Assessment of immediate and owner perceived recovery following three different premedication drugs in dogs undergoing anaesthesia for radiotherapy

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Abstract

Veterinary radiotherapy requires frequent, short duration general anaesthesia to perform the treatment. All anaesthetic drugs affect recovery to varying degrees and potential side effects of these drugs may impact both the animal and the owner's perception of the treatment.

Numerous studies have investigated the speed and quality of recovery following different anaesthetic drugs but few studies have assessed longer duration recovery from anaesthesia. The objectives of this thesis were to: (1) investigate immediate recovery speed and quality following three different premedication drugs; (2) investigate longer term recovery within the home environment following three different premedication drugs. The three premedication drugs investigated were alfentanil/atropine, butorphanol and medetomidine.

Immediate recovery was assessed by video analysis using a self-designed scoring system. Anaesthetic data, such as propofol dose, end tidal sevoflurane concentration, duration and various time points, was also captured. Longer term recovery was assessed by the owners following treatment using a self-designed questionnaire. Comparisons from these outcomes between the different treatment groups were made and other factors were also analysed that could affect the outcomes.

Speed of recovery was significantly affected by premedication. Premedication drug significantly affected time to extubation and the likelihood of dogs reaching sternal or standing position. Quality of immediate recovery was significantly affected by end tidal sevoflurane concentration. When assessing longer term recovery, premedication drug had a significant effect on reported behaviours. A reduction in activity and an increase in sleep were reported more frequently following butorphanol.

This study highlights the effect that premedication can have on both immediate and longer-term recovery from anaesthesia in dogs undergoing radiotherapy.

Table of Contents

List of Tables

List of Figures

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Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Printed name:

Signature:

Definitions and abbreviations

ASA	American Association of Anesthesiologists
CI	confidence interval
ED	emergence delirium
hr	hour
kg	kilogram
kPa	kilopascal
L	litre
m^2	square metre
MAC	minimum alveolar concentration
mcg	microgram
mg	milligram
ml	millilitre
ng	nanogram
PONV	postoperative nausea and vomiting
QoL	quality of life
QoR	quality of recovery
SDS	simple descriptive scale
TIVA	total intravenous anaesthesia
VAS	visual analogue scale

1.1 Introduction

Radiotherapy is becoming a more commonly used technique in veterinary oncology to treat a variety of tumour types (Farrelly & Mcentee, 2014). In comparison to human adult radiotherapy, general anaesthesia is a necessity for radiotherapy in veterinary species. It is vital to completely prevent patient movement to allow for accurate positioning and aiming of the radiotherapy beam.

Depending on a variety of factors, including tumour type, patient co-operation and owners' wishes, the course of radiotherapy is fractionated into numerous treatments over several weeks (Nolan & Dobson, 2018). At this institution, treatments are spread out over the week, typically on a Monday, Wednesday and Friday, however certain tumour types may be treated daily. In the majority of cases, there will be multiple short duration anaesthetics and the recovery characteristics will have implications for the owner and patient. The decision to undertake radiotherapy is a complex one with the potential effect of repeated anaesthetic events being a key consideration (Smith et al, 2019).

The anaesthesia is potentially more complex given potential co-morbidities and the requirement for day case anaesthesia. In our institution animals are scheduled for the radiotherapy treatment and then discharged the same day as soon as possible into their owners' care. This is necessary to minimise the impact on the animal's routine and to ensure quick and smooth running of the department. Given these requirements, a fast induction, a smooth transition to maintenance of anaesthesia and then a short recovery period are required. Minimal hangover effect from the anaesthetic drugs is desirable prior to transportation home. These factors determine what drugs and techniques are used to anaesthetise these patients.

Given the frequent anaesthetic episodes every week, the effect of repeated treatments and anaesthetics may impact on the wellbeing of these patients. Optimising the overall anaesthetic event, including the recovery period, for each patient could minimise this potential impact on quality of life and improve the outcome and wellbeing of radiotherapy patients.

The aim of this literature review is to assess the evidence behind the following questions:

- How has quality of life (QoL) been assessed in veterinary species?

- What comparisons for repeated anaesthetics do we have for veterinary patients?
- How does anaesthesia affect our veterinary patients?
- How do we assess recovery from anaesthesia?
- Are certain drugs or techniques associated with reduced side effects?
- Would one drug or combination of drugs be better than another for repeated anaesthesia in dogs?

1.2 Quality of life assessment in animals

In humans, quality of life (QoL) is defined as “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.” (World Health Organisation, 2020). The extrapolation of this definition to animals is challenging and there is a current lack of a consensus definition of QoL in animals (Belshaw et al., 2015). It has been defined as “a balance between pleasant and unpleasant feelings” (McMillan, 2000) and most other descriptions include recognition of the individual nature of QoL (Belshaw et al., 2015; McMillan, 2000; Wojciechowska & Hewson, 2005). As veterinarians we strive to improve the welfare and wellbeing of all animals under our care. QoL may be used as a synonym for welfare and it has been argued that they are one and the same (Broom, 2007).

There are numerous tools and techniques to assess QoL (Belshaw et al., 2015) but there are some areas of complexity when considering QoL assessment in animals compared to humans. There are two main approaches to QoL assessment in animals: mental state approaches which tend to be more subjective by evaluating the emotions of animals and external parameter approaches which tend to be easier to assess but are more objective (Yeates & Main, 2009). Mental state approaches are inherently difficult to assess in veterinary patients because animals are non-verbal. Interpretation of the animal’s behaviour or demeanour is required to assess their mental state and bias or variability in the assessment is a key limiting factor and greatly dependent on the assessor. External parameter approaches are more objective and can generate quantifiable data on which assessment can be made. For example, activity and appetite can be assessed and scored or physiological variables such as heart rate, body mass and blood pressure can be measured. The balance, and difficulty, surrounding assessment is

limiting subjective bias of the observer and also determining the relevance of objective measurements on QoL.

Numerous different scales have been developed to assess QoL (Belshaw et al., 2015). The limitations of these scales include specificity for one disease type or state, for example cardiovascular disease, and potential subjectivity. It is important to recognise who the tool is designed for: the owner or the veterinarian. Owner perceptions on QoL and wellbeing may be very different and more emotionally influenced than those of a veterinarian.

QoL has been investigated in dogs and a validated tool using an owner-based questionnaire has been developed (Wiseman-Orr et al., 2006). The initial tool, GUVquest, assessed several variables associated with chronic pain and the effect on QoL. It involves rating 109 different descriptive words on a 7-point Likert rating scale. A Likert rating scale allows respondents to specify their level of agreement to a statement using a symmetric agree-disagree scale. It allows assessment of the respondents' intensity of feeling for that statement. A complex algorithm then analyses this data using different descriptors and creates a score profile for the dog. Factors that influenced the score included an assessment of activity and interaction and an assessment of appetite. Descriptive words such as listless, lethargic, eager, energetic were found to either positively or negatively load onto these factors. The original GUVquest questionnaire was undertaken by owners of dogs which were grouped into 4 categories - pain free healthy dogs, pain free dogs with lymphoma, chronically painful dogs with a low pain score and chronically painful dogs with a high pain score. The outcomes of each of the descriptors was compared between groups and items which distinguished one group from another were carried forward to the new model. This new model was then tested prospectively and was found to be able to identify dogs in each different group (Reid et al., 2013). A shortened version of GUVquest, which included 60 questions has been used to assess QoL in obese dogs (German et al., 2012) and demonstrated that QoL improved as dogs lost weight. This tool has been shortened to a web-based questionnaire which is more user-friendly and easier for owners to complete (Reid et al., 2013).

1.2.1 Effect of repeated anaesthesia on QoL

None of the scales assess the effect of anaesthesia or repeat anaesthesia on QoL in animals. In

humans there are numerous scales and measures to assess QoL (Garratt et al., 2002) but no reference to the effect of repeated anaesthesia on QoL. One veterinary study assessed the impact of repeated anaesthesia on wellbeing in laboratory beagles (Bert et al., 2008). The basis behind this study was that no guidelines existed for repeat anaesthesia in laboratory animals and there is no regulation for companion animals. The investigators wanted to assess the impact of anaesthesia on "wellbeing". Dogs received five general anaesthetics over an eight-week period using similar drugs but anaesthesia varied greatly in duration from 3 - 7 hours. No procedures were performed during the anaesthetic. The measured parameters to assess "wellbeing" were body weight and heart rate. This was assessed before anaesthesia and during exercise as a measure of exercise tolerance. They found that the dogs tended to lose weight and there was some decreased exercise tolerance following anaesthesia but parameters returned to normal after 1 - 2 weeks after anaesthesia. Based on their findings it was recommended that an interval of 2 weeks between anaesthetics allowed sufficient time for recovery.

There are numerous limitations into extrapolating this conclusion to animals having repeated anaesthesia. Firstly, their measure of "wellbeing", including exercise tolerance and body weight, does not translate into an assessment of QoL of these animals. For example, a reduction in exercise tolerance doesn't necessarily mean the QoL of the animal is affected. A decrease in body weight over two weeks could be due to decreased intake of food either before or after anaesthesia but this again could be a consequence of a variety of factors. Also, anaesthetic technique and duration of recovery following a 3–7-hour anaesthetic may be very different from anaesthetic technique used for veterinary radiotherapy cases making it difficult to make comparisons.

To conclude, there are tools available to assess QoL in animals, but they are still in their infancy with a major limitation being the unavoidable subjectivity. Assessment of anaesthesia and repeat anaesthesia on QoL in humans and animals has only briefly been investigated.

1.3 Human comparisons for repeated anaesthesia

The immediate and long-term effects of anaesthesia on veterinary patients are hard to quantify and assess but more and more data is being published demonstrating the effects of anaesthetic

drugs on the body. For example, there is an increasing body of work investigating the role of inhalational anaesthetic agents in preconditioning and neuro- and cardiac protection (Kunst & Klein, 2015; Wang et al., 2008). Preconditioning refers to changes at a biomolecular level that occur following minor adverse events. As a result, these tissues may be able to tolerate a major adverse event with less deleterious effects (Loveridge & Schroeder, 2010). For example, following mild ischaemia induced by anaesthesia, the heart may be able to tolerate a more severe ischaemic insult. This highlights the potential positive effects of mild homeostatic alterations that anaesthetic agents may induce.

There has been less study into the anaesthetic effects on the emotional and mental wellbeing of patients particularly in veterinary species largely due to the difficulty in assessing these factors. One study assessed the psychological effects of repeated general anaesthesia in children with chronic disease (Kayaalp et al., 2006) and found that repeat anaesthesia in addition to chronic disease does not appear to disturb the child's psychological health. No studies have assessed the impact of repeat anaesthesia compared to healthy children and parallels are hard to draw to a population of veterinary patients. Repeat anaesthesia combined with a chronic oncological disease in canines could negatively impact wellbeing and QoL and altered protocols could minimise these potential impacts.

There are not many comparable situations within human anaesthesia that require frequent repeated anaesthesia but the simplest and most obvious comparison to make would be paediatric radiotherapy. Historically children were sedated for radiotherapy but it is now considered unreliable and unpredictable (Stackhouse, 2013). Anaesthesia is generally necessary for children younger than 3 years old and rarely required when older than 5 years (Fortney et al., 1999). A comparison of sedation and general anaesthesia demonstrated a much higher rate of satisfactory sedation and fewer complications with general anaesthesia. The time from administration of anaesthetic drugs to treatment end was also faster with general anaesthesia (Seiler et al., 2001). A commonly used anaesthetic technique is induction with propofol and maintenance with sevoflurane with no premedication (Stackhouse, 2013). Other techniques include ketamine or total intravenous anaesthesia (TIVA) with propofol (Evans & Chisholm, 2008). However, there have been no randomised studies demonstrating the superiority of one technique based on recovery over another (Evans & Chisholm, 2008).

Another important method commonly employed in paediatric anaesthesia is “play preparation”. This technique involves models, play sets and costumes to demonstrate procedures and outcomes prior to surgery or anaesthesia. Studies have demonstrated that children who received play preparation prior to anaesthesia remained calmer and more co-operative that children who did not (Schwartz & Albino, 1983). Another study showed that the requirement for sedation can be minimised following an appropriate play preparation programme (Scott et al., 2002). While it is unthinkable to suggest that similar techniques could avoid anaesthesia for veterinary radiotherapy, a modified approach could have an important role in reducing stress and improving the wellbeing of animals undergoing such treatments. Considerations to keep the treatment as familiar as possible, such as the same staff and same order of process, may reduce the stress of canine patients undergoing radiotherapy.

1.4 Recovery from anaesthesia

Quality and speed of recovery for veterinary radiotherapy patients is a key area and can have a major impact on decision-making regarding further treatment. Anecdotally, a slow recovery from previous anaesthetics can influence an owner’s decision whether to treat their animal with radiotherapy. The technology and knowledge are available to offer more advanced therapies, but an important factor is patient wellbeing and their QoL. This is even more important in veterinary species as treatments are decided by their owners under the guidance of veterinary surgeons. It is impossible for animals themselves to consent to treatment. If an animal is tolerating the radiotherapy well but the non-radiation side effects, such as lethargy, vomiting and inappetence, are becoming excessive then treatment may need to be stopped (Farrelly & Shi, 2018). These side effects may be related to anaesthetic drugs used, underlying disease or unknown causes. Reducing these potential side effects could improve radiotherapy outcomes. Anaesthetic side effects may also affect the owner’s perception of radiotherapy treatment. If they are severe or prolonged, this could lead to the owner deciding that further treatment is likely to negatively impact the dog’s QoL to such an extent that treatment may be stopped. There is little published data on longer term recovery and potential side effects in dogs. Monitoring the effects of anaesthesia and recovery is important to help ensure that treatment is continued without causing excessive detriment to the patient.

The recovery period is one of the most important times of anaesthesia. Focusing at one

extreme, almost 50% of perioperative anaesthesia-related deaths occurred within the recovery period (Brodbelt et al., 2008). The recovery period was defined as the 48-hour period following anaesthesia and most deaths occurred within 3 hours of the end of anaesthesia. This not only highlights the importance of the recovery period but also how dramatic potential complications can be. For radiotherapy we are sending these patients home very quickly after their treatment. This reduces our ability to monitor closely during the longer recovery period. However, if we kept these dogs within the hospital environment for the day following treatment, this may impact on their QoL to a greater extent. This conflict is a key driver for finding a protocol that ensures a rapid and complete recovery with no residual sedation.

1.4.1 Assessment of recovery

Quality of recovery (QoR) has been investigated in some detail in human medicine and several scoring systems have been described (Bowyer & Royse, 2016; Quinn et al., 1993). A systematic review including 17 studies demonstrated that one system, the QoR-15 scale, which is a shortened form of the QoR-40 scale, is widely used and has been extensively validated to assess quality of recovery (Gornall et al., 2013). This scale is used by the patient to assess recovery and considers factors such as comfort, emotional wellbeing, physical independence and support. This scale has then been used to assess recoveries when comparing different anaesthetic techniques and drugs (Moro et al., 2016). Time scale is a relatively easy objective measure to assess when considering recovery from anaesthesia. Time points, such as time to extubation or time to sternal recumbency, can be measured and then compared between different drugs. Speed, particularly for patients undergoing short procedures, may be a key consideration for recovery but an important distinction between speed and quality of recovery needs to be made. A recovery may be of short duration but of poor quality and a long, smooth recovery may be considered a better overall recovery in comparison. However, determining the importance of quality over speed may be a subjective factor and it may be difficult to determine which factor is more important for an individual.

Another consideration when assessing recovery is the timing of assessment. Following anaesthesia, recovery can be considered in two parts: the immediate recovery following the termination of anaesthesia and longer-term recovery in the following hours. Following day-case anaesthesia, this longer-term recovery often occurs within the home environment

following treatment. The quality of recovery at home may have a greater impact on the animal's QoL and often is an area that the anaesthetist does not see or hear about. Simple factors such as appetite, lethargy and interaction could be assessed at home by the owner to give an indication of longer-term recovery quality. One recent study investigated this area but could only draw limited conclusions due to limited owner compliance (Lehnus & Brearley, 2019). Another study assessed behavioural changes within the home environment for 3 days following day case anaesthesia for surgery (Väisänen et al., 2004). Owners were asked to rate 22 different categories using a Likert scale comparing to their dog's normal behaviour. On the day of surgery, 94% of owners reported changes in 5 or more of these categories which decreased to 58% of owners by day 3. Most common changes in behaviour were related to their dog's demeanour, way of moving, overall activity and contact seeking. Surgical procedure varied in the dogs, ranging from skin tumour removal to open abdominal procedures, and analgesia protocol also varied. Inadequate analgesia in this study resulting in pain is a major confounding factor which may have influenced both the animal's behaviour and also the owner's perception of behaviour.

1.4.2 Scoring systems for recovery in dogs

The veterinary literature assessing recoveries from anaesthesia is more basic. There is no validated scoring system to assess recovery in veterinary patients. Again, a major limiting factor is the inability to directly ask our patients questions and the reliance on proxies to assess recoveries from a subjective viewpoint. Previous studies assessing recovery quality have used visual analogue scales (VAS) (Copeland et al., 2017; Jiménez et al., 2012), numerical rating scales (Dehuisser et al., 2017) or simple descriptive scales (SDS) (Jiménez et al., 2012; Kennedy & Smith, 2015; Love et al., 2007). These scales provide an easy numerical method to compare two techniques however they rely on an individual making a subjective assessment. These unidimensional scales are simple and easy to perform and can then be used to compare and rank outcomes.

Simple descriptive scales list similar adjectives, which describe the measured variable, into categorical groups. An adequate SDS should include the extremes of the measured variable. One major limitation is that these scoring systems group the outcome into categories that may not have similar intervals between categories. For example, the difference between a score of 1 and 2 may not be the same as the difference between a score of 2 and 3. Outcomes from

these scales are categorical so data analysis is limited to nonparametric statistical tests which may be considered another weakness of these scales. The sensitivity of these scales is also limited by the number of categories. The fewer the categories, the less sensitive the scale becomes.

Visual analogue scales assess an outcome based on a line scale from one extreme to the other (Kuhlmann et al., 2017). For example, with recoveries this might consist of “worst possible recovery” to “best possible recovery”. The assessor is asked to mark on a line, usually 100 mm long, where they rate the outcome. This mark can be measured and then converted into a continuous outcome. These scales have many response categories which means they are considered more sensitive to change than simple descriptive scales. A major limitation is that this scoring system may be interpreted differently by different assessors so it may not result in reliable outcomes between assessors (Briggs & Closs, 1999).

Key considerations when designing scoring systems include validity, reliability and compliance. Validity is the ability of a tool to measure what it is supposed to measure (Buckingham, 1921). No scoring systems for immediate recovery have been validated for dogs and designing and validating a scoring system was beyond the scope of this project. However, the use of previously published scoring systems may allow comparison of results between studies (Sánchez et al., 2013). No scoring systems have been validated for owner assessment of recovery. However, a recent study included a self-designed questionnaire to assess owner’s perceptions of recovery (Lehnus & Brearley, 2019).

