

The probit logistic regression model created using the data from this clinical trial estimated a 95% confidence interval of ±7.2% of the final concentration for the EC_{95} value to reduce the pain NRS score by 20/100 points at 30 minutes after the injection of 30 ml of levobupivacaine.

4.10.3 Sensory testing

Sensory testing was included in the protocol in an attempt to reduce the placebo effect attributed to all analgesic procedures. A placebo analgesic effect is possible although great care was taken to explain to the patients that the femoral 3-in-1 nerve block may not give any pain relief. Any change in pain NRS

score at 30 minutes after the injection of the levobupivacaine was regarded as equivocal unless it was accompanied by an appropriate sensory change in one of the two sensory modalities in the cutaneous sensory femoral nerve distribution. The two methods of assessing sensation were (cold sensation to melting ice and sensation to a 25G blunted needle). Two methods of assessing sensation were used as there was very little information in the published literature on the correlation between analgesia and sensation on which to base the protocol.

We found that the decrease in sensation to a blunted 25G needle at 30 minutes after the injection of levobupivacaine was correlated with analgesia (≥20/100 reduction in pain NRS score). We also used a receiver operator curve (ROC) to determine the size of the decrease in sensation to blunt 25G needle that was associated with the highest sensitivity and specificity for a ≥20/100 point reduction in pain NRS scores at 30 minutes. The sensory score of <90/100 to a blunted 25G needle was associated with the highest 96% true positive rate and the lowest 7.1% false positive rate. This is in contrast to the work of Marhofer et al which suggested that an analgesic response in the same patient population was correlated to a ≤30/100 sensory score to 25G blunted needle in comparison to the contra lateral side (Marhofer et al. 1997). In this clinical trial a sensory score to pin prick from blunted 25G needle of ≤90/100 was highly sensitive and specific measure of the analgesic effectiveness of a femoral 3-in-1 nerve block. In contrast to this clinical trial Marhofer et al assessed the cutaneous sensory response but he made no independent measure of the pain (Marhofer et al. 1997). In this clinical trial we used the results to determine if cutaneous sensory response was associated with pain NRS scores however Manhofer simply stated that they were correlated (Marhofer et al. 1997). In summary, cutaneous sensation on the anterior upper thigh to a blunted 25G needle or melting ice was a surrogate measure of analgesic effectiveness for the femoral 3-in-1 nerve block.

4.10.4 Analgesia observed at 10 minutes after injection of levobupivacaine

It is possible to use the placebo effect to explain the decreased pain scores at 10 minutes and then the subsequent increases at 20 and 30 minutes but the limited duration and consistent timing make this explanation less than satisfactory. It is

possible that levobupivacaine acts more rapidly than the 20 to 30 minutes usually quoted however the lack of an associated sensory change at 10 minutes compared to 20 and 30 minutes (using logistic regression analysis) may suggest that the analgesic effects observed at 10 minutes could have a different mechanism. An alternative explanation may be provided by the hydrostatic pressure exerted on the nerve following injection of levobupivacaine. The hydrostatic effect may be limited in duration by the rapid absorption of the injected levobupivacaine and may not be associated with a cutaneous sensory response unlike the local anaesthetic effects of levobupivacaine.

4.10.5 Implications of the low dose need for the EC_{95} dose

This study has produced an estimate of the effective dose required to provide analgesia which implies that the currently used doses are in excess of what is required to provide analgesia. This study will act as the starting point to further work which could allow the safe provision of analgesia to patients with a fractured neck of femur by utilising lower (and therefore safer) doses of levobupivacaine.

4.11 Conclusion

The effective concentration of 30 ml of levobupivacaine required to produce a reduction in pain numerical rating scale (NRS) score of ≥20 points on a 100 point scale in 50% of patients (EC_{50}) with a proximal traumatic fractured neck of femur using an ultrasound guided femoral nerve block was estimated as (μ) EC_{50}=0.0255% with 95% CI of 0.0229% to 0.0284%. The effective concentration in 95% of patients (EC_{95}) was estimated as EC_{95} =0.0357% with 95% CI of 0.0332% to 0.0383%.

4.12 Summary of chapter 4

4.12.1 Aim

The aim of this clinical trial is to determine the dose of levobupivacaine required to provide effective pain relief to patients with a fractured neck of femur using ultrasound to guide needle insertion.

4.12.2 Method

Patients with a fractured neck of femur were recruited prior to surgical fixation. An ultrasound guided femoral 3-in-1 nerve block was used to anaesthetise the nerves supplying the proximal femur. At 10 minute intervals the feeling in the upper leg and pain numerical rating scale (NRS) scores were recorded for a total of 30 minutes. A successful femoral 3-in-1 nerve block was defined as ≥20/100 decease in the pain NRS score at 30 minutes with a sensory change in skin supplied by the femoral nerve. The concentration of levobupivacaine was increased or decreased if the nerve block was ineffective or effective respectively in the previous patient.

4.12.3 Results

The EC_{50} of levobupivacaine was estimated using probit logistic regression analysis at EC_{50}=0.0255% with 95% CI of 0.0229% to 0.0284% for 30 ml of levobupivacaine and the EC_{95}=0.0357% with 95% CI of 0.0332% to 0.0383%.

Chapter 5

5 The duration of analgesia and pharmokinetics of 30 ml. of the effective concentration of levobupivacaine in 95% of patients (EC_{95}) with a fractured neck of femur.

5.1 Aim

To determine the duration of analgesia provided by an ultrasound guided femoral 3-in-1 nerve block when 30 ml of 0.036% levobupivacaine (the EC_{95} concentration) was used to provide analgesia to patients with a fractured neck of femur. The plasma concentration profile was determined to ensure peak serum levels of levobupivacaine were within safe limits.

5.2 Study design

Observational prospective cohort study.

5.3 Study Population

Competent patients with a fractured neck of femur.

5.4 Trial inclusion/exclusion criteria and patient withdrawal criteria

5.4.1 Inclusion criteria

- Patients with a fractured neck of femur
- American Society of Anaesthesiology grading ≤4/5 (Little 1995)
- Capacity to give informed consent
- Resting visual analogue pain score >50 on a 100 scale before recruitment (moderate pain)
- Able to cooperate with sensory testing of lower limb function.

5.4.2 Exclusion criteria

- Acute mental test score of ≤7/10 at any time preoperatively
- Allergy to local anaesthetic
- Signs, symptoms or laboratory evidence of
    - local infection (at intended site of needle insertion)
    - systemic sepsis which would normally preclude regional analgesia
- Pre-existing known neurological deficit (sensory or motor) affecting the lower limb
- Patient with lower limb amputations or other condition affecting sensation in lower limbs.

5.4.3 Criteria for withdrawal of patient from the trial

- Patient initiated withdrawal. Patients could withdraw from the clinical trial at any time.
- Administration of regional anaesthesia or analgesia not in the protocol
- Failure of rescue analgesia 'top-up' with a 20 ml injection of 0.25% levobupivacaine through the catheter sited after the initial injection of 30 ml of levobupivacaine.
- Equivocal sensory and pain test results (see section 5.5 Methodology; for definition of equivocal sensory and pain results)
- A protocol violation leading to a patient safety issue or a quality issue
- An urgent safety issue with the clinical trial protocol.

5.5 Methodology

All patients were recruited preoperatively and were scheduled for fixation of fractured neck of femur. Consented unpremedicated patients were transferred to the operating theatre suite and initial sensory testing and pain NRS scores were performed. Femoral 3-in-1 nerve blocks were inserted preoperatively using ultrasound needle guidance and 30 ml of the EC_{95} concentration of levobupivacaine. Needle placement for the femoral nerve block was guided by ultrasound. Ultrasound images of the common femoral artery, femoral vein and nerve in the short axis were obtained using a linear high frequency ultrasound

probe on a LOGIQe ultrasound machine (supplied by General Electric Ltd.) and a 100 mm or 50 mm 18G Contiplex Tuohy tipped needle (supplied by B-Braun Ltd) which was advanced in plane until the tip of the needle was under the fascia iliacus membrane immediately lateral to the femoral nerve. After a 'negative' aspiration to detect accidental intravascular placement, the local anaesthetic dose was injected. Real time ultrasound images were used to ensure that the injected local anaesthetic (30 ml of levobupivacaine EC_{95}) spread around the femoral nerve with associated 'tenting' of the fascia iliacus membrane. After injection of the levobupivacaine, a catheter was threaded through the Contiplex Tuohy tipped needle and its position confirmed by visualising movement of the catheter under the fascia iliacus membrane. The concentration of levobupivacaine used was 0.036% (EC_{95} of levobupivacaine to 3 decimal places) for all patients recruited to this study. At 10, 20 and 30 minutes after injection of levobupivacaine, pain NRS (numerical rating scale) scores and sensory testing on the upper thigh were recorded. Effective regional analgesia was defined as reduction in pain NRS score of ≥20/100 points with a pre block resting pain NRS score of ≥50/100 in association with a sensory change, 30 minutes after the femoral 3-in-1 nerve block. The sensory change was either a reduction to ≤30/100 of initial sensory stimuli on testing with a blunted needle or altered sensation on testing with melting ice in the area of distribution of femoral nerve in comparison to the contra lateral side. If the sensory response in the anterior upper thigh and the pain NRS score were at odds the response was defined as equivocal and the patient data removed from the final analysis.

The primary end point, in effective blocks was defined as the duration of analgesia (pain NRS score of <30/100 at rest); pain scores were recorded postoperatively until a pain score of ≥30/100 was recorded. Blood samples were taken for venous blood gases and liver function tests before the insertion of the levobupivacaine. A further blood sample was taken before the insertion of the femoral 3-in-1 nerve block and at 5, 10, 20, 30 and 60 minutes post insertion of the femoral 3-in-1 nerve block, from a cannula inserted, to assess the pharmokinetics of serum levobupivacaine. All levobupivacaine blood samples were taken 60 minutes after the femoral 3-in-1 nerve block to the biochemistry

department at the Western Infirmary. The levobupivacaine blood samples were centrifuged and frozen to -20^{0}C for delayed batch analysis.

If the ultrasound guided femoral 3-in-1 nerve block failed to reduce the pain NRS score to <30/100 in 30 minutes then 20 ml of 0.25% levobupivacaine was given via the femoral nerve catheter to achieve a pain NRS score of <30/100. If 30 minutes after the injection of 20 ml of 0.25% levobupivacaine, the pain NRS score was not ≤30/100 the ineffective regional analgesia was attributed to a failure of placement of the initial 30 ml EC_{95} dose of levobupivacaine and intravenous morphine was titrated according to local protocols to achieve a pain NRS score of <30/100.

5.5.1 Estimation of the number of patients needed

The primary outcome of this clinical trial was the duration of analgesia. The standard deviation was estimated at approximately 4 hours (from clinical experience). The standard error of the mean is the standard deviation divided by the square root of the sample size. Hence a sample size of 16 patients would provide a standard error of 1 hour. Therefore, to estimate the mean duration of analgesia with a 95% confidence interval of ±1.96 hours would require a sample size of approximately 16 patients, assuming an approximately normal distribution. It was assumed that the mean duration of analgesia provide by the levobupivacaine EC_{95} would be approximately 12 hours and if the standard error of the mean was ±1.96 hours then the (1.96/12)*100=16.3%. A 16.3% error was considered an acceptable percentage error for estimation of the mean.

5.5.2 Pain score assessment

A pain score measures a patient's pain intensity or other features. Pain scores are based on self-report, observational (behavioral), or physiological data. A self-reported score such as the Numeric Rating Score provides the most accurate data. It may be used for adults and children over 10 years old or older. Pain scores were assessed on a 100 point numerical rating scale (NRS) scoring system. Pain scores were assessed on a 100 point Numerical Rating Scale (NRS). The following verbal descriptions were used to guide patients; 0-29 mild pain, 30-69

moderate pain and 70-100 severe pain. Pain NRS score was used throughout all clinical studies in this thesis as the pain visual analogue scale was found to be difficult to use in patients with a fractured neck of femur.

5.5.3 Assessment of sensory function

The primary sensory response was based on the sensory response of the middle third of the upper thigh. The patient sensory function was assessed by the intensity of a pin prick sensation and cold sensation produced by melting ice. Pin prick sensation was measured using a blunted 25G (orange) needle. The patient was asked to grade the intensity of the sensory response to the 25G needle by verbalising or marking a line from 0 (no sensation) to 100. One hundred was defined as the same intensity of sensation as the contra lateral anterior aspect third of the upper thigh. Melting ice was also used as a stimulus and the patient was asked if the cold sensation was reduced on the side on which nerve block was performed compared with the contra lateral (unblocked side) on the medial (M), anterior (A) and lateral region (L) of the upper thigh (See Figure 5-1).

The change in sensation associated with effective regional analgesia was defined as a reduction in sensation to blunted 25G needle in the anterior aspect of the upper thigh (area marked as A in Figure 5-1) of ≤30/100 or a reduction in cold sensation to melting ice in comparison with the contra lateral area of the thigh in the upper anterior aspect of the thigh.

Figure 5-1: The surface anatomy of the upper thigh: The anterior (A), lateral (L) and medial (M) aspects of the upper thigh are shown in the diagram below.

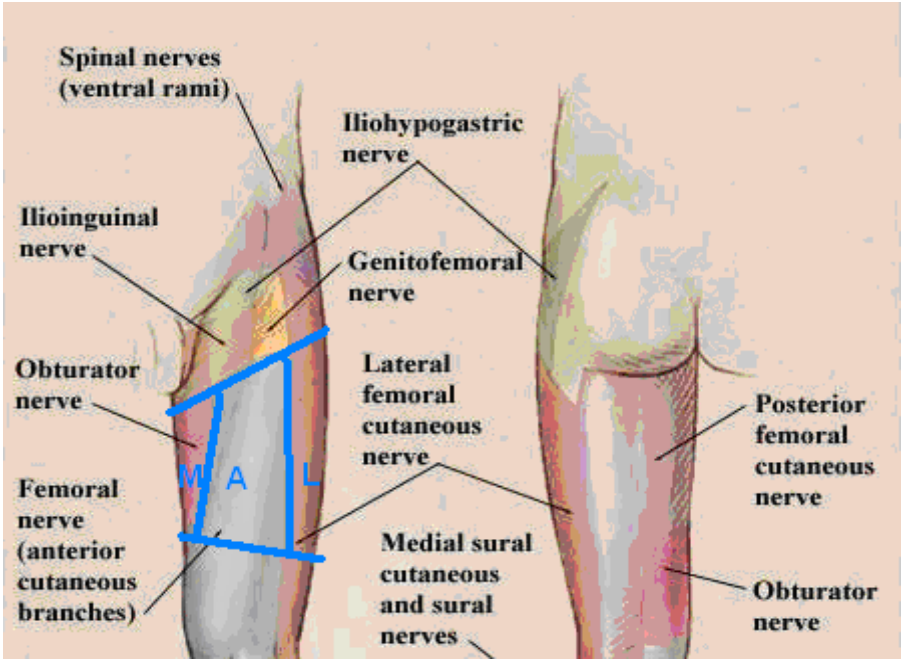


Image from personal collection of Dr Malcolm Watson

5.5.4 Assay of levobupivacaine levels

All blood samples where stored on ice immediately and centrifuged after the collection period and stored at -20^{o}C until they were sent for analysis. Analysis was performed with a specific Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) assay at ABS Laboratories using GLP (good laboratory practice)/GCP (good clinical practice) compliant systems within a GLP accredited laboratory. The levobupivacaine assay used to analyse the plasma samples was calibrated between 1 ng/ml – 5000 ng/ml with an inter sample variability of <5.1% over this range (see Appendix 7).

5.5.5 Secondary end points

- Blood pressure, oxygen saturation, pulse rate and respiratory rate before the femoral 3-in-1 nerve block and every 10 minutes for 30 minutes after insertion of 30 ml of levobupivacaine
- Serum concentrations of levobupivacaine from blood samples taken at 5, 10, 20, 30 and 60 minutes after insertion of the levobupivacaine.
- The pain NRS score was recorded pre femoral 3-in-1 nerve block and at 10, 20 and 30 minutes post block in order to estimate the time to half the pain NRS score. These were modelled using both linear and nonlinear methods to achieve the best fit for the data and therefore the best estimate of half pain time.
- The sensory function of the femoral, obturator and lateral cutaneous nerves was tested at 0 minutes (before insertion of levobupivacaine) and at 10 and 20 minutes post insertion of 30 ml levobupivacaine.
- Venous blood gases and liver function tests results outside the standard range of values.

5.5.6 Standards

This clinical trial was conducted to ICH-GCP (2004)and monitored by Greater Glasgow and Clyde Board (the report is included in Appendix 1) with only minor findings. All Investigational and Medicinal Products were produced by an accredited pharmacy production unit using the batch of levobupivacaine 0.75% assayed in Appendix 8. The clinical research data was recorded and processed

to comply with ISO 9001:2008 and the statistical analysis was supervised by Dr Alex McConnachie, senior statistician at the Robertson Centre for Biostatistics, Glasgow University.

5.6 Results

A total of 14 patients with fractured neck of femur were prospectively recruited preoperatively from 20 November 2010 until 4 March 2011. No patients had equivocal sensory and pain results or ineffective analgesia (≤20/100 decrease in VAS pain scores) therefore no patient's data was excluded.

5.6.1 Demographics

The mean age of all patients recruited was 76 year with a standard deviation of 12 years (median 76 years and interquartile range 72-85 years). Five patients recruited were male and nine were female.

5.6.2 Hospital mortality

All 14 patients recruited survived to hospital discharge.

5.6.3 Time taken to insert a femoral 3-in-1 nerve block

The mean time taken to insert a femoral 3-in-1 nerve block was 71 seconds with a standard deviation of 23 seconds and a median of 75 second and interquartile range of 50 to 84.seconds.

5.6.4 Number of attempts to insert block

Only one skin puncture was required for all patients but an average of 1.3 needle advancements with a standard deviation of 0.5 advancements were required to achieve an ultrasound guided femoral 3-in-1 nerve block.

5.6.5 Physiological observations

The physiological observations of the patients pre-block and at 10, 20 and 30 minutes after the femoral 3-in-1 nerve block are shown in Table 5-1.

Table 5-1: Physiological observations preblock and at 10, 20 and 30 mins. after a femoral 3-in-1 nerve block.

	Pre-block	10 minutes post block	20 minutes post block	30 minutes post block
Median Systolic BP (mmHg), (interquartile range)	152 (136-155)	142.5 (127-145)	137.5 (129-144)	142.5 (132-147)
Median Diastolic BP (mmHg) (interquartile range)	76 (68-85)	73 (70-83)	73 (66-81)	74 (65-84)
Median O_2 saturation (interquartile range)	93 (90-95)	94 (93-96)	94 92-96)	94 (93-96)
Median number of litres of supplementary O_2 (interquartile range)	0 (0-0)	1 (0-2)	1 (0-2)	2 (0-2)
Median Respiratory rate (interquartile range)	14 (12-16)	13 (12-16)	14 (10-15)	12 (10-15)
Median Pulse rate (interquartile range)	88 (77-96)	86 (76-98)	82 (71-96)	86 (72-100)

No statistically significant changes in physiological observations were noted (all interquartile ranges for all the parameters measured overlapped) during the period of observation.

5.7 Part 1: Duration of analgesia following injection of 0.036% levobupivacaine

A summary of the primary end point data (duration of analgesia) from the 14 patients recruited to this clinical trial can be seen in Figure 5-2 and Table 5-2 below.

Figure 5-2: Bar chart for duration of analgesia in individual patients

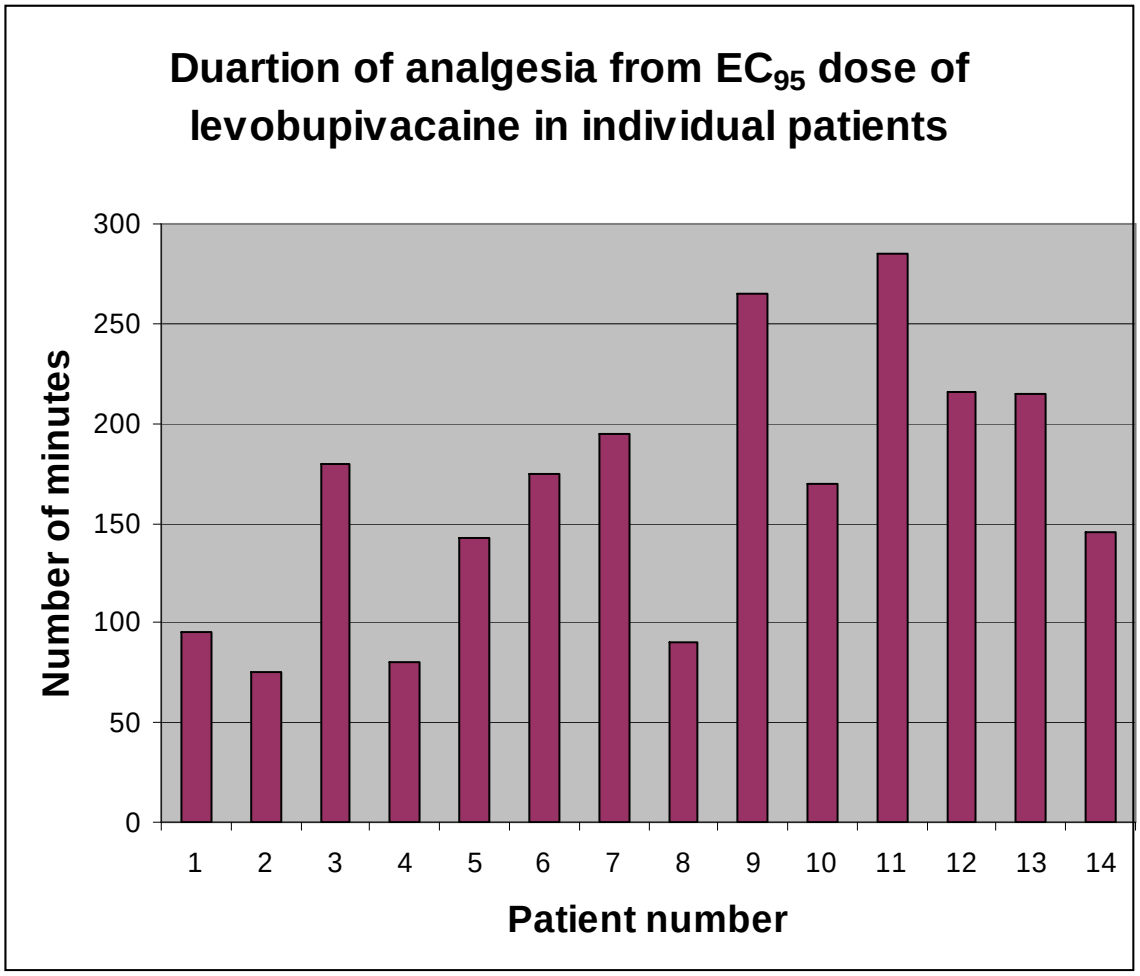


Table 5-2: Summary of data from 14 patient's duration of analgesia in minutes

Mean (median) duration of analgesia	Standard error of the mean	95% confidence interval of standard error of the mean (% of mean duration)	Standard deviation (interquartile range)
166 (177)	18	3 5(21%)	67 (110-210)

5.7.1 Justification of termination of trial after 14 patients had been recruited

This trial was terminated after 14 patients had been recruited when the 95% confidence interval of the standard error of the mean was ±35 minutes. The actual 95% confidence interval of the standard error of the mean was a similar precision to the estimated value from the power calculations (see Table 5-3 Precision of estimation of mean duration of analgesia)

Table 5-3: Precision of estimation of mean duration of analgesia

	Mean duration of analgesia	Standard error (SE)	95% confidence interval (CI)	Percentage (SE)/ mean
Estimated duration of analgesia	12 hours	1 hour	1.96hours	16%
Actual duration of analgesia	166 minutes	18 minutes	35 minutes	21%

A summary of missing data and the adverse event log for this study are shown below in Table 5-4 and Table 5-5, respectively.

Table 5-4: Summary of missing data

Patient number	Problem	Action taken
1	Investigator forgot to take blood sample at 10 minutes post femoral 3-in-1 nerve block	No data available for that time point for serum levobupivacaine levels
5	Faulty glucose electrode on blood gas machine	No data available
11	Unable to aspirate blood from intravenous cannula 30 minutes post block	No data available for that time point for serum levobupivacaine levels

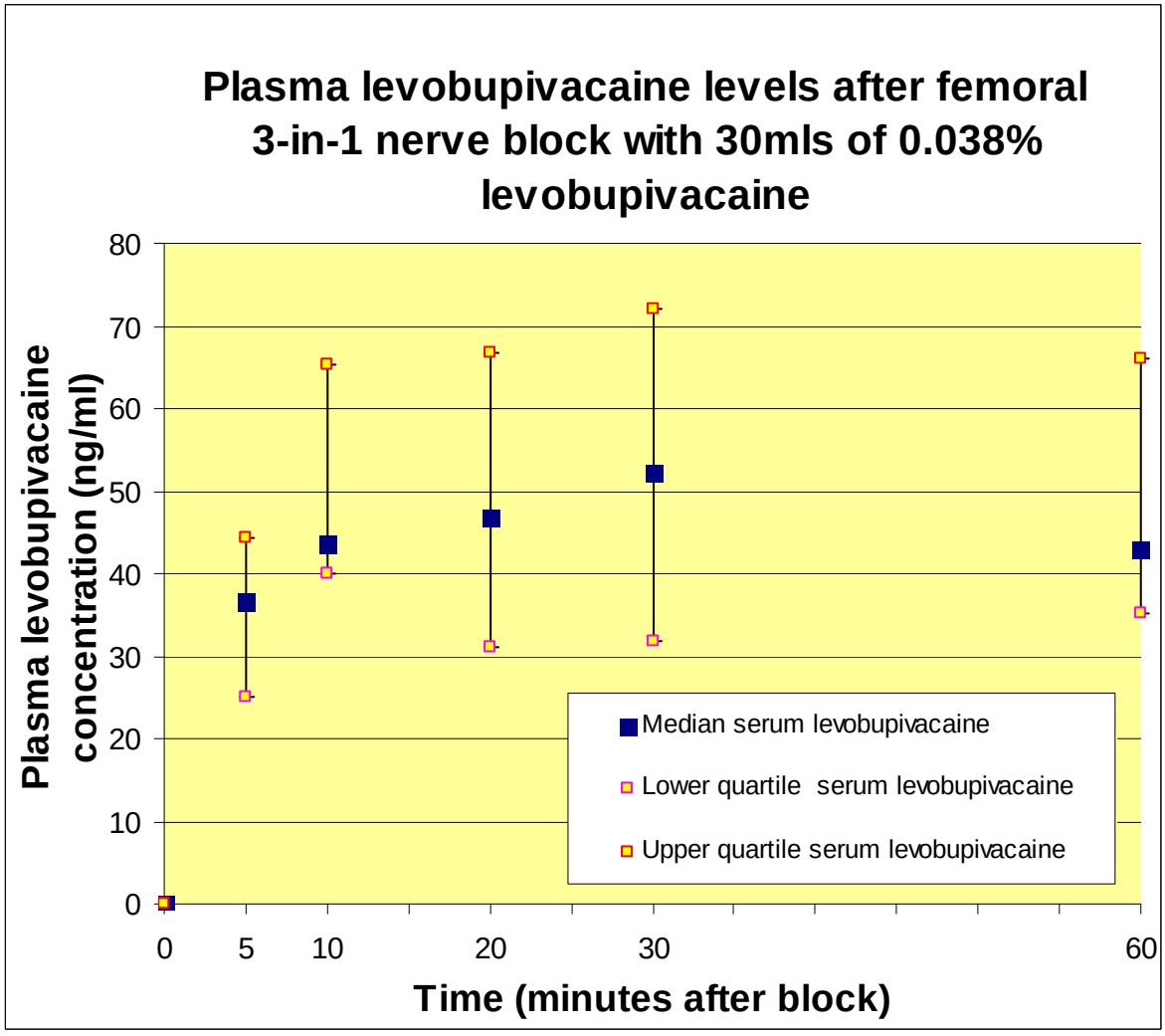
Table 5-5: Adverse event log

Patient number	Adverse event
8	Patient confused overnight for approximately 8 hours after recruitment to study, orientated postoperatively, discharged home 4 days later no treatment given for confusion.

5.8 Part 2 Serum levobupivacaine levels

Blood samples were analysed for serum levobupivacaine concentrations pre-block (0) and at 5, 10, 20, 30 and 60 minutes post femoral 3-in-1 nerve block. The median and upper and lower quartiles of these concentrations have been graphed in Figure 5-3 shown below. The measured serum levobupivacaine concentrations were within the range 9.7-256.6 ng/ml and that the maximum bias in this range was ±2.65% (see appendix 7).

Figure 5-3: Plasma levobupivacaine concentrations against time



The total plasma levobupivacaine concentration increased rapidly to peak after 30 minutes. The highest median level reached (52.3 ng/ml) was substantially lower than the plasma concentration associated with symptoms of central nervous system and cardiovascular system toxicity (2100ng/ml) in the literature (Knudsen et al. 1997). At 30 minutes the range of median concentrations of levobupivacaine was 16-256 ng/ml and a large range was observed at all time points examined in this trial. This may be the result of different absorption patterns from the site of action.

Part 3 Time to half pain scores

The pain NRS scores were recorded before (baseline) the femoral 3-in-1 femoral nerve block and at 10, 20 and 30 minutes after the block in order to estimate the time to half the baseline pain NRS score. This was modelled using both linear and nonlinear models to achieve the best fit for the data.

A linear regression model of time (measured in minutes) for the femoral 3-in-1 nerve block against percentage analgesia based on pre-block pain scores (painRed).
All linear regression equations can be written as

$$y = \beta_0 + \beta_1 x \qquad \underline{OR} \qquad (\text{PainRed}) = \beta_0 + \beta_1(\text{mins})$$

Where y= percentage analgesia and x=time in minutes from nerve block
If we give y the value 50 (50% decease in pain score from pre block levels)
Then the equation could be written

$$50 = \beta_0 + \beta_1 x$$

As rearranged to get x the number of minutes at which the equation predicts that the pain score will have dropped to 50% of there original value

$$X = (50 - \beta_0) / \beta_1$$

We fitted the 3 regression models (see below for a definitions and a summary (Table 5-6) of models 1-3)

- **Model1:** With time in minutes and percentage pain score reduction from baseline
- **Model 2** With time in minutes and Log_e(percentage reduction in pain scores from baseline)
- **Model 3** With Log_e (time in minutes) and Log_e(percentage reduction in pain scores from baseline)

Table 5-6: The R squared and correlation coefficients are shown below

	Model 1	Model 2	Model 3
Regression equation	% pain red =32.0+1.01 minutes	Log_e(% pain red) =3.4+0.02 minutes	Log_e(% pain red) =2.7+0.4 minutes
R squared adjusted	5.3%	6.2%	7.2%
Predicted half pain time	18 minutes	23 minutes	24 minutes

The normal probability plot for residuals for models 1, 2 and 3 are shown below in Figures 5-4, 5-5 and 5-6 respectively.

Figure 5-4: Model 1

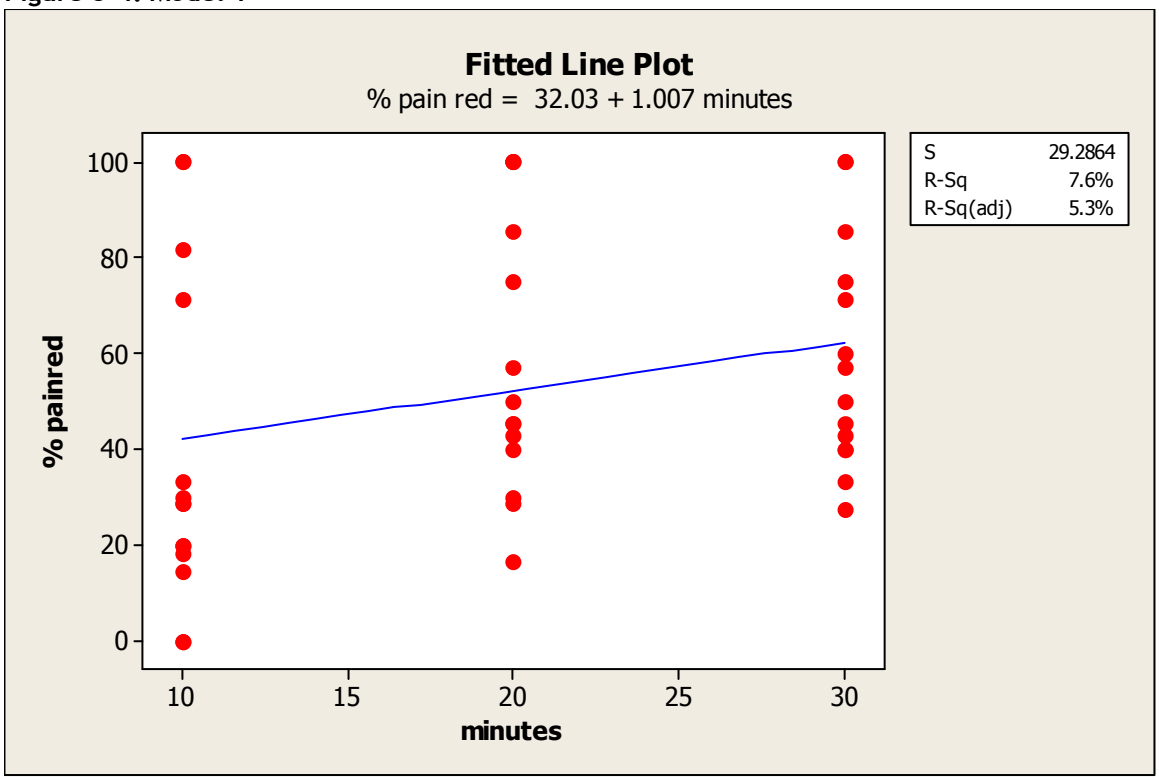


Figure 5-5: Model 2

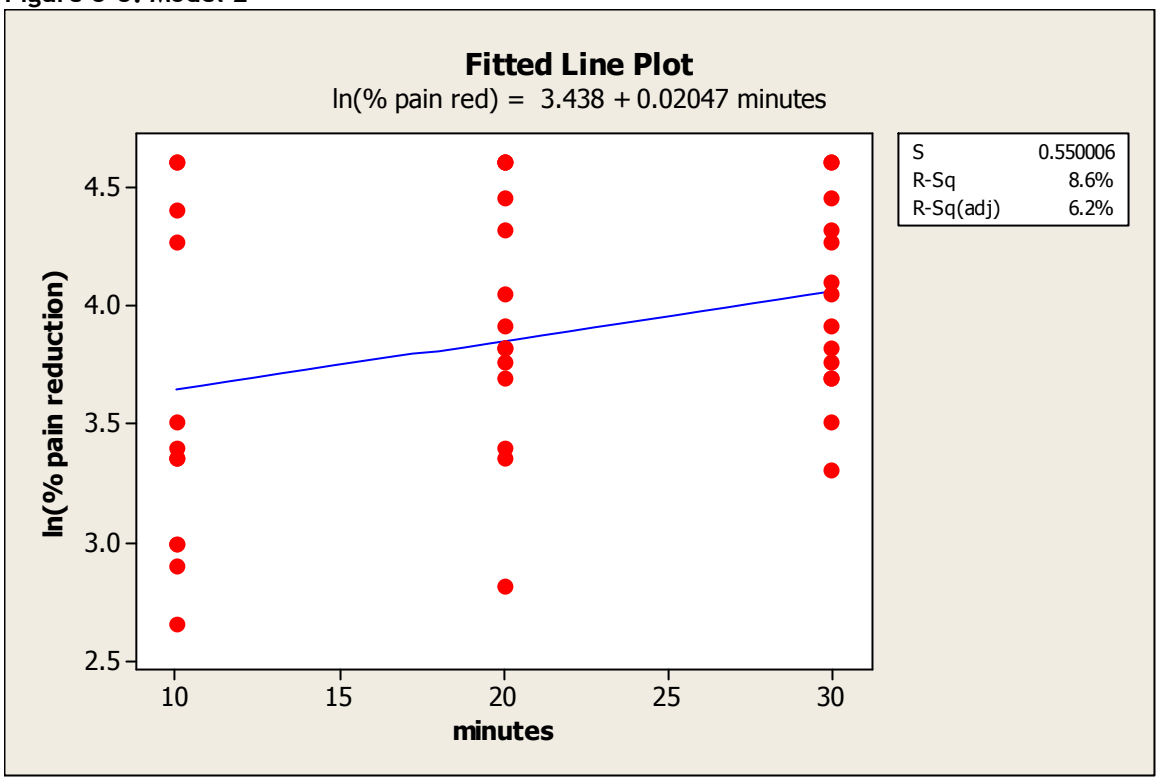
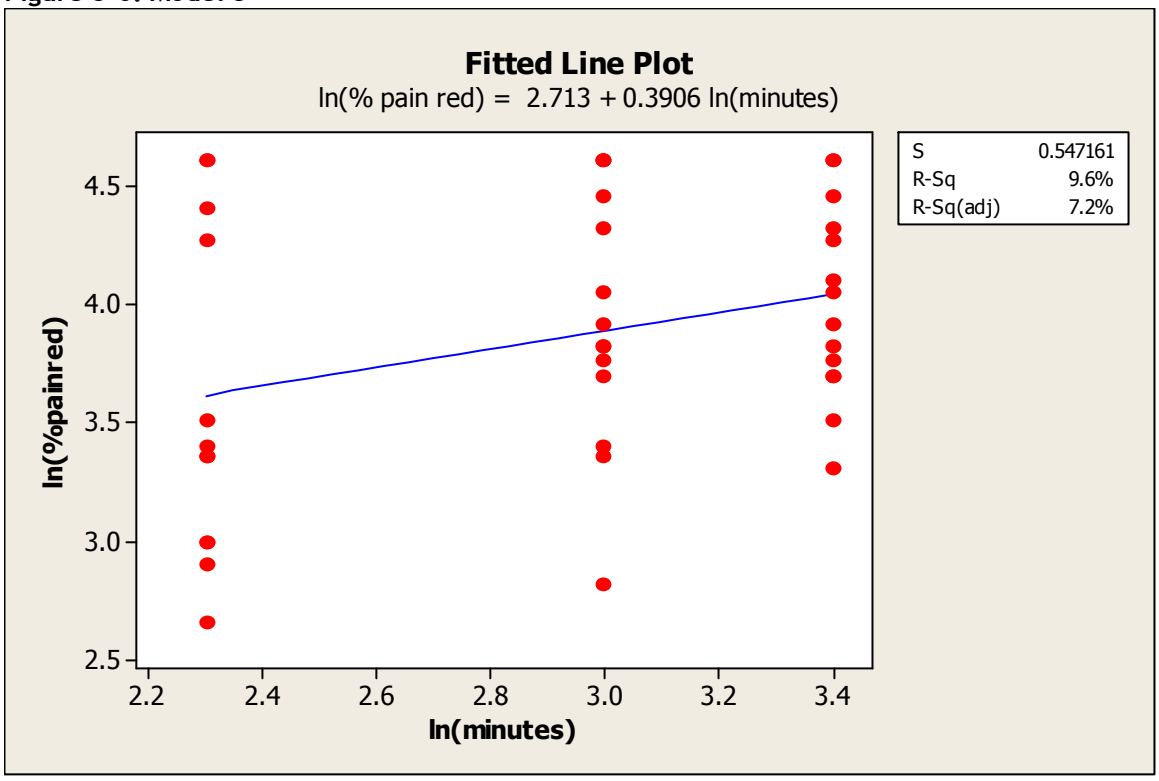


Figure 5-6: Model 3



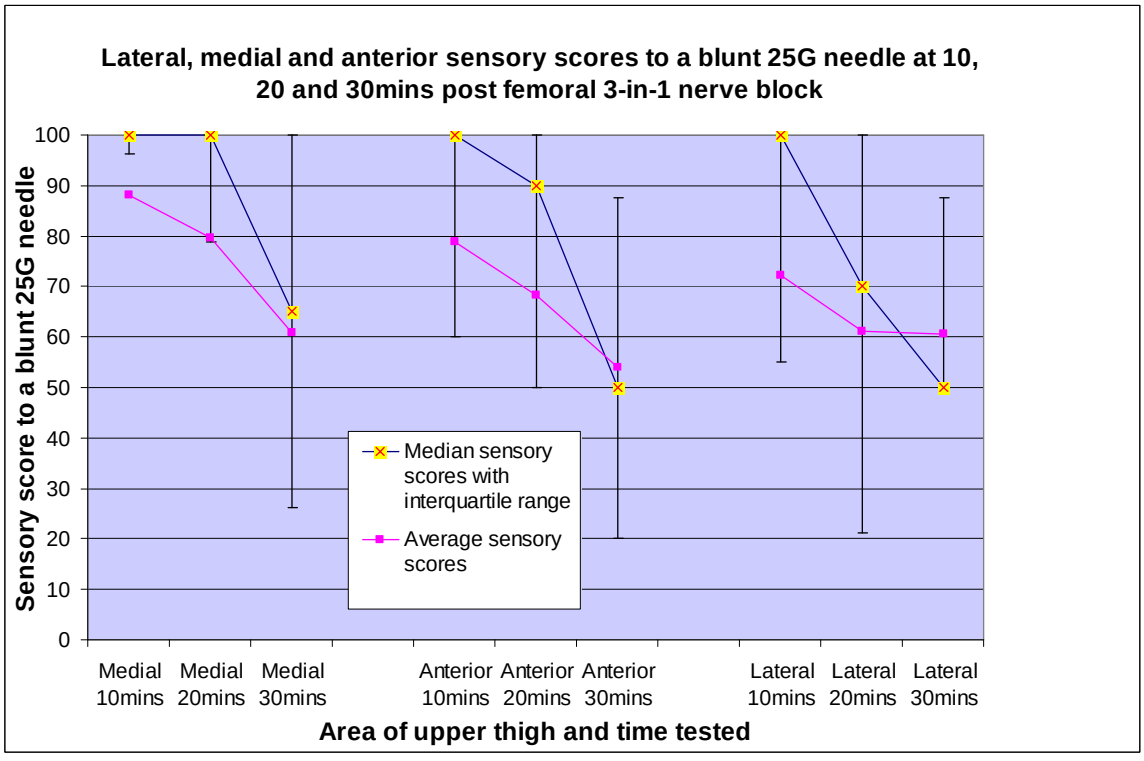
In model one (% pain red=32.0+1.01 minutes) the residuals had a positive skew and the natural $\log_e$ of the data was taken to normalise the residuals and improve the correlation (increase the R squared value). The best fit (least

residuals and highest r squared value) was given by model three. The r squared adjusted value for model three was only 7.2% which implies that only 7.2% of the variance can be explained using this model.

