



Comparison of induction and recovery characteristics in dogs following diazepam-ketamine or propofol administration

By

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Declaration

I, Jacques Ferreira, declare that this dissertation entitled, ‘Comparison of induction and recovery characteristics in dogs following diazepam-ketamine or propofol administration’, which I hereby submit for the degree [MSc (Veterinary Science)] at the University of Pretoria, is my own original work and has not been previously by me for a degree at this or any other tertiary institution.

Signature: _____
Jacques P. Ferreira

Date: _____

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List of abbreviations

ACP	Acepromazine
D	Diazepam
D/K	Diazepam/Ketamine
EEG	Electroencephalography
GABA	Gamma-Aminobutyric Acid
hrs	Hours
IQR	Interquartile range
i/m	Intramuscular
i/v	Intravenous
K	Ketamine
Kg	Kilograms
m	Metres
MAC	Minimum alveolar concentration
NMDA	N-methyl-D-aspartate
P	Propofol
PVC	Polyvinyl chloride
SDS	Simple descriptive scale
SPO ₂	Peripheral oxygen saturation of haemoglobin
TIVA	Total intravenous anaesthesia
μ	Mu
VAS	Visual analogue scale
VOC	Vaporiser out of circuit

DISSERTATION SUMMARY

**COMPARISON OF INDUCTION AND RECOVERY
CHARACTERISTICS IN DOGS FOLLOWING
DIAZEPAM-KETAMINE OR PROPOFOL ADMINISTRATION**

BY

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Degree: MSc (Veterinary Science)

Objective: To compare anaesthetic induction and recovery characteristics of diazepam-ketamine combination to propofol alone in dogs undergoing elective orchidectomy.

Experimental design: Prospective, randomised clinical trial.

Animal population: Thirty six healthy adult male dogs of various breeds weighing 5.5 ± 2.3 kg and aged 26 ± 13 months.

Materials and Methods: After demeanour scoring (simple descriptive scale; (SDS); the dogs were sedated with morphine (0.3mg/kg) and acepromazine (0.02mg/kg) intramuscularly. Forty minutes after administration, a premedication score (SDS) was allocated. Immediately after premedication had been scored, general anaesthesia was induced with either a combination of diazepam and ketamine (D/K) or propofol (P) intravenously to facilitate endotracheal intubation. Anaesthesia was maintained with isoflurane. Scores for the quality of induction, intubation and degree of myoclonus were allocated (SDS). Orchidectomy was performed in a standard way by a single experienced surgeon. Recovery from anaesthesia was scored (SDS). Times to extubation and standing were recorded. Data were analysed for statistically significant differences using the t-test for parametric data and the Wilcoxon Mann-Whitney test for non-parametric data. The Kappa Reliability and Kendall Tau tests were used to assess the degree of agreement between the scorers for the scored characteristics.

Results: There were no statistically significant differences between groups in age, weight, cage rest score, premedication score and duration of maintenance of anaesthesia. Group P was associated with a poorer quality of induction and more pronounced myoclonus; but had better quality of recovery and shorter recovery times compared to group D/K.

Conclusions: Diazepam-ketamine and propofol are associated with acceptable induction and recovery from anaesthesia. Propofol had inferior anaesthetic induction characteristics, but better and quicker recovery from anaesthesia compared to diazepam-ketamine in male dogs premedicated with morphine and acepromazine.

Chapter 1:

Introduction

Diazepam-ketamine and propofol have been used for induction of anaesthesia in healthy and cardiovascularly compromised dogs for years (Green *et al.* 1981, Hellyer *et al.* 1991, White *et al.* 2001, Fayyaz *et al.* 2009, Beteg *et al.* 2010, Henao-Guerrero and Ricc6 2014).

Induction of anaesthesia using diazepam-ketamine provides reliable dissociative anaesthesia facilitating endotracheal intubation in dogs (Wright 1982, Hellyer *et al.* 1991, White *et al.* 2001, Beteg *et al.* 2010). Maintenance of pharyngeal and laryngeal reflexes and hypersalivation are common characteristics of ketamine-based anaesthesia and have reportedly resulted in difficult intubations (White *et al.* 2001). Recovery from diazepam-ketamine is acceptable but delayed and is commonly associated with varying degrees of ataxia. Propofol, on the other hand, is associated with near perfect induction of anaesthesia and recovery from anaesthesia (Amengual *et al.* 2013)

A prospective clinical study comparing diazepam-ketamine to propofol alone will enable direct assessment of this ketamine-based anaesthetic combination against an induction agent associated with rapid and excitement-free induction, easy endotracheal intubation as well as rapid and calm recovery from anaesthesia (Watkins *et al.* 1987, Jim6nez *et al.* 2012, Amengual *et al.* 2013). In doing so; the characteristics of induction and recovery from diazepam-ketamine anaesthesia can be described more broadly.

Chapter 2

Literature on Drugs used in the present study

Acepromazine

Acepromazine (ACP) or 2-acetyl – 10 – (3 – dimethylaminopropyl) is a phenothiazine derivative that is widely used in veterinary practice for premedication prior to induction of general anaesthesia.

The primary neurotransmitter receptor to which the phenothiazines bind are dopaminergic and are mostly located in the basal ganglia and limbic system. The onset of action of ACP is relatively slow with tranquilisation occurring 15 minutes after intramuscular (i/m) injection and peaking at 30-45 minutes after administration (Thurmon *et al.* 1996). While onset of action is considered slow, the duration of action is relatively long (2–3hrs) (Thurmon *et al.* 1996).

The dose range of ACP in dogs is wide at 0.02 to 0.10 mg/kg (Pypendop and Verstegen 1994, Gomes *et al.* 2011). Acepromazine tranquilisation causes inhibition of conditioned avoidance behaviour and decreases voluntary motor activity (Pypendop and Verstegen 1994, Gomes *et al.* 2011).

In addition to its neurological effects; ACP's cardiovascular effects are widely described. The most notable cardiovascular effects of ACP include a decrease in mean arterial pressure and reduction in likelihood of ventricular arrhythmias (Tranquilli *et al.* 2007, Monteiro *et al.* 2009). The respiratory system does not appear to be affected significantly by ACP (Popovic *et al.* 1972; Tranquilli *et al.* 2007). In addition, ACP has an antiemetic effect and induces a state of poikilothermia in dogs (Thurmon *et al.* 1996, Smith *et al.* 2007).

Morphine

Morphine is an opioid with full affinity for the mu (μ)-opioid receptor in both the central as well as peripheral nervous system and is considered the “gold standard” in providing systemic antinociception today (Stanway *et al.* 2002, Gurney 2012).

Morphine’s dose range is wide and it provides dependable analgesia for moderately painful procedures from doses of 0.3 mg/kg upwards (Brodbelt *et al.* 1997a, Monteiro *et al.* 2009). Higher doses of morphine (≥ 0.5 mg/kg) have, in addition to analgesia, been consistently associated with sedation; but there is a risk of vagally-mediated bradycardia and respiratory depression at doses of 1mg/kg in conscious and anaesthetised dogs (Lucas *et al.* 2001, Tranquilli *et al.* 2007). Sedation may be augmented by administration of morphine in combination with acepromazine, with resultant reduction of the required dose of anaesthetic induction and maintenance drugs by as much as 63% (Ilkiw 1992, Brodbelt *et al.* 1997b).

Propofol

Propofol (2, 6-di-isopropylphenol) is a lipid soluble alkylphenol that induces rapid CNS depression through the enhancement of the inhibitory neurotransmitter, gamma-aminobutyric-acid (GABA) (Watkins *et al.* 1987).

Rapid induction may occur 20-30 seconds after intravenous (i/v) commencement of administration of propofol, while loss of muscle tone and reflexes is in accordance with the plane or stage of anaesthesia classification described by Guedel in 1937 with ether administration (Guedel 1937; Tranquilli *et al.* 2007, Hillman *et al.* 2009). Propofol bypasses the early stages of anaesthesia depth, that are often associated with involuntary clonic movements thereby

facilitating routine excitement-free anaesthetic inductions in up to 92.5% of cases (Davies 1991, Glowaski and Wetmore 1999, Tranquilli *et al.* 2007). Adverse induction behaviour characterised by limb paddling, muscle twitches and pain on injection has however been previously described in dogs to which propofol had been administered (Davies 1991, Smith *et al.* 1993).