Reliability describes the consistency of the measurements of a test (Buckingham, 1921). For the scoring system to be useful, the outcome must be reproducible and consistent. Reliability can be assessed using test-retest reliability where the same observer performs the assessment at two separate time points (Krabbe, 2017). An alternative to this is to assess scores between two different assessors and calculate interobserver correlation.

When considering compliance in a medical field, it is often defined as the degree to which the patient follows the advice of a medical practitioner (Osterberg & Blaschke, 2005). Another definition is “the act of obeying an order, rule or request” (Cambridge Dictionary, 2020). When applied to scoring systems, it relates to the extent to which the assessor uses the scoring system in the designed way. The assessor needs to comply with the system to ensure validity and reliability of the outcomes.

1.4.3 Factors affecting recovery in dogs

A large retrospective multi-variant analysis of 900 dogs undergoing anaesthesia investigated the anaesthetic factors that influence time to extubation (Kleine et al., 2014). Importantly only time to extubation was assessed with no description or analysis of the quality or duration of recovery. In their final model several factors were significantly associated with time to extubation. Premedication with acepromazine, compared to alpha$_2$ agonists or benzodiazepines, was associated with a longer time to extubation. Induction with propofol was associated with a shorter time to extubation compared to induction without propofol. Time to extubation was increased with increasing bodyweight, decreasing body temperature and increasing anaesthetic duration.

This study shows that there are numerous ways in which an anaesthetist can reduce time to extubation such as drug choices and managing body temperature. However, time to extubation is only one part of recovery and it may not correlate with quality or duration of the whole recovery period. Also, the large variation of procedures, drug doses and timings, disease status of the animals and other unmeasured variables may have a large impact on these results.

1.4.4 Drug effects on recovery in humans

There are numerous studies in human medicine investigating drug effects on quality and speed of recovery. This is a key area of interest as more and more procedures are performed on a "day case" basis so a quick, complication free recovery is necessary to send patients home. A large systematic review focusing on postoperative recovery and complications using four different anaesthetic techniques in humans demonstrated some interesting findings (Gupta et al., 2004). Comparisons were made between propofol-based anaesthesia and inhalation anaesthesia using isoflurane, sevoflurane and desflurane. In general, there was a higher frequency of postoperative nausea and vomiting (PONV) and requirement for antiemetics in the inhalational groups. PONV was only significantly higher in isoflurane treated groups compared to propofol treated groups. There were no differences between propofol and desflurane or sevoflurane. Early recovery was only marginally quicker with sevoflurane and

desflurane compared to isoflurane and propofol, but they suggested that residual effects of other drugs, such as opioids and neuromuscular blocking agents, may interact with other anaesthetic agents to prolong recovery. Conclusions from this review would suggest that inhalational agents have a higher risk of PONV. In dogs, one study found an incidence of 12.3% in postoperative regurgitation and vomiting and gastrointestinal surgery was the most significant risk factor (Davies et al., 2015). However, there is an inherent difficulty in assessing nausea in non-verbal patients. Interestingly, maintenance with sevoflurane was associated with an increased risk compared to other inhalational agents. Comparison between inhalational agents and intravenous agents for maintenance of anaesthesia were not compared.

Quality of recovery in humans comparing inhalational anaesthesia and propofol TIVA showed similar scores on the QoR-40 scale, similar length of stay in the recovery area and a similar occurrence of PONV (Moro et al., 2016). Speed of recovery comparing propofol TIVA and isoflurane inhalation anaesthesia in dogs premedicated with either acepromazine or diazepam showed a significantly longer time to standing in the TIVA group, 35 minutes compared to 27 minutes in the isoflurane group, and a similar incidence of complications (hypersalivation, excitement and vomiting) in both groups (Tsai et al., 2007). Although only a small increase in recovery time this could be an important factor for veterinary radiotherapy anaesthesia. Comparing human and veterinary studies assessing speed of recovery and PONV needs to be done with care. Human patients rarely received premedication drugs compared to veterinary patients and these premedication drugs can influence these outcomes.

1.4.5 Drug effect on recovery in dogs

Compared to humans, there are no standardised recovery scoring systems which makes direct comparison of different studies difficult. Numerous factors, other than drug selection, can affect recovery quality and time such as duration of anaesthesia, temperature, comorbidities and surgery type (Kleine et al., 2014). Drawing definitive conclusions about the individual drugs is challenging but a review of recent literature on the effects of drug choice on recovery times and quality is given below.

1.4.5.1 Premedication drug

Several veterinary studies have investigated the effect of different premedication drugs on

duration and quality of recovery. In healthy dogs undergoing a range of surgical and diagnostic procedures, comparison of acepromazine (0.03 mg/kg) and two doses of medetomidine (5 or 10 mcg/kg), in combination with buprenorphine intramuscularly, showed no differences in time to recovery with no differences in duration of anaesthesia between groups (Grint et al., 2010). However, there was no assessment of quality of recovery. Another study, involving dogs undergoing anaesthesia for ovariohysterectomy, compared intramuscular buprenorphine combined with either acepromazine (0.05 mg/kg) or dexmedetomidine (10 mcg/kg) followed by induction and maintenance of anaesthesia with an alfaxalone infusion. This study showed similar recovery times, median time of 16 minutes to extubation, between groups but better recovery in acepromazine treated groups (Herbert et al., 2013). Duration of anaesthesia was similar in each group, with a mean time of 130 minutes. Quality of recovery was assessed using a SDS and one possible explanation for the improved quality recovery in the acepromazine group was due to the longer duration of action of acepromazine compared to dexmedetomidine. Another similar study involving dogs undergoing ovariohysterectomy described comparable quality of recovery in acepromazine (0.02 mg/kg) and dexmedetomidine (5 mcg/kg) groups (Dehuisser et al., 2019) following induction and maintenance of anaesthesia with alfaxalone. However, in this study time to extubation following acepromazine was longer than dexmedetomidine, a median time of 32 minutes and 19 minutes respectively. A shorter duration of anaesthesia, 95 minutes compared to 130 minutes in the Herbert study, and the longer duration of acepromazine compared to dexmedetomidine could account for this difference.

An experimental study comparing different doses of dexmedetomidine (1 and 2 mcg/kg) and medetomidine (1, 2 and 4 mcg/kg) showed no significant differences in recovery times between the different treatment groups (Gómez-Villamandos et al., 2006). Anaesthesia was induced with propofol and maintained with desflurane and lasted 90 minutes. Given the duration of anaesthesia and the low doses of short acting premedication drug in this study, the sedative effects of the premedication might not have still been present which could account for the similar recovery times between groups. Interestingly the end tidal desflurane was different between the groups but this didn’t affect recovery times.

1.4.5.2 Induction drug

Induction agents could also influence recovery time and quality. However, an important consideration when assessing these studies is the duration of anaesthesia and administration of other drugs. Induction agents tend to be short onset and short duration drugs so their effect on recovery may be minimal following a long duration anaesthetic. One study comparing propofol, alfaxalone and ketamine-diazepam for induction demonstrated similar recovery qualities between groups (White & Yates, 2017). Healthy dogs undergoing anaesthesia for castration were premedicated with 20 mcg/kg medetomidine and 0.2 mg/kg methadone intramuscularly and anaesthesia was maintained with isoflurane vaporised in oxygen. Recoveries were assessed using an SDS scale. Duration of anaesthesia was similar between groups, 69 – 84 minutes, but end tidal inhalation agent was not reported. One confounding factor that could have limited the effect of induction agent on recovery quality was the profound sedation from the premedication combination.

Comparison of propofol and ketamine-diazepam for induction of anaesthesia following acepromazine (0.02 mg/kg) and morphine (0.3 mg/kg) premedication in healthy dogs undergoing castration showed significant differences in recovery between the groups (Ferreira et al., 2015). Propofol was associated with a superior quality recovery and a shorter time to standing than ketamine-diazepam. Duration of anaesthesia was short (approximately 30 minutes) and a shorter time for redistribution and metabolism of the induction agents might allow the differences between the induction agents to be more apparent.

Comparison of alfaxalone and propofol as induction agents showed significant differences in recovery assessed by SDS and VAS systems (Jiménez et al., 2012). All dogs were premedicated with methadone alone. Early recovery, immediately after extubation, was similar between groups but later recovery, defined as once animals were fully conscious and maintaining sternal recumbency, was significantly worse following alfaxalone. There were no significant differences between groups in sedation score following premedication but dogs that were more sedated had better recoveries. This study highlights the impact of premedication and its effect on the recovery period.

An experimental study assessing the recovery from an induction dose of alfaxalone or propofol demonstrated significantly longer recoveries following alfaxalone (12 +/- 4 minutes

compared to 5 +/- 2 minutes) (Maney et al., 2013). There were no significant differences in quality of recovery, assessed by SDS scales, between groups however there were significantly more undesirable events, such as tremors and twitching, following alfaxalone. In this study no other drugs or procedures were performed which allows direct comparison of the recovery characteristics of these two drugs.

1.4.5.3 Maintenance of anaesthesia

Maintenance of anaesthesia can be achieved via administration of drugs either via inhalation or by TIVA. A major difference between these techniques is how the drugs are metabolised and excreted. Inhalational agents undergo minimal metabolism and their termination of action is by elimination via the lungs (Becker & Rosenberg, 2008). Injectable agents, such as propofol or alfaxalone, differ in that their duration of action is terminated by redistribution of the drug away from the site of action. However, the redistributed drug still needs to be metabolised and excreted from the body. This can be a rate-limiting stage and can impact on the speed of full recovery from anaesthesia.

One prospective study assessing recovery in dogs compared different inhalational agents, isoflurane and sevoflurane (Love et al., 2007). All dogs were anaesthetised for urinary tract imaging and were premedicated with acepromazine (0.03 mg/kg) and pethidine (3 mg/kg) intramuscularly. Anaesthesia was induced with propofol to effect and maintained with either isoflurane or sevoflurane vaporised in oxygen, titrated to maintain a light plane of anaesthesia. They investigated time to extubation and to sternal recumbency and degree of ataxia at 30 and 60 minutes post-extubation. Ataxia and recovery scores were assessed using a VAS. There were no significant differences in timings or ataxia, but recoveries were scored significantly better in the sevoflurane group. Another study comparing sevoflurane and isoflurane for maintenance of anaesthesia in a large group of dogs undergoing anaesthesia for a range of clinical conditions demonstrated similar recovery times with both inhalational agents (Bennett et al., 2008). Duration of anaesthesia was similar between groups and very short procedures were excluded to limit the effect of premedication and induction agents on recovery times. Quality of recovery was not investigated. An experimental study in research dogs assessing cardio-respiratory parameters and recovery times after halothane, isoflurane and sevoflurane at 1.5 and 2 minimum alveolar concentrations demonstrated no significant differences in recovery times between the three inhalational agents (Polis et al., 2001). Dogs were

premedicated with fentanyl-droperidol and duration of anaesthesia was 1 hour.

Comparison of intravenous and inhalational techniques for maintaining anaesthesia demonstrates large differences in recovery speeds. An experimental study comparing propofol infusion and isoflurane maintenance showed a significantly slower time to extubation with propofol (23 +/- 6.3 minutes compared to 8 +/- 3.4 minutes). Depth of anaesthesia was assessed using a scoring system and was similar between groups (Kuusela et al., 2003). Duration of anaesthesia was 4 hours. A clinical study comparing similar maintenance agents showed a similar increased duration of recovery in propofol TIVA group (Tsai et al., 2007) despite differences in premedication and duration of anaesthesia. Studies comparing different drugs for TIVA have shown comparable recovery times and qualities between propofol and alfaxalone (Ambros et al., 2008; Suarez et al., 2012).

1.4.6 Other factors affecting recovery

Delayed recovery is a common consequence of hypothermia which has several potential mechanisms. Decreased body temperature causes central nervous system depression and altered cerebral blood flow which can slow time to full consciousness (Clark-Price, 2015). Altered pharmacokinetics of anaesthestic agents and reduced metabolism can be compounded by direct cardiovascular depression caused by hypothermia which can all lead to a slower recovery from anaesthesia. Heat loss is time dependent with an initial steeper decline, due to redistribution, followed by a decrease in the rate of heat loss. A rate of 0.5-1 °C temperature loss over the first hour of anaesthesia is commonly quoted in humans (Bindu et al., 2017). One study in dogs has shown an increase in recovery time with decreasing body temperature (Pottie et al., 2007). Mean duration of anaesthesia was 75 minutes. However, given the short duration of anaesthesia for radiotherapy, the effect of body temperature on recovery may not be a significant factor.

1.4.7 Emergence delirium and dysphoria

Emergence delirium (ED) is seen following extubation in both humans and animals. In children it is defined as “a disturbance in a child’s awareness or attention to his/her environment with disorientation and perceptual alterations including hypersensitivity to

stimuli and hyperactive motor behaviour in the immediate post anaesthesia period" (Sikich et al., 2004). There is no strict definition in animals. Drug factors can be associated with the incidence of ED but there have been limited studies in veterinary species. In children the use of sevoflurane alone is associated with an increase in prevalence of ED and adjuncts such as alpha$_2$ agonists, opioids and ketamine reduce the risk of ED when compared to sevoflurane alone (Costi et al., 2014). These adjuncts were given during the anaesthetic and premedication with midazolam was not associated with a reduced risk of ED. Comparison of the individual effect of different adjuncts was not assessed. The mechanism for ED is unknown but it could be related to the rapid emergence from anaesthesia with volatile agents (Reduque & Verghese, 2013). ED is associated with a poorer recovery from anaesthesia and different premedication agents may influence the incidence of ED in dogs.

Dysphoria in humans is described as feelings of unpleasantness that may cause a patient to act out against their environment. Dysphoric behaviours in dogs have been described and include vocalisation, hyper-reactivity to external stimuli, agitation and unresponsive to interactions with people (Becker et al., 2013). Opioids in dogs have been associated with post anaesthetic dysphoria with an prevalence ranging from 1 to 22% (Becker et al., 2013). However, there is no clear definition of dysphoria in these studies making comparison difficult. Dysphoria is often confused with pain and analgesics such as fentanyl may alleviate the pain but could also worsen the dysphoria if the animal is truly dysphoric rather than painful. A recent study infused fentanyl (7.5 mcg/kg/hr) to anaesthetised non painful dogs and reported no difference in recovery between dogs receiving fentanyl or saline and no incidences of dysphoria in recovery (Romano et al., 2019).

1.5 Anaesthesia for veterinary radiotherapy

As general anaesthesia is a requirement for veterinary radiotherapy, several studies have investigated different anaesthetic protocols specifically for this patient population. The use of alfentanil (10 mcg/kg) and atropine (0.3mg total) intravenously as premedication, followed by propofol induction in 100 anaesthetics has been reported (Chambers, 1989). Quality of induction was described as poor in only 2% of cases and the mean propofol dose required for intubation was 1.94 mg/kg. Apnoea, persisting for more than 3 minutes, was recorded in 11% of cases. Recovery was smooth and fast in all cases with a small number (exact number not

reported) of dogs being described as “disorientated” for several minutes. They conclude that “if required, dogs may be returned to their owners fully conscious in less than 10 minutes from the end of the procedure” highlighting the apparent rapid and smooth recovery that this anaesthetic protocol can result in.

An observational study described an anaesthetic protocol for radiotherapy (Hall & Peshin, 1996). Anaesthesia was induced with propofol and maintained with halothane vaporised in nitrous oxide/oxygen mixture. No premedication was given. Recovery was described as rapid and smooth with 13 minutes between extubation and walking on average. However, this protocol was described as “not entirely satisfactory” given the relatively high prevalence of tonic-clonic movements during anaesthesia which was attributed to propofol.

A study, assessing different induction agents in dogs undergoing anaesthesia for radiotherapy, used a similar premedication combination (Michou et al., 2012). All dogs received alfentanil (10 mcg/kg) and atropine (20 mcg/kg) intravenously prior to induction. As the primary outcome was assessment of pain on injection of induction agent, no comment was made on the degree of sedation or the quality of recovery.

A recent study compared different techniques of administering alfentanil and propofol for induction of anaesthesia (Lehnus & Brearley, 2019). They compared intravenous premedication with alfentanil (10 mcg/kg) and atropine (12 mcg/kg) followed by induction with propofol to induction with a propofol-alfentanil admixture (9 mg/ml propofol and 45 mcg/ml alfentanil). The premedication group had significantly higher heart rates during anaesthesia but a more frequent incidence of hypotension that the propofol-alfentanil admixture group. Recovery times were similar in both groups with median time to walking 10 minutes from the end of anaesthesia in both groups. Recovery was scored using an SDS and recovery scores were similar in both groups with the majority being described as smooth. Interestingly, agitation or excitement was reported in 18 out of 80 of inductions, with a higher frequency in the admixture group. Overall, this study demonstrates that the use of alfentanil, either as a premedication or in combination with propofol, results in quick, smooth recoveries but potentially with some agitation on induction.

1.6 Conclusions

There are tools to assess the impact of specific disease states on the quality of life of veterinary patients. However, the interaction between anaesthesia and quality of life in veterinary patients is a challenging area to investigate. Recovery from anaesthesia can be influenced by a variety of different factors and, unlike human anaesthesia, there are no validated scales to assess recovery in veterinary patients. Numerous studies have attempted to assess recovery following different anaesthesia drug combinations in animals, but few studies have assessed recovery following repeated anaesthetic events. The limited published data on specific veterinary radiotherapy protocols provides an area for further investigation. Current protocols are based on experience of drug action and outcomes rather than evidence. The main area of interest in this study is the effect that different drugs may have on recovery, primarily assessing the effect of premedication drugs. Premedication is often used in veterinary medicine for sedation, pre-emptive analgesia and for its potential anaesthetic sparing effects. The assessment of different premedication drugs on the quality of induction and recovery will provide further information which may help guide anaesthesia for radiotherapy.

2.1 Introduction to the study

2.1.1 Aims of the study

The overall aim of this study was to investigate the effect of different premedication drugs on recovery from anaesthesia in a population of dogs undergoing radiotherapy. Recovery was assessed at two different time points: within the hospital immediately following anaesthesia and within the home environment. Different aspects of recovery were assessed. Within the hospital both speed and quality of recovery were investigated. Within the home environment, the quality of the longer recovery time was investigated. Characterisation and assessment of recoveries following different premedication drugs may allow determination of optimal drug selection for these patients.

2.1.2 Preliminary investigation of radiotherapy recoveries

A brief retrospective review of the most recent 100 anaesthetics for radiotherapy, comprising of 13 individual patients excluding patients with brain tumours, was performed to investigate which drugs are commonly used in this clinic and what doses are used. All inductions were performed with propofol administered to effect and anaesthesia was maintained with sevoflurane vaporised in oxygen. The two most used premedication drugs were an alpha$_2$ agonist, either medetomidine or dexmedetomidine, in approximately 80% of cases and alfentanil/atropine in the remaining 20%. All premedication drugs were given intravenously. Medetomidine or dexmedetomidine were reversed with atipamezole in approximately 50% of cases. Median dose of medetomidine was 1.7 mcg/kg (range 0.5-3.2) and median dose of dexmedetomidine was 1.0 mcg/kg (range 0.4-2). The dose of alfentanil/atropine was much more standardised with 10 mcg/kg of each drug given in each case.

