# Anaesthetic, analgesic and cardiorespiratory effects of three intramuscular anaesthetic protocols in cats

By

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Submitted in partial fulfilment of the requirements for the degree of MMedVet (Anaes) in the Department of Companion Animal Clinical Studies in the Faculty of Veterinary Science, University of Pretoria

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# Declaration

I, Gareth E. Zeiler, hereby declare that the research presented in this dissertation, was conceived and executed by myself, under guidance from my supervisors.

Neither the substance, nor any part of the dissertation has been submitted in the past, or is to be submitted for a degree at the University of Pretoria or any other University.

This dissertation is presented as partial fulfilment of the requirements for the degree Master of Veterinary Medicine (Anaes).

Signature:_____

Gareth E. Zeiler

Date: 26 November 2013

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# List of Abbreviations

| | |
|---|---|
| MedK | Medetomidine and Ketamine |
| MedKM | Medetomidine, Ketamine and Morphine |
| MedKT | Medetomidine, Ketamine and Tramadol |
| mg | Milligram |
| kg | Kilogram |
| µg | Microgram |
| mL | Millilitre |
| mmHg | Millimetres of Mercury |
| cm | Centimetre |
| min | Minute/s |
| % | Percentage |
| < | Smaller than |
| > | Greater than |
| = | Equal to |
| ≤ | Smaller or Equal to |
| ≥ | Greater or equal to |
| T0 | Time immediately after injection |
| T20 | 20 minutes after injection |
| µ | Mu |
| K | Kappa |
| A | Alpha |
| IV | Intravenous |
| IM | Intramuscular |
| °Celsius | Temperature in degrees Celsius |
| HR | Heart rate (beats per minute) |
| $f_R$ | Respiratory rate (breaths per minute) |
| SABP | Systolic arterial blood pressure |
| $SpO_2$ | Peripheral oxygen haemoglobin saturation |
| ECG | Electrocardiogram |
| $O_2$ | Oxygen |
| $PETCO_2$ | End tidal carbon dioxide (mmHg) |
| $ET_{Iso}$ | End tidal isoflurane concentration |
| $P_AO_2$ | Alveolar partial pressure of oxygen (mmHg) |
| $FiO_2$ | Fractional inspiration of oxygen (%) |
| Hb | Haemoglobin concentration |
| $P_{bar}$ | Barometric air pressure (mmHg) |
| $P_{H2O}$ | Partial pressure of water (mmHg) |
| $PaCO_2$ | Partial pressure of arterial carbon dioxide (mmHg) |
| $PaO_2$ | Partial pressure of arterial oxygen (mmHg) |
| $SaO_2$ | Arterial oxygen saturation of haemoglobin (%) |
| $PvO_2$ | Partial pressure of venous oxygen (mmHg) |
| $SvO_2$ | Venous oxygen saturation of haemoglobin (%) |
| $CaO_2$ | Arterial content of oxygen ( |
| $CvO_2$ | Venous content of oxygen |
| OE | Oxygen extraction ratio |

| | |
|---|---|
| RQ | Respiratory Quotient (0.8) |
| $P(A\text{-}a)O_2$ | Alveolar-arterial oxygen gradient |
| IPPV | Intermittent Positive Pressure Ventilation |
| 2° AV blocks | Second degree atrioventricular blocks |
| ET tube | Endotracheal tube |
| VAS | Visual analogue Scale |
| ASA | American Society of Anaesthesiologists |
| CEPSAF | Confidential Enquiry into Perioperative Small Animal Fatalities |
| OVAH | Onderstepoort Veterinary Academic Hospital |
| SD | Standard deviation |
| IQR | Interquartile range |

# Summary

## Anaesthetic, analgesic and cardiorespiratory effects of three intramuscular anaesthetic protocols in cats

By

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Co-promoter: Prof Tarisai B. Dzikiti

Department: Department of Companion Animal Clinical Studies

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**Objectives** To compare the anaesthetic, analgesic and cardiorespiratory effects of intramuscular medetomidine and ketamine administered alone or combined with morphine or tramadol for orchiectomy in cats.

**Study design** Randomised, blinded, prospective clinical study.

**Animals** Thirty client owned healthy cats.

**Materials and methods** Cats received a combination of medetomidine (60 µg $kg^{-1}$) and ketamine (10 mg $kg^{-1}$) alone (MedK) or combined with morphine (0.2 mg $kg^{-1}$) (MedKM) or tramadol (2 mg $kg^{-1}$) (MedKT) intramuscularly. Time of different events and physiological parameters were recorded by a

blinded researcher. Pre-surgery arterial and venous blood gases were measured. Heart rate (HR), respiration rate ($f_R$), systolic arterial blood pressure (SABP), peripheral haemoglobin saturation ($SpO_2$) and end-tidal carbon dioxide tension ($PETCO_2$) were recorded every 5 minutes of general anaesthesia and at each surgical stage. Post-operative analgesia was evaluated with a visual analogue scale, a multidimensional composite scoring system and a rigid tip von Frey mechanical threshold device every hour from 3 to 8 hours post-injection of the initial combination of drugs. Data were analysed with a linear mixed model, Kruskal Wallis or Chi-square tests ($p < 0.05$).

**Results** Median (range) induction and recovery times (minutes) were not significantly ($P = 0.125$) different among the three combinations: 5.6 (2.7, 8.0), 7.4 (5.1, 9.6) and 8 (5.8, 14.9) for induction and 128 (95, 143), 166 (123, 210) and 143 (123, 180) for recovery, with MedK, MedKT and MedKM, respectively. All three combinations caused similar low partial pressure of arterial oxygen ($PaO_2$) values (mean ± SD: 66.2 ± 1.7 mmHg). Surgery had a significant effect on SABP ($p < 0.001$), $SpO_2$ ($p < 0.001$), $f_R$ ($p = 0.003$) and HR ($p = 0.002$), which increased; and $PETCO_2$ ($p = 0.003$), which decreased, with all combinations. Non-significant differences were found in pain scores and von Frey results among treatments; however, the von Frey changes over time did vary by treatment ($p < 0.001$) with the MedK group returning to baseline values more rapidly than MedKM and MedKT. None of the cats required rescue analgesics.

**Conclusion and clinical relevance** All three protocols provide adequate anaesthesia and analgesia for orchiectomy in cats. However, rescue intervention to maintain surgical anaesthesia such as isoflurane may be required in some cats. Oxygen should be supplemented.

***Keywords*:** feline, medetomidine, ketamine, morphine, tramadol, anaesthesia, orchiectomy

# Literature review

This literature review has highlighted: various commonly used intramuscular regimens administered to cats for general anaesthesia, focusing on the regimens' clinical application and dose rates; information about the individual drugs used in this study and their significance in domestic cats; and the current status on pain scoring of domestic cats.

## Anaesthetic regimens used in practice

### *Tiletamine-zolazepam, Butorphanol, Dexmedetomidine (TTDex) regimen*

Originally this combination was known by the acronym TTD (where T = Telazol, T = Torbugesic and D = Domitor [medetomidine]). Medetomidine was replaced by the newer dexmedetomidine (DexDomitor) in 2008 (Ko et al. 2010). Medetomidine is still in use in countries that do not have dexmedetomidine yet, as in the case of South Africa. This drug combination is usually reconstituted in the tiletamine-zolazepam (Telazol) bottle by adding 2.5 mL of butorphanol (Torbugesic 10 mg $mL^{-1}$) and 2.5 mL of dexmedetomidine (DexDomitor 0.5 mg $mL^{-1}$) as the diluents. The advantage of this anaesthetic regimen is the inclusion of an opioid to increase the analgesic efficacy of the combination. The advantage of butorphanol, a kappa (κ) agonist and mu (μ) antagonist, over μ agonist opioids such as morphine is that it is associated with milder respiratory depression and bradycardia. However, butorphanol induces only mild to moderate analgesia that might not be adequate for certain procedures (e.g. orthopaedic surgery).