Recovery from propofol is rapid, with full return to consciousness occurring 20 minutes after termination of bolus administration (Morey *et al.* 2006; Tranquilli *et al.* 2007). The quality of recovery from propofol TIVA is superior to inhalation maintenance of anaesthesia, although delayed recoveries have been reported in greyhounds (Robertson *et al.* 1992, Tsai *et al.* 2011). Return to consciousness is routinely free of excitement and ataxia but poor recoveries characterised by tremors, opisthotonus, excessive salivation and vomiting have been described during propofol anaesthesia (Robertson *et al.* 1992, Smith *et al.* 1993).

Propofol, at high doses, is associated with adverse effects that mostly affect cardiopulmonary functions. Cardiopulmonary depression characterised by dose-dependent hypotension, cyanosis and apnoea is commonly observed after rapid propofol administration, particularly at doses exceeding 3 mg/kg. (Ilkiw 1992, Smith *et al.* 1993, Bufalari *et al.* 1998, Tranquilli *et al.* 2007, Jiménez *et al.* 2012, Amengual *et al.* 2013, Hall and Clarke 2014). Respiratory depression characterised by neurological depression of ventilatory drive resulting in decreased tidal volume following high doses of propofol has also been reported in dogs (Robertson *et al.* 1992).

Ketamine

Ketamine is a dissociative general anaesthetic drug that causes dose-dependent unconsciousness and analgesia by antagonizing the *N*-methyl-*D*-aspartate (NMDA) receptor (Wright 1982, Tranquilli *et al.* 2007, Hall and Clarke 2014).

Ketamine, when administered alone at doses of 5-10 mg/kg intramuscularly, has occasionally been associated with adverse effects. The effects occur 5-10 minutes after administration and are characterised by: initial behavioural excitement, hypersalivation, maintenance of unguarded laryngeal and pharyngeal reflexes, myoclonus, tonic-clonic convulsions and noise phobias (Green *et al.* 1981, White *et al.* 2001, Jackson *et al.* 2004). Subsequent violent recoveries characterised by ataxia and convulsions have been described following ketamine anaesthesia administered intravenously at doses described above (Jackson *et al.* 2004, Tranquilli *et al.* 2007).

Ketamine has a direct negative inotropy on cardiac muscle but it may increase overall inotropy through indirect endogenous catecholamine release, decreased vagal tone and inhibition of neuronal uptake of catecholamines by sympathetic nerve endings (Kolata 1986, White *et al.* 2001). Ketamine causes negligible depression of the respiratory system and may actually have a stimulating effect on the respiratory centre and peripheral chemoreceptors (Soliman *et al.* 1975).

Diazepam

Diazepam is a non-water – soluble benzodiazepine, whose chemical formula is 7 – chloro – 1,3 – dihydro – 1 - methyl – phenyl – 2H – 1,4 benzodiazepine – 2- one (Tranquilli *et al.* 2011). The high lipid solubility characteristic affords it rapid distribution characteristics and rapid onset of muscle relaxation. This GABA agonist has negligible sedative effect in dogs but may instead

induce paradoxical excitement and dysphoria (Haskins *et al.* 1986, Tranquilli *et al.* 2007). When administered for treatment of noise phobia anxiety at doses of 0.5-2.0 mg/kg orally in dogs, diazepam has reportedly been associated with ataxia, paradoxical excitation and dose-dependent agitation (Herron *et al.* 2008).

Diazepam has minimal effects on the cardiovascular and respiratory systems at therapeutic doses (0.5-2 mg/kg) typified by minimal changes in heart rate, myocardial contractility, cardiac output and arterial blood pressure after i/v administration (Flacke *et al.* 1985, Haskins *et al.* 1986, Heniff *et al.* 1997, Tranquilli *et al.* 2007).

Metabolism of diazepam in the dog is reliant on adequate hepatic function for demethylation and hydroxylation that produces active metabolites (Schwartz *et al.* 1965). The active metabolites produced from diazepam have been associated with delayed recovery from anaesthesia in humans (Baird and Hailey 1972). Similarly, delayed recovery has been reported in dogs administered diazepam prior to induction of anaesthesia; however correlations with plasma metabolite levels have yet to be made (Baird and Hailey 1972, Smith *et al.* 1993).

Diazepam and Ketamine combination for induction of anaesthesia

The combination of diazepam and ketamine is a commonly described induction regimen for anaesthesia in healthy and certain cardiovascularly compromised dogs of various ages (Green *et al.* 1981, Haskins *et al.* 1986, Kolata 1986, Hellyer *et al.* 1991, White *et al.* 2001, Boutureira *et al.* 2011, Hazra *et al.* 2008, Fayyaz *et al.* 2009, Beteg *et al.* 2010). Co-administration of diazepam and ketamine at doses ranging from 0.2-0.5 mg/kg and 5-10 mg/kg respectively; has been associated with excitement-free induction of anaesthesia in dogs (Green *et al.* 1981, Hellyer *et al.* 1991, White *et al.* 2001). The combination is not considered the induction agent of choice

in respiratory compromised cases however, because of the maintenance of pharyngeal and laryngeal reflexes as well as an associated long onset of induction time (40-60 seconds) that might result in hypoxaemia for a long period before endotracheal intubation can be achieved (Hellyer *et al.* 1991, Henao-Guerrero and Ricc6 2014).

Recovery from diazepam-ketamine in dogs has been reported to be free of emergence excitation but ataxia is common (White *et al.* 2001, Beteg *et al.* 2010).

Diazepam-ketamine combination is not without complications, with arrhythmias in the form of ventricular premature contractions and a single case of pulmonary oedema having been reported (Boutureira *et al.* 2007).

Isoflurane

Isoflurane is an inhalation anaesthetic agent whose minimum alveolar concentration (MAC) in dogs is 1.31 %. It is widely used in veterinary practice for maintenance of anaesthesia (Steffey and Howland Jr 1977).

Isoflurane causes dose dependent depression of the cardiorespiratory system, typified by reduced cardiac output, blood pressure and tidal volume. Isoflurane causes increased cerebral blood flow and intracranial pressure (Keegan 2005). Metabolism of isoflurane is low as most of it is exhaled unchanged, with only 0.2% of the administered dose requiring metabolism in the liver (Keegan 2005).

Recovery from isoflurane maintained anaesthesia is rapid and time to standing may be as little as 10 minutes after termination of isoflurane administration (Robinson *et al.* 1999, Yang *et al.* 2006, Tsai *et al.* 2007).

Conclusions from literature review of drugs to be used in the present study

The literature review above justifies further investigation as partly explored in the present study regarding:

1. anaesthetic induction quality of diazepam and ketamine combination compared to propofol in dogs.
2. anaesthetic recovery from diazepam and ketamine combination compared to propofol in dogs.

Chapter 3

Aims and objectives

The aim of the study was to assess and compare anaesthetic effects of two commonly used induction protocols (diazepam-ketamine and propofol) in male dogs undergoing orchidectomy.

Specific objectives of the present study were:

1. Assessment of the anaesthetic induction quality for propofol and diazepam-ketamine in dogs.
2. Assessment of the anaesthetic recovery quality for propofol and diazepam-ketamine in dogs.

Hypotheses

The primary hypotheses were:

H₀: The quality of anaesthetic induction with propofol is similar to diazepam-ketamine in dogs.

H₁: The quality of anaesthetic induction with propofol is different from diazepam-ketamine in dogs.

The secondary hypotheses were:

H₁: The quality of recovery from anaesthetic induction with propofol is similar to diazepam-ketamine in dogs.

H₀: The quality of recovery from anaesthetic induction with propofol is different from diazepam-ketamine in dogs.

Benefits arising from the study

The present study provides information that will help veterinarians understand the expected effects when diazepam-ketamine or propofol are used for induction of anaesthesia in dogs.

Observations from the present study might also help minimise adverse effects associated with anaesthetic induction and recovery in anaesthetic procedures based on these regimens in dogs.

