APPROACHES TO TREATMENT OF MAJOR PEPTIC ULCER HAEMORRHAGE

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Ethical Permission

Studies were approved by the Lothian Medicine and Oncology Ethical Committee . Animal Experimentation was carried out after obtaining a project and personal licence from the Home Office . Studies involving patients were carried out after obtaining a full consent from every patient .

Acknowledgements

Dorris Russell who accommodated me throughout my period of clinical research .

Abstract

In 200 B C , Hippocrates wrote that "those diseases which medicines cannot cure , the knife cures , those which the knife cannot cure , cautery cures and those which cautery cannot cure are reckoned to be wholly incurable" . This dictum applies well to the management of peptic ulcer haemorrhage . In my period of research at the Western General , I aimed to address some aspects of these three corners of management .

I-Cautery :

Endoscopic injection therapy with dilute adrenaline stops bleeding and prevent rebleeding from peptic ulcers . No treatment is perfect , 15-25% of patients rebleed and require urgent surgery .

My work has examined clinical and experimental approaches of improving endoscopic injection treatment .

i-Major peptic ulcer haemorrhage is the consequence of arterial erosion and the focus of therapy is to cause thrombosis of the arterial defect . Whilst adrenaline probably stops bleeding by causing vasoconstriction , a more permanent approach is to inject thrombin into the bleeding ulcer .Therefore , 140 patients with significant peptic ulcer haemorrhage were randomised to endoscopic injection with adrenaline (70 patients , group 1) or to adrenaline plus human thrombin (70 patients , group 2) . Fourteen (20%) group 1 patients and three (4.5%) group 2 patients rebled ($p<0.005$). The 30 day mortality was 10% in group 1 patients and nil in group 2 patients ($p<0.013$) . Combination of adrenaline plus human thrombin injection appears safe and may represent best treatment for bleeding peptic ulcers .

ii-The mechanisms by which endoscopic therapy stops bleeding are unclear , and to explore this,experiments were performed in a validated animal model in which bleeding mucosal ulcers were treated by a range of injection materials . Active ulcer haemorrhage was arrested by an adrenaline/thrombin combination whilst other agents including sclerosants , hypertonic solution and alcohol were only moderately effective . Arterial thrombosis was not effected by any regime , although the thrombin/adrenaline combination caused local submucosal thrombosis of small vessels which probably act as a haemostatic plug .

iii-Whilst the immediate outcome of patients treated endoscopically for ulcer bleeding is well documented , late prognosis is unclear.

121 patients treated endoscopically for severe peptic ulcer haemorrhage were followed for a median period of 36 months ,and outcome was compared with that of age and sex matched controls .

Kaplan-Mieir plots showed reduced survival in ulcer patients (p<0.01) . 30 patients(26%) died during the follow up period , deaths were largely restricted to patients who had co-morbid diseases .

II-Medicines

Acid reducing agents are extensively used in patients with ulcer haemorrhage but there is no evidence that they have any effect on morbidity or mortality . This leaves those who fail endoscopic therapy and are not fit for surgery at a great risk of death . Octreotide has been used to stop variceal bleeding largely by reducing splanchnic blood flow and it was reasoned that this action may be of value in reducing arterial blood loss

from peptic ulcer haemorrhage . Gastroduodenal mucosal blood flow was measured in experimental animals using a Laser Doppler Flowmeter . Intravenous octreotide infusion markedly reduced gastro-duodenal mucosal blood flow in a dose dependent manner , without causing any systemic haemodynamic disturbance . These findings suggest that this agent may be helpful in the management of bleeding from gastroduodenal ulcer disease and gastritis and trials of octreotide in peptic ulcer haemorrhage are in progress .

III-The Knife

The optimal emergency operation to stop haemorrhage from peptic ulcers is a matter of debate , the answer to this debate could be crucial in determining the short and long term outcome.

Sixty seven of 492 patients failed endoscopic therapy for bleeding peptic ulcer and underwent emergency surgery in Edinburgh in the period 1990-1995 . Simple underrunning was done in 28 patients whilst 39 had more radical surgery . The two groups were well matched for risk factors known to influence prognosis . Rebleeding was significantly higher in patients treated by underrunning (7 versus 1)($p<0.015$) . There were fewer deaths in the radically treated group(5 versus 7)(NS) .Patients undergoing surgical operation for severe peptic ulcer haemorrhage after failed endoscopic therapy may be best served by an aggressive approach .

In conclusion , the approaches of Hippocrates remain appropriate in 1996 . Now cautery by endoscopic therapy has become the treatment of choice for bleeding

ulcers . The knife is reserved for failures of endoscopic therapy , although an aggressive scalpel may work better than a conservative one .

Medicines still have little to offer , although novel approaches using drugs which reduce blood flow may be helpful .

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   Kubba et al (SRS)

Chapter 1

Introduction

The role of endoscopy in the treatment of peptic ulcer bleeding

INTRODUCTION

In specialised centres the mortality of peptic ulcer haemorrhage has been greatly reduced and now lies between 2 and 6% (Jeans et al 1991 , Hunt et al 1980 , Zimmerman et al 1995 , Bramley et al 1993). It is difficult to define a single factor responsible for this low mortality and it is unlikely that further reductions will occur since some deaths from ulcer bleeding are an agonal event in terminally ill patients or occur in very frail elderly patients who have severe comorbid diseases. The role of endoscopy in achieving optimum management for patients admitted to hospital because of ulcer bleeding relates to obtaining an early, accurate diagnosis, provision of prognostic information and delivery of haemostatic therapy. Nevertheless it is difficult to prove that diagnostic or therapeutic endoscopy improves survival and it is likely that the best outcome is achieved by concentration of resources and expert personnel upon the critically ill patient leading to proper resuscitation and appropriate use of pharmacological, surgical and endoscopic treatments. Endoscopic therapy is only part of the management jigsaw and best therapy involves a multidisciplinary approach including endoscopists, surgeons, radiologists and experts in intensive care.

Endoscopy is done after the patient has been resuscitated . However out of hours emergency endoscopy in the most severely ill patients is often undertaken by relatively inexperienced endoscopists in suboptimal surroundings without expert nursing assistance. Centres with special interest in gastrointestinal bleeding have properly equipped and manned facilities available 24 hours a day. Although the great majority of cases can be safely endoscoped during the next working day(Choudari et al 1993) , some actively bleeding patients do require out of hours endoscopy and resources must be available to manage them.

Pathophysiology

Major bleeding occurs when a peptic ulcer erodes a large artery. Branches of the gastroduodenal artery may be involved by posterior duodenal ulcers and branches of the left gastric artery can be ruptured by lesser curve ulcers. It is of interest that bleeding from ulcers in these sites tends to be particularly brisk (Swain* et al 1986) . The involved arteries range in size between 0.1 - 1.8mm and it has been shown that breaches greater than 4mm in diameter are unlikely to respond to any form of endoscopic therapy (Swain^ et al 1986) .

Arteritis is commonly seen in vessels involved by ulcers and this makes interpretation of histological changes which follow endoscopic therapy difficult .

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For example it may be impossible to quantify the degree of arteritis or thrombosis associated with endoscopic therapy when similar changes are an inherent feature of the ulcer process. In addition, the relative infrequency of biopsy material and lack of an animal model of ulcer bleeding have greatly limited the ability of researchers to define the effects of endoscopic therapy in man.

Haemostatic mechanisms following ulcer bleeding are unclear . The effect of acid contents upon clotting is largely unknown although it is clear that blood clot stability is impaired by low pH . Detailed understanding of thrombotic mechanisms may result in strategies for developing optimal intragastric conditions for haemostasis and specific agents which could be applied to the bleeding point.

Patient selection

Approximately 80% of patients stop bleeding spontaneously (Bornman et al 1985 , Clason et al 1986) . Endoscopic or surgical therapy is clearly unnecessary and meddlesome in this group. Patients at risk of uncontrolled bleeding tend to be elderly, present with hypotension, tachycardia and anaemia. Mortality is high in patients who have an upper gastrointestinal haemorrhage while hospitalised for other reasons(Zimmerman et al 1994). The presence of significant comorbid disease increases the risk of death, particularly if a surgical operation is necessary

(NIH 1989 , Silverstein et al 1981 , Branicki et al 1990 , Peterson et al 1990) . The most important prognostic factor however is the endoscopic findings (Chang-Chien et al 1988 , Lin et al 1992 , Freeman et al 1993 , Foster et al 1978 , Griffiths et al 1979 , Storey et al 1981 , Wara 1985). Patients who at endoscopy are found to be actively bleeding and who are shocked have an 80% risk of continuing to bleed or of rebleeding during that hospital admission . The presence of a non-bleeding visible vessel (figure 1) is associated with a 50% chance of rebleeding . The "visible vessel" represents either a pseudo-aneurysm of the damaged artery or a sential blood clot (Swain 1990) . Although adequate cleaning of the ulcer base is necessary to define the endoscopic appearances, the endoscopist must be aware that disturbing the "visible vessel" can cause brisk, active bleeding.

Adherent blood clot and "oozing" (figure 2&3) have been associated with a significant risk of rebleeding rate by some authors(Storey et al 1981, Wara 1985) ; others suggest that rebleeding is uncommon and it is my own practice not to treat patients who present with oozing or adherent clots from ulcers endoscopically . A clean ulcer base (figure 4) is not associated with further bleeding.

Some enthusiasts have advocated the use of endoscopic Doppler devices to identify patent arteries within and around the ulcer, and have reported that only

ulcers with a positive Doppler signal should be treated (Beckly et al , Kohler et al 1991 , Fullarton et al 1990) .

Endoscopic stigmata of ulcer haemorrhage are ephemeral; obviously all patients who present with ulcer haemorrhage have active bleeding at some stage, and the frequency with which stigmata are found varies with the timing of endoscopy . For example if endoscopy is performed within 12 hours of admission approximately 70% of ulcers will have important endoscopic stigmata but if endoscopy is delayed after 12 hours these endoscopic findings will only be present in 40% of comparable patients (Foster et al 1978) . The timing of endoscopy is therefore important in interpreting clinical trials of ulcer bleeding therapy.

Despite this observation it is generally agreed that patients who are found to be actively bleeding from the ulcer and those who present with a non-bleeding visible vessel should be treated endoscopically, and those without stigmata should be managed conservatively. Surgery is now reserved for the failures of endoscopy therapy; when access is impossible because of profuse active bleeding or when the patients continues to bleed despite apparently adequate endoscopic therapy.

It is important that the endoscopist knows his/her limitations . Massive bleeding from a major artery does not respond to any endoscopic modality and patients

presenting in this way require early emergency surgery; their operation should not be delayed by endoscopic therapy which has little chance of success. It follows that endoscopic treatments are only valuable in managing moderately severe cases. Minor bleeding will settle with supportive therapy, major haemorrhage requires an emergency operation whilst the intermediate group of patients benefit from endoscopic therapy . This may avoid the need for a surgical operation and may reduce transfusion requirements, but because endoscopic therapy has limited value in the more profusely bleeding patients , its impact upon reducing hospital mortality is only modest.
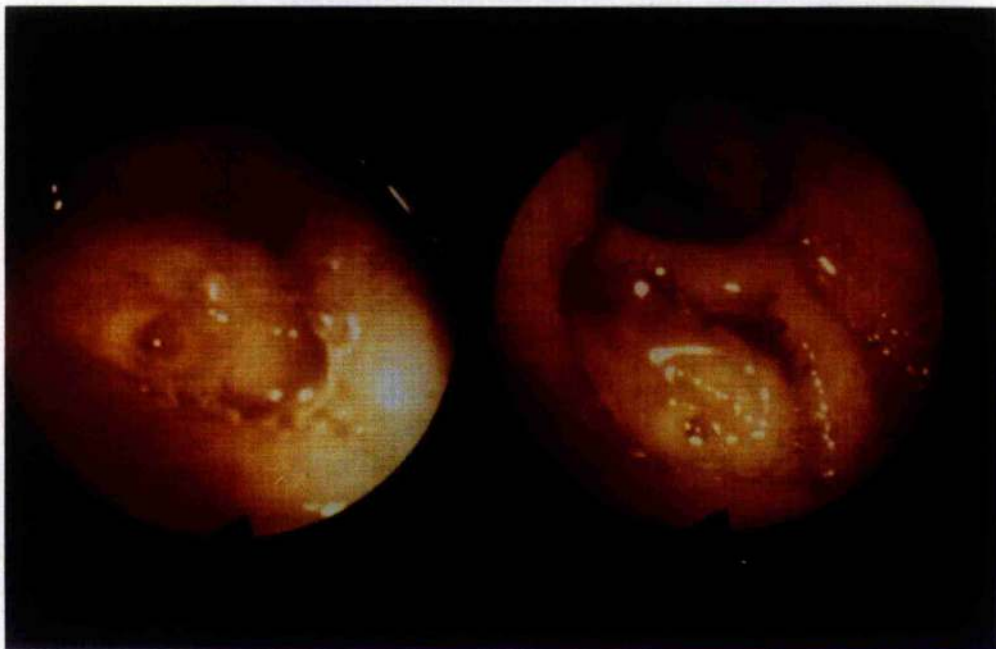
Figure 1 An ulcer with a non bleeding visible vessel

Figure 2 An ulcer with an adherent clot
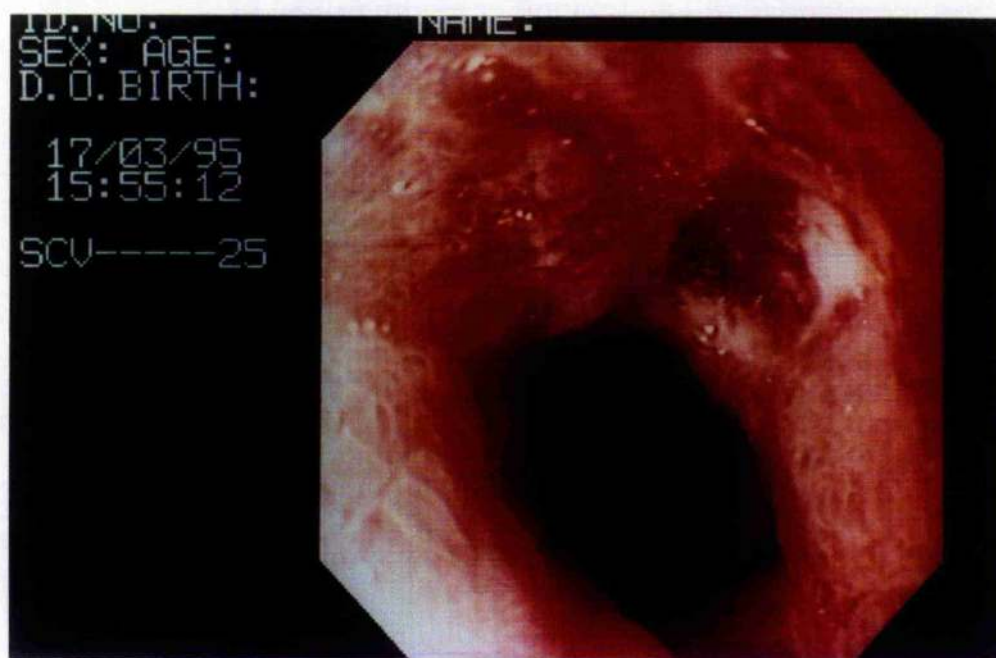
Figure 3 An oozing ulcer

Figure 4 An ulcer with clean base

End Points

The most important and best defined end point is death. Most series report "hospital mortality" although surgical literature generally refers to "30 day mortality".

In some clinical trials patients randomised to conservative therapy have received active treatment once it is clear that they are continuing to bleed or rebleed (Rajgopal et al 1991) . Although this approach to a trial can be criticised on scientific grounds, in clinical practice it is ethically difficult to deny ill patients access to active therapy. These trials therefore show no effect upon mortality although analysis of other end points demonstrates efficacy of therapy.

"Rebleeding" is strongly associated with death and it has been known for many years that the mortality of patients who rebleed in hospital is tenfold increased (Bornman et al 1985) . Rebleeding rates are therefore used in most series to define efficacy of therapy and in many studies rebleeding and uncontrolled bleeding (active bleeding which continues despite therapy) are reported together . Unfortunately it is often difficult to know in clinical practice when rebleeding has occurred . Falls in haemoglobin concentration may be a consequence of haemodilution; the passage of melaena or occult blood positive stool can occur for

days after bleeding has stopped; pulse and blood pressure alterations may be due to a range of causes . It is usual to define rebleeding as the sudden development of haematemesis and/or melaena associated with clinical shock or a rapid fall in haemoglobin concentrations of at least 2g/dl over a 24 hour period .

Other end points are subject to many variables which make them less useful . The need for a surgical operation tends to vary according to institution. For some surgeons, the need to transfuse more than 4 units of blood is an indication for an operation, whilst others will operate only for active bleeding . Transfusion requirements are a crude indication of blood loss, because criteria for transfusion also differ widely between clinicians . Duration of hospital admission is a poor indicator because it tends to relate more to the presence of comorbid disease rather than to the severity of bleeding.

Endoscopic therapy - principles

Haemostatic therapy is based upon the need to thrombose the bleeding artery. This can be attempted by thermal modalities, diathermy, injection of vasoconstricting, sclerosing or clotting factors and by mechanical devices (Table 1).

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TABLE I

Endoscopic treatment for bleeding ulcer

Thermal

    Argon laser

    Neodymium YAG laser

    Heater probe

    Electrocoagulation

Injection

    Adrenaline

    Sclerosants

    Alcohol

    Thrombin

Other

    Topical sprays

    Microwave coagulation

    Mechanical

Thermal devices - laser photocoagulation

The Argon laser emits visible blue-green light energy . Tissue penetration is superficial and high power settings are needed to cause a tissue effect.

Experiments in a canine model of ulcer bleeding showed that haemostasis can be achieved using the Argon laser with low risk of gastric perforation (Silverstein et al 1976) . Three controlled clinical trials involving patients who at endoscopy had major stigmata of peptic ulcer bleeding were published in the 1980s (Swain et al 1981 , Vallon et al 1981 , Jensen et al 1984) (Table II) . Swain et al selected 76 of 330 patients who presented with gastro-intestinal bleeding, 52 of these were randomised to laser photocoagulation or managed conservatively . Rebleeding episodes (8 in the treated group versus 17 controls) and hospital mortality (0 versus 7) were significantly lower in treated patients . This, like many studies of ulcer bleeding suffers from the criticism of small numbers and selection bias . Nevertheless efficacy of Argon laser photocoagulation was also shown by the other 2 studies .

Further animal studies suggested that Nd-Yag laser energy may be a more appropriate haemostatic tool . The depth of penetration is several millimeters, resulting in an immediate obvious tissue effect associated with coagulation within

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vessels, acute inflammation within the mucosa and submucosa leading to eventual scar tissue formation (Silverstein et al 1979) . Studies in mesenteric arteries demonstrated that small and medium sized breaches could be sealed although holes greater than 0.4mm in diameter continued to bleed (Rutgeerts et al 1981) . Perforation of an experimental ulcer required relatively large amounts of energy and an order of magnitude greater than that associated with arterial coagulation (Dixon et al 1979). These characteristics led to the view that Nd-Yag laser treatment was more suitable than Argon photocoagulation but it is of interest that the clinical efficacy of the two modalities is very similar.

Nd-Yag photocoagulation: technical aspects

Nd-Yag lasers produce infra-red light energy at a frequency of 1064nm. Light is transmitted via flexible glass fibres using medium power settings of 25-50 watts . Tissue effects around the bleeding point are achieved without allowing the probe to touch the mucosa . Accurate therapy depends upon assiduous cleaning of the ulcer base and active bleeding increases the difficulty of administering optimal treatment . Standard safety precautions, particularly involving the use of filters and safety locks on doors in the endoscopy suite, are necessary to protect the endoscopist and assistants.

Clinical trials

Several uncontrolled series suggested that Nd-Yag laser photocoagulation of bleeding ulcers is safe and effective . The most notable of these was the large series reported by Kieshaber et al (1990) who reported more than 90% efficacy in 1058 treated patients .

Nine controlled clinical trials of Nd-Yag laser versus conservative therapy have been published (Table III). In common with studies of Argon laser therapy, the number of patients included in any one study is relatively small. Nevertheless criteria for inclusion, particularly endoscopic findings or major stimgata of bleeding, are uniform. Meta-analysis is therefore justified and has shown that laser therapy reduces the rate of rebleeding and decreases hospital mortality (Cook et al 1992 , Henry et al 1988) .

Swain*^ et al(1986) randomised 131 patients to laser or conservative therapy , treatment was administered by one of two experienced endoscopists and objective end points were assessed by independent clinicians . Seven of 70 patients treated by laser rebled and one of these died in hospital . This contrasted with rebleeding in 27 of the 68 conservatively managed patients and eight of these died . These differences were statistically significant . However even in the experienced hands

of these endoscopists, 19% of patients had ulcers which were inaccessible to treatment either because bleeding was severe and obscured the ulcer or because the bleeding ulcer was awkwardly situated .

A contrasting study is that reported by Krejs et al(1987) . This two centre American trial failed to show benefit for Nd-Yag laser therapy . Nineteen of 85 treated patients and 18 of 89 conservatively managed patients rebled and surgical operation rates, hospital mortality and transfusion requirements were virtually identical in the two groups .

The reasons for the different conclusions of these studies illustrate many of the difficulties associated with clinical trials in this field . Although both trials exclusively randomised ulcers associated with major endoscopic stigmata, actively bleeding ("unstable") patients who comprise the highest risk category were few in the American study. This trial thereby compared outcome in a relatively less severe disease group . This is confirmed by a much lower rebleeding rate in the American control group compared to that of the London(Swain) study. Patients in the study of Krejs et al were also relatively young, with a median age of only 49 years; much less than reported in all other bleeding studies. Endoscopic therapy was administered by a small number of experienced endoscopists in the London

study , whilst many more operators were involved in the American trial . It seems likely that some of the American endoscopists were climbing their learning curve whilst the Londoners were established experts .

Whilst the effiacy of Nd-Yag laser therapy varies between trials, the studies are consistent in demonstrating that treatment is safe.   Only one case of laser associated perforation having been reported (Krejs et al) .

Current status

Clinical trials show that both Argon and Nd-Yag photocoagulation are effective treatments for bleeding peptic ulcer . Both modalities are safe and reported complications are very rare.   Laser therapy is at least as versatile as other endoscopic modalities since it is also the treatment of choice for vascular anomalies (Cello et al 1986) and is effective therapy for the Dieulafoy abnormality (Al-Kawas et al 1987) .

Despite these observations, laser is now very little used as haemostatic therapy for bleeding ulcer . This is because the machines are expensive and until recently have been cumbersome and non-portable . Of all available modalities laser is the most demanding for the endoscopist; the no-touch technique and the need to treat circumferentially around the bleeding point present great practical difficulties in

many bleeding patients . This is reflected by the high inaccessibility rate, reported

in the clinical trials . Other endoscopic therapies are at least as effective, tend to be

easier to apply and are cheaper.