5.9 Part 4 Sensory function of the femoral, obturator and lateral cutaneous nerves

The sensory scores to a blunt 25G needle for the medial, anterior and lateral areas of the upper thigh were plotted against time to examine the pattern of onset of the sensory nerve block (please see Figure 5-7). The part of the femoral nerve that supplied the skin on the lateral parts of the thigh was blocked first, then the anterior and finally the medial aspect of the thigh. The order that the median values cross the 90/100 line on the y-axis (sensory scores to a blunt 25G needle) appears to be related to the proximity of the part of the nerve to the injected dose of levobupivacaine.

Figure 5-7: Sensory scores to a 25G needle in medial, anterior and lateral areas of upper thigh at 10, 20 and 30 minutes after a femoral 3-in-1 nerve block.



5.10 Part 5 Venous blood gas and liver function tests

Table 5-7 below lists the mean ± standard deviation, median, interquartile ranges and ranges for the blood results for all 14 patients in the study with the normal reference range. All values outside the normal reference range have been shown in **bold** with an underline. The vast majority of the interquartile ranges are within the reference range. A few range values are out with the reference range and this was expected in a population of patients with multiple co-morbidities.

Table 5-7: Blood results for all patients recruited to the trial

	Mean ± SD	Median	Interquartile range	Range	Reference range
H^+(nmol/L)	41 ± 4.4	42	40.2-43.6	**30**-47	39-49
pCO_2(kPa)	5.6 ± 0.89	5.8	**5.1**-6.25	**3.5**-6.6	5.5-6.8
PO_2 (kPa)	5.8 ± 2.3	5.25	4.2-**6.7**	**3.2**-**11.8**	4.0-5.3
Na^+ (mmol/L)	136 ± 2.4	135	135-137	**131**-140	135-145
K^+ (mmol/L)	4.1 ± 0.34	4.1	4.0-4.3	**3.3**-4.6	3.5-5.0
Haematocrit (%)	36 ± 5	36	**33**-40	**26**-44	40-54
Glucose (mmol/L)	7.2 ± 1.4	7.5	5.8-**8.4**	5.1-**9.1**	3.5-5.5
Lactate (mmol/L)	1.4 ± 0.54	1.1	1-1.8	0.7-2.2	<0.5-2.2
Base excess (mmol/L)	0.45 ± 2.8	1.5	(-1.7)-1.9	(-**5.1**)-**5.7**	±3
HCO_3^- (mmol/L)	25.6 ± 3.1	26.9	23.3-27.7	18.1-28.6	21-28
Urea (mmol/L)	6.1 ± 1.7	5.6	5.2-6.9	3.6-**10.2**	2.5-7.5
Creatinine (µmol/L)	77 ± 24	64	63-85	55-**132**	40-130
Bilirubin (µmol/L)	10.6 ± 5.2	9	7.2-13	4-**22**	<20
AST (U/L)	22.5 ± 13	20	17-23	11-**64**	<40
ALT (U/L)	15 ± 4.2	14	12-16	8-22	<50
γ-GT (U/L)	59 ± 125	20	16-**43**	11-**488**	<40
Alk-PO3 (U/L)	159 ± 263	90	74-122	43-**1069**	40-150
Total protein (g/L)	66 ± 8	66	60-68	55-**89**	60-80
Albumen (g/L)	33 ± 6	34	28-37	**23**-42	32-45
Globulin (g/L)	33 ± 6	32	30-35	23-**47**	23-38

The reference ranges for the majority of the value displayed were taken from Western infirmary, Glasgow biochemistry and haematology laboratories but base excess and H^+, PCO_2 and O_2 in venous blood gases were taken from http://en.wikipedia.org/wiki/Reference_ranges_for_blood_tests which was referenced from brooksidepress.org (12 A.D.).

5.11 Discussion

5.11.1 Safety of levobupivacaine

The measurement of serial plasma levobupivacaine concentrations assessed the safety of the EC_{95} concentration of levobupivacaine when administered to an elderly frail patient population with multiple co-morbidities.

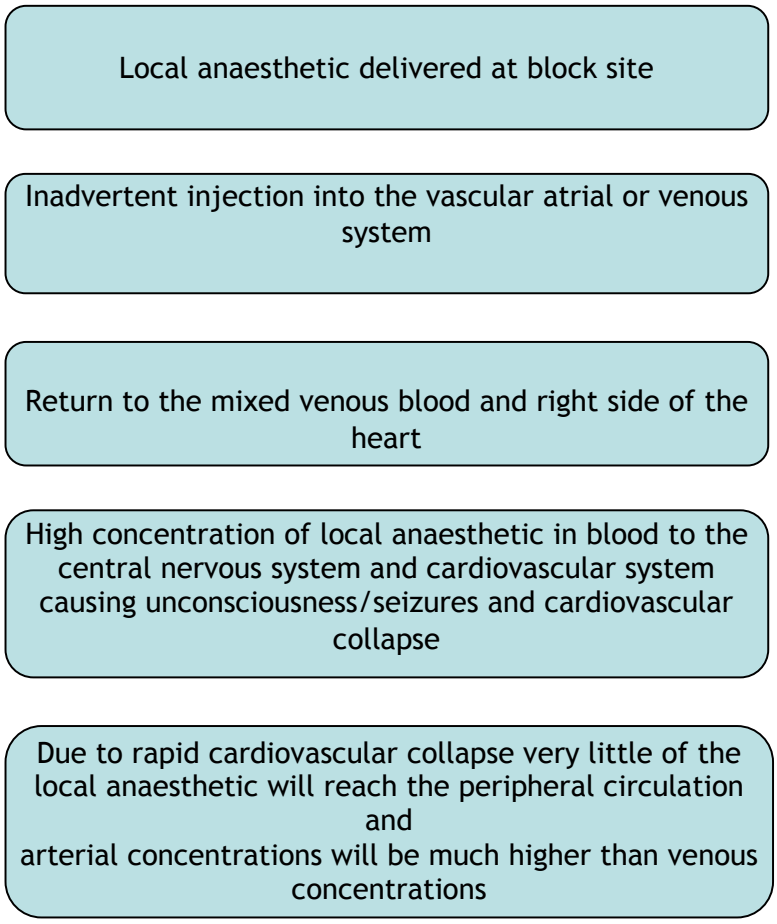
5.11.2 Levobupivacaine plasma concentrations and toxicity

The levobupivacaine venous concentrations increased rapidly after the femoral 3-in-1 nerve block and the highest median plasma concentration was obtained after 30 minutes. Paut et al also noted a rapid increase in venous plasma ropivacaine concentration after femoral 3-in-1 nerve blocks (Paut et al. 2004). In contrast to the study of Paut et al, the peak serum plasma concentrations during this clinical trial were well within the 'safe range' despite a wide variation in the observed plasma levobupivacaine concentrations.

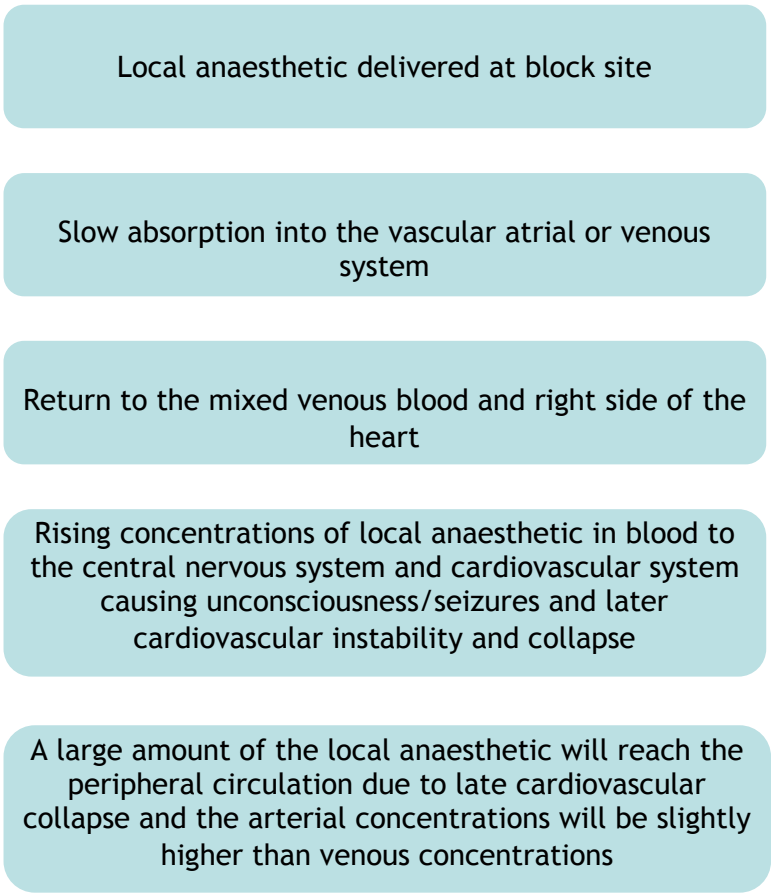
The study by Paut et al was stopped early due to measured serum ropivacaine levels above 2200 ng/ml (Paut et al. 2004) in venous samples. This concentration had been associated with central nervous and cardiovascular toxicity in healthy adult volunteers by Knudsen et al (Knudsen et al. 1997). However Paut et al did not take into account the rapid intravenous infusions which were used in the study by Knudsen et al and the consequent arteriovenous difference in both plasma levobupivacaine and ropivacaine concentrations (Knudsen et al. 1997). In the rapid infusion model, peripheral arterial and venous concentrations will not reflect heart and central nervous system concentrations of local anaesthetic and a large peripheral arteriovenous difference will be present (please see 5.11.3 Rapid infusion system). In a 'slow infusion' model which would be more applicable to the study of Paut et al (Paut et al. 2004) the peripheral concentrations are likely to reflect exposure of the heart and central nervous system and the peripheral arteriovenous concentration difference will be small (please see 5.11.4 Slow infusion system). It is also notable that despite terminating the study early, no child exhibited the signs or symptoms of central nervous system or cardiac toxicity. In contrast, in the healthy volunteers study by Knudsen et al, signs of central nervous system

toxicity were easily observed by the doctors observing the volunteers. It is possible that children are resistant to local anaesthetic toxicity. It is possible that concomitant general anaesthesia masked the signs and symptoms of central nervous system and cardiovascular toxicity.

5.11.3 Rapid infusion system (Injection of local anaesthetic into vascular system



5.11.4 Slow infusion system (Absorption of local anaesthetic into the cardiovascular system)



5.11.5 The relationship between serum local anaesthetic concentration and toxicity

It is often stated that there is a lack of correlation between the serum concentration of local anaesthetic and clinical symptoms and it is likely that other factors play a significant part and these factors are often overlooked in case reports of local anaesthetic toxicity

5.11.6 Venous arterial difference for serum local anaesthetics

The vast majority of reports of local anaesthetic toxicity have reported venous serum concentration of local anaesthetic. In the event of a rapid infusion of

local anaesthetic into the systemic circulation, venous sampling will not correlate well with toxicity (Chazalon *et al*. 2003;Huet *et al*. 2003). The use of venous sampling may be justified if the onset of central nervous or cardiac toxicity is delayed (slow infusion model) following the administration of the local anaesthetic. In the event of a delay of less than 5 minutes (rapid infusion model), arterial sampling will be a more accurate measure of exposure of critical organs (heart and central nervous system) to systemic concentrations of levobupivacaine.

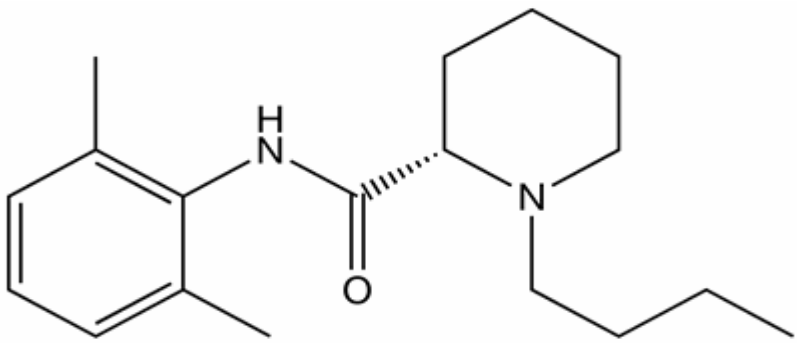
5.11.7 Injection of local anaesthetic directly into the central nervous system

Arterial plasma concentrations may not reflect the direct exposure of the central nervous system to local anaesthetic. Systemic vascular concentrations may have no correlation to the local exposure of the central nervous system as a result of an interscalene approach to the brachial plexus block or to epidural anaesthesia (Dhir et al. 2007;Pasquier et al. 2009;Satsumae et al. 2008). All three case reports the authors were unable to aspirate blood via the needle or catheter. The use of both MRI and ultrasound doppler visualisation by Dhir et al failed to visualise the vascular placement of a interscalene brachial plexus catheter which was associated with seizures (Dhir et al. 2007).

5.11.8 The effect of acid base balance and protein binding

The acid base balance affects the action and the protein binding of levobupivacaine due to the presence of an amino group. The structure of levobupivacaine can be seen below.

Figure 5-8: The chemical structure of levobupivacaine



Levobupivacaine a lipophilic benzene ring (on the right) linked by an intermediate amide linkage to an amide group on the left.

5.11.8.1 Onset of local anaesthesia

The amino group of levobupivacaine, will adopt the tertiary non-polarised) lipophilic or the quaternary (polarised positively charged weak base) water soluble form dependant on the pH. This effect has a practical application in obstetric anaesthesia. Sodium bicarbonate is often added to levobupivacaine to reduce the onset time of an epidural block to facilitate delivery. The explanation of this effect is that if the pH is increased there will be an increase in tertiary (non polarised) molecules. Those molecules cross more easily through the lipophilic axonal membrane to the site of action on the inside of the fast voltage dependant sodium channels. In contrast, in an acidic environment such as an abscess the low pH will result in less tertiary (non-polarised) lipophilic molecules crossing the axon membrane.

5.11.8.2 Protein binding

Acid base balance will also affect the protein binding of levobupivacaine. Levobupivacaine is more than 97% protein bound, mainly to acid α-1-glycoprotein which is an acute phase protein. If the environment is acidic then more levobupivacaine will be in the ionised form and since acid α-1-glycoprotein binds positively charged molecules, a greater percentage of it will be protein bound. The effect; therefore, of a profound acidosis on protein binding would be to decrease the availability of free drug but there are no case reports or studies describing this effect. The effect of protein binding is seen in studies looking at infusions of local anaesthetic and the increase in acid α-1-glycoprotein resulted in the levels of free levobupivacaine remaining unchanged despite increasing levels of total levobupivacaine (Ekatodramis *et al.* 2003). The complex effects of protein binding and acid base balance can be negated if free levobupivacaine levels are measured; however, this is expensive as the samples need to undergo ultrafiltration after centrifugal separation, before freezing and storage of the plasma sample for later analysis.

5.11.9 Free levobupivacaine

It can be argued that free plasma levobupivacaine will be more closely associated with toxicity but during the short time period that this study was conducted (less than 1hour) it can be assumed that no significant change in plasma proteins will have occurred. We recorded cardio-respiratory

measurements, urea and electrolytes, liver function tests and venous blood gases in all patients recruited to this study. The contribution of acid base balance to levobupivacaine toxicity has never been adequately assessed. The amount of free base drug such a levobupivacaine will be influenced by the acid base balance. In the elderly population, the presence of abnormalities will be higher and any assessment of levobupivacaine toxicity should take into account the effect of pH and plasma proteins.

5.11.10 The effect of age on the toxicity of levobupivacaine

If the effect of age is taken into account it is likely that the EC_{95} calculated is only valid for the population of patients recruited to this clinical trial (elderly patients). The efficacy of local anaesthetics in the elderly population has been consistently increased in studies examining central neuraxial (epidural blocks) (Bromage 1969;Simon et al. 2004) and in peripheral nerves (in the brachial plexus) (Paqueron et al. 2002) In contrast, local anaesthetic toxicity is a greater risk in the elderly. Although plasma concentrations of local anaesthetics are unaffected by age (Finucane, Hammonds, & Welch 1987;Veering et al. 1991); however, elderly patients have a reduced plasma clearance (Bromage 1969;Knudsen et al. 1997;Paut et al. 2004) which leads to a greater risk of toxicity.

5.11.11 Pain half time-onset of analgesia

In order for the analgesic effect of femoral 3-in-1 nerve block to be useful, it must be comparable to the alternative analgesic which is morphine in the UK. The anaesthetic text books quote an onset time of 15 to 30 minutes for intravenous morphine (Bromage 1969;Stoelting 2000). This is comparable to the 24 minutes estimated from the time to half pain NRS scores for femoral 3-in-1 nerve block with an EC_{95} concentration of levobupivacaine.

5.11.12 Medial sensory response and time to half pain

The medial sensory response appears to be temporally linked to the time to half the pain NRS score. It is possible this is a coincidental finding but the association between the loss of medial sensation in the upper thigh and analgesia has been previously documented (Dolan et al. 2008). It is possible that

loss of medial sensation in the upper thigh could be used as a surrogate marker of analgesic efficacy.

5.11.13 Quantifiable error in final concentration and volume of IMP

The error associated with the manufacture of a specific volume and concentration of levobupivacaine should be estimated. The IMP (levobupivacaine) was manufactured to good manufacturing practice (GMP) standards in an accredited pharmacy facility.

The stock drug (levobupivacaine 0.75% manufactured by Abbot Ltd.) was diluted with saline 0.9% to produce the 30 ml of the EC_{95} concentration of levobupivacaine. We obtained the concentration assay preformed by Abbot Ltd. on the batch of levobupivacaine marked as 0.75% used in this clinical trial. The actual concentration of levobupivacaine 0.75% used for all 14 doses of levobupivacaine EC_{95} given in this study was 7.605 mg/mL (101.4% of marked concentration) (please see Appendix 8).

The estimated error during manufacture of the IMP arose from two sources, the estimated weight of the saline bag used to dilute the stock levobupivacaine 0.75% (max error=0.88% of final concentration) and the volume of the two syringes used to measure stock 0.75% levobupivacaine concentration and to store and administer the levobupivacaine which will be 3.5% per syringe using data from BD Ltd (please see Appendix 6: The BD Ltd. data sheet). Therefore, the maximal error for the concentration of the IMP and hence the EC_{95}% is ± (1.4%+0.88%+3.5%+3.5%) =± 9.3%. This assumption is likely to be grossly in excess of the true error as it assumes that all the errors were maximal and that they all changed the concentration in the same direction.

A more reasonable calculation is to sum the error squared and get the square root of the result. This assumes that some of the errors will cancel each other out (Taylor 1982).

Therefore Final error=$\sqrt{}(1.4)^2+(0.88)^2+(3.5)^2+(3.5)^2$

$=\sqrt{}(1.96)+(0.7744)+(12.25)+(12.25)$

$=\sqrt{}(27.2344)$

$=5.2\%$

EC_{95}%= 0.0357% maximal error (± 9.3% of the marked concentration) i.e ± 0.003%

or sum of squares(± 5.2% of the marked concentration) i.e ±0.0019%

5.11.14 Total estimated experimental error for duration of analgesia

The standard error of the mean was 36 minutes for the duration of analgesia with an estimated the duration of analgesia of 166 minutes. Therefore, the estimated biological variation and pharmacological error had a 95% confidence interval of ± 21% of the estimated duration of analgesia provided by the EC_{95} concentration of levobupivacaine (0.036%).

5.11.15 Sensory testing

Sensory testing was included in the protocol in an attempt to reduce the placebo effect attributed to the provision of all analgesic procedures. It was possible that a placebo analgesic effect was present although great care was taken to explain to the patients that the procedure (femoral 3-in-1 nerve block) may not give pain relief. In order to minimise the placebo effect a change in the pain NRS score at 30 minutes after the injection of levobupivacaine was regarded as unreliable unless it was accompanied by an appropriate sensory change affecting the femoral nerve distribution. The agreement between the measured analgesic response and the sensory testing with melting ice and a blunted 25G needle makes it less likely that a placebo response was responsible for the analgesic effect measured in this clinical trial.

5.11.16 Further work

This clinical trial has produced an estimate of the effective dose required to provide analgesia (EC_{95}) and the associated duration of the analgesia. This result suggests that the doses of local anaesthetic commonly used in current clinical practice are in excess of what is required to provide analgesia. A similar clinical trial design (the sequential up /down Dixon's methodology) could be used to investigate the dose of levobupivacaine required to provide a clinically useful duration of analgesia (10 hours). The result of this trial would be an estimate of the EC_{95} and the EC_{50} required for 10 hours of analgesia.

5.11.17 Conclusion

The median duration of analgesia from 30 ml of 0.036% (the EC_{95} of levobupivacaine) was 166 minutes with an interquartile range of 110 to 210 minutes. The peak median total serum plasma concentration was reached

at 30 minutes after the block and was 52 ng/ml and it was well within the 'safe range' despite a wide variation in the plasma concentrations observed in this study (range at 30 minutes 16 to 256 ng/ml). It was therefore concluded that the EC_{95} dose of levobupivacaine was safe but provided too short a duration of action to be of clinical value

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3.1 Summary of chapter 5

5.11.18 Aim

The aim of this study was to determine the duration of analgesia provided by the EC_{95} dose of levobupivacaine and ensure that it had a safe pharmacokinetic profile in the patients with a fractured neck of femur.

5.11.19 Method

The duration of analgesia in 14 patients with a fractured neck of femur provided by a femoral 3-in-1 nerve block with 30 ml of 0.036% levobupivacaine (the EC_{95} dose of levobupivacaine) was measured. Blood samples where taken at 5, 10, 20, 30 and 60 minutes after the block to determine the plasma levobupivacaine concentrations.

5.11.20 Results

The median duration of analgesia was 166 minutes with a standard error of 36 minutes. The plasma concentrations of levobupivacaine varied widely but were well within safe limits.

5.11.21 Conclusion

The median duration of analgesia provided by 30 ml of 0.036% levobupivacaine was too short to be clinically useful but the plasma levels of levobupivacaine were within safe limits in the fractured neck of femur population.

6 Can nerve block for hip surgery be improved by ultrasound and nerve stimulator guidance?

6.1 Aim

To determine if the use of ultrasound and nerve stimulator guided femoral 3-in-1 nerve block can improve the effectiveness of this nerve block in comparison to a technique utilising loss of resistance.

6.2 Study design

This study was an assessor-blinded, prospective, randomised controlled study of three techniques to guide the insertion of a femoral 3-in-1 nerve block; ultrasound, nerve stimulator and loss of resistance.

6.3 Study Population

One hundred and eighty competent patients scheduled for elective primary total hip arthroplasty were prospectively recruited to this study between 1st February 2009 and 23rd December 2010 in three hospitals in Glasgow, Scotland.

6.3.1 Inclusion criteria

The following inclusion criteria were used:

- Scheduled for elective primary total hip arthroplasty with spinal anaesthesia
- American Association of Anaesthetists classification (ASA) ≤4 (1963;Little 1995).
- Able to give informed consent
- Able to cooperate with sensory and motor testing of lower limb function

6.3.2 Exclusion criteria

The following exclusion criteria were used:

- Abnormal clotting screen or platelet count, (International Normalised Ratio (INR) >1.4) or (platelets <100,000/mm^3) respectively that would normally preclude regional anaesthesia.
- Acute mental test score of ≤7 at any time pre- or postoperatively
- History of allergy to any local anaesthetic agent
- Signs, symptoms or laboratory evidence of local infection or systemic sepsis that would normally preclude central neuraxial regional anaesthesia
- Known pre-existing neurological deficit (sensory or motor) affecting the lower limb
- Patients with a lower limb amputation

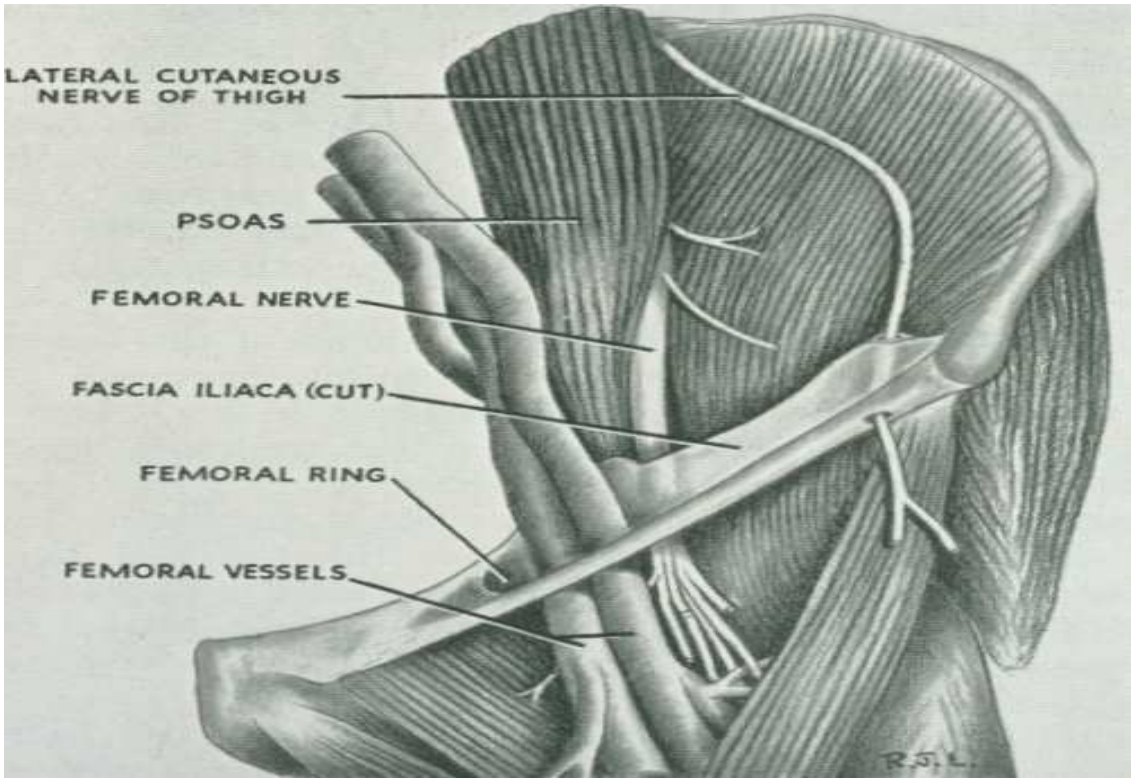
6.3.3 Criteria for withdrawing a patient from the study

- Patients were allowed to withdraw from the study at any time without giving any reason or justification
- Patients with an acute metal test (AMT) ≤7/10 at any time intraoperatively or up to 24 hours postoperatively

6.3.3.1 Summary of clinical anatomy of the femoral nerve

The femoral nerve is formed in the body of the psoas muscle from the anterior primary rami of L2-4, inferiorly it lies on the surface of a groove between iliacus muscle laterally and psoas muscle medially. It is covered by the iliacus fascia which also covers the lateral cutaneous nerve of the thigh and separates both nerves from the femoral artery and vein. The femoral nerve passes under the inguinal ligament and divides into multiple terminal branches. The femoral nerve is therefore best visualised at or just distal to the inguinal ligament before it divides into its terminal branches.

Figure 6-1: Left femoral nerve, vein and artery with fascia lata and superficial structures removed



Adapted from Last's Anatomy Regional And Applied, 4th edition Churchill publishing page 193

6.4 Methodology

6.4.1 Randomisation

Patients recruited to the study were randomised into one of the three techniques in a ratio of 1(loss of resistance):2(nerve stimulator):2(ultrasound) by computer generated block randomisation into groups with random block lengths of 5 or 10 patients. After the patient was consented they were randomised by opening a sealed envelope. The randomisation sequence was held at the Robertson Centre for Biostatistics, Glasgow and only on completion of the study was the full randomisation sequence unblinded and checked against the actual envelopes used to randomise patients recruited to the study.

6.4.2 Preoperatively

Consented unpremedicated patients were transferred to the operating theatre approximately 45 minutes prior to their scheduled operation and initial sensory and motor function testing was performed by an assessor blinded to the allocated technique. A femoral 3-in-1 nerve block was inserted preoperatively using one of the three techniques described with the following local anaesthetic mixture; 10 ml of 0.25% levobupivacaine mixed with 10 ml of 2% lignocaine. The regional needles used were 18G; 50 mm or 100 mm Contiplex Tuohy tipped needles (B. Braun Ltd.) for all femoral 3-in-1 nerve blocks. Lidocaine 1% 0.5 ml was injected intradermally for skin anaesthesia before regional needle skin puncture. The number of skin punctures and time taken to complete the femoral 3-in-1 nerve block was recorded.

6.4.2.1 Methodology for ultrasound guided femoral 3-in-1 nerve block

A LOGIQ e ultrasound machine (GE Ltd.) with a linear broad band (8-12 MHz) probe was used to obtain short axis images of the common femoral artery, vein and nerve, parallel to the inguinal ligament (see Figure 6-2 and Figure 6-3) and the needle was introduced in plane until the tip was positioned lateral to the femoral nerve under the fascia iliacus membrane. After a 'negative' aspiration to detect accidental intravascular placement, 1 ml of local anaesthetic mixture was injected to ensure spread of local anaesthetic around the femoral nerve with associated 'tenting' of the fascia iliacus membrane. If this did not occur

then the needle tip was repositioned and the 1 ml test injection repeated. Only after satisfactory local anaesthetic spread had been achieved and a 'negative' aspiration for inadvertent intravascular placement had been performed was the remaining local anaesthetic injected.

Figure 6-2: Position of ultrasound probe for a left femoral 3-in-1 nerve block

Image from personal collection of Dr Malcolm Watson

Figure 6-3: Short axis ultrasound image of femoral nerve artery and vein

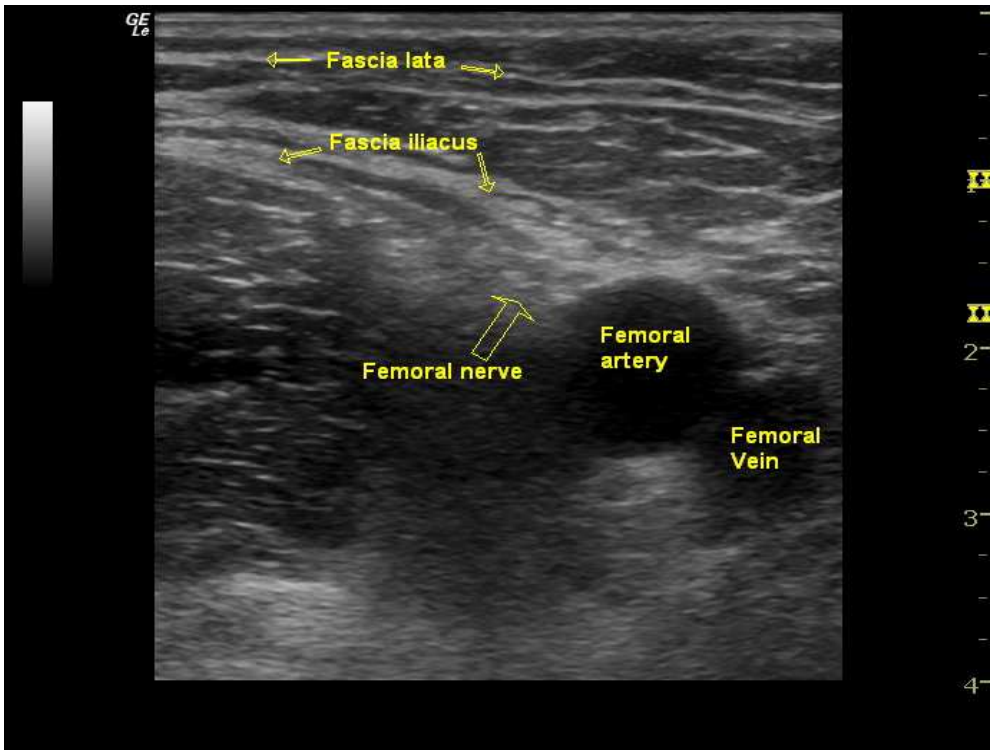


Image from personal collection of Dr Malcolm Watson

6.4.2.2 Methodology for nerve stimulator guided femoral 3-in-1 nerve block

The needle punctured the skin 1 cm lateral to the femoral artery and 1.5 cm below the inguinal ligament. A Stimulpex HNS12 nerve stimulator was used with the starting current set to 1 milliamp (2 Hz frequency and 0.1 millisecond duration) (1963a;Tsui 2007). The needle was positioned to achieve contractions of the quadriceps femoris muscle. Once this motor response had been elicited the current was reduced and the needle positioned until the quadriceps motor response was elicited at less than 0.5 milliamps and disappeared below 0.3 milliamps. After the motor response was achieved and a 'negative' aspiration for inadvertent intravascular placement had been performed, the local anaesthetic dose was injected.

6.4.2.3 Methodology for loss of resistance guided femoral 3-in-1 nerve block

The needle was inserted perpendicular to the skin at a point 1 cm below the junction of the lateral third and medial two thirds of a line that joined the pubic tubercle to the anterior superior iliac spine. The needle was advanced until the '2 losses of resistance' of the fascia lata and the fascia iliacus respectively were felt. After a 'negative' aspiration for inadvertent intravascular placement, the local anaesthetic dose was injected.

6.4.3 Assessment of sensory function

The patient's sensory function was assessed by the intensity of a pin prick sensation using a blunted 25G needle. The patient was asked to grade the intensity of the sensory response to a blunted 25G needle by verbalising or marking a 100 mm line scored from 0 (no sensation) to 100 (normal sensation). A sensory score of 100 was defined as the same intensity of sensation in the corresponding area of the contra lateral thigh. The patient was asked how the sensation to a blunted 25G needle compared to contra lateral (unblocked side) on the medial (M), anterior (A) and lateral region (L) of the upper thigh (See Figure 6-4). The change in sensation associated with effective regional analgesia was initially defined as a reduction in sensation to a blunted 25G needle in the anterior aspect of the upper thigh (which is area marked as A in Figure 6-4) of

≤30/100 in comparison with the contra lateral area in the anterior aspect of the upper thigh (Marhofer et al. 1997). As a result of the clinical trial described in Chapter 4 the definition of an effective femoral 3-in-1 nerve block was amended to a score of ≤90/100 in the anterior aspect of the upper thigh as this sensory response was associated with analgesic efficacy.

Figure 6-4: The surface anatomy of the upper thigh: The anterior (A), lateral (L) and medial (M) aspects of the upper thigh are shown in the diagram below.

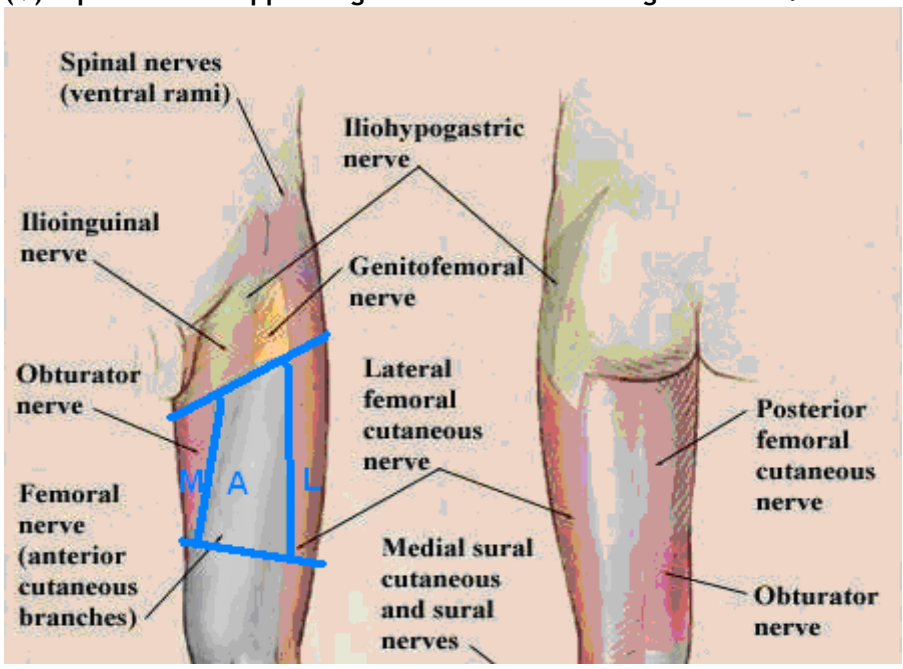


Image from personal collection of Dr Malcolm Watson

6.4.4 Assessment of motor function

6.4.4.1 Assessment of femoral nerve function (quadriceps femoris muscles)

The patient's ability to extend at the knee with the hip semi flexed (to 20 degrees) was assessed and defined as follows:

Grade 4

Patient was able to raise heel from the bed against force applied by assessors arm with assessors elbow flexed at 90 degrees

Grade 3

Patient **not** able to raise heel from the bed against force applied by assessors arm with assessors elbow flexed at 90 degrees but patient was able to raise heel against gravity alone.

Grade 2

Patient able to extend the knee with gravity eliminated

Grade 1

Palpable contraction of quadriceps muscles but no but movement at hip joint

Grade 0

No movement of joint on voluntary contraction of quadriceps muscles

Please see section *'6.5.6 Protocol amendment affecting motor assessments'* for a complete description of all the assessment methods used.

6.4.4.2 Obturator nerve function (hip adductor muscles)

Obturator motor function was assessed using a method described by Lang et al (Lang 1998) which measured the maximal pressure generated on adduction. The patient was asked to adduct both legs with maximal force with the knees and hips extended. The obturator motor function was measured by calculation the average of three maximal pressures generated by a manometer cuff inflated to a starting pressure of 40 mmHg on the upper thigh. An obturator nerve block was defined as a decrease in pre-block average maximal pressure of ≥20% (Lang et al. 1993).

6.4.5 Intra operatively

All patients recruited to the study were scheduled for central neuraxial spinal anaesthesia using 'heavy 0.5% bupivacaine'. The volume of 'heavy 0.5% bupivacaine' used was decided by the attending consultant anaesthetist. Sedation was also used at the discretion of the attending anaesthetist (midazolam, propofol or a low dose volatile agent (<1.5 minimum anaesthetic concentration [MAC]). The airway management was determined by the attending anaesthetist. All patients received paracetamol 1 g every six hours unless contraindicated. Intra operative morphine was administered at the discretion of the attending consultant anaesthetist and was guided by local protocols.

6.4.6 Postoperatively

6.4.6.1 Assessment of pain scores

A pain score measures a patient's pain intensity or other features. Pain scores are based on self-report, observational (behavioral), or physiological data. A

self-reported score such as the Numeric Rating Score provides the most accurate data. It may be used for adults and children over 10 years old or older. Pain scores were assessed on a 100 point numerical rating scale (NRS) scoring system. Pain scores were assessed on a 100 point numerical rating scale (NRS). The following verbal descriptions were used to guide patients; 0-29 mild pain, 30-69 moderate pain and 70-100 severe pain. Pain NRS scores were used throughout all clinical studies in this thesis as the pain visual analogue scale (VAS) was found to be difficult to use in patients with a fractured neck of femur. The use of the pain NRS scores in both elective hip arthroplasty patients and patients with a fractured neck of femur allowed comparison of the data from both studies.

6.4.7 Estimation of the number of patients needed to answer research questions

The expected percentage of effective femoral 3-in-1 nerve blocks in the three groups was 95% (ultrasound), 75% (nerve stimulator) and 50% (loss of resistance) (Dolan et al. 2008;Marhofer et al. 1997). The p value was split for the two comparisons (Abdi 2007;Tsui 2007), for the ultrasound group and nerve stimulator group versus loss of resistance group the alpha error was set at 0.025 and for the ultrasound versus nerve stimulator comparison the alpha error was set at 0.025. If the Fisher exact method and a two sided comparison were used then 72 patients per group need to be recruited to the ultrasound and nerve stimulator groups and 36 patients to the loss of resistance group to adequately power the study. The loss of resistance versus nerve stimulator and ultrasound comparison would have a 90% power to detect a difference between the groups. The ultrasound and nerve stimulator versus loss of resistance comparison would have an 80% power to detect a difference between the groups. It was therefore estimated that the study needed to recruit a total of 180 patients in the ratio 2 (ultrasound):2 (nerve stimulator):1 (loss of resistance).

6.4.8 Primary end point

Effective regional analgesia was defined as ≤90/100 of initial sensory stimuli to a blunted 25G needle in area of skin supplied by the femoral nerve (anterior aspect of upper thigh) and/or evidence of loss of motor power in the quadriceps muscles (inability to raise the heel from bed with hip flexed to 20 degrees

against the assessors arm) ≤3/4 motor score at 30 minutes post insertion of local anaesthetic.

6.4.9 Secondary end points

- Sensory function of the anterior, lateral and medial areas of the upper thigh at 10 and 20 minutes after insertion of local anaesthetic block.
- Motor function of the knee extensors and hip adductors at 10 and 20 minutes after insertion of local anaesthetic block.
- Sensory function at 30 minutes in the lateral and medial areas of the upper thigh and the hip adductor muscle function at 30 minutes.
- Time taken and number of attempts to insert femoral 3-in-1 nerve block
- Acute mental test scores six hours postoperatively and at 24 hours post-anaesthesia
- Morphine usage six hours post-anaesthesia, and 24 hours post-operatively
- Patient satisfaction score six hours and 24 hours post-operatively
- The day and time the patient was mobilised on hip joint by physiotherapy.
- Hospital mortality

6.4.9.1 Standards and quality control

The current study was conducted to the standards detailed in the guidelines by the Chief scientist office, Scotland in 'Research Governance Framework for Health and Community Care' 2nd edition published in February 2006 (2006). This study was audited by NHS Greater Glasgow and Clyde Heath Board (report included in Appendix 9) and the data was recorded, stored and processed to comply with the Data Protection Act 2008 (Data protection act 2008).

6.4.10 Summary of data management

Case Report Forms (CRFs) which contained the original study data and all identifiable patient data were stored in a locked filing cabinet in a locked office. Original data was entered without any personally identifiable data into a password protected computer database to which the chief investigator has never had access. On completion of the study, the data in the database was error checked by two investigators involved in the study (not the chief investigator) against the data on the CRFs. Patient case notes were requested when necessary to obtain the most complete data set. The chief investigator was

given access to a copy of the complete data set, for analysis To allow future audit of this study a complete copy of the original complete data set has been retained to which the chief investigator will never have access.

6.4.11 Standardisation of assessments and study procedures

To minimise the bias from different assessment methods only four assessors carried out all the sensory and motor assessments (please see Appendix 10) and all were trained by Dr Malcolm J Watson and supervised for the first five assessments to ensure accuracy and consistency. The assessor of the primary and secondary end points was blinded to the method used to site the femoral 3-in 1 nerve block (i.e. assessor blinded).