An attempt was made to compare recoveries based on description by the anaesthetist. Words commonly used, such as smooth, calm, dysphoric and excited, were ranked and a simple descriptive scale was designed based on which words were used in the description (Table 2.1). Only 64/100 recoveries were described.

Table 2.1- Table to show categorisation of recovery quality based on descriptive terms extracted from anaesthetic records

scale of quality
1 - good/smooth
2 - mild agitation
3 - paddling, dysphoric, vocalisation, ataxia
4 - poor

Based on this scale, 5/13 (38%) recoveries following alfentanil/atropine had the descriptors "paddling, dysphoric, vocalisation, ataxia" compared to 4/51 (8%) recoveries following an alpha$_2$ agonist. When assessing speed of recovery, 53/100 were described. Following alfentanil/atropine 11/12 (92%) described recoveries included the words "rapid" or "quick" compared to 20/41 (48%) following an alpha$_2$ agonist.

Statistical analysis using Chi-Square tests showed significant differences in these reported outcomes. The words "paddling, dysphoric, vocalisation, ataxia" were used to describe recoveries following alfentanil/atropine significantly more frequently than medetomidine (p = 0.002). Following alfentanil/atropine, recoveries were described as "quick" significantly more frequently than following an alpha$_2$ agonist (p = 0.008).

Subjective clinical experience would seem to support the information gained from this retrospective observation of anaesthetic records. Following alfentanil/atropine, dogs tend to recover quickly but may vocalise or paddle more than when compared to dogs receiving an alpha$_2$ agonist. Therefore, one aim of this study was to assess immediate recovery to determine if there were significant differences in speed and quality.

2.1.3 Premedication selection

Ideal characteristics of premedication drugs for short duration anaesthesia include quick onset of action, short duration and potentially reversible. Appropriate premedication can aid a rapid, smooth induction and recovery. The drugs that were chosen to be investigated in this study were medetomidine, alfentanil/atropine and butorphanol. The characteristics of these drugs are described below which outlines partly why these drugs were chosen.

Alfentanil is a full mu opioid agonist with a very short onset and duration of action (Ilkiw et al., 1991). However, when given as an intravenous bolus, it can cause pronounced bradycardia and cardiac arrest (Flecknell et al., 1990) so it is usually combined with an anticholinergic drug (Chambers, 1989). Atropine is preferred over glycopyrrolate because it has a faster onset of action (Hendrix & Robinson, 1997) which enables administration of alfentanil and atropine at the same time. A dose of 10 mcg/kg of alfentanil and 10 mcg/kg atropine for premedication has previously been described (Chambers, 1989). The degree of sedation is often mild and it is

not commonly used as a premedication agent outside of radiotherapy (Chambers, 1989; Lehnus & Brearley, 2019). Previous studies have assessed alfentanil as an adjunct for intravenous anaesthesia and sedation and described a propofol sparing effect (Auckburally et al., 2008; Montefiori et al., 2016). When combined with propofol for sedation it provided a smooth quality of sedation compared to propofol alone but a higher incidence of hypoxaemia (Montefiori et al., 2016). It is not licensed in the UK for use in dogs.

Medetomidine is an alpha$_2$ agonist which provides dose dependent, reliable sedation. It is a commonly used premedication and sedation drug (Gómez-Villamandos et al., 2005; Hellebrekers & Sap, 1997). Following intravenous administration, onset of sedation is reported to be 1 minute (Sinclair, 2003). Duration of action is also dose dependent and its action can be reversed with the use of atipamezole, a competitive alpha$_2$ adrenergic antagonist (Vaha-Vahe, 1990). Cardiovascular effects of alpha$_2$ agonists have been well described and include intense peripheral vasoconstriction and a reflex bradycardia (Bloor et al., 1992; Murrell & Hellebrekers, 2005). Cardiac output is dramatically reduced by up to 50% with dose dependent cardiovascular effects only seen with lower doses (1-2 mcg/kg) (Pypendop & Verstegen, 1998). This class of drugs should be used with caution with patients with cardiovascular disease.

Butorphanol is a mu opioid receptor agonist-antagonist and a kappa opioid receptor agonist (Walsh et al, 2008). It is considered to have mild analgesic effects in dogs but can cause moderate dose-dependent sedation (Trim 1983). It has been shown to have better sedative effects than other opioids when combined with an alpha$_2$ agonist (Trimble et al., 2018). Antinociceptive effects are reported to last 45 minutes (Houghton et al., 1991) with peak sedation within 15 minutes. It is more frequently used in combination with other drugs to enhance the sedative effect and it has minimal cardiovascular effects. Doses of 0.1 - 0.4 mg/kg are commonly used for premedication (KuKanich & Wiese, 2015).

2.2 Materials and methods

2.2.1 Ethical approval and test certificate

Ethical approval for the study was obtained from the School of Veterinary Medicine, University of Glasgow Research Ethics committee. An Animal Test Certificate (Type S) was obtained from the Veterinary Medicines Directorate for the off-license use of alfentanil hydrochloride in dogs prior to initiation of the study (Animal Test Certificate No: ATC-S-092). Informed owner consent was also obtained prior to enrolment in the study (Appendix 1).

2.2.2 Animals

American Society of Anesthesiologists (ASA) grade 1 or 2 client-owned dogs undergoing at least 4 treatments for radiotherapy were considered for enrolment. Exclusion criteria included radiotherapy for brain tumours, systemic disease other than the tumour undergoing radiation or dogs whose temperament was overly stressed, anxious or aggressive. This was based on clinical assessment by the primary anaesthetist. Any dogs that received steroids as part of their radiotherapy treatment were also excluded.

2.2.3 Study design

Dogs were allocated in sequence to one of three treatment groups based on a repeating block Latin square design (Figure 2.1). All dogs received all three premedication drugs in a predetermined order. The initial aim was to recruit at least 12 dogs.

Figure 2.1 - schematic to show drug allocation for successive patients using a repeating block Latin square design showing first 5 dogs. One block consisted of 3 dogs and this was then repeated A – alfentanil/atropine, B – butorphanol, M – medetomidine

Dog 1	A	B	M
Dog 2	B	M	A
Dog 3	M	A	B
Dog 4	A	B	M
Dog 5	B	M	A

The three treatment groups consisted of:
Group A received 10 mcg/kg alfentanil (Rapifen 500 mcg/ml; Piramal Critical Care Limited, West Drayton, UK) combined with 10 mcg/kg atropine (Atropine Sulphate 600mcg/ml; Martindale Pharma, High Wycombe, UK)
Group B received 0.2 mg/kg butorphanol (Torbugesic 10mg/ml; Zoetis UK Limited, Leatherhead, UK)
Group M received 2 mcg/kg medetomidine (Domitor 1 mg/ml; Vetoquinol UK Limited, Towcester, UK)

All premedication drugs were given intravenously. Dogs in group M received 10 mcg/kg atipamezole (Antisedan 5 mg/ml; Vetoquinol UK Limited, Towcester, UK) intramuscularly administered at the end of anaesthesia (when the vaporiser was switched off).

Dogs were included in the study from their second radiotherapy treatment for three consecutive treatments. The anaesthetist who performed the anaesthetic was not blinded to the treatment group. During the radiotherapy protocol, the first treatment is often longer due to unfamiliarity of the patient, patient preparation and positioning, including placing an intravenous cannula, and setting up the radiotherapy beams for the first time. Therefore, it was decided to include dogs from the second treatment to prevent the influence of these factors on the study.

2.2.4 Anaesthetic protocol

A schematic overview of the study timeline is shown in Figure 2.2. The dog entered the radiotherapy suite and a clinical exam was performed by the anaesthetist. An intravenous cannula (Biovalve Safe; Vygon Ltd, Swindon, UK) was placed into a peripheral vein if necessary. Cannulas were placed on the first treatment of the week and were maintained patent with a stylet (Stylet; Vygon Ltd, Swindon, UK). This was to minimise repeated restraint and potential stress that may occur if new cannulas were placed at each treatment.

With the patient standing on a mattress on the floor, the predetermined premedication was administered intravenously. Two minutes elapsed prior to induction. During this time period,

the patient was gently restrained if required but interaction was minimised. The dog was then placed on a table and preoxygenated for one minute via face mask prior to induction of anaesthesia with propofol (PropoFlo Plus 1 % emulsion; Zoetis UK, Leatherhead, UK) administered intravenously slowly to effect until conditions were suitable for tracheal intubation. This consisted of loss of palpebral reflex, ventromedial rotation of the eye and loss of jaw tone. The trachea was intubated with an appropriately sized endotracheal tube and the cuff was inflated. Following intubation, the endotracheal tube was attached to a circle breathing system and anaesthesia was maintained with sevoflurane (SevoFlo 100% inhalational vapour; Zoetis UK, Leatherhead, UK) vaporised in 100% oxygen. Fresh gas flow was initially 4 L/minute and this was reduced to 1 L/minute after 10 minutes. The vaporiser was initially set to deliver an initial end tidal sevoflurane concentration of 2.3%. Vaporiser settings were then titrated to maintain an appropriate plane of anaesthesia. The dog was positioned on the radiotherapy table as required for the treatment and mechanical ventilation (Blease 8200S Ventilator; Blease Medical Equipment Limited, Chesham, UK) was initiated with a tidal volume of 10 ml/kg and a rate to maintain normocapnia (4.5 - 6 kPa). Monitoring during anaesthesia included pulse oximetry, capnography, electrocardiography, non-invasive oscillometric blood pressure monitoring and anaesthetic agent analysis (Datex-Ohmeda S5; Datex-Ohmeda Ltd, Hatfield, UK).

At the end of the radiotherapy treatment the vaporiser and ventilator were turned off and the fresh gas flow was increased to 4 L/minute. This was defined as the end of anaesthesia. A stopwatch was also started. If patients were apnoeic for greater than 30 seconds, intermittent manual positive pressure ventilation at a rate of 2 breaths per minute, was initiated until spontaneous ventilation resumed. Monitoring equipment was removed and once the dog was spontaneously breathing and the end tidal sevoflurane concentration was less than 1.0%, the patient was moved, while still intubated, to an orthopaedic mattress on the floor. The dog was positioned in lateral recumbency. Extubation was performed when first attempts to swallow were noted and restraint or support was provided by an assistant only if required otherwise the patient was not otherwise stimulated. Times from end of anaesthesia to extubation, to sternal recumbency and to standing were recorded. If the dog had a duration of recovery of greater than 20 minutes from the end of anaesthesia, attempts were then made to stimulate and rouse the patient. This was decided to minimise the impact of slow recoveries on the running of the radiotherapy schedule. All dogs were discharged from the hospital to their owner’s care once

walking unaided.

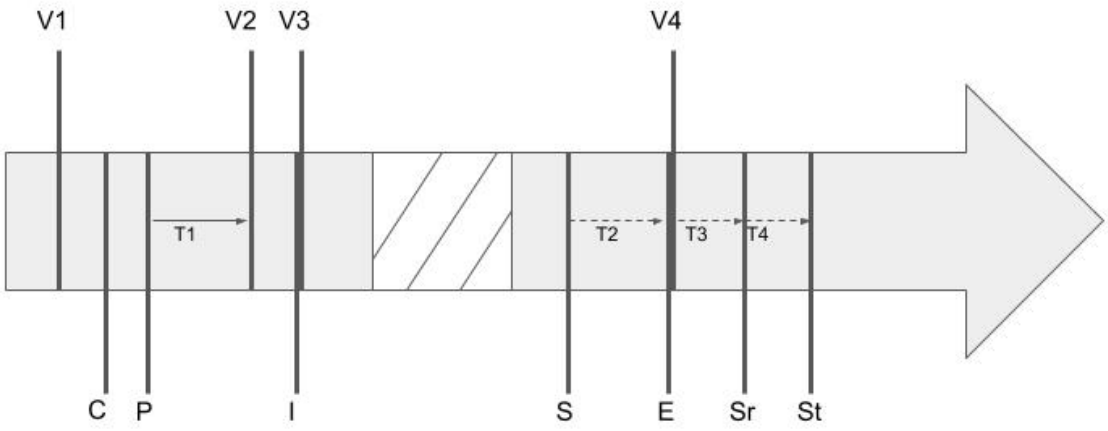
2.2.5 Video recording

Four videos were recorded during each anaesthetic period. These included a demeanour video, a sedation video, an induction video and a recovery video. The demeanour video was recorded for 30 seconds once the dog entered the radiotherapy suite and standing on the mattress prior to any interaction with the patient. The sedation video was recorded 2 minutes following administration of the premedication drug for 30 seconds with the dog still positioned on the mattress on the floor. The induction video was recorded from the start of propofol administration until endotracheal intubation. The recovery video was recorded from extubation until either the patient reached standing or 20 minutes had elapsed from the end of anaesthesia. The four video recordings from each treatment were anonymously labelled and viewed in a randomised order at a later date by two assessors who were blinded to the treatment groups. Scores were assigned for each video based on the simple descriptive (SDS) and visual analogue scales (VAS) in Appendix 2. Each assessor was an experienced board-certified clinical anaesthetist (DipECVAA).

2.2.6 Owner questionnaire

Owners, who were unaware what premedication drug their dog had received, were asked to assess the recovery of their dog following the treatment. They were asked to complete the questionnaire on the morning after the anaesthetic to give an overall impression of the recovery during the preceding afternoon and night. A single owner was asked to complete all questionnaires for their dog to limit interobserver variation.

Figure 2.2 Study timeline. V1 - video 1 to assess demeanour score, V2 - video 2 to assess sedation score, V3 - video 3 to assess induction score, V4 - to assess recovery score, C - clinical examination and cannula placement (if necessary), P - premedication, I - induction, S - end of anaesthesia, E - extubation, Sr - dog achieves sternal position, St - dog stands. T1 - time between administration of premedication and V2 (2 minutes). T2 – time to extubation (from end of anaesthesia (S) to extubation (E)). T3 – time to sternal (from end of anaesthesia (S) to sternal position (Sr)). T4 – time to standing (from end of anaesthesia (S) to standing (St)).



2.2.7 Design of scoring systems

2.2.7.1 Video scoring system

For the demeanour, sedation and induction videos, previously published SDS were modified for use (Holton et al, 2001, Sánchez et al, 2013, Jimenez et al, 2012). A VAS was also used to assess the induction to allow analysis of a continuous variable. For the recovery videos, commonly seen recovery behaviours and actions were considered and included in the scoring system. These aspects were restraint, vocalisation, paddling, ataxia and excitement. These were rated as present or absent and if present, ranked on 3-point scale (from a little to a lot). Finally, the overall recovery was assessed using a visual analogue scale between worst imaginable recovery and best possible recovery. Assessment of validity was beyond the scope of this study. Reliability was assessed by analysing interobserver variation in scores. The scoring system is included in Appendix 2.

2.2.7.2 Owner assessment questionnaire

Following consideration of potential areas that may concern an owner, four areas were assessed for the owner questionnaire. Commonly reported issues following anaesthesia included lethargy, poor appetite and excessive sleep. Therefore, areas included in the owner questionnaire were appetite, activity levels, sleep and attention seeking behaviour. The owners were asked to rank these based on a Likert-type scale as less than normal, normal or more than normal. An open text box for comments was also provided to try and capture other descriptive data. The owners were also asked to rank the three recoveries from best to worst. The questionnaire was purposely designed to be simple and quick to perform to maximise owner compliance. The owner questionnaire is included in Appendix 3.

2.2.8 Main outcome measures

2.2.8.1 Anaesthetic period

During the treatment the main anaesthetic parameters recorded included the propofol dose (mg/kg) required for endotracheal intubation, the end tidal sevoflurane at end of anaesthesia

(%) and the duration of anaesthesia (minutes).

2.2.8.2 Immediate recovery period

Time to reach certain predetermined points were also recorded for the recovery period. All time points were recorded from the end of anaesthesia, defined as when the vaporiser was turned off. These included time to extubation, time to reach sternal position and time to reach standing and were all measured in minutes.

2.2.8.3 Video analysis

Four videos were recorded for each treatment. A scoring system (Appendix 2) was used to generate scores for each video. These included a demeanour score prior to interaction with the patient; a sedation score following premedication; an induction score and VAS score to assess induction and a recovery VAS score. Behaviours were also rated in recovery and these included paddling, vocalisation, restraint, ataxia and overall if the recovery was smooth or excited. These scores are termed recovery behaviour scores.

2.2.8.4 Owner assessment

Four categories were assessed and a score for each category was assigned by the owner. These included scores for activity, appetite, sleep patterns and attention seeking behaviour (Appendix 3).

2.3 Statistics

Following advice from a statistician, it was not possible to perform a power calculation to determine the required sample size due to the Latin square study design. Initially 12 dogs were recruited however, this was increased to 15 dogs. This resulted in 45 individual treatments. Data was inserted into an Excel spreadsheet (Microsoft) and uploaded into Minitab (version 19) and SPSS (version 26) for statistical analysis. Data was assessed for normality using Anderson Darling plots.

Data is presented as mean (± standard deviation) for normally distributed data or median (range) for non-normally distributed data. A level of significance was set at a p value < 0.05.

2.3.1 Descriptive data

Descriptive statistics were performed for age and body mass including mean, median, standard deviation and range.

2.3.2 Generalised linear mixed models

2.3.2.1 Continuous outcomes

Continuous outcomes were analysed using mixed effects models (Minitab version 19) with the patient as the random effect. Possible explanatory factors were put into each model to analyse their effect on the outcome and a backwards stepwise approach was used to refine the model. Interaction terms between certain factors were also included, based on clinical reasoning. Continuous outcomes analysed included propofol dose for induction, duration of anaesthesia, end tidal sevoflurane concentration, time to extubation, video scores for induction VAS and recovery VAS.

2.3.2.2 Categorical outcomes

Categorical outcomes were analysed using linear mixed effect models (SPSS version 26) with the patient as the random effect. As for the continuous outcomes, possible explanatory factors were put into each model and a backwards stepwise approach was used to refine the model.

Interaction terms between certain factors were also included based on clinical reasoning. Categorical outcomes included demeanour score, sedation score, induction score, number of dogs reaching sternal position, number of dogs reaching standing position, recovery behaviour scores and owner assessment scores.

For both continuous and categorical outcomes model summaries are presented for significant factors to show the effect that the factor has on the outcome. A positive coefficient indicates that the factor increases the likelihood of that outcome whereas a negative coefficient indicates a decreased likelihood of that outcome. The *p* value indicates the level of significance.

2.3.3 Interobserver agreement

For the video analysis, interobserver agreement was assessed using Cohen's kappa for categorical outcomes and Spearman's correlation for continuous data. Bland Altman plots were generated for the induction and recovery VAS to assess interobserver agreement.

2.4 Results

Normally distributed data included body mass, age, propofol dose, time to extubation, time to sternal and time to standing. Non-normally distributed data included duration of anaesthesia, end tidal sevoflurane, video assessment scores (including induction SDS and recovery behaviour videos), video VAS scores and owner questionnaire scores.