Table II

Controlled trials of Argon laser therapy

Author (year)	Number randomised	Further/uncontrolled Bleeding			Comments
		Laser	Controls		
Swain et al (1981)	75 (52 with major stigmata)	8/20	17/28	P < .05	Benefit only in patients with major stigmata
		3/19	8/16	NS	Reduced mortality in treated group (0 versus 7 deaths)
Vallon et al (1981)	136 35 NBVV 28 active bleeding 73 spots	8/19 5/15	8/19 9/13	NS P < .05	Benefit only in actively bleeding patients
		2/34	4/39	NS	
Jensen et al (1984)	16	2/7	7/9	NS	Overall morbidity score lower in treated patients

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Table III
Controlled trials of Nd-Yag laser photocoagulation

Author (year)	Number randomised	Further/Uncontrolled bleeding			Comments
		laser	Control		
Swain** et al (1986)	138 NBVV 59 Active bleeding 20 Other stigmata 69	4/28 2/10 1/32	15/31 8/10 6/27	P < .001 P < .002 NS	Active treatment associated with improved mortality (1/70 v 8/65, P < .005)
Rutgeerts et al (1982)	152 23 actively bleeding not randomised: 20 controlled bleeding 70 oozing 43 NBVV	3/38 5/14	9/38 12/22	P < .01 NS	Also includes patients bleeding from other sources no effect on mortality
Krejs et al (1987)	174 32 active bleeding 142 other stigmata	5/29 14/85	5/33 13/89	NS NS	Many exclusions because of "instability". See text.
Mathewson et al (1990)	143	9/44	18/24	P < .05	Also included group of patients treated by heater probe
Rohde et al (1980)	105	35/62	25/43	NS	Reported in abstract form: details of therapy and randomisation unavailable
Buset et al (1985)	88	6/44	28/44	P < .05	Other end points not reported

Study	n							Comments
Ihre et al (1981)	66	32 active bleeding 42 other stigmata	6/18 3/19		5/14 4/23	NS NS		Details unclear; other causes of bleeding included in paper
Escourrou et al (1981)	83		7/40		12/43	NS		
Homer et al (1983)	42		4/21		5/21	NS		No other end points

Heater Probe

The heater probe comprises a portable power source in which preset amounts of heat energy are transmitted to the teflon coated metal tip of an endoscopically positioned catheter; best results are obtained using larger diameter probes at medium power settings . The catheter is also fitted with a powerful water jet which cleans and irrigates the bleeding point and prevents the tip sticking to the ulcer crater. Tamponade can be administered to aid haemostasis and, unlike the laser, heat can be applied by tangential application.

Haemostasis probably results from a combination of heat and tamponade . Experiments in animals showed that the heater probe was more effective than injection therapy in arresting bleeding from canine arteries (Rutgeerts* et al 1989)

.

Uncontrolled series suggested that the heater probe was effective in clinical practice (Storey 1983 , Shorvon et al 1985). In the 1980s small controlled series from Fullerton et al (1989) and from Jensen et al(1988) confirmed that haemostasis of actively bleeding ulcers can usually be achieved, and that rebleeding is infrequent following therapy (Table IV). Tekant et al (1995) performed a much larger controlled trial in which 153 patients exhibiting a range

of endoscopic stigmata associated with peptic ulcer bleeding were randomised to a combination of adrenaline and heater probe thermocoagulation or to no endoscopic treatment . The two groups were well matched with regard to usual risk factors for rebleeding and death, although some patients in both groups had minor stigmata such as red or black spots which are not regarded as having adverse prognostic significance . Haemostasis was achieved by the heater probe in all actively bleeding patients and rebleeding was significantly less common in treated patients (5 versus 16 rebleeds, $P < .01$) .

The heater probe and laser have been compared in two clinical trials (Johnston et al 1985 , Jensen et al 1984) but neither included sufficient patients to show differences in outcome. Pap(1987) also failed to show differences in efficacy between the heater probe and multipolar coagulation . These trials, limited as they are, therefore show little to choose between thermal methods for controlling ulcer bleeding . The lower cost, ability to apply tamponade and to coagulate using tangential application suggest that heater probe is a better buy than laser for treating ulcer haemorrhage.

The more important comparison is between the heater probe and injection therapy. The first clinical trial which compared these approaches was reported by Lin et

al(1990) .One hundred and thirty seven patients who presented with active bleeding or a non-bleeding visible vessel were randomised to heater probe, injections with absolute alcohol or conservative (no intervention) therapy. Initial control of bleeding was better with the heater probe than with injection (98% versus 67%, P <0.04) and permanent haemostasis was achieved significantly more often in patients treated by the heater probe, than injection or conservative management (91%, 67% and 52% respectively). The efficacy of injection treatment described in this study is rather less than reported in most other series. No complications followed endoscopic intervention. The second study, reported by Chung et al(1991), randomised 132 patients who had endoscopic evidence of active bleeding to injection with dilute adrenaline or to the heater probe. Bleeding was initially controlled in 83% of injected patients compared to 95% of heater probe treated patients (P < .05). The apparent advantage of the thermal method has to be balanced by the development of ulcer perforation in two patients who received heater probe therapy. The third study reported by Choudari et al(1992) randomised 120 patients who presented with a range of endoscopic stigmata to 1:100,000 adrenaline plus 5% ethanolamine or heater probe coagulation. Permanent haemostasis was achieved in 87% of injected patients and

85% of heater probe treated patients . Other end points were similar in the two groups . No complication of therapy occurred in any patient.

These studies therefore suggest that the heater probe and dilute adrenaline have similar efficacy and (although data are rather limited) that the heater probe is superior to sclerosant injection . In clinical practice however these differences are not always clearcut and the techniques are complementary . For example the capacity of the heater probe to apply tamponade and its powerful irrigation channel make it suitable for some ulcers which have a large amount of semi-adherent blood clot and which makes the ulcer difficult to inject. On the other hand the heater probe may be rather awkward to manoeuvre within a deformed duodenal cap whilst injection treatment can sometimes be more easily administered . A well equipped bleeding unit should therefore have equipment and expertise for both modalities.

Table IV

Controlled trials of heater probe treatment

Author	Number randomised	Rebleeding/uncontrolled bleeding			Comments
		Heater probe	Sham	Other endoscopic therapy	
Fullarton et al (1989)	43	39 active bleeding	4 NBVV	0/18 0/2	21/21 0/2		p < .002 Heater probe treatment associated with perforation in one patients. Some "inaccessible" ulcers excluded
Jensen et al (1988)	94	38 active bleeding	56 NBVV	22%	72%	(BICAP) 44%	Heater probe superior to other approaches. Details scanty (abstract form only)
Tekant et al (1995)	153	55 actively bleeding	198 other stigmata	3/31 2/43	4/22 12/72		p < .05 Heater probe combined with adrenaline injection. More shocked patients in heater probe group

Study	n				Outcome
Flach et al (1996)	104	27 actively bleeding	2/14	2/13(adrenaline+polidocanol)	NS
		39 NBVV	4/20	3/19	NS
		21 oozing bleed	3/11	3/10	NS
		17 adherent clot	3/8	2/9	NS
Lin et al (1990)	137	71 actively bleeding	2/29	15/24 (alcohol)	Heater probe significantly more effective in active bleeding (p < >002)
		66 NBVV	2/16	7/22	
Chung et al (1991)	132	actively bleeding	11/64	3/68 (adrenaline p < .05)	2 perforations with heater probe
Choudari et al (1992)	120	57 actively bleeding	5/57	6/58 (adrenaline) NS	No difference in relation to endoscopic stigmata
		63 NBVV			

Electrocoagulation

Electrocoagulation devices aim to stop bleeding by passing an electric current through the bleeding area.

Monopolar units apply a ball tipped probe to the bleeding area and the electrical circuit is completed through a plate attached to the patient . The earlier probes often precipitated bleeding because they adhered to the ulcer bed . These probes were also associated with unpredictable tissue damage and the need to frequently clean the tip . The liquid monopolar probe has an electrical conducting fluid between the tip and the mucosa and this largely overcomes the problem of tissue adherence . Three studies have examined monopolar probes in the context of controlled clinical trials (Table V) . The largest study was reported by Freitas et al(1985) who randomised 78 patients presenting with a range of endoscopic findings to electrocoagulation using a liquid monopolar electrode or to sham treatment. Permanent haemostasis was achieved in 19 of 36 treated patients, but a high proportion of the control group had spontaneously stopped bleeding and did not rebleed.

These rather unimpressive results, associated with an unpredictable tissue damage has largely resulted in monopolar electrocoagulation being superseded by other contact methods, particularly the multipolar coagulation system.

Bipolar coagulation works by completing an electrical circuit between probes applied to the mucosa. The patient plate is unnecessary; tissue penetration and damage is more predictable than that associated with monopolar electrocoagulation . In experimental animals, the best system is the multipolar electrocoagulation pulse, known as BICAP (Laine 1991) . This has three pairs of electrodes on its side and tip and electrocoagulation occurs if any pair of electrodes are in tissue contact, allowing tangential treatment . Power settings of 7-8 lasting 1 second are applied circumferentially around the bleeding point until blanching occurs, and the probe is then directly applied to the bleeding point.

Controlled clinical trials with BICAP have reported varying outcome (Table VI) . O'Brien et al(1986) randomised 204 patients who were found at endoscopy to have either active bleeding or a non-bleeding visible vessel. Seventeen of 101 treated patients continued to bleed or rebled compared to 34 of 103 sham treated conservative patients, P < .01. The greatest benefit was found in the subset of patients who had active bleeding; haemostasis was achieved in 24 of 40 patients

with spurting haemorrhage whilst spontaneous haemostasis occurred in only 8 of 13 actively bleeding controls . These, and other authors, commented that bleeding can be precipitated by application of the probe . This can usually be stopped by further BICAP treatment, although this is not invariably possible and catastrophic bleeding has followed BICAP therapy.

Brearley et al(1987) examined the BICAP in 41 bleeding patients and found no benefit for active treatment. Similar lack of benefit was reported by Goudie et al(1984) and by Kernohan et al (1984) .

In contrast, Laine(1987&1989) reported two trials in which prognosis was improved using BICAP . In the first of these , he studied 44 patients who presented with severe gastrointestinal bleeding from a range of causes . Twenty four of these patients were actively bleeding from peptic ulcers . Blood transfusion was less in the 10 treated ulcer patients compared to the 14 control ulcer subjects. The duration of hospital admission and costs of hospitalisation were also less in the treated group. Clearly this very small study is insufficient to confirm efficacy, but benefit was also reported in a larger study performed by the same author . In a clinical trial involving 75 patients who exclusively had non-bleeding visible vessels within ulcers, patients were randomised to BICAP or sham treatment.

Rebleeding occurred in 18% of treated patients compared to 41% of controls; blood transfusion requirements and need for surgery were lower in the BICAP group. Subsequently Laine(1990) and Waring et al(1991) reported similar outcome for patients treated using BICAP or injection sclerotherapy.

It therefore appears that European experience of BICAP is disappointing compared to that reported in the USA . The reasons for these differences may relate to trial design; certainly the number of patients included in European trials are greater than those reported by Laine. It is possible that the expertise of a single therapeutic endoscopist is a factor in the American studies . An important consideration relates to probe size which was larger in the series reported by Laine (3.2 versus 2.3mm) and this may have allowed better tamponade and more effective coagulation . Technical details are often scantily reported in these papers, but it does appear that Laine applied more electrical treatment than was given in the European studies.

In summary it is probable that electrocoagulation carries modest benefit in ulcer bleeding . It may be most suitable for active bleeding . Worries include precipitation of active haemorrhage by the probe and one reported perforation after BICAP therapy.

Table V : Controlled trials of Monopolar Coagulation

Author (Year)	Number Randomised	Bleeding/Uncontrolled Bleeding			Comments
		Coagulation	Controls		
Freits et al (1985)	78 21 active bleeding 57 other stigmata	2/11 3/25	6/10 8/25	p < .05	Fewer operations in endoscopically treated patients -liquid monopolar probe
Moreto et al (1987)	37	1/16	11/21	p < .05	Fewer operations in treated patients liquid monpolar probe
Pap (1982)	32	1/16	13/15	p < .05	Reduced operations rate and duration of hospital admission in treated patients: dry monopolar probe

Table VI : Controlled trials of multipolar coagulation

Author (Year)	Number Randomised	Rebleeding/Uncontrolled Bleeding		Comments
		BICAP	Control	
O'Brien et al (1986)	61 active bleeding	6/40	13/21 $P < .05$	7F Probe. More patients in treated group with active bleeding. One perforation
Goudie et al (1984)	46	7/21	5/25 NS	2.3mm probe. Bleeding precipitated by BICAP in one patient
Kernohan et al (1984)	45	9/21	7/24 NS	"Inadequate coagulation" reported in 10 patients randomised to BICAP
Laine (1987)	34 active bleeding	2/21	10/13 $P < .0001$	Included patients bleeding from several sources (24 ulcers). Reduced blood transfusions operative intervention and hospital stay in treated patients
Laine (1989)	75 NBVV	7/38	15/37 $P < .05$	Less operative intervention and cost in BICAP group

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INJECTION THERAPY

Injection therapy for peptic ulcer bleeding is now widely used as first line treatment . Clinical trials show that the approach is as effective as other options and that treatment is safe and cheap.

Many questions remain unanswered however; these include the mechanism of action, the optimum injection solution and whether injection should be combined with other approaches including thermal modalities.

It is not clear how injection therapy stops active bleeding and prevents rebleeding. This is because operative specimens following injection therapy are rarely available and it is difficult to differentiate the effects of treatment from the histological characteristics of a chronic ulcer. Inflammation, vasculitis and thrombosis of vessels are an inherent feature of peptic ulcer . Furthermore an appropriate reproducible animal model of bleeding peptic ulcer is unavailable.
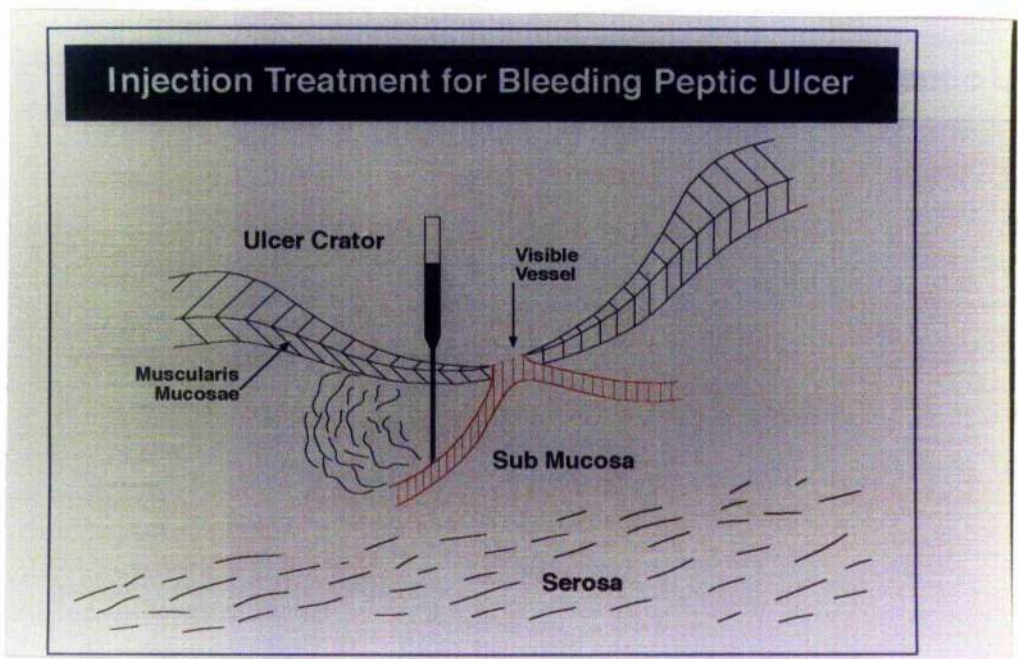
Figure 5 1-The ulcer bleed is due to erosion of a major submucosal artery and disruption of the Muscularis Mucosae
2-The serosa is rarely involved
3-Injection is usually directed beside the visible vessel to induce tamponade , vasoconstriction , dehydration or sclerosis

The efficacy of injection therapy may be due to one or all of the following mechanism.

(i)-Tamponade : Injection of fluid into a fibrotic, rigid ulcer causes compression of the bleeding vessel. This hypothesis is supported by the results of the clinical trial reported by Lin et al(1993) in which injections of saline or dilute dextrose into bleeding ulcers were more effective than conservative therapy and had similar efficacy to absolute alcohol injections . Similar conclusions were reported by Lai et al (1994) who showed that endoscopic injection of water stopped bleeding and prevented ulcer rebleeding . Fleig et al(1994) speculated whether the efficacy of injection therapy was due to the tamponade effect of the solute rather than the pharmacological effect of the solvent .

In animal models of gastrointestinal bleeding it is not possible to show that haemostasis can be achieved by injection of inert fluids , (Rutgeerts* et al 1989 , Rajgopal 1992) although these models do not involve chronic ulceration and fibrosis, limiting any tamponade effect . Larger clinical trials are needed to examine the effect of injection therapy using inert substances.

(ii)-Vasoconstriction : Dilute adrenaline stops active bleeding in models of gastrointestinal bleeding (Rutgeerts* et al 1989 , Rajgopal 1992) and in clinical practice (Chung^ et al 1988 , Steele et al 1989) . This is presumed to be due to vasoconstriction of the bleeding artery although atheromatous change in the vessel, peri-vascular fibrosis and inflammation may reduce the capacity of the artery to contract . Most endoscopists inject relatively large volumes of dilute adrenaline and tamponade may also be important. Blanching around the injected area occurs at the time of adrenaline injection; the gastric mucosa of dogs looked "cyanotic" when injected with dilute adrenaline (Rutgeerts* et al 1989) . In these experiments histological examination showed that inflammation is completely localised to the injected area and that necrosis and vascular changes rarely occur after injection of adrenaline.

Whether adrenaline is effective entirely by causing vasoconstriction is unclear . In clinical trials dilute adrenaline injections not only stop active bleeding, but also largely prevents rebleeding (Choudari et al 1994 , Chung et al 1993) suggesting that it may thrombose the ruptured artery . This is likely to be simply a consequence of vasoconstriction, but adrenaline induced alteration of platelet

function (Chung* et al 1988 , O'Brien 1963)and stimulation of the coagulation

cascade may also be a factor.(figure 6)
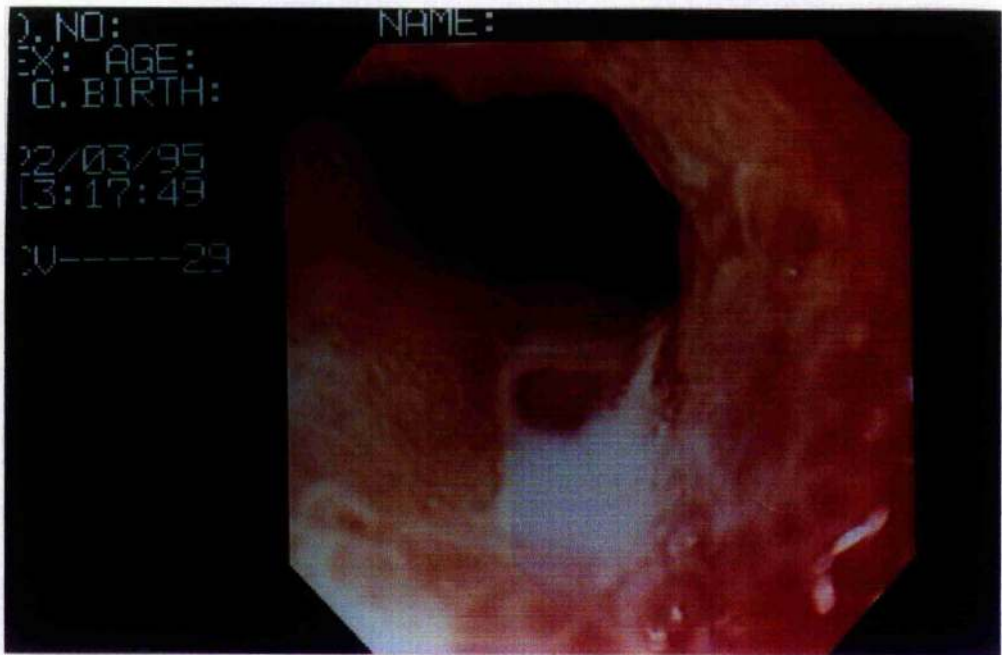
Figure 6 Tissue oedema and blanching after the submucosal injection of a bleeding ulcer with dilute adrenaline

(iii)-Sclerosants : Polidocanol, ethanolamine and sodium tetradecyl sulphate are widely used sclerosants . When injected into the gastric mucosa of dogs differing concentrations of polidocanol caused extensive necrosis and deep ulcers in a dose dependent manner (Rutgeerts* et al 1989 , Randall et al 1989) .Venous thrombosis invariably follows sclerosant injection but endarteritis and arterial thrombosis occurs less often . Indeed in a rabbit model , ethanolamine injections temporarily increased the rate of bleeding and were not associated with thrombosis of major arteries (Rajgopal et al 1992) .

One clinical trial has reported that sclerosant injections are useful in stopping active bleeding(Wordehoff et al 1982) but most authorities consider that if sclerosants have a role it is likely to be in prevention of rebleeding rather than treating active bleeding.

(iv)-Alcohol : 98% ethanol injections cause profound dehydration of tissues leading to vigorous inflammation, extensive necrosis and ulcer formation (Rutgeerts* et al 1989 , Randall et al 1989) . Surrounding areas are congested and hyperaemic and blood vessels are partially thrombosed, yet often permiable . In experimental models active bleeding is rarely stopped by alcohol injection .

(v)-Clotting factors : Injections of bovine thrombin initiate the clotting cascade. Several small studies show value for injection of bleeding peptic ulcers(Benedetti et al 1991 , Balanzo et al 1990 , Groitle et al 1987 , Herold et al 1994) although no study has been large enough to define comparative efficacy with other modalities.

Controlled clinical trials

Many uncontrolled series performed in the 1980s suggested that injection therapy improved outcome in patients who presented with major ulcer bleeding . Inclusion criteria are often poorly defined in these reports which are subject to the usual criticisms of open trials, but their conclusions have largely been confirmed by randomised controlled clinical trials.

Relatively few studies have compared injection with no-injection in matched groups of patients but clear advantage for injection has emerged and it can be argued that trials which include a no-treatment control arm have become unethical.

The optimum injection regime stops active bleeding, prevents rebleeding and has no complications. Many combinations of injection solutions have been examined but none as yet completely fulfils these requirements.

a)-Dilute Adrenaline : Chung and collegues have pioneered the use of dilute adrenaline . In a controlled trial patients who presented with actively bleeding ulcers were randomised to endoscopic injection with 1:10,000 adrenaline or were managed without endoscopic therapy (Table VII) . Injected patients required significantly less blood transfusion, needed fewer emergency surgical operations

and had a shorter hospital stay than conservatively managed patients . "Rebleeding" is not reported in this paper and mortality was similar in both groups.