**Current recommended intramuscular dosages for surgical anaesthesia in cats:**

Tiletamine: 3 mg $kg^{-1}$; Zolazepam: 3 mg $kg^{-1}$; Butorphanol: 0.15 mg $kg^{-1}$; Dexmedetomidine: 7.5 μg $kg^{-1}$ (Ko et al. 2010)

### *Dexmedetomidine, Ketamine, Butorphanol (DKB) regimen*

In this regimen, dexmedetomidine may be substituted with medetomidine with the same effect. This regimen necessitates the use of lower dosages of ketamine and dexmedetomidine when compared to ketamine and xylazine anaesthetic regimens, thus minimising their adverse effects (Carbone 2012). Literature suggests that dexmedetomidine and butorphanol should not be mixed in the same syringe (Martin et al. 2010, Plumb. 2008) while others suggest they can (Ko et al. 2010). This combination lacks a benzodiazepine derivative like zolazepam when compared to the TTDex regimen.

**Current recommended intramuscular dosages for surgical anaesthesia in cats**

Ketamine: 5 to 7.5 mg $kg^{-1}$ IM; Dexmedetomidine: 25 to 37.5 µg $kg^{-1}$ IM; Butorphanol: 0.4 to 0.6 mg $kg^{-1}$ (Martin et al. 2010)

### *Medetomidine, Ketamine (DK) regimen*

This anaesthetic regimen has been described over a decade ago where a combination of a dissociative anaesthetic (ketamine) is combined with an $\alpha_2$-adrenoreceptor agonist (medetomidine) (Verstegen et al. 1989). The earlier combination that was well-described was made up of ketamine and xylazine (Verstegen et al. 1990). Ever since the commercialisation of medetomidine in 2002 (Ko et al. 2010) it has largely replaced xylazine because of its high specificity for $\alpha_2$-adrenoreceptors and less adverse effects (Cullen 1996). Xylazine (1 mg $kg^{-1}$) and ketamine (10 mg $kg^{-1}$) combination is associated with higher incidences of apnoea and cardiovascular depression compared to a ketamine and medetomidine combination (Cullen 1996). The DK protocol is still used today in many private veterinary practices and welfare clinics in South Africa.

**Current recommended intramuscular dosages for surgical anaesthesia in cats**

Ketamine: 2.5 to 10 mg $kg^{-1}$; Medetomidine: 80 µg $kg^{-1}$ (Cullen 1996)

***Tiletamine-zolazepam, Ketamine, Xylazine (TKX) regimen***

The TTD regimen, described previously, replaced the TKX regimen in 2002 when Domitor (medetomidine) was commercialised (Ko et al. 2010). However, the TKX regimen is still used today in many private veterinary practices and welfare clinics around the World. It is favoured due to its ease of administration and reasonable cost. Cistola and colleagues (2004) suggested a need for the development of newer anaesthetic regimens for mass sterilisations of cats, hence the development of the TTDex and DKB regimens described above (Cistola et al. 2004).

**Current recommended intramuscular dosages for surgical anaesthesia in cats**

Tiletamine: 4 mg $kg^{-1}$; Zolazepam: 4 mg $kg^{-1}$; Ketamine: 7 mg $kg^{-1}$; Xylazine: 1.8 mg $kg^{-1}$ (Cistola et al. 2004)

There are many other intramuscular regimens that include ketamine that are used in cats for surgical anaesthesia. These regimens include (Kastner 2007):

- Acepromazine (0.02 to 0.05 mg $kg^{-1}$), buprenorphine (0.01 mg $kg^{-1}$) or butorphanol (0.2 to 0.4 mg $kg^{-1}$), ketamine (20 to 30 mg $kg^{-1}$)
- Xylazine (1 mg $kg^{-1}$), ketamine (5 to 10 mg $kg^{-1}$)
- Medetomidine (20 µg $kg^{-1}$), butorphanol (0.1 mg $kg^{-1}$), ketamine (5 mg $kg^{-1}$)
- Romifidine (0.05 to 0.1 mg $kg^{-1}$), ketamine (10 to 20 mg $kg^{-1}$)
- Midazolam (0.25 mg $kg^{-1}$), ketamine (10 to 20 mg $kg^{-1}$)

The possible intramuscularly administered drug regimens for surgical anaesthesia in cats are numerous. Despite this, most have not undergone clinical research trials and the dosages are often inferred from

clinical experience or extrapolated from other species. Even though these regimens accomplish the task of keeping the cat immobile during invasive surgery, there is little published scientific evidence confirming the regimens' anaesthetic and analgesic properties in this species. Analgesic properties are a challenge to accurately measure and interpret due to the difficulty in assessing pain levels and the lack of validated pain scoring systems in cats. Anaesthetic quality has been subjectively evaluated by monitoring the frequency of emesis, pain and excitement on injection, and monitoring various physiological parameters such as blood pressure, heart and respiratory rate.

## Drugs of interest

The present study compared combinations including medetomidine and ketamine alone or in combination with morphine or tramadol. Information on the pharmacokinetic and pharmacodynamics effects of the anaesthetic regimens in cats is scant. Opioids are the key element in peri-operative analgesia (Robertson et al. 2004, Robertson 2005). Morphine and tramadol are better analgesics than partial (buprenorphine) mu (μ) agonists or mixed (butorphanol) kappa (κ) agonist/ mu (μ) antagonist opioids (Hall et al. 2001, Tranquilli et al. 2007) and therefore deserve being studied in cats under clinically relevant conditions.

### General effects of the drugs of interest

**Medetomidine** has the following main attributes (Cullen 1996, Sinclair 2003):

1. Good somatic and visceral analgesia mediated through central $\alpha_2$-adrenoreceptors.
2. Good muscle relaxation.
3. Substantial anaesthetic sparing effects of up to 80%.

4. Biphasic changes in blood pressure, initially hypertension (increase in peripheral vascular resistance due to peripheral vasoconstriction via peripheral $\alpha_1$-adrenoreceptor stimulation) followed by normotension or mild hypotension.
5. Decrease in cardiac output.
6. Dose-dependent respiratory depression.
7. Arterial oxygen and carbon dioxide tensions remain within acceptable physiological ranges in domestic species.
8. Species dependent emesis (common in cats).
9. Increase in diuresis due to decreased anti-diuretic hormone release.
10. Transient hyperglycaemia due to decreased insulin release.
11. Effects are reversible with atipamezole.

**Ketamine** has the following main attributes (Kastner 2007, Jaspar et al. 1983):

1. Good somatic analgesia.
2. Increase in heart rate, blood pressure and cardiac output indirectly through endogenous catecholamine release.
3. Decrease in lacrimation leading to dry eye.
4. Anaesthetic depth difficult to determine due to intact eye and laryngeal reflexes and increased muscle tone.
5. Increase in intra-cranial and intra-ocular pressures.
6. Painful intramuscular and subcutaneous injection.
7. Cannot be reversed.
8. Shorter acting than tiletamine.