Two digital manometers were used to record the motor power of the obturator never during this study. The accuracy and precision of the BP cuffs used for obturator (adductor) motor power testing was recorded before they were used in the study, after 50 patients had been recruited and at the end of the study when all 180 patients had been recruited. The final quality assurance reports for both manometers are included in Appendix 11. The variation in manometer precision and accuracy was <1 mmHg throughout the study for both manometers.

6.4.12 Statistical methods

All statistical tests used to analyse the results of this study were non-parametric; however, both parametric and non-parametric methods where used to describe the distribution of values. The results of this study were analysed using Minitab (Version 15). The statistical analysis was conducted by Dr Malcolm Watson and supervised by Dr Alex McConnachie, a senior statistician at the Robertson Centre for Biostatistics, Glasgow University.

6.5 Results

A total of 180 patients scheduled for elective primary hip replacement were prospectively recruited from 1 February 2008 to 23 December 2010. Seventy one patients were recruited and randomised to the nerve stimulator group, 72 patients to the ultrasound group and 37 patients to the loss of resistance group.

6.5.1 Demographics

Tables 6-1 and 6-2 show the demographics of the patients recruited in this study. Table 6-1 shows the percentage of patients recruited at each site. Table 6-2 shows the age, gender, weight, height and BMI of patients of the patients with respect to the technique used to guide the femoral 3-in-1 nerve block.

Table 6-1: The number of patients recruited on each site

	Gartnavel General hospital	Glasgow Royal Infirmary	Golden jubilee hospital
Number of patients recruited/total	120/180	31/180	29/180
Percentage of total recruitment	66.7%	17.2%	16.1%

Table 6-2: The age, weight, height and BMI* of patients recruited to the study

	Loss of resistance	Nerve stimulator	Ultrasound
Median age (Ave. ± SD)	62.6 (64.0 ± 12.7)	64.1 (64.2 ± 12.7)	65.5 (63.9 ± 12.3)
Gender			
Male, n(%)	12/37(32.4)	28/71(39.4)	28/72(38.9)
Female, n(%)	25/37(67.6)	43/71(60.6)	44/72(61.1)
Median Weight (Kg), (mean ± SD)	73.6 (74.7 ± 13.3)	80 (78.4 ±18.6)	75.5 (78.4 ± 16.6)
Median Height (m) (mean ± SD)	1.63 (1.63 ± 0.085)	1.64 (1.66 ± 0.094)	1.635 (1.65 ± 0.085)
Median BMI* (Kg/m^2) (mean ± SD)	27.7 (28.1 ± 4.0)	29.7 (28.5 ± 6.1)	28.2 (28.8 ± 5.2)

***BMI-Body mass index = weight in Kg/ (height in metres)^2**

6.5.2 Hospital mortality

All 180 patients recruited survived to hospital discharge.

6.5.3 Time taken to insert femoral 3-in-1 nerve block

Table 6-3 shows the time taken to insert the femoral 3-in-1 nerve block from skin puncture to completion of local anaesthetic injection. A statistically significant difference was seen in the time taken to complete the femoral 3-in-1 nerve block between the techniques when compared to the ultrasound group; loss of resistance took the least time, ultrasound was the next quickest and nerve stimulator took the most time. The statistical significant differences in time taken to insert femoral 3-in-1 nerve block are not clinically significant.

Table 6-3: Time taken to insert femoral 3-in-1 nerve blocks

	Loss of resistance	Nerve stimulator	Ultrasound
Time (seconds)			
median interquartile range (mean ± SD)	38 30-46.25 (41 ± 20)	86 56-146 (130 ±127)	51 44-75 (66± 46)
Mann Whitney test against time to insert ultrasound guided block	P= 0.0001	P= 0.0001	

6.5.4 Number of skin punctures and needle advancements

Table 6-4 shows the number of skin punctures and needle advancements required to complete the femoral 3-in-1 nerve block. A statistically significant difference was seen between the ultrasound and nerve stimulator techniques. Significantly fewer skin punctures and needle advancements were needed to complete a femoral 3-in-1 nerve block using ultrasound compared with nerve stimulator (p=0.0001).

Table 6-4: Number of skin punctures to insert femoral 3-in-1 nerve blocks

	Loss of resistance	Nerve stimulator	Ultrasound
Number of patients:			
with data	36	70	72
with missing data	1	1	0
Median number of skin punctures	1	1	1
Interquartile range (mean ± SD)	1-1 (1.02 ± 0.167)	1-2 (1.54 ± 1.151)	1-1 (1.04 ± 0.201)
Mann Whitney test against ultrasound guided skin punctures	0.7273	0.0002	
Median number of needle advancements	1	1	1
Interquartile range (mean ± SD)	1-1 (1.14 ± 0.35)	1-3 (2.51 ± 2.65)	1-1 (1.30 ± 0.68)
Mann Whitney test against ultrasound guided advancements	0.2657	0.0001	

6.5.5 Adverse event log

Table 6-5 shows a sequential list of all the adverse events in the study and the associated randomisation number of the patient. No causal relationship was observed between any of the adverse events and this clinical study.

Table 6-5: Adverse event log

Patient randomisation number	Description of adverse event
26	Postoperative pulmonary thromboembolism
28	Respiratory infection
34	Postoperative pulmonary thromboembolism
52	Bilateral postoperative pulmonary thromboembolism on CTPA scan, treated with heparin and then warfarin
56	Atheromatous plaque discovered incidentally, in the right common femoral artery
57	Morphine PCA discontinued on day 0, 15:00 due to patient inability to use equipment. AMT score 10/10 (as assessed by chief investigator), but ward staff and family believed patient to be confused.
89	Developed renal failure postoperatively. The maximum. creatinine was 540 µmol/L and urea 15.4 mmol/L on day 3 postoperatively; electrolytes improved to normal on day 10 postoperatively. Renal dialysis was not required
117	Haematemesis postoperatively. transferred to Western Infirmary
127	Episode of congestive cardiac failure postoperatively, treated with single dose of frusemide of 20 mg.
154	Blisters on heel on same side as hip hemiarthroplasty
157	Pus in joint-primary hemiarthroplasty not done, 1st stage revision completed

6.5.6 Protocol amendment affecting motor assessments

For patient allocations 1 to 15 the following grading system was used:

- **Grade 3:** Patient was able to raise heel from the bed against force applied by assessors arm with assessors elbow flexed at 90 degrees
- **Grade 2:** Patient **not** able to raise heel from the bed against force applied by assessors arm with assessors elbow flexed at 90 degrees but are able to raise heel against gravity alone.
- **Grade 1:** Patient able to extend the knee with gravity eliminated (lying on their side)
- **Grade 0:** No movement of joints on voluntary contraction of quadriceps muscle

It was felt that this grading system lacked sensitivity as had no motor grading between 'movement with gravity eliminated' and 'no movement'. Therefore, a protocol amendment was made to include the following grade.

- **Grade 1** Palpable contraction of joint but no but movement at hip joint (lying on their side)

Therefore, the motor assessment utilised for patient allocations 16-180 was:

- **Grade 4:** Patient was able to raise heel from the bed against force applied by assessors arm with assessors elbow flexed at 90 degrees
- **Grade 3:** Patient **not** able to raise heel from the bed against force applied by assessors arm with assessors elbow flexed at 90 degrees but are able to raise heel against gravity alone
- **Grade 2:** Patient able to extend the knee with gravity eliminated (lying on their side)
- **Grade 1:** Palpable contraction of quadriceps muscle but no but movement at hip joint (lying on their side)
- **Grade 0:** No movement of joints on voluntary contraction of quadriceps muscle

6.5.6.1 Action taken to utilise data from patient allocations 1 to 15

To take account of this in the final analysis for the first 15 patients; 1 was added to all the motor scores of 1 or more to allow the motor data to be used in the final analysis.

6.5.7 Data anomalies and missing data

The subjective nature of the sensory and motor assessment, assessor and patient error combined to produce a variety of anomalous responses. The nature of these responses and the actions taken to reduce bias on the final result analysis are summarised below in 'anomalous sensory scores', 'anomalous motor scores' and Table 6-6: Summary of missing data.

6.5.7.1 Anomalous sensory scores

The sensory score for the contra lateral side was defined as 100 and as a result the baseline sensory score (for the ipsilateral lower limb) was higher or lower than 100 in 8 patients. The sensory scores for these 8 patients were adjusted so that in effect the starting ipsilateral limb sensory score was 100. This was achieved by dividing the patient's 10, 20 and 30 minute sensory scores by the ipsilateral pre-block score and multiplying by 100 (to rebase the score to 100). Effective regional analgesia was then defined as a score ≤90/100 of initial ipsilateral sensory response to blunted 25G needle in area of skin supplied by the femoral nerve (anterior aspect of the upper thigh).

6.5.7.2 Anomalous motor scores

A total of 35 patients were recruited to the study with a pre block motor score of 3/4 or less which would have fulfilled the criteria for effective regional analgesia with no change in femoral nerve motor power.

The primary end point was redefined as a sensory change of ≤90/100 in the anterior upper thigh or a motor score of 3/4 or less if the starting score was 4/4. Thus effective regional analgesia was defined only on the sensory response in these 35 patients.

6.5.7.3 Missing data

Table 6-6: Summary of missing data

Patient allocation number	Problem	Action
5	Sensory records recorded on a scale of 0-5	Score were rebased to scale of 0-100
91,123	Missing number of skin punctures, needle advancements and time for femoral 3-in-1 nerve block	Primary analysis performed without this patients motor data
102	No motor scores recorded for 20 and 30 minutes	Patient excluded from the motor analysis
150,128,148,156,163,173, 153,169,175,176,179	Unable to perform adductor power measurements due to pain, muscle wasting or poor patient cooperation	The results of these patients were excluded from the final analysis of obturator nerve function

6.5.8 Results Part 1-Primary endpoint:

6.5.8.1 Effective and ineffective regional analgesia using sensory scores and motor scores for the femoral nerve at 30 minutes

The primary end point used combined femoral nerve motor and sensory end points to assess the effectiveness of three techniques to site a femoral 3-in-1 nerve block. However, although nerve stimulator is routinely used for femoral 3-in-1 nerve blocks for elective arthroplasty it is unlikely to be used for patients with a fractured neck of femur due to the electrical stimulation of the femoral nerve and resultant movement of an unfixed fracture. The important clinical and research question was whether loss of resistance was an effective alternative to ultrasound. Loss of resistance represents a significantly simpler technique to guide a femoral 3-in-1 nerve block than ultrasound. A total of 17 practitioners were used, all of whom were considered competent to site a femoral 3-in-1 nerve block (Please see Appendix 10) as is unlikely that an expert practitioner would be available.

The first research question was whether loss of resistance was as effective at providing a femoral 3-in-1 femoral nerve block as techniques using nerve stimulator and ultrasound. The second research question was whether the nerve stimulator or ultrasound was most effective at providing a femoral 3-in-1 femoral nerve block. The first question is arguably the most important as the use of the nerve stimulator in patients with a proximal femoral fracture would result in significant discomfort and potential displacement of an unfixed fracture. Two primary end points were used to answer these two research questions and using the Bonferroni correction (Abdi 2007) the p-value was set at $p<0.025$) for each primary comparisons.

6.5.8.2 Summary of primary end points

Question 1: Is loss of resistance as effective as nerve stimulator and ultrasound?

and

Question 2: Is ultrasound as effective as nerve stimulator?

6.5.9 Question 1:

Is loss of resistance as effective as nerve stimulator and ultrasound?

A total of 35 patients recruited to this study had a starting motor score of 3/4 or less and as a result of the original chosen definitions of effective and ineffective regional analgesia these patients were all defined as effective even if their motor and sensory scores did not change from their starting values. The chosen sensory end point was correlated with analgesia but there is no evidence of an association between motor scores and analgesia.

Table 6-7 shows the primary end point results if the 35 patients (with pre-block motor scores of ≤3/4) were included in the primary analysis (for research question 1) and their outcome was based only on their sensory data.

Table 6-7: The primary end point as originally defined for sensory and motor scores for 143 patients. However in the 35 patients with a starting motor score of 3 or less the primary end point was only defined by their sensory scores

	Ultrasound and nerve stimulator	Loss of resistance
Number of patients (Ineffective)	28	15
Number of patients (Effective)	114	22
Total	**142**	**37**
Percentage effective blocks	80.3%	59.5%
p-value (using Fisher exact, p ≤0.025)	p=0.0159	

(NB patient 102 allocated to the ultrasound group was not included in the combined motor and sensory analysis as no motor end point data was recorded for this patient)

6.5.10 Question 2:

Is Ultrasound as effective as nerve stimulator?

Table 6-8 shows the primary end point results if the 35 patients were included in the primary analysis (for research question 2) and their outcome was based only on their sensory data.

Table 6-8: Primary end point using motor and sensory scores (with patients with a starting motor score of ≤3/4 the primary end point was defined only by their sensory scores)

	Ultrasound	Nerve stimulator
Number of patients (Ineffective)	16	12
Number of patients (Effective)	55	59
Total	**71**	**71**
Percentage effective blocks	77.5%	83.1%
p-value (using Fisher exact p ≤0.025)	p=0.527	

(NB patient 102 allocated to the ultrasound group was not included in the combined motor and sensory analysis as no motor end point data was recorded for this patient)

6.5.10.1 Alternative definition for the motor endpoint for an effective femoral 3-in-1 nerve block

It would have been possible to use a one point drop in the motor score as the motor endpoint (see Table 6-9); however, the motor scale was not linear (see section 6.5.12 Results Part 3, Analysis of efficacy of femoral 3-in-1 block by femoral motor data). There is no evidence that a one point drop in the motor score from 3/4 to 2/4 would be equivalent to the original primary end point (a decrease from 4/4 to 3/4). Table 6-9 shows the results with an effective motor end point defined as a one point drop in the femoral motor score.

Table 6-9: Primary end point using motor and sensory scores (redefined motor end point as one point drop in motor score or greater defined as effective regional analgesia)

	Ultrasound and nerve stimulator	Loss of resistance
Number of patients (ineffective)	19	9
Number of patients (effective)	123	28
Total	**142**	**37**
Percentage effective blocks	86.6%	75.7%
p-value (using Fisher exact, $p \leq 0.025$)	p=0.127	

(NB patient 102 allocated to the ultrasound group was not included in the combined motor and sensory analysis as no motor end point data was recorded for this patient)

6.5.11 Results Part 2:

Primary end point efficacy of femoral 3-in-1 nerve block defined by sensory scores

The results of Chapter 4 suggested that a pin prick sensory score in the anterior upper thigh of ≤90/100 was associated with analgesia with a sensitivity and specificity of 93.3% and 92.6%, respectively. Table 6-10 and 6-11 show the primary end point analysis to answer research questions 1 and 2 using only sensory data.

6.5.11.1 Research question 1:

Is loss of resistance as effective as nerve stimulator and ultrasound?

Table 6-10: Primary end point with effective and Ineffective regional analgesia defined only using sensory data

	Ultrasound and nerve stimulator	Loss of resistance
Number of patients (Ineffective)	42	18
Number of patients (Effective)	101	19
Total	**143**	**37**
Percentage of effective blocks	70.6%	51.4%
p-value (using Fisher exact, Sign p≤0.025)	p=0.0321	

6.5.11.2 Research question 2:

Is ultrasound as effective as nerve stimulator?

Table 6-11: Primary end point with effective and Ineffective regional analgesia defined only using sensory data

	Ultrasound	Nerve stimulator
Number of patients (Ineffective)	25	17
Number of patients (Effective)	47	54
Total	**72**	**71**
Percentage of effective blocks	65.3%	76.1%
p-value(using Fisher exact, p ≤0.025)	p=0.199	

If the efficacy of the femoral 3-in-1 nerve block is defined by sensory data a larger difference was observed (10.8% in comparison to 5.6% in Table 6-10) between ultrasound and nerve stimulator treatment groups in comparison to the use of the combined motor and sensory end points used in Results part 1. This suggests that that the inclusion of the femoral motor (knee extensor) data to define the efficacy of a femoral 3-in-1 nerve block may have reduced the ability of the study to discriminate between the treatment groups.

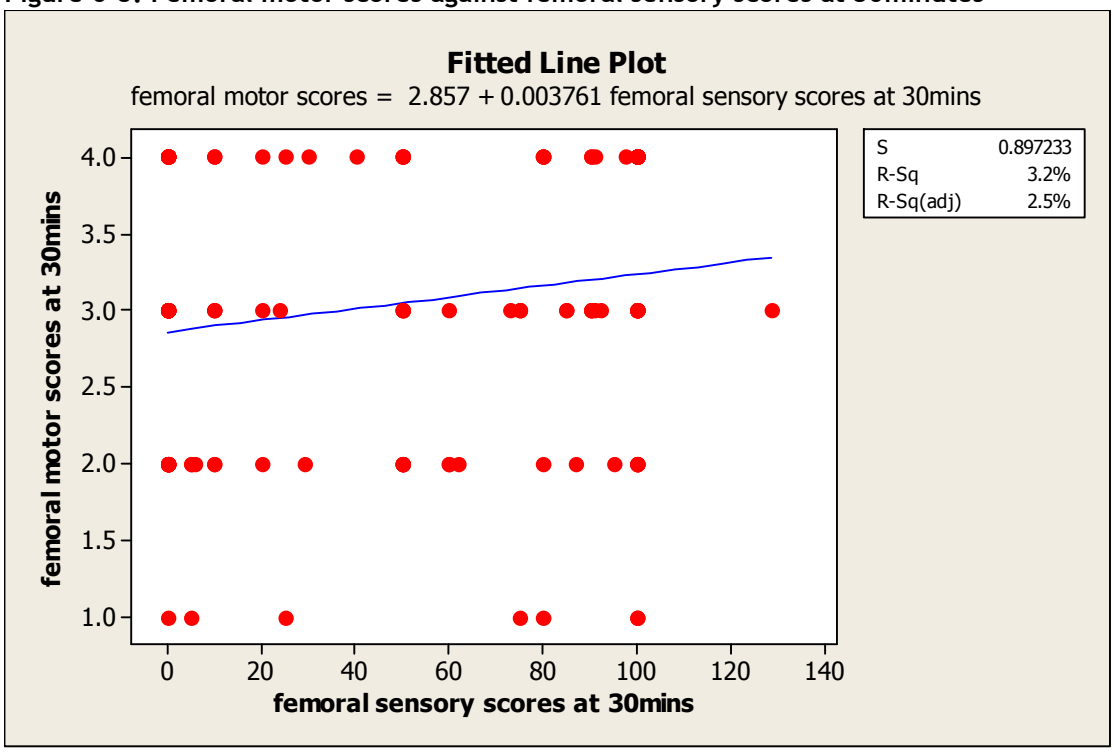
6.5.12 Results Part 3:

Analysis of femoral 3-in-1 nerve block by femoral motor response

The motor power of two nerves was tested during the study; the femoral and the obturator nerve. The femoral motor response (extension of a flexed knee against resistance with the hip flexed to 20 degrees) formed one part of the assessment for the primary outcome. In contrast to the sensory data which was correlated with an analgesic response, there is no evidence in the literature of a correlation between femoral nerve motor scores and analgesia.

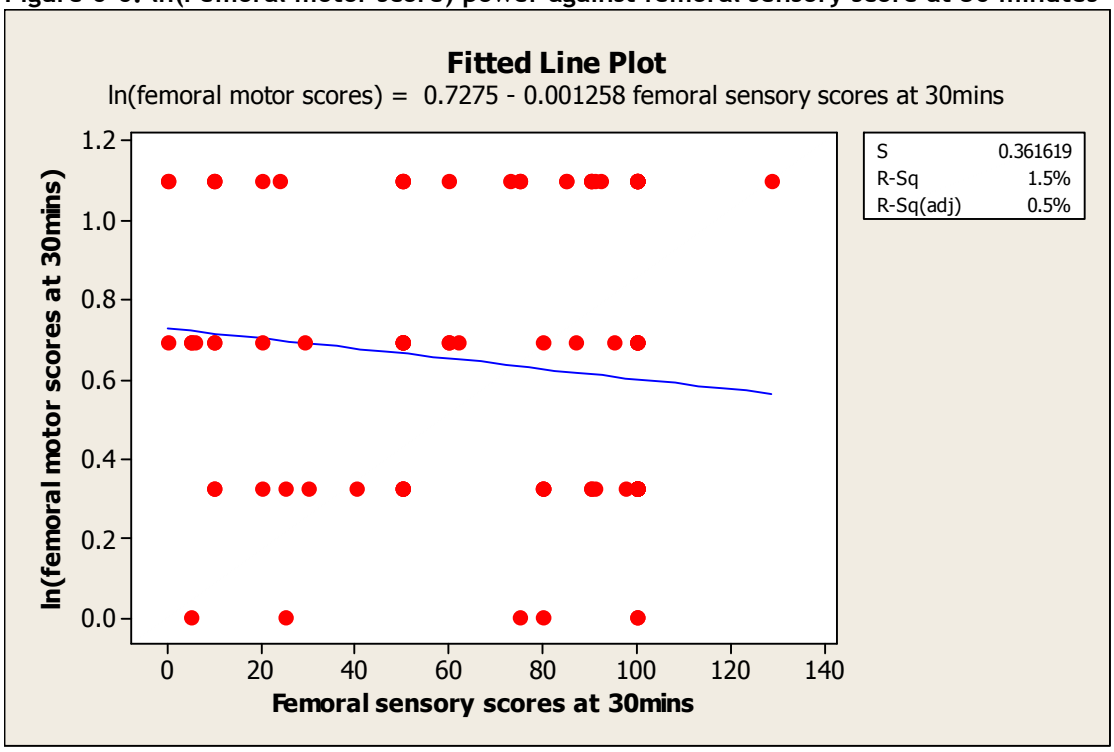
The correlation between the femoral motor score at 30 minutes and the sensory score (to a blunt 25G needle on the anterior upper thigh) was investigated to find the best fit model. Thirty five patients with pre-block motor scores of three or less were excluded and one patient had no motor scores recorded (patient 102) was also excluded. The remaining 143 patients were analysed using the spearman rank correlation coefficient to determine the best fit model. A linear relationship between the motor scores and the sensory scores gave an r squared value of 3.2% or r squared adjusted of 2.5% which implied that the relationship was very weak (see Figure 6-5). This implies that 2.5% of the all the changes in value of the motor scores can be explained by the sensory scores by using a simple linear relationship.

Figure 6-5: Femoral motor scores against femoral sensory scores at 30minutes



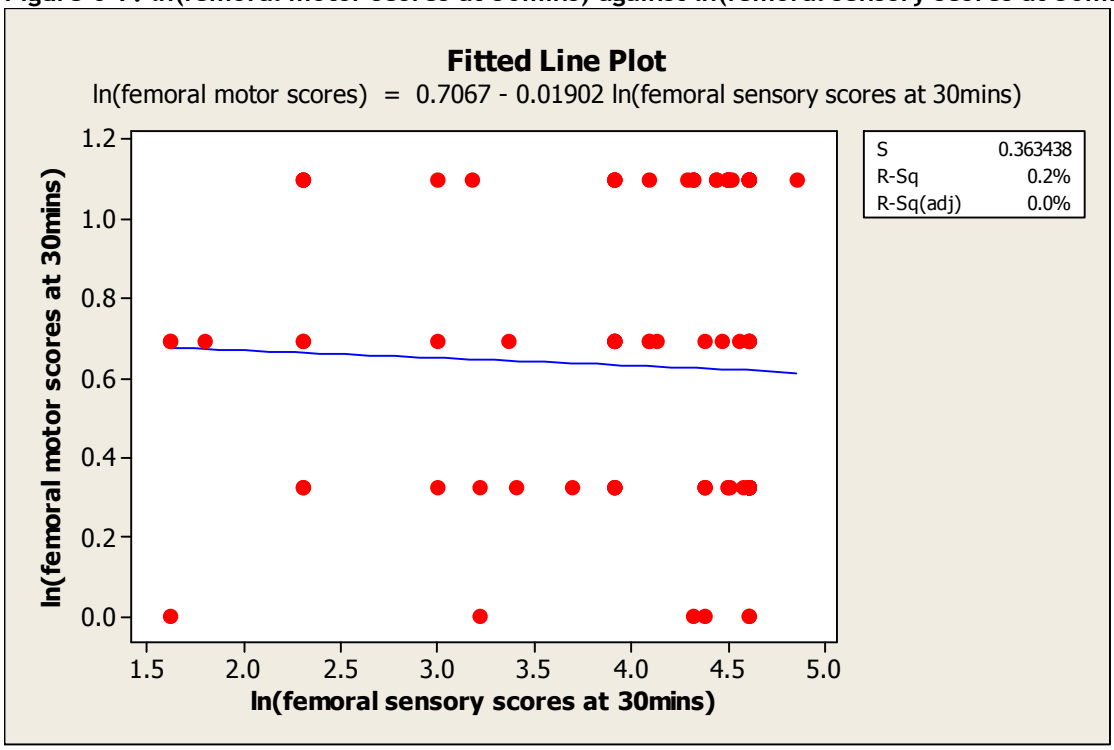
If the natural log of the femoral motor scores is calculated (omitting the two motor scores of 0 (as the natural log of 0 can not be calculated then the Pearson correlation coefficient was r=0.151 and the r-squared value was 1.5% and r squared adjusted was 0.5%.

Figure 6-6: ln(Femoral motor score) power against femoral sensory score at 30 minutes



Patients with a sensory score of 0 were excluded from the analysis. If the natural log is taken of the remaining sensory scores and the motor scores (106 patients were analysed) then the r value was r=-0.0430 and the r squared value was 0.2% and an r squared adjusted of 0% (see Figure 6-7).

Figure 6-7: ln(femoral motor scores at 30mins) against ln(femoral sensory scores at 30mins)



The femoral motor scores at thirty minutes do not correlate to the femoral sensory scores to a blunt 25G needle at 30 minutes. Sensory scores to blunted 25G needle are correlated to analgesia (please see Chapter 4). It is therefore likely that if the motor scores are correlated to analgesia the relationship is independent of the relationship between femoral sensory scores and analgesia. The inclusion of the motor scores in the primary outcome may have decreased the sensitivity and specificity of the primary analysis.

6.5.12.1 The obturator motor response

The obturator nerve has a limited cutaneous sensory distribution to the upper medial aspect of the thigh in a minority of patients (Bouaziz et al. 2002b); as a result, it is accepted that the only reliable way of determining obturator nerve block is by testing for a weakness in adductor power (Lang et al. 1993). The results of testing for adductor motor power reduction are summarised in table 6-12.

Table 6-12: Obturator nerve involvement assessed using adductor strength measured by thigh manometer cuff using the method of Lang et al (Lang 1998).

	Loss of resistance	Nerve stimulator	Ultrasound
Number of patients effective	2	10	7
Number of patients ineffective	34	56	60
Excluded (patient unable to cooperate)	1	5	5
Total	**37**	**71**	**72**
Percentage obturator block	5.9%	17.9%	11.7%

In this study, <20% of patients had motor evidence of an obturator nerve block using the definition first described by Lang et al (Lang et al. 1993). In this study, the nerve stimulator technique had the highest incidence of obturator nerve block.

6.5.13 Results Part 4

Trends in sensory scores over time

We analysed the trends in sensory scores over time for the different methods of guiding a femoral 3-in-1 nerve block. The null hypothesis was that if all methods of guiding local anaesthetic administration acted on the nerves in the same way then the sensory change onset and profile would not be significantly different for each of the three techniques. We analysed only effective sensory blocks as arguably ineffective blocks were not sited correctly. Figure 6-8 and 6-9 show the mean and median sensory scores, respectively, plotted against time and lateral, medial or anterior position on anterior upper thigh for all effective femoral 3-in-1 nerve blocks.

Figure 6-8: Mean sensory scores for all effective femoral 3-in-1 nerve blocks against time

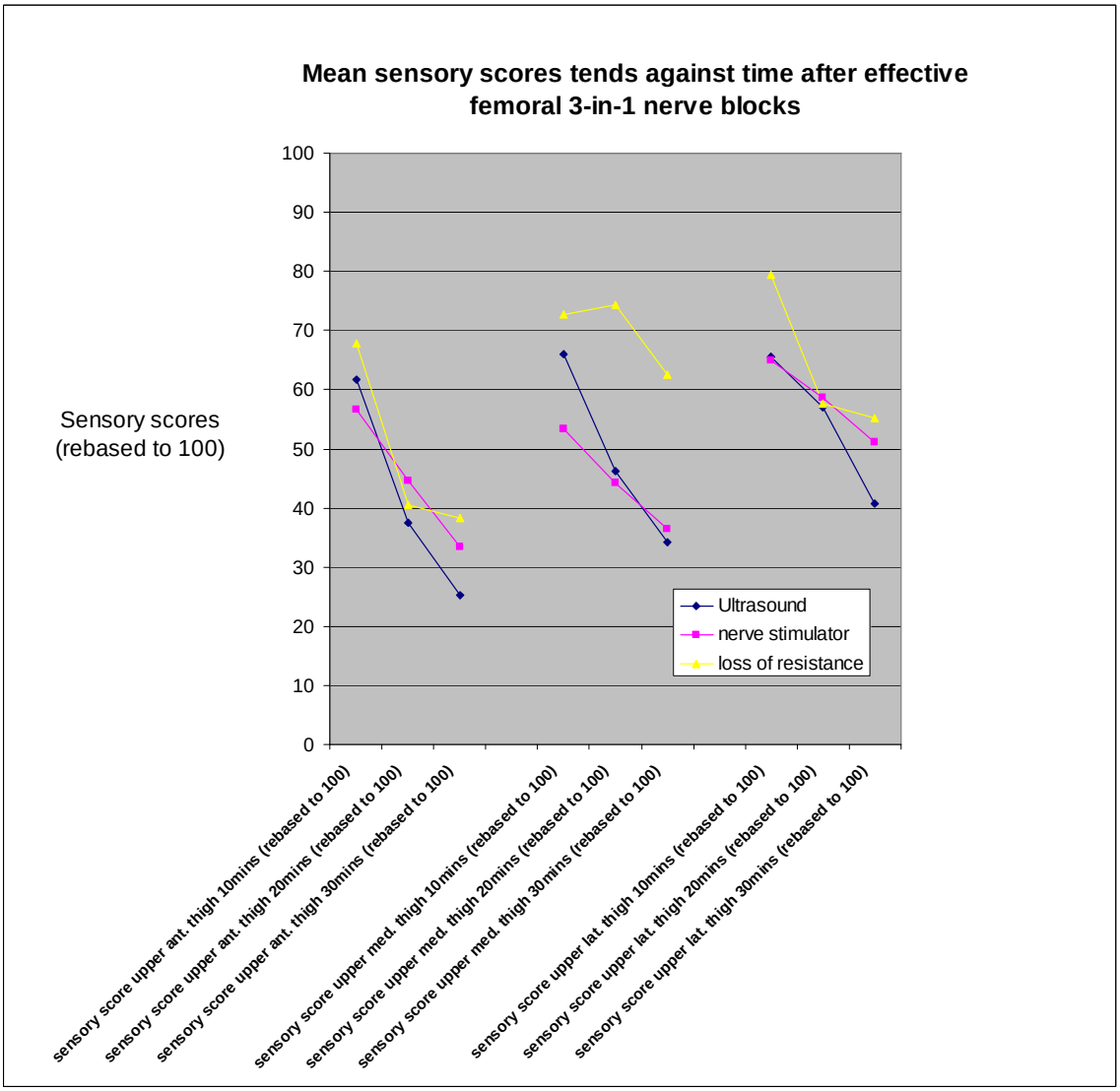
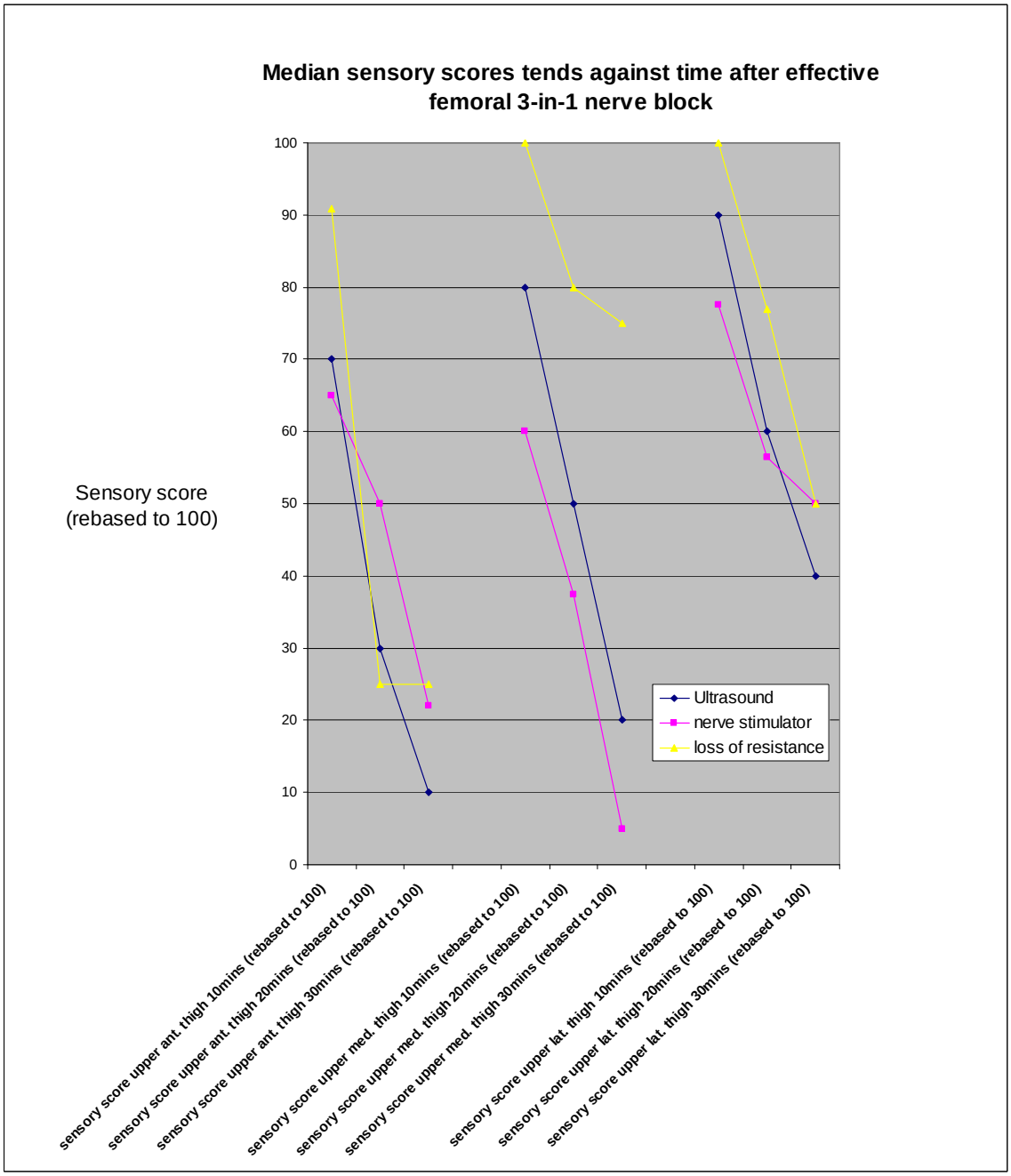


Figure 6-9: Median sensory scores for all effective femoral 3-in-1 nerve blocks against time



6.5.14 Sensory score against technique used for femoral 3-in-1 nerve block

The distribution of sensory scores was very wide indicating a large variation in the sensory scores reported by unpremedicated elective primary hip arthroplasty patients (see Table 6-13). A statistically significant difference was noted in the sensory scores at 10, 20 and 30 minutes in the medial section of the upper thigh for the loss of resistance technique in comparison to the nerve stimulator technique. A statistically significant difference was also recorded in the sensory scores at 20 and 30 minutes in the medial section of the upper thigh for the loss of resistance technique in comparison to use of ultrasound (see Table 6-14). There was no statistically significant difference in sensory scores between ultrasound and nerve stimulator techniques. This implies that there was no difference between the techniques in terms of their effect on sensory scores and, by association, no difference in analgesic efficacy.

Table 6-13: Summary of the results for sensory scores for all effective femoral 3-in-1 nerve blocks (/100)

	Loss of resistance			Nerve stimulation			Ultrasound		
Sensory score	**Medial**	**Anterior**	**Lateral**	**Medial**	**Anterior**	**Lateral**	**Medial**	**Anterior**	**Lateral**
10 minutes									
Median (mean ± SD)	100 (73±44)	91 (68±38)	100 (79±36)	60 (53±43	65 (57±41)	78 (65±45)	80 (66±39)	70 (62±38)	90 66±39
20 minutes									
Median (mean ± SD)	80 (74±41)	25 (40±37)	77 (58±38)	38 (44±42)	50 (45±39)	56.5 (59±45)	50 (46±40)	30 (38±36)	60 57±39
30 minutes									
Median (mean ± SD)	75 (63±47)	25 (38±35)	50 (55±40)	5 (36±42)	22 (34±34)	50 (52±44)	20 (34±38)	10 (25±30)	40 (41±36)

Table 6-14: Summary of statistical analysis of methods used for a femoral 3-in-1 nerve block and sensory scores (comparisons with a p<0.05 are shown in bold)

Statistical test used	Comparison	p-value
Mann Whitney between sensory scores at 30 minutes in medial area of the upper thigh	Loss of resistance and nerve stimulator	**0.0097**
	Loss of resistance and ultrasound	**0.0161**
Mann Whitney between sensory scores at 20 minutes in medial area of the upper thigh	Loss of resistance and nerve stimulator	**0.0100**
	Loss of resistance and ultrasound	**0.0152**
Mann Whitney between sensory scores at 10 minutes in medial area of the upper thigh	Loss of resistance and nerve stimulator	**0.0480**
	Loss of resistance and ultrasound	0.3278

6.5.15 Results Part 5:

Secondary end point analysis: pain NRS scores, morphine consumption, acute metal test scores and patient satisfaction scores at 6 and 24 hours after a femoral 3-in-1 nerve block.

This part of the results section will examine the secondary end points of pain numerical response scale (NRS) scores, AMT scores, morphine consumption and patient's satisfaction scores at six and 24 hours after femoral 3-in-1 nerve block. The definition of effective and ineffective femoral 3-in-1 nerve block relied on a surrogate end point which assessed femoral nerve cutaneous sensation and motor power. The relationship between sensory and motor score and analgesia is complex and it has not been fully described by the previous studies by Dolan, Marhofer and Urbanek (Dolan et al. 2008;Marhofer et al. 1997;Marhofer et al. 1998;Urbanek et al. 2003). As a result of this the definition of an effective femoral 3-in-1 nerve block was altered during the study and after its completion. If the starting motor score was 3/4 or less then only the sensory score to a 25G blunted needle was used to define an effective femoral 3-in-1 nerve block (results part 1) this definition was used to define an effective regional analgesia in this section of the results.

The secondary end points of pain numerical response scale (NRS) scores, AMT scores, morphine consumption and patient's satisfaction scores at six and 24 hours after femoral 3-in-1 nerve block where analysed against the technique used to insert a femoral 3-in-1 nerve block and shown in Tables 6-17 and 6-18.

In this section efficacy was defined using sensory score (<90/100) and/or femoral motor score using four different definitions (please see Table 6-15 for the definitions).

Table 6-15: The femoral motor score definition of a effective femoral 3-in-1 nerve block was defined in the following four ways

Number	Motor definition of an effective femoral 3-in-1 nerve block
1	The efficacy of the femoral 3-in-1 block in patients with pre-testing motor scores of ≤3/4 was defined only by their sensory data
2	In patients with pre block motor scores of ≤3/4 an effective motor block was defined by a reduction in femoral motor score of 1 or more and/or a sensory response
3	Patients with pre block motor scores of ≤3/4 were defined as ineffective
4	Patients with pre-block motor scores of ≤3/4 were excluded from all analysis

In this chapter the secondary end points in Tables 6-17 and 6-18 were analysed using the combined sensory and motor end points as defined in method 1 in Table 6-15 and as used in results part 1 for the primary end point analysis. The data handling for patients with serious protocol violations has been detailed in Table 6-16. The secondary end points results using the femoral motor definition of efficacy described in method 2, 3 and 4 (see Table 6-15) are detailed in Tables 12-1 to 12-6 in Appendix 12.

6.5.15.1 Analysis of secondary end points against efficacy with data from those patients with serious protocol violations treated

Table 6-16 contains a list of the patients with violations of the protocol and a summary of the violation and the action taken with respect to the secondary end point analysis.

Table 6-16: Patients with serious protocol violations and the action taken

Patients	Protocol violation	Action
119,120,179 and 180	Wound infiltration performed by surgeon	All six and 24 hour AMT, patient satisfaction, morphine usage and pain scores and mobilisation times removed from analysis
82,89 and 93	Patient had General Anaesthesia due to failed spinal	All six and 24 hour AMT, patient satisfaction, morphine usage and pain scores and mobilisation times removed from analysis
155	Venflon tissued six and 24 hour scores invalid	All six and 24 hour AMT, patient satisfaction, morphine usage and pain scores and mobilisation times removed from analysis
130	Diamorphine in spinal anaesthesia	All six and 24 hour AMT, patient satisfaction, morphine usage and pain scores and mobilisation times removed from analysis
160	Morphine not used for postoperative pain relief	All six and 24 hour AMT, patient satisfaction, morphine usage, pain scores and mobilisation times removed from analysis
157	Pus in joint, 1st stage revision done 105	All results included in analysis
28	Ward staff pressed morphine PCA which they though was not working (once)	All results included in analysis
62	Morphine PCA disconnected at 18.5 hours after block, started on oxycontin and oxynorm but no doses given.	All results included in analysis

6.5.15.2 Analysis of secondary end points against efficacy for a femoral 3-in-1 nerve block (with data from those patients with serious protocol violations treated as described in Table 6-16)

Tables 6-17 and 6-18 shows the results of the analysis of secondary end points with protocol violations treated as described in Table 6-16. The efficacy of the femoral 3-in-1 block in patients with pre-testing motor scores of ≤3/4 was defined only by their sensory data)

Table 6-17: Summary of secondary end points against efficacy at six hours

	Number of patients Ineffective/Effective	Ineffective	Effective	Mann Whitney (p-value)
Pain NRS score (0-100)				
median (interquartile range)	36/133	42.5 (19-60)	40 (20-60)	0.8896
AMT(1-10)				
median (interquartile range)	35/130	10 (10-10)	10 (10-10)	0.6235
Morphine consumption(mg)				
median (interquartile range)	36/133	11 (7-16)	10 (5-16)	0.7322
Patient satisfaction(1-10)				
median (interquartile range)	36/131	10 (8-10)	10 (8-10)	0.8828

Table 6-18: Summary of secondary end points against efficacy at 24 hours

	Number of patients Ineffective/Effective	Ineffective	Effective	Mann Whitney (p-value)
Pain NRS score (0-100)				
Median (interquartile range)	36/131	25 (10-50)	30 (11-50)	0.5133
AMT(1-10)				
median (interquartile range)	35/131	10 (10-10)	10 (10-10)	1.0
Morphine consumption(mg)				
median (interquartile range)	36/131	31 (18-42)	30 (17-46)	1.0
Patient satisfaction(1-10)				
Median (interquartile range)	36/130	9 (8-10)	9 (8-10)	0.9121

6.5.15.3 Summary of secondary endpoints against efficacy

The secondary endpoint results were not significantly affected by the inclusion or exclusion of data from patients with serious protocol violations and by the definition of efficacy of a femoral 3-in-1 nerve block. Please see Appendix 12 tables 12-1 to 12-6 for multiple analyses of the secondary endpoints using different definitions of effective and ineffective analgesia.