Several groups subsequently performed trials in which adrenaline was combined with injections of sclerosants (Rajgopal et al 1991 , Panes et al 1987 , Balanzo et al 1988 , Oxner et al 1992). This was done because of the preconception, supported by experiments in animal models that adrenaline would not cause thrombosis of the bleeding artery . Whilst adrenaline should stop active haemorrhage by causing vasoconstriction, the argument ran that a sclerosant was necessary to induce vascular damage and promote intra-arterial thrombosis. To test this assertion, two clinical trials compared outcome in patients treated with dilute adrenaline with that of matched patients treated by a combination of adrenaline and a sclerosant . Chung et al (1993) randomised 200 actively bleeding patients to injection with 1:10,000 adrenaline (99 patients) or to adrenaline followed by 3% sodium tetradecyl sulphate (101 patients). The groups were well matched in all relevant respects . Initial haemostasis was achieved in almost all patients, in fact the only failures were those in whom torrential bleeding prevented visualisation and injection of the bleeding ulcer . After initial control of bleeding

only two patients in each group rebled in hospital. Similar conclusions were reached by Choudari et al (1994) who randomised 107 patients who presented with a range of major endoscopic stigmata to injection with 1:100,000 adrenaline or to adrenaline plus an injection of 5% ethanolamine. Permanent haemostasis was achieved in 85% of patients in both groups.

These two studies clearly show that the addition of a sclerosant to an injection of adrenaline is unnecessary. This suggests that in clinical practice, adrenaline does induce thrombosis of the bleeding vessel, underlying deficiencies in animal models of ulcer bleeding.

Other series have compared the outcome of patients treated by injection therapy with patients treated using thermal methods . Loizou et al(1991) randomised 42 patients to 1:10,000 adrenaline or a combination of adrenaline and Nd-Yag laser photocoagulation . Not surprisingly this small study had insufficient power to show significant differences between these treatments although there was a tendency for combination therapy to be more effective, as suggested by a 25% rebleeding rate in the injected group compared to a 14% rebleeding rate following laser and injection . Carter et al(1994) compared adrenaline injection with Nd-Yag laser therapy . Permanent haemostasis was achieved in 96% of laser treated

patients and 81% of injected patients but this apparent difference was not statistically significant because of small sample size (44 patients).

The effective concentration of adrenaline is not known . The Hong Kong group have used a concentration of 1:10,000 whilst the Edinburgh group have favoured a 1:100,000 solution . The results of endoscopic therapy are very similar in trials reported by these two centres. Significant and potentially important increases in plasma adrenaline concentrations follow endoscopic injection with 1:10,000 adrenaline solutions(Sung et al 1994) , and this could have adverse efffects in patients who have co-existing cardiac diseases . In clinical practice no significant complications have been reported following adrenaline treatment.

Dilute adrenaline is the injection treatment of choice for active ulcer bleeding and clinical trials show it to be at least as good as any other approach . For patients with non-bleeding visible vessels there seems little to choose between adrenaline and alternative therapies. Combination of adrenaline injection and a thermal method is attractive because the bleeding source is treated by several approaches . As yet few clinical trials have adopted this approach although Chung et al (1994) and Tekant et al(1995) have shown that combination of adrenaline and the heater probe is safe and effective . Studies proving that combination treatment is better

than a single agent approach will require large numbers and almost certainly

multicentre participation.

Table VII : Dilute adrenaline injection versus conservative treatment

Author	Number Randomised	Operation for failed haemostasis		Comments
		Injected	Controls	
Chung et al (1988)	68 active bleeding	4/34	14/34 P < .02	Initial haemostasis in all injected patients. Shorter hospital stay and reduced blood transfusion in the treated group

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Table VIII : Controlled trials of adrenaline plus sclerosant versus conservative treatment

Author (Year)	Number Randomised		Rebleeding/Uncontrolled haemorrhage		Comments
			Injection	Control	
Rajgopal + Palmer (1991)	109	9 active bleeding 100 other stigmata	7/52	25/53 $P < .001$	1:100,000 adrenaline plus 5% etharolamine. Some control patients injected after rebleeding
Panes et al (1987)	113	28 active bleeding	3/15	10/13 $P < .01$	1:10,000 adrenaline plus 1% polidocanol. Reduced transfusion need in injected patients
		46 oozing/clot	0/22	14/24 $P < .05$	
		39 NBVV	8/18	15/21 $P < .01$	
Balanzo et al (1988)	72		7/36	15/36 $P < .05$	1:10,000 adrenaline plus 1% polidocanol. Reduced surgical intervention and transfusion needs in injected group
Oxner et al (1992)	93	5 active bleeding 88 other stigmata	8/48	21/45 $P < .05$	1:10,000 adrenaline plus 1% polidocanol. Fewer deaths in injected patients (4 v. 9, NS)

(b)-Sclerosants : A range of sclerosing agents have been injected directly into and around bleeding ulcers to try and stop active bleeding and prevent rebleeding . These include 1% polidocanol, 5% ethanolamine and 3% sodium tetradecyl sulphate.

Several uncontrolled series (Sohendra et al 1985 , Kortan et al 1986) performed in the early 1980s suggested that injection of these agents was effective and safe . There are however no controlled trials in which outcome has been assessed in patients randomised to sclerosants or to conservative (no injection) treatment.

Several trials have compared the efficacy of sclerosant injection with other haemostatic methods . For example Benedetti et al(1991) randomised patients presenting with bleeding from a range of sources to injection with 1% polidocanol or to thrombin injection and showed similar haemostatic effect for these treatments . Strohm et al(1994) randomised patients to one of four treatment arms (fibrin glue, 1% polidocanol, dilute adrenaline or adrenaline plus polidocanol) and showed little advantage for any one approach . These two trials have insufficient power to demonstrate that polidocanol injection is better than other approaches but even in the small numbers involved in these studies, low rebleeding following 1% polidocanal injection in patients with endoscopic stigmata of major bleeding

does suggest that this agent is effective . Pulancic et al (1995) randomised 315

patients with peptic ulcer haemorrhage (Forrest Class Ia&b and IIa&b) to injection

with 1% polidocanol (n–160) or Nd YAG Laser(n=155) ., they reported a success

rate(permanent haemostasis of 90 and 94 per cent respectively(NS) . Finally

Rutgeerts^ et al(1989) also showed that injection of polidocanol is as effective as

Nd-Yag laser photocoagulation therapy in patients with ulcer bleeding.

More studies have examined the effectiveness of combination adrenaline and

sclerosant regimes. (Table VIII) The controlled trial reported by Panes et al (1987)

involved 113 patients who were randomised to a combination of 1:10,000

adrenaline plus 1% polidocanol or to no injection. Recurrent bleeding occurred in

5.5% of injected patients, compared to 43% of controls (P< .001), with

corresponding reduction in need for emergency surgery, blood transfusion and

duration of hospital admission . Rajgopal et al(1991) subsequently showed that the

combination of 1:100,000 adrenaline plus 5% ethanolamine reduced rebleeding

rates (12.5 versus 47%, P < .001) in patients who had a range of major endoscopic

stigmata . In this study some control patients were injected when they rebled, most

then avoided emergency surgery, but this questionable defect of trial design

resulted in loss of potential difference in other possible end points . Moreto et

al(1992) showed in a small clinical trial (38 patients) that haemostasis was achieved in patients treated by a combination of ethanolamine plus thrombin injections (one of 19 treated patients developed uncontrolled bleeding, compared to further bleeding in eight of 19 controls).

The role of the sclerosant in these trials is difficult to interpret for two major reasons . Firstly because the trials suffer from the common problem of small sample size . Secondly, because the sclerosant has invariably been injected in combination with another agent which has proven therapeutic value . To try and define the role of the sclerosants three studies have compared outcome in patients randomised to adrenaline injection with that following a combination of adrenaline and a sclerosant.

As previously described, the trials reported by Chung et al(1993) and by Choudari et al (1994) showed little advantage for combination therapy over an injection of adrenaline alone . A third study reported by Villanueva* et al(1993) showed similar outcome following injection with adrenaline plus polidocanol or treatment with adrenaline alone. (Table IX) No study has compared haemostasis in patients treated by dilute adrenaline with that achieved by injection of a sclerosant alone.

Sclerosant injections have been associated with serious complications . These presumably occur as a consequence of extensive thrombosis of arteries serving the upper gastrointestinal tract . Levy et al (1991) reported a fatal case of gastric antral necrosis following injection with a combination of adrenaline and sodium tetradecyl sulphate . Similar complications following sclerosant injections have been reported by several authors (Loperfids et al 1990 , Chester et al 1990) . Luman et al (1995) reported common bile duct stricturing causing obstructive jaundice after repeated injection of a posterior duodenal ulcer with adrenaline and 5% ethanolamine.

Because sclerosants appear to offer no advantage over injection with adrenaline alone and because of these unusual but potentially serious side effects, I do not believe that sclerosants have a role as injection therapy for bleeding ulcers.

Table IX: Combination of adrenaline plus sclerosant versus adrenaline alone

Author (Year)	Number Randomised	Rebleeding/Uncontrolled haemorrhage		Comments
		Combination	Adrenaline alone	
Chung et al (1993)	200 active bleeding	14/98	16/98 NS	Numbers refer to operations for further bleeding. Injection with 1:10,000 adrenaline ± STD
Choudari & Palmer (1994)	107	57 active bleeding 5/28	7/29 NS	1:100,000 adrenaline + 5% ethanolamine
		50 NBVV 1/24	1/26 NS	
Villanueva et al (1993)	63	8/33	4/30 NS	1:100,000 adrenaline + 1% polidocanol

(c)-Alcohol : The efficacy of injections of 98% ethanol has been examined in several clinical trials (Table X). Sugawa et al (1986) reported effective haemostasis in actively bleeding ulcers and this was confirmed in a randomised trial performed by Pascu et al (1989) . More recently Lazo et al (1992) reported a study of 39 patients who were found at endoscopy to have non-bleeding visible vessels within the ulcer base . Twenty five patients were treated by alcohol injection and 14 acted as non-injected controls . Rebleeding was significantly less common in the injected group (8 versus 57%, P < .01) . Lin et al (1993) reported that alcohol injection stopped active bleeding and prevented rebleeding in 86% of patients whose ulcers were injected with alcohol although a similar proportion of ulcers treated with 3% sodium chloride (68%), 50% dextrose (78%) and normal saline (78%) also achieved permanent haemostasis.

As already stated (Rutgeerts* et al 1989 , Randall et al 1989) injection of alcohol into the gastric mucosa of dogs caused deep ulcers and such ulcers also commonly occur in the human oesophagus following injection sclerotherapy for varices . It is perhaps not surprising therefore that ulcer perforation has been reported following alcohol injection into a bleeding ulcer (Lin et al 1993) .

One small study (Chiozzini et al 1989) has compared the efficacy of alcohol with dilute adrenaline injection therapy (but had insufficient power to detect differences in efficacy). A much larger study is needed . The evidence that alcohol stops active bleeding and prevents rebleeding is more convincing than that for the sclerosants ethanolamine, polidocanol and STD . The potential for side effects induced by injection is probably higher for alcohol than for adrenaline, and this may deter such a study.

Table X: Controlled trials involving alcohol injection

Author (Year)	Number Randomised	Number Rebleeding/ Uncontrolled Bleeding			Comments
		Alcohol	Control		
Pascu et al (1989)	143	2/65	10/78	P < .05	"Rebleeding" relates to need for surgical intervention. Reduced mortality in injected patients.
Lazo et al (1992)	66 patients 39 NBVV	2/52	8/14	P < .001	Reduced need for surgical intervention in treated patients.
Chiozzini et al (1989)	35 5 active bleeding 47 other stigmata	2/16 active bleeding	5/19	NS	15 further patients randomised to 1:100,000 adrenaline (2 rebled)

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(d)-Thrombin : Direct injection of thrombin into a bleeding ulcer may represent the most effective method of sealing the bleeding vessel . Groitl et al (1987) injected bovine thrombin into ulcers of 11 patients halting active bleeding and prevented rebleeding . They also suggested that the agent may have value in sealing anastomotic leakage.

Balanzo et al (1990) randomised 64 patients who presented with active ulcer bleeding to 1:10,000 adrenaline or to a combination of 1:10,000 adrenaline plus thrombin . Permanent haemostasis was achieved in 81 and 84% of both groups respectively .   Benedetti et al (1991) randomised 82 consecutive patients who presented with peptic ulcer bleeding to 1% polidocanol (n=28) or thrombin (n=54) injections . Permanent haemostasis was achieved in 82% of polidocanol injected patients and 87% of thrombin treated patients . (Table XI)

Thrombin injection therefore does seem at least as effective as other modalities, although the clinical trials have insufficient power to show whether it is any better (or worse) than other approaches . A trial which could define such differences would have to be extremely large since standard injection treatment is relatively effective and because at least some of the failures of each modality are due to

inaccurate localisation of the injected material rather than to differences in the capacity of these materials to thrombose vessels.

A particular risk of thrombin injection is that it could precipitate extensive intravascular thrombosis . In clinical practice this has not been observed either in patients injected for peptic ulcer or variceal bleeding . Bovine thrombin also carries the theoretical risk of inducing anaphylaxis and it may be unwise to repeatedly inject the same patient with this material.

Table XI : Controlled trials involving injection with thrombin

Author (Year)	Number Randomised		Uncontrolled haemorrhage or rebleeding		Comments
			Thrombin	Other	
Balanzo et al (1990)	64		6/32	5/32	(NS) (Thrombin plus 1:100,000 adrenaline)
Benedetti et al (1991)	82	20 active bleeding 62 NBVV	8/54	5/28 (1% polidocanol) (NS)	
Moretto et al (1992)	38		1/19	8/19 (no injection)	P < .005. Thrombin injected with 5% ethanolamine

Other approaches Endoscopic haemostasis has been attempted by topical application of a range of substances including collagen haemostat (Feld et al 1981), clotting factors (Linscheer et al 1977) , cyanoacrylate tissue glues (Peura et al 1982) and metallic slurries as part of ferromagnetic tamponade (Smith et al 1990 , Carlson et al 1990) . Experience in animals and man has largely been disappointing but is rather limited.

Mechanical approaches have included metal clips (Binmoeller et al 1993) , rubber band ligation (Swain et al 1985) , balloon tamponade (Taylor et al 1996) and sewing (Escourrow et al 1990) . Each has its enthusiasts but cannot as yet be recommended in clinical practice.

A microwave coagulation method has been devised for endoscopic use . Microwave energy produces heat dielectrically based on molecular motion produced by ultra-high frequency excitation . The electrical field is well localised to the tip of the electrode and risk of perforation is theoretically low. In experimental models microwave coagulation performs as well as the heater probe and BICAP and better than injection with adrenaline and 1% polidocanol (Michaeltz et al 1989) . One prospective clinical trial (Panes et al 1991) involving 127 patients presenting with a range of endoscopic findings associated with peptic

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ulcer bleeding, randomised patients to endoscopic sclerosis using adrenaline and polidocanol or to microwave coagulation . No complications occurred in either group and rebleeding, surgical operation and transfusion rates were similar in both groups .

The main drawback of the microwave coagulation probe is adherence to the bleeding point. Although this can be usually overcome by application of a dissociation electrical current, precipitation of further bleeding can sometimes be serious. A no-contact method in which sparking across to the bleeding point has been studied in experimental animals but has not yet been applied to man (Kalabakas et al 1993) .

Failures of endoscopic therapy

It can be argued that endoscopists can adversely affect outcome in patient who fail endoscopic therapy . Repeated endoscopy, large blood transfusion and delayed surgical operation in patients who ultimately fail attempted endoscopic haemostasis all increase risks of death . Unfortunately we cannot predict the failures of endoscopic treatment . Clearly patients with the most active, profuse haemorrhage are the least likely to respond to non-operative approaches both because massive bleeding can make adminstration of endoscopic therapy

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impossible and because large holes in major arteries are unlikely to respond to any endoscopic therapy . Thus, patients who are shocked with active bleeding from a large(>2cm in diameter) posterior duodenal ulcer tend to comprise the failures in clinical trials (Choudari et al 1994 , Villaneuva^ et al 1993 , Brullet et al 1991&1996) . Nevertheless even in these patients the Edinburgh group reported 75% success with treatment by injection or heater probe (Choudari et al 1994) .

One approach in the highest risk patients is early repeat endoscopy with further treatment even in the absence of rebleeding . Villanueva et al (1994) suggested that such a policy might improve outcome .

Best policy in patients who rebleed after endoscopic treatment is not clear . Many endoscopists tend to retreat such patients, whilst others believe that rebleeding is an indication for surgical intervention . Clinical trials do not tell us when to operate and although an aggressive, early surgical approach has been reported to be best for elderly patients presenting with major ulcer bleeding (Morris et al 1984) , we have no data supporting this for patients receiving endoscopic therapy . No study has compared surgical against endoscopic therapy . Most trials of endoscopic therapy define need for a surgical operation as a treatment failure . An alterntive view is that endoscopic control of bleeding facilitates safe, early elective

surgery . A successful outcome in an individual patient often depends upon a

combination of endoscopic and surgical approaches and good management is a

team approach .

Chapter 2

Experimental studies of injection in ulcer haemorrhage

Introduction

Peptic ulcer haemorrhage can be stopped by a range of endoscopic injection therapies . A variety of solutions have been used but in a series of clinical trials , the best regime has not been defined . Furthermore , the mechanisms by which injection therapy thromboses the bleeding artery within the ulcer bed are unclear . Such mechanisms may include (i)-vasoconstriction(Rutgeerts et al 1989 , Pinkas et al 1995) ; (ii)-compression of the bleeding vessel by local oedema "tamponade" , Lai et al (1994) demonstrated that local tamponade with distilled water is as effective as diluted adrenaline in the treatment of patients with ulcer bleeding) , (iii)-sclerosis and endarteritis (demonstrated by Rutgeerts after injection of polidocanol) and (iv)-dehydration (Leung et al 1991&1989 , Chung* et al 1991) .

It is difficult to study these effects because an adequate animal model of peptic ulcer bleeding is unavailable . Experiments have largely involved gastric mucosal bleeding induced by various ulcer making devices (Rajgopal et al 1992 , Whittle et al 1991 , Protell et al 1978 , Chung et al 1991) and this is far removed from the clinical situation of bleeding from a chronic ulcer in which a major artery is eroded by a chronic inflammatory process . Nevertheless experiments involving bleeding from acute ulcers have yielded valuable information concerning the effect of endoscopic treatments and these have stimulated clinical trials of injection therapy in man .

In a previous study Rajgopal et al 1991 showed that injections of dilute adrenaline (but not saline) stopped active bleeding from acute gastric mucosal ulcers in anticoagulated rabbits , whilst sclerosants increased the rate of bleeding . Histological examination showed that adrenaline did not cause arterial thrombosis and that sclerosants induced severe local inflammation , necrosis and venous thrombosis but these changes were not followed by endarteritis or arterial thrombosis .

These experiments prompted a clinical trial in which it was demonstrated in patients admitted to hospital because of bleeding peptic ulcer that a combination of adrenaline and ethanolamine conferred no extra advantage over injection with adrenaline alone (Choudari et al 1994) .

Adrenaline does not always stop ulcer bleeding ; failures are likely to be due to continued patency of the defect within the bleeding artery . One approach to thrombosing the artery is local injection of thrombin . In this study I have compared the acute haemostatic effect of injection with dilute adrenaline , the sclerosant ethanolamine and human thrombin using a previously validated (Rajgopal et al 1991) model of acute mucosal bleeding .

Methods

Gastric mucosal injury was induced in anaesthetised rabbits and the effects of injections were observed in acute and semi acute experiments .

(1)-Acute bleeding experiments

Experiments were carried out in 6 NewZealand white rabbits with a median weight of 3.22kg (2.3-3.75 kg) . Intravenous midazolam 0.6 mg/kg and intramuscular fentanyl citrate 0.315 mg/ml and Fluanison 10mg/ml (0.22 ml/kg) was used to induce anaesthesia . All animals received continuous supplementary oxygen through a face mask at 6 l/min .

The animals received two 300 mg Aspirin tablets , 24 and 12 hours before the procedures and also received a bolus injection of 500 U of intravenous heparin , followed by 500 units/kg/hour of heparin injection into an ear vein . A median laparotomy and anterior gastrotomy were performed with careful haemostasis . Ulcers were created by excising mucosal discs of 2.5-4mm in diameter using a scalpel . Randomly chosen discs were examined by an independent histologist (A.Lessells.) . This revealed mucosa alone in all cases . Bleeding from each wound was initially measured by a volumetric beaker and as the bleeding volume decreased by a pre-weighed segment of blotting paper . Measurements were carried out at 1, 2,3,4,5,10,20 and 30 minutes after ulcer induction . Only wounds bleeding in excess of 1.5 ml/min (basal blood loss) for one minute were studied .

A total of thirty eight ulcers(blood loss>1.5ml/min) were created in 6 rabbits .

These were then randomised to

(a)-Control-no injection .

(b)-Two 1 ml injections of 50% dextrose around the mucosal wound .

(c)-2 mls of 1 : 100,000 adrenaline .

(d)-2 mls 5% ethanolamine .

(e)-2 mls human thrombin (400 IU) suspended in 16 mM calcium chloride

(donated by Scottish Blood Transfusion Service) .

(f)-1 ml of human thrombin (200 IU) plus 1 ml of human fibrinogen (50 mg) .

(g)-Spray of thrombin/fibrinogen mixture (2 mls) within 3 mm of the ulcer .

This was done using a double channel sclerotherapy injection needle which

allow simultaneous discharge of the injected material which was sprayed over a

30 second period .

Injections were given in random order (different treatments were used in ulcers

created in the same animal) using a standard 25G needle with an outer diameter

of 0.6 mm . At the end of the experiment , the animals were killed by an

overdose of barbiturate . The stomach was removed , fixed in formalin and

examined by an independent histo-pathologist (A.L.) who was unaware of the

injection given .

(2)-Semi-acute experiments

Four further rabbits with a median weight of 3.2 kg (range 3.1-3.3 kg) were intubated and ventilated . Upper gastrointestinal endoscopy was performed using an Olympus P 10 paediatric forward viewing gastroscope (Olympus , Keymed , South end on sea , UK) . Superficial mucosal injury was induced using a standard biopsy forceps (26N) (Olympus , Japan) in the body and antrum of stomach . The ulcerated areas were then injected endoscopically with 1 ml of 1: 100,000 adrenaline plus 1 ml thrombin (200IU)(n=2) , 2 ml 5% ethanolamine or 2 ml 98% alcohol . Injections were carried out using a variceal sclerotherapy needle (25G) . Injection sites were marked with methylene blue. Two out of those four animals survived post operatively and were killed after 1 hour and 60 hours respectively . The other two animals (injected with 98% alcohol and 5% ethanolamine respectively) suffered an anyphalactic reaction and died 4 hours post-operatively . This occurred despite the presence of a Home Office veterinary surgeon who intubated and ventilated the animals and supervised the procedure . It was her opinion that the anaphylactic reaction and death was secondary to the injected material rather than other technical factors .