**Morphine** has the following main attributes (Murrell 2007, Feldberg et al. 1986):

1. High affinity for mu (μ) receptors, mild affinity for kappa (κ) and delta (δ) receptors, thus excellent somatic and visceral analgesia.
2. Dose-dependent respiratory depression.
3. Bradycardia via vagal nerve stimulation.
4. Species dependent emesis is common.
5. Enhances sedation of $\alpha_2$-adrenoreceptor agonists.
6. Effects can be reversed with naloxone.

**Tramadol** has the following main attributes:

1. Tramadol and its metabolites are active at the mu (μ) opioid receptor sites, contributing to its analgesic effect.
2. Inhibits serotonin (by dextro-tramadol metabolite and the metabolite O-desmethyltramadol or M1) and noradrenalin (by levo-tramadol metabolite) re-uptake which may suppress the nociceptive pathways in the spinal cord (Brondani et al. 2009).
3. Levo-tramadol metabolite acts indirectly on postsynaptic $\alpha_2$-adrenoreceptors (Brondani et al. 2009).
4. Effects can be reversed with naloxone (Teppema et al. 2003).
5. A dose-dependent respiratory depression has been described (Teppema et al. 2003).
6. The current studies do not indicate any pronounced cardiovascular depression.

## Relevant literature on the drugs' effect on cats

Two research studies on the effects of intramuscular injected morphine, medetomidine and ketamine in small animals were found in the literature search and are referenced here.

The first study was based on dogs (Ueyama et al. 2008). The authors suggest that intramuscular administration of these drugs produced a good dose-dependent anaesthesia and analgesia in the dogs. Hemodynamic data, including heart rate, cardiac index and blood pressure were within acceptable physiological limits. Effects of the combination due to the medetomidine may be partially reversed by administering atipamezole. The final conclusion was that this combination may be used for short minor medical and surgical procedures, but it is not recommended for medical or surgical procedures that are painful.

The study by Ueyama et al. (2008) used dosages of the drugs (medetomidine 20 µg $kg^{-1}$, ketamine 5 mg $kg^{-1}$, morphine 0.2 mg $kg^{-1}$) that induced a light general anaesthesia. The study concluded that the dosages induced a light general anaesthesia which should not be considered for noxious procedures and that higher dosages may achieve a deeper plane of general anaesthesia. Noxious stimulation was achieved by clamping of the rear limb metatarsus and tail base with a 22 cm Pean intestinal clamp for 10 to 60 seconds. This is a common method of inducing a noxious stimulus in research trials. This makes clinical interpretation difficult as clinical noxious stimulation is often more complex.

The second study was based on cats (Wiese et al. 2007). The results suggest that the combination of medetomidine (60 µg $kg^{-1}$), morphine (0.2 mg $kg^{-1}$) and ketamine (5 mg $kg^{-1}$) injected intramuscularly produced excellent short-term anaesthesia and analgesia with minimal cardiopulmonary (heart rate, blood pressure, respiratory rate, minute volume and tidal volume) depression. The adverse effects of the combination may be partially reversed using atipamezole. The authors suggest a need for further clinical trials to verify their findings. This trial also made use of a noxious stimulation applied to the rear

limb metatarsus and tail base using a 22 cm Pean intestinal clamp. This study set the basis for determination of the dosages that could be safely used in a clinical trial using this protocol.

There are a few studies on the use of tramadol in domestic cats (Brondani et al. 2009, Cagnardi et al. 2011, Castro et al. 2009, Teppema et al. 2003, Brondani et al. 2009, Chanthawan et al. 2010, Pypendop et al. 2008, Pypendop et al. 2009, Steagall et al. 2008), including two that discuss the pharmacokinetics of tramadol in domestic cats (Cagnardi et al. 2011, Pypendop et al. 2008). These previous studies helped us determine the most appropriate dosage to use in the present study.

One study determined the pharmacokinetics of an intra-operative intravenous dosage of 2 mg $kg^{-1}$ of tramadol (Cagnardi et al. 2011). The time course of tramadol after intravenous administration was described by a two-compartment open model. The time course of O-desmethyltramadol was described by a non-compartmental model based on serum concentrations. There were no sex-related differences for these variables. The clinical effect of tramadol at an intravenous dosage of 2 mg $kg^{-1}$ did not produce any evident intra-operative cardiorespiratory adverse effects. The authors of this article suggested that additional investigations on the analgesic effects of tramadol were needed. The cats undergoing gonadectomy in this study received atropine sulphate (0.03 mg $kg^{-1}$) and acepromazine maleate (0.05 mg $kg^{-1}$) as a premedication, and inhalation induction and maintenance with isoflurane; thus the cardiovascular results may be biased in this study due to the cardiovascular effects of atropine (sinus tachycardia) and acepromazine (vasodilation) (Hall et al. 2001, Tranquilli et al. 2007). The second study assessed the pharmacokinetics of tramadol administered to cats comparing the oral (5 mg $kg^{-1}$) and intravenous (2 mg $kg^{-1}$) routes (Pypendop et al. 2008). A two-compartment model best described the disposition of tramadol in cats. A first-order absorption in the central compartment model for the oral administration tramadol was used. The authors of this article concluded that tramadol and its metabolite O-desmethyltramadol disposition in cats is characterized by a large volume of distribution

and a relatively low clearance, perhaps due to the cat's poor ability to glucuronidate compounds. They also suggested that there is a need for further pharmacodynamic studies to correlate the clinical effects to the kinetics of tramadol in cats. The cats appeared to be euphoric for several hours post administration.

A study conducted on tramadol and its effects on the cat's respiratory system determined that respiratory depression is mediated through opioid receptors (Teppema et al. 2003). An intravenous dosage of 4 mg $kg^{-1}$ was associated with marked respiratory depression and apnoea due to a decreased sensitivity to carbon dioxide and a shift in the apnoea point in the respiratory center. Tramadol reduces the patient's response to hypoxic and hypercapnic loads. Naloxone was used to reverse the adverse effects of tramadol on the respiratory system. This suggests that the opioid receptors are involved in the respiratory depression effects of tramadol.

A study on the thermal anti-nociception properties of tramadol concluded that oral dosages of 2 to 4 mg $kg^{-1}$ were necessary for inducing a significant and sustained analgesic effect (Pypendop et al. 2009). A tramadol dose of 4 mg $kg^{-1}$ orally every 6 hours produced the maximum analgesic effect of tramadol to noxious heat stimulation. A study into the analgesic effects of tramadol determined that using a subcutaneous dosage of 1 mg $kg^{-1}$ in cats had limited effect on thermal and pressure nociception, but that it was enhanced by adding acepromazine (0.1 mg $kg^{-1}$) (Steagall et al. 2008).

A study on the analgesic effects of subcutaneously injected tramadol (2 mg $kg^{-1}$) alone or subcutaneously administered tramadol combined with oral vedaprofen (0.5 mg $kg^{-1}$) or oral vedaprofen (0.5 mg kg-1) alone in cats undergoing ovariohysterectomy suggested that a multimodal analgesic plan was superior to tramadol treatment alone (Brondani et al. 2009). In this study, the vedaprofen only group had 16 patients requiring rescue analgesics, the tramadol only group had 5 patients requiring

rescue analgesics, while the vedaprofen with tramadol group did not require any rescue analgesic, proving that a multimodal analgesic approach is superior. In this study, tramadol did not modify the haemostatic, biochemical and gastrointestinal function of cats at a dosage of 2 mg $kg^{-1}$ subcutaneously (Brondani et al. 2009), this suggests that tramadol administered at this dose is safe in cats.