6.5.15.4 Secondary end points against technique for femoral 3-in-1 nerve block

Table 6-19: Secondary endpoints for techniques of ultrasound, nerve stimulator and loss of resistance at six hours

Technique used (Number of patients analysed)	Loss of resistance (34)	Nerve stimulator (67-69)	Ultrasound (66-64)
Pain NRS score (0-100)			
median (interquartile range)	47.5 (20-60)	42 (20-70)	30 (20-50)
AMT(1-10)			
median (interquartile range)	10 (10-10)	10 (10-10)	10 (10-10)
Morphine consumption(mg)			
median (interquartile range)	9.5 (6-16)	10 (5-15)	11 (5-18)
Patient satisfaction(1-10)			
median (interquartile range)	9 (8-10)	10 (8-10)	10 (8-10)

Table 6-20: Secondary endpoints for techniques of ultrasound, nerve stimulator and loss of resistance at 24 hours

Technique used (Number of patients analysed)	Loss of resistance (34)	Nerve stimulator (68-69)	Ultrasound (64)
Pain NRS score (0-100)			
median	35	30	28
(interquartile range)	(10-58)	(20-50)	(10-50)
AMT(1-10)			
median	10	10	10
(interquartile range)	(10-10)	(10-10)	(10-10)
Morphine consumption(mg)			
median	32	29	29
(interquartile range)	(18-42)	(17-48)	(17-42)
Patient satisfaction(1-10)			
median	9	9	10
(interquartile range)	(8-10)	(8-10)	(8-10)

6.5.15.5 Summary of secondary endpoints against technique analysis

No statistically significant differences were observed in the secondary end points against the technique used; however, a trend towards higher pain NRS scores and morphine usage was associated in the loss of resistance group of patients at six and 24 hours (please see Tables 6-19 and 6-20 and tables 12-1 to 12-6).

Results Part 6: Day postoperatively first mobilised on hip joint by physiotherapy

This section of the results will examine the effect of a femoral 3-in-1 nerve block had on mobilisation after hip joint arthroplasty. Data on mobilisation times were available for 174 patients, 35 in loss of resistance group, 68 in nerve stimulator group and 71 in ultrasound group. Ten patients were excluded for protocol violations (see Table 6-16). The inclusion or exclusion of those patients with serious protocol violations did not affect the statistical significance of this outcome.

Table 6-21: Method 1 table 6-15 used to define effective and ineffective block

	Number of patients ineffective/ effective	Ineffective Median (interquartile range) hours	Effective Median (interquartile range) hours	Mann Whitney (p-value)
Mobilisation times in hours all patients included	37/137	23.8 (21.7-24.7)	24.3 (21.9-26.4)	0.2739
Mobilisation times in hours (10 patients excluded for protocol violations)	34/131	23.9 (21.6-24.9)	24.3 (21.9-26.4)	0.3479

Table 6-22: All patients included (no protocol violation removed)

	Loss of resistance (35 patients)	Nerve stimulator (68 patients)	Ultrasound (71 patients)
Time from nerve block to first mobilisation in hours			
Median (interquartile range)	24.7 (21.9-27.4)	23.2 (21.5-26.3)	24.2 (22.25-25.6)

No statistically significant differences where observed in mobilisation time as a result of the efficacy of the femoral 3-in-1 nerve block or the technique of insertion. The vast majority of the 180 patients in this study mobilised at around 24 hours from their operation.

6.6 Discussion:

6.6.1.1 Study design

This study was designed to determine which method we should use to guide the needle insertion for a femoral 3-in-1 nerve block in patients with a traumatic fractured neck of femur. Elective total primary hip arthroplasty patients were the chosen as the population for the following reasons:

- Initial power calculations estimated that a large number of patients (180 patients) would be required.

- It was deemed necessary to undertake multi-site recruitment due to the large number of patients required.

- Less that half of the patients admitted with a fractured neck of femur have capacity to cooperate with sensory and motor testing.

- Patients with a fractured neck of femur are admitted as an emergency to hospital which would have made recruitment of large numbers difficult.

The nerve stimulator technique was included because the study population was elective primary hip arthroplasty patients. The use of a nerve stimulator on patients with an unfixed fracture would be considered unjustifiable when less painful techniques are available. It was; however, considered to be unethical not to include a nerve stimulator treatment group as it was the 'gold standard' for patients scheduled for elective hip arthroplasty.

The primary research question to be answered by this study is (research question 1 chapter 1) is '*Which method do we use to site the local anaesthetic in patients with a fractured neck of femur?*' This study therefore had a split primary end point. The two end points used were

1 Loss of resistance treatment group against a combined nerve stimulator and ultrasound treatment groups.

2 Nerve stimulator treatment group against the ultrasound treatment group.

In retrospect it would have been better to have used a single primary end point to answer the first research question. This single end point should have been a comparison of the loss of resistance treatment group against the ultrasound treatment group. The comparison of the nerve stimulator group to ultrasound group or loss of resistance group should have been included as a secondary end point.

6.6.1.2 Sensory and motor testing

The primary end point in this study, which was used to define effective or ineffective femoral 3-in-1 nerve block, was the sensory and motor testing after the insertion of the local anaesthetic. The vast majority of prior work into analgesic effectiveness of nerve blockade has used the requirement for supplementary anaesthesia or analgesia as the primary end point (Abrahams et al. 2009). Prior to the start of this study the only studies to use sensory scoring as the primary end point for a effective blockade were studies of Marhofer et al and Kapral et al (Dolan et al. 2008;Marhofer et al. 1997;Marhofer et al. 1998;Urbanek et al. 2003) and only one study used a combined motor and sensory end point to determined whether the blockade was effective or ineffective (Dolan et al. 2008). The results from Chapter 4 of this thesis provided evidence of a correlation between the sensory changes and an analgesic response with a 96% sensitivity and 92.9% specificity. This evidence was used to alter the primary outcome in a substantial ethics amendment before the final patient was recruited and the data was unblinded and analysed.

The motor component for the efficacy of the femoral 3-in-1 nerve block did not have any independent validation. The motor scores recorded were not recorded on a linear or congruent scale and it is not possible to convert those 35 patients with a starting motor score of 3/4 or less to be analogous to those patients with a starting motor score of 4/4. The motor definition of an effective femoral 3-in-1 nerve block was derived from the motor endpoint used in the study by Dolan et al prior to its publication (Dolan et al. 2008). In order to prevent the results of those 35 patients with motor score of 3/4 or less from biasing the study in those 35 patients efficacy was defined solely on the patient's sensory score at 30 minutes. The decision to analyse the femoral motor scores in this way was made after the final patient was recruited and the data was unblinded. In results part

3 the correlation between the sensory scores and femoral motor scores was very low. This implied that either the femoral motor scores were not associated with analgesia or that the relationship between femoral motor score and analgesia was independent of the relationship between sensory scores and analgesia.

6.6.1.3 Primary end point: Efficacy of the femoral 3-in-1 nerve block

The primary analysis has shown that the loss of resistance technique was statistically significantly less effective than nerve stimulator or ultrasound guided techniques for a femoral 3-in-1 nerve block. The study also showed that ultrasound was less effective than nerve stimulator at guiding a femoral 3-in-1 nerve block but this result was not statistically significant. These blocks were sited by 17 different anaesthetists (see Appendix 10) so the results reflect the general skill levels of practicing anaesthetists who stated that they were competent to site a femoral 3-in-1 nerve block using all three methods with no assistance. The high efficacy of the nerve stimulator group may perhaps be explained by the assessment method. It has been claimed that the use of a nerve stimulator may be associated with an increased incidence of intra-neuronal injection due to the unreliability of threshold current at determining intra-neuronal placement and the lack of clinical evidence of motor or sensory deficit following intra-neuronal injection (Lupu et al. 2010;Robards et al. 2009). It was hypothesized that intra-neuronal injection of local anaesthetic may be associated with a more rapid onset and profound sensory anaesthesia than and extra-neuronal injections due to shorter diffusion distances. There was no significant difference between the sensory changes in the upper thigh to blunted 25G needle associated with nerve stimulator and ultrasound treatment groups. These methods were equal in terms of sensory testing and there was no evidence that the nerve stimulator produced a rapid onset sensory blockade

In summary, the loss of resistance treatment group had a higher incidence of effective blocks and the ultrasound was less effective than was expected. A number of factors may be responsible but the large number of operators used in this study may have influenced this outcome. Ultrasound guided femoral 3-in-1 nerve block may be more technically demanding than generally appreciated and loss of resistance may have a relatively high efficacy when performed by non-experts. The use of a nerve stimulator and/or ultrasound improved the

effectiveness of the femoral 3-in-1 block by a statistically significant absolute difference of 20.8%. It is likely that in clinical practice the relative efficacy of nerve stimulator, loss of resistance and ultrasound techniques for a femoral 3-in—1 nerve block appears to differ significantly from the reported efficacy of experts.

6.6.1.4 Secondary end points

The medial sensory area in the upper thigh had a significantly less sensory anaesthesia for the loss of resistance group than for ultrasound and nerve stimulator groups at 20 and 30 minutes post insertion of the femoral 3-in-1 nerve block. The most likely explanation for this was the anatomical distance of the needle insertion point from the medial aspect of the femoral nerve in comparison to the other two techniques.

The obturator nerve involvement in the femoral 3-in-1 nerve block has been debated since Winnie et al first proposed the 3-in-1 block (Winnie, Ramamurthy, & Durrani 1973). It was accepted that the obturator nerve is only blocked in a minority of cases following femoral 3-in-1 nerve block using nerve stimulator and loss of resistance methods (Bouaziz et al. 2002;Lang 1998). A recent publication by Dolan et al implied that the use of ultrasound may significantly increase the incidence of obturator motor block to 44% (Dolan et al. 2008). Obturator nerve involvement was less than 20% for all the femoral 3-in-1 nerve block techniques in this study, this correlated very well with the work of Lang et al (Lang et al. 1993) but conflicts with the findings of Dolan et al (Dolan et al. 2008). The reason for this may be that the assessors used by Dolan et al did not keep the patient's knee fully extended during the assessment (Dolan et al. 2008). Failure to do so would have resulted in recruitment of the quadriceps femoris muscles and increased pre-block pressures. Therefore, reduced pressure measurement would be the result of a femoral nerve block not an obturator nerve motor block. Higher average pressures were generated by Dolan et al patients with a mean of 120 mmHg and standard deviation of 46 mmHg. In contrast to the patients in this study generated a mean pressure of 64 mmHg with a standard deviation of 15 mmHg (Dolan et al. 2008). It is therefore possible that the relatively high incidence of obturator block reported by Dolan et al was as a result of the methods used to measure obturator (adductor) motor function.

The secondary end points showed a slight reduction in opiate requirements (1-2 mg) of morphine at six hours and at 24 hours in effective femoral 3-in-1 nerve blocks. This reduction was not statistically or clinically significant and was not a consistent finding depending on the definition of effective and ineffective femoral 3-in-1 nerve block used (see tables 6-17, 6-18 and 12-1 to 12-6). The time to first active weight bearing mobilisation on the replaced hip joint did not vary with the different methods used to insert a femoral 3-in-1 nerve block. No patient had delayed mobilisation due to prolonged motor blockade in this large patient cohort with multiple operators undertaking the femoral 3-in-1 nerve blocks.

6.7 Conclusion

The first research question was whether loss of resistance was as effective at providing analgesia as techniques using nerve stimulator and ultrasound.
The combined efficacy for the ultrasound and nerve stimulator techniques was 80.3% and the efficacy of the loss of resistance technique was 59.5% with a $p=0.016$ using fisher exact test ($p \leq 0.025$). The null hypothesis was therefore rejected and a statistically significant difference accepted between the efficacy of the loss of resistance technique and combined ultrasound and nerve stimulator techniques.

The second research question was whether the nerve stimulator or ultrasound was the most effective at providing analgesia. The efficacy of the ultrasound technique was 77.5%, the nerve stimulator technique was 83.1% with a $p=0.527$ using fisher exact ($p \leq 0.025$). The null hypothesis was therefore accepted for the comparison between the efficacy of the ultrasound and nerve stimulator techniques.

Chapter 7

7 The anatomy of the femoral 3-in 1 block

7.1 Research question

What is the maximal distribution of local anaesthetic injected using the inguinal paravascular lumbar plexus block technique as described by Winnie et al (Winnie, Ramamurthy, & Durrani 1973), which is better known as the 'femoral 3-in-1 nerve block'?

7.2 Aim

To determine the maximal anatomical distribution of 30 ml of black 10% latex injected using ultrasound guidance lateral to the femoral nerve under the fascia iliacus membrane in unembalmed cadavers.

7.3 Study design

A pilot dissection study on two cadavers after ultrasound guided femoral 3-in-1 block with 30 ml of black 10% latex.

7.4 Study Population

Two cadavers were dissected in Glasgow University Anatomy Department after injection with 30ml of black 10% latex dye and fixation by embalming using the right carotid artery and internal jugular route.

7.5 Introduction

Twenty eight years ago Winnie et al described the inguinal paravascular lumbar plexus block technique, which is better known as 'the femoral 3-in-1 nerve block' and hypothesised the existence of a fascial sheath around the femoral nerve (Winnie, Ramamurthy, & Durrani 1973). Winnie hypothesised that this fascial sheath could conduct local anaesthetic from below the inguinal ligament to the lumbar plexus, anaesthetising the femoral, lateral cutaneous, and obturator nerves. Winnie et al claimed that, 'if a volume of 20 ml or more is utilised, anaesthesia of all three nerves is virtually assured'. Although the anatomical existence of a fascial sheath around the femoral nerve has been confirmed it does not appear to consistently act as a conduit for proximal spread of local anaesthetic injected under the fascia iliacus membrane. The majority

of investigators have been unable to consistently anaesthetise the femoral, obturator and lateral cutaneous nerves with a single injection (Capdevila et al. 1998;Lang et al. 1993;Madej, Ellis, & Halsall 1989;Parkinson et al. 1989;Ritter 1995;Spillane 1992;Winnie, Ramamurthy, & Durrani 1973). The course of the obturator nerve is anatomically distant from the site of injection (see Figure 7-1A and B) of the 3-in-1 nerve block (Ritter 1995). It is difficult to envisage how the obturator nerve could be consistently anaesthetised by an injection at this level without proximal spread.

A recently published study by Dolan et al reignited this debate by demonstrating a motor block of the obturator nerve in 44% of cases and a loss of sensation in the medial aspect of the upper thigh in 60% of ultrasound guided femoral 3-in-1 nerve blocks (Dolan et al. 2008). It is possible that retrograde spread to the lumbar plexus and anaesthesia of the obturator nerve resulted in the motor and sensory blockade of the adductors muscles and medial aspect of the upper thigh as described by Dolan et al.

Figure 7-1A and 7-1B: Anatomy of upper thigh

The left image (1A) shows the skin, superficial fascia, fascia lata and fascia iliacus have been removed to show the femoral vein, artery and nerve from medial to lateral.

The right image (1B) shows pectinus muscle reflected to reveal the anterior division of obturator nerve emerging from obturator foramina piercing obturator externus muscle and lying on abductor brevis (NB the posterior division is posterior to adductor brevis).

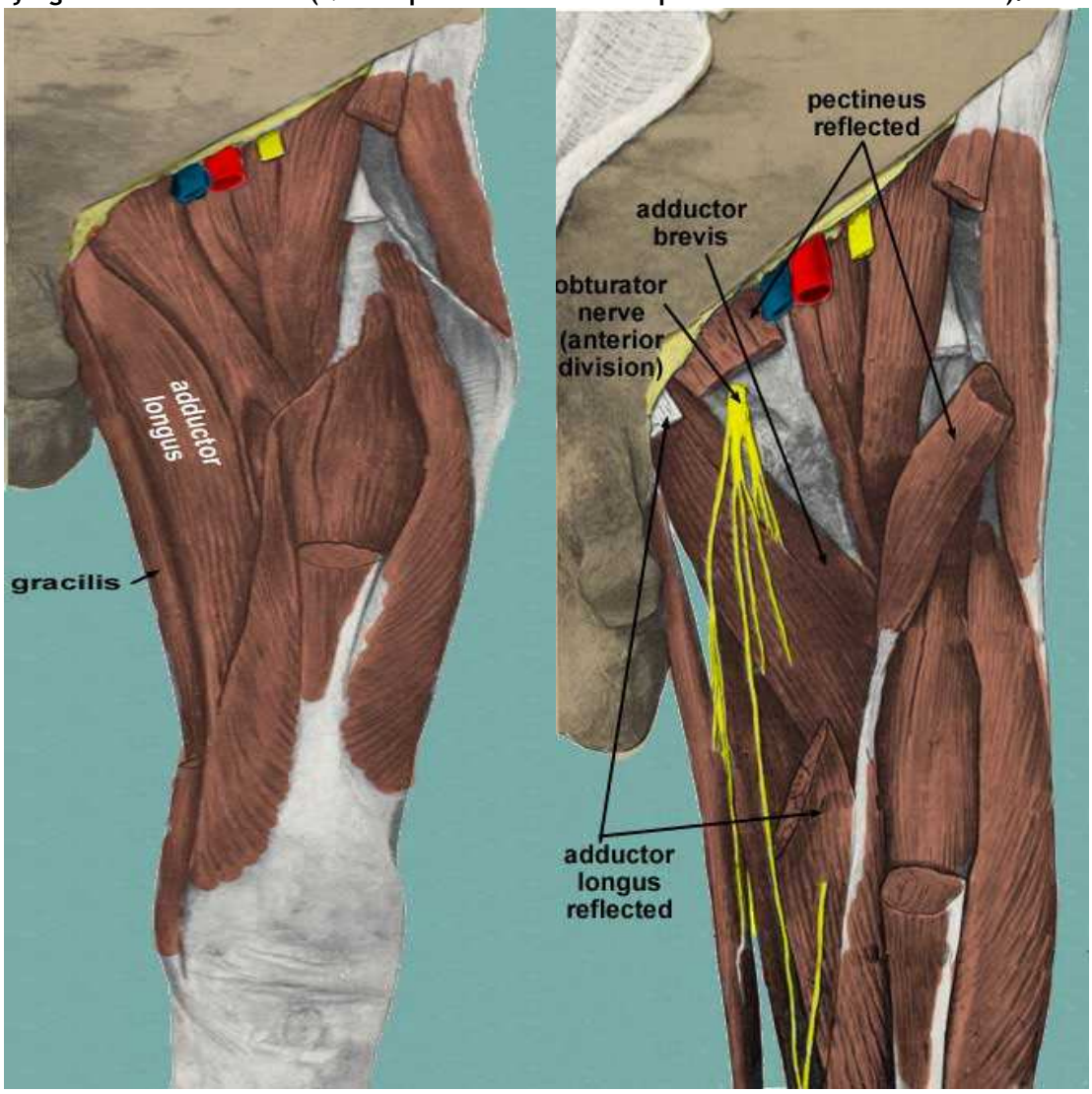


Image from personal collection of Dr Malcolm Watson

7.6 Methodology

7.6.1 Injection and fixation

This work was performed in the Anatomy Department of Glasgow University which is licensed under the Anatomy Act 1984 (1984). Two adult female cadavers who had donated their bodies to medical science where used for this study. The two cadavers studied had no external evidence of surgery, pathology or invasive procedures to the lower abdomen, pelvis, inguinal regions or lower limbs. Immediately before fixation of both cadavers, the tip of an 18G Tuohy needle was sited under ultrasound guidance (using a GE logiq E ultrasound machine with an 8-12 MHz linear probe) under the fascia iliacus membrane lateral to the femoral nerve. Thirty ml of black 10% by volume liquid latex was injected bilaterally. The two cadavers were then embalmed by injection under pressure into the right carotid artery and internal; jugular vein within 1 hour of the ultrasound guided black 10% latex injection. The embalming fluid used was the Cambridge formulation, which contained by volume 62.5 % water, 12.5 % phenol (80%), 7.5% formaldehyde (37%), 17.5% and 0.5% phenoexetol. Three months later both cadavers were dissected to determine the distribution of the black 10% latex.

7.6.2 Dissection

7.6.2.1 Methodology of the dissection

The four dissections were performed using the method described below. A transverse incision was made one centimetre below and parallel to the inguinal ligament and a vertical incision was made down the centre of the thigh. The skin was reflected and the superficial fascia, fat and fascia lata removed. The femoral, lateral cutaneous nerve of the thigh, medial cutaneous nerve of the thigh were all identified and traced proximally and distally to determine if they had been stained with black 10% latex. The nerves stained with black 10% latex were then traced proximally and distally. To determine the proximal extent the abdominal cavity was opened and following reflection of the bowel and peritoneum the branches of the lumbar plexus on the iliacus and in the psoas muscle in the abdomen were examined. The distal spread was determined by dissecting the Hunter's (adductor) canal and the sciatic nerves and its terminal

branches in the popliteal fossa. The medial cutaneous nerve of thigh and the obturator nerve and its terminal branches were examined by reflecting pectineus and adductor brevis muscles.

7.7 Results

7.7.1 Summary table

Table 7-1: Summary of result of dissection

	Femoral nerve	Lateral cutaneous nerve	Sciatic nerve at popliteal fossa	Proximal spread to stain obturator nerve	Distal spread to Sciatic nerve	Distal spread down Hunter's canal
Number of nerves stained/total	4/4	4/4	4/4	0/4	4/4	4/4
Percentage staining	100%	100%	100%	0%	100%	100%

7.8 Description of results

In all four dissections the black 10% latex stained the femoral nerve (Figure 7-2: femoral nerve) and spread distally to the adductor or Hunter's canal (Figure 7-3: subsartorial spread into the Hunter's canal) through the adductor hiatus in the adductor magus muscle into the popliteal fossa. The distal spread resulted in staining the sciatic nerve and its terminal branches at the apex of the popliteal fossa (Figure 7-4: Sciatic nerve at the apex of the popliteal fossa). The lateral cutaneous nerve (Figure 7-5: lateral cutaneous nerve) and the medial cutaneous nerve of thigh (Figure 7-6: medial cutaneous nerve of thigh) were both consistently stained but no dye was found around the obturator nerve (Figure 7-7: Obturator nerve) or its terminal branches.

Figure 7-2: Femoral nerve

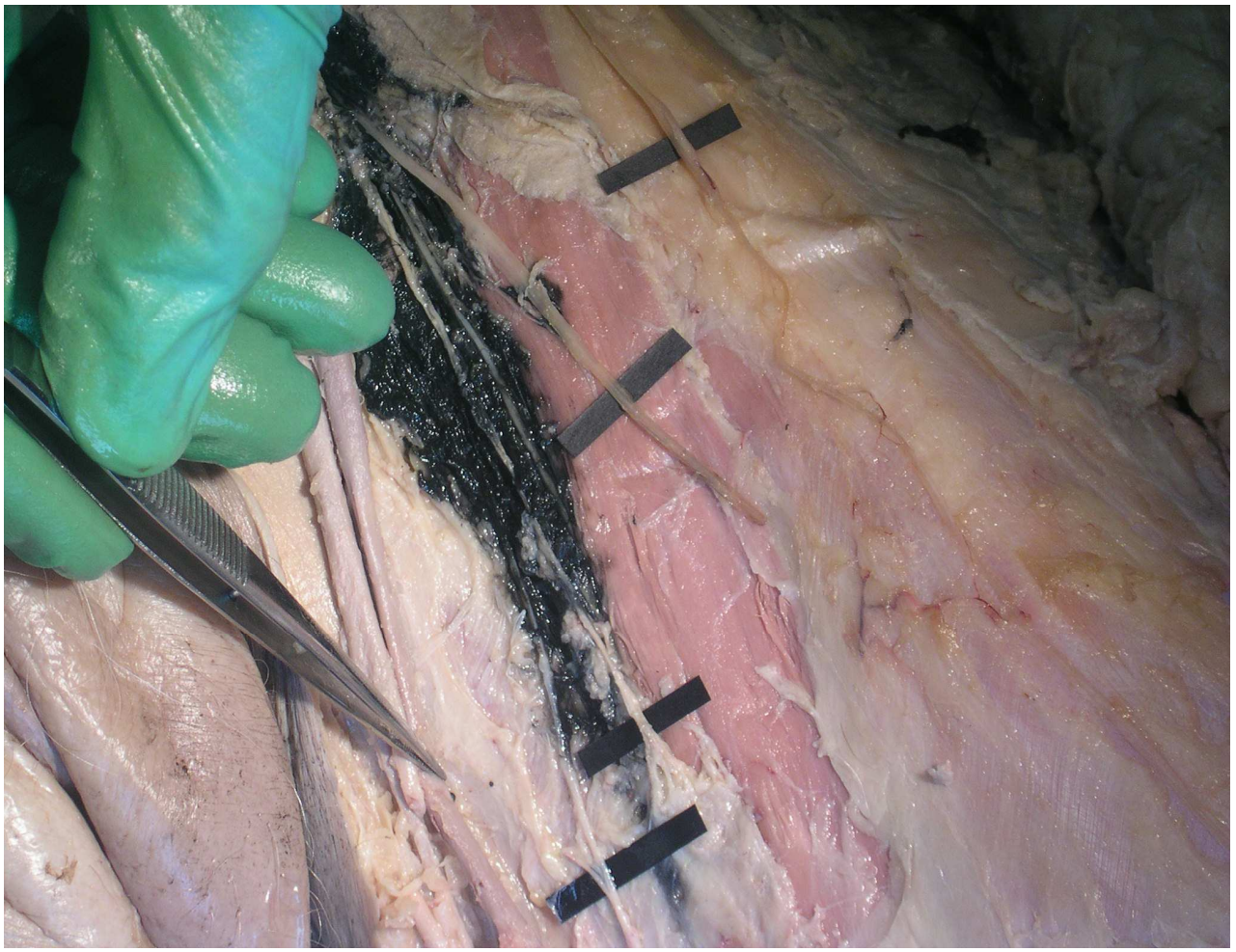


Image from personal collection of Dr Malcolm Watson

Significant staining was observed of femoral nerve and its branches below the inguinal ligament. The staining was limited by the iliopsoas muscle inferiorly and the fascia iliacus superiorly. The femoral vein can be seen pushed medially by the forceps.

Figure 7-3: Sub sartorial spread into the Hunter's canal

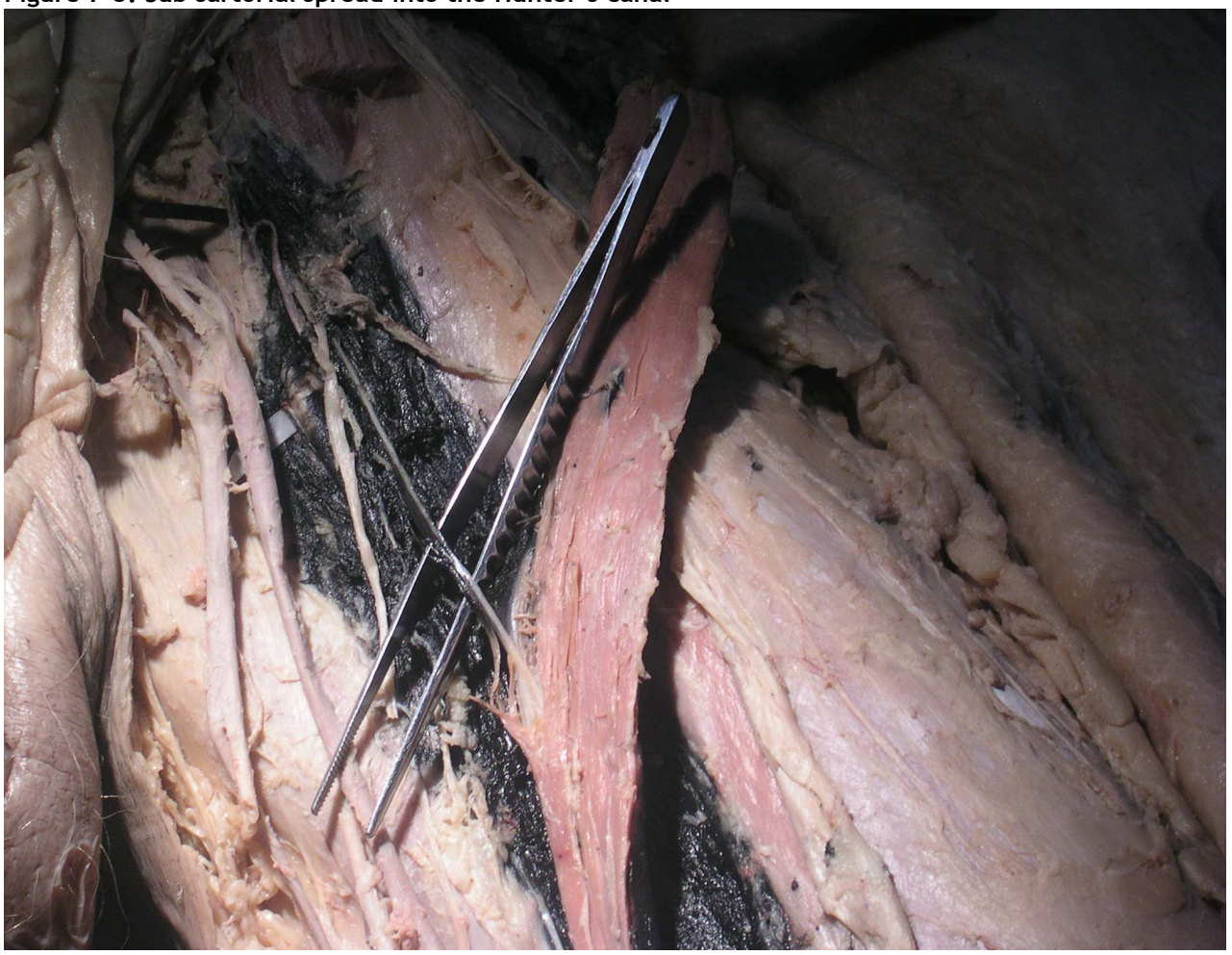


Image from personal collection of Dr Malcolm Watson

Dense staining by black 10% latex can be seen in the adductor (Hunter's) canal with associated staining of the nerves supplying the sartorius muscle. The femoral artery can be seen (with white paper underneath it) and further medially and superficially the tributaries of the femoral vein can be seen. The sartorius muscle has been reflected and the forceps are placed under a motor branch to the sartorius muscle.

Figure 7-4: Sciatic nerve at the apex of the popliteal fossa

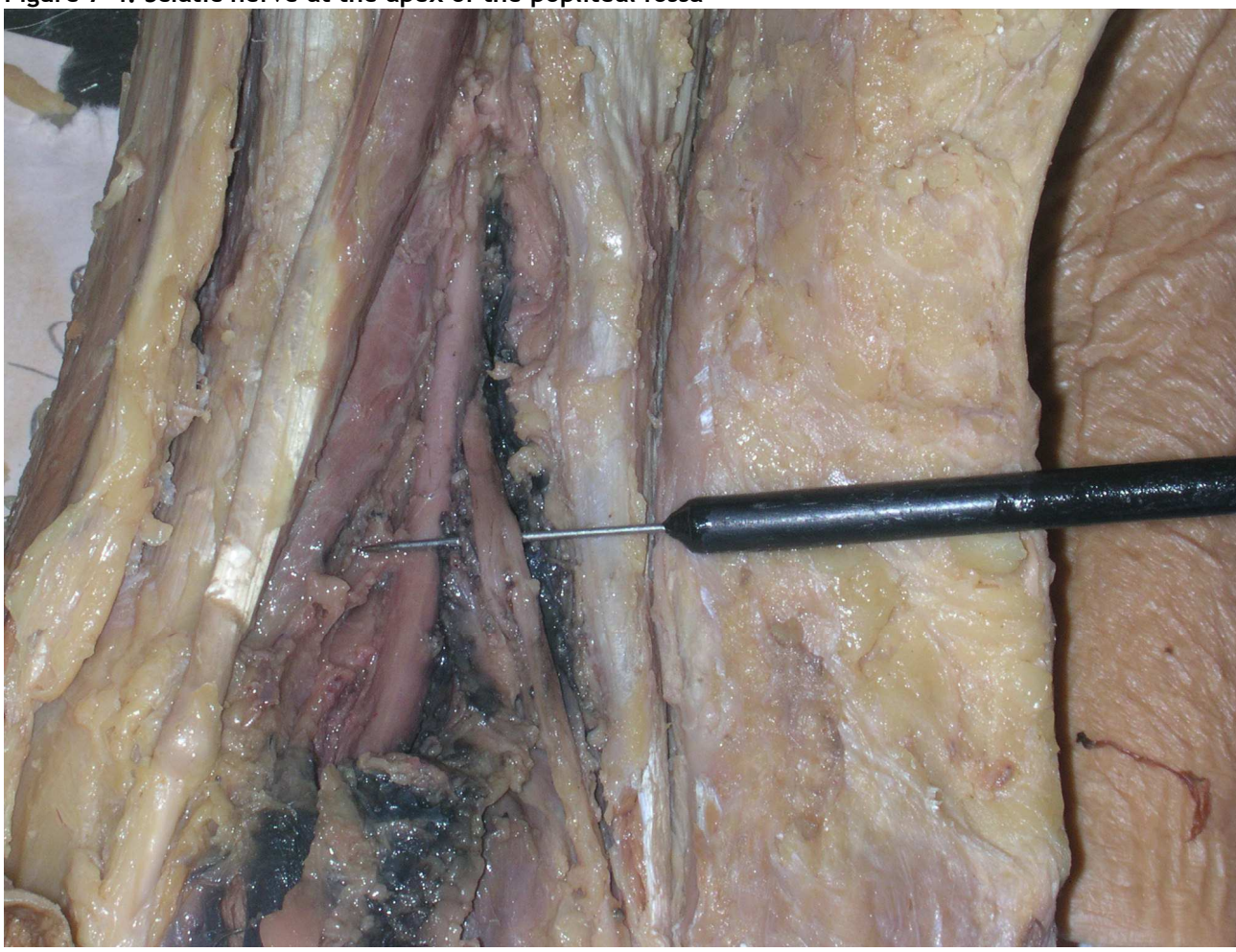


Image from personal collection of Dr Malcolm Watson

After injection at the level of the inguinal ligament the black 10% latex has spread distally down the adductor (Hunter's) canal and through the adductor hiatus into the popliteal fossa and around the terminal divisions of the sciatic nerve (the common peroneal and tibial nerves). The probe is under the common peroneal nerve and over the tibial nerve with the undivided sciatic nerve superiorly.

Figure 7-5: Lateral cutaneous nerve

Image from personal collection of Dr Malcolm Watson

The lateral cutaneous nerve is seen under the forceps. The probe has pierced and holding back the fascia ilaicus membrane.

Figure 7-6: Medial cutaneous nerve of thigh

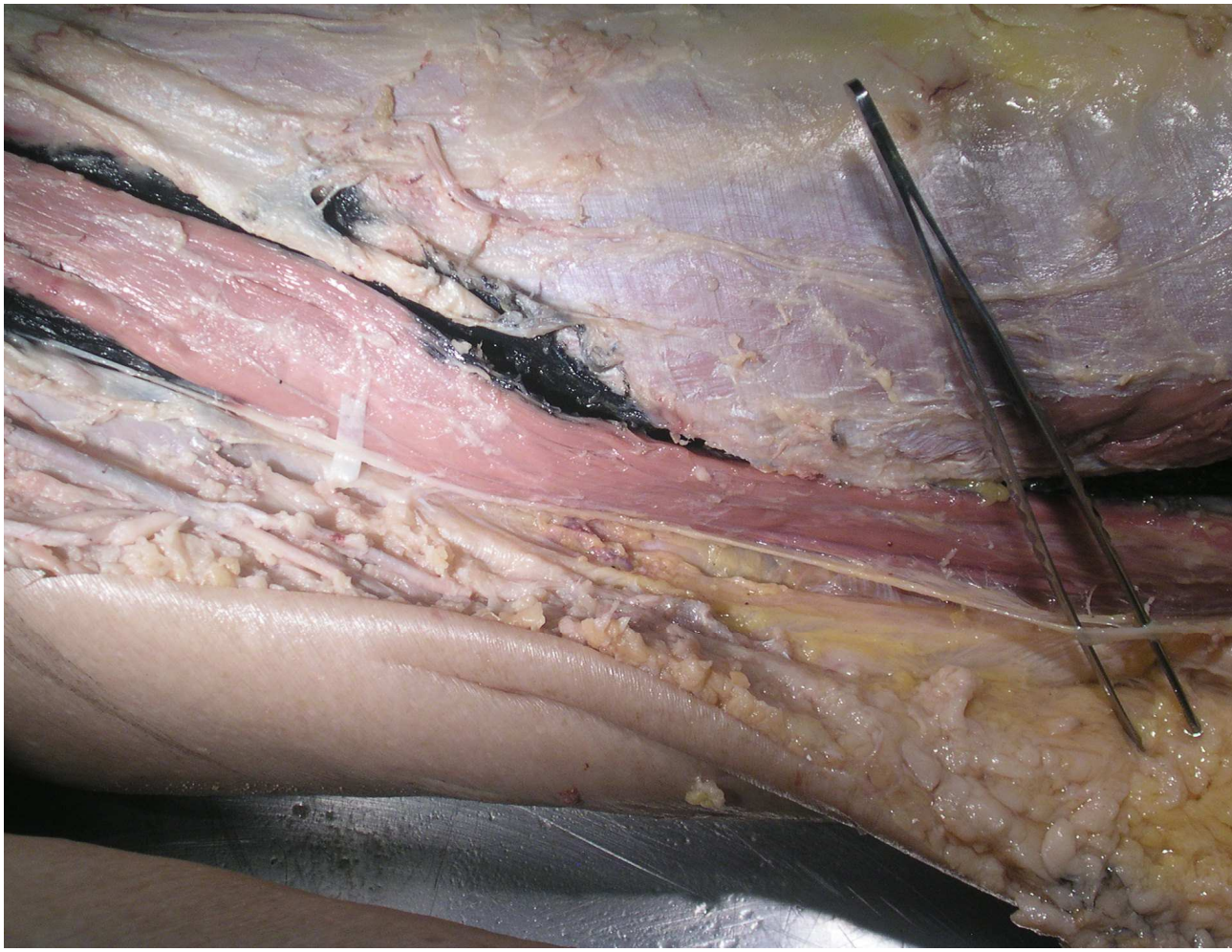


Image from personal collection of Dr Malcolm Watson

The medial cutaneous nerve of the thigh, a branch of the femoral nerve, can be seen emerging from the black 10% latex.

Figure 7-7: Obturator nerve

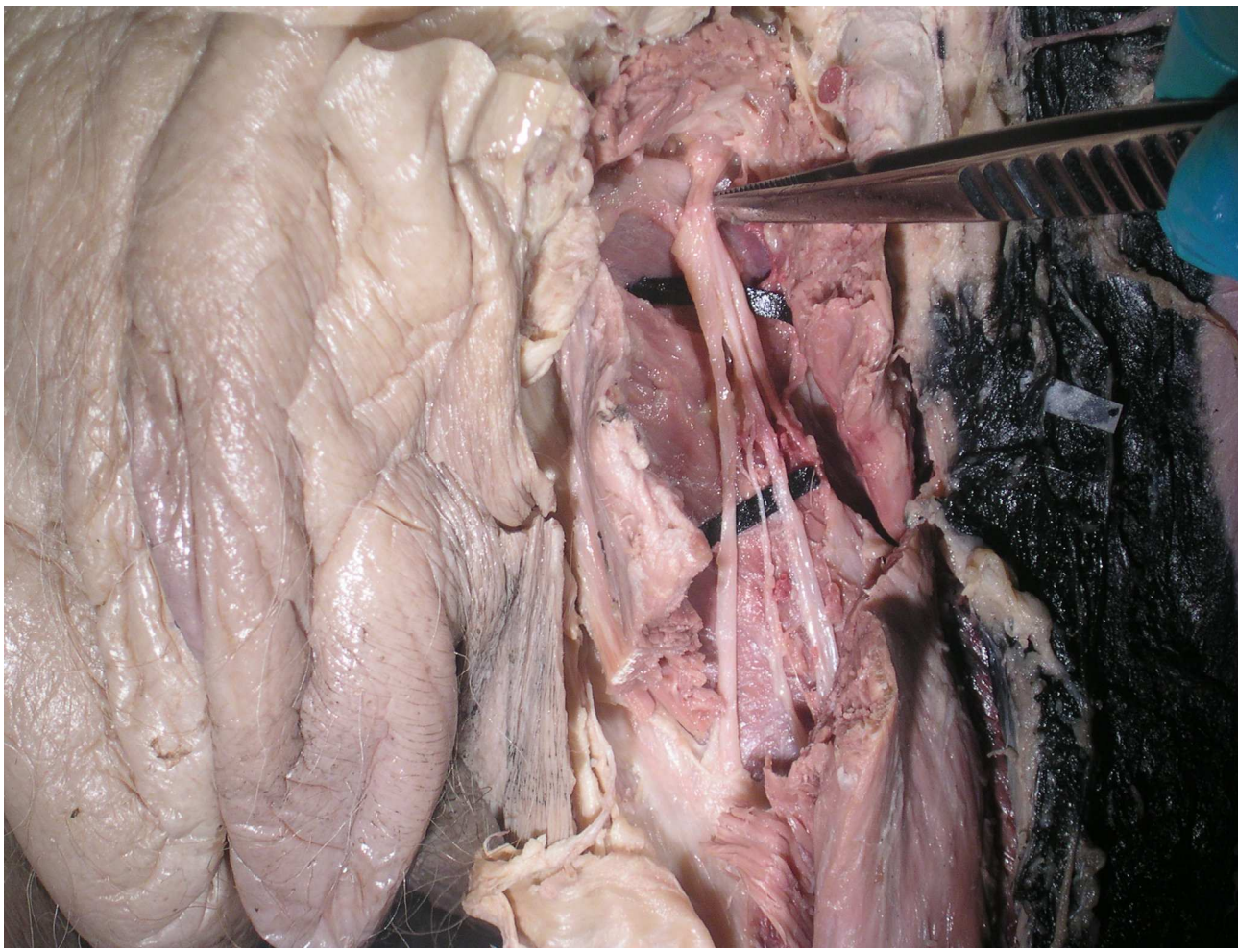


Image from personal collection of Dr Malcolm Watson

The obturator nerve is seen piercing the obturator externus muscle and dividing into the anterior (black paper beneath the anterior division lying on the obturator brevis muscle) and posterior division (below the adductor brevis muscle).