(3)-Experiments involving peripheral (ear) arteries

In 5 rabbits(also used for gastro-intestinal experiments) injections of 2 ml of 1:100,000 adrenaline alone , adrenaline plus thrombin(200 IU) , 5% ethanolamine , 98% alcohol , fibrinogen(100mg) and 50% dextrose were randomly placed next to the ear central

artery . Animals were killed 2 hours(3 rabbits) or 56 hours(2 rabbits) later and the ear sections examined histologically .

Statistical Analysis

Changes in bleeding volume were plotted out and the integrated blood loss for each modality was measured as the area under the curve . Statistical difference between the various groups was measured using the Mann-Whitney U test . Significance level was considered as $p<0.05$.
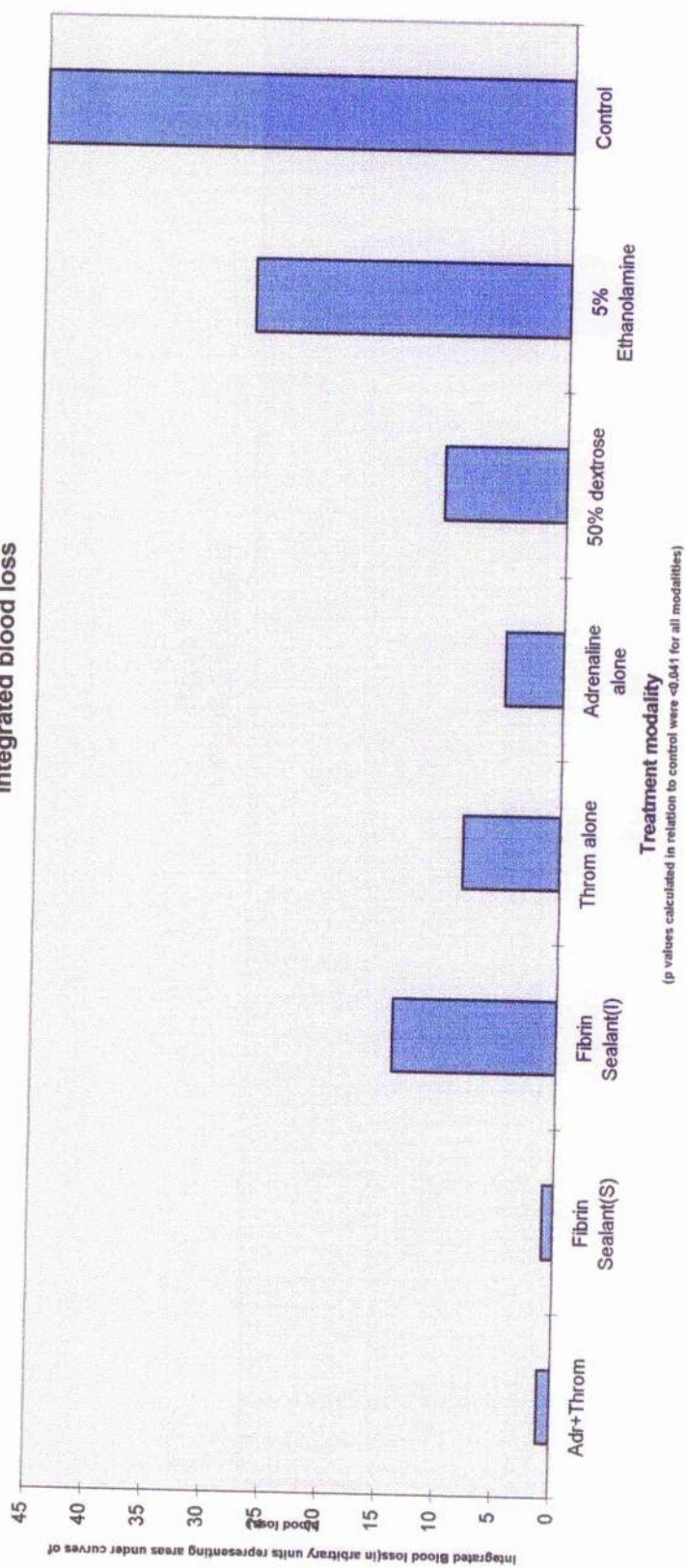
Results

(1)- Acute bleeding experiments

Basal blood loss was similar in all ulcers , mean 1.87(SD=0.31) ml/min (n=38) with the exception of 2 ulcers which were subsequently injected with 50% dextrose . By chance these ulcers bled more profusely than controls and those receiving other treatments .

Bleeding rate was relatively constant in control ulcers over a 30 minutes period (Table1) .

All haemostatic agents significantly reduced integrated blood loss although adrenaline plus thrombin and sprayed fibrin sealant tended to be the most effective . The difference between the various modalities did not achieve statistical significance (Table 1& figure 1) . Indeed both of these rapidly stopped active bleeding and this did not recur over the experimental period . Injected fibrin sealant , 5% ethanolamine and 50% dextrose injections did not significantly decrease initial blood loss , but did tend to reduce bleeding rates within 20 minutes . As anticipated adrenaline alone immediately reduced bleeding rates , albeit less impressively than the combination of adrenaline plus thrombin (Table 1) .

Table 1
Mean blood loss(ml/min)

Agent	No of ulcers	0 min	1 min	2 min	3 min	4 min	5 min	10 min	20 min	30 min	p values(MWU)
Adr+Throm	4	1.85	0.2	0	0	0	0*	0	0	0	0.0036
Fibrin Sealant(S)	4	1.65	0.075	0	0	0	0*	0	0	0	0.0014
Fibrin Sealant(f)	4	1.65	1.2	1	1	0.65	0.8	0.5	0.2	0.25	0.023
Throm alone	6	1.76	1.03	0.9	0.98	0.62	0.3	0.27	0.05	0.06	0.0047
Adrenaline alone	8	1.75	0.33	0.11	0.025	0.0125	0.025	0.16	0.18	0.11	0.004
50% dextrose	4	2.56	1.5	1	0.5	0.4	0.36	0.3	0.2	0.1	0.0132
5% Ethanolamine	4	1.9	1.55	1.4	1.43	1.4	1.4**	1.1	0.63	0.43	0.041
Control	4	1.9	1.7	1.75	1.5	1.5	1.55	1.45	1.7	1.2	

SD<1 in all blood flow measurements

*$p < 0.001$

**$p = 0.4$

p values are calculated in relation to controls

Figure 1
Integrated blood loss

(p values calculated in relation to control were <0.041 for all modalities)

Treatment modality

Integrated Blood loss(in arbitrary units representing areas under curves of blood loss)

Gross examination of gastric mucosal tears injected by the various substances and removed 1 hour after injection therapy revealed oedema and blanching but no other gross abnormalities . Microscopic appearance was similar in all cases(showing oedema and submucosal haemorrhage) other than where fibrin sealant was injected . This showed an amorphous acellular eosinophilic material occupying the submucosa at the site of injection . (figure 2,3) In addition in one case where a combination of adrenaline and human thrombin were used , an area of significant inflammatory reaction , involving large numbers of polymorphs was seen within the mucosa , spilling over into the muscularis propria . However , as the animal had been killed within one hour of the injection , the surprising extent of the inflammation noted raises doubt whether this observation was secondary to injection therapy or as part of an incidental area of mucosal erosion (figure 4,5) .

(2)-Semi-acute experiments

Gross examination of the stomach removed 60 hours after injection with adrenaline plus thrombin revealed no major gross changes . Microscopic examination showed submucosal haemorrhage , dilated veins with thrombosis and local necrosis of walls . However no significant changes in the arteries were seen .
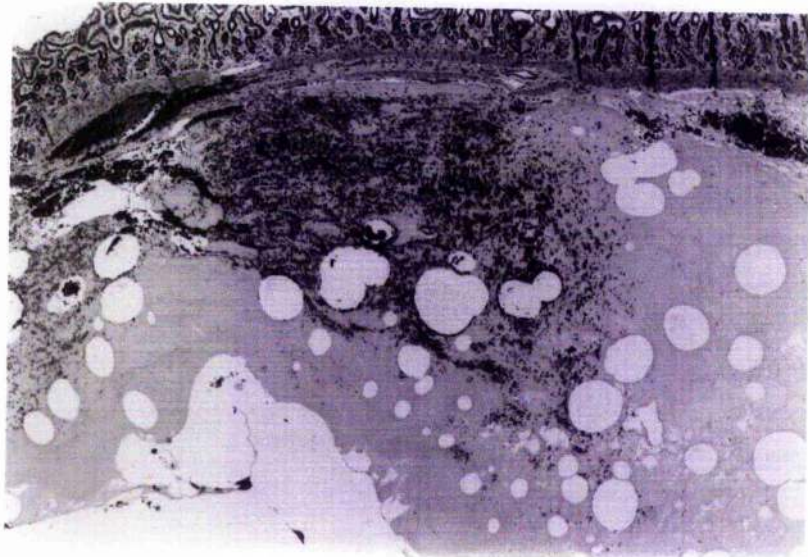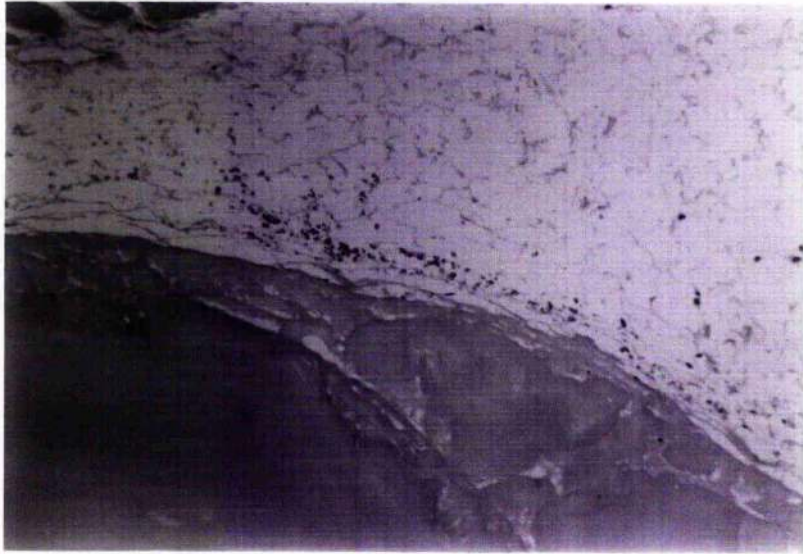
Figures 2&3 Experimental ulcer injected with fibrin sealant

(Acellular amorphous eosinophilic material occupying the submucosa represents the

injected fibrin sealant)
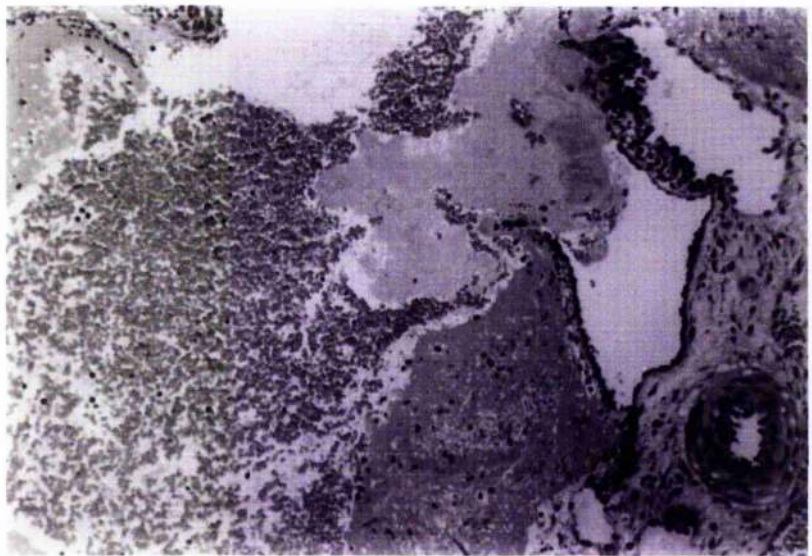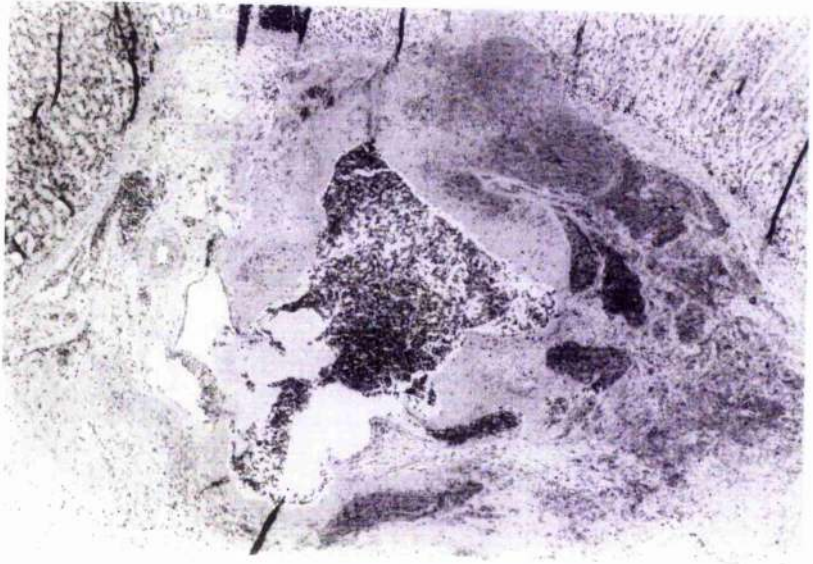
Figures 4&5 Experimental ulcer injected with adrenaline plus thrombin

(3)-Experiments involving peripheral (ear) arteries

Acute changes(2 hour after injection)

Adrenaline , fibrinogen , 50% dextrose , 98% alcohol and a mixture of adrenaline plus thrombin caused haemorrhage around the central artery , non occlusive venous thrombosis but no arterial thrombosis (figure 6,7,8).

Chronic changes(56 hours after injection)

(a)- Adrenaline plus thrombin caused non occlusive venous thrombosis without ischaemic necrosis of the overlying skin (figure 9).

(b)-Ethanolamine(5%) caused extensive occlusive venous thrombosis and ischaemic necrosis of adjacent skin (figure 10,11) .
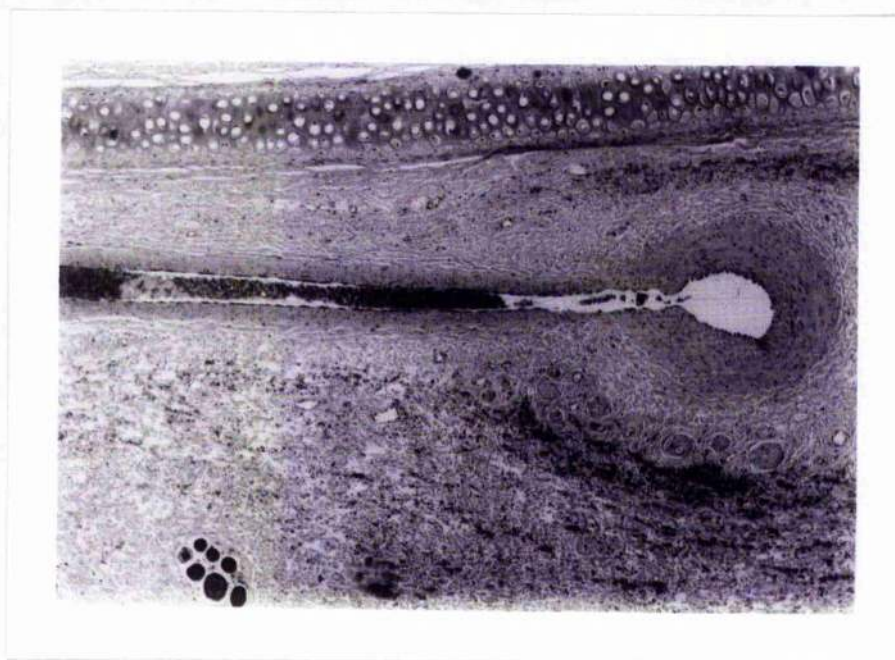
Figure 6 Section of ear injected with adrenaline(showing non occlusive venous thrombosis but no tissue necrosis)
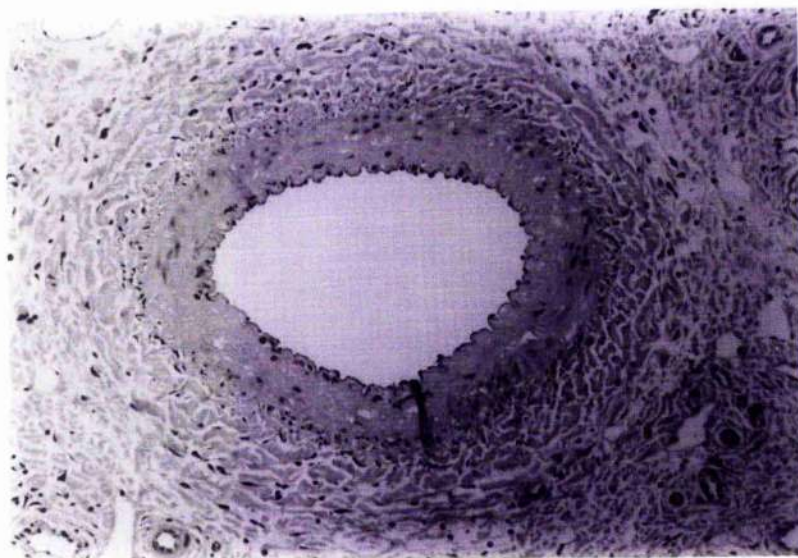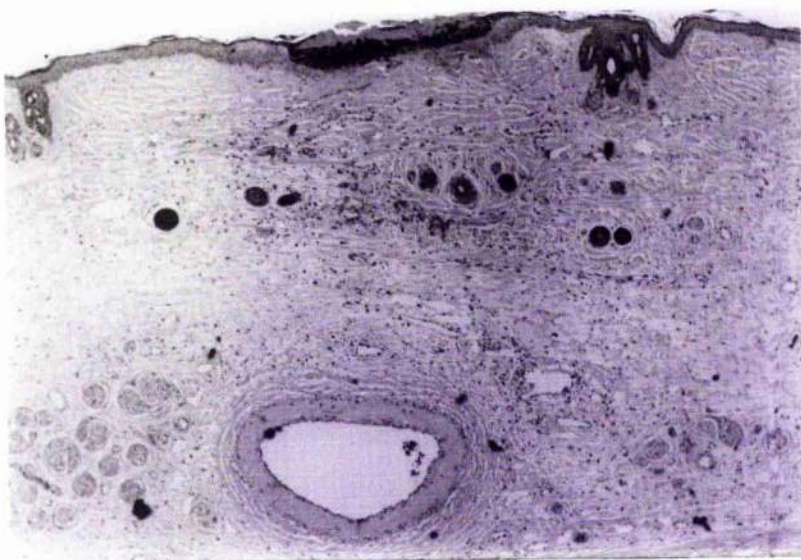
Figure 7&8 Section of ear 2 hours after injection with adrenaline plus thrombin(showing no arterial thrombosis and no tissue necrosis)
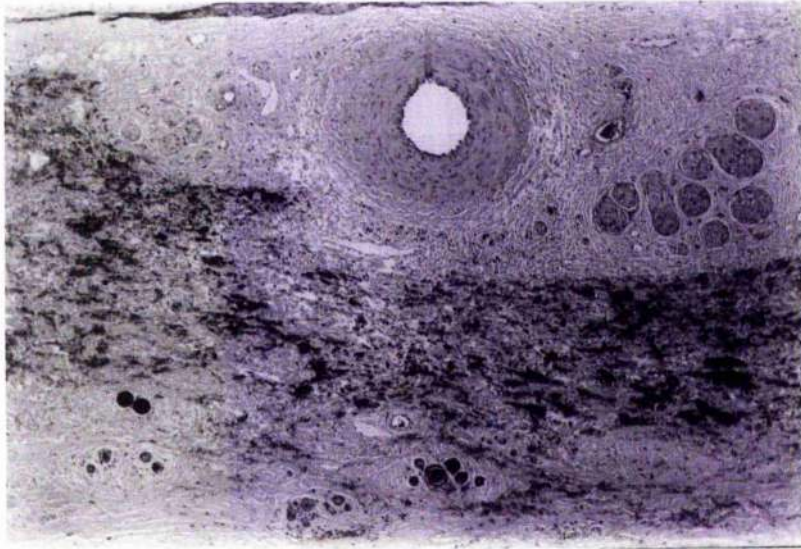
Figure 9 Section of ear 56 hours after injection with adrenaline plus thrombin(no ischaemic

necrosis occurred)
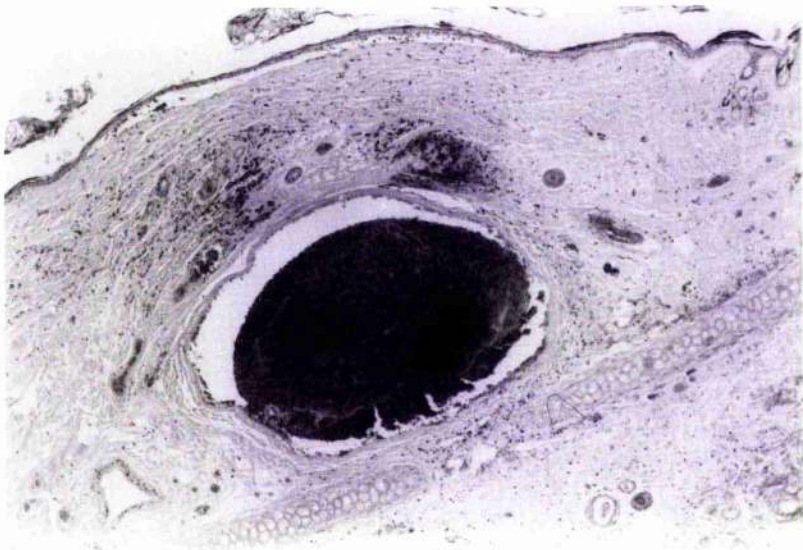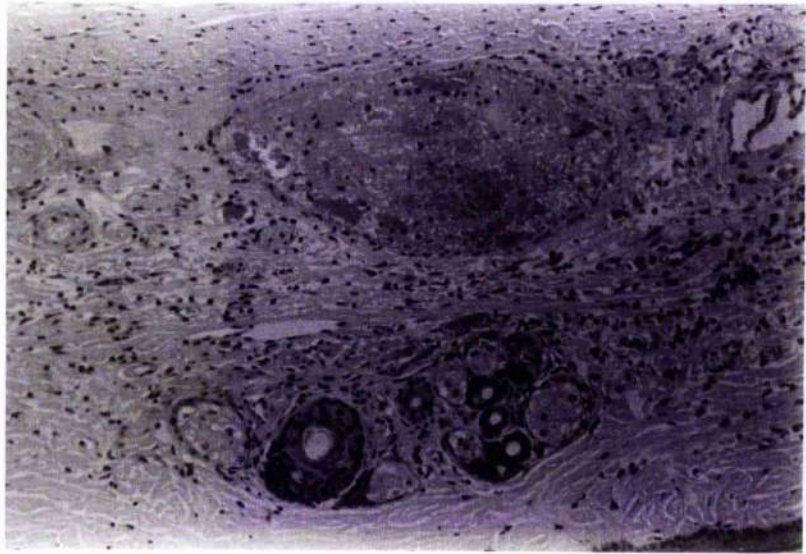
Figure 10&11 Section of ear 56 hours after injection with 5% ethanolamine(extensive tissue necrosis)

Discussion

In a rabbit model of acute gastric mucosal bleeding , prompt haemostasis was effected by injection of adrenaline plus thrombin and by sprayed fibrin sealant . Adrenaline injected alone also stopped active bleeding , albeit less conclusively than these modalities . Other agents ; thrombin alone , injected fibrin sealant , 50% dextrose and 5% ethanolamine did not immediately stop bleeding but all exerted a modest delayed haemostatic effect . Histological examination of injected tissues did not reveal the mechanism by which haemostasis was achieved . No agent was shown to cause arterial thrombosis .