2.4.1 Study population

Fifteen dogs were enrolled in the study and all completed all three treatments. This resulted in 45 individual treatments. Dog breeds included 6 mixed-breed, 4 Labradors, 1 Border Terrier, 1 Cocker Spaniel, 1 English Pointer, 1 Hungarian Vizla and 1 Shih Tzu. Mean age was 8.2 years (± 2.2 years) and body mass was 25.8 kg (± 9.6 kg). All owner questionnaires were completed and returned. Indications for radiotherapy were varied and included 7 cutaneous appendicular tumours (mast cell tumour right hock, mast cell tumour right shoulder, mast cell tumour left carpus, mast cell tumour left thigh, soft tissue sarcoma right hock, soft tissue sarcoma right pelvis, soft tissue sarcoma left thigh), 5 oral/nasal/facial tumours (ocular tumour, oral epitheliotrophic lymphoma, nasal osteosarcoma, nasal adenocarcinoma, nasal epitheliotrophic lymphoma), 2 cutaneous trunk tumours (soft tissue sarcoma chest wall, soft tissue sarcoma dorsum) and 1 anal sac adenocarcinoma. All dogs received 12 fractions of radiation.

Duration of anaesthesia was similar between groups (Table 2.2) with a median duration of 15 minutes (10-35 minutes) and was not affected by treatment order or treatment group.

There is missing data in certain areas. Following medetomidine, one dog regurgitated following extubation so the recovery data and video data is not available for that dog. Due to technical issues with the video recording, certain videos are missing for some patients. A total of 168 videos were included for analysis (out of a possible 180). Where data is missing, numbers in each group are shown in the various tables.
Outliers, defined as greater than 1.5 times the interquartile range from the upper or lower quartile are indicated in the boxplots but were included in the analysis.

2.4.2 Re-categorisation of data

Following some treatments, data were missing because the dog had not reached the end point within 20 minutes of the end of anaesthesia (Table 2.2). For two outcomes, time to sternal recumbency and standing, it was not possible to analyse these data points using a mixed effect model due to numerous missing data points. These two outcomes were recoded as binary outcomes (did the dog reach sternal – yes or no, did the dog stand – yes or no). This data is shown in Table 2.10.

Owner scoring systems for activity, appetite, sleep patterns and attention seeking behaviour were originally categorised into 3 outcomes – less than normal, normal or more than normal (Table 2.17). Owner scores were re-categorised into two groups based on clinically relevant outcomes. For activity and appetite, normal or more than normal were grouped together and compared to less than normal. For sleep patterns and attention seeking behaviour, less than normal and normal were grouped together and compared to more than normal. This data is shown in Table 2.18.

*Table 2.2. Table showing anaesthetic variables and immediate recovery times following each treatment. A – alfentanil/atropine, B – butorphanol, M – medetomidine. Data presented as mean (+/- standard deviation) or median (range). n indicates number of animals in each group. ETSevo – end tidal sevoflurane concentration. * indicates significant difference between other treatment groups (p value < 0.05)*

	Treatment group A	**Treatment group B**	**Treatment group M**
Propofol dose (mg/kg)	4.4 (± 0.6)	4.0 (± 0.8)	2.5 (± 0.7) *
ETSevo (%)	2.1 (2.0-2.3) *	2.1 (1.9-2.2)	1.8 (1.7-1.9)
Duration (minutes)	15 (10-35)	15 (10-30)	15 (5-20)
Time to extubation (minutes)	6.5 (± 2.5) * n = 15	9.0 (± 3.7) n = 15	9.5 (± 4.1) n = 15
Time to sternal (minutes)	9.6 (± 3.9) n = 14	12.3 (± 3.7) n = 7	12.9 (± 4.1) n = 12
Time to standing (minutes)	10.9 (± 3.8) n = 13	12.3 (± 4.7) n = 4	14.1 (± 4.2) n = 11

2.4.3 Video assessment results

2.4.3.1 Interobserver agreement

For the video analysis interobserver correlation and agreement were calculated (Table 2.3). Following grouping of some categories, correlation improved (Table 2.3). Recovery behaviour scores for paddling, vocalisation, restraint and ataxia, were grouped into present or absent during recovery. This improved the correlation between observers. Interobserver correlation for the VAS scores (Table 2.4), both for induction and recovery, showed moderate correlation.

Interobserver agreement for the induction and recovery VAS scores were assessed via Bland-Altman plots (Figure 2.3 and Figure 2.4). For the induction video, the bias was –14 and there was a wide level of agreement. Generally, the majority of the videos were scored between 80 – 90 but there was improvement of agreement at this level. For the recovery video, the bias was -15 and again there was a wide level of agreement. In videos that were scored higher, there tended to be more agreement between observers.

2.4.3.2 Grouping of video assessment data

Due to the moderate correlation between the two observers' scores, outcomes from certain categories were regrouped for analysis. For demeanour, sedation and induction videos, scores 1 and 2 were grouped and scores 3 and 4 were grouped. Recovery behaviour scores for paddling, vocalisation, restraint, ataxia and excitement, were grouped into present or absent during recovery. These grouped scores were taken forward into the models as described below. To account for the variation in the observers' scores, scores from both observers were put in the models. When assessing recovery behaviour video scores as primary outcomes, the effect of the observer was included in the model as a fixed effect.

Induction and recovery VAS scores were continuous outcomes so the average score from the two observers was used for analysis.

Table 2.3. Table showing correlation for categorical data between observers for each video category. The third column shows the correlation between observers following regrouping of raw video scores (demeanour, sedation, induction – scores 1 and 2 = 0, scores 3 and 4 = 1. Paddling, vocalisation, restraint, ataxia, excitement 0 = absent, 1 = present)

	Cohen's Kappa	**Cohen's Kappa for grouped scores**	**Number of videos analysed**
Demeanour	0.26	0.40	43
Sedation	0.21	0.40	43
Induction	0.81	0.65	43
Paddling	0.69	0.85	27
Vocalisation	0.54	0.84	27
Restraint	0.23	0.73	27
Ataxia	0.19	0.42	27
Smooth/excited	0.21	0.49	27

Table 2.4. Table showing correlation for continuous data between observers for induction and recovery visual analogue scales. CI – confidence interval

	Spearman's correlation r	**CI**	**Number of videos analysed**
Induction	0.594	0.326 – 0.773	43
Recovery	0.681	0.390 – 0.848	27

Figure 2.3. Bland Altman plot for Induction VAS scores (n = 42). The red line shows the mean difference of the scores (level of bias) and the dashed black lines show the mean ± 2 standard deviations (level of agreement)

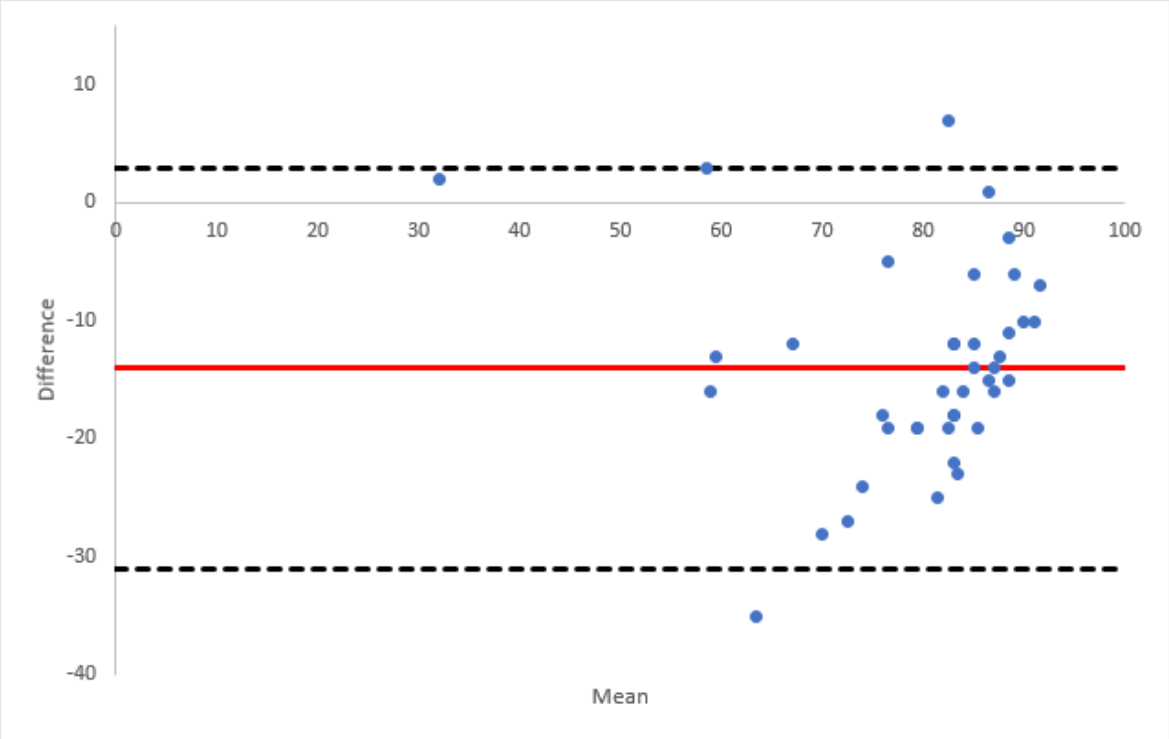


Figure 2.4. Bland Altman plot for Recovery VAS scores (n = 27). The red line shows the mean difference of the scores (level of bias) and the dashed black lines show the mean ± 2 standard deviations (level of agreement)

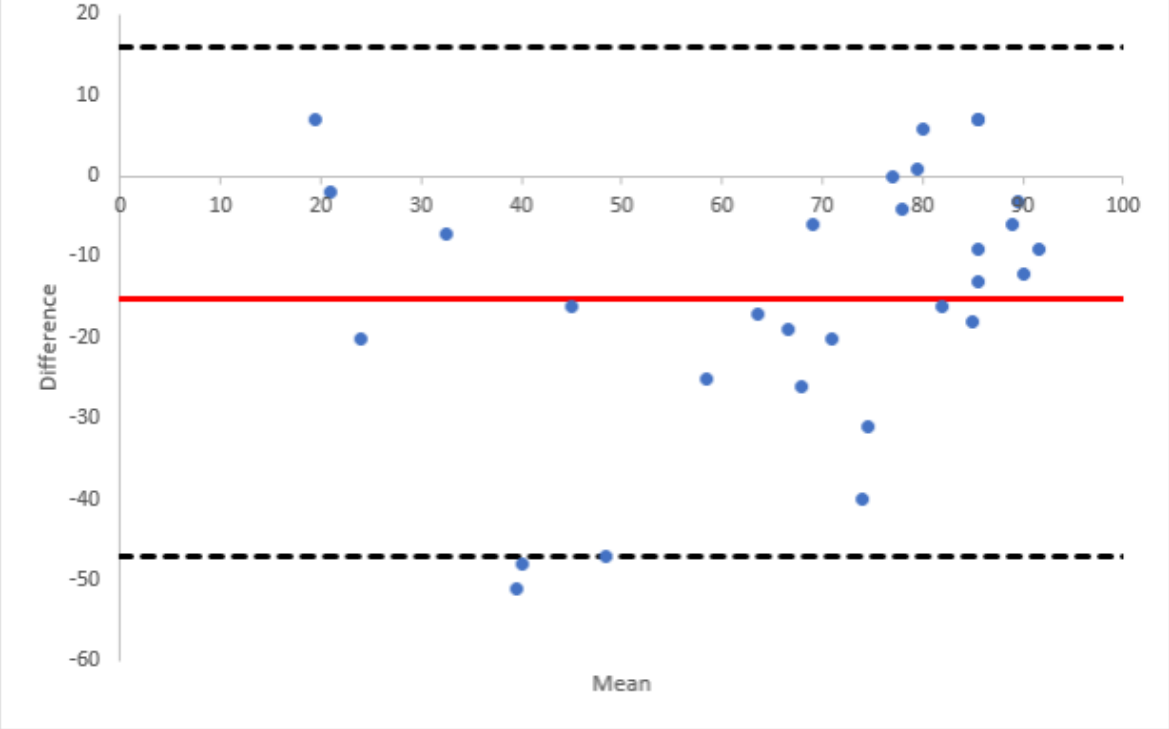


Table 2.5. Table showing median (range) video assessment scores from simple descriptive scales from both observers. A – alfentanil/atropine, B – butorphanol, M – medetomidine. n indicated number of videos analysed for each group

	Treatment group	**n**	**Observer 1**	**Observer 2**
Demeanour	A	15	2 (1-4)	2 (1-3)
	B	14	2 (1-4)	2 (1-4)
	M	14	2 (1-3)	2 (1-4)
Sedation	A	15	2 (1-3)	2 (1-3)
	B	15	2 (1-3)	2 (1-3)
	M	14	3 (1-3)	2 (1-3)
Induction	A	14	1 (1-3)	1 (1-2)
	B	13	1 (1-3)	1 (1-3)
	M	14	1 (1-2)	1 (1-2)

2.4.4 Demeanour

Median demeanour score is shown in Table 2.5. Data from the scores was grouped for analysis and shown in table 2.6. With grouped demeanour score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, observer and an interaction term between treatment group and treatment order. Patient was a random factor.
Demeanour score was not affected by any factor and did not differ between treatment groups.

2.4.5 Sedation

Median sedation score for each treatment is shown in Table 2.5. Data from the scores was grouped for analysis and shown in Table 2.7. With grouped sedation score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, observer and an interaction term between treatment group and treatment order. Patient was a random factor.
Sedation score was not significantly affected by any factor and did not differ between treatment groups.

2.4.6 Induction of anaesthesia

2.4.6.1 Propofol dose

Mean dose of propofol required for intubation for each treatment is shown in Table 2.2 and Figure 2.5. With propofol dose as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order and an interaction term between treatment group and treatment order. Patient was a random factor.
Treatment group was the only significant factor in the model ($p < 0.001$). Alfentanil/atropine and butorphanol were associated with a significantly increased propofol dose required for intubation compared to medetomidine.

Final model summary

Model term	**Co-efficient**	***p value***
Treatment group - M	*Reference*	
Treatment group - A	0.778	< 0.001
Treatment group - B	0.384	0.015

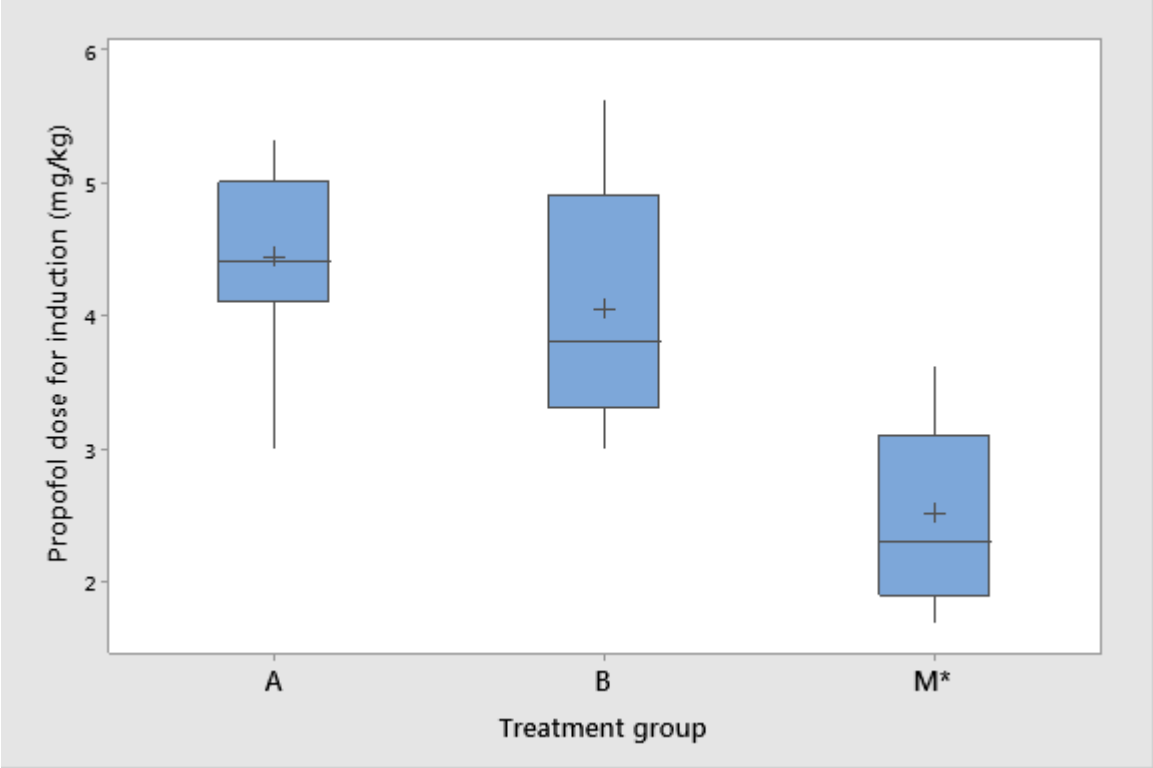
Table 2.6 showing grouped demeanour score and frequency of reported descriptors from each observer for each treatment group. A – alfentanil/atropine, B – butorphanol, M – medetomidine. Numbers in columns indicate dogs categorised for each descriptor

Grouped Demeanour score	**Treatment group**	**Observer 1**	**Observer 2**
0 - nervous/quiet	A	12	7
1 - content/bouncy		3	8
0 - nervous/quiet	B	12	3
1 - content/bouncy		3	12
0 - nervous/quiet	M	12	5
1 - content/bouncy		3	10

Table 2.7 showing grouped sedation score and frequency of reported descriptors from each observer for each treatment group. A – alfentanil/atropine, B – butorphanol, M – medetomidine. Numbers in columns indicate dogs categorised for each descriptor

Grouped Sedation score	**Treatment group**	**Observer 1**	**Observer 2**
0 - not very/slight sedation	A	9	11
1 - sedated/very sedated		6	4
0 - not very/slight sedation	B	9	10
1 - sedated/very sedated		6	5
0 - not very/slight sedation	M	5	5
1 - sedated/very sedated		10	10

*Figure 2.5 – Boxplot showing propofol dose (mg/kg) required for intubation in the different treatment groups. A – alfentanil/atropine, B – butorphanol, M – medetomidine. The whiskers indicate the range in each group, the edge of the boxes indicate the interquartile range and the horizontal line indicates the median. + indicates the mean. * indicates significantly different from the other treatment groups*



2.4.6.2 Induction score

Median induction score for each treatment is shown in Table 2.5. Data from the scores was grouped for analysis and shown in Table 2.8. With grouped induction score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, observer and an interaction term between treatment group and treatment order. Patient was a random factor.

Induction score was not significantly affected by any factor.

2.4.6.3 Induction VAS

Mean induction VAS score for each treatment group is shown in Table 2.9 and Figure 2.6. With mean induction VAS score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order and an interaction term between treatment group and treatment order. Patient was a random factor.

Induction score was significantly affected by treatment group ($p = 0.011$). Following alfentanil/atropine dogs had a significantly lower induction score compared to medetomidine. There were no differences between medetomidine and butorphanol.