7.9 Discussion:

The femoral 3-in-1 nerve block is performed frequently but the anatomical maximal extent of the local anaesthetic distribution is currently unknown. If the femoral 3-in-1 nerve block is to be utilised to improve analgesia for patients, the anatomy of a femoral nerve block must be understood. Previous work on the anatomical basis of the femoral 3-in-1 block by Ritter et al (Ritter 1995) focused on the proximal spread of methylene blue to test the hypothesises of Winnie et al (Winnie, Ramamurthy, & Durrani 1973). The complete distribution of the methylene blue dye was not described. In order to correct this omission the full extent of the spread of black 10% latex in the two cadavers was dissected. The anatomical model used in this study (injection of black 10% latex) was most likely to represent the maximal extent of spread rather than the average distribution following injection of local anaesthetic under the fascia iliacus membrane and lateral to the femoral nerve. It is also arguable that black 10% latex is a better model for maximal local anaesthetic distribution as it is a very large molecule which leaves a residue in the tissue plane rather than staining the adjacent tissues. The distal spread may explain the occasional clinical observation of sciatic nerve motor weakness following an ultrasound guided femoral 3-in-1 nerve block (personal observation by Dr Malcolm J Watson). The use of unembalmed cadavers should have given a realistic model in comparison to using embalmed cadavers however the effect of arterial perfusion in the tissue compartments on local anaesthetic spread is unknown.

This pilot study confirmed the widely held belief that distal spread and a 2-in-1 block (femoral and lateral cutaneous nerves) is the most likely outcome of an injection underneath the fascia iliacus and lateral to the femoral nerve. The lack of obturator involvement is further supported by the paucity of obturator motor (adductor muscle involvement) in Chapter 6)

The preliminary dissection work in this chapter and the results of Chapter 6 may give an alternative explanation of the motor and sensory changes observed by Dolan et al (Dolan et al. 2008). The sensory anaesthesia described by Dolan et al. on the medial part of the upper thigh may have been due to anaesthesia of the medial cutaneous nerve of the thigh (a branch of the femoral nerve). The obturator (adductor) motor blockade demonstrated was possibly due to

anaesthesia of the obturator nerve as it travelled distally in the adductor canal as part of the subsartorial plexus or simply a difference in the assessment methods used to determine obturator motor block (see discussion in Chapter 6 section 6.6.1.4 Secondary end points).

In order to provide analgesia for a total knee arthroplasty, both the sciatic and the femoral nerves (which both supply the knee joint) should be anaesthetised. The distal spread to the branches of the sciatic nerve in the popliteal fossa observed in this study may explain the effectiveness of a femoral 3-in-1 nerve block for total knee arthroplasty.

7.10 Conclusion

The distribution of 30 ml of black 10% latex in two unembalmed adult cadavers injected lateral to the femoral nerve under the fascia iliacus membrane was to stain the lateral cutaneous and femoral nerve and to travel distally in the Hunter's canal through the adductor hiatus into the popliteal fossa to stain the sciatic nerve and its terminal branches.

7.11 Chapter summary

7.11.1 Background

Since the publication by Winnie in 1972 of the femoral 3-in-1 nerve block, there has been a debate about the distribution of the local anaesthetic and the inclusion of the obturator nerve.

7.11.2 Aim:

To determine the distribution of 30 ml of black 10% latex following an injection under the fascia iliacus membrane lateral to the femoral nerve.

7.11.3 Method

Two unfixed fresh cadavers were injected with 30 ml of black 10% latex under the fascia iliacus membrane lateral to the femoral nerve using ultrasound guidance. These cadavers were then fixed using the Cambridge formulation embalming fluid within one hour of injection and dissected three months later to determine the spread of the black 10% latex.

7.11.4 Results

In this model using black 10% latex and unfixed cadavers significant distal spread was observed but no evidence of proximal spread of the black 10% latex was seen. This result was consistent with the results of Chapter 6 and the clinical findings of the majority of other workers.

7.11.5 Conclusion

This preliminary dissection study confirms that the majority of the spread of black 10% latex dye injected under the fascia iliacus membrane is likely to be distal.

Chapter 8

8 Summary of results and future work

8.1 Introduction

Fractured neck of femur is a significant cause of morbidity and mortality in the developed world. The majority of the mortality and morbidity associated with traumatic fracture neck of femur was due to cardiac and respiratory complications (Perez et al. 1995). The use of regional anaesthetic techniques in patients with a high risk of cadiorespiratory complications has tended to show an outcome benefit (Scott et al. 2001;Yeager et al. 1987). However, the impact on mortality has diminished as improvements in surgical and anaesthetic techniques have also resulted in a reduction in the overall mortality. The mortality from high risk elective surgery is now less than 5%; therefore, to quantify the effect of regional analgesia higher incidence secondary outcome measures (i.e. lower respiratory tract infections, the need for ventilation and combined cardiac end points) have been used (Rigg et al. 2002). In contrast to the marked improvements in mortality for elective surgery, the overall mortality from emergency surgery and in particular surgery for fractured neck of femur patients has remained unchanged (Bottle & Aylin 2006;Heikkinen, Parker, & Jalovaara 2001).

It is possible that effective regional analgesia could improve outcome if delivered to patients with a fractured neck of femur early in their admission to hospital. The femoral 3-in-1 nerve block (also called the femoral nerve fascia iliacus block or anterior psoas compartment block) appeared to offer a viable solution to provide analgesia to patients with a fractured neck of femur prior to definitive surgical fixation. The nerve block is technically undemanding in contrast to epidural anaesthesia which requires extensive training of practitioners and continuous cardio-respiratory monitoring and increased nursing care. Ultrasound guidance may increase the block success rate and lower complication rates but it is associated with the extra cost of the ultrasound machine, disposables and staff training. In contrast, loss of resistance is technically simple and cheap but potentially inaccurate and, as a result, less effective. The use of the nerve stimulator is the current gold standard for elective femoral 3-in-1 nerve blocks but if used on patients with a fractured neck of femur it is likely to cause unnecessary discomfort in a limb with an

unfixed fracture. In order to determine the comparative efficacy of all three methods of guiding femoral 3-in-1 nerve blocks we performed femoral 3-in-1 nerve blocks in 180 patients scheduled for elective primary total hip arthroplasty.

Further work on levobupivacaine dosing was then undertaken and this work utilised ultrasound to guide femoral 3-in-1 nerve blocks to determine the effective dose and duration of analgesia provided. This information was needed as no levobupivacaine dosing information was available for fractured neck of femur patients. The further information on dosing based on efficacy and duration of action will allow a reduction in dose and hence an improvement in safety of the femoral 3-in-1 nerve block.

8.2 Summary of primary end points of this project

In Chapter 3, six research questions to be answered by this PhD project were defined. The second question was answered by undertaking a literature review and the summary of the answers to questions one, and three to six are provided below.

8.2.1 Question 1: Which method do we use to site the local anaesthetic?

From Chapter 6

The success rates of methods of guiding insertion of a femoral 3-in-1 nerve block were as follows in table 8.1.

Table 8-1: Percentage of successful femoral 3-in 1 nerve blocks in elective hemiarthroplasty patients

Method:	Ultrasound	Nerve stimulator	Loss of resistance
Number of patients(ineffective)	16	12	15
Number of patients(effective)	55	59	22
Total analysed	71	71	37
Percentage successful blocks	77.5%	83.1%	59.4%

***The definition of a successful block was cutaneous sensory response of <90/100 and/or a motor score decrease of <1 with a starting value of 4/4(in patients with a starting values of <3/4 the efficacy of the block was determined by the sensory change).**

The use of ultrasound or a nerve stimulator resulted in a statistically significant absolute increase in the effectiveness of the femoral 3-in-1 femoral nerve block by 20.8% (p=0.0159) respectively in comparison to loss of resistance giving a number needed to treat to see a difference of approximately 5. It is difficult to advocate the use of a nerve stimulator on a limb with an unfixed fracture for analgesia; therefore, ultrasound is the most effective viable guidance method for the femoral 3-in-1 nerve block in patients with a fractured neck of femur.

8.2.2 Question 3: What is the effective dose of levobupivacaine for a femoral 3-in-1 femoral nerve block?

From Chapter 4

The effective concentration of 30 ml of levobupivacaine required to produce a reduction in pain numerical rating scale (NRS) of ≥20 points on a 100 point scale in 50% of patients (EC_{50}) with a fractured neck of femur using an ultrasound guided femoral nerve block was EC_{50}=0.0255% with 95% confidence interval (CI) of 0.0229% to 0.0284%. The effective concentration of levobupivacaine in 95% of patients (EC_{95}) was calculated as EC_{95}=0.0357% with 95% CI of 0.0332% to 0.0383%.

8.2.3 Question 4: What is the duration of analgesia from the EC_{95} dose of levobupivacaine?

From Chapter 5

The median duration of analgesia from 30 ml of 0.036% (the EC_{95} of levobupivacaine) was 177 minutes and the interquartile range of the duration of analgesia was 110 to 210 minutes. The mean duration of analgesia was 166 minutes with a standard error of the mean of ±18 minutes and a standard deviation was ± 67 minutes.

8.2.4 Question 5: What is the pharmacokinetic profile of levobupivacaine in the population of patients with a fractured neck of femur?

From Chapter 5

The peak median total serum plasma concentration of levobupivacaine was reached at 30 minutes after the femoral 3-in-1 nerve block was 52 ng/ml with 95% confidence interval (CI) of 16-256 ng/ml which is within the 'safe range' (of <2100ng/ml).

8.2.5 Question 6: What is the clinical anatomy of the femoral 3-in-1 nerve block

From Chapter 7

The distribution of 30 ml of black 10% latex in two unembalmed adult cadavers injected lateral to the femoral nerve under the fascia iliacus membrane was investigated by dissection. In all four dissections the lateral cutaneous and femoral nerves were stained and the black 10% latex travelled distally in the Hunter's canal (or adductor canal) through the adductor hiatus into the popliteal fossa to stain the sciatic nerve and its terminal branches.

8.3 Summary of primary end points

The use of ultrasound and nerve stimulator for the delivery of local anaesthetic in the femoral 3-in-1 nerve block for elective total hip replacement was statistically significantly more effective than loss of resistance with a number needed to treat of 5. There was no statistically significant difference in the success of using the nerve stimulator and ultrasound to guide insertion of a femoral 3-in-1 nerve block. Since the use of nerve stimulator would result in unnecessary discomfort in patients with an unfixed fractured neck of femur we concluded that ultrasound was the optimal technique in this population. The estimated effective dose in 95% of patients (EC_{95}) of levobupivacaine for the femoral 3-in-1 nerve block in patients with a fractured neck of femur was (0.036%); however, the mean duration of analgesia was short (166 minutes with a standard error of the mean of ±18 minutes). The plasma levels of levobupivacaine observed while using the estimated EC_{95} were well within 'safe' limits. The total peak median plasma levobupivacaine concentration observed (52 ng/ml) indicated that if the dose of levobupivacaine was increased to provide a clinically useful duration of analgesia (i.e. ≥10 hours) then the plasma levels were likely to be within safe limits (<2100ng/ml) (Knudsen et al. 1997). The results of the 4 cadaveric dissections following ultrasound guided femoral 3-in-1 nerve block injections of black 10% latex suggest the site of action of local anaesthetic may be distal to the point of injection contrary to the currently held belief.

8.4 Summary of secondary end points

In elective total hip arthroplasty patients there was a slight reduction (not statistically significant) in both pain NRS scores (10-20 points on a 100 point scale) and opiate requirements (1 to 2 mg) at six hours. No change in pain NRS score or opiate requirement was observed at 24 hours in successful femoral 3-in-1 nerve blocks. The reductions in pain NRS and opiate requirement at six hours were not clinically significant. The time to first active weight bearing mobilisation on the replaced hip joint did not vary with the different method used or efficacy of the femoral 3-in-1 nerve block.

The correlation observed between reduced sensation to melting ice and pin prick sensation (<90/100) to a blunted 25G needle with analgesia in patients with a fractured neck of femur may be a useful surrogate measure for analgesia in other patient populations. The pain half time (estimated time for pain (NRS) score to reduce to half the original value) with the EC_{95} levobupivacaine dose was 24 minutes (P=0.052). The association of sensory changes with pain (NRS) scores at 10, 20 and 30 minutes implied that levobupivacaine has a delayed onset and that analgesic effects seen before 20 minutes may be due to another mechanisms such as hydrostatic pressure. Wide variations in the plasma concentrations of levobupivacaine were observed (maximal median value of 52 ng/ml with a range of 16-256 ng/ml at 30 minutes after the femoral 3-in-1 nerve block) despite stringent controls on the administration and production of the levobupivacaine. The wide variation may represent variable absorption of levobupivacaine from the site of action.

8.5 Further work-

To estimate the dose of levobupivacaine required to provide analgesia for greater than 10 hours

The EC_{95} of levobupivacaine did provide an estimate of the effective dose but as the effective dose was relatively low the duration of analgesia was too short to be clinically useful. In order to provide a clinically useful duration of analgesia the EC_{95} and EC_{50} to provide ≥10 hours of analgesia will need to be determined.

The sequential up/down Dixon's method (Dixon 1965) may be utilised to determine the concentration of levobupivacaine necessary to provide 10 hours of analgesia. The binary end point will be the successful provision of 10 hours of analgesia (with pain NRS <50/100).The number of patients required to obtain a precise estimate for levobupivacaine EC_{95} and EC_{50} will be decreased by the use of iterative re-estimate of the optimal stepping value (δ).

The review article by Pace et al provided a number of improvements to the original Dixon up/down methodology (Pace & Stylianou 2007). Pace et al suggested the use of the Bias coin method of patient allocation to target the EC_{95} instead of targeting the EC_{50} of levobupivacaine. In order to estimate the

EC_{95} with the same precision as the EC_{50} 20 times the number of patients would need to be recruited, as every failure will be accompanied by 19 successes at the EC_{95} concentration. If a sequential up/down Dixon's method dosing study requires 20 to 40 patients to estimate the EC_{5o} then 400 to 800 patients would be required to estimate EC_{95} with the same precision.

In Chapter 4 the stepping value was altered on the basis of an interim probit regression analysis to achieve increased accuracy with a reduced number of patients. If the interim analysis used in Chapter 4 was repeated several times during the clinical trial it would theoretically result in an improvement in accuracy with a reduced number of patients in comparison to the traditional sequential up/down Dixon's method. The protocol for the dosing study in Chapter 4 initially set a large stepping value (δ) (difference between the concentrations of levobupivacaine used) and decreased it after 16 patients had been recruited so that the stepping value (δ) was between 2/3 and 3/2 of the estimated standard deviation (σ) using the probit regression analysis techniques to model the concentration against chance of a successful femoral 3-in-1 nerve block. If this process had been repeated on multiple occasions during the trial progressively better estimations for the stepping value could have been obtained. Iterative re-calculation of the mean and standard deviation (σ) would have resulted in progressively increased precision when fitting a probit model to estimate the EC_{50} and EC_{95} for levobupivacaine.

The **iterative re-calculation** of **σ (standard deviation)** and **μ (the estimated EC_{50})** would have several other advantages:

- The initial **stepping value (δ)** can be relatively large which will result in a decrease in the number of patients required to reach a **turning point** (change in direction from effective to ineffective or vice versa)
- The number of patients needed would be less dependent on the **starting concentration**
- Repeated measures of **μ (the estimated EC_{50})** will give a measure of variation and therefore **stability** of the model and therefore the precision of the final estimate of the levobupivacaine EC_{50} and EC_{95}

- Objective criteria for stopping the trial can be set at the beginning of the trial which will relate to the **stability** of the probit model created using probit binary regression analysis.

The following assumptions have been made when designing the protocol to use iterative re-calculation of the stepping value (δ).

- The iterative calculation of (δ) will only yield a different result if the test result has reached a **turning point**.
    - If the **turning point** has been reached then, if a further 2 patients are recruited, the information from these will allow determination of whether the turning point was above the mean, below the mean or at the mean.
    - Therefore, an **iterative re-calculation** of the **Standard deviation (σ)** and the estimated mean **μ (the estimated EC_{50})** will be made after a turning point has been reached and 2 further patients have been recruited and the stepping value(δ) concentration will be adjusted to be within 3/2 and 2/3 of the σ.
    - The new starting concentration after recalculation will be the estimated mean plus the new **stepping value (δ).**
    - The result of the iterative process will be rounded to achieve the most accurate result possible within the error limits imposed by the pharmaceutical manufacturing process (see Chapter 4, discussion section 4.10.1 Quantifiable error in final concentration and volume of IMP, manufacturing errors were estimated at 5.1% of stated concentration.
    - The iterative process will be repeated after recruiting two patients after each turning point until agreement is reached between three estimations of **μ (the estimated EC_{50})** within a predetermined precision (<10% variance). This will imply that the probit regression model is stable and that a reliable estimate of EC_{95} and EC50 can be derived.
    - Utilising these principles a protocol for a clinical trial to determine the dose required for ≥10hours analgesia and to ensure its safety has been written (please see appendix 13)

In summary, the use of iterative probit analysis techniques to set the setting value will decrease the number of patients needed to provide an accurate and precise answer to the EC_{50} and EC_{95} dosing question. It will also provide objective criteria to stop the trial once it has achieved a stable probit binary regression model.

8.6 Further work

Outcome benefit of femoral 3-in-1 nerve blocks for patients with a fractured neck of femur

This reason for undertaking this PhD project was to develop a method of improving analgesia for patients with a traumatic fractured neck of femur. The results of the project have done the majority of that development work; however, it may be that by improving analgesia we may also improve the patient outcome. A multicentre clinical trial will be needed to determine if improved analgesia could result in an improvement in outcome. In order to design a protocol the following research questions need to be answered.

Research questions:

1. Which adverse event should be measured?
2. What is the current incidence and timing of the adverse event?
3. What impact could the intervention make on the adverse event?

A power calculation can then be made to estimate the number of patients that need to be recruited to the study.

8.6.1 Which adverse events should be measured?

The principal aetiology of mortality and morbidity early (in the first 48-72 hours) after a fractured neck of femur was cardiac (Perez et al. 1995) and the risk was further increased in those patients with a history of cardiac disease (Marsch et al. 1992). In contrast, bronchopneumonia and pulmonary embolism accounted for the majority of late deaths (7-14 days after fractured neck of femur) (Perez et al. 1995). Early surgical fixation, early mobilisation, antibiotics, and

prophylactic anticoagulation have been shown to reduce death from bronchopneumonia and pulmonary embolism after hip fracture (Morrison, Chassin, & Siu 1998;Perez et al. 1995). An intervention which reduced the early severe pain associated with a fractured neck of femur would potentially reduce the harmful stress response with a concomitant improvement in early (first 72 hours after injury) morbidity and mortality from adverse cardiac outcomes. Mangano et al and other research groups have used beta-blockers (ß-blockers) or alpha 2 (α_2) blockers to reduce stress and improved cardiac outcomes in non-cardiac patients (Mangano et al. 1996;Stuhmeier et al. 1996;Wallace et al. 1998). The use of the femoral 3-in-1 nerve block could reduce the pain and hence 'stress response' of patients with a fractured neck of femur and would have the potential to improve early adverse cardiac outcomes (Matot et al. 2003;Scheinin et al. 2000)

8.6.2 What is Incidence and timing of adverse events?

Marsch et al found a 31% incidence of perioperative ischaemic events measured using Holter monitors which were fitted to patients preoperatively up to six days postoperatively in an unselected population of patients admitted with fractured neck of femur (Marsch et al. 1992). The majority of the ischaemic episodes occurred preoperatively, intraoperatively and the first 48 hours postoperatively. Scheinin et al found an incidence of myocardial ischaemia detected by Holter monitors in the control group (prescribed opiate and non steroidal anti inflammatory drugs (NSAIDS) for analgesia) varied between 27% to 42% (Scheinin et al. 2000). Matot et al (Matot et al. 2003). Matot et al examined a combined cardiac end point (cardiac death, myocardial infarction, unstable angina, congestive heart failure (CHF), and new-onset atrial fibrillation) based on the definitions used by Magano et al (Mangano et al. 1996). Matot et al found that the control group (prescribed intramuscular meperidine) had and preoperative incidence of combined cardiac end points of 20% (Matot et al. 2003).

The use of epidural analgesia by Scheinin et al and Matot et al reduced both the combined cardiac end points and ischaemic episodes in the preoperative, intraoperative and immediate postoperative period (48 hours after hip fixation) (Matot et al. 2003;Scheinin et al. 2000). The use of serial sensitive troponin measurement has replaced Holter monitoring in detecting cardiac ischaemia

episodes. Troponin has been well validated as a sensitive specific test and elevated levels have been associated with adverse cardiac outcomes in vascular and cardiac surgery patients populations (Christenson & Phillips 2011;Flu et al. 2010;Mair 1997;Marsch et al. 1992;Sadony et al. 1998).

If combined cardiac end points and serial troponin measurement are used then an incidence of adverse events of 30-40% can be expected in the control population. The preoperative, intraoperative and immediate postoperative (48 hours after fixation of the hip) periods are the most susceptible to intervention based on previous study by Marsch et al (Marsch et al. 1992).

8.6.3 What impact could a femoral 3-in-1 nerve block make on pre and intraoperative cardiac events?

Scheinin et al observed an absolute reduction in ischaemic episodes of 17% preoperatively, 27% intraoperatively and 9% postoperatively in those patients treated with epidural analgesia (Scheinin et al. 2000). Matot observed an absolute reduction in combined cardiac end points of 20% preoperatively and a 6.6% reduction postoperatively (Matot et al. 2003). It should be assumed that femoral 3-in-1 nerve blocks will be less effective than epidural analgesia as no sympatholyic cardiac effect will be observed with peripheral nerve blocks in contrast with neuraxial blocks. The power curve plots for various sample sizes are shown below in figure 8-1 and table 8-2 for an absolute reduction in combined cardiac end points and elevated troponin measurements of 5%, 7.5% and 10% with an alpha error of 0.05.

8.6.4 Power calculation if combined cardiac end points and troponin was used as the primary endpoint

If it is assumed that the control group have an incidence of combined cardiac end points and elevated serial troponin measurements of 35%. The power curves shown below show the number of patients to achieve an 80% and 90% power and an alpha error of 0.05. The sample sizes required for an 80% and 90% power and a 5%, 7.5% and 10% percentage change in combined cardiac end points and elevated serial troponin measurement with an alpha error of 0.05 are shown above in Figure 8-1 and below in Table 8-2.

Figure 8-1: Combined cardiac end points and elevated serial troponin measurement cardiac morbidity (as a proportion) (x-axis) is plotted against the power of the study to detect the difference (y-axis).

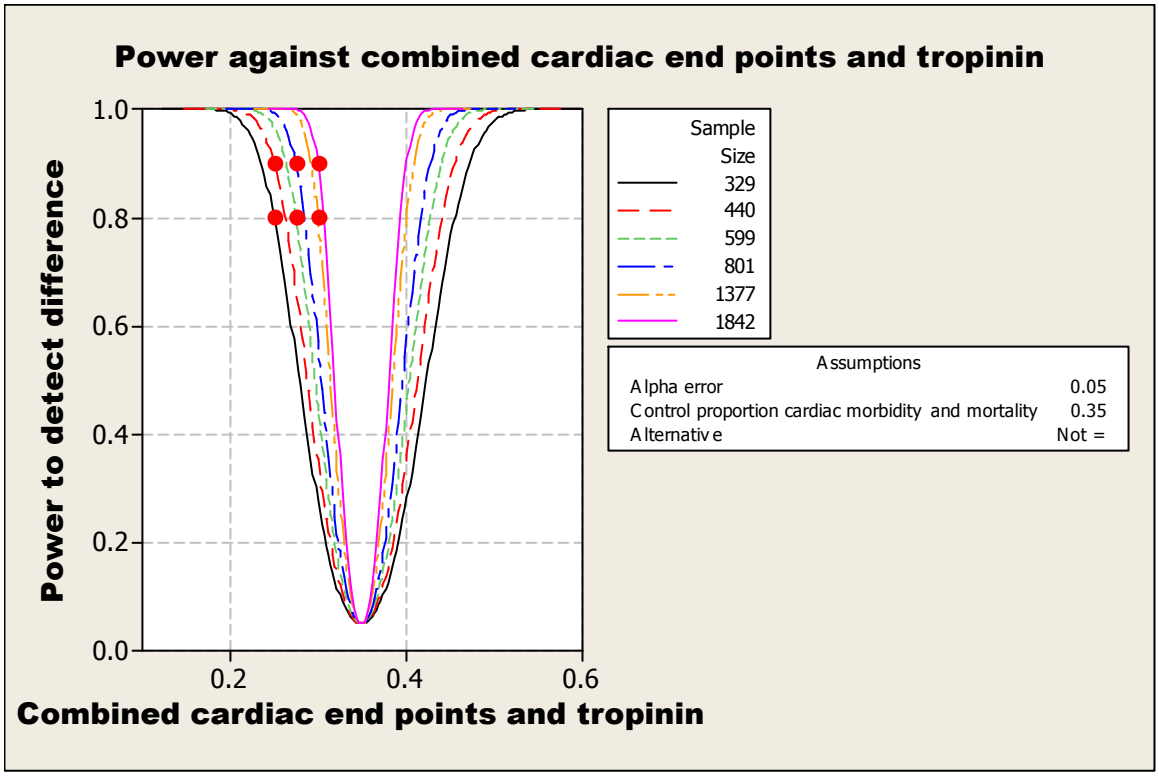


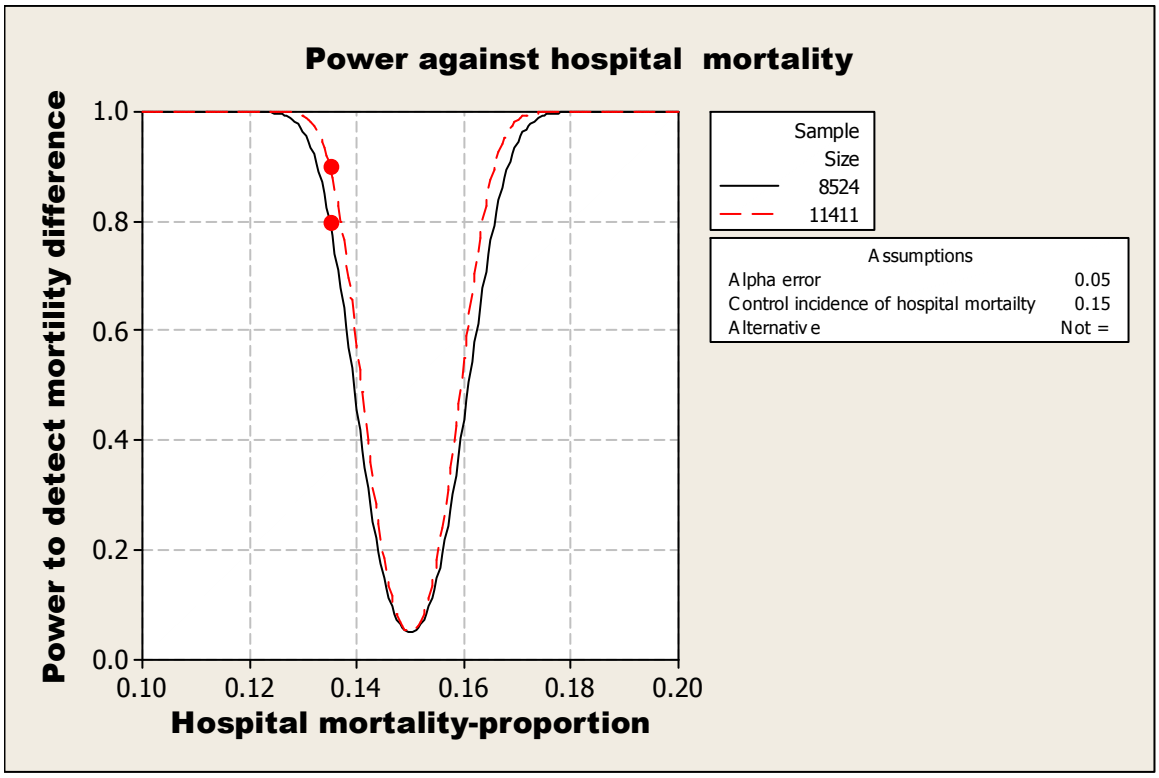
Table 8-2: Number of patients required in each group to power trial for 5%, 7.5% and 10% difference in combined cardiac end points and elevated serial troponin measurement and p=0.05

	Difference in combined cardiac end points and elevated serial troponin measurement		
	5%	7.5%	10%
80% power of trial	1377 Patients in each group	599 Patients in each group	329 Patients in each group
90% power of trial	1842 Patients in each group	801 Patients in each group	440 Patients in each group

8.6.4.1 Power calculation if hospital mortality is used as the primary outcome

If it is assumed that the effect of the femoral 3-in-1 nerve block was a 10% relative reduction in hospital mortality from 14.6% (Bottle & Aylin 2006) (i.e. 1.5% absolute reduction). If hospital mortality is used as the end point of an outcome study then 8524 patients would be needed (for an 80% power and an alpha error of 0.05) in each group to detect a 10% relative mortality benefit in comparison to 329 patients for the combined morbidity and mortality end point and serial troponin testing (or Holter monitoring)(please see figure 8.2 for sample size calculation). Therefore, combined cardiac end points and elevated serial troponin measurement could provide an end point for a clinical trial which has an achievable patient recruitment target due to a relatively high event rate and potentially relatively large intervention effect.

Figure 8-2: The power graph demonstrates the number of patients in each group needed to give the study an 80% (8524 patients) and 90% (11411 patients) power with an alpha error of 0.05.



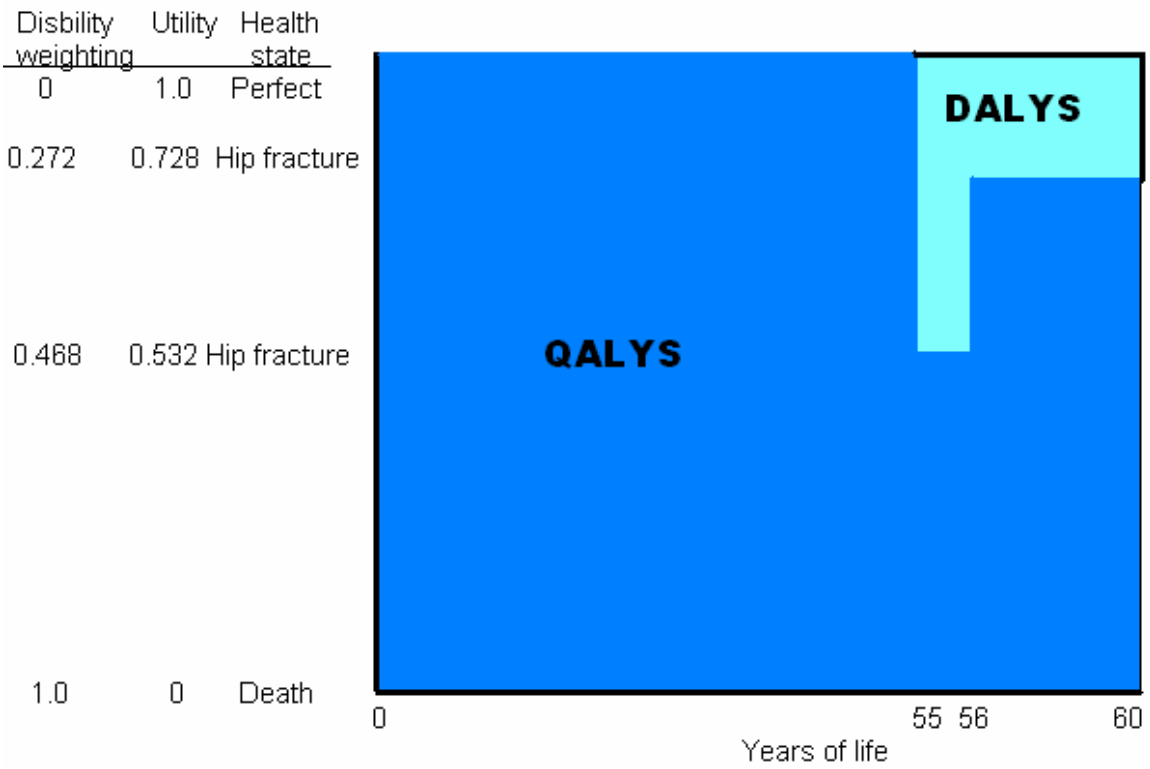
8.7 Medical/economic arguments for the use of ultrasound guided femoral 3-in-1 femoral nerve blocks in fractured neck of femur patients

8.7.1 DALYs and QALYs

In order to asses the potential benefits of any intervention it is necessary to assess the harm directly attributable to the disease process in terms of increased morbidity and mortality in DALYs (disability adjusted life years). The beneficial effects of any intervention are usually measured in reduced morbidity and mortality in QALYs (quality adjusted life years) gained. These two measures are complementary, QALYs measure the number of healthy years gained and DALYs (disability adjusted life years) combines information about morbidity and mortality in numbers of healthy years lost. In both the DALYs and QALYs approach, each state of health is assigned a disability or utility weighting respectively on a scale from zero (perfect health-DALYs or death-QALYs) to one (death-DALYS to perfect health-QALYs) by an expert panel. In summary, QALYs are years of healthy life lived; DALYs are years of healthy life lost. If QALYs and DALYs are displayed graphically (see Figure 8-3) multiply the number of years (x axis) by the quality of those years (y axis). QALYs use "utility" weights of health states; DALYs use "disability weights" to reflect the burden of disease states. The use of DALYs by the World Bank and World Health Organisation has been controversial due to the discounting of future disability weights at a rate of 3% per year, and the practice of using a lifetime weighting so that years of life in childhood and old age are weighted less (Arnesen & Nord 1999).

If we use the example of a patient suffering a fractured neck of femur at age 55 with previously perfect health the disability weighting would be 0.468 (Kanis *et al*. 2001) in the first year and 0.272 (Murray & Lopez 1997) for subsequent years therefore the utility weighting is 1-0.468=0.532 for the first year and 1-0.272=0.728 for subsequent years. If that patient then had a myocardial infraction and died at 60 then Figure 8-3 shows the QALYs and DALYs.

Figure 8-3: QUALY and DALYS for fractured neck of femur patient



8.7.1.1 Summary of DALYS and QUALYS:

DALYs lost due to fractured hip=0.468*1+0.272*4=1.556 in 5 years due to fractured hip

QALYs gained after hip fracture=1*5-1.556=3.444 in 5 years following the fractured hip

8.7.2 Cost over 10 years (ultrasound machine, extra disposables, medical and nursing time and training)

NICE consider that the threshold cost/benefit for an intervention to be considered cost effective is 1 QALYs =£20000 or less (2012). The costs of providing ultrasound guided regional analgesia in a small hospital are detailed below.

- Equipment: Ultrasound machine with an equipment life span of 10 years will treat 300 patients per year in an average size hospital (i.e. Western infirmary, Glasgow). Total cost **£24000**
- Extra disposables:

  (Costs from procurement system in NHS GGC, 6th June 2010)

  - £5.00 per sterile pack
  - £2.00 per ultrasound probe sheath
  - £15.00 per needle
  - £2.00 per sachet of ultrasound gel
  - £1.00 0.5% Chorohexidine with 70% alcohol skin preparation
- **Total cost over 10 years** of disposables would be £25 multiplied by 3000 patients=**£75000 in total**
- **Total equipment and disposables cost** over 10years = £99,000
- Extra medical and nursing time for 3000 patients
  - 10 mins, extra consultant time, consultant, paypoint 5 (2011)
    - 30000minutes/255minutes(1 PA)= 118 PAs extra at £161 per PA (Programmed Activity)= **£19000 in total**
  - 10 minutes of extra nursing time, band 6 paypoint 5 (2011)
    - banding 6 (29,464/52=566.62
    - 566.62/37.5 hours=£15.11/per hour)
    - 30000 minutes/60 minutes= 500 hours at £15.11per hour= **£7555 in total**

8.7.3 Training costs

- Cost of course £250 per day for 10 days= **£2500 in total**
- Cost of back filling post: 2.5 PA (Programmed Activity) per day with 5 years seniority (consultant salary scale 2010-2011)= 83,829/10 = **8380 in total**
- 8,382.90/52=£161.21 per PA=£403.02 per day
  10 days in 10 years= **£4030 in total**

Total extra cost =£132910 for 10 years in Western Infirmary, Glasgow

8.7.4 Outcome benefit versus cost of treatment:

If we use the costs calculated above and apply the improvements (QALYs) needed by NICE to justify automatic inclusion as a guideline **(£132910 (total cost)** over 10 years /£20000 = 6.6 QALYs or more would be needed by NICE (2012b) in the total population over 10 years to justify the cost of treatment.

8.7.5 The benefit associated with ultrasound guided femoral 3-in-1 nerve block needs to be greater than 6.6 QALYs

In order to determine if 6.6 QALYs is an achievable benefit we need to examine the total QALYs lost due to a hip fracture. In the first year after a hip fracture 0.468 QALYs are lost (Kanis, Oden, Johnell, Jonsson, de Laet, & Dawson 2001). It may only be possible to improve 10% of the total disability in the first year (therefore 0.0468 QALYs will be gained per patient in the first year for a 10% relative reduction. If this effect is achieved for all 3000 patients then a total of 140 QALYs will be gained.

Another way of examining the 'achievable benefit' question would be to examine the effect of the pathologies that a femoral 3-in-1 nerve block may prevent. The combined mortality and morbidity effect of one myocardial infarction is the loss of 5.14 QALYs (Hong *et al*. 2011). If ultrasound guided femoral 3-in-1 nerve blocks prevented 2 myocardial infarctions in ten years then it would be a cost effective intervention (2012).

In this cost benefit analysis all possible costs have been included and rounded up. Since the cost of the ultrasound machine is a fixed cost and the largest cost

then if more patients are treated then the number of QALYs required will decrease. I therefore conclude that the use of ultrasound guided femoral 3-in-1 nerve blocks would only require a small improvement in morbidity and morality for it to represent a cost effective intervention using current NICE guidance.

8.8 Final summary of thesis

Patients with a fractured neck of femur have a significant morbidity and mortality: the hospital mortality in this patients group is approximately 1 in 7 patients. Regional anaesthesia and analgesia appeared to offer benefits to almost all patient populations studied. Although epidural analgesia and has been shown to offer improved outcomes for patients with a fractured neck of femur this has not led to a change in practice. It is unlikely that the resources required to implement epidural analgesia for all patients with a fractured neck of femur will ever be available within this NHS. The use of femoral 3-in-1 nerve block to provide analgesia would require increased training in accident and emergency departments but should not increase nursing or medical staff workload and could result in improved outcome for patients.

The aim of this PhD was to develop a method of providing safe, effective regional analgesia to the 60,000 to 70,000 patients admitted annually to UK hospitals with a traumatic fractured neck of femur. It was hypothesised that ultrasound guided femoral 3-in-1 nerve blocks could provide a superior method of analgesia to the current standard of care (parenteral opiates).

An initial randomised trial compared the efficacy of using ultrasound and traditional insertion techniques to guide the needle for the femoral 3-in-1 nerve blocks in elective primary total hip arthroplasty patients. The most successful method was nerve stimulator however this was not statistically significant and it is unlikely to be widely utilised for preoperative analgesia in the fractured neck of femur patients. The use of ultrasound or nerve stimulator improved the efficacy of the technique over loss of resistance by 20.8%, giving a number needed to treat of approximately five patients although this was also not statistically significant.

We determined the levobupivacaine dosing using a sequential Dixon's up/down study. A femoral 3-in-1 nerve block was performed and the concentration of levobupivacaine was increased or decreasing for an ineffective or effective nerve block respectively. The EC_{50} of levobupivacaine was calculated as EC_{50}=0.0255% with 95% confidence interval (CI) of 0.0229% to 0.0284%. The effective concentration in 95% of patients (EC_{95}) was calculated as EC_{95}=0.0357% with 95% CI of 0.0332% to 0.0383%.

A final clinical trial assessed local anaesthetic pharmacokinetics (to ensure that serum levels of the EC_{95} dose of levobupivacaine were within the safe range) and pharmacodynamics (to assess duration of analgesia) in fractured neck of femur patients using serial blood sampling and by monitoring pain scores respectively. The peak median total serum plasma concentration was reached at 30 minutes after the block and was 52ng/ml. This concentration of levobupivacaine was well within the 'safe range' for levobupivacaine and the mean duration of analgesia was two hours and 46 minutes with a standard error of the mean of ± 18minutes.

The dissection of 2 cadavers following ultrasound guided femoral 3-in-1 nerve blocks and injection of 30 ml of black 10% latex dye showed that the dye did not spread proximally as Winnie et al (Winnie, Ramamurt .S, & Durrani 1973) hypothesised. In all cases it tracked distally through the Hunters canal and through into the adductor hiatus to stain the sciatic nerve and its terminal branches in the popliteal fossa.

This PhD project was funded by a Chief Scientist Office fellowship award which paid all the research costs and the salary of the chief investigator for three years. A total of 234 patients were recruited between 1 February 2009 and 4 March 2011 in four Glasgow hospitals. It required the completion of one multi site clinical study ethics application with four substantial amendments and one ethics application for a clinical trial of an investigational and medicinal product with an associated MHRA (Medicines and Healthcare Regulatory Agency) application and one substantial amendment. It was the first comparative study of all three methods of guiding a femoral 3-in-1 nerve block and provided new information on the association of sensory and motor changes with analgesia for

the femoral 3-in-1 nerve block and an assessment of the effect of a femoral 3-in-1 nerve block on mobilisation, analgesia and morphine consumption. The clinical trial provided the first estimate of the minimum effective dose of levobupivacaine to provide analgesia in patients with a fractured neck of femur and the estimated the duration of analgesia and pharmokinetics of levobupivacaine. As a result of this PhD project improvements have been made to the sequential up/down Dixon's methodology which should reduce the number of patients needed and increase precision and accuracy of this method. The dissection provided initial data on the maximal distribution of a 30 ml volume injected under the fascia iliacus membrane, lateral to the femoral nerve. In summary, this project provided new information which could provide analgesia to 60000 to 70000 patients admitted annually to UK hospitals with a fractured neck of femur.