Various methods have been employed in the creation of experimental ulcers . They include ; mechanical methods (by excision of disk shaped segments of mucosa or small mucosal incisions with a scalpel) , chemical methods (by submucosal injection of 98% ethanol) and the use of " the ulcer maker " (Rajgopal et al 1992 , Whittle et al 1991 , Protell et al 1978 , Chung et al 1991). Unfortunately an appropriate animal model of peptic ulcer bleeding has not been developed and the experimental situation of acute mucosal tears is far removed from the clinical state of patients presenting to hospital with ulcer haemorrhage . The rabbit stomach was chosen because it is an animal with gastric anatomy and physiology similar to that of man (Wara et al 1957) and an animal successfully used by others in ulcer bleeding experiments (Rajgopal et al 1991 , Wara et al 1957 , Dilley et al 1995 , Kivilaakso et al 1981) .

Nevertheless , the experiments described in this study do suggest that an adrenaline/thrombin combination might be appropriate for active bleeding . The efficacy of this mixture contrasts with the relatively poor haemostatic efficacy of ethanolamine , 50% dextrose and thrombin injected alone . Thus , adrenaline is the most effective drug for treating active bleeding but its temporary vasoconstricting activity might be expected to be associated with rebleeding . The combination with an agent (such as thrombin) which may cause thrombosis is therefore logical . The failure of thrombin (or any other agent) to thrombose arteries may be a defect of the experimental model since one would only expect arterial thrombosis to occur if the injection is directed into the arterial lumen . In clinical practice , endoscopists may attempt an intra-arterial injection into the bleeding artery , whilst this was not possible in my experimental model .

The injected substances produced a range of macroscopic and histological effects . These were relatively mild following adrenaline and thrombin , but considerable delayed necrosis was associated with 5% ethanolamine injections . In addition , its relative ineffectiveness in stopping mucosal bleeding suggest that sclerosants may not be optimal agents for treating ulcer bleeding in man . This conclusion is reinforced by case reports of major complications following their use in clinical practice (Meissner et al 1993 , Farrell et al 1993 , Goldberg et al 1993 , Loperfids et al 1990 , Pousset et al 1992 , Roul et al 1991 , Levy et al 1991 , Lumen et al 1994) . In contrast adrenaline and thrombin injection have

not been associated with complications in clinical pracice . The use of adrenaline is now established in clinical practice(Choudari et al 1994 , Chung et al 1988 , Villanueva et al 1993 , Chung et al 1993) ; that of thrombin is controversial and is worthy of further study .

In these experiments sprayed fibrin sealant proved to be an effective haemostatic agent and may be worthy of further study . Unfortunately , and in contrast to injected agents , sprays are difficult to use in clinical practice , although a combination of adrenaline injection(to stop active bleeding) followed by a fibrin spray(to stimulate thrombosis within the bleeding vessel or to form a plug which seales the hole in the bleeding vessel) could represent a viable approach .

Chapter 3

Endoscopic injection for bleeding peptic ulcer ; a comparison of Adrenaline alone with Adrenaline plus human Thrombin

Introduction

The prognosis of patients who present to hospital because of major peptic ulcer haemorrhage is improved by endoscopic injection therapy . A range of solutions have been injected and all have similar efficacy in reducing the rate of rebleeding , operation and mortality (Panes et al 1987 , Lazo et al 1992 , Balanzo et al 1988 , Rajgopal et al 1991) . In controlled trials , Choudari et al (1994) and Chung et al (1993) showed that diluted adrenaline (1 : 100,000 or 1 : 10,000) is at least as effective as alternative regimes and in contrast to sclerosants injections (Loperfido et al 1990 , Pousset et al 1992 , Roul et al 1991 , Levy et al 1991) , adrenaline has not been associated with systemic or local complications .

Unfortunately 15-20% of patients continue to bleed despite technically successful injection therapy (Panes et al 1987 , Lazo et al 1992 , Balanzo et al 1988 , Rajgopal et al 1991 ,Lin et al 1993) . This may be because the bleeding artery is not thrombosed ; indeed experiments in animals fail to show arterial thrombosis following adrenaline injection (Rajgopal et al 1992 , Chung*et al 1988 , Rutgeerts*et al 1989) .

Bovine thrombin has been injected into gastro-duodenal bleeding lesions to stop bleeding and prevent rebleeding (Juszkiewicz et al 1993 , Moreto et al 1992 , Balanzo et al 1990 , Benedetti et al 1991 , Koyama et al 1995) . Although the use of thrombin is attractive because it represents the best theoretical approach to causing thrombosis , trials have not shown that this is better than injection using alternative injection solutions(Balanzo et al 1990 , Benedetti et al 1991 , Koyama et al 1995) . This may be because studies have involved small numbers of patients , a suboptimal dose of thrombin , inappropriate patient selection and because some high risk patients have been excluded .

Since the results of my own experimental studies demonstrated that a combination of adrenaline plus thrombin may be the most potent modality in inducing haemostasis , in this study I have examined the efficacy of a combination of adrenaline plus thrombin extracted from pooled human plasma as injection therapy for bleeding peptic ulcer , comparing it with 1 : 100,000 adrenaline injections . As shown to in the introduction (Chung^ et al 1988 & Rajgopal et al 1991) , the clinical efficacy of endoscopic haemostatic therapy using 1:100,000 and 1: 10,000 adrenaline are similar .

Patients and Methods

Design and Inclusion Criteria

Between October 1994 and November 1995 , consecutive patients presenting with severe gastrointestinal haemorrhage were considered for this study . These patients were admitted to the four acute receiving units in the Lothian region of Scotland (Western General Hospital , Edinburgh , Edinburgh Royal Infirmary , St John's Hospital , Livingston and the Eastern General Hospital , Edinburgh) . The admitting teams then contacted me , using an air call pager . After resuscitation endoscopy was performed in all cases by myself* using an Olympus XQ10 forward viewing gastroscope . Patients who were found to have a peptic ulcer that was either actively bleeding or had a non bleeding visible vessel were included in the study if they had one other clinical risk factor . These risk factors were age over 60 years , initial haemoglobin concentration of less than 10 g/dl or shock , defined as a pulse rate greater than 100 beats/min or a systolic blood pressure less than 100 mm Hg , or both . A history of non steroidal anti-inflammatory drug (NSAID) use , previous history of peptic ulcer disease and Helicobacter pylori status were recorded . Patients who were admitted to hospital because of peptic ulcer haemorrhage (primary bleeders) and patients who bled after admission for other medical conditions(secondary bleeders)were recruited .Comorbidity was assessed in each patient .

*I had done 500 upper GI endoscopies while working as SHO in General surgery as part of my basic surgical training , some were therapeutic procedures . Furthermore , I received intensive training by Dr KR Palmer in August and September 1994 during which a further 200 endoscopies were carried out by myself .

Cardiovascular morbidity was defined as previous myocardial infarction with recurrent angina attacks and/or the presence of congestive cardiac failure . Respiratory comorbidity was defined as the presence of chronic obstructive airways disease sufficient to limit normal daily activity and or pneumonia at the time of bleeding . Renal comorbidity comprised chronic elevation of serum creatinine to greater than 500 mM/l . Neurological disability was defined as central nervous system disease resulting in loss of physical independence ; it encompasses chronic disability due to stroke , demylination or other degenerative neurological disease . Post operative phase was defined as the period in which a patient was in hospital after a major operative procedure . Mental and physical handicapped individuals were those institutionalised for cerebro-vascular disease or cerebral palsy .

Over the study period 289 patients were endoscoped and 149 were excluded , because they had bled from other causes(n=91) , did not have major stigmata of recent haemorrhage within an ulcer bed(n=55) , had significant liver disease(1 patient) or were receiving anticoagulant drugs(2 patients) . Patients were randomised by opening a sealed envelope to receive either injection with dilute adrenaline (group 1) or adrenaline plus human thrombin (group 2) *. The randomisation was carried out during the endoscopy , after examination of the peptic ulcer , before injection of dilute adrenaline . In many cases it was necessary to wash the ulcer bed using endoscopically positioned catheters in order to demonstrate major stigmata of haemorrhage.

Informed Consent :

This study was given ethical permission by the Medicine&Oncology ethical subcommittee of the Lothian Healthboard . When possible informed written consent was obtained from each patient or a relative prior to endoscopy . It was recognised by the subcommittee and myself that this is nevertheless not truly informed since an acutely ill patient or the relatives are not in a position to electively consider the implications of trial participation .

Endoscopic technique

Injections were administered using a disposable 4mm , 23 gauge injection needle (Keymed Ltd , Southend upon sea , UK) . Group 1 were treated with multiple injections (each 1-2 ml) of 1 : 100,000 adrenaline into and around the bleeding vessel . Group 2 patients were injected with 1 : 100,000 adrenaline in exactly the same manner followed by at least 2.8 ml (600 IU) injection of human thrombin injected into the vessel .

Human thrombin used in this trial was manufactured from pooled human plasma and was donated on a named patient basis (as a component of a fibrin sealant kit) by the Scottish National Blood Transfusion Service .

The volume of injection was similar in groups 1 and 2 . Group 1 patients received 4-18 mls(median 10 mls) of 1:100,000 adrenaline . Group 2 patients received 4-12 mls (median 7 mls) adrenaline , plus 2.8-4.5mls(median 3.5mls) of thrombin suspended in 40 mM calcium chloride , representing 600-1000 IU of human thrombin *(I intentionally aimed to give those receiving combination therapy smaller volume of adrenaline . The volume of adrenaline injected depended on the size of ulcer , the control of bleeding and the patient's tolerance of the endoscopic procedure)* . This dose of thrombin is similar to that which has been shown to reduce blood loss when injected into anastamosis during vascular surgery(Milne et al 1995&1996) .

Management following endoscopy was left in the hands of the admitting teams who were unaware of what was injected . The success or otherwise of the endoscopic therapy was communicated to these doctors .

Decision regarding blood transfusion and need for emergency surgery were made independently by those teams .

End points

The following endpoints were determined :

(1)-Re-bleeding , defined as fresh haematemesis or melaena , or both with either shock (pulse rate greater than 100 beat /min and systolic blood pressure less than 100 mm Hg) or a fall of haemoglobin concentration of at least 2 g/dl over a 24 hour period . Re-bleeding was in every case confirmed by endoscopy or emergency surgery .

(2)-Surgical operation . Re-bleeding was the only indication for surgery .

(3)-Units of blood transfused .

(4)-Duration of hospital stay

(5)-Thirty day mortality (from the time of admission) .

Repeat Endoscopy

This was performed in one of these situations

(1)-If in my opinion of , the initial endoscopic injection was felt to be suboptimal ; because blood made therapy difficult or because of an awkuad ulcer position .Repeat endoscopy was then undertaken within 24 hours as a planned elective procedure .

(2)-To confirm rebleeding

(3)-At the request of admitting teams if there was doubt concerning rebleeding .

Policy after re-bleeding

Re-bleeding was treated either by surgical operation or by endoscopic therapy (if requested by the admitting team) . Endoscopically treated re-bleeding patients received the same form of endoscopic therapy as was given at the time of admission .

Statistical Analysis

Differences in rebleeding and mortality rates were analysed using the chi square test and Fisher's Exact test respectively . Differences in blood transfusion was carried out using the (t) test .

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Results

One hundred and forty patients fulfilled the inclusion criteria and were randomised Two patients (one in each group) in whom initial treatment was thought by myself to be suboptimal had elective repeat endoscopic therapy(using the same injection materials) within 36 hours . Both patients presented with active bleeding and although initial haemostasis was effected in both cases , anatomical distortion and the presence of blood resulted in uncertainty about the adequacy of the procedure .

Table 1 shows the characteristics of the randomised patients . The two groups were well matched with regard to age , sex , NSAID intake , ulcer type and risk factors for re-bleeding (admission haemoglobin concentration , shock , serious co-morbid disease and endoscopic stigmata) .

Table 1
Patient Characteristics

	Adrenaline alone group 1 =70		Adrenaline+Thrombin group 2 =70	
	Active bleeding (n=24)	Non-bleeding vessel (n=46)	Active bleeding (n=27)	Non-bleeding vessel (n=43)
Median age , (range) years	71.0 (42-90)	71.0 (26-91)	68.0 (27-83)	69.5 (33-92)
Sex (M:F)	15 : 9	34 :12	17 :10	27 : 16
Mean admission haemoglobin concentration (SD), g/dl	8.4 (2.2)	8.5 (2.0)	8.9 (2.1)	8.5 (1.9)
Number in shock	14	18	20	20
NSAID users	16	22	13	21
Oesophageal ulcers	4	2	2	2
Gastric ulcers	7	20	9	16
Duodenal ulcers	13	24	16	25
Number with co-morbid disease	18	27	17	21
H.Pylori +ve/-ve	03/21	15 / 31	13/14	19 / 24
Primary : secondary bleeders	20/04	40 / 6	23/04	36 / 7

The nature of comorbid diseases is shown in table 2 .

Table 3 shows outcome in the two groups . Fourteen group 1 patients (20%) and three group 2 patients (4.5%) rebled during their hospital admission (p<0.005) . Those who rebled included significantly greater number of patients who presented with active bleeding than those who at endoscopy had a non bleeding visible vessel (11 versus 6) (p<0.036) . Ten group 1 patients who rebled were re treated with adrenaline alone and permanent haemostasis was achieved in five . Permanent haemostasis was not achieved by endoscopic therapy in seven group 1 patients . Five of these underwent urgent surgery , one died from exsanguination before a surgical operation could be performed and a further patient who was unfit for surgery because of a recent myocardial infarction had no further bleeding following an intravenous infusion of octreotide .

A total of eight patients from groups 1 and 2 who continued to bleed had emergency surgery . All but one recovered , although all had serious post operative complications . One patient died six days after emergency surgery of adult respiratory distress syndrome .

Table 2		
Type and distribution of co morbid disease		
	Group 1(45)	Group 2(38)
Cardiovascular	9	6
Respiratory	6	5
Cardiovascular& Respiratory	13	15
Cardiovascular Respiratory&Renal	2	4
Neurological	3	1
Renal	2	1
Post-operative	6	4
Mental&physical handicap	4	2

Table 3
Results of treatment

	Adrenaline alone group 1 =70		Adrenaline+Thrombin group 2 =70	
	Active bleeding (n=24)	Non-bleeding vessel (n=46)	Active bleeding (n=27)	Non-bleeding vessel (n=43)
Number re-bleeding*	9	5	2	1
Number re-treated	6	4	1	0
permanent haemostasis	20	43	25	42
Emergency surgery	3	2	2	1
Median units transfused (range)	2 (0-17)	3 (0-10)	4 (0-9)	3 (0-6)
Median duration of hospital stay (range)	6 (2-37)	7 (3-65)	6 (2-25)	6 (4-35)
Death**	3	4	0	0

* $p<0.005$
** $p<0.013$

Although median transfusion requirements were similar in both groups ,
significantly more total units were transfused in group 1 compared to group 2
(297 versus 219 , p<0.041) . The duration of hospital stay was similar in both
groups .

Seven group 1 patients died but there were no fatalities among group 2 patients
(p<0.013) . Deaths were restricted to patients who had severe comorbid
disease , and three of these occurred in secondary bleeders who had been
admitted to hospital because of unrelated serious medical problems . One of
these died from bleeding which occurred in association with multiple
complications associated with total cystectomy for invasive transitional cell
carcinoma . A second patient suffering from congestive cardiac failure due to
ischaemic heart disease rebled and died in congestive heart failure . A third
patients died from recurrent bleeding in association with chronic renal failure
and disseminated intravascular coagulation . A fourth elderly patients was
admitted because of upper gastrointestinal bleeding in association with lobar
pneumonia and died seven days later of respiratory failure despite successful
treatment of her bleeding ulcer . A fifth patient had unsuccessful injection
therapy for bleeding ulcer followed by two laparotomies for gangrenous
appendicitis and septicaemia . One other death followed emergency ulcer
surgery . A final patient exsanguinated from ulcer bleeding before an operation
could be performed .

No complications followed endoscopic therapy in either group . The presence
of Helicobacter pylori on biopsies did not influence outcome .

Discussion

In this trial of patients presenting with major peptic ulcer haemorrhage , combination injection treatment with dilute adrenaline plus human thrombin achieved significantly greater permanent haemostasis and improved mortality compared to patients treated by adrenaline alone .

Previous studies had shown that conservatively managed patients who have major endoscopic stigmata of bleeding have a high risk of uncontrolled bleeding and rebleeding (Chang-Chin et al 1988 , Brearly et al 1985 , Bornman et al 1985 , Clason et al 1986) . Others have shown that this risk is greatly reduced by endoscopic therapy (Panes et al 1987 , Lazo et al 1992 , Balanzo et al 1988 , Rajgopal et al 1991) . Consequently I felt it unethical to include a control (no endoscopic treatment arm) in the current study .

All patients who died had significant medical comorbidity and three deaths occurred in patients who bled following admission to hospital for illness unrelated to peptic ulcer . It is clearly possible that these patients would have inevitably died as a consequence of their cardiorespiratory or other diseases , that bleeding ulcer was an agonal incidental event and by chance all of these were randomised to group 1 . It is likely however that uncontrolled bleeding in each case contributed to decompensation of comorbid illness and was an important contributor to death . If the deaths in group I which were not directly due to exsanguination are excluded , the mortality difference between the two groups become non significant . However because the analysis was based upon "intention to treat" and because it is likely that rebleeding contributed to death by excacerbating comorbid disease , such exclusions are inappropriate .

In this study the severity of comorbid disease was not quantified ; nevertheless the definition of comorbidity was such that these patients had severe illness with significant physical disability . The distribution of comorbid disease , including the presence of multiple conditions was very similar in the two groups and differences in outcome following endoscopic therapy are unlikely to have been due to unequal distribution of severity or number of these .

Although permanent haemostasis was achieved more often with combination therapy than by injection of dilute adrenaline alone , the median blood

transfusion requirements and median duration of hospital stay were similar in the two groups .

The length of hospital stay is frequently dependent upon social factors and the course of unrelated medical illness and it is therefore not surprising that duration of hospital stay was similar in the two groups . The observation that total transfusion requirements was less in group 2 , yet median transfused units was similar in both groups reflects the wide range of transfusion necessary in this study .

Lin et al (1993) showed in clinical trial that haemostasis from bleeding ulcer can be as readily achieved by injection of inert substances as by injection of sclerosants and adrenaline . This suggested that a "tamponade effect" in which a relatively large volume of fluid injected into the rigid confines of a chronic ulcer , can stop bleeding by compressing the bleeding vessel . Others(Leung et al 1987 , Chung*et al 1988 , Lai et al 1994) have also referred to this possible mechanism . In the current study the median total injected volume was similar in the two groups . Therefore although a "tamponade effect" may have contributed to haemostasis in many patients , I have demonstrated an additional specific effect for human thrombin .

The efficacy of injected bovine thrombin (alone or in combination with other agents) has been examined in several clinical trials with varying conclusions . Juszkiewicz et al (1993) randomised 50 patients who presented with non-bleeding visible vessels within peptic ulcers to either no endoscopic therapy or injection with 200 IU of "animal thrombin" and reported a rebleeding rate of 4% in the treated group compared to 40% in the control group . Whilst this difference is statistically significant($p<0.01$) and encouraging , there must be reservations about the conclusions of such a small study . This criticism also applies to the trial reported by Moreto et al (1992) who randomised 38 patients(with spurting , oozing or non bleeding visible vessel) to conservative therapy or injection with ethanolamine plus 50 IU of bovine thrombin . Re-

bleeding in the treated group was 5 .3% compared to 57.9% in the control group .

The clinical trial which is most comparable to my own is that reported by Balanzo et al (1990) who randomised 64 patients who had been admitted to hospital because of ulcer bleeding and were found at endoscopy to have active bleeding or a non bleeding visible vessel to adrenaline alone(1:10,000) or adrenaline plus 150-300 IU of bovine thrombin . Re-bleeding rates (18.7% vs 15.6%) and other end points in both groups were very similar . It is likely that this trial eliminated some high risk cases since patients aged over 80 years and those unable to give written consents were excluded . The number of patients included was less than in our study and the amount of injected thrombin was approximately 25% of that used by ourselves . Other studies of thrombin are not comparable with the current study and do not clarify the value of thrombin . For example , Koyama et al (1995) reported a trial involving 62 patients who were found to have a non bleeding visible vessel within a gastric ulcer . All ulcers were sprayed with a mixture of dilute adrenaline plus 20,000 IU of "thrombin" and half were randomised to absolute alcohol injection . Perhaps not surprisingly the injected group had a lower rebleeding rate than the group who were not injected(12 versus 34.5%) .

Benedetti et al (1991) studied 82 patients injected with either 1% polidocanol (28 patients) or 100 IU of bovine thrombin (54 patients) . They excluded patients with "giant ulcers covered by a large blood clots" , those with firm sclerotic ulcers and those with deep ulcers . The remaining patients had ulcers which were either active bleeding , had a non bleeding visible vessel , were oozing or had an adherent clot . Rebleeding rate was similar in both groups (17.8% vs 14.8% respectively) .

Other trials have compared the efficacy of adrenaline injection with that of adrenaline in combination with sclerosants (Choudari et al 1994 , Chung et al 1993 , Villaneuva et al 1993) . These studies do not show advantages for combination therapy using either ethanolamine(Choudari) , sodium tetradecyle sulphate (Chung) or polidocanol(Villaneuva) with almost identical rates of uncontrolled bleeding , rebleeding , surgical intervention and death . The approach to haemostasis of injection plus a thermal modality is theoretically attractive and many clinicians use combination injection with bipolar electrocautery , heater probe or less frequently Laser photocoagulation although these approaches have only been evaluated in a small number of patients (Loizou et al 1991) . Trials are necessary to compare these options and a comparison of adrenaline plus thrombin versus adrenaline plus a thermal modality has merit .