Chapter 4

Materials and Methods

Study Design

The study was approved prior to commencement by both the Research and Animal Ethics Committee of the University of Pretoria (V017-33).

Animals

Thirty six healthy male dogs with a mean age of were used in the study. In order to be included in the trial the dogs had to meet the following criteria:

- clinically healthy with no physical, biochemical or haematological abnormalities
- within the age range of 6 to 60 months.
- intact males with fully descended testes
- free of history of severe illness or overt testicular pathology
- good-natured with no history of aggression.

The owners of each dog had to concede consent through signing a comprehensive form (Addendum 1) prior to recruitment of their dog into the experimental trial.

Initial preparation of the dogs for the trial

Upon admittance each dog was weighed, assigned a number (e.g. dog 1) and had an identification collar fitted around its neck. Shortly after being placed in their allotted enclosures, the dogs underwent a clinical examination (24 hours prior to anaesthesia) to ensure they were

suitably healthy (Addendum 2). The clinical examination consisted of measurement of heart rate, respiratory rate, capillary refill time, mucous membrane colour and rectal temperature. Palpation of external lymph nodes and determination that both testes were present in the scrotum was also performed. After completion of the clinical exam, blood was drawn from the jugular vein using a 21 G hypodermic needle (Terumo, Terumo Medical) attached to a 3 mL syringe (Omnifix, B Braun). The sample was immediately divided into serum and ethylenediaminetetraacetic acid (EDTA) blood collection tubes (BD Vacutainer, BD). Serum creatinine and haematological evaluation was performed using a chemical analyser (Cobas Integra 400 Plus, Roche) and haematological analyser (ADVIA 2120 Haematology system, Siemens), respectively. If the observations from clinical examination, haematological and serum chemical analyses were within normal limits, the dog was included in the experimental trial. An anaesthetic regimen was then randomly assigned to the dog. Each dog was starved of food and water for 8 hours and 1 hour, respectively, prior to premedication.

Experimental Period

Each dog was placed in a quiet and warm enclosure for a minimum of 30 minutes to settle down prior to administration of premedication drugs. Once the 30-minute period had elapsed, the dog were allocated a habitus score between 0-3 (Table 1) by the primary investigator.

Table 1: Scoring system used for patient habitus during cage rest in dogs

Score	Sign Elicited
0	Severely anxious and/or aggressive, vocalising and body tremors
1	Anxious and vocalising, no body tremors
2	Anxious but responsive to auditory stimuli [‡]
3	Calm and responsive to auditory stimuli [‡]

[‡]= vocalising and hand clapping

Once the habitus had been scored, premedication drugs (acepromazine ACP (Neurotranq, Alfasan) at 0.02 mg/kg and morphine (morphine sulphate Fresenius PF, Fresenius Kabi) at 0.3mg/kg) were administered into the accessory gluteal muscle of the right leg. Each drug was administered separately after an aspiration attempt to ensure the needle was not placed into a vein. The dogs were then left in the same cage for a period of 40 minutes to allow the premedication drugs sufficient time for maximum sedation effect. Once the 40 minute waiting period had passed, the degree of sedation was scored (Table 2).

Table 2: Scoring system used for degree of sedation following premedication with acepromazine 0.02 mg/kg and morphine 0.3 mg/kg intramuscularly in dogs

Score	Sign Elicited
0	No change from pre-sedation behavior
1	Slight sedation, still able to walk
2	Ataxic and heavily sedated, able to walk [‡]
3	Very heavily sedated, unable to walk [‡]

[‡]= Dog walked from cage to preparation room approximately 2m in distance.

Table adapted from Amengual *et al.* 2013

During the 40 minute post-premedication period, the primary investigator and co-investigator prepared the equipment required for induction and maintenance of general anaesthesia. The extension set (Perfusor IV Extension, B.Braun) connecting the induction syringe and the patient's catheter was covered with 25 mm non-transparent adhesive plaster (Leukoplast, BSN Medical) to ensure blinding of the video-based quality of induction assessor to the induction agent. The induction agents were drawn up into a 10 mL syringe (Omnifix, B Braun) and placed in a syringe driver (Perfusor, B Braun).

Once the sedation score had been allocated, a 22 G indwelling cannula (Jelco, Smiths Medical) was placed percutaneously into the right cephalic vein of the dog. The cannula was secured using an adhesive plaster (Leukoplast, BSN Medical) following which it was flushed with 1 mL of sterile saline 0.9% drawn up into a 5 mL syringe (Omnifix, B Braun).

Thirty seconds prior to induction of general anaesthesia, a hand-held digital video recorder began recording the induction phase until the dog was successfully intubated and placed on the breathing system for maintenance of anaesthesia.

For induction of general anaesthesia, each dog was randomly assigned to an induction regimen of either propofol (Group P) or diazepam-ketamine (Group D/K) using spreadsheet randomization and sort functions (=RANDBETWEEN(1,36); Microsoft Excel 2007; Microsoft). This was performed prior to the patient being cage rested. Group P dogs were induced with an initial propofol (Propofol 1% Fresenius, Fresenius Kabi) dose of 2 mg/kg. Group D/K dogs were induced with an initial dose of a combination of diazepam (A-Lennon Diazepam 10mg/2mL, Pharmacare Ltd) and ketamine (Ketamine Fresenius 100mg/mL, Fresenius Kabi) of 0.375mg/kg and 5mg/kg respectively. Diazepam and ketamine were drawn up separately before being mixed into one 10 mL syringe and administered. The induction drugs were administered intravenously at the initial calculated bolus via a volumetric infusion pump system (Braun Perfusor, B. Braun) operated by the primary investigator. The bolus was administered over a 30-second period. After administration of the bolus, the catheter was flushed with 1 mL of sterile saline 0.9% by the co-investigator to ensure the complete bolus entered the bloodstream efficiently.

Thirty seconds after the administration of induction bolus of P or D/K had been terminated, the dogs were assessed for depth of anaesthesia. The testing of the lateral and medial palpebral reflex, menace reflex and muscle tone was performed solely by the co-investigator. The lateral and medial palpebral reflex was deemed absent if three palpations of the lateral and medial canthus of the eye failed to illicit a blink response. A menace reflex was performed and deemed absent if the slow movement of a finger toward the dog's eye did not elicit a blink response. Muscle tone was assessed by testing the ease of opening of the dog's mouth with the thumb and forefinger of the same hand.

If depth of anaesthesia was deemed insufficient (co-investigator evaluated) for endotracheal intubation, a follow-up bolus was administered. Group P dogs received a follow-up

bolus of 1mg/kg, while the Group D/K dogs received a follow-up bolus of 0.175mg/kg and 2.5mg/kg of diazepam and ketamine respectively, administered from the same syringe. All follow-up boli were administered over 30 seconds using the same volumetric infusion pump that had been used for the initial bolus.

Propofol and diazepam-ketamine follow-up boli were administered until an anaesthetic depth was adequate for tracheal intubation. The total doses of drugs and the number of follow up boli required for induction were recorded on the data capture sheet.

All tracheal intubations were performed by the co-investigator. During tracheal intubations, the dogs were positioned in sternal recumbency with the head supported by grasping the scruff of the neck and using gauze bandage looped behind the maxillary canine teeth. A laryngoscope (Welch Allyn) with adequate sized illuminated blade was placed rostral to the base of epiglottis and depressed ventrally to allow the rima glottis to be visualised. A polyvinyl chloride (PVC), disposable, single use, cuffed endotracheal tube (Intersurgical) of the appropriate size was selected based on each dog's weight and visual inspection of the rima glottis. The tip of the endotracheal tube was palpated to ensure it did not advance beyond the thoracic inlet. The endotracheal tube was secured with gauze bandage and the dogs immediately connected to the breathing system. The cuff of the endotracheal tube was inflated with room air to ensure gas did not leak past the cuff when positive pressure ventilation of 20 cmH₂O was applied to the breathing system. The time at the end of induction was recorded on the data capture sheet.