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Appendix 1: NHS GGC monitoring report

Research and Development Department
Acute Services Division
Western Infirmary

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Tennent Institute
R&D Management
1st Floor
Western Infirmary
Glasgow G11 6NT

Dr Malcolm Watson
Specialist Registrar in Anaesthesia
Western Infirmary
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Enquiries to Michael McLaughlin / Lynsay Dickov
Extension
Direct Line 0141 211 6313
E Mail Michael.McLaughlin@ggc.scot.nhs.uk / Lynsay.Dickov@ggc.scot.nhs.uk
Date 13 January 2011

Dear Dr Watson,

Subject: **Monitoring Visit FU Letter – visit on 30 November 2010**
Title: **Dose Finding Study for Pain Relief of a Broken Hip**
R&D Number: **GN09AN334**

Thanks for taking the time to organise our visit, prepare the files, and ensure your room was available for us to conduct our visit. During the visit, we covered the following:

- Site File review
- 100% ICF (Informed Consent Form) verification
- 10% SDV (Source Data Verification)
- Safety Reporting
- Preparation for Part B

Site File review

Firstly, we reviewed all essential documents and approvals. Please see our comments below:

Document	Current Version	Version in site file
Protocol	V 3.0 30-Aug-10	V 3.0 30-Aug-10*
PIS parts A & B	V 3.0 15-Sep-10	V 3.0 15-Sep-10*
ICF Parts A & B	V 2.0 29-Jul-09	V 2.0 29-Jul-09
Data Collection Form A&B	09-Aug-10	09-Aug-10
GP Letter Parts A & B	V 1.0 20-Jun-09	V 1.0 20-Jun-09
Initial R&D Approval	17-Nov-09	17-Nov-09
Initial Ethics Approval	08-Jul-09	08-Jul-09
Initial MHRA Approval	28-Sep-09	28-Sep-09
Am R&D approval	13-Oct-10	13-Oct-10
Am Ethics approval	08-Sep-10	08-Sep-10
Am MHRA approval	22-Sep-10	22/09/2010*
Sponsor letter	16-Nov-09	16-Nov-09
Pharmacy authorisation	07-Oct-09	**
SoPC Chirocaine	13-May-10	16-May-07
CSO Award letter	07-Jan-08	07-Jan-08
SAE form	GCTU V 3.2	GCTU V 3.2* (pages 2-4 V3.1)

* indicates documents we found in a separate file, with original documents in the site file. The site file should contain the current versions of study documents, with superseded versions filed separately where there is no space within the main site file. File notes should be inserted into the relevant sections detailing the locations of superseded documents.

** indicates document missing from the file. A copy of the email with pharmacy authorisation will be attached with this letter. Please file in the pharmacy section of the site file.

1

We comprehensively reviewed your site file and found it to be well organised, indexed and appropriately sectioned as follows:

Introductory section	Standard index, list locating documents not in the site file (completed case report forms and consent forms, logs, prescriptions, amendment documentation, GCP and training documentation).
Section 1	Sponsor details, your contact details and 24 hour contact details
Section 2	Correspondence section with file note - correspondence elsewhere
Section 3	Protocol version 1. Subsequent versions elsewhere
Section 4	Ethics sections. Signed REC application, receipt of annual progress report August 2010, amendment approval, initial committee list of members, initial favourable opinion, acknowledgement of minor amendments letter 30-Jul-09, Annual Safety Report cover letter 2010, SOPs version 3.5 May 2008, file note locating submitted documents of July 2010.
Section 5	R&D section. Signed R&D application, signed site specific information, R&D management approval, file note locating submitted documents of July 2010, signed risk assessment, CSO award letter, Robertson Centre advisory letter, CSO documents and a monitoring log (signed at the visit).
Section 6	Regulatory section. Signed CTA application, CTA amendment approval letter, acknowledgements of amendment 24-Aug-10 and 07-Sep-10, file note locating submitted documents of July 2010, letter to MHRA 10-Sep-09, EudraCT number issue form, MHRA non-acceptance letter 03-Sep-09, letter summarising actions taken following CTA non-acceptance, MHRA receipt, MHRA acknowledgement 10-Aug-09, MHRA submission cover letter 05-Aug-09 and other general correspondence.
Section 7	Critical documents. GCP certificates, CVs and staff responsibilities, including a summary table, sample drug label, prescription form.
Section 8	Trial documents: Part A. PIS version 2.0 29-Jul-09, PIS version 1.0 20-Jun-09, ICF version 2.0 29-Jul-09, ICF version 1.0 20-Jun-09 and GP letter version 1.0 20-Jun-09. Trial documents: Part B. PIS version 1.0 20-Jun-09, ICF version 2.0 29-Jul-09, ICF version 1.0 20-Jun-09 and GP letter version 1.0 20-Jun-09.
Section 9	Pharmacovigilance section. Annual safety report 2010, SAE form and monitoring correspondence.
Section 10	CRF section. Note locating locked subject files (with CRFs) and sample data forms for parts A&B.
Section 11	Laboratory section. Certificate of calibration of temperature data logger and mounting probe 03-Feb-10, temperature logs, file note explaining lost temperature data from 07-Apr-10 to 22-Jun-10.
Section 12	GCP section. Declaration of Helsinki - Seoul 2008, blank site training log.
Section 13	Pharmacy section. Manufacturer's authorisation, Summary of Product Characteristics (SoPC) for Chirocaine, local procedures for managing IMP, IMP management and accountability information for sponsor (Part A only) version 30-Nov-09, copy of the batch release form, copy of the authorisation of first release of IMP, file note detailing error on clinical trial supplies order form version 1, study site IMP start up report, sample IMP accountability log (one copy for site and one for Pharmacy Production Unit), shipment notice form, certificate of calibration for digital temperature indicating instrument 06-Oct-09.
Section 14	SOP section. Glasgow Clinical Trials Unit (GCTU) safety reporting definitions (AEs, SAEs etc), SOPs for Parts A&B.

In addition to points already raised the following minor discrepancies were discovered:

Section 3: Protocol version 1.0 - cover page dated 20-Jun-09 but other pages were dated 18-Jun-09. Your signature is dated 04/12/10

Section 4: Ethics Committee list of members includes Alexander Binning, a co-investigator on the study. It is not clear if he had any involvement in the decision process or not. This should be clarified and documented.

Section 7: Dr Binning's GCP certificate is dated September 2008. There should be evidence of certification within the 2 years prior to any involvement in the trial.

You have not signed off the delegation of responsibilities log.

The following names appeared on the responsibilities log, however no CVs or GCP certificates were found, and no dates are specified for period of study involvement. Ideally, all personnel named on the log should have CVs and GCP certificates files in the site file. Alternatively, a file note can be created to verify that those staff members are GCP qualified, stating the location of CVs and GCP certificates (e.g. Pharmacy file).

- Marie Pollock
- GK Conkie
- Louise Taylor
- David Donald
- Catherine MacLeod
- Michelle Dunn
- Kathryn MacCormick

IMP sample label contains the subject's name. The use of identifying information should be avoided, however if this is not practical, then a file note should be created and filed explaining that the IMP container is disposed of at site or returned to pharmacy for disposal.

Section 9: Filed copy of the SAE form contains a mixture of pages from versions 3.1 and 3.2.

Section 12: The site training log is blank. This is a very useful tool for demonstrating trial, protocol and GCP training, as well as providing a tracking tool for training needs (e.g. when GCP updates are required).

Section 13: Summary of Product Characteristics (SoPC) for Chirocaine in the site file is a superseded version. R&D pharmacy will provide advice on the current version.

Study logs: The screening log lists 2 patients who did not consent to the study. The log includes the patients' names, hospital numbers and birth dates. This information should be removed/obliterated as no identifying information should be stored for any person who did not give consent.

100% ICF Verification

We checked all consent forms for subjects on this study for completeness and accuracy. Our findings are summarised in the table below:

Appendix 1

Subject Number	Initials	Date of Consent	ICF Version	PIS Version	Person taking consent	Comments
1	WK	01-Feb-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
2	AB	11-Feb-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
3	PM	21-Feb-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
4	AD	22-Feb-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
5	PJ	24-Feb-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
6	RB	01-Mar-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
7	LB	06-Mar-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
8	EH	08-Mar-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
9	RR	11-Mar-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
10	MW	29-Mar-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
11	CB	08-Apr-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
12	RW	19-Apr-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
13	RW	19-Apr-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
14	AS	21-Apr-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	Subject not printed their name - signed in both places
15	EG	23-Apr-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Emily Walker	
16	MM	04-May-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
17	MH	11-May-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	Create a file note to file with the ICF to explain who the POA is and why they have signed the form
18	CM	17-May-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
19	GR	19-May-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	Subject not printed their name - signed in both places
20	DP	07-Jun-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	Subject number amended on the form (overwritten) - should be amended as per GCP guidelines

21	RA	14-Jun-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	Ticked in boxes, not initialled
22	MR	16-Jun-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
23	BM	21-Jun-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	Subject date given as 21 6 1020
24	WC	07-Jul-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	Subject number has been corrected - initialled but not dated
25	JT	08-Jul-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
26	LJ	09-Jul-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
27	WG	13-Jul-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	note underneath date 'requested by patient' - this is unclear to read and also to understand what it means
28	MM	15-Jul-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	Subjects printed name corrected - not signed or dated
29	AM	18-Jul-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
30	MA	02-Aug-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
31	MT	03-Aug-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
32	LM	22-Aug-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
33	RM	29-Aug-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	Date of consent listed as 28 Aug 10 on log. Signed by the subject's son - not on the ICF that subject has broken right wrist. ICF witnessed by subject. Boxes not ticked or initialled - just blank.
34	RR	17-Oct-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
35	JM	18-Oct-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	Hospital label on the poly-pocket that contains the consent form - identifies the patient. Should be removed
36	WW	20-Oct-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	Note above date stating that the subject had asked the CI to complete the date on their behalf
37	NB	06-Nov-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
38	OM	09-Nov-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
39	AM	13-Nov-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	
40	JG	17-Nov-10	V2.0 29 Jul 10	V2.0 29 Jul 09	Malcolm Watson	

***General comment - appears that Investigator is printing the subjects name on the ICF on some occasions - this should be completed only by the subject.** In any instance where the subject requested assistance with completing the consent form, this has to be clearly documented. Ideally, when subjects need assistance with completing the forms, this assistance should be witnessed (with name, date and signature) by other study staff. A general file note should be generated explaining the circumstances in which subjects require help with consent as, technically, this practice constitutes GCP and protocol non-compliance.

You should, where possible, endeavour to correct the errors highlighted in the table above, but we understand this will often not be feasible. A file note listing those errors that are not corrected with reasons (e.g. inconvenience to the subjects), would demonstrate that you have acknowledged the errors and attempted to resolve them.

10% Source Data Verification

We chose 4 subjects at random to perform Source Data Verification (SDV) – subjects 1, 3, 16 and 30. The case notes for these subjects were pulled for us on the day of our visit. However, due to time constraints we were able to complete SDV for subject 1 and partially complete for subject 16.

Subject 1 was admitted as an emergency on 28-Jan-10. We were able to verify that the subject met the inclusion criteria as per protocol. We were unable to verify the exclusions of abnormal clotting or acute mental test less than or equal to 7. All other criteria were verified. The subject was medically assessed, signed the Informed Consent Form on 01-Feb-10 and received surgical treatment as planned on 02-Feb-10. After

admission the patient was started on antibiotics for a lower respiratory tract infection. In our preliminary follow up letter we asked you clarify whether or not this constituted a systemic infection that would have excluded the subject. During a subsequent telephone call you assured us that this exclusion referred to infections that related to the site of injury/surgery. During the subject's hospital stay, as well the respiratory infection mentioned above, the subject suffered seizures. The subject was transferred to another ward on10-Feb-10 and finally discharged on 05-Mar-10.

The study data was captured on an individual data sheet. The data sheets contain identifying information which should be removed/obliterated, leaving the subject number, initials (if applicable) and date of birth only as identification. We were unable to verify SaO2 (oxygen saturation) measurements in the case notes. Measurements recorded in the multidisciplinary care plan corresponded with the data sheet but the care plan itself was not dated. The data sheet was not signed off therefore we could not identify who had entered/reviewed the data.

There was an IMP prescription form but no further documentation of dispensing, receiving at site, administration or disposal. We will arrange a pharmacy visit in the near future to verify the accountability of the IMP.

There was evidence of participation in the study within the case notes and we found the GP letter and a copy of the consent form, however no study label was found on the case notes cover. We were not able to verify the dose of IMP from the case records as there was no evidence of IMP administration. The anaesthetic record was not dated and we could not, from the record, identify the anaesthetist.

Subject 16 was admitted as an emergency on 04-May-10. We were able to verify that the subject met the inclusion criteria as per protocol. We were unable to verify the exclusions of abnormal clotting or acute mental test less than or equal to 7. All other criteria were verified. The subject was medically assessed, signed the Informed Consent Form on 04-May-10 and received surgical treatment as planned on 04-May-10. The subject was discharged on 11-May-10. From the case records the subjects stay in hospital was uncomplicated.

The study data was captured on an individual data sheet. The data sheets contain identifying information which should be removed/obliterated, leaving the subject number, initials (if applicable) and date of birth only as identification.

There was an IMP prescription form but no further documentation of dispensing, receiving at site, administration or disposal. We will arrange a pharmacy visit in the near future to verify the accountability of the IMP.

There was evidence of participation in the study within the case notes and we found the GP letter and a copy of the consent form, however no study label was found on the case notes cover. We were able to verify the administration and dose of the IMP. Case notes differ from the data sheet on the formulation of Chirocaine (0.25% in case notes but 0.025% on the data sheet).

We were unclear as to what happens with the data sheets now the study has ended and how the data will be analysed, and by whom.

Safety Reporting

There have been 2 reported SAEs for this study:

Subject 13 Death as a result of metastatic breast cancer - onset 26-May-10. From the SAE report form the date of the report appears to be 04-May-10, preceding the event. You assessed the event as expected, not related and fatal. The report was complete, signed and concluded.

Subject 27 Pulmonary tuberculosis - onset 12-Jul-10. From the report form you reported the event on 12-Aug-10. You assessed the event as expected, not related and recovered. The serious criteria was hospitalisation. The report was complete, signed and concluded.

On reviewing subject 1, we discovered that the subject suffered complications following surgery. Specifically, the subject suffered seizures post-operatively. The subject subsequently remained in hospital for a total of 5 weeks. As hospitalisation was prolonged, this should be reported as an SAE, detailing the event(s) that led to the prolonged stay, treatment and outcome.

The SAE form in your site file is mixture of pages from 2 separate versions. This should be replaced with version 3.2 in its entirety.

Preparation for Part B

The site file has been prepared for the follow up part of the study. You will be spinning blood samples at site and the centrifuge is in place, however you have yet to receive additional equipment for use with the centrifuge. You have refrigerated storage and temperature calibration in place also. You expect to recruit approximately 16 patients within good time.

We will circulate this letter also to Maureen Travers, Trial Coordinator and, in this case, Dr Robert Hunter for Governance overview.

Thanks again for your assistance and cooperation, and for giving us some further insight onto your study. Please contact us if you have any queries or comments regarding this letter.

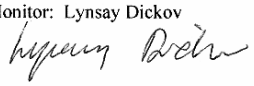
Kind regards,

Michael McLaughlin
Clinical Trials Monitor
NHS Greater Glasgow and Clyde
Research and Development Department

Lynsay Dickov
Clinical Trials Monitor
NHS Greater Glasgow and Clyde
Research and Development Department

ACTIONS	For resolution and by whom
Investigator Site File	
File all current (latest) documents in the site file. Superseded versions can be filed separately as long as there is a file note within the site file stating their location.	CI
Provide a copy of email form R&D Pharmacy with authorisation.	Monitors
File R&D Pharmacy authorisation e mail in site file.	CI
Section 3: protocol version 1.0 is signed, but signature is dated 04-12-10. Correct with note explaining error and initial and date correction in real time.	CI
Section 4: add file-note clarifying A. Binnings role on the Ethics Committee list of members.	CI/PI
Section 7: obtain and file an updated GCP certificate for A. Binning. sign off the responsibilities log. create file note explaining use and disposal of IMP containers labelled with subject's names.	CI/PI CI CI
Section 9: replace currently filed SAE form pages with entire version 3.2.	CI
Section 13: R&D Pharmacy can advise on correct version of SoPC. Correct version should replace currently filed version if applicable.	CI/Pharmacy
Study logs: Identifying information for subjects who have not consented for the study should be obliterated.	CI
Informed Consent Forms File note 1: for subjects 14, 19, 20, 21, 23, 24, 28, and 33. If errors can be corrected in accordance with GCP, this should be effected. If errors are subject errors and it is not feasible to correct them, a file note listing those errors and explaining why they cannot be corrected should be filed in the relevant section of the site file.	CI
File note 2: for subjects 17, 27, 33 and 36. Where subjects required assistance to complete the consent form, a file note should be created explaining the reasons why assistance was needed, and who provided this help. This note should be filed in the relevant section of the site file.	CI
Subject 35: remove or obliterate subject identifiers.	CI

Source Data Verification Subject 1: Remove identifiers from data sheet (number, initials and date of birth only). Please verify that subject met the exclusion criteria relating to abnormal clotting and acute mental status. Subject admitted with respiratory tract infection. Please confirm that this did not meet the exclusion of systemic infection. The subject experienced seizures post-operatively and remained in hospital for 5 weeks. Please consider whether or not this constituted an event that led to delayed discharge. If so, this should be reported as an SAE as soon as possible. If not, please record in case records why this does not meet the SAE reporting criteria. Anaesthetic record for SDV purposes was not dated and the anaesthetist could not be identified. Please ensure the case records providing source data are clearly dated and signed off by appropriate personnel. Subject 16: Remove identifiers from data sheet (number, initials and date of birth only). Please verify that subject met the exclusion criteria relating to abnormal clotting and acute mental status. Please verify the correct concentration of Chirocaine used and correct either the case notes or the data sheet as appropriate.	CI CI CI CI CI CI CI CI
Data Management Please advise how the data sheets are reconciled, the data analysed and by whom.	CI
Safety Subject 1: SAE as above File full copy of version 3.2 SAE form as above.	
Recommendations	
Consider using the Site Training log for documenting the study/protocol and GCP training of all staff involved in the study. This can give you good oversight of training status and when updates are due.	
If it is anticipated that some subjects are likely to have difficulties with providing written consent, consider in future including alternative processes in the protocol; e.g. relatives giving assent. For now, if there is a need to assist with written consent, consider having someone witness this.	
Consider in future using study labels for case note covers to alert others that the patient is on a clinical trial.	

SIGNATURES
Date: 13 Jan 10
Name of Monitor: Michael McLaughlin
Signature:
Date: 13 Jan 10
Name of Monitor: Lynsay Dickov
Signature: 

Encl: Pharmacy authorisation email

CC Dr R Hunter Associate R&D Director
Maureen Travers Trial Coordinator

Appendix 2: Statistical justification of sample size and interim analysis

Dixon's up/down methodology explained

The Up-Down study design requires the specification of an initial dose ($x_{0)}$, and the difference between successive doses (δ). The first experiment takes place at dose x_0: if it is a success, the second experiment takes place at dose x_0-δ; if it is a failure the second experiment takes place at x_0+δ. The dose for each successive patient is therefore determined by the success or failure of the previous patient and as a result the dose will tend to move towards a value where 50% of patients are successful and 50% fail and oscillate around that value.

Estimation of sample size (Dixon)

It is assumed that for a given log (dose), x, the probability, P(x), that the dose will be effective is

$$P(x) = \Phi\left(\frac{x-\mu}{\sigma}\right)$$

where Φ is the cumulative density function of a standard Normal distribution. μ is the concentration at which 50% of the population would achieve pain relief, or EC_{50}, since $P(\mu) = \Phi(0) = ½$.

If the numbers of successes is less than the number of failures, then $\hat{\mu} = \bar{y}_1 - \delta/2$, where $\bar{y}_1$ is the mean concentration over the successful experiments; otherwise $\hat{\mu} = \bar{y}_0 + \delta/2$, with $\bar{y}_0$ being the mean concentration over experiments that were failures.

The standard error of $\hat{\mu}$ is estimated by

$$\mathrm{SE}(\hat{\mu}) = G\sigma / \sqrt{n_k}$$

with σ estimated by

$$\hat{\sigma} = 1.620\delta\left(\frac{s_k^2}{\delta^2} + 0.029\right)$$

and k = 1 or 0 depending on whether $\hat{\mu}$ was estimated from the successful or unsuccessful experiments, s_k^2 is the sample variance of the concentration levels and n_k is the number of experiments used in the estimation of $\hat{\mu}$. The constant G is an approximately linear function of δ/σ: for $\delta=\sigma$, $G\approx1$; for $\delta=2\sigma$, $G\approx1.2$. Since n_k is approximately ½N, where N is the total number of experiments conducted, the required sample size for a study can be calculated depending upon the desired width of the confidence interval for μ, relative to σ. Since the 95% CI for μ will be approximately $\hat{\mu} \pm 2\mathrm{SE}$, the required sample size will be $N = 8\Delta^2$, if $\delta\approx\sigma$, where $\pm\Delta$ is the width of the 95% CI required for μ in units of σ, i.e. the 95% CI for μ is $\hat{\mu} \pm \Delta\sigma$. Thus for a 95% CI of ½$\sigma$ each way, the required sample size will be about 32.

Appendix 2

Estimation of percentiles other than the 50th, e.g. the concentration at which 95% of patients would achieve pain relief, or EC_{95}, is given by

$$\mu + z_{0.95}\sigma$$

where $z_{0.95}$=1.645 is the 95th percentile point of a standard Normal distribution. The standard error of this estimate is

$$\sqrt{SE(\mu)^2 + z_{0.95}^2 SE(\sigma)^2}$$

where $SE(\sigma) = H\sigma / \sqrt{n_k}$, with H following an approximately quadratic function of $\delta\sigma$, taking its smallest values over the range $\sigma<\delta<2\sigma$, where H≈1.3-1.4.

Comments

The estimation method as described by Dixon is straightforward in the sense that it provides an estimate of μ based on a mean concentration, and leads to a simple sample size calculation. However, many of the steps taken to reach parameter estimates and their standard errors are not transparent, and the estimates of standard errors involve multiplication by factors (G and H) that are not well defined. Furthermore, the standard error estimate for quartiles other than the EC_{50} does not take account of the correlation between estimates for μ and σ.

Justification of interim analysis

Number of patients needed

An interim analysis will be performed at 16 patients to ensure that δ (the incremental change in the concentration i.e. 0.025) is approximately ½ σ (the standard error of the mean for the EC50) and δ will be altered if necessary to increase the accuracy of the estimate obtained for the EC_{50} concentration and hence the estimate of EC_{95}.

The number of patient needed is affected by two variables:

1- A suitable starting value for x_0

2- A value for the concentration change between experiments (δ) which should ideally be in the region of σ-1.5σ.

Recommendations

The formula $N = 4\Delta^2$ should be used as an initial estimate of the required sample size for a study.

The appropriateness of the value used for δ should be modified throughout the study based on the accrued evidence, and modified if necessary.

Appendix 3: Interim probit logistic regression analysis after 16 patients had been recruited

FRACTURE NECK OF FEMUR UP-DOWN DOSE FINDING STUDY

Interim Analysis

Alex McConnachie, 11th May 2010

Objective

The aim of the interim analysis was to estimate the parameter σ from the probit model for the dose-response relationship, given by

$$P(x) = \Phi\left(\frac{x-\mu}{\sigma}\right)$$

where x is the concentration administered, and P(x) is the probability of success. The optimal stepping value for varying the concentration for successive patients is in the region of σ. Initially, σ was set at 0.025; this will be revised based on the results of this analysis.

Data

The data from the first 16 patients are shown below.

Patient number	Concentration	successful-1, unsuccessful-0
1	0.1	1
2	0.075	1
3	0.05	1
4	0.025	equivocal
5	0.025	0
6	0.05	1
7	0.025	1
8	0.025	0
9	0.05	1
10	0.025	0
11	0.05	1
12	0.025	1
13	0.025	0
14	0.05	1
15	0.025	1
16	0.025	1

For the analysis, the outcome for patient 4 was defined as unsuccessful. The probit regression model is fitted as a generalised linear model:

$$P(x) = \pi$$
$$\Phi^{-1}(\pi) = \beta_0 + \beta_1 x$$

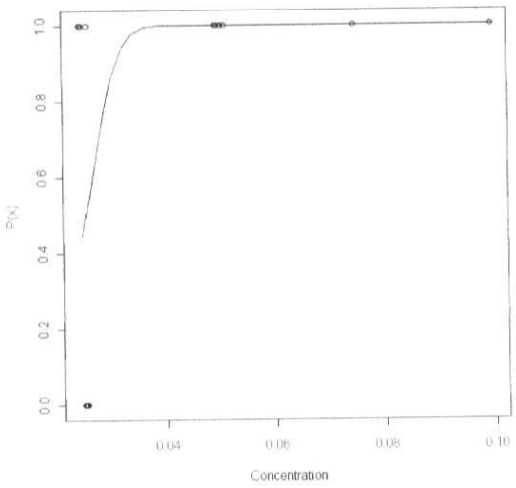
from which σ and μ can be calculated by $\sigma = 1/\beta_1$ and $\mu = -\beta_0/\beta_1$.

Results

Fitting the probit regression model gave the following parameter estimates:

	Estimate	SE	z	p-value
β_0	-5.982	615.746	-0.010	0.992
β_1	233.706	24629.804	0.009	0.992

The model fit was apparently unstable, with large standard errors and a correlation between the estimates of β_0 and β_1 of virtually 1, due to all tests at concentrations of 0.05 or above being successful:



However, repeating the analysis with concentrations of 0.1 and 0.075 removed gave similar results. Whilst all patients administered a concentration of 0.05 were successful, these cannot also be removed as only those patients with concentrations of 0.025 would remain, and the model would be inestimable.

From these results, the estimate of σ was 0.00428, and for μ was 0.0256.

Conclusion

The study should continue with a concentration step size of 0.005. Currently, it is estimated that the EC_{50} will be in the region 0.025. For the final analysis, the sensitivity of the results to the exclusion of patients given concentrations of 0.1 and 0.075, and possibly 0.05, should be considered.

Appendix 4: List of Amendments to the Protocol for the clinical trial

Table 1: Summary of Substantive amendments

	Area of study and part of study affected	Summary of amendment
1	Storage of IMP	Extend shelf life of IMP(levobupivacaine) from 7 days to 28 days
2	Insertion of catheter	Insertion of catheter and bolus dose of levobupivacaine to provide analgesia (pain NRS<30/100) for 12 hours and confirm correct positioning of initial dose of IMP
3	Inclusion/Exclusion criteria	Inclusion of patients with proximal femoral fractures treated non operatively and patients with peri-prosthetic proximal femoral factures
4	Minimum concentration of IMP	Reduce the minimum concentration of the IMP(levobupivacaine) from 0.025% to 0.005%
5	Data collection sheet(CRF)	Improved layout to record data
6	End point of study	A reduction in sensory stimuli to pin prick of <50/100 in two or more regions out of three (medial, anterior and lateral of upper thigh) with an associated reduction in cold sensation (to melting ice) in the same region will be the minimum sensory change associated with successful analgesia (=>20/100 point drop in pain NRS scores)

Amendment 1 -Storage of IMP

Justification of amendment

Storage and of IMP-

Further information regarding the shelf life and temperature stability was made available to the research team after the initial ethics submission in October 2009.

See attached paper:

'Stability of sufentanil and levobupivacaine solutions and a mixture in a 0.9% sodium chloride infusion stored in polypropylene syringes.'[1]

Please see summary of information in paper

'the levobupivacaine hydrochloride solution maintained chemical stability for 28 days at 4°C and 21°C, 8°C and for 23 days at 36 °C .'

We will store the drug at 4-8 (°C) degrees Celsius in a temperature monitored environment (the temperature is recorded every 5 minutes using a Testo® 175-T2 temperature data logger, with 2 channels with internal and external sensor; ISO calibrated to 2 °C degrees and 8°C) for up to 28 days. Due to the temperature stability of this drug we will not report temperature deviations of less than 2 degrees for less than ten temperature recordings at 5 minute intervals. This will not affect the stability of the IMP (levobupivacaine) and is safe practice in terms of bacteriological considerations please see attached letter from Graham Conkie from the Pharmacy Production Unit at the Western Infirmary Glasgow dated the 22nd of May 2008.

Supporting documentation

Stability of sufentanil and levobupivacaine solutions and a mixture in a 0.9% sodium chloride infusion stored in polypropylene syringes.
Jappinen A. Turpeinen M. Kokki H. Rasi A. Ojanen T. Pelkonen O. Naaranlahti T.
European Journal of Pharmaceutical Sciences. 19(1):31-6, 2003 May.
[Journal Article]
UI: 12729859

See letter dated 22/05/2008 from Graham P Conkie qualified person of the Pharmacy Production Unit.

Amendment 2 – Insertion of catheter and bolus dose of levobupivacaine to provide analgesia

Justification of amendment

The patients recruited to this clinical trial are in moderate to severe pain and despite the analgesia provided by the IMP (levobupivacaine) they will require further analgesia. The insertion of a catheter at the end of the injection of the bolus dose of IMP will allow multiple doses of local anaesthetic to be given to provide analgesia using standard protocols for up to 3 days. This amendment also increase the scientific value of the trial as a failure of the local anaesthetic injected using the catheter to provide analgesia would indicate that the bolus dose of the IMP is likely to have been incorrectly sited. This will allow exclusion of these patients' results from the final analysis and increase the accuracy of the primary end point.

Amendment 3 – Inclusion of non operatively managed patients and patients with peri-prosthetic fractures

Justification of amendment

The inclusion criteria have been broadened to include those patients with proximal femoral fractures managed non-operatively and patients with a previous hip joint replacement with a fracture of the femur (peri-prosthetic fractures). Femoral nerve blocks provide effective analgesia for both these groups of patients and both these groups of patients could benefit from the regional analgesia provided by the study.

Amendment 4 - Minimum concentration of IMP

Justification of amendment

After recruiting 16 patients to the study an interim analysis was performed as stated in the protocol version 1. The results of that analysis are stated in the attached letter from Dr Alex McConnachie (senior consultant statistician at the Robertson centre Glasgow university) dated 11/05/2010.

In summary

The calculated effective concentration in 50% was(EC50) of patients(estimated μ= 0.0256) is probably close to the original minimum concentration set in the protocol version 1 (0.025%) so in order to determine the distribution of concentrations around the EC50 Dr Alex McConnachie (senior consultant statistician at the Robertson Centre Glasgow university) suggested decreasing the interval between IMP concentrations to 0.005% (which has been done as allowed in the original protocol) and decreasing the minimum concentration to 0.005%. The maximum concentration has been set to 0.1% to reduce the dosage that can be given by following the protocol as the protocol now allows for a bolus of 0.25 % levobupivacaine via the catheter if the original concentration of IMP (levobupivacaine) does not reduce the pain NRS score to < 30/100 at 30 minutes after the injection.

Supporting documentation

A Letter from Alex McConnachie (senior consultant statistician at the Robertson centre Glasgow University) dated 11th of May 2010, Title 'Fracture neck of femur up down dosing finding study interim analysis'

A letter dated (11th May 2010) from Dr Alex McConnachie (senior consultant statistician at the Robertson centre Glasgow University) is attached.

A further letter dated (16th July 2010) from Dr Alex McConnachie (senior consultant statistician at the Robertson centre Glasgow university) is attached.

Amendment 5 - Data collection sheet (clinical research form, CRF)

Justification of amendment

In order to facilitate accurate data recording minor changes should be incorporated in the Data collection sheets for part A and B of the study (CRF Part A and B). In addition in part A the response to an additional dose via a catheter sited after injection of the IMP dose (see amendment 2) would provide evidence of correct placement of the IMP dose if an analgesic response was seen(pain NRS score <30/100 at 30minutes after bolus dose).

Specific changes to data collection form (CRF):

- Record if the visual analogue pain score of < 30/100 is achieved by administration of 20ml of 0.25% levobupivacaine 30minutes after the administration of IMP dose of levobupivacaine.

- Record the division of the sensory changes to pin prick sensation into the medial, anterior and lateral regions of the upper thigh and the

response to cold stimuli in the same area (medial, anterior and lateral segments of the upper thigh).
- Increase in the area for recording the cardiovascular and respiratory observations.

Amendment 6 - End point of study

Justification of amendment
I have been unable to replicate the 30% drop in sensory score (using a blunted 25G needle compared to the contra lateral side) following a successful (> or =2 point drop in the visual analogue pain scores femoral nerve block) reported by Manhofer et al[1]. Manhofer et al have never provided any clinical or statistical justification for the choice of 30% as the determinant of a femoral nerve block associated with analgesia but it did appear to be a consistent result from in the study in published in 1997.

I have recorded that a significant analgesic effect is consistently associated with a less profound sensory change than originally reported by Manhofer et al[1] in a similar study population. The result of the first 31 patients recruited to the current clinical trial show that the analgesic effect (>=20 point reduction in pain NRS) has been associated with a change to cold sensation (melting ice). The association of analgesia and altered sensation to melting ice has been recorded consistently in the previous 31 patients. There is currently no need to change the protocol as the analgesic effect has been consistently associated with a sensory change (to melting ice) and inconsistencies between the sensory(tested by both cold and pin prick sensation) and analgesic response have been treated by repeating the concentration.

I therefore propose to model the sensory scores (using a blunted 25G needle compared to the contra lateral side) using the analgesic(pain NRS) and sensory responses to melting ice to determine if they add predictive value and at what pattern of sensory score response to pin prick is associated with analgesic outcome. This will allow a more detailed analysis of my other study (see below).

Short title: Can nerve block for hip surgery be improved by ultrasound guidance?

Ethics reference number 08/S0703/122

The current offices are beginning renovated for use by the Research and development department and the ultrasound research office and laboratory has been moved to F-block, Lower Ground Floor, Western Infirmary General, 38 Church Street, Glasgow, G11 6NT

Appendix 5: Actual conc^{n} of Levobupivacaine 0.75%

Date Prepared/manufact	WIG B.N.	Abbott B.N.	Conc. from C of A
Batch 1 of levobupivacaine 0.75%			
	011826	**124756W02**	**99.6% = 7.47mg/mL**
1-10/11/10	011816	124756W02	
2-08/11/10	011811	124756W02	
3-21/10/10	010829	124756W02	
4-19/10/10	010825	124756W02	
5-18/10/10	010823	124756W02	
Batch 2 of levobupivacaine 0.75%			
	010821	**119612W01**	**101.4% = 7.605mg/mL**
6-25/08/10	008853	119612W01	
7-17/08/10	008834	119612W01	
8-05/08/10	008813	119612W01	
9-03/08/10	008806	119612W01	
10-29/07/10	007866	119612W01	
11-20/07/10	007845	119612W01	
12-16/07/10	007841	119612W01	
Batch 3 of levobupivacaine 0.75%			
	007834	**119612W03**	**100.5% = 7.537mg/mL**
13-08/07/10	007821	119612W03	
14-09/07/10	007824	119612W03	
15-13/07/10	007831	119612W03	
16-01/07/10	007803	119612W03	
17-22/06/10	006856	119612W03	
18-17/06/10	006845	119612W03	
19-16/06/10	006840	119612W03	
20-09/06/10	006820	119612W03	
21-31/05/10	005880	119612W03	
22-18/05/10	005842	119612W03	
23-12/05/10	005829	119612W03	
24-07/05/10	005814	119612W03	
25-30/04/10	004876	119612W03	
26-23/04/10	004861	119612W03	
27-22/04/10	004854	119612W03	
28-21/04/10	004848	119612W03	
29-19/04/10	004837	119612W03	
Batch 4 of levobupivacaine 0.75%			
	004833	**107885W01**	**101.2% = 7.59mg/mL**
30-09/04/10	004816	107885W01	
31-07/04/10	004807	107885W01	
32-31/03/10	003883	107885W01	
33-29/03/10	003873	107885W01	

34-12/03/10	003832	107885W01
35-09/03/10	003825	107885W01
36-08/03/10	003821	107885W01
37-02/03/10	003803	107885W01
38-25/02/10	002953	107885W01

Batch 5 of levobupivacaine 0.75%

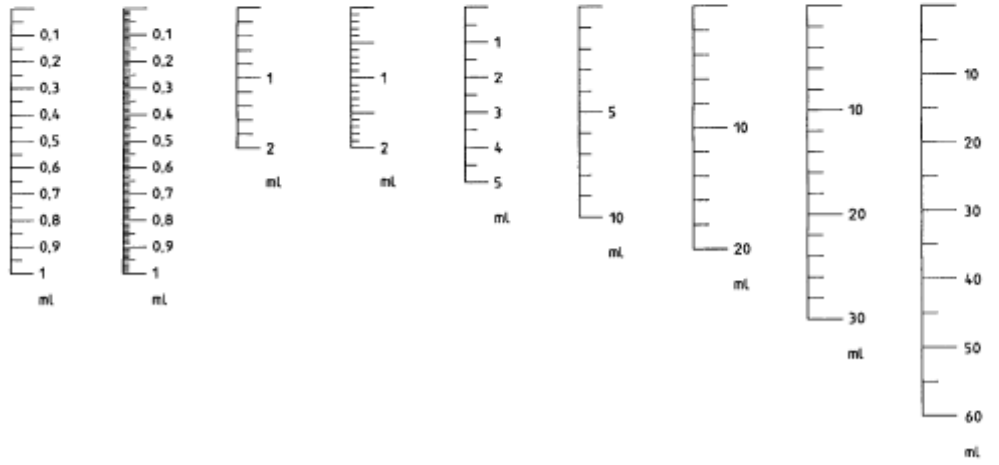
002947 **106734W02** **99.8% = 7.485mg/mL**

39-22/02/10	002940	106734W02
40-16/02/10	002921	106734W02
41-09/02/10	002896	106734W02
42-02/02/10	002876	106734W02
43-26/01/10	001857	106734W02

Appendix 6: Tolerances for syringes used to prepare levobupivacaine from BD Ltd.

Table 1 — Capacity tolerance, dead space, scale dimensions and test forces

Nominal capacity of syringe, V	Tolerance on any graduated capacity		Maximum dead space	Minimum overall length of scale to nominal capacity mark	Scale interval	Increment between graduation lines to be numbered	Force for leaking testing (see Annex D)	
	Less than half nominal capacity	Equal to or greater than half nominal capacity					Side force (≙ 5 %)	Axial pressure (gauge) (≙ 5 %)
ml			ml	mm	ml	ml	N	KPa
$V < 2$	≙ (1,5 % of V + 2 % of expelled volume)	≙ 5 % of expelled volume	0,07	57	0,05	0,1	0,25	300
$2 \leqslant V < 5$	≙ (1,5 % of V + 2 % of expelled volume)	≙ 5 % of expelled volume	0,07	27	0,2	0,5 or 1	1,0	300
$5 \leqslant V < 10$	≙ (1,5 % of V + 1 % of expelled volume)	≙ 4 % of expelled volume	0,075	36	0,5	1	2,0	300
$10 \leqslant V < 20$	≙ (1,5 % of V + 1 % of expelled volume)	≙ 4 % expelled volume	0,10	44	1,0	5	3,0	300
$20 \leqslant V < 30$	≙ (1,5 % of V + 1% of expelled volume)	≙ 4 % of expelled volume	0,15	52	2,0	10	3,0	200
$30 \leqslant V < 50$	≙ (1,5 % of V + 1 % of expelled volume)	≙ 4 % of expelled volume	0,17	67	2,0	10	3,0	200
$50 \leqslant V$	≙ (1,5 % of V + 1 % of expelled volume)	≙ 4 % of expelled volume	0,20	75	5,0	10	3,0	200



NOTE The vertical line of the scale may be omitted.
Not to scale.

Figure 2 — Examples of scale graduations

Appendix 7: Calibration of analysis for levobupivacaine by ABS laboratories

Advanced Bioanalytical Service Laboratories
BioPark
Broadwater Road
Welwyn Garden City
Hertfordshire, AL7 3AX
Telephone:+44(0)1707 358666 Fax:+44(0)1707 358667
Email: abslabs@biopark.org.uk

Analytical Report for ABS Laboratories Ref. ABS/39/11

Client:	**Dr Malcolm Watson** ***Department of Anaesthesia*** ***30 Shelley Court*** ***Gartnavel Hospital*** ***Glasgow*** ***G12 0YN***	Date of Sample Receipt:	10-May-2011
		Date of Analysis:	19 to 20-May 2011
		Date of Report:	14-Jul-2011
Contact:	Dr Malcolm Watson		
Project Name:	Analysis of human plasma samples to quantify the presence of levobupivacaine		
Client Project Number:	Not known		
ABS Project Number:	ABS/39/11		

Client Sample Identity and Method Summary	ABS Sample Number

Samples were generated from a Clinical study conducted by Dr Malcolm Watson. The client supplied these samples directly to ABS Laboratories in a frozen condition. These samples were stored below -15°C prior to analysis. The samples were analysed using a method set up and validated to the FDA guidelines for the validation of Bioanalytical methods by ABS Laboratories' personnel, Method SOP 5-77.2. This method describes the determination and quantification of bupivacaine using mepivacaine to internally standardise the procedure. The analytes are precipitated from the plasma proteins using acetonitrile, reduced to dryness under nitrogen, and reconstituted in 0.05% formic acid for quantitative determination using liquid chromatography tandem mass spectrometry (LC-MS/MS) with multiple reactions monitoring (MRM). The samples were analysed in two batches with duplicate calibration standards containing levobupivacaine in control human plasma at 0 (blank), 1.0, 2.0, 5.0, 10.0, 25.0, 50, 100, 250 and 500 ng/m and duplicate quality control samples (QCs) at 3, 75 and 300 ng/mL (These were prepared in bulk and stored frozen at approximately -20°C until required.) Stability of levobupivacaine has been demonstrated at -20ºC for 3 months in K^{3+} EDTA human plasma, and for 24 months in lithium heparin human plasma. Samples were analysed by LC-MS/MS on system API4000D using the following MRM transitions, levobupivacaine m/z 289.2 > 140.2 and mepivacaine m/z 247.2 > 98.2.	1 to 82

Results

Quantification was performed by analyzing the calibration standards in duplicate with one series being analyzed at the beginning of a batch and one series being analyzed at the end of a batch. At least 75% of the calibration standards should have back-calculated values <± 15% of their nominal concentration except at the lower limit of quantification (LLOQ) where it should be <± 20%. The LLOQ and upper limit of quantification (ULOQ) must be present from at least one series of the calibration standards. The correlation coefficient (r) should be >0.98 for each calibration curve. The actual back calculated calibration standards in this study are shown in Table 8. In addition the accuracy (% bias) of the method should be <± 15% for 2/3rds of the spiked control sample concentrations. The actual back calculated concentrations of the QCs analyzed in this study are shown in Table 8.
Example MRM chromatograms from 1 and 500 ng/mL calibration standards and a test sample ABS No. 50 are shown in Tables 8 and 9 respectively.