The current study clarifies the value of adrenaline plus thrombin injection therapy in patients who exhibit major stigmata of haemorrhage . Unlike many previous studies , the highest risk patients were not excluded , an adequate sample size was studied and endoscopic therapy was undertaken by a single endoscopist using a standard technique and a relatively high dose of human thrombin . The injected dose of human thrombin used in the current study was at least 60% greater than that employed in other clinical trials of bleeding peptic ulcer . This dose of human thrombin was chosen because of experience in vascular surgery . When injected in combination with fibrinogen as a fibrin sealant , 600-1000 IU thrombin significantly reduced bleeding from anastomosis fashioned during carotid endarterectomy (Milne et al 1995) and peripheral vascular surgery (Milne et al 1996) . Furthermore although no formal , sequential studies of intravascular thrombosis have been undertaken in these trials neither local nor systemic thrombosis nor embolisation have occurred .

It is possible that both bovine and human thrombin could provoke anaphylactic reaction , particularly in repeated injection are administered . However such reactions have not been reported despite relatively extensive use of thrombin in vascular surgery (Milne et al 1995&1996 , Kram et al 1988) , as well as therapy for gastric and oesophageal varices () and in the current and other trials of peptic ulcer bleeding .

The thrombin used in this trial was manufactured from pooled human plasma . The extraction procedure includes a solvent-detergent virus step which has a good safety record (Bennet et al 1993) . In addition this product has been used as part of fibrin sealant in a number of clinical trials and no evidence of virus transmission was found over a six month serological follow up period (Mine et al 1995 , Bennet et al 1993)) .

Recombinant thrombin is currently being manufactured by the Scottish Blood Transfusion Service and concerns relating to viral transmission are therefore likely to be completely eliminated in the near future .

The current study encourages us to believe that injection with a combination of dilute adrenaline plus human thrombin is a significant therapeutic advance in the management of major peptic ulcer bleeding . This conclusion must be confirmed by larger studies and issues of toxicity relating to possible thrombotic complications and viral transmission must be addressed .

Chapter 4

The outcome of urgent surgery for major Peptic Ulcer Haemorrhage

Introduction

The management of major peptic ulcer haemorrhage has been transformed by therapeutic endoscopy . In most centres injection or thermal methods of haemostasis are applied to actively bleeding ulcers and to ulcers which contain a visible vessel . These approaches usually stop active bleeding and prevent rebleeding (Panes et al 1987 , Swain*^ et al 1986 , Chung et al 1989 , Liane 1987) , but are not always successful and patients who continue to bleed require urgent surgical intervention .

The choice of surgical operation for bleeding ulcer is controversial . Some centres favour a relatively aggressive surgical approach including vagotomy and pyloroplasty , ulcer excision or partial gastrectomy rather than underrunning the bleeding vessel alone . This is supported by series reporting better outcome following definitive surgery (Humphrey 1982 , Dronfield et al 1979 , Poxon et al 1991) .

Poxon and colleagues reported a multicerntre randomised prospective trial comparing minimal surgery(under-running or ulcer excision and adjutant intravenous Ranitidine) with conventional ulcer surgery(vagotomy and pyloroplasty or partial gastrectomy) for the treatment of peptic ulcer haemorrhage . One hundred and twenty nine patients were randomised to conservative therapy(n=62) or conventional surgery(n=67) . Twenty nine patients died , 16(26%) after conservative surgery and 13(19%) after conventional surgery . The only significant difference between the two groups was the incidence of fatal rebleeding , which occurred in six

patients after conservative surgery compared with none after conventional surgery (p<0.02) .

Dronfield and colleagues retrospectively compared the outcome of patients undergoing ulcer surgery in two hospital in Nottingham . They reported that for bleeding gastric ulcers , partial gastrectomy was associated with 21% mortality compared to 50% mortality after conservative surgery(oversewing , local excision with or without vagotomy and pyloroplasty) . However the role of radical surgery for bleeding duodenal ulcers was questionable in this study(mortality following vagotomy and drainage was 12% compared to 44% after partial gastrectomy) . This study could be critised in being retrospective . Furthermore only 3 out of 110 patients had under-running alone . Humphrey reviewed the surgical literature and concluded in an authoritative surgical textbook that undersewing is an inadequate treatment which frequently led to recurrent haemorrhage .

Others argue for a minimalist surgical approach because major surgery is associated with high morbidity and mortality . Powerful drug therapy eliminates gastric acid output and helicobacter pylori infection and previous studies reported better outcome in patients treated by underrunning and drug therapy (Rogers et al 1988 , Hunt et al 1979) . Rogers and colleagues reported the outcome of 61 patients who underwent surgery for bleeding gastric ulcers at Glasgow's Western Infirmary . Surgery included partial gastrectomy(n=19) , under-sewing plus vagotomy and pyloroplasty(n=20) and under-running alone(n=20) . All groups were similar in terms of age ,

severity of haemorrhage , delay before surgery and grade of surgeon performing the procedure . Mortality in the three groups was 26 , 45 and 10 per cent respectively .

In this study I report the Edinburgh experience of patients who underwent urgent surgical intervention following failure of endoscopic therapy for bleeding peptic ulcers between 1990-1995 .

Patients and Methods

Between June 1990 and December 1995 , 1142 patients were referred for urgent upper gastrointestinal endoscopy because of upper gastrointestinal haemorrhage and of these 492 patients(333 men and 159 woman) with significant peptic ulcer haemorrhage were considered for inclusion in clinical trials . These patients were admitted to the four acute receiving units in the Lothian region of Scotland(Western General Hospital , Royal Infirmary/Edinburgh , Eastern General Hospital and St. John's Hospital at Howden) . They were referred to myself or 2 previous research fellows from the Western General Hospital for endoscopic therapy(injection or heater probe therapy) . Patients had peptic ulcers which were actively bleeding or had a non bleeding visible vessel . In addition , patients had one other clinical risk factor . These risk factors were age over 60 years , initial haemoglobin concentration of less than 10 g/dl or shock , defined as a pulse rate of greater than 100 beats/min or a systolic blood pressure less than 100mm Hg , or both . A history of non steroidal anti-inflammatory drug (NSAID) use and evidence of serious co morbid disease were documented .

Of these patients , 67(13.6%) patients had emergency surgery due to torrential bleeding which made accurate diagnosis and endoscopic therapy impossible(n=9) , continuous uncontrolled active bleeding(n=5) or rebleeding (n=53) following endoscopic therapy . These surgical operations

were carried out by different surgeons in four hospitals . None had a specific policy as to the type of operation which should be performed . The clinical characteristics of these patients , the type of surgery undertaken and outcome in terms of rebleeding and mortality were compared . This was done by examining completed audit forms , case notes and individual follow up by the three research fellows . I compared the group of patients receiving conservative therapy(underrunning alone)(n=28) with those receiving other operations (underrunning plus vagotomy&pyloroplasty (n=24) , excision alone (n=3) , excision plus vagotomy&drainage (n=3) and partial gastrectomy/antrectomy(n=9) .

Statistical analysis

Comparison between the study groups was carried out using the chi square test and results considered significant for p<0.05 .

Results

Table 1 shows the characteristics of the study groups and the type of operation carried out . The two groups were well matched for age , sex , non steroidal anti-inflammatory drugs intake and ulcer type . In addition , the severity of bleeding (haemoglobin concentration , presence of shock and proportion of patients with serious comorbid disease) were similar . Twenty eight patients underwent conservative surgical therapy defined as underrunning of the ulcer without a further surgical procedure (group 1). Thirty nine patients underwent radical operative intervention ; 24 had underrunning with vagotomy & pyloroplasty(V&P) , 3 had ulcer excision , 3 had excision plus V&P and 9 had partial gastrectomy / antrectomy (group 2).

Table 2 shows outcome in the two groups in terms of rebleeding and death . Seven(25%) group 1 patients rebled after conservative surgery . One patient(2.5%) from group 2 (the radical group) had further bleeding (p<0.015) . There were 7(25%) post operative deaths in group 1 patients and 5(12.8%) deaths in group 2 (NS/ p=0.2) . The overall post operative mortality was 18% .

The ratio of consultant to non consultants performing these operations was (18/10) in group 1 and (25/14) in group 2 .

Twenty nine (8.7%) men and 38(23.8%) women underwent urgent surgery after failed endoscopic therapy (p<0.0001) .

Table 1
Patients Characteristics

Type of surgery	No of patients	Median age(range)	Sex(M : F)	Haemoglobin(g/dl)	Ulcer(Duodenal/Gastric)	Shock	comorbid disease
Underrunning alone(group1)	28	70(41-86)	10:18	7.1(4.1-10.9)	20:08	24(86%)	24(86%)
Other surgery(group 2)	39	68(41-88)	19:20	7.5(4.2-10.2)	21:18	34(87%)	32(82%)

Table 2
Results of surgery

	No of patients	Re-bleeding	Death
Underrun alone(group 1)	28	7(25%)	7(25%)*
Other surgery(group 2)	39	1(2.5%)	5(12.8%)**

*$p < 0.015$
**NS/ $p = 0.2$

Discussion

Rebleeding and hospital post operative mortality were higher in patients treated by simple underrunning of the bleeding ulcer than in those treated by more radical surgery. This finding was not due to differences in case mix. Risk factors for rebleeding and death, particularly age, admission haemoglobin concentration, the presence of shock and severe comorbid medical diseases were very similar in the patient groups. Thus, poor outcome in conservatively treated patients was not attributable to a greater need to perform a rapid, simpler operation because of differences in bleeding severity and comorbid illnesses. It is worthy of note that there was a greater number of gastric ulcers treated by radical surgery than by underrunning alone(46% vs 30%). This did not achieve statistical significance (p=0.32). Outcome was not influenced by seniority of the surgeon since the proportion of operations performed by consultants and non consultants was similar. The specialist interest of the general surgeons involved was not recorded. It is possible that those with interest in Gastroenterology would obtain better results but we have no evidence to support this possibility.

It is not clear why more radical surgery proved more effective than simple underrunning in this series. However my findings reflect those of Dronfield et al(1979) and Poxon et al(1991) who also reported a trend toward better outcome with an aggressive surgical approach. Whilst one can understand that partial gastrectomy or excision which remove the bleeding ulcer effectively prevent rebleeding, one has difficulty with the observation that vagotomy and pyloroplasty with underrunning proved superior to underrunning alone. All patients received powerful ulcer healing drugs before and after surgery and if acid plays any role in ulcer bleeding, it is

surprising that conservatively treated patients faired relatively poorly .

Perhaps the anatomical aspects of pyloroplasty are important , since these

could influence the vascular supply of the duodenum , and may allow

greater surgical access to the bleeding lesion compared with a small

duodenotomy .

Most patients undergoing surgery in this series had been subjected to

endoscopic injection or heater probe therapy ; in a minority torrential

bleeding or failure of access prevented this . It is possible that endoscopic

therapy influences the outcome of surgery . Local oedema commonly

occurs at injection sites , but this did not apparently increase the difficulty

of the surgical operation . Nevertheless , it is possible that this could have

made undersewing less effective . My policy has been to avoid sclerosant

injections which can cause local necrosis (Laperfido et al 1990 , Pousset et

al 1992) , and are more likely to exacerbate the difficulties of surgery .

Only a minority (5.8%) of patients admitted to hospital because of non

variceal bleeding failed to respond to conservative medical or endoscopic

therapy and required a surgical operation . This may reflect the efficacy of

endoscopic treatment , particularly as the patients in this study were a

selective high risk group since they had stigmata of recent haemorrhage .

Patients without these endoscopic findings invariably have a good

prognosis and only rarely require surgical intervention (Clason et al 1986 ,

Chang-Chen et al 1988 , Kohler et al 1993) . One potential problem of

endoscopic therapy is that patients who fail to respond could be put at

increased risk of death following abortive endoscopic treatment . Patients

who fail endoscopic therapy undergo delayed surgical operation , which

may be less successful than early surgery , receive more blood transfusion

and are more prone to prolonged and repeated hypotensive episodes than

patients who undergo an early operation (Morris et al 1984 , Hunt 1987) .

This study reassures us that these potential problems do not apparently lead

to excessive mortality . In this series overall post operative mortality was

18% and this compares favourably with that reported elsewhere (Welch et

al 1986 , Park et al 1994 , Schein et al 1989) .

Our finding that the outcome of females with major peptic ulcer

haemorrhage is poorer than males was an unexpected incidental finding . It

could be because the median age of female patients is higher than males (73

versus 69 years) or because of greater use of NSAID among women (72%

versus 43.6%) . This trend was also noted by Rockhall et al (1995) who

reviewed 4185 patients with upper gastrointestinal haemorrhage and found

that both the overall mortality and the age standardised mortality was higher

in women compared to men .

The type of surgery performed will ultimately depend on several factors ;

the location and chronicity of the ulcer , the haemodynamic and

cardiorespiratory state of the patient after initial resuscitation and the

experience and skills of the surgeons available . Effective emergency ulcer

surgery must be tailored to the individual patient and their pathology but

our findings suggest that a conservative surgical operation is a less effective

option than a more radical approach .

Chapter 5

Reduced long term survival following major peptic ulcer haemorrhage

Introduction

The late outcome of patients who are discharged from hospital after receiving endoscopic therapy for bleeding ulcers is uncertain.

Smart et al (1986) reported that 26% of patients who had bled from gastric ulcers died within a four to eight year follow up period, usually from causes unrelated to ulcer and that 16% suffered rebleeding episodes.

Rorbaek-Madsen et al (1994) also found that late mortality in bleeding gastric ulcer patients is high, most deaths being related to co-morbid disease rather than further ulcer complications. Hudson et al (1995) followed up 487 patients(aged>60) who presented with peptic ulcer bleeding for a mean duration of 34 months. This included patients with minor and major bleeding and none received endoscopic haemostatic therapy. They reported a mortality of 29% in the study group compared to 12% in an aged and sex matched controls. These reports concentrated upon survival determined by case notes review and death registry check; little is known of prognosis in terms of subsequent ulcer symptoms and their relationship to bleeding events and death. In this study I have examined late outcome in a series of patients who received endoscopic therapy for major peptic ulcer bleeding. The purpose of this was to define causes of death and to examine morbidity from further bleeding and other ulcer related events.

Patients and Methods

The study group was recruited from patient cohorts who took part in two clinical trials between Dec 1988 and May 1992 . In the first of these(Rajgopal et al 1991) , 109 patients were randomised to endoscopic injection therapy with dilute adrenaline and ethanolamine or to conservative management . Fifty six of these received endoscopic therapy , two died in hospital and long term information from 54 was available . The second clinical trial(Choudari et al 1992) involved 120 patients who were randomised to endoscopic therapy using the heater probe or injection sclerotherapy with a combination of dilute adrenaline and ethanolamine . Eighty two of these were treated before May 1992 and were considered for long term follow up , 5 died in hospital , no follow up information was available from 10 patients because their medical records could not be traced and long term information was available from the remaining 67 .

The study group thus comprised 121 patients . All of these had presented either with active bleeding or a non bleeding visible vessel at endoscopy . In addition they had at least one other adverse prognostic factor from age over 60 years , serum haemoglobin concentration less than 10 g/dl or shock (defined as a pulse rate greater than 100 beats/minute or a systolic blood pressure less than 100 mm Hg).

Demographic details of the study group and of patients who could not be contacted are shown in table 1.

Table 1
Risk factors in patients who were followed up and those who could not be traced

	Traced (121)	Non-traced (10)
Male	64%	70%
Median age(range) years	68(20-96)	68(23-78)
Gastric ulcer	37%	30%
Duodenal ulcer	62%	70%
Others	1%	0%
Active bleeding	53%	60%
Stigmata of recent haemorrhage	47%	40%
Patients on NSAID	37%	20%
Mean haemoglobin(SD) g/dl	8.8(2)	8.5(2.2)
Co-morbid disease	46%	40%

Fifty five patients in the study group had serious co-morbid disease as defined by admitting medical teams.(table 2)

Table 2
Co-morbid disease in the study group

Co-morbid disease-Total	55(46%)
Cardiovascular	32
Respiratory	15
Neurological	5
Renal	1
Others	2

Endoscopic therapy was successful in 119 patients ; the two remaining patients underwent emergency surgery.

As previously reported , the short term outcome of patients treated by injection or the heater probe was similar (Choudari et al 1992) .

Follow up

Median length of follow up was 36 months(range 30-76) . Causes of death were obtained from hospital records and surviving patients were contacted by postal questionnaires . General practitioners were contacted when information was uncertain.

The postal questionnaire addressed the need for further hospital admission including endoscopy , recurrent bleeding and details of drug therapy . A simple dyspepsia questionnaire was used to quantitate indigestion(figure 1) . This was validated in 100 outpatients attending for routine upper gastrointestinal endoscopy.(table 3)

Table 3 -Validation of dyspepsia questionnaire

Dyspepsia score	0-2	3-5	>5
Patients with *positive findings	5	38	15
Patients with negative findings	35	2	5

Sensitivity = 91% / Specificity = 83%
p<0.0001
*positive findings refer to the presence of ulcer or untreated oesophagitis

Confidence interval(CI) is between 0.84-0.98

Long term outcome in peptic ulcer bleeding Questionnaire

A- Please Tick or put a Circle as appropriate:

1-After your hospitalisation at -- in ------/------/------ :
(a)- Have you had any further hospital admissions for any reason?.

             YES   NO

If the answer is YES , please state the name of the hospital : --

(b)-Have you had any further Endoscopy (the telescope test into the stomach) ?.

             YES   NO

If the answer is YES , please state the month and the year of the procedure

----

		YES	NO
(c)-Have you had further :	Vomiting of blood	--------	-------
	Passing of black motions	--------	-------

If the answer is YES to either of the above two questions , have these episodes been severe enough for you to report them to a doctor ?.

Dyspepsia Questionnaire

Do you frequently suffer from:

	Not at all (0)	Alittle (1)	A lot (2)
a-Tummy pain			
b- Heart burn			
c- Acid reflux			
d- Nausea			
e- vomiting			

B- Please list any symptoms you suffer from which may be related to your condition
_____
_____

C- Can you list your present medications that you have obtained from your GP or the Hospital (please state dose and duration)
_____
_____

Can you list any medicines that you felt the need to buy over the counter (that is without prescription)
_____
_____

D- How often did you seek help from your GP regarding this condition over the last year?

Never   Occasionally(1-2 times)   Frequently(more than twice)

How often did you attend a Hospital regarding this problem (Number of times over the last year)

..   _____/ year

E-How many cigarettes have you smoked in the last week? _____/ week

F-How much alcohol did you consume over the last week? _____ unit/ week

Statistical analysis

Mortality in the study group was analysed using the Kaplan-Mieir method , comparing survival with that of the age and sex matched Scottish population (Scottish Health Statistics 1993) .

Results

Survival

Late mortality is presented as life table analysis in figure 2 . Survival was significantly less than that of the matched Scottish population($p < 0.01$) . Figure 3 shows that deaths were almost all restricted to patients who had significant co-morbid disease at their initial hospital admission for peptic ulcer bleeding ($p < 0.001$) . Thirty patients died during the follow up period . The causes of death are summarised in table 4 . Five patients had autopsy , 23 died in hospital and 7 died at home . Only two patients died from complications of peptic ulcer surgery ; one aged 79 years died at home from myocardial infarction 30 days after surgery , the other died at the age of 82 from pulmonary thromboembolism 26 days after surgery.

The median age of patients who died was 79 years(range 52-96) , that of long term survivors was 66 years(range 20-92).

Recurrent bleeding

Eight out of the surviving 91 patients (9%) had hospital admissions , because of recurrent peptic ulcer bleeding .Only two of these patients were receiving maintenance acid suppressing therapy , none had Helicobacter pylori eradication and two others were concurrently receiving therapy with non steroidal anti-inflammatory drugs without ulcer prophylaxis .
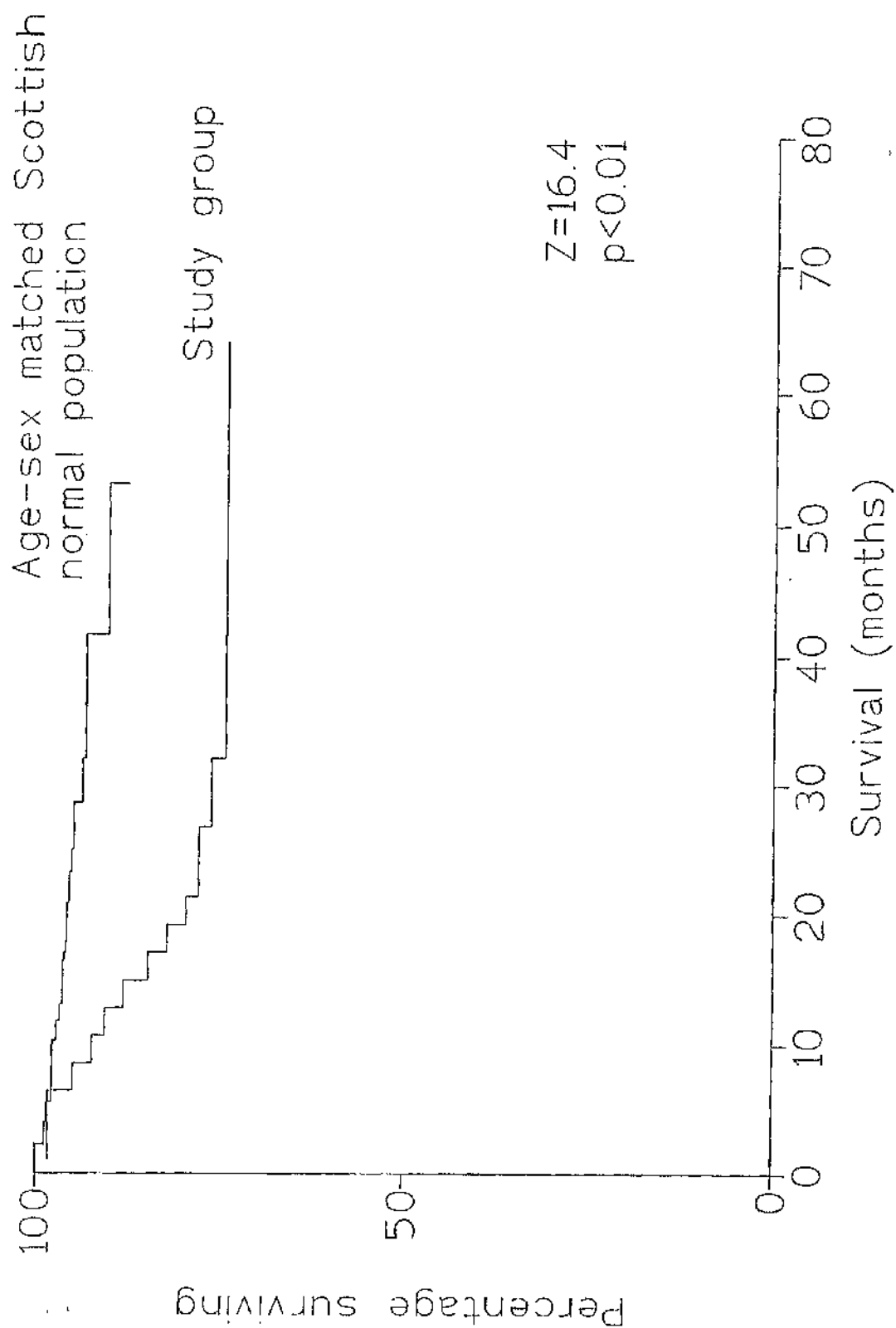
Morbidity

Twenty two patients (24%) had an average of two hospital admissions for reasons unrelated to peptic ulcer disease . The indication for admission principally related to cardio-respiratory and cerebro-vascular diseases.