The authors of this clinical trial (Brondani et al. 2009) re-evaluated the data captured during this study and found that some of the pain score scale criteria used to determine the level of post-operative pain was not considered valid due to a lack of difference between non-painful and painful cats. This result did not alter the outcome of the study but rather refined the scale to include parameters that were considered more appropriate markers of increased pain in cats. The revised version of the multidimensional composite pain scoring scale was used in the present study (Brondani et al. 2011). The topic of pain scoring systems in cats will be discussed under the "Pain Scoring" section of this literature review.

A study on the anaesthetic quality of a combination of tiletamine-zolazepam (5 mg $kg^{-1}$), tramadol (4 mg $kg^{-1}$) and dexmedetomidine (10 µg $kg^{-1}$) injected intramuscularly concluded that this combination provides excellent immobilization and surgical plane of anaesthesia in cats (Chanthawan et al. 2010). This study was presented as a short communication and therefore, there is not enough scientific data published to evaluate these claims. Relatively high intramuscular tramadol dosages were used in this study without any apparent negative effect.

## Pain scoring

Peri-operative and traumatic pain management in domestic cats has been neglected and under-treated in the past. Possible reasons include the difficulty to recognise pain, lack of licensed analgesic drugs, fear of toxic side effects and lack of information specific to cats (Robertson 2005). Pain assessment in cats is

challenging and the development and validation of a pain scoring system is yet to be formulated, and it remains a very important and necessary field of study (Robertson 2005).

There are several types of pain scoring systems in animals, including: visual analogue scale (VAS), numerical rating scale (NRS), simple descriptive scale (SDS), composite scoring system and multidimensional scoring system (Price et al. 2007). No pain scoring system in cats has been validated under clinical conditions yet. Assessment of post-operative pain should be based on interactive methods, including wound palpation. The findings should be appropriately weighted in the overall assessment of pain scoring (Grint et al. 2006).

It has been shown that pain is proportional to increasing levels of circulating cytokines (Hellyer et al. 2007). Pro-inflammatory cytokines such as interleukin 6 (IL-6) and tumour necrosis factor (TNF-α) in the acute phase may help interpret and quantify the acute pain and inflammatory response in the cat. Cortisol levels are regarded as unreliable due to so many influencing factors in its circulating plasma concentration, especially in cats, which often stress in hospital environments (Robertson 2005).

Opioids are associated with an increase in body temperature and mydriasis in cats (Robertson et al. 2004). This is important information for preventing errors in pain scoring when opioids have been administered, as some scales may use pupil diameter and rectal temperature as variables.

Brondani et al. (2011) have evaluated and refined a multidimensional composite pain scoring scale in cats. This article suggests that the respiratory rate and pattern are unreliable in determining severity of pain. Heart rate changes are also not regarded as significant. Psychomotor change (posture, comfort, activity, mental status and miscellaneous behaviours), protection of wound area (reaction to palpation of the surgical wound and palpation of the abdomen and flank), physiological variables (systolic arterial blood pressure and appetite) are considered the most important attributes in any cat's pain scoring

system. Vocal expression of pain is not a consistent finding, but if seen, it is an excellent marker for pain (Brondani et al. 2011). The multidimensional composite pain scoring scale for cats described by these authors was used in the present study.

## Outcome of the literature review

Based on the reviewed literature there are several areas that need to be further studied:

1. Objective assessment of the anaesthetic and analgesic qualities as well as cardiorespiratory effects of the medetomidine and ketamine combination of drugs injected intramuscularly to induce surgical anaesthesia in cats.
2. Objective assessment of analgesic effects of tramadol in combination with medetomidine and ketamine during surgery and the immediate post-operative period in cats.
3. Objective assessment of analgesic effects of morphine in combination with medetomidine and ketamine during surgery and the immediate post-operative period in cats.

# Introduction

Many different combinations of intramuscularly injected drugs are used in private veterinary practices and welfare clinics to anaesthetise domestic cats for routine surgical procedures. Some are based on excellent anaesthetic and analgesic principles, while others might lack analgesia (Hewson et al. 2006) or do not conform to current recommended good anaesthetic and analgesic practices (Hall et al. 2001, Tranquilli et al. 2007). The Confidential Enquiry into Perioperative Small Animal Fatalities (CEPSAF) study conducted in the United Kingdom between 2002 and 2004 showed that the overall risk of anaesthetic and sedation-related death in cats was 0.24%, with the risk in healthy cats (American Society of Anaesthesiologists [ASA] score I and II) being 0.11% (Brodbelt et al. 2007; Brodbelt et al. 2008). This is markedly higher than a risk of 0.05% reported in healthy dogs (Brodbelt et al. 2007; Brodbelt et al. 2008). The major concerns raised by the CEPSAF study were drug overdose, poor pre-anaesthetic examination, lack of or inadequate anaesthetic monitoring, endotracheal intubation with an intact laryngeal reflex, and fluid overloading. More than 63% of deaths were due to cardiovascular and respiratory related causes. The high incidence of anaesthetic accidents reported by the CEPSAF strengthens the need to investigate whether there are anaesthetic combinations that are more reliable, predictable and safer for routine procedures in cats. Cats are unique and it is difficult to accurately extrapolate research data on drug pharmacodynamics, pharmacokinetics, efficacy and pain scoring systems from other species (Taylor et al. 2004).

Routine use of analgesics in cats is often neglected due to fears of undesirable outcomes such as the inability to metabolise non-steroidal anti-inflammatory drugs or excitement when opioids such as morphine are used (Taylor et al. 2004, Robertson et al. 2004, Robertson. 2005). Morphine (Wiese et al. 2007) and tramadol (Brondani et al. 2009, Cagnardi et al. 2011, Castro et al. 2009) have been investigated in cats and have been shown to provide comparable analgesia in various research and clinical trials; however, their use within a medetomidine and ketamine combination under clinical

conditions have not been explored to determine whether better cardiorespiratory stability and/or analgesia may be achieved. A medetomidine and ketamine combination is used routinely in clinical practice for elective gonadectomy in cats, frequently without any monitoring. However, there is a lack of evidence-based literature describing the cardiorespiratory and analgesic effects of this combination, especially when combined with an opioid drug. Routine use of analgesics in other species has demonstrated benefits such as faster recuperation after surgery (Taylor et al. 2004). Despite the known benefits, the analgesic effect of a drug is difficult to assess or quantify as there are few published reports validating pain scoring systems for domestic cats (Brondani et al. 2011). Subjective pain scoring tools demonstrate high inter-user variability (Brondani et al. 2011), which may be caused by differences in experience in working with domestic cats, understanding of their demeanour, and individual interpretation of pain.

The present study aimed to compare the anaesthetic, analgesic and cardiorespiratory effects of a combination of medetomidine and ketamine alone or in combination with morphine or tramadol administered by the intramuscular route to induce surgical anaesthesia for routine orchiectomy in domestic cats.

## Aims and objectives

This study aimed to determine the anaesthetic, cardiorespiratory and analgesic properties of three drug combinations including medetomidine and ketamine alone or including morphine or tramadol in cats undergoing routine bilateral orchiectomy.

The specific goals of the present study were the following:

1. Determination of the anaesthetic quality of each of the combinations.
2. Determination of basic cardiovascular effects of each of the combinations.