Table 2: Results of the calibration standards from ABS/39/11

Run ID	Bupivacaine (ng/mL)							
	1.000	2.000	5.000	10.000	25.000	50.000	100.000	250.000
20110519AB2.rdb	1.020	2.058	4.976	10.224	25.002	52.580	100.759	247.974
	0.954	2.022	5.057	9.966	25.369	52.266	101.610	243.583
20110520AB2.rdb	1.090	1.890	5.017	10.049	26.192	51.969	103.812	266.676
	0.940	1.975	5.154	9.631	23.728	48.481	102.249	236.629
Mean	1.00	1.99	5.05	9.97	25.07	51.32	102.11	248.72
SD	0.07	0.07	0.08	0.25	1.03	1.91	1.29	12.85
CV%	6.88	3.66	1.51	2.50	4.09	3.72	1.26	5.17
%Bias	0.10	-0.69	1.02	-0.33	0.29	2.65	2.11	-0.51

Table 3: Results of the quality control samples from ABS/39/11

Date	Run ID	Bupivacaine (ng/mL)		
		3.000	75.000	300.000
20110519	20110519AB2.rdb	3.083	76.156	312.136
		2.938	77.930	306.403
20110520	20110520AB2.rdb	3.138	76.308	317.781
		3.136	79.858	323.840
Mean		3.07	77.56	315.04
SD		0.09	1.73	7.48
CV%		3.06	2.23	2.38
% Bias		2.46	3.42	5.01

Comments: There are no additional comments for this study

Analyst **Date**

: A. E. Bryant **14-Jul-2011**

Reviewed by Laboratory & QA Date

Appendix 7

Manager

M. V. Doig **14-Jul-2011**

Appendix 8: Concentrations of 0.75% levobupivacaine batch used to prepare EC_{95} levobupivacaine batches

Date Prepared	WIG B.N.	Abbott B.N.	Conc. from C of A
1st Dec 2010	all Batches	128787W01	101.4% = 7.605mg/mL

Appendix 9: Research audit report

The study was selected for audit from the R&D database in line with NHS Greater Glasgow & Clyde Research & Development quality assurance process.

A site file audit was conducted to reconstruct the study and to measure compliance with the study protocol and the principles of good clinical practice in line with the Research Governance Framework for Health and Community Care (2006).

Table 1 summarises the overall total of audit observations audit findings and category rating.

See definitions of categories.

Table 1

Results	
Number of observations	**4**
Number of findings	**10**
Overall category	**1**

Definitions

Finding: Requires action/response by auditee

Observation: Requires no action by auditee but may require a response

Category 1: Minor issues detected

Minor issues of non-compliance of an administrative or technical nature are detected that do not compromise patient safety or the integrity of the data.

Category 2: Major issues detected

Major issues are detected that could affect the conduct of the study but do not constitute a serious breach of GCP or the protocol.

Category 3: Serious issues detected

Serious issues are detected that may impact on patient safety and/or the integrity of the data. This may include potential serious breaches of GCP or the protocol.

Category 4: Critical issues detected

Critical issues are detected that have a significant and/or immediate impact on patient safety or the integrity of the data. This may include potential serious breaches of GCP or the protocol.

Findings/Observations/Corrective Actions

1.

Area of non compliance	**Site file documentation**

Finding(s)	Corrective action(s)/response
No 1: Study correspondence starts 25th March 2009	Ensure all relevant study correspondence is filed in appropriate sections in site file from start of study
No 2 Grant application and grant award letter not in file	Source grant application and award letter and file
Observation(s)	
No 1 IRAS form unsigned and not dated	Ensure all forms are signed and dated as appropriate for subsequent studies
Corrective action/response by:	**Date:**
Corrective action/response accepted:	**Date:**

2.

Area of non compliance	Ethics
Finding(s)	**Corrective action(s)/response**
No 1: Annual progress report not in file	Annual progress report requires to be submitted to ethics and copy filed
No 2: Letter from west ethics committee (2nd Sept) giving provisional opinion not in file	Source letter and file in site file
Corrective action/response by:	**Date:**
Corrective action/response accepted:	**Date:**

3.

Area of non compliance	Critical documents
Finding(s)	**Corrective action(s)/response**
No 1: Original delegation log not in file	Source original delegation log and file. Complete file note if original delegation log cannot be sourced. File note template attached with report.
Observation(s)	
No 1: Cv's in file not all signed and dated	For subsequent studies, ensure all CVs are signed and dated – Robert Zimmer, J Dolan and M Watson are unsigned, M Watson is undated.
Corrective action/response by:	**Date:**
Corrective action/response accepted:	**Date:**

4.

Area of non compliance	Study documentation
Observation(s)	**Corrective action(s)/response**

No 1: Data collection form 1 v5 has fields for name, date of birth and hospital number for the study participant. Data collection form 2 does not have patient identifiable data fields but does not have any fields for CI to sign off and date completed form or who completed the data collection **No 2:**Enrolment log has field for hospital number	For subsequent studies, data collection forms should be reviewed with the R&D coordinator and /or appropriate member of the Research Governance team. Only the patient identification log should have fields for patient identifiable data For this study and at this stage, documentation with identifiable data should remain on NHS premises and only be amended and pseudo anonymised if leaving NHS premises
Corrective action/response by:	**Date:**
Corrective action/response accepted:	**Date:**

5.

Area of non compliance	**Consent**
Finding(s)	**Corrective action(s)/response**
No 1: Not all individuals taking consent are on the IRAS application or responsibilities log	Participant no 83 consented by Emily Walker. Confirm status in study.
No 2: Participant no 51 has illegible date which does not appear to be dated same day as consent by Malcolm Watson	Clarify date of consent. Participant not returning to clinic. Complete file note to explain and file with consent form.
No 3: Incorrect year date by study participant no 60	Participant not returning to clinic. Complete file note to explain and file with consent form.
No 4: Incorrect date by study participant no 71Clarify who has signed and dated amendment. Signature unclear	Complete file note to explain and file with consent form
Corrective action/response by:	**Date:**
Corrective action/response accepted:	**Date:**

6.

Area of non compliance	**SOP**
Finding(s)	**Corrective action(s)/response**
No 1: Study specific clinical SOP prepared by Karen Allen has not been reviewed, approved, numbered or dated	Uncontrolled document. Refer to author. Not recommended to be followed until control procedures in place.
Corrective action/response by:	**Date:**
Corrective action/response accepted:	**Date:**

Once all corrective actions/preventative actions have been addressed, the auditor or audit administrator should be informed by a member of the study team either by email, post or return of report.

Please advise the audit administrator if you prefer to track your actions using the report so it can be resent in word format.

Thank you

Internal Audit Proforma

Research Governance Study

This report is confidential and may not be communicated to any third party without permission from NHS GG&C

Sponsor	NHS Greater Glasgow & Clyde
R&D ref	WN08AN198
Type and purpose of audit	Scheduled site file audit of non CTIMP
Title of study	Can the use of ultrasound to guide the insertion of a needle for an anterior psoas compartment nerve block increase its efficacy in comparison to traditional techniques utilising loss of resistance and nerve stimulation?
R&D Coordinator	Dr Erica Packard Erica. Packard@ggc.scot.nhs.uk 0141 211 6208
Chief Investigator/Auditee	Dr M Watson
Audit number	10/PISV6
Date of audit	24 08 10
Auditor(s)	Ms Eileen McCafferty
Main personnel involved	Dr M Watson Ms Eileen McCafferty
Date of initial report	26 08 10
Date of report sent for factual accuracy	
Date returned with factual accuracy information	
Report reviewed by R&D Senior Manager	
Date final version sent to auditee and R&D Coordinator	
Date/version returned with Corrective Actions/Preventative Actions addressed	
Distribution	Dr Caroline Watson Dr M Watson Dr Erica Packard
Date audit closed	
Audit closed by	

The final report should be filed in the appropriate section of the site file

Summary

Internal Audit Proforma

Research Governance Study

This report is confidential and may not be communicated to any third party without permission from NHS GG&C

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Auditor(s)	Ms Eileen McCafferty
Main personnel involved	Dr M Watson Ms Eileen McCafferty
Date of initial report	26 08 10
Date of report sent for factual accuracy	
Date returned with factual accuracy information	
Report reviewed by R&D Senior Manager	
Date final version sent to auditee and R&D Coordinator	
Date/version returned with Corrective Actions/Preventative Actions addressed	
Distribution	Dr Caroline Watson Dr M Watson Dr Erica Packard
Date audit closed	
Audit closed by	

The final report should be filed in the appropriate section of the site file

Summary

Appendix 10: List of operators and assessors for clinical study

List of operators (sitting femoral 3-in-1 nerve blocks)

1. Dr Malcolm Watson
2. Dr Robert Zimmer
3. Dr John Luck
4. Dr Neil Storey
5. Dr Emily Walker
6. Dr Simone Rowell
7. Dr Judith Ramsey
8. Dr John Dolan
9. Dr Kenneth O'Conner
10. Dr Sarah Ramsey
11. Dr Jane Duffty
12. Dr Judith Todd
13. Dr Marcin Ciechomski
14. Dr Graeme Hilditch
15. Dr Julia Roberston
16. Dr Carole Gray
17. Dr Colin Rae

List of assessors of motor and sensory function

1. Dr Malcolm Watson
2. Dr Alison Wood
3. Kate Lochran
4. Karen Allen

Appendix 11: Blood pressure cuff quality assurance reports

DCPB - WG GGH — **Job No. : 1245881**

Caller:	malcom watson	**Job started:**	03/08/2011
Call date:		**Technician:**	DAVID GAFFNEY
Taken by:	DAVID GAFFNEY	**Job Status:**	Finished

Details: MALCOM WATSON REQUESTS P.P.M.
Notes:

Equipment No.: 15780a

Serial No.:	5080900843	**Category:**	SPHYGMOMANOMETER
Status:	Active	**Model:**	UM-101
Guarantee:	28/07/2009	**Manufr.:**	A&D INSTRUMENTS
Installed:	28/07/2009	**Agent:**	PROACT MEDICAL
Contract:		**Location:**	, GARTNAVEL GENERAL HOSPITAL
Accessories:			

Diagnosis / Action / Comments
P.P.M. PERFORMED AS PER TCP 23. UNIT CHECKED AT UPER AND LOWER AND MEDIUM LIMITS
NO RESULT DEVIATED BY +/_ 1 MM HG

External Services / Parts

Order Nos.:			
Order Date:	**Service Rpt.No.:**	**Labour cost:**	£0.00
Delivered:	**Contract job::** No	**Travel cost:**	£0.00
		Other charges:	£0.00

Parts Fitted:	Qty.	Cost

Parts cost:	£0.00
Total cost ex.VAT:	£0.00
Total cost inc. VAT:	£0.00
In-house hours:	1.00

Job type:	PPM
Fault type:	No Fault Found
Finish date:	03/08/2011

Checks Completed:	
Visual Inspection	Completed
Calibration	Completed
Functional Check	Completed

Testers Used:	Eq.No.
5103 - TEST,GAUGE,PRESSURE,DIGITAL	5412A

DCPB - WG GGH — **Job No. : 1245934**

Caller:	malcom watson	**Job started:**	03/08/2011
Call date:		**Technician:**	DAVID GAFFNEY
Taken by:	DAVID GAFFNEY	**Job Status:**	Finished

Details: MALCOM WATSON REQUESTS P.P.M.
Notes:

Equipment No.: 15086a

Serial No.:	5080300861	**Category:**	SPHYGMOMANOMETER
Status:	Active	**Model:**	UM-101
Guarantee:	15/12/2009	**Manufr.:**	A&D INSTRUMENTS
Installed:	15/12/2008	**Agent:**	PROACT MEDICAL
Contract:		**Location:**	, GARTNAVEL GENERAL HOSPITAL
Accessories:			

Diagnosis / Action / Comments
P.P.M. PERFORMED AS PER TCP 23. UNIT CHECKED AT UPER AND LOWER AND MEDIUM LIMITS
NO RESULT DEVIATED BY +/_ 1 MM HG

External Services / Parts

Order Nos.:			
Order Date:	**Service Rpt.No.:**	**Labour cost:**	£0.00
Delivered:	**Contract job::** No	**Travel cost:**	£0.00
		Other charges:	£0.00

Parts Fitted:	Qty.	Cost

Parts cost:	£0.00
Total cost ex.VAT:	£0.00
Total cost inc. VAT:	£0.00
In-house hours:	1.00

Job type:	PPM
Fault type:	No Fault Found
Finish date:	03/08/2011

Checks Completed:	
Visual Inspection	Completed
Functional Check	Completed
Calibration	Completed

Testers Used:	Eq.No.
5103 - TEST,GAUGE,PRESSURE,DIGITAL	5412A

Appendix 12: Secondary endpoints against efficacy

See table 6-15 femoral motor definition 2

Analysis of secondary end points effective against block efficacy with patients with data from those patients with serious protocol violations treated as described in table 6-16. In patients with pre block motor scores of ≤3/4 an effective motor block was defined by a reduction in femoral motor score of 1 or more and/or a sensory response.

Table 12-1: Summary of secondary end points against efficacy at 6 hours, definition 2

	Number of patients Ineffective/effective	Ineffective	Effective	Mann Whitney (p-value)
Pain scores-median (0-100) (interquartile range)	28/140	50 (18.8-62.5)	40 (20-60)	P=0.5595
AMT(1-10) median(interquartile range)	28/136	10 (10-10)	10 (10-10)	P=0.4686
Morphine consumption(mg) median(interquartile range)	28/140	12.5 (7-16.5)	10 (5-16)	P=0.3344
Patient satisfaction(1-10) median(interquartile range)	28/138	10 (8-10)	10 (8-10)	P=0.9698

Table 12-2: Summary of secondary end points against efficacy at 24 hours, definition 2

	Number of patients ineffective/effective	Ineffective	Effective	Mann Whitney (p-value)
Pain scores (0-100), median(interquartile range)	28/139	20 (8-50)	30 (11-50)	P=0.2268
AMT(1-10) median(interquartile range)	28/138	10 (10-10)	10 (10-10)	No difference
Morphine consumption(mg) median(interquartile range)	28/139	34 (18.75-43)	29 (17-45)	P=0.5996
Patient satisfaction (1-10)median (interquartile range)	28/138	9 (8-10)	9 (8-10)	P=0.5854

See table 6-15: femoral motor definition 3

Analysis of secondary end points effective against block efficacy with patients with data from those patients with serious protocol violations treated as described in table 6-16. Analysis of secondary end points with patients with pre testing motor scores of ≤3 or less all treated as failures.

Table 12-3: Summary of secondary end points against efficacy at 6 hours, definition 3

	Number of patients Ineffective/effective	Ineffective	effective	Mann Whitney (p-value)
Pain scores-median (0-100) (interquartile range)	59/110	37.5 (22.5-70)	36.5 (20-60)	P=0.0665
AMT(1-10) median(interquartile range)	57/108	10 (10-10)	10 (10-10)	P=0.2481
Morphine consumption(mg) median(interquartile range)	59/110	11 (7-17.5)	10 (4.25-16)	P=0.2384
Patient satisfaction(1-10) median(interquartile range)	58/109	9.5 (8-10)	10 (8-10)	P=0.600

Table 12-4: Summary of secondary end points against efficacy at 24 hours, definition 3

	Number of patients ineffective/effective	Ineffective	Effective	Mann Whitney (p-value)
Pain scores (0-100), median(interquartile range)	59/108	20 (10-50)	30 (10-50)	P=0.9879
AMT(1-10) Median (interquartile range)	59/109	10 (10-10)	10 (10-10)	No difference
Morphine consumption(mg) Median (interquartile range)	59/108	29 (18-52)	28.5 (17-42)	P=0.2061
Patient satisfaction (1-10) Median (interquartile range)	58/108	8.75 (8-10)	9.0 (8-10)	P=0.9040

See table 6-15: femoral motor definition 4

Analysis of secondary end points effective against block efficacy with patients with data from those patients with serious protocol violations treated as described in table 6-16. Patients with pre-block motor scores of ≤3/4 were excluded from all analysis

Table 12-5: Summary of secondary end points against efficacy at 6 hours, definition 4

	Number of patients ineffective/effective	Ineffective	Effective	Mann Whitney (p-value)
Pain scores-(0-100) Median (interquartile range)	25/109	40 (15-50)	38 (20-55)	P=0.8588
AMT(1-10) median(interquartile range)	25/107	10 (10-10)	10 (10-10)	P=0.2722
Morphine consumption(mg) median(interquartile range)	25/109	11 (7-16)	10 (4-16)	P= 0.586
Patient satisfaction(1-10) median(interquartile range)	25/108	10 (8-10)	10 (8-10)	P=0.7282

Table 12-6: Summary of secondary end points against efficacy at 24 hours, definition 4

	Number of patients ineffective/effective	Ineffective	effective	Mann Whitney(p-value)
Pain scores (0-100), median (interquartile range)	25/108	20 (10-50)	30 (10-50)	P=0.2325
AMT (1-10)Median (interquartile range)	25/108	10 (10-10)	10 (10-10)	No difference
Morphine consumption(mg) Median (interquartile range)	25/108	34 (18-42)	28.5 (17-42.5)	P=0.7123
Patient satisfaction (1-10)Median (interquartile range)	25/111	9(8-10)	9 (8-10)	P=0.7503

Appendix 13, Protocol: A dose finding study to determine the duration of pain relief for patients with a broken hip

Protocol

Short title: A dose finding study to determine the duration of pain relief for patients with a broken hip

Full title: A dose finding study to determine the duration of analgesia provided by an ultrasound guided femoral 3-in1 nerve block in patients with a fractured neck of femur

Sponsor: Greater Glasgow and Clyde Health Board

Funder:

Public data base registration:
At http://www.clinicaltrials.gov/ct2/home:

Ethics reference number:
EUDRACT Number:
Research and development number:
Compound:
levobupivacaine
Sponsors Protocol Number: **MW001**
Version Number

This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and The Medicines for Human Use (Clinical Trials) Regulations, 2004 SI 2004:1031 (as amended) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

Chief investigator

Dr Malcolm J. Watson MB ChB, BSc, MRCP, FRCA

Principal investigator

Co-investigators

Recruitment sites

Western Infirmary, Glasgow, Scotland

Appendix 13

Index of contents

4 Contact details

5 Dr Malcolm Watson Sp.R. in Anaesthesia

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Email: mwatson@doctors.org.uk

6 Chief investigator:

7 Dr Malcolm Watson Sp.R. in Anaesthesia

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Email: mwatson@doctors.org.uk

Trial statistician:

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University of Glasgow
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Sponsor of clinical trial

NHS Greater Glasgow and Clyde Health Board
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Academic Research coordinator
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Research and Development central office,
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38 Church Street,
Western Infirmary, Glasgow
G11 6NT
Tel. 0141 211 8544
Fax. 0141 211 2811
Email maureen.travers@ggc.scot.nhs.uk

Funder of clinical trial

Appendix 13

Protocol Approval

Short title: A dose finding study to determine the duration of pain relief for patients with a broken hip

Full title: A dose finding study to determine the duration of analgesia provided by an ultrasound guided femoral 3-in1 nerve block in patients with a fractured neck of femur

Chief Investigator:

Address of Chief Investigator:

Signature:

Date:

Participating legal organisation: NHS Greater Glasgow and Clyde Health Board

Site name: Western Infirmary. Glasgow,

Principal Investigator at site:

Signature:

Date:

Abbreviations

AE	Adverse event
CRF	Case report form
EC	Ethics Committee
GP	General Practitioner
ICH GCP	International Conference on Harmonization of Good Clinical Practice
SAE	Serious adverse event
SUSAR	Suspected Unexpected Serious Adverse Reaction
SOP	Standard Operating Procedure
pain VAS	Pain Visual Analogue Score
EC_{50}	Effective concentration in 50% of patients
EC_{95}	effective concentration in 95% of patients
ASA	American Society of Anesthesiologists
US	Ultrasound
IV	Intravenous
US	Ultrasound
SmPC	Summary of Product Characteristics
IB	Investigator's Brochure
CTIMP	Clinical trial of an investigational and/or medicinal product
IMP	Investigational and/or medicinal product
CI	Confidence Interval

Appendix 13

Terminology	Definition
Sequential Dixon's up down methodology	In order construct a probability response curve for a binary outcome against concentration patients will be allocated to the next concentration dependant on the response of the previous patient
Stepping value (δ)	The difference between sequential concentrations in Dixon's up/down methodology
Standard deviation (σ)	The estimated standard deviation of probability data using probit logistic regression analysis
Turning point	If the analysis result changed from successful to unsuccessful or vice a versa
Interim analysis using probit logistic regression analysis	Probit logistic regression re-analysis of the data will be undertaken two patients after each turning point
Effective analgesia	Pain score decreased by ≥20/100, associated sensory changes in femoral nerve distribution, 30 minutes after femoral 3-in-1 nerve block
Ineffective analgesia	Pain score decreased by <20/100 with no associated sensory changes in the femoral nerve distribution, 30 minutes after femoral 3-in-1 nerve block
Equivocal block	Pain scores and sensory changes conflict
Successful block	Pain score ≤50/100 for greater than 10 hours
Unsuccessful block	Pain score >50/100 for greater than 10 hours

Appendix 13

Clinical question

What dose of levobupivacaine is required to provide pain relief for greater than or equal to 10 hours in patients with a broken hip using an ultrasound to guided femoral 3-in-1 nerve block?

Overall study design

The first 32(range 16-50) patients eligible for recruitment will be recruited to ***Part A***

The next 16 (range5-30) patients eligible for recruitment will be recruited to ***Part B***

Clinical trial Synopsis-*PART A*

Aim

Part A: To estimate (using probit logistic regression analysis) the levobupivacaine EC_{50} (concentration required to provide analgesia for greater than or equal to 10 hours in 50% of patients) using an ultrasound guided femoral 3-in-1 nerve block. Probit logistic regression analysis will then be used to estimate the levobupivacaine EC_{95} (concentration required to provide **successful** analgesia in 95% of patients).

Primary outcome

Part A: EC_{50} and EC_{95} concentrations of 30mls of levobupivacaine for ≥10hours of analgesia after a femoral 3-in-1 nerve block.

Methodology

Part A: An ultrasound guided femoral 3-in-1 nerve block will be performed pre-operatively with a catheter left in-situ. An **effective block** will be defined as reduction in resting pain VAS of 20 points or more with a pre block resting pain VAS of greater than or equal to 50/100 (defined as effective analgesia if also associated with sensory change). To ensure the validity of an effective block the patient must also be associated with a <90% of initial sensory stimuli on testing with a blunted needle or altered sensation on testing with melting ice in central area of distribution of femoral nerve in comparison to the contra lateral side at 30 minutes after the insertion of local anaesthetic. An **ineffective** block will have a less than 20 point reduction in pain scores with no change in sensation. If the sensory testing and pain scores changes conflict then the concentration will be repeated and the femoral 3-in-1 nerve block will be defined as **equivocal**. If the block is **ineffective** then confirmation of correct position of the IMP (levobupivacaine) dose will be given by the reduction in resting pain VAS scores to <30/100 after rescue dosing of 20mls of 0.25% levobupivacaine via the femoral nerve block catheter. A **successful** block will provide analgesia for ≥10 hours with VAS pain scores less than or equal to 50/100. An **unsuccessful block** will provide analgesia for <10 hours.

Rescue analgesia

Part A: If the ultrasound guided femoral 3-in-1 nerve block fails to reduce the resting pain VAS by <20/100 in 30 minutes **(ineffective block**) then 20mls of 0.25% levobupivacaine will be given via a femoral nerve catheter to achieve a resting pain VAS of <30/100 and if necessary intravenous morphine will be titrated according to local protocols to achieve a resting pain VAS of <30/100.

Study design

Part A: Sequential Dixon's up/down study

Femoral 3-in-1 nerve blocks will be performed and the concentration of levobupivacaine will be increased or decreased for an **unsuccessful** or **successful** nerve block respectively until the concentration of local anaesthetic is **successful** (effective analgesia for ≥10 hours in 50% of patients (EC_{50})). The stepping value (δ) will be recalculated two patients after each turning point has been reached and changed to increase the accuracy of the final estimate for the EC_{50} of levobupivacaine.

Inclusion criteria

Part A:

Emergency proximal fractured neck of femur
Resting pain VAS at rest of ≥50mm on a 100mm scale before recruitment
American Society of Anaesthesiology (ASA) grading ≤4
Able to give informed consent
Patient is able to cooperate with sensory testing of lower limb function

Exclusion criteria

Part A:

Acute mental test score of <7 at any time pre-operatively
Allergy to local anaesthetic
Contra-indication to levobupivacaine
No pre-existing neurological deficit (sensory or motor) affecting the lower limb
Patients with lower limb amputations
Patients with a history of chronic pain

Number of patients needed

Part A: A single 30ml dose of levobupivacaine prepared by the pharmacy production unit (PPU) at the Western Infirmary, Glasgow with the levobupivacaine concentration increased (by_the stepping value δ) after an unsuccessful femoral 3-in-1 nerve block and decreased (by the stepping value δ) following an effective femoral 3-in-1 nerve block and starting dose of 0.20%. An effective femoral 3-in-1 nerve block (reduction in resting pain VAS of ≥20/100 with an associated sensory change) will be defined as providing successful analgesia (resting pain VAS <30/100 at rest) for greater than 10 hours. The total number of patients needed will be approximately 32 (estimated range 25-50) successful and unsuccessful blocks (Please see attached sample size justification in a letter from Dr Alex McConnachie senior statistician at the Robertson centre, Glasgow University). Multiple interim re-analyses will be performed in 2 patients after each turning point to ensure that δ (the stepping value) is approximately 2/3 to 3/2 σ of (the standard deviation of the mean for the EC_{50} calculated using probit logistic regression analysis) an δ will be altered if necessary to increase the accuracy of the estimate obtained for the EC_{50} and EC_{95} concentration. (Please refer to section '3.8 Statistical justification of sample size **Part A'** for more details)

Appendix 13

Clinical trial synopsis-*PART B*

Aim

Part B: To estimate the duration of analgesia provided by the EC_{95} concentration of levobupivacaine estimated (using probit logistic regression analysis) to provide ≥10 hours of analgesia from part A of this clinical trial and to determine if the peak plasma levobupivacaine concentrations are within safe limits.

Methodology

Part B: Femoral 3-in-1 nerve blocks will be performed pre-operatively using ultrasound to guide needle insertion with a catheter left in-situ. A effective block will be defined as reduction in resting pain VAS of greater than or equal to 20/100 points with a pre block resting pain VAS of greater than or equal to 50/100 with an associated sensory change. To confirm an **effective** femoral 3-in-1 nerve block, the patient must also have <90% of initial sensory stimuli on testing with a blunted needle or altered sensation on testing with melting ice in the central area of distribution of femoral nerve in comparison to the contra lateral side at 30 minutes after the insertion of levobupivacaine.
The primary end point, in **effective** femoral 3-in-1 nerve blocks will be the duration of analgesia (resting pain VAS ≤50/100 at rest); pain scores will be recorded hourly postoperatively from awake patients only. Blood samples will be taken before the insertion of the levobupivacaine and at 10, 20, 30 and 60 minutes post insertion of levobupivacaine from a cannula inserted to assess peak serum levels of levobupivacaine. Blood samples will be taken for venous blood gases and liver function tests before the insertion of the levobupivacaine. Once all the blood samples have been taken 60 minutes after the femoral 3-in-1 block all the blood samples will be taken to biochemistry at the Western infirmary liver function and venous blood gases will be analysed immediately. The levobupivacaine samples will be centrifuged and frozen to minus 20 degrees Celsius for delayed analysis as a batch.

Rescue analgesia

Part B: If the ultrasound guided femoral 3-in-1 nerve block fails to reduce the resting pain VAS by <20/100 in 30 minutes (failed analgesia, ineffective nerve block) then 20mls of 0.25% levobupivacaine will be given via a femoral nerve catheter to achieve a resting pain VAS of <30/100 and if necessary intravenous morphine will be titrated to achieve a resting pain VAS of <30/100.

Study design

Part B: Observation prospective cohort study
Femoral 3-in-1 nerve blocks will be performed with the levobupivacaine concentration estimated to be effective in 95% of patients from part A (EC_{95}).
The duration of analgesia will be the primary end point for this part of the study and 5 blood samples will be taken to determine the blood serum concentration of levobupivacaine. It is estimated that the time taken to half the pain score in the patients recruited to part B of the study (see statistical considerations, Part B, 3.6 Secondary end points)

Inclusion criteria

Part B:

Emergency proximal fractured neck of femur
Visual analogue pain score at rest of ≥50mm on a 100mm scale before recruitment.
American Society of Anaesthesiology grading ≤4
Able to give informed consent
Patient is able to cooperate with sensory testing of lower limb function

Exclusion criteria

Part B

Acute mental test score of <7 at any time preoperatively
Allergy to local anaesthetic
Contra-indication to levobupivacaine
Pre-existing neurological deficit (sensory or motor) affecting the lower limb
Patient with lower limb amputations or other condition affecting sensation in lower limbs
Patient with a history of chronic pain

Number of patients needed

Part B: The primary outcome of this study will be the duration of analgesia. The standard deviation is approximately 4 hours (from clinical experience). The standard error of the mean is the standard deviation divided by the square root of the sample size. Hence a sample size of approximately 16 (range 5-30) will provide a standard error of 1 hour (assumed mean duration of approximately 10 hours). Therefore to estimate the mean duration of analgesia with a 95% confidence interval of ± 2 hours will require a sample size of approximately 16 patients (estimated range 5-30) with successful blocks, assuming an approximately normal distribution.

Primary outcome

Part B: Duration of analgesia (resting pain VAS<50/100 at rest) provided by estimated EC_{95} concentration of levobupivacaine from part A.

Appendix 13

1.0 Introduction

1.1 Background

Burden of disease caused by fractured neck of femur

Fractured neck of femur or proximal femoral fracture is a significant cause of morbidity and mortality in the population of the developed world. Johnell et al calculated that hip fracture was associated with 1.75 million disability adjusted life years (DALYS) which represents 1.4% of the total disease burden calculated in DALYS for women in established market economies in 1990 (Johnell and Kanis 897-902). Disability adjusted life years are a sum of years lost due to premature mortality and disability directly related to hip fracture for the number of years that the patient survives multiplied by a disability factor between 0 (no disability) to 1 (death). The disability weight expressed as a fraction describes the range of disutility between death (=1) and perfect health (=0) and has been estimated for hip fracture by expert panels at 0.272 for each year of illness (Murray and Lopez 1347-52). Fractured neck of femur represents a greater burden of disease in established market economies for women than cirrhosis of the liver (1.1%), stomach cancer (0.9%) or ovarian cancer (0.9%) (Johnell and Kanis 897-902). Gullberg et al estimated that worldwide the total number of hip fractures in men and women in 1990 was 338,000 and 917,000 respectively, a total of 1.26 million(Gullberg, Johnell, and Kanis 407-13). Gullberg also estimated that the number of hip fractures will double to 2.6 million by the year 2025, and 4.5 million by the year 2050 with a 95% confidence interval of between 7.3 and 21.3 million if we assume no change in the age and sex specific incidence.

Prognosis and historical perspective operative /non-operative management

The prognosis for patients with a fractured neck of femur in the UK is poor. The overall 1 year survival is approximately 25% (Heikkinen, Parker, and Jalovaara 349-54) and a hospital mortality is 14.3% for those patients admitted from home (Bottle and Aylin 947-51). The one year mortality has however improved significantly since Beals reported a 50%, 1 year mortality in a surgically managed cohort of patients recruited between 1956 and 1961(Beals 235-44). Roberts et al retrospectively analysed the mortality rates for 32590 patients with a fractured neck of femur between 1968 and 1998(Roberts & Goldacre, 771-775). Roberts concluded that the mortality reduction between 1968 and 1983 was associated with the introduction of surgical management. No significant fall in mortality has been observed since 1983. Non-operative management of fractured neck of femur is associated with significantly higher 30 day mortality (18%) than operative management(11%)(odds ratio 1.7, 95% confidence interval (CI) 1.6 - 1.8), in a review of 50235 fractured neck of femur patients over 7 years in Ontario Canada (Jain, Basinski, and Kreder 11-17).

Prognosis and delay in definitive surgical management

Delay in definitive surgical fracture fixation is also associated with an increased risk of mortality. Bottle et al examined a retrospective cohort of 129522 patients from 151 Trusts in England and Wales between April 2001 and March 2004 (Bottle and Aylin 947-51). Bottle et al found an independent association between delayed operative treatment and an increased risk of death in hospital. For all deaths in hospital, the odds ratio for more than one day's delay relative to one day or less was 1.27(95% confidence interval 1.23 to 1.32) after adjustment for co morbidity. It is interesting to note that if the death rates in patients with at most one day's delay had been repeated throughout all 151 Trusts in this study, there would have been an average of 581 (478 to 683) fewer deaths per year. The association between delay in surgical treatment and

increased mortality was also shown by Moran et al(Moran et al. 483-89). Moran et al conducted a prospective observational study examining the mortality rates for 2660 patients in Nottingham, UK and he concluded that that if patients who were otherwise judged to be fit for surgery were delayed more than four days it was associated with a significant increase in mortality at 30 days (hazard ratio 2.4; p>0.001) and 1year (hazard ratio 2.25; p>0.001). Fox et al did not find that a delay of up to 48 hours had an affect on outcome in a relatively small cohort of 142 patients(Fox et al. 297-300;Perez et al. 237-40).

Prognosis and aetiology for fractured neck of femur patients

The aetiology of this poor prognosis is multifactorial; a review of multiple post mortem studies suggested that the principal cause of death was bronchopneumonia in 46% of patients, cardiac failure and myocardial infarction (23%) and pulmonary embolism (in 14%) (Perez et al. 237-40). Mortality from bronchopneumonia and pulmonary embolism was also significantly reduced in those patients who were operated on within 24hours (Perez et al. 237-40) but cardiac failure was not altered by surgery within 24 hours of admission.

Safe serum levels of levobupivacaine

Currently, there is no known serum level for levobupivacaine that can be considered toxic but levobupivacaine itself may be inherently safer than racemic bupivacaine and current practice to use a single dose of up to a 150mg in a volume of between 20mls and 40mls in fractured neck of femur patients. Kopacz and Allen reported an accidental intravenous injection of 142.5 mg of levobupivacaine into a patient during attempted epidural anaesthesia (Kopacz and Allen 1027). Transient agitation was the only symptom of systemic toxicity and the patient recovered fully however, blood samples were taken after the injection and analysed retrospectively for serum levobupivacaine. The levobupivacaine serum concentrations measured at 14 minutes and at 120 minutes were 2.7μg/mL and 1.1μg/mL respectively. Further evidence for reduced toxicity of levobupivacaine compared to the racemic bupivacaine can be found in a cross-over study of slow (10 mg/min) IV infusion of levobupivacaine in 12 healthy volunteers, central nervous system symptoms first appeared at a larger mean total dose (54.0 mg versus 45.6 mg), producing a higher resultant plasma level (2.38 μg/mL versus 1.87μg/mL) than for racemic bupivacaine (Gristwood et al. 1209 –12). In contrast to the case described by Kopacz at al previous cases of accidental intravenous racemic bupivacaine injection in which seizures or severe cardiac arrhythmias occurred at serum levels as low as 1.8 μg/mL (Rosenburg et al 95–8), 2.74 μg/mL (Moore et al 230–2), and 2.3 μg/mL (Ryan. 907–8) of racemic bupivacaine have been detected within 5 minutes of injecting patients having seizures. It is possible that the toxicity of levobupivacaine may be dependant not only on the total concentration of levobupivacaine but on the amount of free levobupivacaine which is dependant on the acid base status of the patient. It is known that acidosis increases the cardiotoxicity of intravenous local anaesthetics (Moore. 109 –21). The incidence of systemic toxicity from local anaesthetics is very rare and a recent review estimated the incidence to be 1 in 10000 (Cox et al 111-36).

1.2 Current practice and results from previous clinical trials and studies

Current practice:
The hospital mortality for patients admitted to hospital from home in the UK with a fractured hip is 14.3% (Bottle and Aylin 947-51). The current techniques for analgesia rely on parentral morphine, paracetamol and non-steroidal anti-inflammatory (NSAIDS) drugs that frequently provide inadequate pain relief with multiple side effects despite this multimodal approach. Studies have suggested a link with effective pain relief and a reduced risk of death. Effective analgesia can be provided by ultrasound guided nerve blocks as this has been associated with an increased success rate, and shorter onset times than traditional regional anaesthesia techniques. The aim of this project is to develop a safe method that will allow Accident and Emergency doctors to provide effective pain relief to those patients with a fractured hip.

General Plan and background of PhD project:
This clinical trial is part of an NRS career researcher award by the Chief Scientists office (CSO):

7.1 Summary of results for clinical academic fellowship (PhD) CAF 05/07

The results of the clinical academic fellowship clinical trial and clinical study are listed below with their associated research questions:

7.1.1.1 Which method do we use to site the local anaesthetic from a femoral 3-in-1 block?

The success rates of methods of guiding insertion of a femoral 3-in-1 nerve block are as follows. The exact percentage of successful blocks depended on the definition (*) of the primary end point used (sensory and motor changes) but the order and magnitude of the difference between each of the procedures is approximately the same which ever definition of the primary end point (sensory and motor changes) was used.
Table 1: Success rate for 3 methods of guiding a femoral 3-in-1 nerve block

Method used	Ultrasound	Nerve stimulator	Loss of resistance
Number of patients(Failed)	16	12	15
Number of patients(Successful)	55	59	22
Total analysed	71	71	37
Percentage successful blocks	77.5%	83.1%	59.4%

*The definition of a successful block was sensory change <90/100 and/or a motor score decrease of <1 with a starting value of 4/4(starting values of <3/4 did not influence the outcome and success or failure was determined by the sensory change)

The use of ultrasound or a nerve stimulator resulted in an absolute increase in the effectiveness of the block by 17% or 23% respectively giving a number needed to treat to see a difference of approximately 5 (p=0.0159).

7.1.1.2 What dose of levobupivacaine?

The effective concentration of 30mls of levobupivacaine required to produce a reduction in pain verbal analogue score (VAS) of ≥20 points on a 100 point scale in 50% of patients (EC_{50}) with a proximal traumatic fractured neck of femur using an ultrasound guided femoral 3-in-1 nerve block was EC_{50}=0.0255% with 95% confidence interval of 0.0229% to 0.0284%. The effective concentration of levobupivacaine in 95% of patients (EC_{95}) was estimated using probit regression techniques as EC_{95}=0.0357% with 95% confidence interval of 0.0332% to 0.0383%.

7.1.1.3 What duration of analgesia from the dose of levobupivacaine?

The median duration of analgesia from 30mls of 0.036% (the EC_{95} of levobupivacaine) is 166 minutes with an interquartile range of 110 to 210 minutes.

7.1.1.4 What is the pharmacokinetic profile of the dose of levobupivacaine used in the population of patients with a fractured neck of femur?

The peak median total serum plasma concentration was reached at 30mins after the block and was 52ng/ml ('safe range of <2000ng/ml').

7.2 Current clinical trial

7.3 To estimate the dose of levobupivacaine required to provide analgesia for greater than 10 hours

The EC_{95} levobupivacaine concentration from the clinical trial 'A dose finding study for pain relief of a broken hip', ethics reference 09/S0703/87, EUDRACT number 2009-013462-25 did provide an estimate of the effective concentration to provide analgesia. The effective concentration to provide analgesia was relatively low and therefore the duration of analgesia was too short to be clinically useful. In order to provide a clinically useful duration of analgesia the EC_{95} and EC_{50} of levobupivacaine required to provide 10 hours of analgesia using a sequential Dixon up/down methodology needs to be determined.

The review article by Pace et al provided a number of improvements to the original sequential Dixon's up/down methodology. Pace et al suggested using the bias coin method of patient allocation to target the EC_{95} instead of targeting the ED_{50} concentration of levobupivacaine. This appears to be a very attractive option but as every failure will be accompanied by 19 successes, at the EC_{95} concentration in order to estimate the EC_{95} with the same precision as the ED_{50} 20 times the number of patients will need to be recruited. If the average dosing study needs 20 to 40 patients then 800 to 1600 patients would be required for the same precision as a traditional sequential Dixon's up/down methodology targeting EC_{50}. This is not an efficient method of determining the EC_{95} and I propose to adapt the techniques used in the sequential Dixon's up/ down methodology to estimate the effective levobupivacaine concentration 'A dose finding study for pain relief of a broken hip', ethics reference 09/S0703/87, EUDRACT number 2009-013462-25 in which the stepping value was altered on the basis of an interim probit logistic regression analysis.

The sequential up/down Dixon's method may be utilised to determine the concentration of levobupivacaine necessary to provide 10 hours of analgesia. The binary end point will be the successful provision of 10 hours of analgesia (with pain scores ≤50/100 on awake patients). The number of patients required to obtain a precise estimate for EC_{95} and EC_{50} could be decreased by the use of iterative re-estimation of the optimal stepping value stepping value(δ).

The protocol for 'A dose finding study for pain relief of a broken hip', ethics reference 09/S0703/87, EUDRACT number 2009-013462-25 started with a large stepping value (difference between the concentrations of levobupivacaine) which was decreased after 16 patients had been recruited so that the stepping value (δ) was between 2/3 and 3/2 of the estimated standard deviation (σ) using the probit logistic regression analysis techniques. A better method would be to repeat this process on multiple occasions (iterative technique) during the trial to obtain progressively better estimations for the stepping value. Iterative re-calculation of the mean and σ and adjustment of the δ will result in increased precision when creating a probability model to estimate levobupivacaine EC_{50} and EC_{95}

The iterative re-calculation of σ would have several other advantages:

- The initial **stepping value (δ)** can be relatively large which will result in decease in the number of patients required to reach the first turning point
- The number of patients will be less dependant on the **starting concentration**
- Repeated measures of the **standard deviation (σ)** will give a measure of the **stability** of the model and therefore the precision of the final estimate of levobupivacaine EC_{50} and EC_{95}.
- Objective criteria for stopping the trial can be set at the beginning of the trial which will be dependant to the **stability** of the model created using probit logistic regression analysis.

I have made the following assumptions when designing the protocol to use iterative re-calculation of the stepping value (δ).