Final model summary

Model term	**Co-efficient**	***p value***
Treatment group - M	*Reference*	
Treatment group - A	-5.59	0.003
Treatment group - B	1.88	0.294

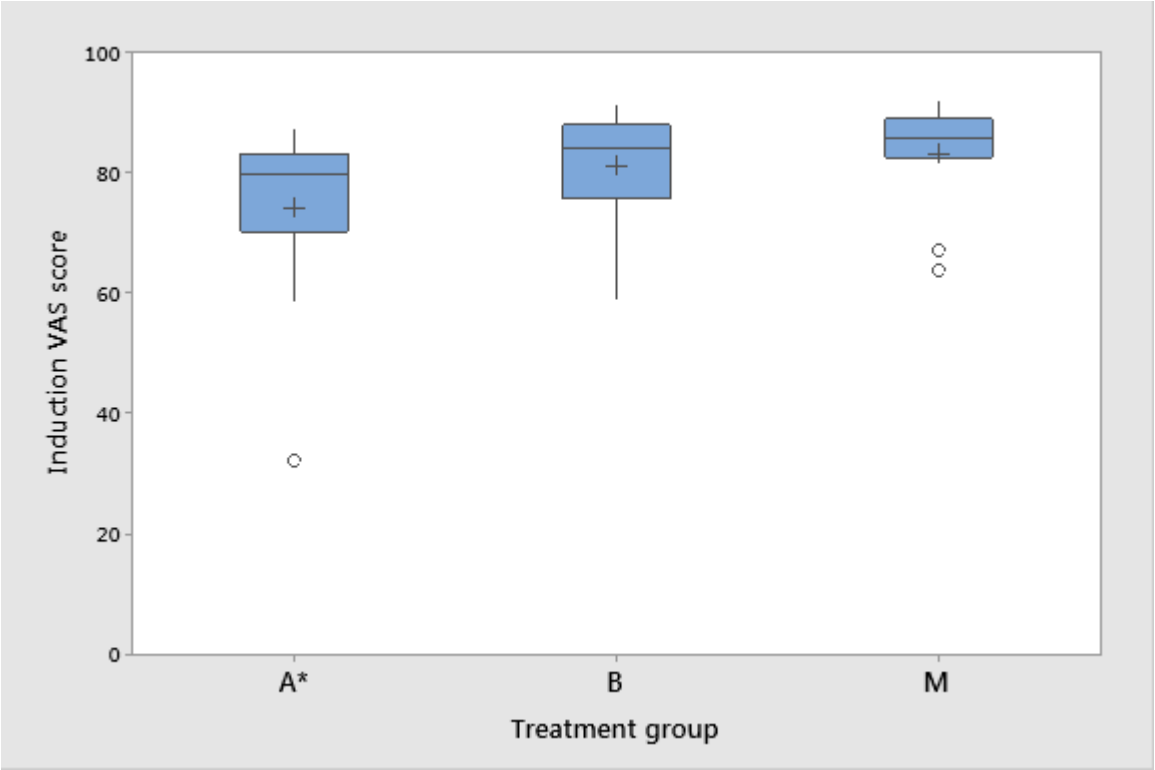
Table 2.8 showing grouped induction score and frequency of reported descriptors from each observer for each treatment group. A – alfentanil/atropine, B – butorphanol, M – medetomidine. Numbers in columns indicate dogs categorised for each descriptor

Grouped Induction score	**Treatment group**	**Observer 1**	**Observer 2**
0 - smooth/fair	A	14	14
1 – poor/very poor		1	1
0 - smooth/fair	B	15	15
1 – poor/very poor		0	0
0 - smooth/fair	M	15	15
1 – poor/very poor		0	0

Table 2.9 – Table showing mean (± standard deviation) VAS scores for induction and recovery videos from both observers. A – alfentanil/atropine, B – butorphanol, M – medetomidine. n column indicates number of dogs included in each group

Treatment group	**Induction VAS**		**Recovery VAS**	
	Score	**n**	**Score**	**n**
A	74 (± 14)	15	54 (±25)	13
B	81 (± 9)	14	61 (± 17)	4
M	83 (± 8)	13	81 (± 14)	10

*Figure 2.6 - Boxplot showing mean induction VAS score from both observers for each treatment group. A – alfentanil/atropine, B – butorphanol, M – medetomidine. The whiskers indicate the range in each group, the edge of the boxes indicate the interquartile range and the horizontal line indicates the median. + indicates the mean. ○ indicates outliers (greater than 1.5 times the interquartile range from the upper or lower quartile). * indicates significantly different from other treatment groups*



2.4.7 Maintenance of anaesthesia

2.4.7.1 ET sevoflurane concentration

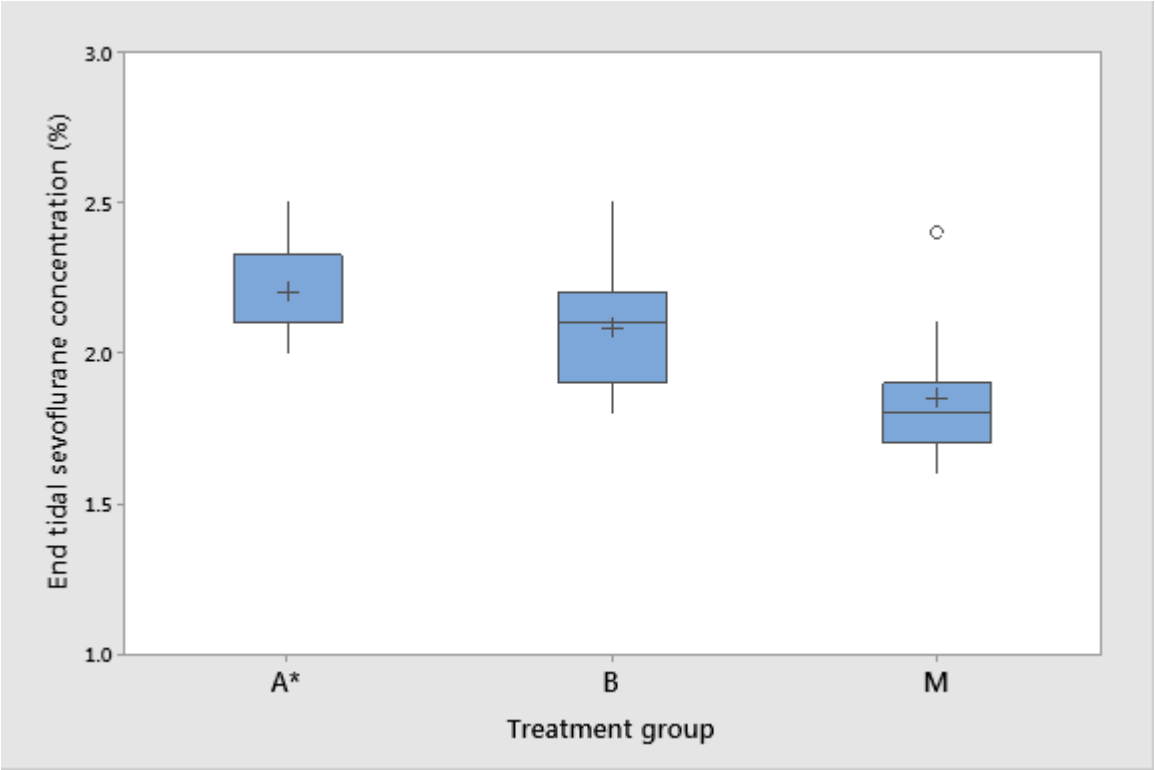
Median end tidal sevoflurane concentration for each treatment group is shown in Table 2.2 and Figure 2.7. With median end tidal sevoflurane concentration as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, propofol and interaction terms between treatment group and treatment order and treatment group and propofol. Patient was a random factor.

End tidal sevoflurane was significantly affected by treatment group ($p < 0.001$). Alfentanil/atropine was associated with a significantly higher end tidal sevoflurane concentration compared to medetomidine. There was no difference between butorphanol and medetomidine.

Final model summary

Model term	**Co-efficient**	***p value***
Treatment group - M	*Reference*	
Treatment group - A	0.159	< 0.001
Treatment group - B	0.037	0.338

*Figure 2.7 – Boxplot showing end tidal sevoflurane concentration (%) at the end of anaesthesia in the different treatment groups. A – alfentanil/atropine, B – butorphanol, M – medetomidine. The whiskers indicate the range in each group, the edge of the boxes indicate the interquartile range and the horizontal line indicates the median. + indicates the mean. ○ indicates outliers (greater than 1.5 times the interquartile range from the upper or lower quartile). * indicates significantly different from other treatment groups*



2.4.8 Recovery

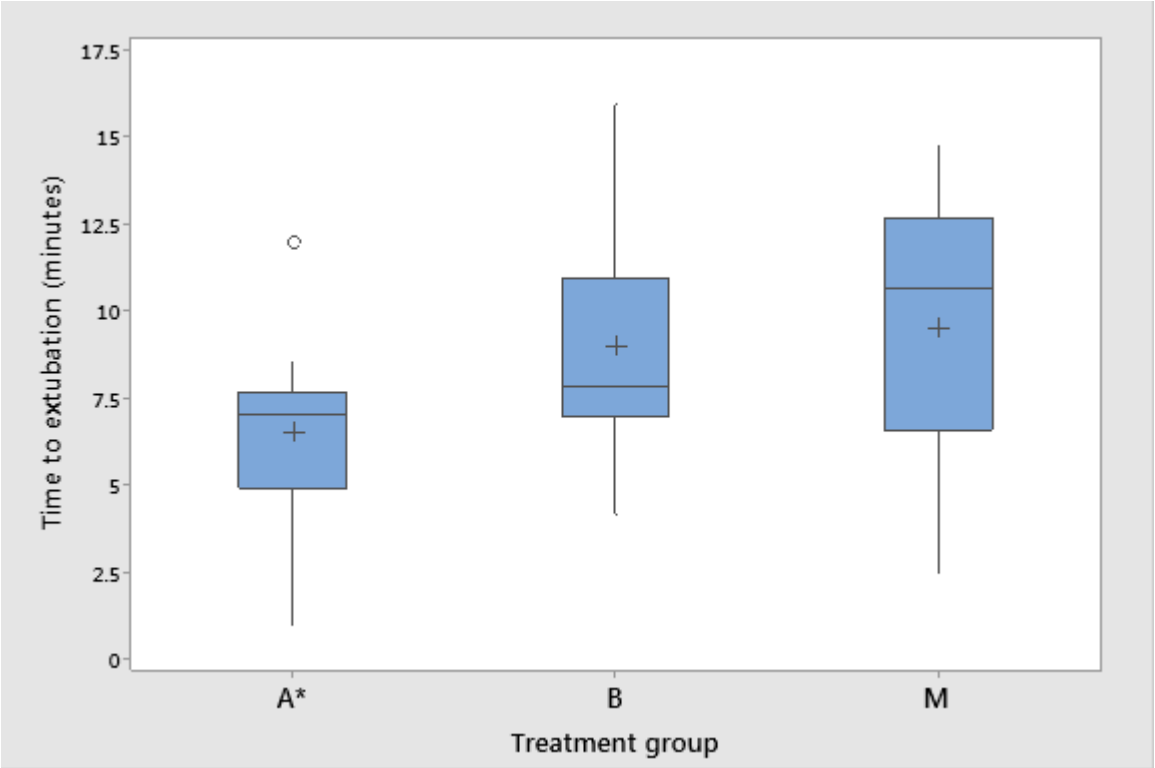
2.4.8.1 Time to extubation

Mean time to extubation for each treatment group is shown in Table 2.2 and Figure 2.8. With time to extubation as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, propofol dose for induction and end tidal sevoflurane concentration. The following interaction terms were also included: treatment group and treatment order, treatment group and propofol, treatment group and end tidal sevoflurane concentration, treatment order and propofol, treatment order and end tidal sevoflurane and propofol and end tidal sevoflurane. Patient was a random factor.
Time to extubation was significantly affected by treatment group ($p = 0.034$).
Alfentanil/atropine was associated with a significantly faster time to extubation compared to medetomidine and there was no difference between butorphanol and medetomidine.

Final model summary

Model term	**Co-efficient**	***p value***
Treatment group - M	*Reference*	
Treatment group - A	-109.742	0.011
Treatment group - B	41.35	0.322

*Figure 2.8 – Boxplot showing time to extubation (minutes) from the end of anaesthesia for the different treatment groups. A – alfentanil/atropine, B – butorphanol, M – medetomidine. The whiskers indicate the range in each group, the edge of the boxes indicate the interquartile range and the horizontal line indicates the median. + indicates the mean. ○ indicates outliers (greater than 1.5 times the interquartile range from the upper or lower quartile). * indicates significantly different from other treatment groups*



2.4.8.2 Number achieving sternal position

Time to reach sternal position is shown in Table 2.2. Due to the difference in the number of dogs reaching sternal position within 20 minutes of the end of anaesthesia following the different treatments, this data was re-categorised into whether dogs reached sternal position. Numbers achieving sternal position within 20 minutes of the end of anaesthesia for each treatment group are shown in Table 2.10. With achieving sternal position as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, propofol dose for induction and end tidal sevoflurane concentration. The following interaction terms were included: treatment group and treatment order, treatment group and propofol, treatment group and end tidal sevoflurane concentration, treatment order and propofol, treatment order and end tidal sevoflurane and propofol and end tidal sevoflurane. Patient was a random factor.

Overall, achieving sternal position was significantly affected by treatment group ($p = 0.033$). However, there were no significant differences between individual treatment groups. Following butorphanol, fewer dogs achieved sternal position compared to medetomidine, but this was not statistically significant ($p = 0.069$). There was no difference between alfentanil/atropine and medetomidine.

Final model summary

Model term	**Co-efficient**	***p* value**
Treatment group - M	*Reference*	
Treatment group - A	-1.273	0.306
Treatment group - B	1.568	0.069

Table 2.10. Table showing numbers of animals reaching sternal recumbency or standing within 20 minutes of the end of anaesthesia. A – alfentanil/atropine, B – butorphanol, M – medetomidine

	A	**B**	**M**
Achieve sternal position	14/15	7/15	12/14
Achieve standing position	13/15	4/15	11/14

2.4.8.3 Number achieving standing position

Time to reach standing position is shown in Table 2.2. Due to the difference in the number of dogs reaching standing position within 20 minutes of the end of anaesthesia following the different treatments, this data was re-categorised into whether dogs reached standing position. Numbers achieving standing position within 20 minutes of the end of anaesthesia for each treatment group are shown in Table 2.10. With achieving sternal position as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, propofol dose for induction and end tidal sevoflurane concentration. The following interaction terms were included: treatment group and treatment order, treatment group and propofol, treatment group and end tidal sevoflurane concentration, treatment order and propofol, treatment order and end tidal sevoflurane and propofol and end tidal sevoflurane. Patient was a random factor.

Achieving standing position was significantly affected by treatment group (p = 0.009). Following butorphanol, dogs were significantly less likely to achieve standing position compared to medetomidine (p = 0.018). There was no difference between alfentanil/atropine and medetomidine. Based on the coefficients, following alfentanil/atropine, dogs were more likely to reach standing. However, following butorphanol, dogs were less likely to reach standing.

Final model summary

Model term	**Co-efficient**	***p* value**
Treatment group - M	*Reference*	
Treatment group - A	-0.862	0.374
Treatment group - B	2.030	0.018

2.4.8.4 Recovery VAS

Mean recovery VAS score for each treatment is shown in Table 2.9 and Figure 2.9. With mean recovery VAS score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, propofol dose for induction and end tidal sevoflurane concentration. The following interaction terms were included in the model: treatment group and treatment order, treatment group and propofol, treatment group

and end tidal sevoflurane concentration, treatment order and propofol, treatment order and end tidal sevoflurane and propofol and end tidal sevoflurane. Patient was a random factor. Mean recovery VAS score was significantly affected by end tidal sevoflurane concentration *(p* = 0.003), independent of any other factor. As end tidal sevoflurane decreased, recovery score increased. Figure 2.10 shows the relationship between end tidal sevoflurane and recovery VAS score.

Final model summary

Model term	**Co-efficient**	***p* value**
End tidal sevoflurane	-50.448	0.003

Figure 2.9 - Boxplot showing mean recovery VAS score from both observers for each treatment group. A – alfentanil/atropine, B – butorphanol, M – medetomidine. The whiskers indicate the range in each group, the edge of the boxes indicate the interquartile range and the horizontal line indicates the median. + indicates the mean. ○ indicates outliers (greater than 1.5 times the interquartile range from the upper or lower quartile)