3. Determination of the respiratory effects of each of the combinations.
4. Assessment of post-operative analgesia of the drug combinations.

## Hypotheses

The Primary Hypothesis was:

$H_1$: The MKM and MKT groups would have ≤ 5% spike in one or more of the following cardiorespiratory parameters: heart rate, respiration rate and arterial blood pressure; while the MK group would have ≥ 15% spike in these parameters, over baseline values during surgical stimulation in cats undergoing routine bilateral orchiectomy.

The Secondary Hypotheses were:

$H_1$: The MK group would have higher arterial and venous oxygen tensions, a higher pulse oximeter reading and a lower arterial carbon dioxide tension, when breathing room air, compared to the MKM and MKT groups, in cats during routine bilateral orchiectomy.

$H_1$: The MK group would have higher mean post-operative pain scores at 3, 4, 5, 6, 7, and 8 hours post injection compared to the MKM and MKT groups in cats following routine bilateral orchiectomy.

$H_0$: Cats treated with tramadol would have similar intraoperative cardiorespiratory parameters as well as similar post-operative pain scores compared to cats treated with morphine following routine bilateral orchiectomy.

### Benefits arising from the study

The main benefit of this study is to further knowledge and understanding of anaesthetic and analgesic clinical properties of intramuscularly injected protocols that include opioid drugs in domestic cats, which may help improve the perioperative pain management in this species.

## Materials and methods

### Animals

The study was performed with the approval of both the University of Pretoria Research Committee and the University of Pretoria Animal Ethics Committee (V044-11). The sample size was calculated to total 30 male cats, calculations are discussed in the "Statistical Analysis" section of Materials and Methods. The 30 client owned cats were obtained from either Wolmer, Pretoria North in collaboration with a local spay and neuter campaign initiated by a local pet welfare interest group or the Onderstepoort Veterinary Academic Hospital (OVAH) staff members, students and clients. All owners of cats participating in the study had to sign a comprehensive informed consent form before enrolling their cat into the study.

The cats had to meet certain criteria before being enrolled into the study, as follows:

1. Healthy and free from obvious diseases and clinical signs such as snuffles and diarrhoea based on a thorough clinical examination and observation.
2. Normal body condition (neither emaciated nor obese).
3. Intact with two testicles visible inside the two scrotums.
4. Not have been vaccinated or treated against external and/or internal parasites within the last 14 days.
5. Friendly and non-aggressive towards human handling.

6. A minimum weight of 2 kg.

Cats that conformed to the criteria were enrolled into the study in a chronological order. Every research week 2 to 4 cats (depending on availability and the week's activity) would be enrolled and were kept for a 3 to 5 day period before they were returned home after the last data collection time point. The data collection phase of the study spanned from the 23rd of January to the 23rd of May 2012. All cats were housed in a dedicated cat enclosure in the OVAH wards (Photo 1). The cats were housed under conditions accepted by the OVAH; fresh food and water was provided throughout the day by the primary investigator; the litter box (tray) was regularly inspected each day and exchanged for a clean litter box (tray) when needed; environmental enrichment was provided by encouraging ward visitors to interact with the cats as well as providing catnip interactive toys for stimulation. The first day was used to run various health screening tests. The cats underwent surgery either the following day or up to 4 days post health screening tests depending on the number of cats enrolled during the week.

**Photo 1.** Study cat housed in the dedicated cat ward of the OVAH.

On day one all of the cats underwent a thorough clinical examination and approximately 2 mL of blood was drawn from either the left or right jugular vein. The blood volume was equally divided and decanted into an Ethylenediaminetetraacetic acid (EDTA) tube and serum tube for haematology (full blood count) and serum chemistry (total serum protein, creatinine) analysis, respectively by daily calibrated machines

used by the Section of Clinical Pathology Laboratory of the OVAH. A 20 µL volume of whole blood from the serum tube was used to run a Feline Immunodeficiency Virus (FIV) and Feline Leukaemia Virus (FeLV) snap test (Antigen Rapid FIV Ab/FeLV Ag Test Kit; BioNote, Inc.; Gyeonggi-do, Korea). All of the cats underwent an echocardiogram to rule out heart pathology such as concentric hypertrophic cardiomyopathy; examinations were done by a specialist veterinary radiologist, on duty, of the Section of Diagnostic Imaging of the OVAH (Photo 2). A faecal flotation was done once the cat passed a stool in the litter box. The data collected during the health exam was used to confirm ASA 1 score (a physical status scoring system from 1 to 5 developed by the American Society of Anaesthesiologists [ASA] where 1 is classed as being healthy with no risk to undergo general anaesthesia for an elective procedure, while 5 is classed as being moribund with the highest risk to undergo general anaesthesia). If patients had a positive faecal float and blood work that indicated a severe verminosis (hypoproteinemia, eosinophilia and/or anaemia) they were treated with a broad spectrum wormer (Quantel; Schering-Plough Animal Health; Isando, South Africa) and excluded from the study for 20 days. Cats with abnormal echocardiograms that suggested an increased or unacceptable anaesthetic risk were excluded completely from the study. Cats that were FIV and/or FeLV positive on snap test were only excluded if the blood results and clinical examination suggested a systemic illness.

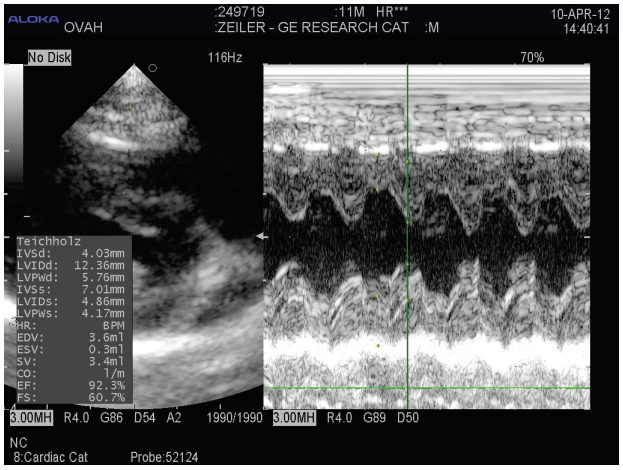


**Photo 2.** Photo of an echocardiogram that the study cats underwent during the health examination.

## Study design

The study was designed as a blinded, randomised, controlled, comparative clinical study used to investigate three different general anaesthetic drug combinations in domestic cats. A co-investigator (Dr Brighton Dzikiti) was responsible for randomly assigning each of the 30 cats equally into the three groups and to draw up the drug combination on the day of the surgery. The randomisation list was generated by entering the number of groups, names of groups and sample size in a software package (Randomisation Allocation Software Version 1, May 2004; M. Saghaei; Department of Anaesthesia, Isfahan University of Medical Science, Iran).