Seventy six patients(84%) replied to my questionnaire , information was only available from the case notes and general practitioners in the remaining 15 survivors .

Sixty three patients (83%) scored 0-2 on the dyspepsia questionnaire (have had very little or no symptoms) . Thirty one (50%) of these patients were receiving maintenance therapy , (comprising Ranitidine 150mg bd or cimetidine 400 mg bd in 84% and Omeprazole 20 mg in the rest) . Nine patients(12%) scored 3-5 (had moderate symptoms) and Four patients(5%) scored more than 5 (had severe symptoms) . Three out of these were taking maintenance acid suppression therapy and one of these had also received Helicobacter Pylori eradication therapy six months prior to rebleeding .

Survival curves comparing the study group
with the normal Scottish population

Age-sex matched Scottish
normal population

Study group

Z=16.4
p<0.01

100

50

0

0   10   20   30   40   50   60   70   80

Survival (months)

Percentage surviving

SURVIVAL CURVES OF THOSE WITHOUT AND WITH CO-MORBID ILLNESS

$\chi^2 = 27.6$
p <0.0001
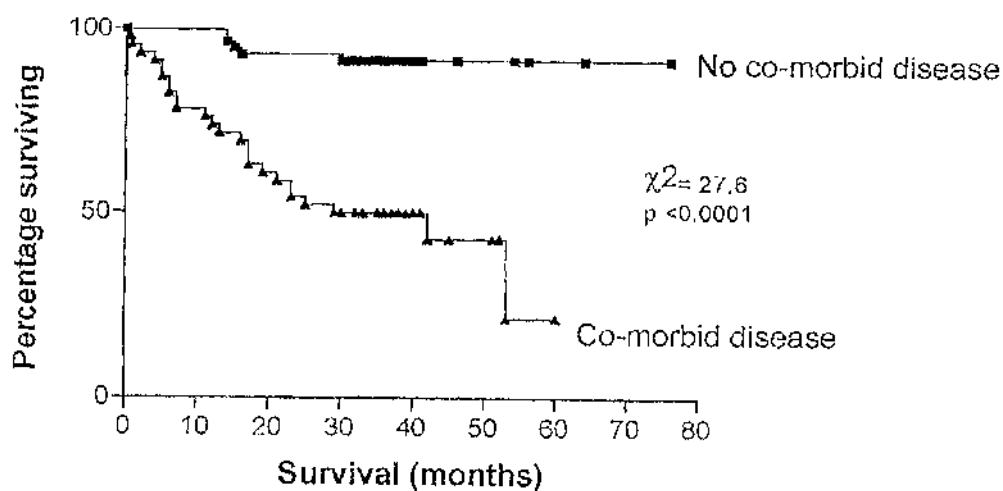
Table 4
Causes of death of the deceased group

Cause of death	Number(total=30)
Cardiovascular(total)	20
myocardial infarction	7
cerebrovascular accident	6
congestive cardiac failure	5
peripheral vascular disease	2
pneumonia and chronic obstructive airways disease	5
Malignant(total)	3
Oral	1
Leukaemia	1
Breast	1
Peptic ulcer	2

Discussion

This study shows that the duration of survival for patients discharged from hospital following endoscopic therapy for major peptic ulcer haemorrhage is lower than that of the age and sex matched Scottish population . Deaths are due to serious co-morbid disease or complications of emergency operations . Post mortem confirmation was available in only a minority of patients . The majority of patients died in hospital and I am confident that the cause of death was accurately defined .

High late mortality in the series was not surprising because of the high prevalence of co-morbid disease in the study group . The presence of concomitant diseases is likely to predispose to a more severe presenting episode ; for example patients with significant cardiovascular disease may withstand a serious haemorrhage poorly and those with an atheromatous bleeding artery within the ulcer bed will probably bleed more extensively than patients with relatively elastic vessels . Most studies of patients presenting with major ulcer bleeding contain a high proportion of patients who have serious co-morbid disease (Panes et al 1987 , Swain*^ et al 1986 , Chung et al 1989 , Liane 1987 , Rajgopal et al 1991 , Choudari et al 1992) .

There was no evidence that endoscopic therapy contributed to mortality and previous studies have shown that successful endoscopic haemostatic therapy does not impair ulcer healing (Rajgopal C et al 1993) . In contrast the morbidity of emergency surgery is high ; early postoperative complications are common and may be fatal (Poxon et al 1991 , Park et al 1994) . In this study two patients died within 30 days of emergency gastric surgery despite being fit enough to be discharged from hospital care . Five other patients admitted with peptic ulcer bleeding during the course of our studies also died post

operatively (a post operative mortality of 23.6%) . However this study only deals with patients who were discharged from hospital after treatment for peptic ulcer haemorrhage and therefore excludes these early post operative deaths.

Many patients who present with peptic ulcer bleeding give no history of antecedent dyspepsia and it is therefore perhaps not surprising that the majority of patients (83%) had very little or no symptoms . Less than half of these were receiving maintenance therapy . Recurrent ulcer bleeding was uncommon , the rate of rebleeding in this series was lower than that reported from other centres (Rorbaek-Madsen et al 1994 , Graham et al 1993 , Egan et al 1991) and most patients who rebled had no symptoms of indigestion (Ming et al 1990) .

Recurrent bleeding was not related to gender , site of ulcer or age , but it is worthy of note that the majority of these re-bleeds occurred in patients who had not received long term ulcer healing therapy.

Penston et al (1993) suggest that the widespread use of long-term continuos therapy with H2 antagonists significantly reduces the level of both uncomplicated and complicated ulcer disease and others have suggested that Helicobacter Pylori eradication should be undertaken following ulcer bleeding (Graham et al 1993) . I found only a low prevalence of rebleeding , but because recurrent bleeding in the presence of co-morbid disease represent a life threatening event and because symptoms do not predict rebleeding , I believe it reasonable to recommend long term healing therapy in all patients who present with bleeding ulcers until the results of large randomised controlled trials comparing long term maintenance with Helicobacter pylori eradication(where appropriate) are available.

Chapter 6

The effect of octreotide on gastroduodenal blood flow

measured by Laser Doppler Flowmetry in rabbits .

Introduction

Changes in gastroduodenal mucosal blood flow (GDMBF) may play a role in the pathogenesis of gastroduodenal ulceration in humans and experimental animals (Piaceski et al 1989 , Cherry et al 1986). In 1842 Curling (1842) observed acute ulceration of the duodenum associated with burns . Cushing(1932) described similar findings in patients undergoing brain surgery .

Sato et al (1979) induced haemorrhagic shock in rats . They demonstrated that disturbed energy metabolism in the gastric mucosa associated with a decline in gastric mucosal blood flow(measured by in vivo reflectance spectrophotometry) resulted in gastric mucosal ulceration . Kamada et al (1982) compared a group of patients who suffered gastric ulceration while in hospital because of major burns or head injury with eight healthy volunteers. They found a significant decrease in gastric mucosal perfusion(measured by reflectance spectrophotometry) in the study group and concluded that mucosal ischaemia following head injury and burns is the main cause of acute gastric ulceration .

It is now clear that septic or hypovolaemic shock with consequent impaired blood flow regularly causes gastric ulceration in experimental animals (Harjola et al 1966 , Hottenrott et al 1978 , Kivilaakso et al 1978) .

Sato et al (1995) found that the administration of indomethacin and 40% ethanol solution to dogs and rats results in a decrease in gastric mucosal blood flow(measured by reflectance spectrophotometry and H2 gas clearance respectively) and concluded that decreased GDMBF may also play an important role in non steroidal anti-inflammatory drugs and alcohol induced gastric mucosal lesions. In contrast portal hypertensive gastropathy is an important cause of upper gastrointestinal haemorrhage in cirrhotic patients (Taransky et al 1994) and has been shown to be associated with increased GDMBF (Panes et al 1992) .

Until recently measurement of GDMBF (based upon reflectance spectrophotometry , neutral red clearance and microspheres clearance) has been complex and unreliable . Laser Doppler Flowmeter(LDF) is a new method of measuring GDMBF . This instrument measures microvascular perfusion through tissue using the doppler shift(this is the frequency change that light and other radiation of a wave nature undergo when interacting with objects in motion , such as red blood cells . Since velocity = wave frequency x wave length , therefore , when the frequency changes the wavelength change as will the quality by which we receive the radiation in lights its colour , in sound its pitch) . The instrument consists of 3 components ; a processor containing the laser mounted on a 2 mm endoscopic probe , an output section transferring information to a computer which processes the data and a display section

which also contains the controls necessary to operate the instrument.(figure 1,2) .

Octreotide is a long-acting somatostatin analogue , SMS 201-995 , Sandostatin , Sandoz Inc , It has the advantage over somastatin in having a half life of 90 minutes compared to 1-3 minutes of somatostatin itself Clinical trials performed in the 1980s suggested that intravenous infusion of octreotide tended to improve the outcome of patients with peptic ulcer haemorrhage (Linberg et al 1980 , Kayasseh et al 1980 , Jenkins et al 1992)

Linberg et al found that somatostatin was successful in stopping bleeding from gastric and duodenal ulcers of 8 out of 10 patients with major haemorrhage compared to 1 out of 10 when cimetidine alone was used . Kayasseh et al randomised 20 patients with major ulcer haemorrhage to cimetidine or somatostatin and found that the success rate in stopping haemorrhage was 2/10 and 7/10 respectively . Jenkins et al found octreotide to be effective in treating 5 patients with ulcer haemorrhage who failed to respond to medical treatment and were unfit for surgery . However , others have refuted this assertion (see summary of clinical trials)(Burrough et al 1993) . The mechanism whereby octreotide might stop peptic ulcer bleeding is unclear . Octreotide significantly reduces splanchnic blood flow in experimental animals (Jenkins et al 1985&1985*) and in healthy subjects (Wahern et al 1986). For example

Cooper et al (1991) showed that octreotide reduced superior mesenteric and portal blood flow by 59 and 49% respectively.

The purpose of this study was to assess the effects of octreotide upon gastric and duodenal mucosal blood flow (GDMBF) in experimental animals using Laser Doppler Flowmetry.

Summary of trials of somatostatin or octreotide for peptic ulcer haemorrhage

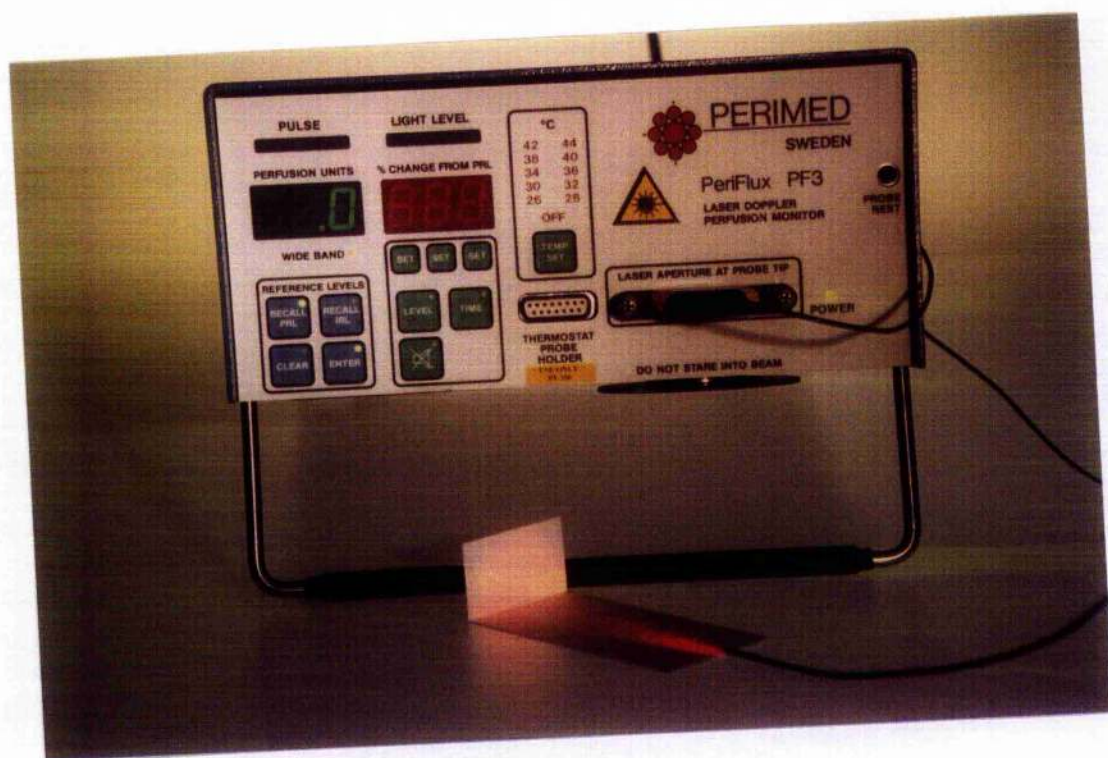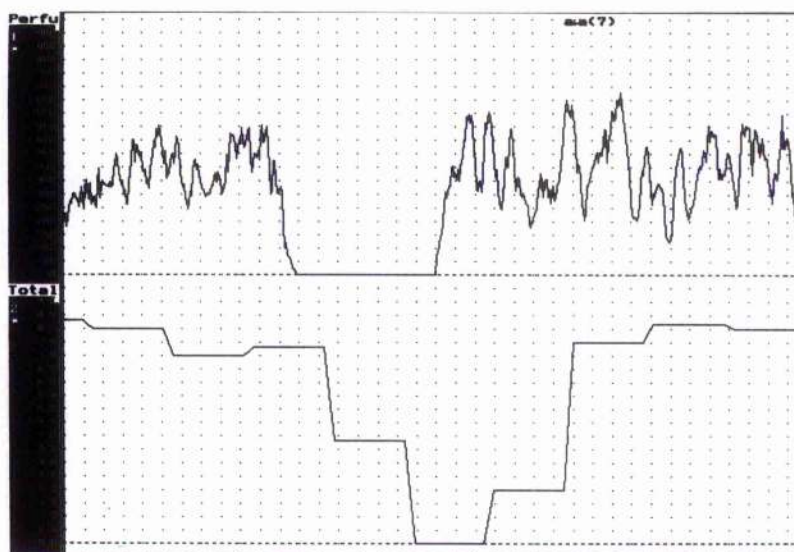| Octreotide more effective than control		No effect of octreotide compared to control	
Author&Year	*No of patients*	*Author&Year*	*No of patients*
Kayasseh (1980)	20	Somerville (1985)	630
Basile (1984)	99	Basso (1986)	96
Corragio (1984)	60	Saperas (1988)	92
Magnusson (1985)	95	Christainsen (1989)	241
Antonioli (1986)	56		
Torres (1986)	60		
Tulassuy (1989)	67		

Figure 1 Laser Doppler Flowmeter

Figure 2 Typical traces which appear in the computer screen attached to the

LDF

Methods

Experiments were carried out in 8 NewZealand white rabbits with a median weight of 3.25kg (2.95-3.95 kg) . Intravenous midazolam , (0.5 mg/kg) and intramuscular fentanyl citrate (0.315 mg/ml) and Fluanison (10mg/ml) 0.22 ml/kg were used to induce anaesthesia . Further injections of intravenous midazolam were used as required to maintain anaesthesia . All animals received continuous supplementary oxygen through a face mask or via an endotracheal tube (size 2) at 6 l/min . All experiments were carried out on an electrically heated pad at body temperature . GDMBF was measured using LDF *(Perimed , Jarfalla , Sweden) via an endoscopic probe (PF 309 , diameter 1.9 mm) .

The operator (myself) who positioned the LDF probe was blinded to the measurement recorded by the LDF . A co-worker (G.Haydon) recorded the measurements and analysed the signals yet was blinded to the type and concentration of substances injected .

GDMBF was measured in the body and antrum of the stomach and duodenum . Systemic haemodynamic changes(HC) were monitored by measuring pulse rate at the cardiac apex (beats per minute)and ear lobe skin perfusion using LDF . Intragastric pH was measured using 2 multistix reagent strips (Bayer Diagnostics , Basingstoke , Hampshire , UK) at the beginning and end of the procedure .

Animal 1 : One animal was intubated then ventilated and an upper gastrointestinal endoscopy was performed using an Olympus P 10

paediatric forward viewing gastroscope (Olympus , Keymed , South end on sea , UK) . Serial measurements of GDMBF were carried out over 30 minutes . The same animal was extubated and allowed to breathe spontaneously through a face mask delivering 6 L of oxygen . Thereafter laparotomy through a 3 cm upper midline incision was carried out and an anterior 4 mm diameter gastrostomy was made . The LDF probe was introduced through the gastrostomy and serial measurements of GDMBF were carried out over 30 minutes .

After this experiment , all measurements of GDMBF were carried out via gastrostomy.

Animal 2 : GDMBF and HC assessed over 60 minutes .

Animal 3 : GDMBF and HC assessed over 60 minutes while receiving intravenous injections of 1 ml of normal saline (total of 7 ml) .

Animal 4 : GDMBF and HC assessed over 60 minutes before and after an intravenous bolus injection of vasopressin (1 mg/kg) of body weight .

Animals 5,6&7 : GDMBF and HC assessed over 20 minutes before and 60 minutes after an intravenous bolus injection of octreotide (40 microgram/kg) of body weight .

Animal 8 : GDMBF and HC assessed over 100 minutes while receiving intravenous doses of octreotide of 10 microgram/kg every 20 minutes reaching a cumulative dose of 50 microgram/kg . This was to study a dose response relationship .

The animals were killed at the end of the procedure with an overdose of phenobarbitone .

Statistical Analysis

The values for perfusion at each of the different sites were quoted as mean +/- standard error of the mean(SEM) . Comparison between the study group and control were calculated using the Mann-Whitney-U test . Significance was established at a level of $p<0.05$.

Figure3
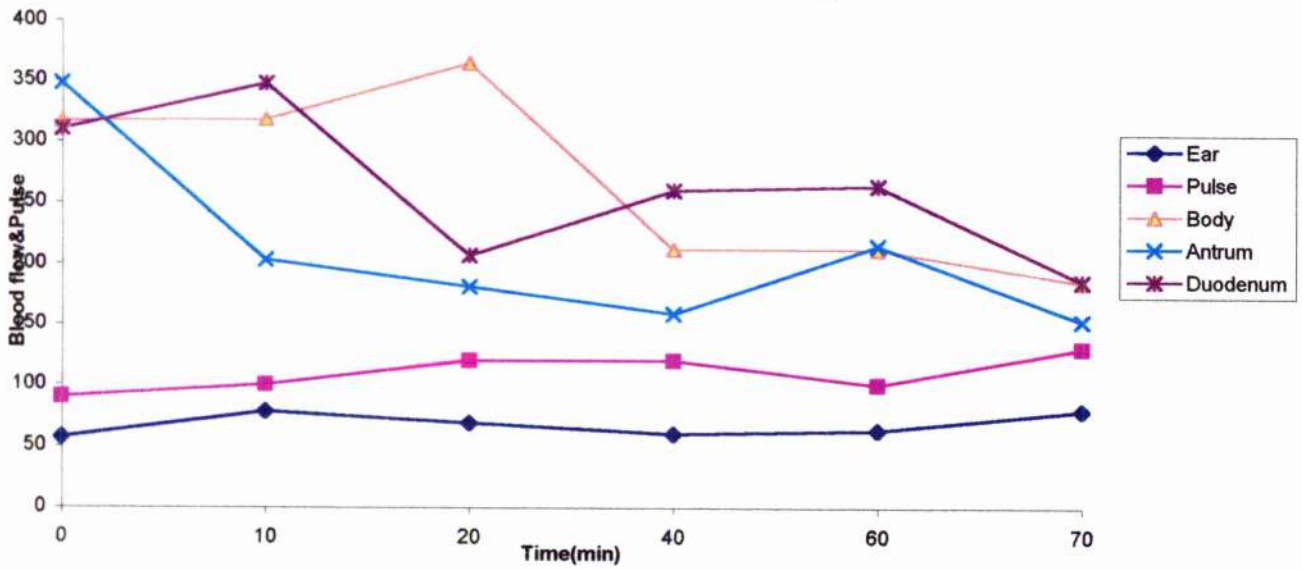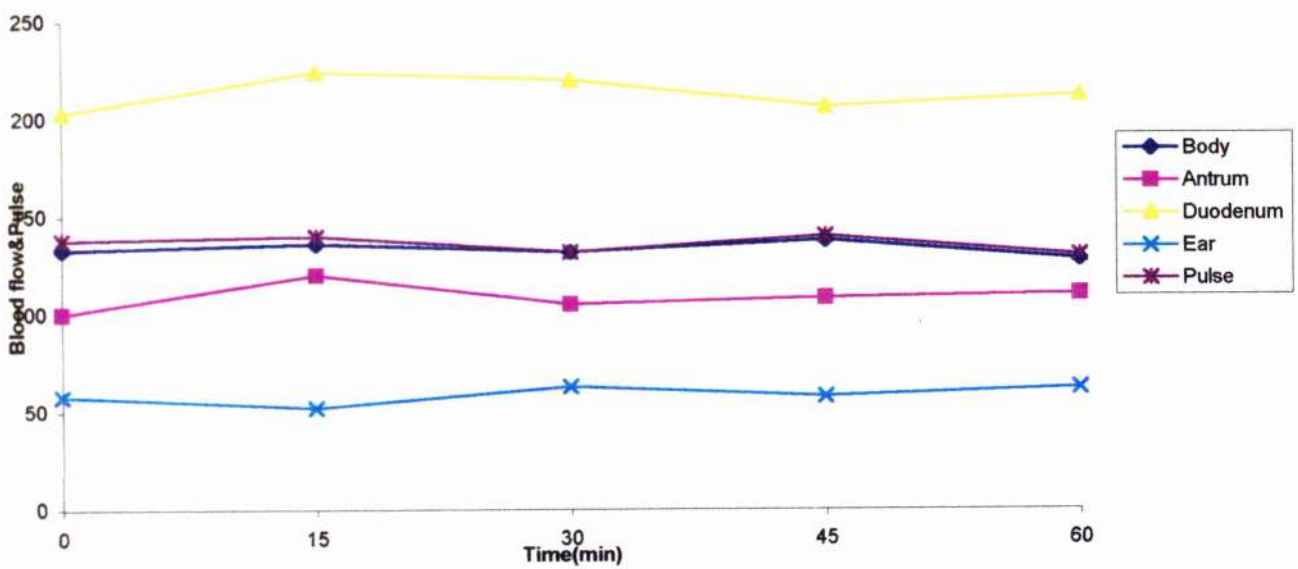**Blood flow&Pulse in one rabbit receiving saline only**