The quality of anaesthetic induction was scored based on three aspects. The first was the overall induction response of the dog with respect to whole body movements and presence of vocalisation. The greater the whole body movements and presence of vocalisation, the higher the

score and vice versa for a perfect induction with minimal overt body movements (Table 3). The second aspect was assessment of ease of intubation. A score of 0-3 (Table 3) was allocated where 0 was a perfect intubation and 3 was allocated if the dog did not allow intubation. Only the last attempt at intubation was scored. The third and final aspect was assessment of the presence and degree of myoclonus. A score of 0-3 (Table 3) was allocated based on the degree of the muscle twitches and rigidity observed.

Once intubation was successful, video recording was stopped. In addition to the score allocated by the primary investigator, retrospective (based on video recordings) scoring of the induction, intubation and degree of myoclonus was performed by a single specialist anaesthetist. Scores were allocated as per the SDS described in Table 3.

Table 3: Scoring systems used to categorise different aspects of anaesthetic induction, including the subjective quality of induction (Induction score), the ease of intubation (Intubation score) and the occurrence of adverse effects such as muscle twitching (Myoclonus score)

Score	Description
Induction score	
0	Calm transition with no paddling
1	Occasional slow paddling movements
2	Moderate sustained paddling movements
3	Marked paddling, struggling or vocalization
Intubation score	
0	Easy intubation
1	Mild coughing
2	Pronounced coughing
3	Swallowing, coughing and gagging
Myoclonus Score	
0	No twitching
1	Occasional mild muscle twitching
2	Moderate sustained muscle twitching
3	Severe muscle twitching with opisthotonus and/or extensor rigidity

[†] assessed from commencement of administration of induction protocol until initiation of isoflurane administration

Adapted from Amengual *et al.* 2013

Once the dogs had been induced and intubated, the endotracheal tube was connected to a modified Mapleson type- F breathing system (Infant T piece breathing system, Intersurgical) and

the dogs allowed to breathe spontaneously. The oxygen flow rate was calculated according the dog's minute volume requirements of 600mL/kg/min. The breathing system delivered isoflurane (Isofor, Safeline pharmaceuticals) in oxygen administered via an out-of-circuit (VOC) precision vaporiser (Tec 5, Vetequip) initially set at 2%.

The anaesthetised dogs were monitored continuously to ensure maintenance of normal physiological parameters and anaesthetic depth. The data that recorded was for purposes of monitoring vital physiological systems during the experimental trial are not of relevance to the present study and are not referred to any further.

A balanced crystalloid (Lactated Ringer's solution, Fresenius Kabi) was administered intraoperatively at a rate of 10 mL/ kg/ hr.

The dogs were surgically prepared for the orchidectomy and moved to a designated surgical theatre. Once in the surgical theatre, the dogs were placed in dorsal recumbency on an electrical heating blanket system (Hot Dog, Augustine Medical). The orchidectomy was performed by a specialist surgeon and once completed, all dogs were allowed to recover.

Once surgery was complete, isoflurane and oxygen administration was stopped and the dogs were allowed to recover. The duration of the surgical and recovery times were recorded. The recovery start time was recorded from termination of the isoflurane and oxygen administration. The dogs were moved to a designated recovery area and positioned in right lateral recumbency and covered with a blanket. All dogs were warmed using a forced air heating device (Bair Hugger[®], Arizant Healthcare Inc.) set to 37 °C.

Extubation was performed once the dog had regained the swallowing reflex. Once extubated, the quality of recovery from anaesthesia was scored on a 0-6 scale (Table 4). The recovery was scored by the primary investigator and an additional investigator present. Once the

recovery had been scored, carprofen (Rimadyl, Zoetis) 4.4 mg/kg was administered subcutaneously for post-operative analgesia.

Table 4: Scoring system used for quality of recovery[‡] from anaesthesia in dogs induced with either diazepam-ketamine or propofol and maintained on isoflurane

Category	Description
1	Early- Extubated, calm transition to alertness, coordinated movement, calm Late: Alert, coordinated movement, calm
2	Early – fairly calm transition, holds head up, no body movement attempted Late – Holds head up, no body movement
3	Early- Unremarkable transition, routine extubation, some incoordination, does not startle, generally quiet Late: Some uncoordinated movements, generally very quiet
4	Early- Unremarkable transition, routine extubation, limited muscle control, startles, may paddle or whine Late – Uncoordinated whole body movement, startles, vocalizes
5	Early- Struggling during transition, difficult extubation with chewing and coughing elicited, uncoordinated whole body movements, startles, vocalises Late – Uncoordinated whole body movements. Startles, vocalizes
6	Early – Violent transition, restraint required for extubation, emergence delirium, thrashing, cannot restrain easily Late – Emergence delirium, thrashing, cannot restrain easily

[‡] observed from termination of isoflurane anaesthesia onwards.

Table adapted from Jiménez *et al.* 2012

After complete recovery from anaesthesia, the dogs were taken outside the hospital building and allowed to move around freely. The dogs were observed for any signs of pain

(vocalisation and/or reluctance to urinate or defaecate) during this phase. The dogs were given unlimited access to water and food post operatively and kept in the hospital overnight for observation. The following day, a final clinical examination was performed by the primary investigator to ensure the wound was clean and sutures still in place. The dogs were discharged into the owners' care one day after surgery.

Statistical analysis

Sample size calculation determined that a minimum of 36 dogs split into two groups of 18 were required to achieve 81% power to detect difference of 1.0 between the null hypothesis mean difference of 0.0 and the actual mean difference of -1.0 at the 0.05 significance level (alpha).

Before statistical analysis, data were sub-divided into Group P and Group D/K so that the observations from the 2 groups could be compared. Data were tested for normality using histogram analyses.

Parametric data (age, weight, anaesthetic maintenance period, extubation time and time to standing) are presented as (mean \pm standard deviation) and were analysed for differences between groups using the t-test, while non-parametric data (all scores) are presented as median (range) and were analysed for differences using the Wilcoxon-Mann-Whitney test.

Agreement between the observers (primary investigator versus specialist anaesthetist regarding scores for induction, intubation and degree of myoclonus and primary investigator versus co-investigator regarding recovery scores) was tested using the Kappa reliability or the Kendall tau B tests. The Kappa reliability test results are categorised into the 6 different levels of association (Table 5). The Kappa reliability ranges from 0.00 to 1.00 with 0.00 having no agreement and 1.00 having complete agreement. Kendall tau B test measures the correlation

between two ordinal level variables ranging from 0.00 – 1.00, where 0.00 has no agreement and 1.00 has perfect agreement. The level of agreement is interpreted in the same manner as the Kappa reliability test (Table 5).

Table 5: Agreement and correlation measures for categorical data for the Kappa reliability and Kendall tau B tests

Kappa Statistic	Strength of Agreement
<0.00	Poor
0.0-0.2	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost Perfect

Landis and Koch 1977

Chapter 5

Results

There were no significant differences between Group P and D/K with regards to average age and weight (Table 6). Additionally, there were no significant differences with regards to cage rest score, sedation score and duration of anaesthetic maintenance (Table 6).

Induction scores were significantly different between the two groups ($P = 0.014$), with Group D/K having better induction scores depicted by shorter induction times and requirement of fewer follow-up boli to achieve endotracheal intubation (Table 6 and Figure 1). There was one dog in Group D/K that was an outlier (inferior score) on induction (Figure 1). No significant differences were observed with regards to intubation score

Table 6: Peri-trial observations on dogs presented for orchidectomy in which anaesthesia was induced with either diazepam-ketamine (Group D/K, $n = 18$) or propofol (Group P, $n = 18$) prior to maintenance with isoflurane

Observation	Group D/K	Group P
Age (months)	24 ± 14	26 ± 12
Weight (kg)	6.4 ± 2.1	4.9 ± 2.2
Cage rest score	2 (0-3)	2 (0-3)
Sedation score	1 (0-3)	1 (0-1)
Total induction dose (mg/kg) [↓]	D: 0.56 ± 1.18 K: 7.36 ± 0.14	P: 5.94(1.9-10)
Number of follow-up boli [‡]	1 (0-2)	3 (0-8)
Intubation score	2 (0-3)	2 (0-3)
Myoclonus score	0 (0-1)	1 (0-3)
Anaesthetic maintenance period (minutes) [Ⓜ]	31.0 ± 4.7	32.3 ± 8.8
Extubation time (minutes) [¥]	9.6 ± 3.7	9.7 ± 3.4
Time to standing (minutes) [¥]	19.0 ± 4.2 [*]	13.7 ± 3.7 [*]