- The iterative calculation of (δ) will only yield a different result if the test result has reached a turning point(i.e. from failure to success or vice a versa)
- If the turning point has been reached then if a further 2 patients are recruited then the results from these patients will allow determination of whether the turning point was above the mean, below the mean or at the mean.
- Therefore an iterative re-calculation will take place 2 patients after a turning point. The standard deviation(σ) and the estimated mean will be made and the stepping value(δ) adjusted to be within 3/2 and 2/3 of the σ
- The new starting concentration after recalculation will be estimated using the equation (mean + the new stepping value (δ)).
- The result of the iterative process should be rounded to achieve the most accurate result possible within the limits of error imposed by the pharmaceutical manufacturing process (with errors of approximately ±5.1% according to previous work of chief investigator)
- The iterative process will be repeated after recruiting two patients after each turning point until agreement is reached between three estimations of the mean and standard deviation within a predetermined precision (<10%). This will imply that the probit logistic regression model is stable and that it will give a reliable estimation of levobupivacaine EC_{95} and EC_{50}.
- The application of these principles have allowed the development of the protocol for a clinical trial to determine the dose of levobupivacaine required for 10 hours analgesia and to ensure its safety.

In summary the use of iterative re-calculation of the stepping value will decrease the number of patients needed to provide an accurate and precise answer to the levobupivacaine EC_{50} and EC_{95}. It will also provide objective criteria to stop the trial once it has achieved a stable endpoint.

Current clinical trial: Part-A and Part-B

Part A

The dosing of the femoral 3-in-1 nerve block required to produce 10 hours of analgesia will be determined in the fractured neck of femur population. Levobupivacaine dosing will be determined by a sequential Dixon's up/down methodology. Femoral 3-in-1 nerve blocks will be performed and the concentration of levobupivacaine will be increased or decreased for an unsuccessful or successful nerve block respectively until the concentration of levobupivacaine is effective in 50% of patients (EC_{50}). The data from part-A can then be used to estimate, using probit logistic regression analysis, the effective concentration in 95% (EC_{95}) of patients.

Part B

Pharmacodynamics will be determined by monitoring pain scores to determine the actual duration of analgesia provided by the concentration calculated to provide ≥10 hours of analgesia in 95% (EC_{95}) of fractured neck of femur patients. The plasma levels of levobupivacaine will also be measured in sequential blood samples to ensure that EC_{95} dose provides pharmacokinetics that are within the safe range.

1.3 Research question

Can we determine the effective dose of levobupivacaine to provide ≥10 hours of pain relief in patients with a broken hip using ultrasound to guide needle insertion?

1.4 Major risk/benefits of trial to patients

Risks-

1 Ultrasound (US) is a relatively new technology for guiding needles to site local anaesthetic nerve blocks but a recent meta-analysis of 14 clinical trials (Abrahams et al, 408-17) found that nerve blocks performed using US guidance were:

1-more likely to be successful with a risk ratio (RR) for block failure of 0.41, (95% confidence interval (CI) 0.26–0.66, P=0.001)

2-took less time to perform with a mean difference of approximately 1 min less to perform with US, (95% CI 0.4–1.7 min, P=0.003)

3-had a 29% faster onset time, (95% CI 45–12%, P=0.001

4-had longer duration (mean difference 25% longer, (95% CI 12–38%, P=0.001) than those performed with PNS guidance.

5-US guidance also decreased the risk of vascular puncture during block performance (RR 0.16, 95% CI 0.05–0.47, P=0.001)

2 Nerve damage is a risk with all types of nerve blocks but the risk is relatively small with femoral 3-in-1 nerve blocks. The biggest single study to

estimate the level of risk of complications was a French study by Auroy et al which surveyed 158083 regional anaesthetic procedures performed by 487 anaesthetists over a 10 month period (Auroy et al 1724-80). 10309 femoral 3-in-1 nerve blocks were performed during this study; no deaths , no cardiac arrests, no episodes of respiratory failure and no seizures were reported and only 3 peripheral neuropathies were reported all of which had completely recovered by 3 weeks. The study estimated that the true incidence of deaths, cardiac arrests, episodes of respiratory failure or seizures associated with the femoral 3-in-1 nerve block using loss of resistance and nerve stimulation was 0-2.9/10000 with a 95 % CI and the recorded incidence of transient neurological complications was 2.9/10000 with 95% CI of 0-7.8/10000. The incidence of adverse events using ultrasound guidance to guide a femoral 3-in-1 nerve block should be less than 2.9/10000 as the femoral nerve and vessels can be directly visualised and it should therefore be possible to avoid inadvertent intraneuronal or intravascular injection.

3 Local anaesthetic toxicity may be a risk; however the femoral 3-in-1 nerve block is currently used in standard clinical practice to provide preoperative analgesia to fractured neck of femur patients with the standard dose (40mls of 0.375% bupivacaine). We will use levobupivacaine instead of racaemic bupivacaine as it is generally accepted to have a lower cardiac toxicity. 20% Intralipid is the current standard treatment for cardiac arrest or collapse as a result of local anaesthetic toxicity and is immediately available in all areas where local anaesthetic is administered including the emergency theatres at the Western Infirmary, Glasgow.

Benefits-

1 The clinical trial will provide analgesia (resting pain VAS<30/100) to a group of frail elderly patients who have suffered a traumatic fractured neck of femur with resting pain VAS scores of greater than 50/100. Morrison et al found that in 411 patients with surgically treated proximal femoral fractures that higher pain scores at rest were associated (Morrison et al 303-11):

- with significantly longer hospital lengths of stay (P=0.03),
- were significantly more likely to have physical therapy sessions missed or shortened (P=0.002),
- were significantly less likely to be ambulating by post-operative day 3 (P<0.001),
- took significantly longer to ambulate past a bedside chair (P=0.01), and
- had significantly lower locomotion scores at 6 months (P=0.02).

Morrison et al concluded that untreated pain was also a significant risk factor for delirium in a further study of 541 surgically treated proximal fractured neck of femur patients (Morrison et al 76–81).

2 Reduced opiate requirement postoperatively which will result in a reduction is opiates associated complications i.e. sedation, respiratory depression, delirium, nausea vomiting and constipation.

3 Reduced volatile anaesthetic requirements intra operatively

2.0 Study Procedures

2.1 Aim

Part A

To determine the effective concentration of 30mls of levobupivacaine required to produce a reduction in resting pain VAS of ≤20/100 (effective block) and keep the pain scores ≤50/100 for ≥10 hours (successful block) in patients with a proximal traumatic fractured neck of femur (EC_{50}) using an ultrasound guided needle placement below the facia iliacus membrane (femoral 3-in-1 nerve block).

Part B

To determine the duration of analgesia provided by the EC_{95} of levobupivacaine and to study the pharmacokinetics of levobupivacaine to ensure peak serum levels are within safe limits.

2.2 Study design

Part A

A prospective sequential Dixon's up down dose finding study for ultrasound guided femoral 3-in-1 nerve block

Part B

Observation prospective cohort study of the duration of analgesia provided by an ultrasound guided femoral 3-in-1 nerve block

2.3 Study Population

Part A and Part B

Competent patients with proximal traumatic fractured neck of femur

2.4 Lay summary of trial

Studies have suggested a link with effective pain relief and reduced illness and death in high risk patients. Ultrasound guided nerve blocks have been associated with an increased success rate and allow visualisation of all the anatomical structures and the distribution of the local anaesthetic on injection. The hospital mortality for patients admitted to hospital from home in the UK in 2006 with a fractured hip was 14.3% (Bottle and Aylin 947-51).

The aim of this clinical trial is to determine the effective dose of local anaesthetic to provide pain relief to patients for ≥10 hours with a broken hip using ultrasound to guide needle insertion. Patients with a broken hip will be recruited after admission to hospital and prior to surgical fixation. All patients recruited to this study will receive appropriate standard anaesthesia, analgesia and surgical or non surgical management of their broken hip as dictated by their clinical condition.

The trial can be divided into sequential two parts; the results of part A will provide an amount of local anaesthetic which will relieve pain of a broken hip in 50% of all patients for ≥10 hours. Part B will determine the actual duration of pain relief provided by the amount of local anaesthetic from part A and blood levels of local anaesthetic.

In parts A and B a standard pain relieving nerve block to numb the nerves supplying the hip joint will be administered using ultrasound to guide the injection of local anaesthetic. The patient will then be observed for 30 minutes during which time the feeling in the upper leg and pain scores will be recorded.

Patients with ineffective and equivocal nerve blocks will be given immediate pain relief and withdrawn from further participation in the study.

In part A the amount of levobupivacaine for the next patient will be increased or decreased if the nerve block is unsuccessful (≤10 hours analgesia) or successful (≥10 hours) respectively.

In part B the dose required to provide successful pain relief for greater than 10 hours in 95% of patients will be given to all patients. Blood samples will be taken before the pain relieving nerve block and at 10, 20, 30 and 60 minutes afterwards. In order to determine the duration of pain relief pain scores will be recorded in awake patients hourly for up to 24 hours.

2.5 Inclusion criteria

Part A and Part B

Emergency hospital admission with proximal fractured neck of femur
Visual analogue pain score at rest of ≥50/100
American Society of Anaesthesiology grading ≤4
Able to give informed consent
A resting pain VAS of greater than 50mm on a 100mm scale before recruitment
Patient is able to cooperate with sensory testing of lower limb function

2.6 Exclusion criteria

Part A and Part B

Acute mental test score of ≤7 at any time preoperatively
Allergy to local anaesthetic
Contra-indication to levobupivacaine
No pre-existing neurological deficit (sensory or motor) affecting the lower limb
Patient with lower limb amputations or other condition affecting sensation in lower limbs
Patient with a history of chronic pain

2.7 Criteria for withdrawing a patient from the study

Part A and Part B

Patients who were administered regional anaesthesia or analgesia not specified in the protocol.
Any patient may withdraw from the study at any time without giving any reason or justification.

A significant protocol violation which would endanger the patient's safety or invalidate the results from that patient will result in the patient being immediately withdrawn from the trial. However we reserve the right to analyse all data collected prior to the patient's withdrawal from the study.

2.8 Methodology

Part A

Patients consented for the study will be transferred to the operating theatre suite prior to their operation and initial sensory function testing will be performed (time 0). Femoral 3-in-1 nerve blocks will be inserted preoperatively using ultrasound needle guidance with 30mls of levobupivacaine (IMP) the concentration of which will be determined by the response of the previous patient. A femoral 3-in-1 nerve block will be undertaken using ultrasound to obtain images of the femoral artery, vein and nerve in the short axis and a 100mm or 50mm 18G Contiplex® Tuohy needle (B-Braun) will be advanced in plane until the tip of the needle is under the fascia iliacus membrane immediately lateral to the femoral nerve. 30mls of levobupivacaine (IMP) will then be injected while imaging to ensure the correct spread of local anaesthetic (around the femoral nerve with 'tenting' of the fascia iliacus membrane). A catheter will be advanced via the Contiplex® Tuohy needle and the needle removed to leave 4 to 5cm beyond the original site of the needle tip. Full aseptic technique will be used during the injection of the levobupivacaine (IMP) and the insertion of the catheter. The concentration of levobupivacaine (IMP) will be 0.20% for the first patient. If the first patient has evidence of a sensory block and a ≥20/100 point reduction in resting pain score (an **effective block**), and the patient has analgesia for ≥10 hours (resting pain VAS ≤50/100**)(a successful block**) then the concentration of levobupivacaine will be decreased by 0.025% for the next patient recruited. If the first patient has evidence of a sensory block and a ≥20/100 point reduction in resting pain VAS (an effective block), and the patient has analgesia for <10 hours (resting pain VAS ≤50/100) **(an unsuccessful block**) then the concentration of levobupivacaine will be increased by 0.025% for the next patient recruited. Conversely, if no sensory block is present and the pain score does not increase (an **ineffective block**) then 20mls of 0.25% levobupivacaine will be given via the catheter and the concentration will be repeated. If the resting pain VAS is not <30/100 30minutes after the injection via the catheter the morphine will be titrated to reduce the resting pain VAS to <30/100. Therefore the concentration of levobupivacaine for each patient will be dependent on the changes observed in the previous patient. A valid change in pain score must be accompanied by an associated change in sensation or the concentration will be repeated (**equivocal block**). If the ultrasound guided femoral 3-in-1 nerve block fails to reduce the resting pain VAS to <30/100 in 30 minutes 20mls of 0.25% levobupivacaine will be given via a femoral nerve catheter to achieve a resting pain VAS of < 30/100 and if necessary intravenous morphine will be titrated according to local protocols to achieve a resting pain VAS of <30/100. The duration of analgesia will be measured by recording hourly resting pain VAS scores for up to 24 hours post femoral 3-in-1 nerve block. If the patient is sleeping the resting pain scores will be recorded as 'S' and the patient will not be woken to assess pain scores.

Part-B

Patients consented for the clinical trial will be transferred to the operating theatre suite prior to their operation and initial sensory function testing will be performed (time 0) and a single set of venous blood gases, baseline levobupivacaine levels and liver function tests will be taken. A femoral 3-in-1 nerve block will be undertaken using ultrasound to obtain images of the femoral artery, vein and nerve in the short axis and a 100mm or 50mm 18G Contiplex® Tuohy needle (B-Braun) will be advanced in plane until the tip of the needle is under the fascia iliacus membrane immediately lateral to the femoral nerve.

30mls of levobupivacaine (IMP) will then be injected while imaging to ensure the correct spread of local anaesthetic (around the femoral nerve with 'tenting' of the fascia iliacus membrane). A catheter will be advanced via the Contiplex® Tuohy needle and the needle removed to leave 4 to 5cm beyond the original site of the needle tip. Full aseptic technique will be used during the injection of the levobupivacaine (IMP) and the insertion of the catheter. The EC_{95} of levobupivacaine for ≥10 hours of analgesia which will be determined by the patient's response to part-A will be administered as the IMP. A valid change in pain score must be accompanied by an associated change in sensation or the patient will be excluded from the study (ineffective block). If the patient does not have a resting pain score of <30/100 then intravenous morphine will be administered according to local protocol to achieve a resting pain VAS of less than 30/100. Patients with a valid change in pain score associated with a sensory change will have blood samples taken before the insertion of the local anaesthetic nerve block and at 10, 20, 30 and 60 minutes post insertion of local anaesthetic block, from a cannula inserted, to assess peak serum levels of levobupivacaine. The primary end point, in successful blocks will be the duration of analgesia (resting pain VAS <30/100 at rest); acute pain scores will be recorded hourly postoperatively for up to 24 hours. If the block is ineffective or equivocal appropriate rescue analgesia will be given (20ml 0.25% levobupivacaine via a femoral nerve block catheter or intravenous morphine will be titrated according to local protocols to achieve a resting pain VAS of <30/100). If the patient is sleeping the pain scores will be recorded as 'S' and the patient will not be woken to assess resting pain VAS.

2.9 Anaesthesia and analgesia for hip replacement or fixation

Part A and Part B

Intra operative anaesthesia:	No restriction but total bupivacaine and levobupivacaine given as part of spinal or general anaesthesia will always be less than 2mg/Kg
Sedation:	May be used at the discretion of the attending anaesthetist using target controlled infusion (TCI) propofol
Airway management:	As determined by attending anaesthetist.
Intraoperative/post operative analgesia:	Paracetamol-1g IV, morphine IV as per local practice
Rescue analgesia (resting pain VAS<30/100)	20mls of levobupivacaine via femoral nerve catheter or morphine IV by local protocol to achieve resting pain VAS<30/100
Post operative analgesia:	Paracetamol 1g QID and Morphine IV by local protocol to achieve resting pain VAS<30/100

2.10 Assessment of sensory function for femoral 3-in-1 nerve block

Part A and Part B

The patient's sensory function will be assessed by the intensity of a pin prick sensation and cold sensation produced by melting ice. Pin prick sensation will be measured using a blunted 25G orange needle. The patient will be asked to grade the intensity of the sensory response to a blunted 25G 'orange' needle by marking a line from 0 (no sensation) to 100. 100 will be defined as the same intensity of sensation as the contra lateral upper middle third of the thigh. Melting ice will also be used as a stimulus and a valid response will be taken as a reduced cold sensation on the side on which are nerve block was performed compared with the contra lateral (unblocked side) on the middle third of the upper thigh. The area of skin to be assessed will be the middle third of the upper thigh which is thought to be supplied by the femoral nerve. To fulfil the definition of effective analgesia as well as having a decrease in resting pain VAS of ≥20/100 the patient must also have <90% of initial sensory stimuli on testing with a blunted needle or altered sensation on testing with melting ice in central area of distribution of femoral nerve in comparison to the contra lateral side at 30 minutes after the insertion of levobupivacaine (IMP).

3.0 Statistical considerations

Part A

3.1 Primary end point

Effective or ineffective analgesia

Effective analgesia is defined by a 20/100 point or greater reduction in resting pain score (resting pain VAS) and an associated sensory change at 30 minutes post insertion of femoral 3-in-1 nerve block. A change in resting pain score (resting pain VAS) must be accompanied by an associated change in sensation (please see '2.10 **Assessment of sensory function for femoral 3-in-1 nerve block'** for a definition of an appropriate sensory change). Only **effective** femoral 3-in-1 nerve blocks can be successful or unsuccessful. Ineffective regional analgesia will be defined by a less than 20/100 point reduction in resting pain score (resting pain VAS) with no associated sensory changes and the levobupivacaine concentration will be recruited.

Successful and unsuccessful block

An effective femoral 3-in-1 nerve block may be successful or unsuccessful dependant on the duration of analgesia. A **successful** block will provide analgesia for ≥10 hours with resting pain VAS less than or equal to 50/100. An **unsuccessful block** will provide analgesia for ≤10 hours. A successful or unsuccessful nerve block will result in a decrease or and an increase respectively in the concentration of the levobupivacaine for the next patient. If the analgesia and sensory changes recorded conflict (equivocal) or 20mls of 0.25% levobupivacaine fails to provide analgesia (technical failure of femoral 3-in-1 nerve block) the concentration will be repeated. This will give an estimate of the EC_{50} concentration at which 50% of patients have successful (≥10 hours duration) and 50% have unsuccessful (≤10 hours duration) analgesia.

3.2 Secondary end points

- Sensory function of the femoral nerves will be tested at 0mins (pre insertion of levobupivacaine) and at 10 and 20 minutes post insertion of 30mls of levobupivacaine.
- Time taken and number of attempts to insert femoral 3-in-1 nerve block
- Blood pressure, oxygen saturation, pulse rate and respiratory rate before insertion of 30mls of levobupivacaine and at 10, 20 and 30minutes afterwards.

3.3 Number of patients needed

A single 30ml dose of levobupivacaine prepared by pharmacy production unit (PPU) at the Western Infirmary, Glasgow with the levobupivacaine concentration increased (by the stepping value δ) after an unsuccessful femoral 3-in-1 nerve block and decreased (by the stepping value δ) following a successful femoral 3-in-1 nerve block and starting dose of 0.20%. The total number of patients required will be approximately 32 (estimated range 25-50) (Please see attached sample size justification in a letter for Dr Alex McConnachie senior statistician at the Robertson centre, Glasgow University). Multiple interim analyses will be performed 2 patients after each turning to ensure that δ (the incremental change in the concentration which will initially be set at. 0.025%) is approximately 2/3 to 3/2 of the σ (the standard deviation of the normal distribution for the EC_{50}) an δ will be altered if necessary to increase the accuracy of the estimate obtained for the EC_{50} concentration and hence the estimate of EC_{95}.

3.4 Statistical considerations

Part B

3.5 Primary end point

The duration of analgesia following a successful femoral 3-in-1 block with the 30ml of levobupivacaine at a concentration calculated to provide analgesia for ≥10 hours to 95% of patients (EC_{95}) with a fracture neck of femur (derived from the results of part A).

3.6 Secondary end points

- Sensory function of the femoral, obturator and lateral cutaneous nerves will be tested at 0 minutes (pre insertion of levobupivacaine) and at 10 and 20 minutes post insertion of 30mls of levobupivacaine.
- The resting pain VAS score will be recorded pre femoral 3-in-1 nerve block and at 10 minutes, 20 minutes and 30 minutes post block in order to estimate the time to half the resting pain VAS score. This will be modelled using both linear and nonlinear statistics with fixed and random effects to achieve the best fit for the data and therefore the best estimate of half pain time.
- Time taken and number of attempts to insert femoral 3-in-1 nerve block.
- Blood pressure, oxygen saturation, pulse rate and respiratory rate pre and 30 minutes after insertion of 30mls of levobupivacaine.
- Serum concentrations of levobupivacaine from blood samples taken at 5, 10, 20, 30 and 60 minutes after insertion of the local anaesthetic.
- Venous blood gases and liver function tests.

3.7 Number of patients needed

The primary outcome of this study is the duration of analgesia. The standard deviation is approximately 4 hours (from clinical experience). The standard error of the mean is the standard deviation divided by the square root of the sample size. Hence a sample size of 16 will provide a standard error of 1 hour (assumed mean duration of approximately 10 hours). Therefore to estimate the mean duration of analgesia with a 95% confidence interval of ±2 hours will require a sample size of approximately 16 (estimated range 5-30) patients, assuming an approximately Normal distribution.

3.8 Statistical justification of sample size

Part A

8 Use of up down study design

The Up-Down study design requires the specification of an initial dose x_0, and δ, the difference between successive doses. Dose is usually measured on a log scale. The first experiment takes place at dose x_0: if it is a success, the second experiment takes place at dose x_0-δ; if it is a failure the second experiment takes place at x_0+δ. The sequence of experiments continues in this way, with the dose reduced by δ whenever an experiment is successful or increased by δ whenever an experiment fails.

Standard Estimation (Dixon & Massey)

It is assumed that for a given (log) dose, x, the probability, P(x), that the dose will be effective is

$$P(x) = \Phi\left(\frac{x - \mu}{\sigma}\right)$$

where Φ is the cumulative density function of a standard Normal distribution. μ is the dose at which $_{50}$% of the population would achieve pain relief, or EC_{50}, since $P(\mu) = \Phi(0) = ½$.

If the numbers of successes is less than the number of failures, then $\hat{\mu} = \bar{y}_1 - \delta/2$, where $\bar{y}_1$ is the mean dose over the successful experiments; otherwise $\hat{\mu} = \bar{y}_0 + \delta/2$, with $\bar{y}_0$ being the mean dose over experiments that were failures.

The standard error of $\hat{\mu}$ is estimated by

$$SE(\hat{\mu}) = G\sigma/\sqrt{n_k}$$

with σ estimated by

$$\hat{\sigma} = 1.620\delta\left(\frac{s_k^2}{\delta^2} + 0.029\right)$$

and k = 1 or 0 depending on whether $\hat{\mu}$ was estimated from the successful or unsuccessful experiments, s_k^2 is the sample variance of the dose levels and n_k is the number of experiments used in the estimation of $\hat{\mu}$. The constant G is an approximately linear function of δ/σ: for $\delta=\sigma$, G≈1; for $\delta=2\sigma$, G≈1.2.

Since n_k is approximately ½N, where N is the total number of experiments conducted, the required sample size for a study can be calculated depending upon the desired width of the confidence interval for μ, relative to σ. Since the 95% CI for μ will be approximately $\hat{\mu} \pm 2\mathrm{SE}$, the required sample size will be $N = 8/\Delta^2$, if δ≈σ, where ±Δ is the width of the 95% CI required for μ in units of σ, i.e. the 95% CI for μ is $\hat{\mu} \pm \Delta\sigma$. Thus for a 95% CI of ½σ each way, the required sample size will be about 32. A sample size of 32 patients is the best estimate of the minimum number of patients needed to determine the EC_{50} and 95% confidence intervals. The actual sample size needed may vary from the current estimate of 32 patients. The estimated range of the population required will be 35-50 patients using the information from the clinical trial data of the patients that have been recruited.
Estimation of percentiles other than the 50th, e.g. the dose at which 95% of patients would achieve pain relief, or EC_{95}, is given by

$$\hat{\mu} + z_{0.95}\hat{\sigma}$$

where $z_{0.95}$=1.645 is the 95th percentile point of a standard Normal distribution. The standard error of this estimate is

$$\sqrt{\mathrm{SE}(\hat{\mu})^2 + z_{0.95}^2 \mathrm{SE}(\hat{\sigma})^2}$$

where $\mathrm{SE}(\hat{\sigma}) = H\sigma/\sqrt{n_k}$, with H following an approximately quadratic function of δ/σ, taking its smallest values over the range σ<δ<2σ, where H≈1.3-1.4.

Comments
The estimation method as described in Dixon & Massey is straightforward in the sense that it provides an estimate of μ based on a mean dose, and leads to a simple sample size calculation. However, many of the steps taken to reach parameter estimates and their standard errors are not transparent, and the estimates of standard errors involve multiplication by factors (G and H) that are not well defined. Furthermore, the standard error estimate for quartiles other than the EC_{50} does not take account of the correlation between estimates for μ and σ.

Justification of interim analysis of part A
The number of patients needed is affected by two variables:

1- A suitable starting value for x_0
2- A value for the dose change between experiments (δ) which should ideally be in the region of σ-1.5σ.

Recommendations:

The formula $N = 4/\Delta^2$ should be used as an initial estimate of the required sample size for a study.

The appropriateness of the value used for δ should be modified throughout the study based on the accrued evidence, and modified if necessary.

Statistical justification of sample size of part B
Part B of the proposal seeks to estimate the mean duration of analgesia. Based on an assumption that the standard deviation of this outcome is 4 hours, then to estimate the mean duration of analgesia with a 95% confidence interval of ±2 hours will require a sample size of approximately 16 patients with successful blocks, assuming an approximately Normal distribution. Assuming a mean duration of analgesia of approximately 12 hours, an estimate of ±2 hours will be adequately precise. This sample size calculation depends on several factors which are impossible to estimate accurately prior to conducting the trial and the actual sample size needed may vary considerably from the current estimate of 16 patients. The estimated range of the population required will be 5-30 patients using the information from the clinical trial data of the patients that have been recruited.'

3.9 Pharmacy

Study medication

The investigational medicinal product in this study is levobupivacaine. All doses of levobupivacaine will be prepared, using levobupivacaine that is commercially available within the United Kingdom, by the Pharmacy Production Unit (PPU) at the Western Infirmary, Glasgow. Each 30ml dose will be prepared aseptically in a 50ml capped syringe as a batch (n=1) using 0.9% sodium chloride as a diluent and will be subject to a QP batch release. Prepared study supplies of levobupivacaine with a protective sleeve will be stored in a secure location in a temperature monitored refrigerator at 2-8°C and deviations of >2°C for greater than $_{50}$ minutes will be reported. The expiry date from preparation will be a maximum of 28 days.

- Supplies of levobupivacaine will be labelled with the following information as a minimum:
- Information on sponsor and chief investigator
- Drug, formulation, strength and quantity
- Route of administration
- Statement 'for clinical trial use only'
- Storage and administration instructions
- Batch number
- Expiry date

Part A:

The initial concentration of levobupivacaine will be 0.20%. The levobupivacaine concentration will then be increased by the stepping value which will initially be

0.025% after an unsuccessful femoral 3-in-1 nerve block and decreased by the stepping value which will initially be set at 0.025% following a successful femoral 3-in-1 nerve block as outlined in section 2.8 above. The maximum and minimum concentration of levobupivacaine to be used in the study will be 0.375% and 0.005% respectively. The total volume of all levobupivacaine (IMP) doses will be 30ml.

Part B:

PPU will prepare a fixed concentration of 30ml levobupivacaine for use in patients recruited to part B based on the outcome of part A. The chief investigator will be responsible for informing sponsor and PPU in writing of the calculated EC_{95} dose prior to the dosing of any patients under part B.

Storage and supply will be under the control of PPU. Study drug will only be supplied from pharmacy once all the appropriate regulatory and governance approvals are in place. Only those supplies intended for use in the study can be administered to study participants.

A record of all study drug movements will be maintained for accountability purposes. Drug accountability records for all used and unused supplies will include:

- An inventory at the site
- Use by each patient
- Return and disposal

The records should include dates, quantities, batch numbers and expiry dates. The study specific IMP destruction form must be completed prior to the destruction of any excess, expired or patient returns of study medication. The inventories must be made available for inspection by the study sponsor or their designee and the regulatory authorities. All concomitant medications prior to and during the study period will be collected.

4.0 Study site staff and responsibilities log

See associated document ‘study site staff and responsibilities log’ version-1 dated 20/04/12

5.0 Adverse events-Pharmacovigilance

Definitions

Adverse Event (AE)
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any adverse event or adverse reaction that

a. results in death
b. is life threatening
c. requires hospitalisation or prolongation of existing hospitalisation
d. results in persistent or significant disability or incapacity
e. consists of a congenital anomaly or birth defect.
f. is otherwise considered medically significant by the investigator

Suspected Serious Adverse Reaction (SSAR)
Any adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) or the Investigator's Brochure (IB)

Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) or the Investigator's Brochure (IB)

Detection, Recording, and Reporting of Adverse Events

5.1 Expected SAES

The adverse events expected during the study are those commonly associated with hip hemi-arthroplasty and hip fixation using dynamic hip screw, spinal anaesthesia, general anaesthesia, sedation and anterior psoas compartment nerve block.

5.2 Femoral 3-in-1 nerve block

Those associated with femoral nerve block include failure, either to develop a satisfactory block for the surgery to commence or for the duration of the block to be greater than 2 days.

5.3 Spinal anaesthesia

Spinal anaesthesia may be very rarely associated with spinal cord damage; haematomas or abscesses around the site of nerve block; hypotension after onset of the block; adverse drug reactions including allergy, rash, headache.

5.4 Surgical fixation of fractured neck of femur

Adverse events commonly associated with surgical fixation of a proximal femoral fracture include: death, dislocation of hip, peri-prosthetic fracture, readmission to hospital, haemorrhage, deep venous thrombosis and pulmonary embolism; wound infection and wound haematoma, cardiac failure, cardiac arrhythmias, sepsis, respiratory failure, paralytic ileus of the gut, bleeding or perforated gastric or duodenal ulceration. The patients often develop an acute confessional state or suffer the exacerbation of a chronic confessional state during there admission to hospital. Patients also commonly require long term care or an increased level of input from nursing and social services after a hip fracture.

5.5 Non surgical management of fractured neck of femur

Adverse events commonly associated with non surgical management of a proximal femoral fracture include: death, pressure sores, readmission to hospital, haemorrhage, deep venous thrombosis, pulmonary embolism, cardiac failure, cardiac arrhythmias, myocardial ischaemia or infarction, sepsis, respiratory failure or infection, paralytic ileus of the gut or constipation, bleeding or perforated gastric or duodenal ulceration and cerebrovascular accident (intracranial haemorrhage or ischaemia). The patients often develop an acute confessional state or suffer the exacerbation of a chronic confessional state during their admission to hospital. Patients also commonly require long term care or an increased level of input from nursing and social services after a hip fracture and due to the high incidence of osteoporosis they often fracture other bones.

5.6 Sedation and general anaesthesia

Adverse events associated with sedation and general anaesthesia include post operative nausea and vomiting, post operative respiratory depression, respiratory infection, hypotension, aspiration and sedation.

5.7 Recording, Assessment and Reporting of SAEs

Part A

Adverse events occurring after discharge from theatre recovery will only be reported and recorded if they are causally related to the anterior psoas compartment nerve block.

Part B

Adverse events occurring after the final pain scores are recorded (up to 24 hours later) will only be reported and recorded if they are causally related to the anterior psoas compartment nerve block.

Full details of all adverse events (including the nature of the event, start and stop dates, severity, relationship to study drug and outcome) will be recorded in the patient case notes and the study case report forms, signed and dated and Dr. Malcolm J. Watson will be informed

AEs will be monitored and followed up until satisfactory resolution or stabilisation.

Serious Adverse Events other than those listed in Section 6.1 above must be reported to the sponsor as detailed below.

NB: Any AE that is assessed as **serious**, is suspected of having a **causal relationship** to the trial medication and is **unexpected** is a **SUSAR** and will require expedited reporting to the MHRA/ Ethics Committee.

5.8 Assessment of adverse events

All adverse events must be assessed for seriousness, causality, expectedness and severity. This assessment is the responsibility of the Chief Investigator

Assessment of Seriousness

An adverse event is serious if it:

a. results in death
b. is life threatening
c. requires hospitalisation or prolongation of existing hospitalisation
d. results in persistent or significant disability or incapacity, or
e. consists of a congenital anomaly or birth defect.
f. is otherwise considered medically significant by the investigator

Assessment of causality i.e. does it have a "reasonable causal relationship" with trial medication?

Assessment for expectedness. (i.e. is the reaction a recognised adverse effect of the medication or is it unexpected?)

Expected: consistent with the toxicity of the (Investigational Medicinal Product (IMP) listed in the Summary of Product Characteristics (SmPC) or Investigator's Brochure (IB)

Unexpected: not consistent with the toxicity of the IMP listed in the SmPC or IB

Assessment of severity

This should be assessed and described using the following categories:
Mild-awareness of event but easily tolerated
Moderate-discomfort enough to cause some interference with usual activity
Severe-inability to carry out usual activity

5.9 Reporting of serious adverse events

Once the Chief Investigator Dr Malcolm J Watson becomes aware that a SAE (not listed in 5.1 above) has occurred in a trial participant he is required to inform the sponsor (via the Glasgow Clinical Trials Unit Pharmacovigilance office) immediately (24-48 hours),

For all such SAEs, a Serious Adverse Event form should be completed and forwarded to the GCTU Pharmacovigilance Office following the procedure detailed on the GCTU website http://glasgowctu.org/for-investigators.aspx

All **SUSARS** must be reported in an expedited fashion to the MHRA and Ethics Committee as follows:

Fatal or life threatening SUSARs: not later than 7 days after the CI had information that the case fulfilled the criteria for a fatal or life threatening SUSAR, and any follow up information within a further 8 days.

All other SUSARs: not later than 15 days after the CI had information that the case fulfilled the criteria for a SUSAR.

5.10 Annual Safety Report

An Annual Safety Report is required to be submitted to MHRA and REC on the anniversary of the issue of the Clinical Trials Authorisation. The Chief Investigator will submit this report on behalf of the sponsor as per GCTU SOP 18.003.

6.0 Data handling and record keeping

All electronic data will be stored on hospital computers and any other electronic copies will have any identifiable patient details removed. Unidentifiable patient data may be stored on NHS, university computer, web sites and personal computers with built in redundancy or back up procedures to prevent data loss and all such data will be password protected and encrypted. The paper records containing the personal identifiable data of the patients and their unique sequential identifier will be stored on paper for 1 year after completion of the trial in a locked metal filing cabinet in the Ultrasound research office, F-block, Lower Ground Floor, Western Infirmary General, 38 Church Street, Glasgow, G11 6NT. Only the chief investigator will have access to this data.

7.0 Indemnity and insurance

This study is sponsored by NHS Greater Glasgow and Clyde Health Board and all the researchers named in this protocol are full time NHS employees therefore patients' recruited to this clinical trial will be covered for negligent harm through the NHS CNORIS indemnity scheme.

8.0 Definition of the start and end of the trial

The trial will be terminated when the last patient is recruited and treated in the study.

9.0 Publication Plan

The data from this study will be published in peer review journals (i.e. British Journal of Anaesthesia, Anaesthesia or Regional Anaesthesia and Pain Medicine). Prior to publication it will be presented in poster and abstract form at the annual ESRA meeting.

10.0 Data Monitoring

10.1 Data monitoring committee

The data monitoring committee will comprise of Dr Michael Serpell and Dr Alex McConnachie of the Robertson centre, Glasgow University. They will meet every 3 months to review the data gathered by the trial and adverse events recorded.

11.0 Archiving of data

Data will be archived in accordance with the NHS Greater Glasgow and Clyde Health Board policies 5 years after the end of the study.

12.0 Updates to protocol or changes to paper work

We will seek approval from the 'The West Glasgow (1) Research Ethics Committee', the MHRA and Research and Development at NHSGGC before any changes are made to the protocol, procedures, personnel or paperwork associated with this trial.

Appendix 13

13.0 References

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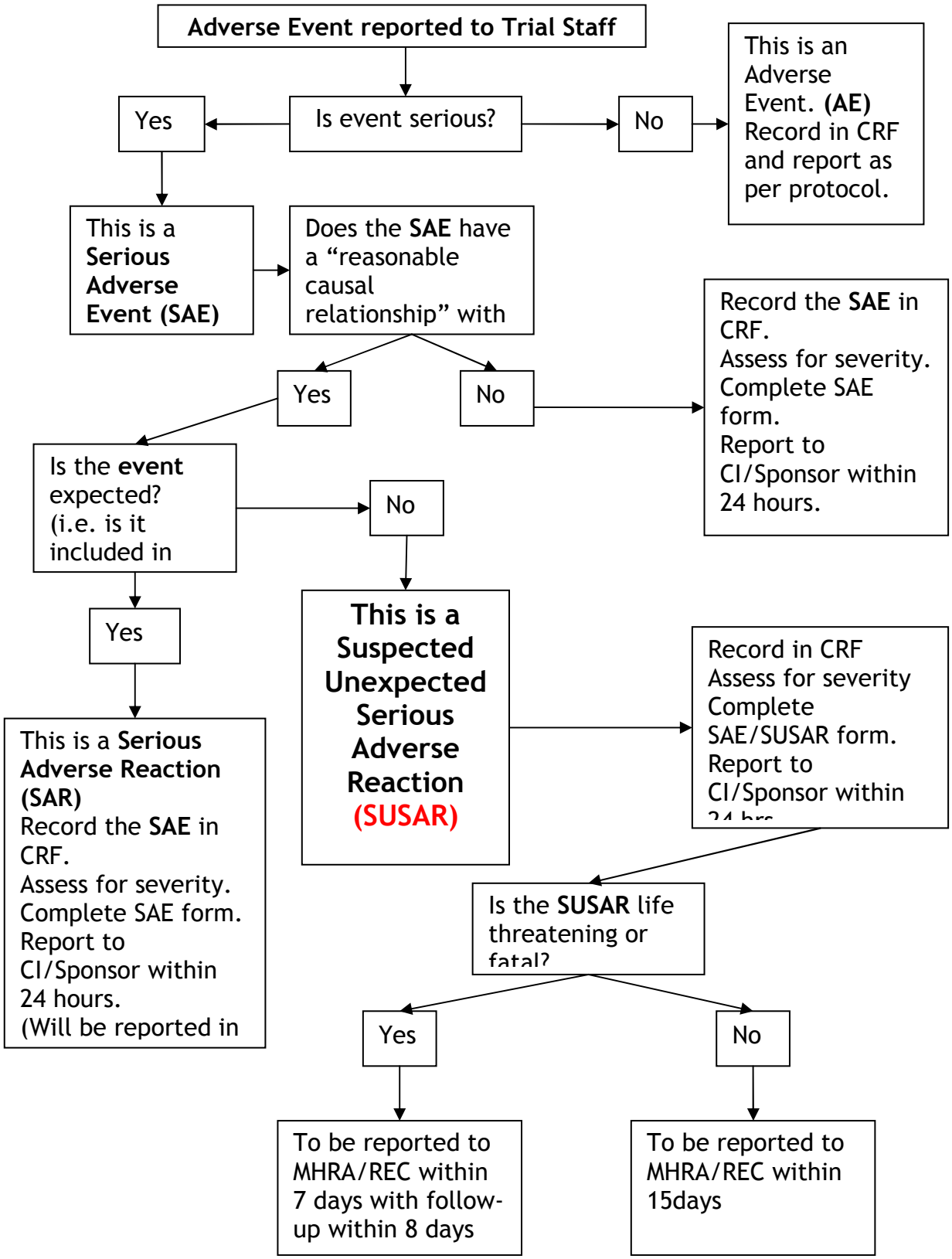
Appendix 1: Flowchart for Assessing and Reporting Adverse Events in IMPs



Appendix 2: Flow chart summary of study

-Part A-

The first approximately 32 (35-50) patients to be recruited to study

Time	Patient pathway
-12 to -9 hours	Patient falls and fractures hip at home
-9 to -8 hours	Transferred to Accident and Emergency via ambulance
-8 to-5 hours	Admitted to Orthopaedic ward
-5 to -4 hours	Investigator called by ward medical or nursing staff
-4 to -2 hours	Attend ward to give verbal and written information about study
-2 to -1 hours	Written consent taken
-1 hours	Patient transferred to theatre suite continuous cardiorespiratory monitoring started
-2minutes	Baseline resting pain scores and sensory scores (25G needle and melting ice)
0 hours	Ultrasound guided femoral 3-in-1 block and catheter inserted by Malcolm Watson
+10minutes	10 minutes resting pain scores and sensory scores (25G needle and melting ice)
+20minutes	20 minutes resting pain scores and sensory scores (25G needle and melting ice)
+30minutes	30 minutes resting pain scores and sensory scores (25G needle and melting ice)
+35minutes	If resting pain VAS >30/100, Patient given rescue analgesia , 20mls of 0.25% levobupivacaine via femoral nerve catheter
+1 to +24 hours	Returned to ward for standard cardio respiratory monitoring and hourly VAS pain scores
+24hours	Patient has induction of Anaesthesia (general or regional) and surgical fixation of hip or returned to ward for non surgical management of proximal femoral fracture

After approximately 32 (35-50) patients have been recruited with effective femoral 3-in-1 nerve blocks the levobupivacaine EC_{50} and EC_{95} will be estimated

-Part B-

The next approximately 16 (5-30) patients with effective nerve blocks with the levobupivacaine EC_{95} will be recruited to part B

Time	Patient pathway
-12 to -9 hours	Patient falls and fractures hip at home
-9 to -8 hours	Transferred to Accident and Emergency via ambulance
-8 to-5 hours	Admitted to Orthopaedic ward
-5 to -4 hours	Investigator called by ward medical or nursing staff
-4 to -2 hours	Attend ward to give verbal and written information about study
-2 to -1 hours	Written consent taken on morning of scheduled hip fixation surgery
-1 hours	Patient transferred to theatre suite continuous cardiorespiratory monitoring started
-2minutes	Baseline resting pain scores and sensory scores (25G needle and melting ice). Blood sample taken for levobupivacaine concentration
0 hours	Ultrasound guided femoral 3-in-1 block and catheter inserted by Investigator
+10minutes	10 minutes resting pain scores and sensory scores (25G needle and melting ice). Blood sample taken for levobupivacaine concentration
+20minutes	20 minutes resting pain scores and sensory scores (25G needle and melting ice). Blood sample taken for levobupivacaine concentration
+30minutes	30 minutes resting pain scores and sensory scores (25G needle and melting ice). Blood sample taken for levobupivacaine concentration
+35minutes	If resting pain VAS >30/100, Patient given rescue analgesia , 20mls of 0.25% levobupivacaine via femoral nerve catheter
+1 to +24 hours	Returned to ward for standard cardio respiratory monitoring and hourly resting pain VAS
+24hours	Patient has induction of anaesthesia (general or regional) and surgical fixation of hip or returned to ward for non surgical management of proximal femoral fracture