Figure 4
Blood flow&Pulse in one rabbit receiving normal saline

Results

Table 1 shows that GDMBF in the duodenum , body and antrum of the stomach presented in arbitrary units were not significantly different whether measurements were obtained endoscopically or at gastrostomy . Infusion of saline did not influence mucosal blood flow in the gastric body(p=0.29) , antrum(p=0.14) and duodenum(p=0.46) and this was well maintained over a 60 minutes period (n= 2) . Pulse rate at the cardiac apex and skin perfusion were also unchanged (table 2) . (figures 3 / 4)

Table 1			
Mean(+/-SE) GDMBF in a single rabbit, measured endoscopically and at gastrostomy/Units(SE)			
	Duration of measurement(min)	Mean GDMBF(SE),Units	
		Endoscopic	Gastrostomy
Body	5	212(4.9)	189(3.1)
Antrum	5	174(2.9)	171(2.4)
Duodenum	5	169(2.1)	129(1.8)

Table 2					
Mean GDMBF,Ear perfusion&Pulse rate during a 60 min period of control in 2 rabbits					
Time(min)	0	10	25	40	60
Site					
Pulse(bpm)	120	124	120	128	110
Skin(SE)	90(2.8)	100(2.2)	69(1.2)	60(1.9)	63(0.6)*
Body(SE)	194(3.2)	189(4.6)	251(6.9)	212(6.3)	212(4.0)**
Antrum(SE)	182(4.8)	145(3.1)	143(3.6)	159(3.9)	205(5.8)^
Duodenum(SE)	222(6.2)	271(6.6)	214(10.1)	260(4.8)	264(3.1)^^

*,**,^,^^NS
*p=0.29
**p=0.06
^p=0.14
^^p=0.46

Figure 5
Blood flow&Pulse in one rabbit receiving vasopressin
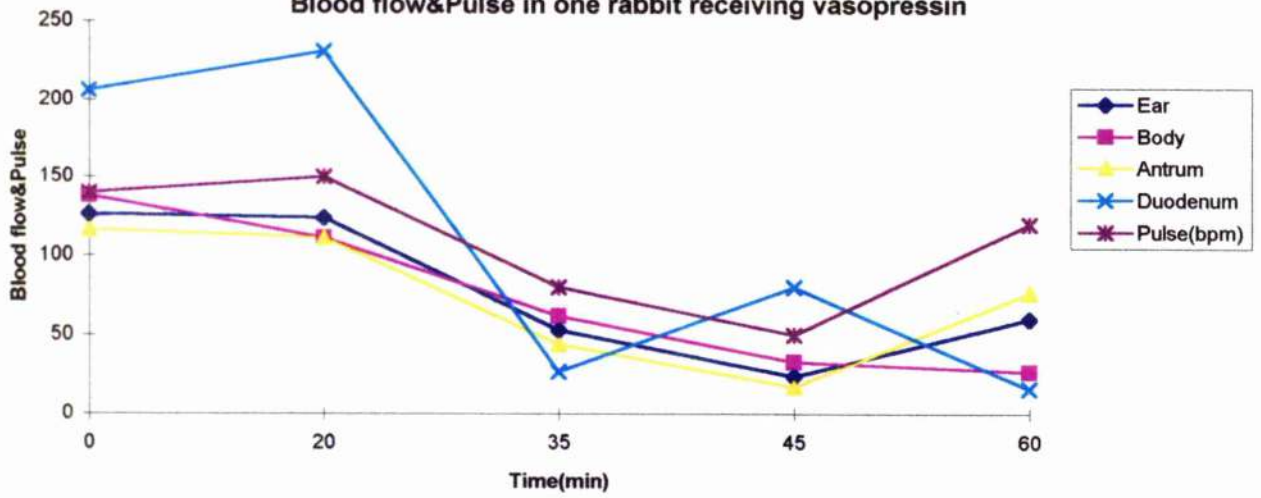

Figure 6
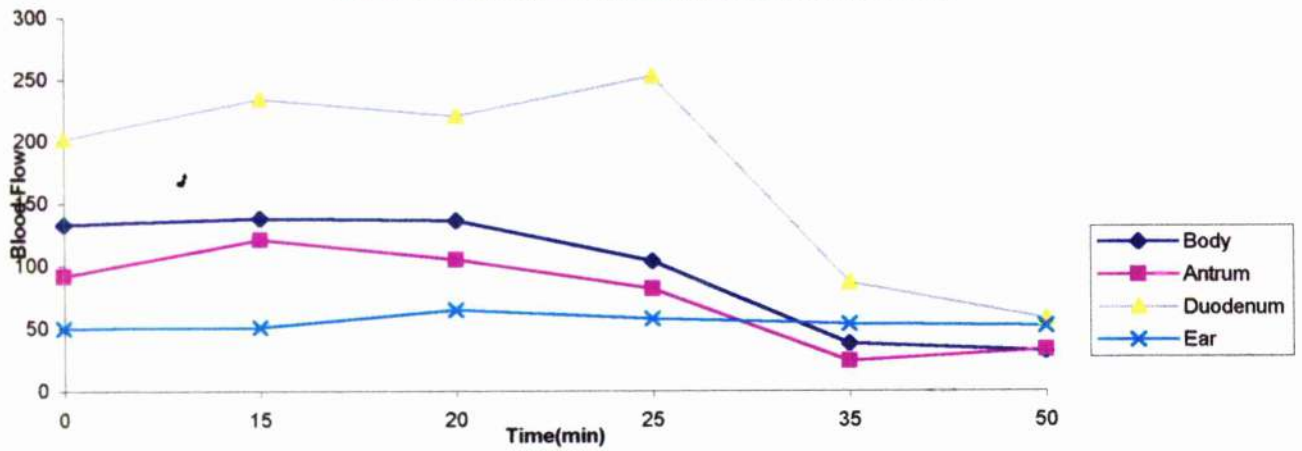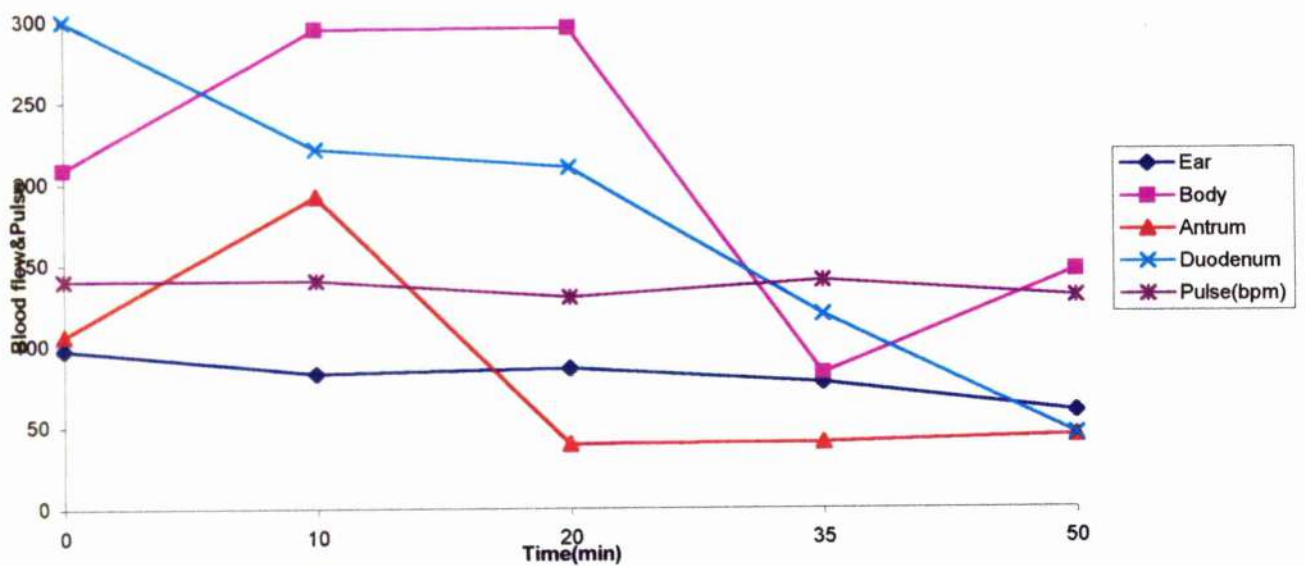**Blood flow in a single rabbit receiving octreotide at 20 minutes**

Figure 7
Blood flow&Pulse in one rabbit given octreotide at 10 mins

Intravenous Vasopressin(1 mg/kg) caused significant reduction in

GDMBF associated with bradycardia and decreased skin perfusion (table

3) (figure 5) .

A bolus injection of Octreotide(40 microgram/kg) significantly

decreased GDMBF (n=3) without affecting pulse rate or skin

perfusion(table 4) (figures 8#/ 6,7) .

Intragastric pH increased from 2 to 6.5 in all three animals following

octreotide but not in control animals or in the animal receiving

vasopressin . A dose relationship for octreotide and GDMBF was

demonstrated between 10-50 microgram/kg of octreotide (figure9) .

Table 3
Mean GDMBF , Ear perfusion & Pulse rate during a 60 min period involving bolus injection of Vasopressin(1 mg/kg)

Min after bolus injection of vasopressin				15	25	40
	Time(min)	0	20	35	45	60
Pulse(bpm)		140	150	80	50^	120
Ear(SE)		126(6.4)	124(6.4)	53(2.46)	24(0.77)^^	60(3.17)
GDMBF(U)						
Body(SE)		138(10.31)	111(10.6)	62(7.37)*	33(1.97)	27(2.16)
Antrum(SE)		116(9.6)	111(9.4)	44(3.66)**	17(1.2)	76(8.3)
Duodenum(SE)		206(8.6)	231(12.4)	27(1.8)***	80(2.9)	16(0.78)

*p<0.03 ^p<0.005
**p<0.02 ^^p<0.02
***p<0.05

Table 4
Mean GDMBF,Ear perfusion&Pulse rate in 3 rabbits over 60 mins after a bolus injection of octreotide(40 microgram/kg)

Time(min)	0	10	25	40	60
Site					
Ear(SE)	70(2.1)	68(0.8)	63(0.6)	53(1.2)	60(1.1)*
Pulse(bpm)	124	120	130	120	120
Body(SE)	178(3.1)	126(2.2)	77(3.1)	82(2.8)	66(0.8)**
Antrum(SE)	152(2.8)	67(1.2)	44(1.6)	41(1.9)	40(1.5)***
Duodenum(SE)	220(6.6)	184(4.1)	79(2.9)	46(1.4)	48(1.9)****

*NS,p=0.65
**p<0.008
***p<0.02
****p<0.016

Figure 8
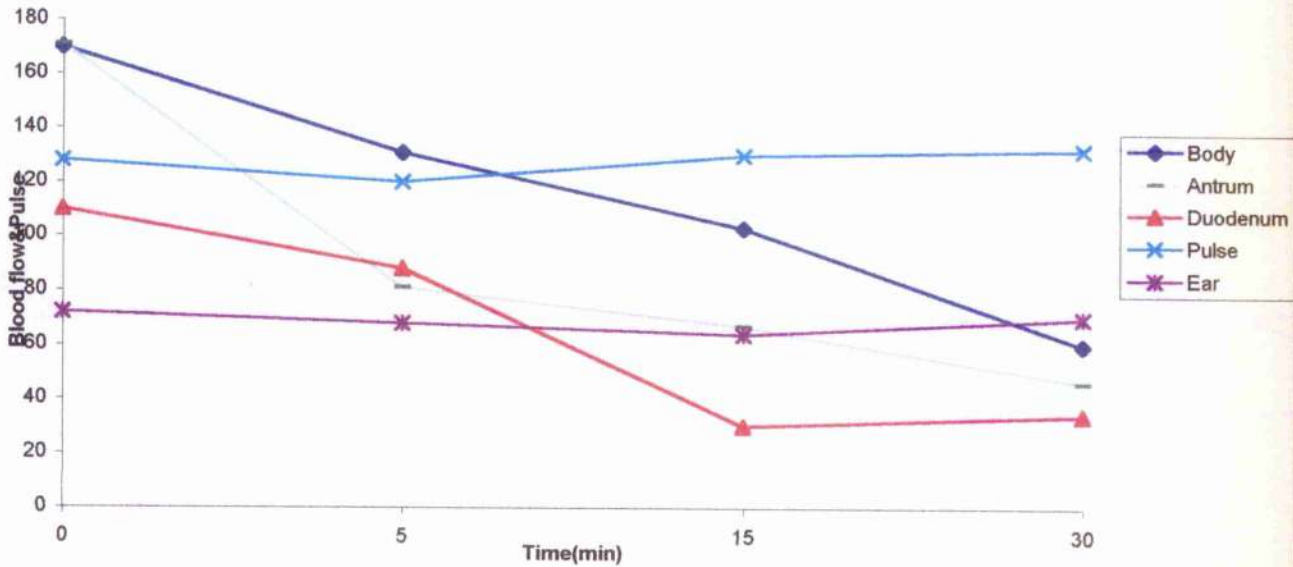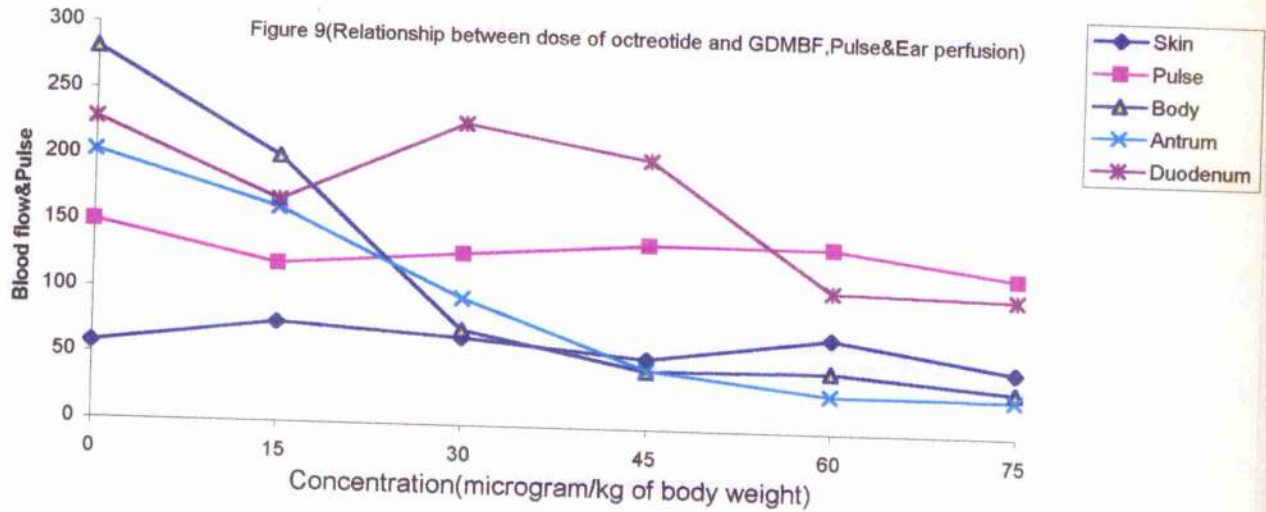### Blood flow&Pulse in one rabbit receiving octreotide

Figure 9(Relationship between dose of octreotide and GDMBF,Pulse&Ear perfusion)

Discussion

This study demonstrated that LDF can be used to measure GDMBF easily , directly and continuously in experimental animals . Octreotide decreased GDMBF and intragastric acidity without causing systemic haemodynamic changes . A dose-response relationship between GDMBF and octreotide concentration was demonstrated , although this was clearer for gastric mucosal blood flow than duodenal blood flow . Vasopressin was used as a positive control since it is known that it decreases GDMBF , although as expected its use was associated with significant haemodynamic changes . Such changes did not occur following octreotide infusion .

The mechanisms of action of octreotide on GDMBF is unknown . It may be a direct consequence of decreasing splanchnic blood flow , a direct vascular effect or an indirect effect mediated by suppression of vasoactive intestinal hormones .

Many problems were encountered by previous researchers when measuring GDMBF . Previous methods were invasive , indirect , not reproducible and were not applicable to man . Becker et al (1982) found that somatostatin significantly decreases gastric but not duodenal blood flow . They and others(Starlinger et al 1987) used the radioactive microspheres method of assessing blood flow which allowed measurements for only a few minutes . These measurements do not represent focal blood flow but are a measure of total gastric tissue

perfusion . Furthermore this method requires the animals to be killed

before assessment of blood flow can be histologically determined .

GDMBF has been measured by neutral red clearance (Sonnenberg et al

1983) . This method is also invasive and indirect , necessitating

intravenous injection of neutral red , multiple venous blood sampling ,

naso-gastric aspiration of gastric contents for analysis and complicated

calculations .

In contrast LDF is a validated method of measuring GMBF (Sato et al

1995 , Gana et al 1987) . It is non invasive , easy to use , safe with

excellent reproducibility and can be used in man (Lunde et al 1988) .

The technique allows repeated measurement of blood flow without

access to venous or arterial blood . It offers instantaneous and continuous

focal blood flow measurement . The main disadvantages are

maintenance of probe-mucosa contact and the lack of calibration in

absolute flow values . In fact probe-mucosal proximity can be easily

maintained both at gastrostomy and endoscopy with minimal practice

and reproducible values can be obtained . Unfortunately the arbitrary

values for blood flow cannot be translated to actual blood flow(mls/min)

because the doppler signal reflects velocity rather than volume . The

LDF is therefore most useful for defining changes in blood flow

following specific intervention .

The relationship between intagastric acidity and GDMBF is uncertain .

Previous studies have demonstrated a positive relationship between

GDMBF and acid concentration up to a value of 80mM , beyond which
the relationship becomes negative (Starlinger et al 1987&1981) . The
observation that octreotide infusion was associated with increased
intragastric pH was an incidental finding in this study and further
assessment of this relationship using more accurate measurements of
gastric acid secretion is warranted .

This study does suggest that octreotide infusion could be of value in the
treatment of mucosal bleeding from the upper gastrointestinal tract and
further clinical and pharmacological studies are necessary .

Chapter 7

Summary , Conclusions and Future Plans

Peptic ulcer haemorrhage remains a common problem in clinical practice and continues to present challenges to clinicians .

Endoscopic therapy is now well established as a very useful and often a first line method of managing high risk patients who present with major peptic ulcer haemorrhage and active bleeding or non bleeding visible vessels . Endoscopic injection therapy is effective in a majority of patients . Furthermore this method appears to be easy to use , cheap and accessible to most units .

I have demonstrated that injection therapy using a combination of adrenaline plus human thrombin is an effective modality ; in experimental animals it proved to be the most potent agent in stopping bleeding and in my clinical trial it stopped active bleeding and prevented rebleeding in over 95% of patients without causing complications .

The experimental bleeding model studies also confirmed that sclerosants are ineffective in stopping active bleeding and induce tissue necrosis .

Therefore since published clinical trials do not demonstrate an additional specific benefit for sclerosants , their use should be abandoned in clinical practice .

The bleeding ulcer model I used in my research remains far removed from the human scenario of a chronic ulcer with a large vessel in its base , therefore my successors should attempt to create new ulcer models . This may be attempted by repeated endoscopic injections of 98% alcohol into the gastroduodenal mucosa of animals and could be linked to the administration

of NSAIDs and anticoagulants over a longer period of time . I have already designed the protocol for such a study .

Although I have demonstrated that a combination of adrenaline plus thrombin is superior to adrenaline alone in treating patients who present with major peptic ulcer haemorrhage , this needs to be confirmed in a larger study . Such a study could be further improved if it was double blinded i.e. if an inert solution is injected in stead of thrombin into the bleeding vessel of ulcers in the control(adrenaline alone) group . Furthermore the issue of safety of human thrombin should be further addressed . In order to study the systemic effect of thrombin upon the coagulation factors present in the circulation I collected venous blood samples from 24 patients randomised to adrenaline plus thrombin and 12 controls (patients receiving adrenaline alone) . This was done before and 20 minutes after injection therapy . Colleagues at the Scottish Blood Transfusion Service are assessing the concentration of d Dimers , thrombin/ antithrombin complexes and alpha thrombin in these samples and I hope and believe that this study will be the subject of future publications .

The optimum concentration of thrombin which should be used in clinical practice should be adequately assessed . This may be carried out by injection of different doses of thrombin into clamped serosal vessels of animals and or into synthetic vessels of known size .

Surgery remains an important tool in the management of patients in whom endoscopic therapy is not possible or those who continue to bleed or rebleed despite endoscopic therapy . My retrospective analysis of the outcome of

surgery for peptic ulcer haemorrhage in the Lothian region since the advent of endoscopic therapy showed that underrunning of the bleeding vessel alone is associated with a high rebleeding rate and is associated with high morbidity and mortality . However these results must be treated (like those of any retrospective analysis) with caution . Negotiations are underway to design a randomised controlled trial to compare underrunning alone with definitive ulcer surgery . Furthermore there is a growing suspicion that we are witnessing an atrophy of surgical experience with ulcer surgery which may be related to poorer outcome reported after surgery in this extremely high risk population . This will inevitably contribute to the debate concerning the development of bleeding units staffed by experienced gastroenterologists and surgeons with special interest in upper gastrointestinal bleeding .

Reduced long term survival of patients who survive a hospital admission for major peptic ulcer haemorrhage is a reflection an elderly population with many comorbid diseases . It is reassuring to find that endoscopic therapy was not associated with increased long term morbidity or mortality . The observation that dyspepsia is uncommon amongst patients who have late recurrent ulcer bleeding has important implications for follow up in this group since secondary prophylactic treatment couldnot be based upon symptoms . This adds to the debate regarding optimum prophylaxis against ulcer bleeding and may open the way to a multi-centre trial in the north and east of Scotland comparing conventional acid reducing long term prophylaxis versus helicobacter pylori eradication therapy .

Laser Doppler Flowmetry represents the method of choice for assessing gastroduodenal perfusion in animals and man . My successor plans to study the effect of injection therapy upon GDMBF in patients being treated for major peptic ulcer haemorrhage . This may reveal important information concerning vasoconstriction , tissue oedema and arterial thrombosis following injection .

The role of gastroduodenal blood flow in ulcer genesis and healing may be important . Therefore I have already started a clinical study to measure gastroduodenal mucosal blood flow in patients with ulcer disease , comparing GDMBF between the centre and periphery of the ulcerated lesions .

For those patients who fail endoscopic therapy and are deemed unfit for surgical intervention the risk of death is grave . Therefore the search must continue for an agent which may stop bleeding . Octreotide was useful in treating such patients in my own practice but inevitably the number of patients involved is very small . I have personally used intravenous octreotide infusion in the treatment of four patients with uncontrolled ulcer haemorrhage who were deemed unfit for surgery with encouraging success (4 out of 4) (see publication list for a case report on this matter in press) . Clearly further research is required in this field

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