Data expressed as mean and standard deviation or median and range where applicable

[↓]= Average induction dose to achieve intubation

[‡]= Average number of follow-up boluses required to achieve intubation

[Ⓜ]= Measured from commencement of isoflurane administration until termination of administration

[¥]= Time recorded from termination of isoflurane administration

D= diazepam

K= ketamine

P= propofol

^{*} = $P < 0.05$

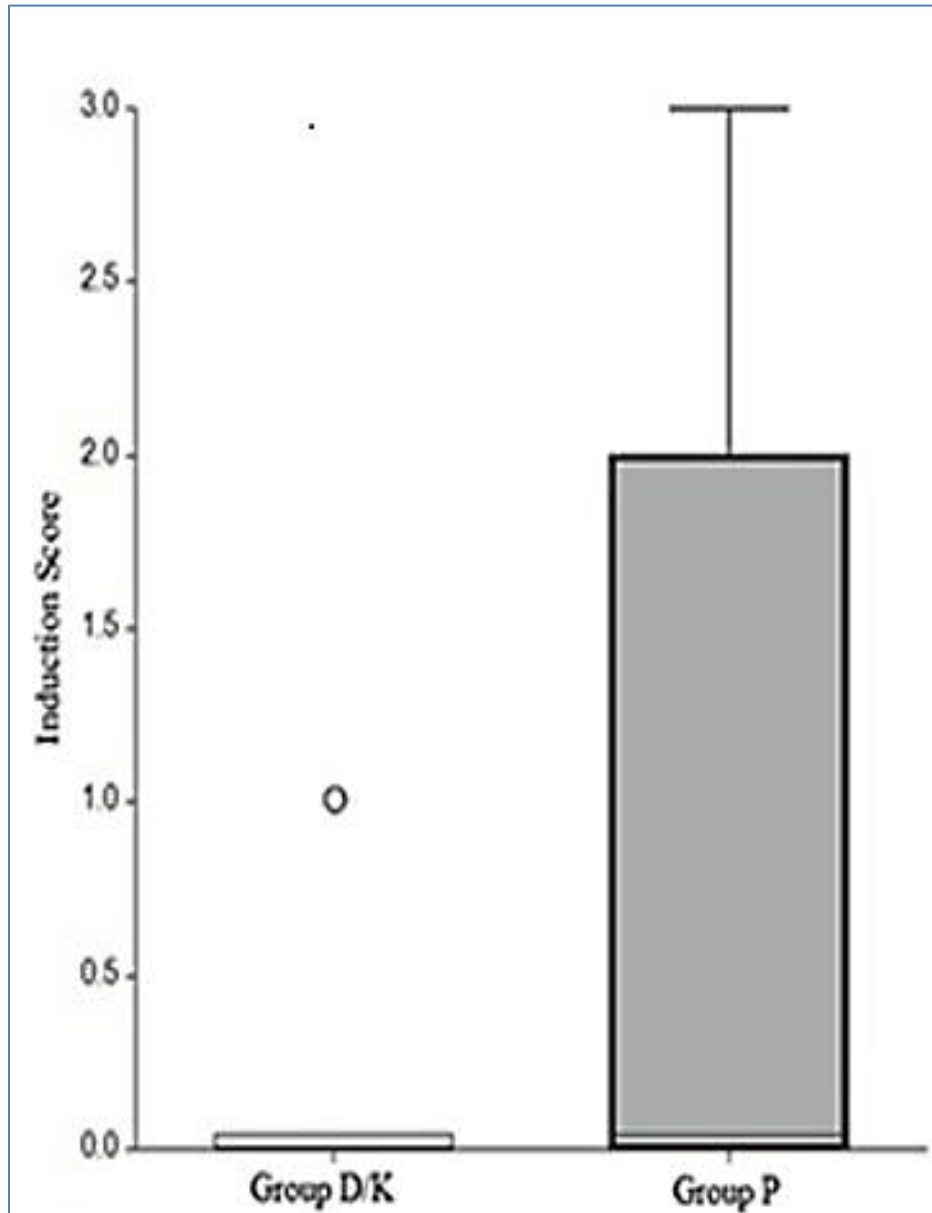


Figure 1: Comparison of induction scores (SDS) of dogs anaesthetised with diazepam-ketamine (Group D/K) or propofol (Group P) for orchidectomy. The score allocation ranged from 0 to 3, 0 representing the perfect induction (calm transition through stages of anaesthesia, no paddling) and 3 representing an undesired induction (Very poor transition through stages of anaesthesia, characterised by marked paddling and vocalisation requiring restraint). Boxes and whiskers represent median (IQR) and range, respectively.

Group P had a greater incidence of myoclonus than Group D/K ($p = 0.003$) with 9 dogs in Group P ($n = 18$) being observed to have myoclonus versus only one dog displaying muscle twitches in Group D/K.

Quality of recovery from anaesthesia was significantly different between the groups ($p = 0.001$). Group P had significantly better recoveries when compared to Group D/K. (Figure 2). Group D/K dogs had, in general, less than perfect recoveries from anaesthesia with 15 of the 18 dogs showing ataxia of varying degrees (7 of the 15 elicited paddling on recovery). One dog in Group P scored poorly on recovery.