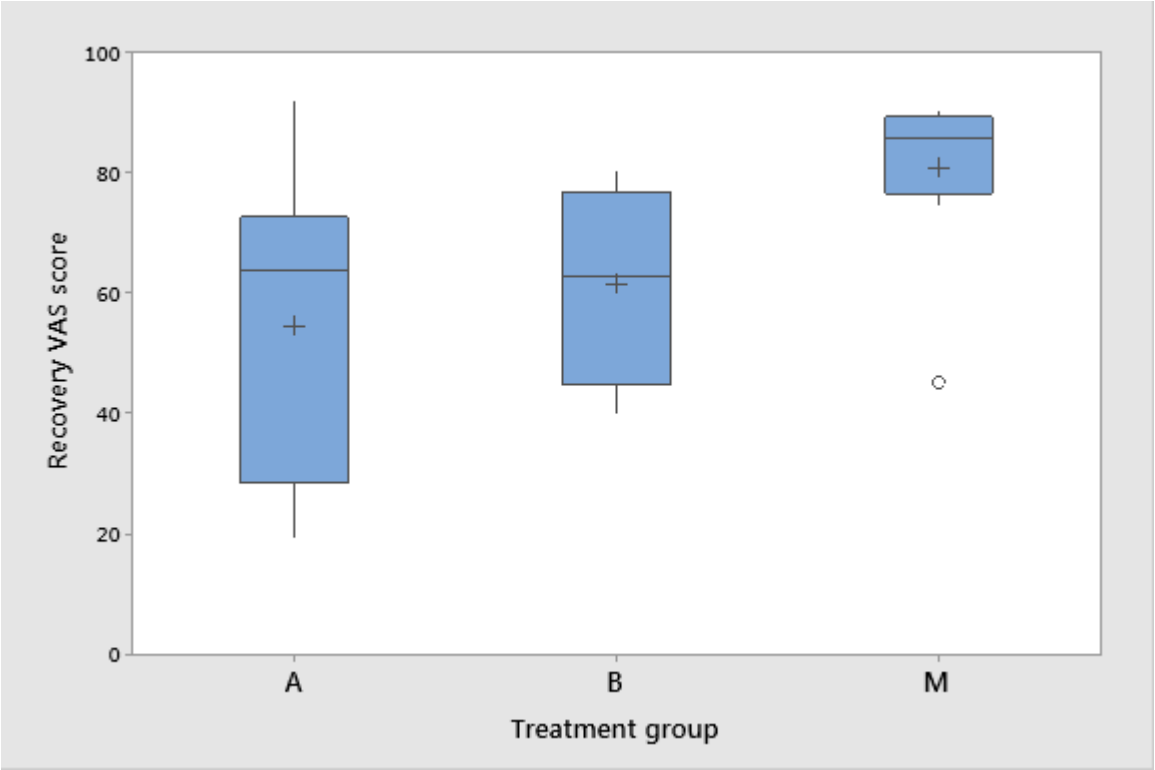
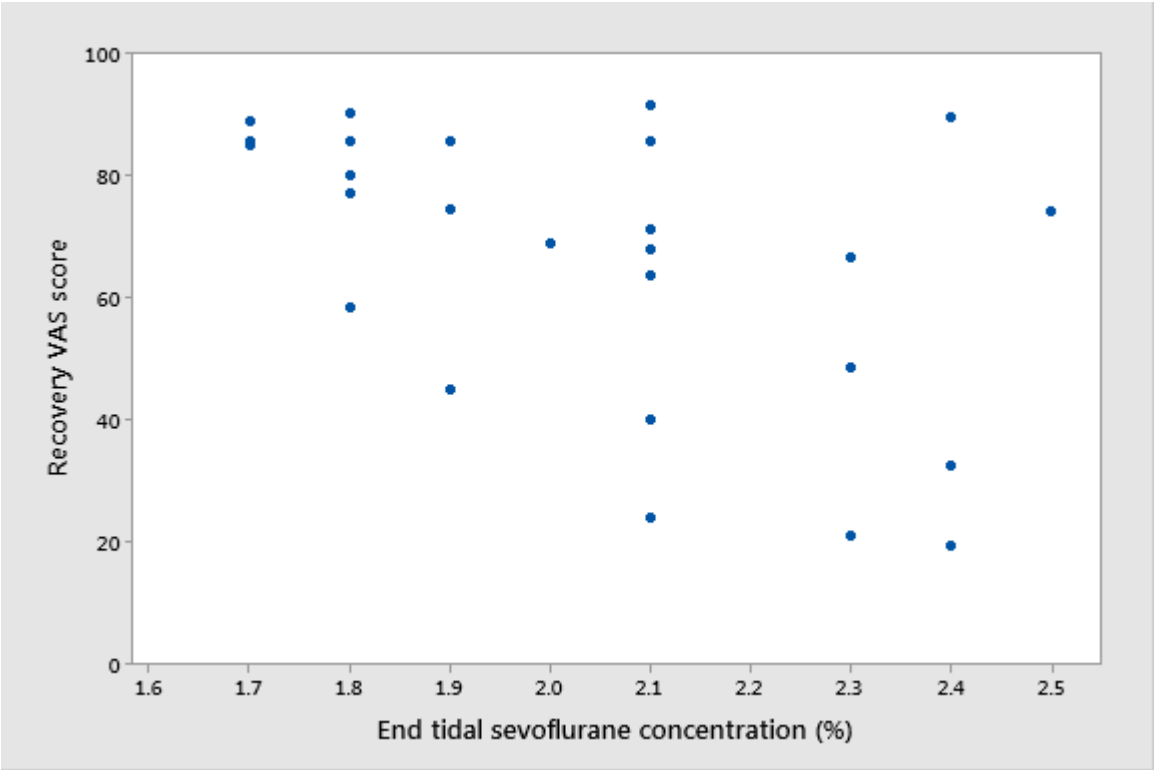


Figure 2.10 – Scatterplot showing end tidal sevoflurane concentration and mean recovery VAS score (n = 26)



2.4.8.5 Recovery behaviour score - paddling

Median paddling score from each observer for each treatment is shown in Table 2.11. Grouped data for paddling score for each observer is shown in Table 2.12. With grouped paddling score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, propofol dose for induction and end tidal sevoflurane concentration. The following interaction terms were included in the model: treatment group and treatment order, treatment group and propofol, treatment group and end tidal sevoflurane concentration, treatment order and propofol, treatment order and end tidal sevoflurane and propofol and end tidal sevoflurane. Patient was a random factor.

Paddling in recovery was significantly affected by end tidal sevoflurane concentration (p = 0.009). As end tidal sevoflurane increased, paddling score trended away from a score of 0. A score of 0 was no paddling and a score of 1 indicated paddling. Figure 2.11 shows the relationship between end tidal sevoflurane and paddling score.

Final model summary

Model term	**Co-efficient**	***p* value**
End tidal sevoflurane	-6.841	0.009

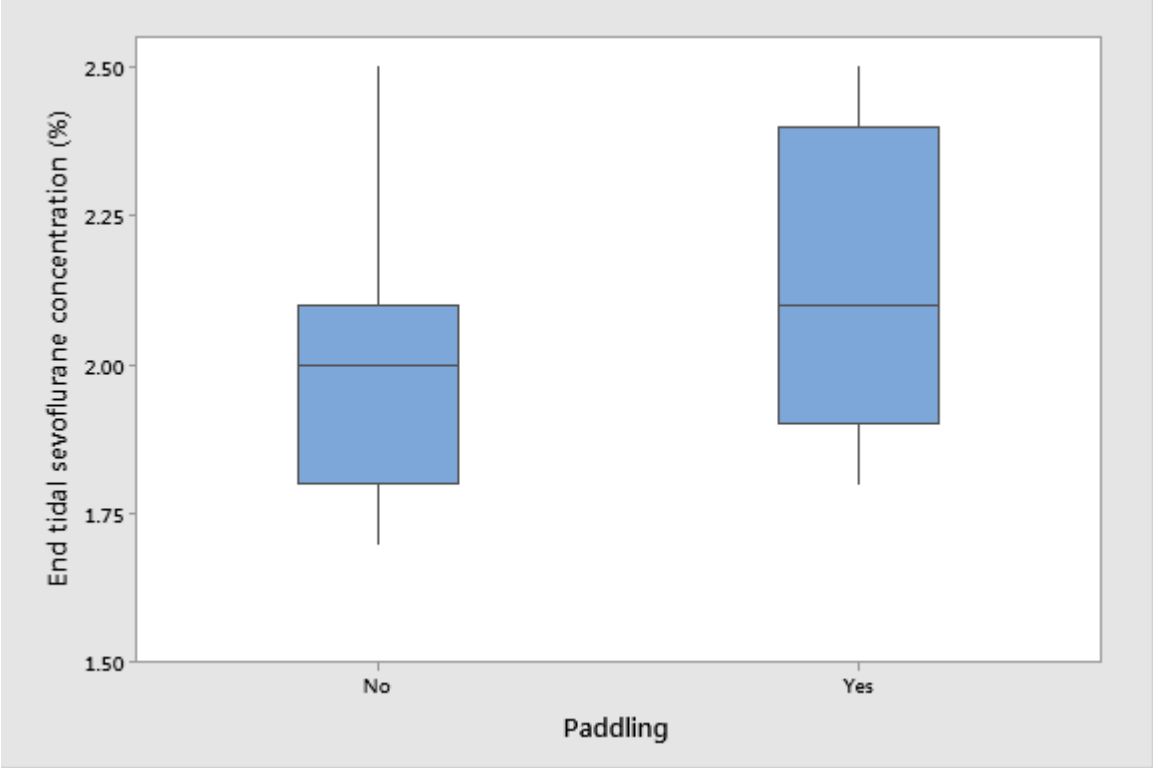
Table 2.11. Table showing median (range) recovery video scores from simple descriptive scales for each observer. A – alfentanil/atropine, B – butorphanol, M – medetomidine. n indicated number of videos analysed for each group

	Treatment	**n**	**Observer 1**	**Observer 2**
Paddling	A	13	0 (0-3)	0 (0-3)
	B	4	0 (0-2)	0 (0-2)
	M	10	0 (0-3)	0 (0-2)
Vocalisation	A	13	0 (0-1)	0 (0-1)
	B	4	0 (0-3)	0 (0-3)
	M	10	0 (0-3)	0 (0-2)
Restraint	A	13	1 (0-3)	0 (0-1)
	M	4	1 (0-2)	0 (0-1)
	B	10	0 (0-3)	0 (0-2)
Ataxia	A	13	2 (0-3)	1 (0-2)
	B	4	1 (0-3)	1 (0-2)
	M	10	1 (0-3)	0 (0-2)
Excitement	A	13	1 (0-3)	0 (0-2)
	B	4	1 (0-3)	0 (0-2)
	M	10	1 (0-3)	0 (0-2)

*Table 2.12 Table showing regrouped data for paddling score. Columns indicate frequency of paddling incidence following the different treatment groups for both observer*s

Treatment group	**Observer 1**		**Observer 2**	
	Yes	**No**	**Yes**	**No**
A	5	8	4	9
B	2	2	2	2
M	1	9	1	9

Figure 2.11 – Boxplot showing end tidal sevoflurane concentration (%) for grouped paddling recovery score. "No" indicates paddling was absent from recovery. "Yes" indicates paddling was present during recovery. The whiskers indicate the range in each category, the edge of the boxes indicate the interquartile range and the horizontal line indicates the median



2.4.8.6 Recovery behaviour score - vocalisation

Median vocalisation score from each observer for each treatment is shown in Table 2.11. Grouped data for vocalisation score for each observer is shown in Table 2.13. With grouped vocalisation score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, propofol dose for induction and end tidal sevoflurane concentration. The following interaction terms were included in the model: treatment group and treatment order, treatment group and propofol, treatment group and end tidal sevoflurane concentration, treatment order and propofol, treatment order and end tidal sevoflurane and propofol and end tidal sevoflurane. Patient was a random factor.

Vocalisation score was significantly affected by end tidal sevoflurane concentration (p = 0.009). As end tidal sevoflurane increased, vocalisation score trended away from a score of 0. A score of 0 was no vocalisation and a score of 1 indicated vocalisation. Figure 2.11 shows the relationship between end tidal sevoflurane concentration and vocalisation score.

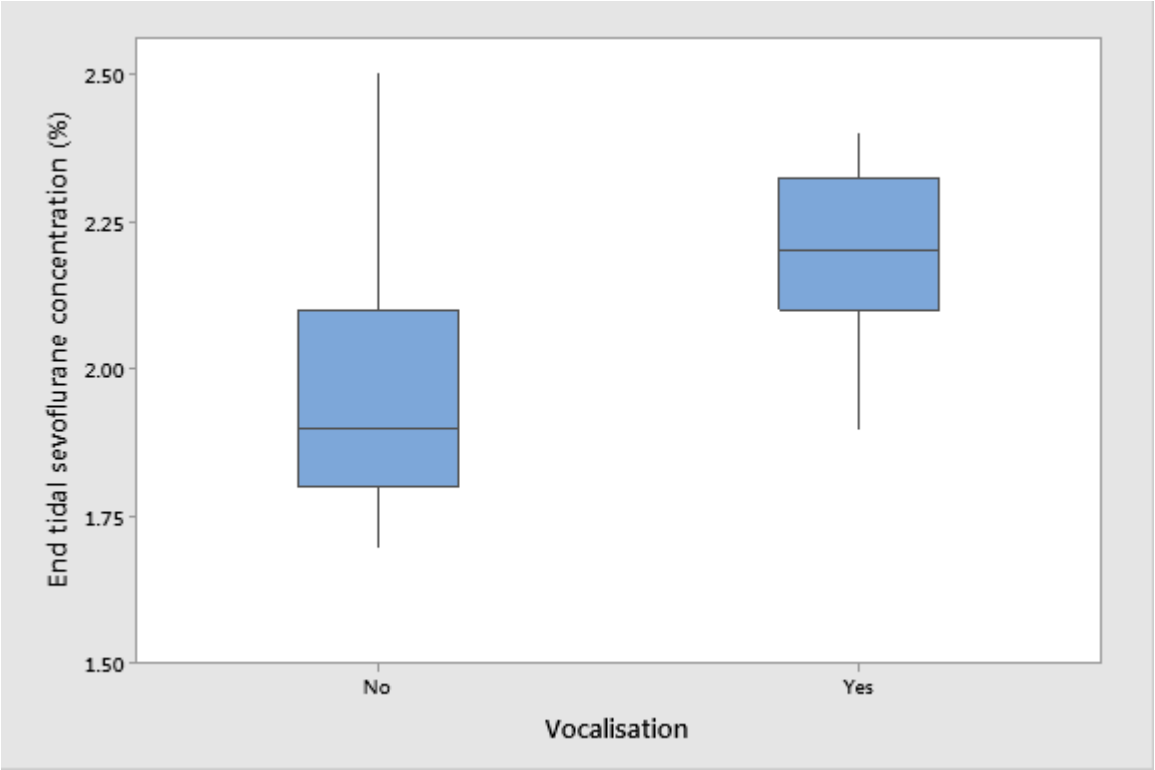
Final model summary

Model term	**Co-efficient**	***p* value**
End tidal sevoflurane	-7.032	0.009

Table 2.13 Table showing regrouped data for vocalisation score. Columns indicate frequency of vocalisation incidence following the different treatment groups for both observers

Treatment group	**Observer 1**		**Observer 2**	
	Yes	**No**	**Yes**	**No**
A	5	8	4	9
B	2	2	2	2
M	1	9	1	9

Figure 2.12 – Boxplot showing end tidal sevoflurane concentration (%) for grouped vocalisation recovery score. "No" indicates vocalisation was absent during recovery, "Yes" indicated vocalisation was present during recovery. The whiskers indicate the range in each category, the edge of the boxes indicate the interquartile range and the horizontal line indicates the median



2.4.8.7 Recovery behaviour score - restraint

Median restraint score for each treatment is shown in Table 2.11. Grouped data for restraint score for each observer is shown in Table 2.14. With grouped restraint score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, propofol dose for induction and end tidal sevoflurane concentration. The following interaction terms were included in the model: treatment group and treatment order, treatment group and propofol, treatment group and end tidal sevoflurane concentration, treatment order and propofol, treatment order and end tidal sevoflurane and propofol and end tidal sevoflurane. Patient was a random factor.

Restraint score was significantly affected by end tidal sevoflurane concentration (*p* = 0.003). As sevoflurane concentration increased, restraint score trended away from 0. A score of 0 was no restraint and a score of 1 indicated restraint. Figure 2.13 shows the relationship between end tidal sevoflurane concentration and restraint.

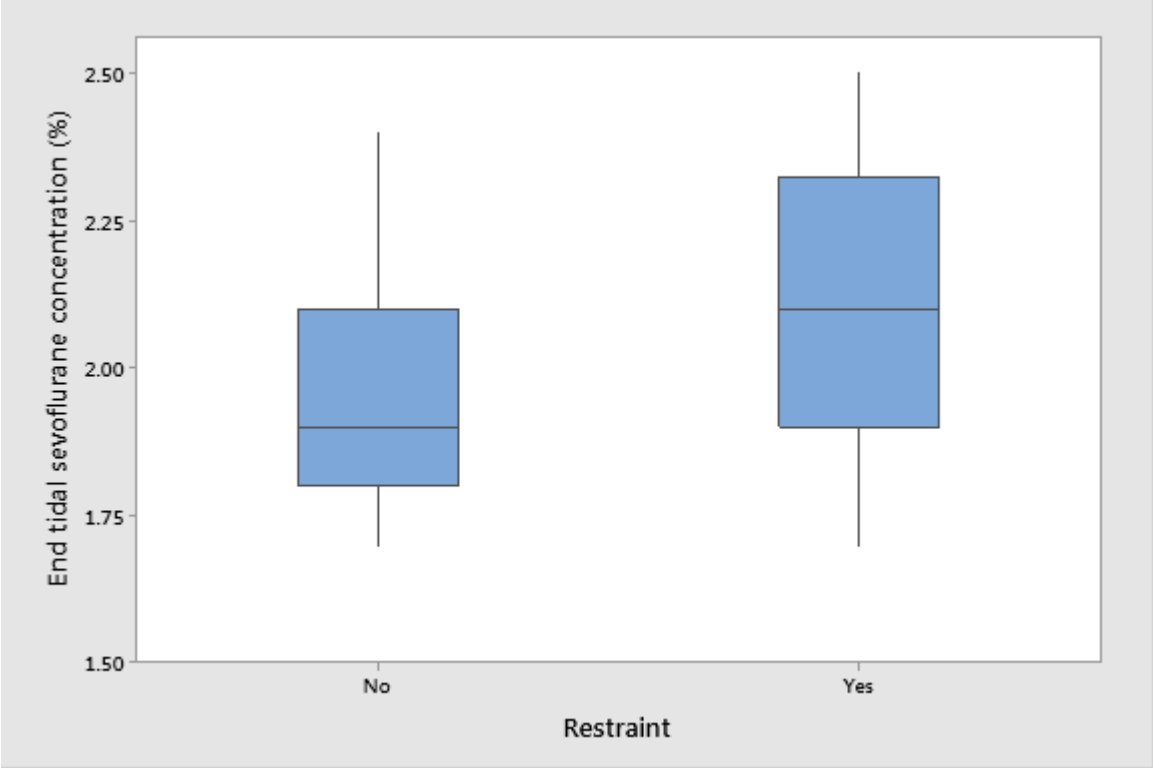
Final model summary

Model term	**Co-efficient**	***p* value**
End tidal sevoflurane	-6.993	0.003

Table 2.14 Table showing regrouped data for restraint score. Columns indicate frequency of restraint requirement following the different treatment groups for both observers

Treatment group	**Observer 1**		**Observer 2**	
	Yes	**No**	**Yes**	**No**
A	9	4	8	5
B	3	1	3	1
M	4	6	1	9

Figure 2.13 – Boxplot showing end tidal sevoflurane concentration (%) for grouped restraint recovery score. "No" indicates restraint wasn't required, "Yes" indicates restraint was required. The whiskers indicate the range in each category, the edge of the boxes indicate the interquartile range and the horizontal line indicates the median



2.4.8.8 Recovery behaviour score - ataxia

There was poor correlation between observers even in the grouped data (Table 2.3). Median ataxia score for each treatment is shown in Table 2.11. Grouped data for ataxia score for each observer is shown in table 2.15. With grouped ataxia score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, propofol dose for induction and end tidal sevoflurane concentration. The following interaction terms were included in the model: treatment group and treatment order, treatment group and propofol, treatment group and end tidal sevoflurane concentration, treatment order and propofol, treatment order and end tidal sevoflurane and propofol and end tidal sevoflurane. Patient was a random factor.

Ataxia score was not significantly affected by any factor.

2.4.8.9 Recovery behaviour score - smooth/excited

There was poor correlation between observers even in the grouped data (Table 2.3). Median smooth/excited score for each treatment is shown in Table 2.11. Grouped smooth/excited score for each observer is shown in Table 2.16. With grouped score (categorised as either smooth or excited) as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order, propofol dose for induction and end tidal sevoflurane concentration. Interaction terms between treatment group and treatment order, treatment group and propofol, treatment group and end tidal sevoflurane concentration, treatment order and propofol, treatment order and end tidal sevoflurane and propofol and end tidal sevoflurane. Patient was a random factor.

This score was significantly affected by end tidal sevoflurane concentration ($p = 0.006$). As end tidal sevoflurane increased, the score trended away from 0. A score of 0 indicated a smooth recovery and a score of 1 indicated an excited recovery. Figure 2.14 shows the relationship between end tidal sevoflurane and smooth/excited score.