## Anaesthetic protocols

Three different general anaesthetic protocols for routine bilateral orchiectomy in domestic cats administered via a single intramuscular injection were studied as follows:

**Group MedK:** cats received an intramuscular dose of medetomidine (60 µg $kg^{-1}$ IM; Domitor; Pfizer Laboratories Pty. Ltd.; Sandton, South Africa) and ketamine (10 mg $kg^{-1}$ IM; Ketamine – Fresenius; Intramed; Port Elizabeth, South Africa)

**Group MedKM:** cats received an intramuscular dose of medetomidine (60 µg $kg^{-1}$ IM), ketamine (10 mg $kg^{-1}$ IM) and morphine (0.2 mg $kg^{-1}$ IM; Morphine Sulphate – Fresenius PF; Intramed; Port Elizabeth, South Africa)

**Group MedKT:** cats received an intramuscular dose of medetomidine (60 µg $kg^{-1}$ IM), ketamine (10 mg $kg^{-1}$ IM) and tramadol (2 mg $kg^{-1}$ IM; Tramahexal Injectable; Janssen Pharmaceutica Pty. Ltd.; Halfway House, South Africa)

The drug combination was drawn up into a single 1 mL syringe with a concentric, elongated plunger that entered the needle hub of the syringe. None of the injected agents in the combination were antagonised at the end of the procedure, unless indicated by the emergency rescue intervention guidelines. This allowed for determination of the total recovery time and quality of the various combinations.

Cat safety was the priority during the study and the following emergency rescue interventions were enforced during the study:

### Emergency rescue intervention during the induction phase

Immediate action was taken if the cat had one or more of the following:

1. A reliable pulse oximeter reading of < 90% for 1 minute
2. Heart rate of < 100 beats per minute
3. Apnoea for ≥ 1 minute
4. Doppler systolic arterial blood pressure of < 75 mmHg in 5 consecutive readings
5. $PaO_2$ of < 70 mmHg
6. $PaCO_2$ of > 55 mmHg

The following actions were taken:

a. In the event number 1, 3, 5 or 6: ET tube was connected to 100% oxygen at a 1 L $min^{-1}$ flow rate using a modified T-Tube semi-open anaesthetic breathing system (Intersurgical Complete Respiratory Systems; Intersurgical Ltd.; Berkshire, UK). If rebreathing of carbon dioxide was evident on capnography then the oxygen flow rate was increased. Intermittent Positive Pressure Ventilation (IPPV) was immediately instituted at 4 to 6 breaths per minute in the event number 3.

b. In the event number 4: Increase crystalloid flow rate and/or administer 3 mL $kg^{-1}$ IV colloids (Voluven; Fresenius Kabi; Halfway House, Midrand, South Africa) via the jugular intravenous catheter. If fluids did not correct hypotension, 0.2 mg $kg^{-1}$ IV ephedrine (Ephedrine Sulphate Injection; Abbott Laboratories S.A. Pty. Ltd.; Johannesburg, South Africa) was injected intravenously to increase blood pressure.
c. In the event number 2 or 4 not responding to action b: reversal of the effects of medetomidine by administering atipamezole (Antisedan; Pfizer Laboratories Pty. Ltd.; Sandton, South Africa) either intravenously or intramuscularly based on cat's clinical parameters and the cat was excluded from the study.

### Emergency rescue intervention during the surgical and maintenance phase

The same events and actions described in the induction phase were applied to this phase. The depth of anaesthesia was closely monitored while surgery was being carried out. The cat was considered to be too light if any of the following occurred:

1. Heart rate and/or respiration rate spiked by more than 30% from induction baseline values within 1 minute
2. Purposeful movement during surgery

The following actions were taken if the cat was considered too light during surgery:

a. In the event number 1 or 2 with minor movement: connected ET tube to a modified T-Tube semi-open anaesthetic breathing system and administered isoflurane (Isofor; Safeline Pharmaceuticals Pty. Ltd.; Roodepoort, South Africa) in oxygen, dispensed

through a precision vaporiser-out-of-circuit (Ohmeda Isotec 5; BOC Health Care; West Yorkshire, England) initially set to 1% and titrated to clinical effect.

b. In the event number 2 with major movement: administered propofol (Propofol 1% Fresenius Injection; Fresenius Kabi South Africa Pty. Ltd.; Halfway House, South Africa) or alfaxalone (Alfaxan-CD RTU; Kyron Labratories; South Africa) at an initial dosage of 0.5 mg $kg^{-1}$ IV until desired depth of anaesthesia was achieved and connected ET tube to a modified T-Tube semi-open anaesthetic breathing system and administered isoflurane in oxygen to effect.

### Emergency rescue intervention during the anaesthetic recovery phase

The recovery phase was closely monitored until the cat had fully recovered. The same events and actions described in the induction phase were applied to this phase. If the cat presented with a rectal temperature < 37˚Celsius, a warm water bottle and/or hot air device (Bair Hugger Warming Unit, Model 505; Augustine Medical SA Pty. Ltd.; Cape Town, South Africa) was used until body temperature reached 37˚ Celsius.

Once the cat was fully recovered (considered to be when it was able to lift the head and had a rectal temperature of ≥ 37˚Celsius), the cephalic catheter was removed and the cat was moved to the enclosure allocated to it at the beginning of the study in the cat wards.

## Instrumentation

On the day of the surgery the cat received the IM injection of the combination into the lumbar epaxial muscle group. On completion of the IM injection two stop watches were started to record the time. T0 (time zero) was considered as the time immediately post injection. Once the cat was induced into an adequate depth of general anaesthesia it was shaved inside the enclosure where it received the injection. The following areas were shaved to allow instrumentation and intravascular cannulation: both dorsal antibrachial areas, both ventral neck regions over the jugular grooves, both palmer metacarpal regions, both dorso-medial metatarsal regions, both medial femoral regions, and the ventral tail base from approximately the 5$^{th}$ coccygeal vertebra proximally. The cat was then moved to the surgical theatre post shaving. The cat was placed on a 40° Celsius preheated warm water blanket (Micro-Temp LT Model 749 Localized Therapy Unit; Cincinnati Sub-Zero Products, Inc.; Cincinnati, USA) (Photo 3). One of the cephalic veins was aseptically cannulated using a Teflon IV cannula (22G Jelco I.V. Catheter Radiopaque; Smiths Medical; Lancashire, UK). If the one vein could not be cannulated then the opposite cephalic vein was attempted. Once the cannula was secured in place an isotonic crystalloid infusion (Intramed Ringer-Lactate Solution 200 mL; Intramed; Port Elizabeth, South Africa) was connected and infused at 5 mL kg$^{-1}$ hr$^{-1}$ using a controlled infusion device (Infusomat Space; B Braun; Midrand, South Africa). Standard orotracheal intubation was attempted, first by inspecting the glottis with the aid of an illuminated laryngeal scope, then spraying the glottis with a single puff of local anaesthetic spray (Xylocaine Spray; AstraZeneca