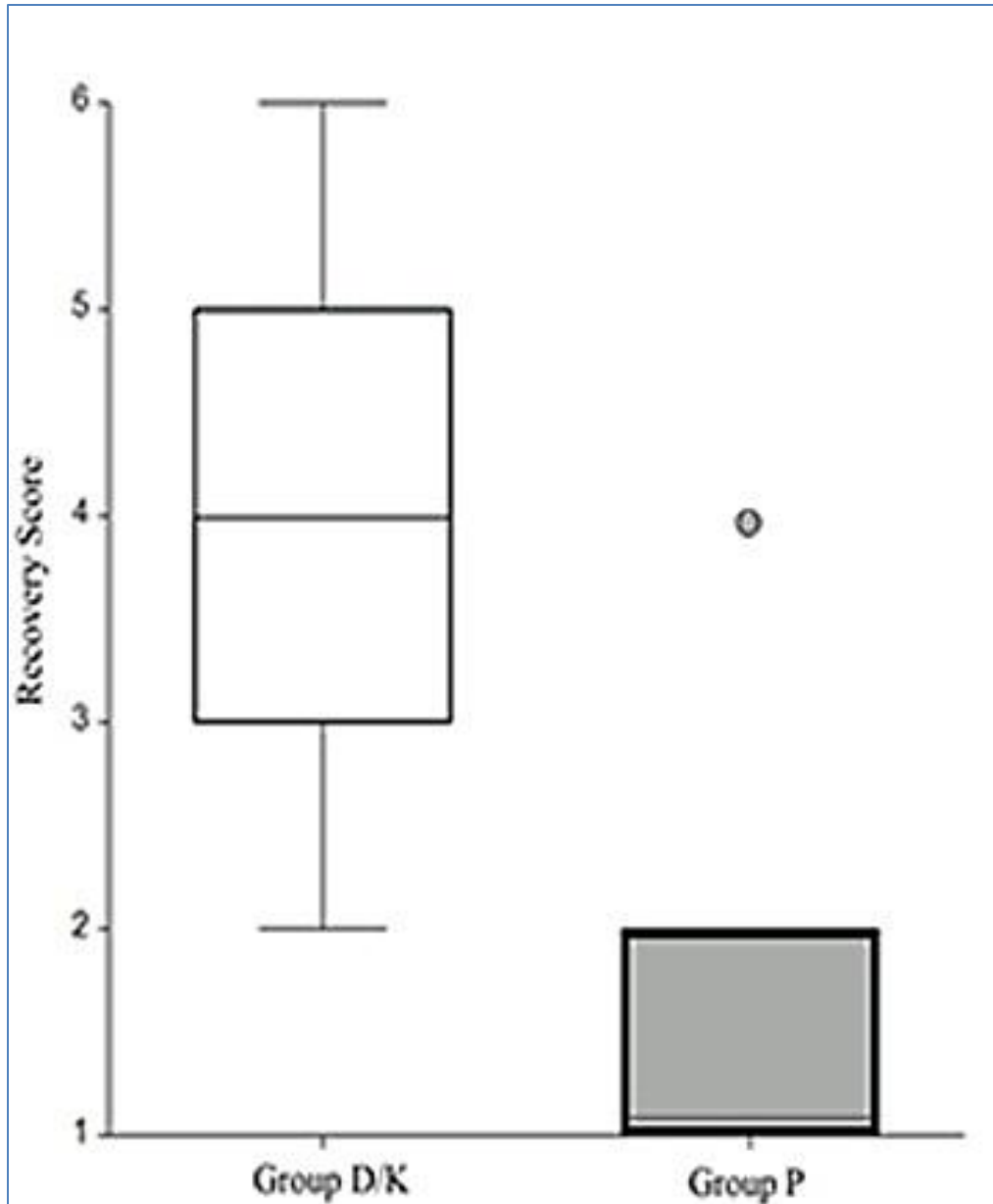


Figure 2: Comparison of recovery scores of dogs anaesthetised with diazepam-ketamine (Group D/K) or propofol (Group P) for orchidectomy. The scores ranged from 1-6, with 1 representing the perfect recovery (calm transition to alertness, coordinated movements) and 6 representing the worst possible recovery (Violent transition requiring restraint). The boxes and whiskers represent the median (IQR) and range respectively.

There was no statistically significant difference in time from termination of isoflurane to extubation of the patients in Group P and Group D/K, but time to standing was significantly shorter in Group P ($p = 0.035$) (Table 6).

The level of agreement between observers was moderate to substantial (0.40-0.75) in all categories of induction and recovery scoring barring the intubation scoring where Kendall's tau test indicated fair agreement (0.32).

Chapter 6

Discussion

The results of the study demonstrate that diazepam-ketamine combination is associated with better induction scores and less myoclonus during induction when compared propofol. The observations of the present study also demonstrate that recovery from anaesthesia is inferior and of a longer duration for diazepam-ketamine combination compared to propofol alone.

Induction of anaesthesia using diazepam-ketamine combination or propofol alone in dogs has been widely described (Green *et al.* 1981, Haskins *et al.* 1986, Kolata 1986, Hall and Chambers 1987, Weaver and Raptopoulos 1990, Hellyer *et al.* 1991, Zoran *et al.* 1993, Bufalari *et al.* 1998, White *et al.* 2001, Hazra *et al.* 2008, Hofmeister *et al.* 2008, Fayyaz *et al.* 2009, Beteg *et al.* 2010, Amengual *et al.* 2013, Henao-Guerrero and Ricc6 2014). Propofol induction of anaesthesia has been described as rapid and excitement-free, facilitating simple endotracheal intubation (Haskins *et al.* 1986). Diazepam-ketamine anaesthesia generally permits simple endotracheal intubation in dogs (Hellyer *et al.* 1991). Excitatory behaviour, persistent laryngeal muscle activity and hypersalivation have been previously described in dogs anaesthetised with diazepam-ketamine and have resulted in relatively slow (60-90 seconds) and challenging endotracheal intubations being reported (Hellyer *et al.* 1991, White *et al.* 2001). The observations of the present study demonstrate acceptable anaesthetic induction with both anaesthetic regimens, although statistically, diazepam-ketamine was superior to propofol, requiring less follow-up boli and shorter induction time to achieve endotracheal intubation.

The quality of induction observed during diazepam-ketamine in the present study is in line with current literature (Hellyer *et al.* 1991, White *et al.* 2001, Beteg *et al.* 2010). Ketamine administered alone in dogs has been associated with, maintenance of muscle tone, salivation and convulsions (Haskins *et al.* 1986). Similarly, diazepam administered alone in dogs fails to provide sedation, but instead may cause excitement (Haskins *et al.* 1986). The co-administration of both agents however; has been reported to produce excitement-free anaesthesia with adequate muscle relaxation to permit endotracheal intubation in dogs (Hellyer *et al.* 1991, White *et al.* 2001). Maintenance of pharyngeal and laryngeal reflexes is expected with ketamine anaesthesia and although difficult endotracheal intubations have been reported, adequate doses of both agents (diazepam: 0.5-1.0 mg/kg; ketamine: 5-10 mg/kg) as described in the present study facilitate short and almost excitement-free induction of general anaesthesia associated with simple endotracheal intubation (Haskins *et al.* 1986, White *et al.* 2001, Jackson *et al.* 2004).

The observation of inferior induction scores during propofol anaesthesia in the present study when compared to diazepam-ketamine anaesthesia is contrary to current literature (Hall and Chambers 1987, Bufalari *et al.* 1998, Hofmeister *et al.* 2008, Amengual *et al.* 2013). The present study's design involved the comparison of two commonly used clinical protocols, under clinical conditions. Statistically the quality of induction with propofol was inferior to diazepam-ketamine; however the mean induction scores obtained in the dogs anaesthetised with propofol were less than 1 (allocated to dogs exhibiting occasional paddling movements) and only 7 dogs failed to score perfectly during propofol induction of anaesthesia. As a result, even though the differences observed between the two anaesthetic regimens were statistically significant, clinically both anaesthetic regimes are acceptable.

Induction of anaesthesia with propofol in the present study was statistically longer and required more follow-up boli to achieve endotracheal intubation when compared diazepam-ketamine. Such observations are contrary to Watkins *et al.* (1987) and Amengual *et al.* (2013) who reported rapid induction of anaesthesia that facilitated easy endotracheal intubation. The apparently inferior induction characteristics associated with propofol in the present study may be attributed to: 1) the induction technique (induction dose and rate of administration), 2) the degree of preanaesthetic sedation achieved, 3) clinician inexperience, 4) the scoring system used and 5) the signalment of the dogs that took part in the trial.

Propofol dose range described for anaesthetic induction in dogs is wide and dependent on the type of preanaesthetic medication used (Jiménez *et al.* 2012, Robinson and Borer-Weir 2013). In a study performed by Robinson *et al.* (2013), dogs premedicated with 0.4 mg/kg midazolam were induced with an initial propofol dose of 1mg/kg titrated to effect. Jiménez *et al.* (2012) described induction doses of propofol ranging from 1.9- 6.9 mg/kg after premedication with 0.1 mg/kg methadone. In addition to the dose, the rate of propofol administration is also an important component to the associated quality of anaesthetic induction. The propofol infusion rate serves mainly to achieve adequate depth of anaesthesia while minimising the risk of development of adverse effects such as induction apnoea and cardiovascular depression. Slow administration of propofol induction doses over a period as long as 90 seconds has been recommended in an endeavour to minimise the severity of associated adverse effects while still attaining induction within a reasonable period (Ilkiw 1992, Smith *et al.* 1993, Glowaski and Wetmore 1999, Keates and Whitem 2012, Amengual *et al.* 2013). Inadequate depth of anaesthesia due to partial recovery from propofol prior to endotracheal intubation was a possible cause for the poor induction scores and prolonged induction times observed for propofol in the

present study. Propofol is associated with rapid onset of anaesthesia and subsequent recovery (Nolan and Reid 1993). Ribeiro *et al.* (2009) reported a period of 30 seconds to attainment of hypnosis following commencement of a propofol 1% infusion at 200 mL/hour to be an adequate waiting period before assessing anaesthetic depth and attempting intubation (Fresenius-Kabi 1998). Thus partial recovery from propofol anaesthesia prior to endotracheal intubation was unlikely to have contributed to the statistically worse scores obtained.