Final model summary

Model term	**Co-efficient**	***p* value**
End tidal sevoflurane	-6.313	0.006

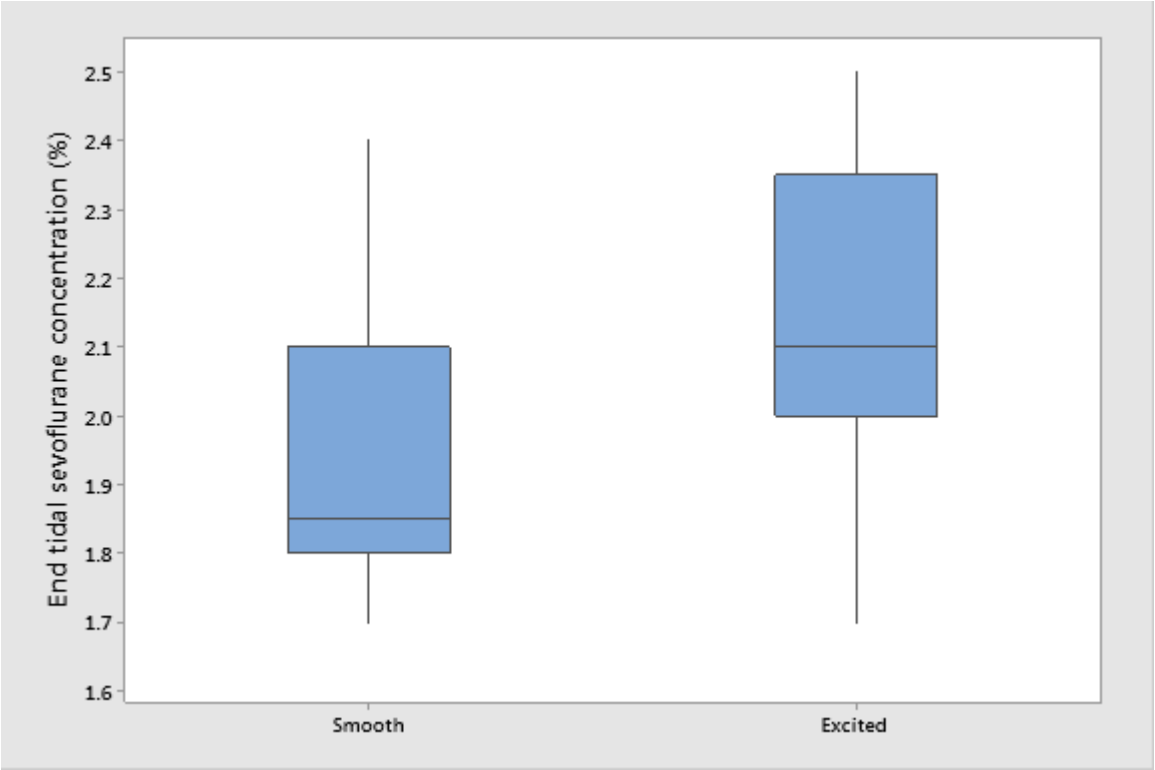
Table 2.15 Table showing regrouped data for ataxia score. Columns indicate frequency of ataxia incidence following the different treatment groups for both observers

Treatment group	**Observer 1**		**Observer 2**	
	Yes	**No**	**Yes**	**No**
A	11	2	10	3
B	3	1	3	1
M	8	2	3	7

Table 2.16 Table showing regrouped data for smooth/excited score. Columns indicate frequency of recovery description (smooth or excited recovery) following the different treatment groups for both observers

Treatment group	**Observer 1**		**Observer 2**	
	Smooth	**Excited**	**Smooth**	**Excited**
A	2	11	5	8
B	0	4	2	2
M	8	2	8	2

Figure 2.14 – Boxplot showing end tidal sevoflurane concentration (%) for grouped smooth/excited recovery score. "Smooth" indicates the recovery was classified as smooth, "Excited" indicates the recovery was classified as excited. The whiskers indicate the range in each category, the edge of the boxes indicate the interquartile range and the horizontal line indicates the median



2.4.9 Owner questionnaire results

All owner questionnaires (45 in total) were completed and returned. Median scores for the three treatment groups are shown in Table 2.17. For each question, owner scores were re-categorised into two groups (see 2.4.4 Re-categorisation of data section). This data is presented as frequency of reported behaviours following re-categorisation in Table 2.18.

2.4.9.1 Activity

Median scores and frequency of reported behaviours are presented in Table 2.17 and Table 2.18 respectively. With grouped activity score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order and an interaction term between treatment group and treatment order. Patient was a random factor. Treatment group significantly affected activity score ($p = 0.013$). With medetomidine as the reference group, a decrease in activity was reported significantly more frequently following butorphanol ($p = 0.007$) but not alfentanil/atropine ($p = 0.190$).

Final model summary

Model term	**Co-efficient**	***p* value**
Treatment group - M	*Reference*	
Treatment group - A	-1.531	0.190
Treatment group - B	-3.230	0.007

Table 2.17. Table showing median (range) scores for each treatment group from the owner questionnaire. A – alfentanil/atropine, B – butorphanol, M – medetomidine

	Treatment group A	**Treatment group B**	**Treatment group M**
Activity	2 (1-2)	1(1-3)	2 (1-3)
Appetite	2 (2-3)	2 (1-2)	2 (1-3)
Sleep	2 (2-3)	3 (2-3)	2 (2-3)
Attention	2 (1-2)	2 (1-3)	2 (1-2)

Table 2.18. Table showing frequency out of total group size of reported behaviours from owner questionnaires following categorisation into clinically relevant categories. A – alfentanil/atropine, B – butorphanol, M – medetomidine

	Treatment group A	**Treatment group B**	**Treatment group M**
Reduced activity	4/15	10/15	1/15
Reduced appetite	0/15	6/15	1/15
Increased sleep	6/15	12/15	5/15
Increased attention	1/15	1/15	1/15

2.4.9.2 Appetite

Median scores and frequency of reported behaviours are presented in Table 2.17 and Table 2.18 respectively. With grouped appetite score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order and an interaction term between treatment group and treatment order. Patient was a random factor. Reported appetite was not affected by any factor.

2.4.9.3 Sleep patterns

Median scores and frequency of reported behaviours are presented in Table 2.17 and Table 2.18 respectively. With grouped sleep score as the primary outcome, the following factors were considered in the model as fixed effects: treatment group, treatment order and an interaction term between treatment group and treatment order. Patient was a random factor. Treatment group significantly affected sleep score ($p = 0.039$). With medetomidine as the reference group, an increased in sleep pattern was reported significantly more frequently following butorphanol ($p = 0.016$) but not alfentanil/atropine ($p = 0.701$).

Final model summary

Model term	**Co-efficient**	***p* value**
Treatment group - M	*Reference*	
Treatment group - A	-0.299	0.701
Treatment group - B	-2.155	0.016

2.4.9.4 Attention seeking

Median scores and frequency of reported behaviours are presented in Table 2.17 and Table 2.18 respectively. When re-categorised into two groups, the scores for all dogs were the same. Therefore, it was not possible to analyse this data statistically.

2.4.9.5 Owner comments

There were two other sections on the owner recovery questionnaire. One section asked the owners about any comments they had on the recovery from anaesthesia and the final section asked the owners to rank the treatments from best to worst. Comments were only completed for 23/45 questionnaires from 11/15 owners. 9/15 owners gave rankings for the three

treatments. Butorphanol was ranked the “worst” treatment most frequently (7 out of 9 owners that ranked the treatments). Comments following butorphanol included “very slow to recover, very sleepy”, “more vocal”, “crying and disorientated” and “very groggy and lethargic”. Whereas comments following medetomidine included “no adverse effects from this anaesthetic” and “it didn't seem like he'd even had an anaesthetic”. Comments following alfentanil/atropine included “back to normal within a few hours” and “usual self at home”. Analysis was not performed on this data due to the incomplete data set and the variation in responses so the significance of these reported outcomes between the different premedication drugs cannot be assessed.

2.5 Discussion

2.5.1 Study population

All dogs undergoing at least four radiotherapy treatments were considered for enrolment in the study, however dogs were excluded based on the following exclusion criteria. These included dogs undergoing radiotherapy for brain tumours, dogs with systemic disease other than the tumour undergoing radiation or dogs whose temperament may make handling or restraining when unsedated stressful. Any dogs that received steroids as part of their radiotherapy treatment were also excluded. Dogs with brain tumours or other systemic disease were excluded because clinical signs, which may be a consequence of the underlying disease, may influence recovery characteristics. For example, a dog with a brain tumour may have altered mentation resulting in excessive sleep behaviours. Or a dog with an endocrinopathy may have increased appetite and thirst which would affect assessment of these behaviours in the recovery period. Dogs receiving steroids were also excluded due to the potential side effects of steroids. These include an increase in thirst and appetite (Ramsey, 2014) which could have influenced the owner assessment questionnaire.

The selection of dogs based on their temperament was a subjective assessment made by the primary investigator. This may have resulted in a selection-bias which may not reflect a representative cross section of the radiotherapy population. Dogs who were not stressed by handling or restraint may be more likely to have calm recoveries which may influence the variation in recovery characteristics seen. Selection of dogs based on these exclusion criteria was deemed necessary however on ethical and welfare grounds. Handling and restraining stressed or anxious animals without sedation to gain intravenous access may cause unnecessary distress to these patients. With stressed patients, normal clinical practice would involve intramuscular administration of sedative drugs prior to gaining intravenous access. Therefore, for this study, these patients were not enrolled.

The dogs enrolled were of varying ages, breeds, sizes and with different tumour types. This variation reflects the population of dogs that present for radiotherapy at this institution. Extrapolating the results from this study should be done with caution as this study group of animals will not be representative of a wider population of dogs.

2.5.2 Treatment group effects on anaesthetic requirement

One aim of premedication is to reduce the amount of other anaesthetic drugs that the patient requires (Rankin, 2015). Premedication can also aid handling of the patient and smooth induction of anaesthesia. The effects of the premedication may continue into the recovery period which may also smooth recovery. In this study, treatment group was the only significant factor that affected other anaesthetic drug requirements.

2.5.2.1 Propofol dose for intubation

The dose of propofol required for intubation was significantly affected by treatment group. However, propofol dose requirements for intubation were within clinically expected ranges in all dogs (1.7 - 5.6 mg/kg) (Morgan and Legge, 1989). Dogs receiving medetomidine required significantly less propofol compared to dogs receiving alfentanil/atropine or butorphanol. Based on clinical experience of these drugs this was not a surprising outcome. Previous studies have shown marked propofol sparing effects following alpha$_2$ agonists (Canfrán et al., 2016; Sano et al., 2003) Following 3 mcg/kg (100 mcg/m^2) medetomidine intramuscularly, the propofol dose required for intubation was 2.2 mg/kg (± 1.1) (Sano et al., 2003). This was a 64% reduction in propofol requirements compared to dogs that received no premedication. Canfrán et al. found dogs required 2.9 mg/kg propofol for intubation after 5 mcg/kg dexmedetomidine administered intramuscularly. Interestingly the dose used in our study (2 mcg/kg) was lower than these two studies but a similar propofol dose was required for induction. However, the route of administration and time elapsed between premedication and induction differed which may account for the differences seen in the studies.

Few studies have assessed alfentanil as a premedication agent as it is more commonly used as a co-induction agent or as an infusion for analgesia and anaesthetic-sparing effects (Auckburally et al., 2008; Hall & Chambers, 1987; Raisis et al., 2007). Following the same dose of alfentanil/atropine, one study reported a mean propofol dose for induction to be 1.94 mg/kg (Chambers, 1989). This is approximately half of the dose required in our study. One major difference in study protocol was the time elapsed between premedication and induction. In the study by Chambers, 30 seconds elapsed compared to 2 minutes in our study. Two minutes was chosen for our study to allow for the onset of all premedication drugs prior to

induction. This onset is likely to be different for the three different drugs and the peak sedative effect of alfentanil may have passed within these two minutes. In humans, onset of action is reported to be within 0.75 minutes with peak effect at 1.5 minutes (Scholz et al, 1996). Alfentanil has a rapid onset of action (Cookson 1984; Ilkiw et al. 1991; Hoke et al. 1996) and based on clinical experience, sedation following alfentanil/atropine is often seen within 30 seconds or so. Changing the study design, to allow for different time periods to elapse between premedication and induction for the different drugs, may have resulted in an induction at the peak effect of the premedication drug.

A previous study found a mean induction dose of propofol to be 4.2 mg/kg (±1.2) following 0.4 mg/kg butorphanol (McFadzean et al., 2017) which is a similar induction dose to the one found in this study.

2.5.2.2 End tidal sevoflurane concentration

Given the significant differences in propofol dose required for intubation following the different treatment groups, it is not surprising that there were significant differences in end tidal sevoflurane. Following medetomidine, dogs required significantly less sevoflurane to maintain anaesthesia. A reduction in inhalant agent required for anaesthesia following alpha$_2$ agonists has been demonstrated in other studies (Moran-Muñoz et al., 2014; Pascoe et al., 2006). Pascoe et al. showed a reduction in isoflurane requirements of 18% with a 0.5 mcg/kg/hr medetomidine infusion. At 3 mcg/kg/hr this reduction was increased to 59%. Moran-Muñoz reported a 46% sevoflurane reduction following 2 mcg/kg/hr dexmedetomidine infusion. There is limited published data on the minimum alveolar concentration (MAC) sparing effects of alfentanil but it is reported to reduce isoflurane requirements by up to 35% in cats (Ilkiw et al., 1997) and enflurane requirements by up to 70% in dogs (Hall et al., 1987). This study used a target-controlled infusion of alfentanil so comparison of doses between studies is difficult. However, this study reported a maximal isoflurane sparing effect at an alfentanil plasma concentration of 500 ng/ml.

2.5.2.3 Blinding of anaesthetist

One potential confounding factor to the propofol and sevoflurane requirements during anaesthesia is the lack of blinding to treatment groups. The anaesthetist who gave all premedication drugs and performed all anaesthetics was aware of the treatment group. The

anaesthetist was not blinded to the treatment groups to enable a smooth running of the treatment. Also, if any complications arose during the treatment, it was necessary for the anaesthetist to be aware of what drugs had been administered. Based on clinical experience, anticipation of propofol requirements may have resulted in administration of propofol at different rates following the different premedication drugs. Previous studies have shown that the rate of administration of induction agent can significantly affect the total dose required for intubation (Bigby et al., 2017; Raillard et al., 2018). Similarly, sevoflurane requirements may have been adjusted based on knowledge of the premedication group. However, as propofol and sevoflurane requirements were not primary outcomes of this study, when designing this study, we thought this lack of blinding may only have a limited effect on the main outcomes. However, the marked differences in propofol and end tidal sevoflurane between the groups may make it difficult to separate effects due to the treatment group and effects due to these variables. Induction quality assessed by a VAS, which was assessed by blinded observers, was significantly different between treatment groups. Following alfentanil/atropine, induction VAS was significantly lower than medetomidine and butorphanol. However, there was no difference between the treatment groups based on the SDS with 43/45 inductions being categorised as smooth. The interpretation of these conflicting results is difficult and may be complicated by the lack of blinding as described above. The unblinded anaesthetist may have influenced these scores by altering rate of administration of propofol which may have affected the quality of induction. For example, the anaesthetist may have inadvertently administered propofol more slowly following medetomidine which may have resulted in a smooth induction.

2.5.3 Immediate recovery

2.5.3.1 Time points during recovery

When assessing various time periods following recovery, the study design had a significant limiting factor on this data. Given the clinical nature of this trial there was a need for the study to have a minimal impact on the running of the normal radiotherapy schedule. Also, it was considered during the study design phase that most dogs would have fully recovered within 20 minutes of the end of anaesthesia. This, in hindsight, was not sufficiently long to fully assess speed of recovery in the hospital. Given that a relatively large number of dogs did not reach the sternal and standing stages of recovery within this timeframe, it was not possible to fully

analyse all this data.

Time to extubation was analysed as there was sufficient data to assess this (44/45 dogs were extubated within 20 minutes of the end of anaesthesia). Following all treatments, the mean time to extubation was approximately 8.3 minutes with a standard deviation of 4 minutes. From a clinical viewpoint, this would seem like a long recovery time considering the short duration of anaesthesia (a median time of 15 minutes). One explanation for this could be the lack of stimulation during the recovery period. During a normal recovery, the anaesthetist may interact with and stimulate the patient to speed up the process. The lack of stimulation in this study could account for these subjectively long recovery times. Other studies have had a standardised stimulation during recovery, such as an ear stroke every minute (Lehnus & Brearley, 2019), which may have resulted in faster times to extubation and more dogs within the study reaching standing within the 20-minute window.

Comparison of duration of recovery with other studies show a variety of outcomes. In a similar study, following an alfentanil-atropine premedication, the median time to sternal was 9 minutes (range 6-14) and walking was 10 minutes (range 9-15) which is comparable to the results from this study (Lehnus & Brearley, 2019). However, time to extubation was shorter compared to our results (3 minutes compared to 6.5 minutes). All time points in this study were measured from when the vaporiser was turned off. Other studies have reported similar recoveries with time to extubation ranging from 5.5 minutes to 10.5 minutes (Grint et al., 2010; Love et al., 2007; Polis et al., 2001) following different premedication drugs and inhalational agents. Variation in methodology between the studies may influence recovery times so making direct comparisons between the studies is difficult. In these studies, premedication drugs included acepromazine and pethidine (Love et al., 2007), acepromazine-buprenorphine or medetomidine-buprenorphine (Grint et al., 2010) and fentanyl-droperidol (Polis et al., 2001). Anaesthesia was maintained with halothane, isoflurane or sevoflurane. Duration of anaesthesia ranged from 60 to 90 minutes.

Studies assessing subsequent time periods following extubation, such as time from end of anaesthesia to sternal position or standing, report a range of durations from 11.4 minutes (Love et al., 2007) and 13 minutes (Grint et al., 2010) to reach sternal position. This is comparable to the animals that reached these time points in this study (median time to sternal

11.5 minutes). Again, numerous factors, as discussed above, influenced this outcome and determining specific factors that affected this is difficult.

The data from our study emphasises that the duration of the recovery period can be a significant part of the total anaesthetic time, even following short duration anaesthetics.

2.5.3.2 Effect of premedication on recovery times

Premedication was the only significant factor that affected recovery times. Dogs receiving alfentanil/atropine had a significantly shorter time to extubation compared to dogs receiving medetomidine. However, there were no significant differences between dogs receiving medetomidine and butorphanol and dogs receiving alfentanil/atropine and butorphanol. Considering the differences in propofol dose required for intubation and end tidal sevoflurane, it is interesting to note that following medetomidine, where dogs required significantly less propofol and end tidal sevoflurane concentrations, these dogs took the longest time to reach extubation. Conversely, dogs that received alfentanil/atropine required a significantly higher propofol dose and end tidal sevoflurane concentration but were quickest to extubation.

A proportion of dogs didn't reach the predetermined recovery end points, time to sternal position and standing, following certain drug treatments. However, when categorised into whether dogs reached these end points, analysis showed that the number of dogs reaching sternal position was significantly affected by treatment group alone. Treatment group had an overall significant effect but when the different treatments were compared, no individual treatment had a significant effect. When analysing the numbers of dogs reaching standing position, significantly fewer dogs receiving butorphanol reached standing compared to dogs receiving medetomidine or alfentanil/atropine.