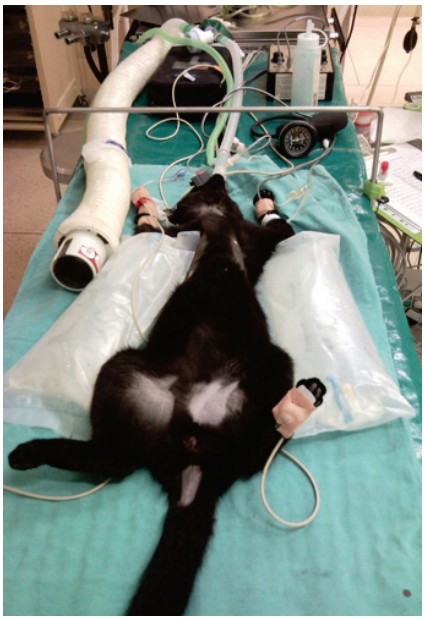

**Photo 3.** Study cat instrumentation during the procedure data collection.

Pharmaceuticals Pty. Ltd.; Wilmington DE, USA) followed by the placement of a size 4 internal diameter, uncuffed, PVC endotracheal tube (ET tube). The ET tube was connected to a straight side stream gas sampler connector, which had a 4 French Gauge (FG) male cat urinary catheter (Buster Cat Catheter, sterile; V Buster; South Africa) inserted through the side stream gas sampling port in the direction of the ET tube connector side (Photo 4). The urinary catheter passed the ET tube connecter side by 55 mm. This allowed deep ET tube gas sampling. The gas sampling line was thus connected to the urinary catheter to measure the end tidal carbon dioxide ($PETCO_2$), and end tidal Isoflurane concentrations ($ET_{Iso}$) when needed during rescue intervention. The cat was allowed to breathe room air during the anaesthetic period. An oesophageal thermometer probe was introduced into the oesophagus until the shoulder region to measure core body temperature. A pulse oximeter probe (Veterinary Pulse Oximeter/CO2 Detector Model 9847V; Nonin Medical, Inc.; Plymouth, USA) was placed on the cat's tongue to measure the peripheral haemoglobin oxygen saturation ($SpO_2$). Two lubricated electrocardiography (ECG) pads (Skintact Premier Paediatric; Leonhard Lang GmbH; Innsbruck, Austria) were placed, one on the right metacarpal pad (positive electrode) and the other on the left metatarsal pad (negative electrode), for lead II ECG trace monitoring. Either the coccygeal or one of the dorsal metatarsal arteries was aseptically cannulated using either a 22G or 24G IV catheter for invasive blood pressure monitoring and arterial blood

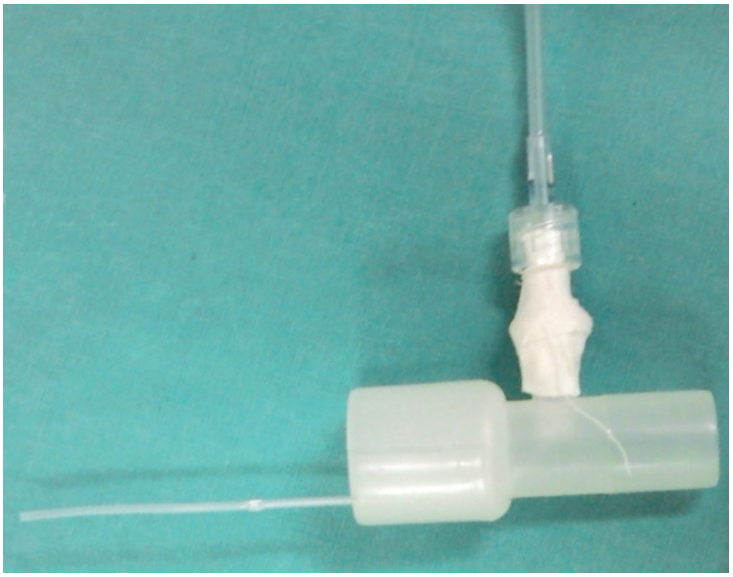

**Photo 4.** Modified straight side stream gas sampler collector.

sampling. A maximum of two attempts per site or up until T20 (i.e. 20 minutes post injection) was allowed for arterial cannulation. If arterial cannulation could not be achieved then direct femoral artery puncture was done using a 24 G needle and a 3 mL pre-heparinised syringe was used for arterial blood gas sampling. The side stream gas sampler (sampling rate: 200 mL $min^{-1}$), oesophageal thermometer probe, invasive blood pressure transducer, and ECG lines were connected to a multiparameter anaesthetic monitoring machine (Datex-Ohmeda S/5 Anesthesia Monitor; GE Healthcare Finland Oy; Helsinki, Finland). A 22G IV cannula was aseptically placed into either the left or right jugular vein for venous blood sampling and rescue intervention if needed during the anaesthetic period. A lubricated Doppler probe (Ultrasonic Doppler Flow Detector Model 811-AL; Parks Medical Electronics, Inc; Aloha, Oregon, USA) was placed on the pre-shaved palmar metacarpal region on the thoracic limb without the cephalic cannula to hear a palmar common digital arterial branch's blood flow. A human digit cuff (Size 1.9) (cuff width was 30 to 40% of the circumference of the limb) was placed in the mid antebrachial region of the thoracic limb fitted with the Doppler probe. The cuff was attached to a manually operated trigger manometer to determine non-invasive systolic blood pressure of the cat. Readings were taken in triplicate at each measurement time point and averaged for data analysis.

Once instrumentation was complete a drape was placed over the cat to improve the thermal control. A hot air device outlet was placed under the drape and operated at a medium to high temperature setting, depending on the oesophageal temperature readings. The target time for full instrumentation was T20 (i.e. 20 minutes post injection time).

## Arterial and venous blood gas analysis

Simultaneous arterial and venous blood samples (1 mL each) were collected anaerobically into lithium heparin syringes via needle puncture of the femoral artery and from a jugular cannula, respectively. Samples were collected just prior to surgery while the cats were spontaneously breathing room air.

Blood gas analysis (α-stat at 37.0 °C) was performed within 3 minutes after collection using an automated blood gas analyser (Rapidlab 348 System; Siemens; South Africa). The alveolar partial pressure of oxygen ($P_AO_2$) was calculated using the standard alveolar gas equation [$P_AO_2 = FiO_2 (P_{bar} – P_{H2O}) – PaCO_2/RQ$]; using a barometric pressure ($P_{bar}$) of 662 mmHg (pressure at altitude of 1252 meters above sea level and ambient temperature of 17 °C in theatre); a partial pressure of water ($P_{H2O}$) of 47 mmHg and a respiratory quotient (RQ) of 0.8 (Cinel et al. 1991). The arterial partial pressure of carbon dioxide ($PaCO_2$) and $PaO_2$ of each cat were used accordingly in the alveolar gas equation and alveolar-arterial oxygen gradient [$P(A\text{-}a)O_2 = PAO_2 – PaO_2$] calculations to compare differences among treatments. Arterial and venous oxygen contents were also calculated using the following equations: $CaO_2 = (Hb \times 1.34 \times SaO_2) + (PaO_2 \times 0.003)$ and $CvO_2 = (Hb \times 1.34 \times SvO_2) + (PvO_2 \times 0.003)$] (Tranquilli et al. 2007), where haemoglobin (Hb) was obtained from the complete blood count, and arterial oxygen saturation of haemoglobin ($SaO_2$), $PaO_2$, venous oxygen saturation of haemoglobin ($SvO_2$), and venous partial pressure of oxygen ($PvO_2$) were obtained from the arterial and venous blood gas analyses, respectively. The oxygen extraction ratio (OE Ratio) was calculated using the following equation: $(CaO_2 – CvO_2)/CaO_2 \times 100$.

## Anaesthetic monitoring and data capture points

A standardised anaesthetic monitoring form was specifically designed for the study to capture data during the induction, maintenance and recovery phases of the anaesthetic period. Standard data points captured during the various phases of anaesthesia were always captured by the primary investigator and are summarised in Table 1 for easy reference. Additional data were captured if the cat had to be rescued, described after Table 1.