Adequate premedication provides anxiolysis, muscle relaxation, analgesia and decreases induction agent dose requirements (Grint *et al.* 2010). Preanaesthetic administration of acepromazine and morphine prior to induction of anaesthesia is common in dogs and produces less sedation than routinely observed with true sedatives such as the α_2 -adrenergic agonists (Heard *et al.* 1986, Pypendop and Verstegen 1994, Brodbelt *et al.* 1997a, Robertson *et al.* 2001, Smith *et al.* 2001, Love *et al.* 2007, Monteiro *et al.* 2009, Grint *et al.* 2010, Gomes *et al.* 2011, Henao-Guerrero and Ricc  2014). The dose range for both premedication agents is wide in dogs (Pypendop and Verstegen 1994, Monteiro *et al.* 2009, Gomes *et al.* 2011). The doses of ACP (0.02 mg/kg) and morphine (0.3 mg/kg) used in the present study were conservative and resulted in a small degree of sedation as demonstrated by the low sedation scores observed in both groups. Had there been more pronounced sedation; the induction dose as well as rate of administration used in the dogs anaesthetised with propofol, it would have most likely been adequate to facilitate easy endotracheal intubation as described by Amengual *et al.* (2013) and resulted in shorter and excitement-free anaesthetic inductions.

Timely assessment of depth of anaesthesia and subsequent intubation requires a moderate degree of experience and skill (Forrest *et al.* 2002). Attainment of intubation was considered the endpoint of the induction period in the present study. Assessment of the depth of anaesthesia and

endotracheal intubation were performed by a veterinary intern (co-investigator) who might have been less experienced for the tasks. An intern may be considered as having less experience and skill than a specialist anaesthetist. In addition, knowledge of upper airway across various breeds may be lacking. This could imply that the ability to perform rapid inductions and intubation is a challenge to inexperienced personnel, and as reported by Robinson and Borer-Weir (2013), could result in prolonged induction times with need for a higher number of follow-up boli of the induction agent in order to be able to successfully perform endotracheal intubation.

Signalment plays a role in the induction dose requirements in dogs (Czerniak 2001, Boveri *et al.* 2013). The dogs enrolled in the present study were all mature, male dogs less than 5 years old and weighing less than 8.4 kg. Gender-based differences in pharmacokinetics have been previously reported and attributed to differences in hepatic metabolism; renal elimination and non-metabolic processes in rats, rabbits and goats (Czerniak 2001). Hepatic metabolism is one of the primary mechanisms responsible for clearance of induction drugs such as propofol from the blood and in doing so lowering its plasma concentration. In a study performed by Hay Kraus *et al.* (2000); male dogs possessed greater hepatic concentration of the primary microsome responsible for propofol metabolism (CYP2B11) and resulted in faster biotransformation of propofol in male compared to female dogs. The exclusively male population in the present study may thus have implied a need for higher initial induction bolus of propofol than used in the present study. Propofol induction requirement in dogs is correlated to body condition score (Boveri *et al.* 2013). In a study performed by Boveri *et al.* (2013), the importance of calculating propofol dose requirements based on lean body mass of the dog and not on its general weight was emphasised. Body condition score was not assessed during the preanaesthetic clinical examination and was another limitation to the present study as it may have provided information

on the induction dose requirements for the dogs, further substantiating the inferior scores obtained.

One dog, induced with diazepam-ketamine, scored poorly on induction. This has been previously reported in dogs induced with diazepam-ketamine (White *et al.* 2001). White *et al.* (2001) attributed the poor induction to the dog's excitable nature and failure to respond to pre-anaesthetic sedation. The outlying dog in the present study was calm on habitus score, but failure to achieve successful pre-anaesthetic sedation may have contributed to the poor score observed. Diazepam-ketamine and propofol have been reported to cause myoclonus during induction of anaesthesia in dogs (Boscan *et al.* 2005, Hofmeister *et al.* 2008, Beteg *et al.* 2010, Amengual *et al.* 2013). Traditionally ketamine has been associated with pronounced myoclonus and propofol associated more commonly with muscle twitches (Hellyer *et al.* 1991, Amengual *et al.* 2013). Clinically myoclonus and muscle twitches can be difficult to distinguish and thus were both scored as myoclonus of varying degrees in the present study (Bagley 1992). Myoclonus was observed in dogs from both groups. The observation of propofol causing worse myoclonus than diazepam-ketamine combination is in line with a study performed by Mair *et al.* (2009) but contrary to observations by Musk *et al.* (2005). The justification for the apparent increased incidence in the Mair *et al.* (2009) study when compared to Musk *et al.* (2005); were the slow rate of propofol administration and increased vigilance of the induction period for specific signs of myoclonus. The same may be said for the present study, where a specific scoring system was used to assess myoclonus. The lower incidence of myoclonus with diazepam-ketamine was in contrast to studies by Hellyer *et al.* (1991) and Beteg *et al.* (2010) where varying degrees of myoclonus after induction with diazepam-ketamine were common findings. A higher dose of diazepam ($0.55 \text{ mg/kg} \pm 0.14$) was used in the present study when compared to the doses used in

the Hellyer *et al.* (1991) and Beteg *et al.* 2010 studies of 0.28 mg/kg and 0.25 mg/kg, respectively. These high doses of diazepam used in the present study may have ameliorated the myoclonus that is often associated with ketamine inductions (Beteg *et al.* 2010). Another reason for the lower incidence of myoclonus with diazepam-ketamine combination in the present study might be administration of preanaesthetic sedation. The present study employed pre-anaesthetic sedation, while Hellyer *et al.* (1991) and Beteg *et al.* (2010) studies did not. The ACP administered pre-anaesthetically may have aided muscle relaxation and prevented myoclonus from manifesting (Tranquilli *et al.* 2011).

Recovery from anaesthetic induction using propofol was statistically superior and shorter when compared to diazepam-ketamine. Propofol has been widely associated with acceptable recoveries and the observations of the present study further support these previous reports (Smith *et al.* 1993, Bufalari *et al.* 1998, Glowaski and Wetmore 1999, Tsai *et al.* 2007, Suarez *et al.* 2012, Amengual *et al.* 2013). Propofol recovery has been described as calm with rapid return to consciousness that is free of ataxia (Zoran *et al.* 1993, Tsai *et al.* 2007, Jiménez *et al.* 2012). This was exemplified by one of the dogs that recovered perfectly (recovery score 1) even after requiring a total propofol dose of as high as 10 mg/kg to achieve endotracheal intubation. On the other hand, one dog induced with propofol scored poorly on recovery (recovery score 4): displaying myoclonus, prolonged inability to maintain sternal recumbency and vocalisation. Propofol has been previously associated with myoclonus, paddling and opisthotonus during the recovery period (Davies 1991, Robertson *et al.* 1992), but not with vocalisation.

Dogs induced with diazepam-ketamine were associated with statistically poor and delayed recoveries when compared to propofol. Clinically however, the quality of recovery from anaesthesia was acceptable for both agents. A median score of 4 (characterised by unremarkable

return to consciousness, routine extubation, occasional paddling and vocalisation) was observed during recovery from diazepam-ketamine in the present study. Such quality of recovery in a clinical setting is considered acceptable as no physical restraint was required and most dogs were able to stand after a relatively short period of 19 ± 4.24 minutes. A study performed by Clarke *et al.* (2001) reported good recovery from anaesthesia in greyhounds induced with diazepam-ketamine. Subjectively poorer recoveries in the present study when compared to Clarke *et al.* (2001) may be attributed to the difference in duration of anaesthetic maintenance between the two studies. The present study observed a relatively short duration of anaesthetic maintenance of 31.3 ± 8.8 minutes. The study performed by Clarke *et al.* (2001) was comparatively longer with an average duration of anaesthetic maintenance of 103 ± 43.8 minutes. The difference in duration of the anaesthetic maintenance period significantly affects the plasma concentrations of diazepam-ketamine present during the recovery period. The half-life of ketamine and diazepam is 61 minutes and 30 minutes, respectively (Greene *et al.* 1992, KuKanich and Naus 2012). The extended period of anaesthesia in the White *et al.* (2001) study may have provided sufficient time for the diazepam-ketamine plasma concentration to be decreased by metabolism and redistribution, lessening the induction agents effects on the duration of the recovery period (Jiménez *et al.* 2012).