Factors that could account for the difference in recovery times following the different premedication drugs could be their mechanism of action, duration of action and degree of sedation. The premedication drugs act at different sites to exert their sedative effects and consequently will cause sedation through different mechanisms. Alfentanil is an agonist at mu opioid receptors and is short acting (Ilkiw et al., 1991). Following 50 mcg/kg in cats, its analgesic onset was reported to be 40 seconds and lasted on average for 20 minutes. Following administration, sedation was apparent for 5 to 40 minutes. Butorphanol is a kappa opioid

receptor agonist and a mu opioid receptor agonist-antagonist and its antinociceptive effects are reported to last 45 minutes (Houghton et al., 1991). In this study they also subjectively assessed sedation which they reported to be mild with a peak sedation at 15 minutes following administration of 0.1 mg/kg butorphanol intravenously. Medetomidine is an alpha$_2$ adrenoreceptor agonist and its duration is dose dependent (Lamont et al., 2012). However, it can be antagonised by atipamezole and reversal of sedation is reported to occur within 3 – 7 minutes following intramuscular administration (Clarke & England, 1986).

Following medetomidine, time to extubation was longest. This could be due to the greater degree of sedation following medetomidine and the delayed onset of reversal of sedation from atipamezole. However, following premedication, sedation scores between the groups were not significantly different. Another factor could be that the degree of sedation caused by the premedication drug might be different during the recovery phase compared to the sedation assessment phase. Recovery times following alfentanil/atropine were quickest compared to the other premedication groups which may be due to the short duration of action. Interestingly, following butorphanol dogs had a similar time to extubation to dogs receiving medetomidine but significantly fewer dogs reached sternal or standing compared to the other groups. Only 4 dogs out of 15 reached standing within 20 minutes of the end of a short duration of anaesthesia (median time 15 minutes) which was an unexpected finding. This could be accounted by the long duration of action of butorphanol compared to the other treatment drugs. Limiting the duration of the recovery period to 20 minutes highlights that this duration of recovery was not anticipated during the study.

2.5.3.3 Factors affecting recovery quality

Speed of recovery is one consideration, but assessment of the quality and nature of recovery is also of importance. This was assessed using the video recovery scoring system. Overall recovery, assessed by a VAS, was not affected by treatment group but interestingly it was affected by end tidal sevoflurane concentration. Interactions between sevoflurane and other factors, such as treatment group, treatment order and propofol dose, were not significant which would suggest that sevoflurane, independent of these factors, affected the recovery VAS. End tidal sevoflurane concentration was significantly affected by treatment group however the interaction between end tidal sevoflurane and treatment group was not significant in this model. Lower end tidal sevoflurane concentrations were associated with higher recovery

quality scores (Figure 2.10). This outcome is surprising and hard to explain based on clinical experience and may highlight that there are other factors that may influence recovery quality that we did not assess statistically.

Recovery behaviours that were assessed were not significantly affected by treatment group but end tidal sevoflurane, independent of interactions, did significantly affect some behaviours. Incidence of paddling, vocalisation and restraint were all associated with a higher end tidal sevoflurane concentration (Figures 2.11, 2.12, 2.13). Recoveries tended to be classified as excited compared to smooth as end tidal sevoflurane increased (Figure 2.14). Again, these findings are unexpected based on clinical experience but they do correlate with the outcome for the recovery VAS score. A higher end tidal sevoflurane was associated with a lower recovery VAS, therefore a poorer recovery, and characteristics that might signify a poor recovery, such as paddling and vocalisation, were also more likely with a higher end tidal sevoflurane.

There may be several explanations to why end tidal sevoflurane alone had a significant effect on recovery outcomes. Firstly, there was a marked difference between numbers in each treatment group for the recovery outcomes. There were 13 in group A, 4 in group B and 10 in group M. This small sample size, particularly following butorphanol, may have made the data underpowered to detect a treatment group effect. When looking at the reported incidence of these behaviours following the different treatments (Table 2.12 - 2.16), there might be a trend towards these behaviours following alfentanil/atropine. End tidal sevoflurane was significantly affected by treatment group, with a significantly lower end tidal sevoflurane following medetomidine. The significant effect of end tidal sevoflurane on recovery may reflect a treatment group effect that wasn't statistically evident due to the small data set. Secondly, the interobserver variation in the individual scores may have masked other influences on the recovery outcomes.

2.5.3.4 Treatment order effects

The repeating block Latin square study design also allowed the assessment of the effect of repeated treatments on study outcomes. Interestingly, for outcomes, such as propofol dose, end tidal sevoflurane concentrations and time to extubation, treatment order didn't have a significant effect on outcomes. Based on the author's subjective clinical experience, dogs

often require less anaesthetic drug for each treatment as they progress through the treatment course. They often sedate more with the same dose of premedication, require less propofol for induction and have a faster recovery. Numerous factors may play a role but familiarity with the environment and personnel may be the most significant. Dogs are encouraged to have a positive experience during their treatment and this is reinforced with treats and praise. Demeanour score and sedation score were not affected by treatment order which shows that this clinical observation was not proved statistically in this study. There may be several explanations for this. Firstly, the models generated showed that treatment group was the only significant influence on propofol dose and end tidal sevoflurane. Standardising premedication may be required to fully assess the effect of repeat treatment on anaesthetic requirements. Secondly, dogs were included for their second, third and fourth radiation treatments and the effect of repeated treatments on anaesthetic drug requirements may only become apparent over a longer treatment course.

2.5.4 Video analysis as a recovery assessment tool

Recovery was assessed via video analysis by two observers for several reasons. Firstly, it enabled the video assessment to be blinded and to be performed at a convenient time. Secondly, subjectivity that may be associated with this type of assessment, may be reduced by combining the scores from two observers. Also, calculation of interobserver correlation and agreement also enables an assessment of the reliability of video recording as a tool to assess recovery.

Following the design of this study, a paper was published investigating the reliability of video recordings to assess recovery (Copeland et al., 2017). This study assessed both intra-observer variation and inter-observer variation in recovery assessment. Videos were assessed by inexperienced observers and experienced veterinary anaesthetists at two different time points. Recovery was assessed using a simple descriptive scale, visual analogue scale and a numerical rating scale for each recovery. Both intra- and inter- observer agreement was generally low which suggests that video assessment of recovery using these types of scoring system is not a reliable method. However, when the recoveries were categorised as either “good” or “bad” there was perfect agreement between observers. Overall, this paper concluded that assessing recovery using video analysis should be done with caution. In hindsight, a different design for

this study may have avoided the requirement for video analysis which may have allowed a more reliable way of assessing recovery.

In this study, interobserver correlation varied between the different videos and scoring systems but was generally mild to moderate. Correlation improved when the scores were grouped according to clinically relevant outcomes. However, interestingly, when categorised as "paddling - absent or present", there was still not perfect correlation between observers. The correlation between scores for demeanour and sedation was poor (0.40 and 0.40 respectively) even after grouping of scores. One factor that may have contributed to this interobserver variation in this study was the lack of observer training. The descriptors on the video assessment sheets were left to interpretation by the observers. A more detailed description of each behaviour may have reduced this variation. Moderate correlation between observers has also been reported in other studies (Copeland et al., 2017; Lehnus & Brearley, 2019) and the results from this study provide further evidence that video assessment of recovery should be used with caution. The use of VAS to assess induction and recovery demonstrated better correlation between observers in this study. This may be due to the inherent differences between SDS and VAS systems. Given the inter-observer variation in the recovery assessment, both scores and an observer term were put into the models for the SDS scores to account for this difference.

Interestingly, one study assessing inter-observer scores for sedation via video recordings found excellent correlation between observers (Wagner et al., 2017). The sedation scale used in their study was more complex and involved interaction with the patient. The use of simplistic scoring tools in this study may have not been sensitive enough to detected variations in the outcomes which may have impacted the interobserver agreement in this study.

Overall, the results from this study highlight one inherent difficulty in assessing recovery from anaesthesia in veterinary patients. There is an unavoidable subjectivity and variation when observers use scoring systems as an assessment tool. Self-reporting of the recovery experience, if it were possible, using a validated system would be the best way to assess the effect of different premedication drugs on recovery.

2.5.5 Owner assessment of recovery

2.5.5.1 Questionnaire design

Owners were asked to complete the recovery questionnaire the morning after the radiotherapy treatment and return on the subsequent treatment. The owners were blinded to which drug their dog had received. The questionnaire itself was designed to be simple and quick to complete to maximise compliance. All questionnaires were completed and returned which may suggest that this aim was achieved.

When designing the questionnaire, it was decided to look at four areas which may be altered during recovery. As the owners were asked to complete the questionnaire the morning after the treatment, the aim was to get an overview of these areas during the 24 hours following the treatment. There have been no validated owner questionnaires assessing their pet's recovery from anaesthesia. However other owner questionnaires, such as the Helsinki Chronic Pain Index (Hielm-Bjorkman et al., 2009) or the Vetmetrica HRQL tool (Reid et al., 2013), have been designed to gain information from the owner's perspective. However, these tools are related to the impact of pain or other health conditions on QoL and not the effect of anaesthesia. Therefore, we designed our own simple questionnaire. The areas that we considered most relevant to recovery based on clinical experience were activity levels, appetite, sleep patterns and attention seeking behaviour. Owners were asked to categorise these outcomes into three: less than normal, normal and more than normal. This broad categorisation gave quite a crude overview of recovery, but it enabled the owners to make a quick subjective assessment. It also provided data that could be easily grouped to allow statistical analysis.

2.5.5.2 Outcomes

Data from the owner questionnaires was combined into two groups to assess for clinically relevant changes in the 4 categories. A reduction in activity were reported significantly more frequently following butorphanol compared to alfentanil/atropine and medetomidine. An increase in the amount of sleep was reported significantly more frequently following butorphanol compared to alfentanil/atropine and medetomidine. Changes in attention seeking behaviour were not apparent between groups. The premedication drugs included in this study are all short onset and short duration drugs however the results highlight the potential effect

that anaesthetic agents can have on longer duration recovery. The desired effects of drugs, for example degree of sedation, may be of short duration but these drugs may have other characteristics that may be undesirable. These negative characteristics may persist for a longer duration. The significantly higher incidence of negative recovery characteristics seen following butorphanol, combined with the long immediate recovery times would suggest that it is not the idea drug of choice for short duration repeated anaesthetic events.

Butorphanol is a commonly used anaesthetic drug for premedication and sedation. The results from this study might suggest that butorphanol may be associated with negative recovery characteristics. However, extrapolation of these results to a wider population of dogs should be done with caution. This study involved a small population of dogs undergoing a very specific treatment protocol which is not comparable to other anaesthetic events. Further study is required to investigate the recovery characteristics of butorphanol in a larger population of dogs.

However, a recent study at this institution assessing owner perceptions of radiotherapy in their pets before and after treatment highlighted a significant difference in perception regarding repeated anaesthesia (Smith et al., 2019). Prior to the start of their pet's treatment, the median response to the statement "I do NOT have any concerns about the repeat anaesthetics during radiotherapy treatment" was "neutral" but following treatment the median response was "agree". 92% of respondents (45/49 owners) either "agreed" or "strongly agreed" with the statement following completion of radiotherapy. Based on owner perceptions, the majority of patient's had few problems with repeated anaesthetic events. This outcome from this study and the study by Smith et al. may suggest that significant differences are apparent following different premedication drugs but these differences may not cause owners to be worried or concerned about their animal. However, the anaesthetic protocols were not reported so individual drug effects cannot be determined. The data in the Smith et al. study was collected between 2012 and 2015. Based on the retrospective analysis (data gathered between 2015 and early 2016) performed prior to designing this study, 80% dogs received an alpha$_2$ agonist and the remaining 20% received alfentanil/atropine. No dogs received butorphanol. The anaesthetic records for the Smith et al. study period have not been analysed but based on our retrospective data, it may be likely that few dogs received butorphanol during this time period. In this current study, butorphanol was associated with a higher incidence of reported negative

side effects with no differences between the more commonly used medetomidine and alfentanil. Had butorphanol been used frequently during the Smith et al. study period, the owner perception outcomes for repeated anaesthetics may have been different. However, analysis of the anaesthetic records will need to be performed to investigate this further.

Another important consideration is that this was an assessment of recovery within the home environment where the animal may be less stressed and show more natural behaviour. Assessing recovery within the hospital environment may be confounded by numerous factors. The different environment, different people and different routine may all induce stress in the patient that may result in altered behaviours which may or may not be related to the recovery from anaesthesia (Lloyd, 2017). Few studies have investigated owner assessment of recovery from anaesthesia (Lehnus & Brearley, 2019) and it could be an interesting area for further investigation. Given the close nature of the owner-pet relationship, a poor recovery from anaesthesia could have a dramatic influence on the owner's perception of the procedure undertaken. Considering that the vast majority of animals that receive an anaesthetic and are reunited with their owner that same day, any steps that can be made to improve the speed and quality of recovery may have important benefits for both the animal and the owner.

2.5.6 Limitations

The overall outcomes of this study were limited by the lack of power. It was not possible to perform a power calculation due to Latin square study design so it is uncertain if this study was sufficiently powered to detected differences between the groups. Also, the effect of numerous dogs not reaching sternal or standing position had a severely limiting effect on the data collected during the immediate recovery period.

Several limitations have already been discussed in the relevant sections above. Recruitment of dogs for the study may have resulted in selection bias of dogs with a calm demeanour. This may have decreased the variation in recovery characteristics between dogs. Also, this may make the results from this study less applicable to a wider population of animals. The lack of blinding of the anaesthetist to the treatment groups may have influenced the propofol dose for induction and end tidal sevoflurane requirements. However, this lack of blinding was decided during the study design phase to be important for the safety of the anaesthetic. It also made the

study more practical for a clinical setting. An oversight was to administer the propofol at 2 minutes following administration of the premedication drug. As mentioned previously, this may have missed the peak sedation effects of the premedication drug and therefore the propofol and sevoflurane sparing effects. This may have influenced the outcomes of the anaesthetic variations and early recovery characteristics.

Considering the low numbers of dogs reaching sternal and standing position during the study period after certain treatments, capping the recovery period to 20 minutes had a large limiting effect on the data gathered. Changing the study design to either extend the recovery period, or to include a standardised stimulus may have resulted in a larger data set. The small numbers in the study may have masked potential differences between the different treatment groups. As discussed in some detail above, the use of video recording to assess recovery may have limited the outcomes from this study. Finally, the scoring systems used were self-designed and not validated. To limit this potential effect, the recovery scoring systems were adapted from previously published studies

Another area which may have influenced the outcome of this study was a control treatment group. In some radiotherapy centres, dogs are not premedicated and anaesthesia is induced with propofol and maintained with an inhalational agent (Farrelly & Mcentee, 2014; Farrelly & Shi, 2018). If a “no premedication” group had been included, greater differences in recovery times and quality may have been more apparent. However, this was decided during the study design phase and at the ethical review that this study should follow our normal clinical practice as much as possible so a “no premedication” group was not included.

2.5.7 Conclusions

The results from this study have demonstrated detectable differences in speed of immediate recovery and in quality of longer duration recovery following different premedication drugs. Notably, following butorphanol, dogs took significantly longer to recover immediately from anaesthesia. Negative recovery characteristics were reported by owners significantly more frequently following butorphanol. This study gives a glimpse into the longer-term effects that certain anaesthetic drugs may have on recovery that can be detected using a simple owner scoring system. Drugs that are presumed to have short duration sedative effects may exert

other undesirable effects for a longer time period.

Appendix 1 – Owner consent form

UNIVERSITY of GLASGOW

CONSENT FORM: Investigation of the effect of different sedatives on recovery from anaesthesia

DATE	OWNER NAME
CASE NUMBER	PATIENT NAME
BREED	AGE
GONADAL STATUS	REASON FOR RADIOTHERAPY
ANY OTHER RELEVANT INFORMATION	

When anaesthetizing dogs we typically give sedatives first to reduce anxiety.

We would like to try different sedatives in your pet to see which works best. If your pet is included in this study we will administer 3 different sedatives on 3 separate occasions and then compare how well your pet recovers after each. The sedatives that we plan to use are all commonly used in dogs undergoing anaesthesia in our hospital.

We are also interested in your assessment of how your dog has recovered once you leave the hospital and will ask you to fill in a short questionnaire after each of the 3 study anaesthetics.

We would be very grateful if you would consent to your pet being part of this study.

I understand what is written above and give my consent to my pet participating in this study.

Signed: ……..Date ……..

University of Glasgow Veterinary School
Bearsden Rd, Bearsden Glasgow G61 1QH

Appendix 2 – video assessment sheet

Video assessment sheet

Patient ID (letter)	Treatment number

Please circle the most appropriate number for each category

Video 1 - Demeanour score

1 - nervous/anxious - worried expression, pacing
2 - quiet - remaining still, will look when spoken to but not respond
3 - content - interested in surroundings and people, responsive and alert
4 - bouncy - wagging tail, jumping, vocalising with happy and excited noise

Video 2 - Sedation score

1 - not very sedated - able to stand, fully responsive
2 - slightly sedated - able to stand, mild drowsiness
3 - sedated - unable to stand, can maintain position in sternal, moderate drowsiness
4 - very sedated, unable to maintain position in sternal, unresponsive to stimuli

Video 3 - Induction score

1 - smooth - no paddling
2 - fair - mild and transient paddling, mild excitement
3 - poor - moderate and transient paddling, moderate excitement
4 - very poor - marked and prolonged paddling, severe excitement

Worst imaginable induction — Best imaginable induction

Video 4 - Recovery score (please circle Y or N - if Y then please circle appropriate amount)

Restraint	Y / N	if restraint was required was it	a little / a moderate amount / a lot
Vocalisation	Y / N	if vocalised was it	mild / moderate / severe
Ataxia	Y / N	if ataxic was it	mild / moderate / severe
Paddling	Y / N	if paddling was present was it	mild / moderate / severe
Smooth / Excited		if excited was it	mild / moderate / severe

Worst imaginable recovery — Best imaginable recovery

Appendix 3 – Owner assessment sheet

Date:

Client's name	Dog's name	Case number

As part of this study, investigating recovery from anaesthesia, we are interested in your assessment of your pet. Thank you for being willing to take part & for contributing to this project.

- Please fill in this questionnaire the morning after your dog's radiotherapy treatment
- There will be three questionnaires to complete, each corresponding to a different study anaesthetic
- It is important that the same person completes the questionnaire each time

Please circle the response that best fits the question.

❑ **Following treatment was your dog's activity level**

Less than normal Normal More than normal

❑ **Following treatment was your dog's appetite**

Less than normal Normal More than normal

❑ **Following treatment has your dog slept**

Less than normal Normal More than normal

❑ **Following treatment has your dog been attention-seeking**

Less than normal Normal More than normal

Do you have any other comments on your dog's recovery following this treatment? If this was your last treatment are you able to compare the recovery from the 3 anaesthetics and state which was best and which was worst?

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