The subjective scoring systems incorporated in the present study successfully differentiated the quality of induction and recovery obtainable from the assessed anaesthetic regimens with a moderate to good level of agreement between different observers achieved. The simple descriptive scale (SDS) scoring systems used to score induction and recovery from anaesthesia have been previously described in literature but have not been validated (Jiménez *et al.* 2012, Amengual *et al.* 2013). Amengual *et al.* (2013) first described the induction SDS used

in the present study in which the quality of induction obtainable from propofol and alfaxalone in dogs were compared. Jiménez *et al.* (2012) first described recovery SDS used in the present study in which recovery from propofol and alfaxalone anaesthesia in dogs were compared. The validity of the SDS scores used in the Jiménez *et al.* (2012) study was recently questioned by Ferchichi *et al.* (2013). Ferchichi *et al.* (2013) questioned the methodology of associating induction and recovery characteristics to a single agent, without confirming adequate plasma concentrations of the induction agent/s. During induction in particular; Ferchichi *et al.* (2013) questioned the strength of comparing induction scores from two induction agents where administrations of the agents were not at equipotent doses. Concern was also raised when remarking on the quality of anaesthetic recovery from a specific induction agent, without demonstrating the presence of the drug in adequate concentrations in plasma. This argument raised valid concerns and demonstrates limitations in the present study as well. The results in the present study are however still relevant in the clinical setting, where subjectively assessed anaesthetic depth provides the end-point for titration of induction agents prior to intubation. Similarly during the recovery period; the worse recovery scores consistently associated with diazepam-ketamine when compared to the near perfect recoveries observed in dogs induced with propofol even at very high doses in the present study have to be heeded.

Multiple observers were used to score the induction and subsequent recovery from anaesthesia. The primary observer scored both the induction and recovery period; while the additional observers scored either induction or recovery. A moderate level of agreement was obtained when the scores were compared to the primary assessor's scores and a higher agreement may have been achieved if only two observers assessed both phases. Finally, only one recovery score was allocated for the overall quality of recovery from anaesthesia. Scoring the early phase

and late phase of recovery separately would have improved the assessment accuracy during the recovery period and provided more information on the recovery phase shortly after termination of isoflurane as well as the period from endotracheal extubation until standing was achieved.

Conclusion

Diazepam-ketamine combination or propofol alone produce clinically acceptable induction of anaesthesia in dogs with diazepam-ketamine being the seemingly superior induction regimen. Recovery from anaesthesia induced with either diazepam-ketamine combination or propofol is acceptable (excitement-free and short) with propofol associated with less ataxia and quicker recoveries.

Chapter 7

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Chapter 8

Addendum:

Addendum 1: Informed consent form

This form must be completed by a person who has the authority to consent to the use of domestic dogs from the facility in an anaesthetic study conducted at the Onderstepoort Veterinary Academic Hospital, overseen by the Companion Animal Clinical Studies Section, Department of Anaesthesiology.

Brief Overview of Study

Many Veterinary practices throughout South Africa commonly use both Propofol or Ketamine along with Diazepam to anaesthetize patients for routine procedures such as spays and castrations. There has been no consensus reached with Ketamine having potentially more difficult inductions of anaesthesia and some animals showing more complex recoveries. The study intends to prove these induction and recovery characteristics true or false.

Brief Overview of the Procedure

Male dogs will arrive to the Onderstepoort Veterinary Academic Hospital and be examined to ensure he is clinically healthy and suitable for anaesthesia. Blood will be drawn and tested to confirm anaesthetic eligibility for surgery. The castration will take place the next day (Day 2). Data will be collected in the form of subjectively scoring the dogs during induction and recovery. After recovery the dogs will be kept overnight to ensure they are fully recovered and will be discharged from the Onderstepoort Veterinary Academic Hospital on day 3.

Timeframe and Schedule for Dogs

- **Day one:** arrive at Onderstepoort Veterinary Academic Hospital, basic clinical examination, blood drawn for haematology.
- **Day two:** Procedure and subjective scoring of induction and recovery.
- **Day three:** Discharged after final clinical exam.
-

Informed Consent to Provide Dogs for the study

I/We _____
of the _____

Facility give permission and informed consent to provide friendly, young (6 months to 5 years old), unsterilized, healthy domestic male dogs, with normal body condition (not skinny nor obese) to participate in a clinical research study to be performed in the Department of Anaesthesiology Clinical Study under the following terms:

1. Once the dogs are enrolled and collected from your facility they may not, under any circumstances leave the clinical study until they have completed all stages. We anticipate a 3 day timeframe as described in the “Timeframe and Schedule for dogs” section above. If there is a delay in the timeframe you will be notified as soon as reasonably possible.
2. The Department of Anaesthesiology will make all the travel arrangements for the dogs to and from your facility at our costs.
3. Dogs enrolled in the clinical study will undergo a standard, routine orchidectomy.
4. The protocols used to induce general anaesthetics and pain management being tested in this study are safe and are not expected to cause illness or death.
5. The whole procedure will be monitored by several specialist veterinarians to ensure safety of the dogs.
6. The dogs will be kept in an indoor enclosure facility to provide a warm, quiet and friendly environment throughout their stay. They will be allowed in outside runs during the day, will be walked at least twice a day and will be monitored several times each day.
7. If the dogs experience pain post-surgery a rescue analgesic (pain killer) will be administered to ensure pain relief.
8. The dogs will be shaved on their ventral abdomen and at least one legs to allow intravenous catheter placement. The hair is expected to grow back within 6 weeks post study.
9. All dogs will be fed Royal Canine dog food during their stay at our facility.
10. If the dogs have owners, it is your duty to inform them of the study and the potential time delay in getting their dog back from the surgery. The dogs will not, under any circumstances be released from the study at an earlier stage.
11. Aggressive dogs that cannot be safely handled may not be included in the study.
12. In the very unlikely event of a death during the dog’s stay at our facility we will insist on a post-mortem examination to determine the cause of death. You will be informed immediately in the event of a death if the dog needs to be returned to your facility and a comprehensive report will be issued.
13. The Onderstepoort Veterinary Academic Hospital and its entire staff complement cannot be held liable or responsible for any death, loss or negligence of any type or form during the dog’s stay at our facility.
14. This consent form and Form A2 “Admission Information” needs to be signed in double, one record kept at your facility and the other at the Onderstepoort Veterinary Academic Hospital.
15. Our facility will make every effort to provide the best care and attention for the dogs during their stay at the Onderstepoort Veterinary Academic Hospital.
16. Your facility will not be charged (billed, invoiced) for any of the work conducted on the dogs during their enrolment in the trial, this includes the castration surgery, the food and boarding.
17. The veterinarians conducting the study have a right to exclude any dog obtained from your facility that do not conform to the requirements (friendly, healthy, good body condition score, young, unsterilised, male) of the study participants.

As a token of appreciation your facility may be mentioned in the acknowledgment section of all scientific articles published from this study:

- Yes, please add our facility's name to the acknowledgement section of all publications written using the data collected from this study.
- No, please do not add our facility's name to the acknowledgment section of all publications written using the data collected from this study.

Signing of the Informed Consent Form

Authorised Person of Facility

Name: _____

Signature: _____

Date: _____

Authorised Person of Onderstepoort Veterinary Academic Hospital

Name: _____

Signature: _____

Date: _____

Witness

Name: _____

Signature: _____

Date: _____

Addendum 2: Clinical examination form:

Dog Number:.....

Date:.....

Cage Number:.....

Age:.....

Habitus:.....

Intact and descended Testes (Y/N):.....

Heart Rate:.....

Temperature:.....

Respiratory Rate:.....

CRT:.....

Blood Collection Date:.....

Ht:.....

TSP:.....

Crea:.....

Abnormalities:.....

Addendum 3: Score sheet

Dog Number:.....

Date:.....

Group (P or D/K):

Calculated Dose:.....

F/U Dose:.....

F/U (No):.....

Score Sheet		
Cage Rest	Score (0-3)	Comments
Premedication	Score(0-3)	Comments
Induction	Score (0-3)	Comments
<i>Induction</i>		
<i>Intubation</i>		
<i>Myoclonus</i>		
Recovery	Score (1-6)	Early/Late (5 minutes after ext)

Addendum 4: Proposed journal article submission and presentation commitments

Proposed Journal of choice for submission:

- Journal of Small Animal Practice
- or
- Journal of South African Veterinary Association

Proposed Conference for Abstract Presentation

- University of Pretoria Faculty of Veterinary Science- Faculty Day
- Date: 4 September 2014