**Table 1.** Summary of the standard data points captured during the anaesthetic period.

| Parameter | Definition | Comment |
|---|---|---|
| **Note on time points:** T0 was defined as the time immediately after the IM injection of the combination. Time data points were captured according to the time elapsed from T0; recorded in hours, minutes and seconds where T0 is 0 hours: 0 minutes: 0 seconds. | | |
| **Induction Phase** | | |
| Injection reaction | The cat was placed in one of the following categories: No reaction; Runs away; Fights hands of injector; Slowly creeps away. | A note was made if there was excessive grooming of the injection site, as defined in the excitement parameter. |
| Excitement | A subjective observation was made on the cat's level of excitement post injection. Excessive pacing, vocalisation and excessive grooming of the injection site were considered as post injection excitement. | |
| Time to head rests on floor | The time when the head rested on the floor of the enclosure without bobbing up and down. | |
| Time to move into lateral recumbency | The cat had to move its pelvic limbs laterally to one side and rotate its pelvic girdle and lumbar spine to accommodate the laterally placed pelvic limbs, at a minimum, to be considered in lateral recumbency; the thoracic limbs and head were allowed to remain in a sternal configuration. | The primary investigator was allowed to move the cat into lateral recumbency 3 minutes after the head rested on the floor. A note was made if the cat moved into lateral recumbency on its own or with assistance. |
| Time to relaxed limbs | Limbs that are easily extended and flex without resistance to the manipulation. | A period of 1 minute after moving into lateral recumbency was allowed to elapse before determining the rigidity of the limbs. |
| Time to loss of pedal reflex | An active withdrawal of the limb from intense human thumb nail pressure applied to the dorsal aspect of the metacarpal and metatarsal bones was considered a positive withdrawal reflex. | The pedal reflex was tested at 30 second intervals once the limbs were deemed to be in a relaxed state. |
| Vomiting | The cat was placed in one of the following categories: No vomiting; Unproductive retching; Vomiting. | If vomiting was observed then a note of the composition was made such as food or bile. |
| Nausea | The cat was placed in one of the following categories: No nausea; Licking lips; Licking lips and unproductive retching. | A note of excessive salivation was made if the cat began to lick its lips. |

| Maintenance and Surgical phase | | |
|---|---|---|
| Glottis activity on intubation | The cat was placed in one of the following categories: No activity; minor activity with cough and or swallowing when sprayed; active with swallowing and/or partial spasms; too active and awake with purposeful swallowing and head movements, thus could not be intubated. | If the cat experienced an active glottis with partial or full spasm a rescue intervention to deepen anaesthetic level was implemented. |
| 5 minute interval monitoring during maintenance. | The following data were captured at 5 minute intervals: Heart rate; respiration rate; $PETCO_2$; $SpO_2$; Doppler blood pressure; systolic -, diastolic -, and mean arterial pressure (when an arterial catheter could be placed); oesophageal temperature. The ECG tracing was observed for any arrhythmias, which were noted when present. | Data of various parameters were captured as soon as a monitoring device (multiparameter anaesthetic monitoring machine with ECG leads, oesophageal temperature probe, gas line sampler, invasive blood pressure transducer; Doppler probe; $SpO_2$ probe) was connected. Thus most parameters were able to be measured from T10 (10 minutes post injection) in most cats. A target of T20 (20 minutes post injection) was set for full instrumentation. |
| Arterial and venous blood gas determination. | A venous sample was drawn from the placed jugular cannula. An arterial blood sample was drawn from an aseptic femoral artery needle puncture. | Bloods were sent directly to the clinical pathology laboratory for analysis within 3 minutes from blood takes. Time of blood take and $SpO_2$ reading were recorded. |
| Critical surgical stage monitoring during the surgery. | The same data were captured as for the 5 minute interval periods described in “5 minute interval monitoring during maintenance”, except these data sets were recorded during critical stages during the surgery, as follows: plucking of the scrotal hair; first scrotal incision; pulling and tying off of the first testicle; second scrotal incision; pulling and tying off of the second testicle. | Parameters were measured from monitoring devices as described for “5 minute interval monitoring during maintenance” parameter. |
| Time of start and end of surgery. | The starting and ending time of the surgical procedure were recorded. | Surgical length and time frames post injection were determinable. The target surgical start time was T25 (25 minutes post injection). |
| **Recovery phase** | | |
| Time to Extubation | Extubation of the ET tube was performed either when the cat demonstrated purposeful swallowing attempts or when the ear flicked in | The cats were left on the surgical table up until T60 (60 minutes post injection) for data capture. |

| | | |
|---|---|---|
| | response to blowing into the ear canal. | Extubation was performed if the cat awoke before the T60 time point. |
| Time to regain pedal reflex | An active withdrawal of the limb from intense human thumb nail pressure applied to the dorsal aspect of the metacarpal and metatarsal bones was considered a positive withdrawal reflex. | This was tested every 5 minutes post T60 (60 minutes post injection). The withdrawal had to be purposeful and strong, not a gentle retraction of the limb. |
| Time to regain consciousness | A subjective assessment of the cat's state of consciousness by responding to stimulation. Stimulation such as verbal gestures, slow movement of objects in front of the eye, "clicking" of a pen near the ear. The cat was considered conscious when the eyes and/or ears focused and moved towards the stimulation. | This was tested every 10 minutes after T60 (60 minutes post injection). |
| Time to lift head | The cat had to make a purposeful attempt to raise its head and maintain this position for longer than 5 seconds for it to be considered as a head lift. | The thoracic limbs, when resting in lateral recumbency, were often repositioned during this stage of recovery which helped determine a purposeful attempt to raise the head. |
| Time to ambulation | The cat had to ambulate purposefully with at least two leg movements or raise its body for longer than 5 seconds for it to be considered an ambulatory attempt. | The recovery blankets were removed for a short period to determine if the cat could ambulate after the head was raised. If the cat refused to move the blanket was replaced and this exercise was reattempted at 10 minutes intervals. |
| Vomiting | The cat was placed in one of the following categories: No vomiting; Unproductive retching; Vomiting. | If vomiting was observed then a note of the composition was made such as food, foam or bile. |
| Nausea | The cat was placed in one of the following categories: No nausea; Licking lips; Licking lips and unproductive retching. | A note of excessive salivation was made if the cat began to lick its lips. |
| Excitement | The cat was placed in one of the following categories: Relaxed; Excited. | A note to explain the excitement was made on an individual basis. The following were considered excitement during recovery: excessive vocalisation (short meows to long drones or moans); excessive pacing; excessive rolling and stumbling. |

| | | |
|---|---|---|
| Euphoria | The cat was placed in one of the following categories for euphoria: Nothing detected; Playful and kneading floor when touched; Very playful and mock wrestling; Nervous and hypersensitive to touch; Hiding and very sensitive almost seizuring. | This was tested every hour from 3 hours post injection to last data collection point 8 hours post injection. |
| Eye | The cat's eyes were monitored and placed into one of the following categories: No abnormality; Prolapsed third eyelid alone; Mydriasis alone; Prolapsed third eyelid and mydriasis. | This was tested every hour from 3 hours post injection to last data collection point 8 hours post injection. |
| Level of sedation during recovery | The cat was placed in one of the following categories for level of sedation: No sedation; Mild sedation; Moderate sedation; Heavy sedation (cat cannot stand). | This was tested every hour from 3 hours post injection to last data collection point 8 hours post injection. |

Data was captured if an emergency rescue intervention was indicated during the anaesthetic period, as follows:

1. If oxygen support was needed, a note of when oxygen was started and when it was discontinued. The oxygen support manipulated the $SpO_2$ and blood gas $PaO_2$ values, thus it was important to know when and for how long oxygen was supplemented. Oxygen support was administered to hypoxaemic cats after the first arterial blood gas sample was obtained.

2. Additional general anaesthetic support during a rescue intervention due to being considered too light for surgery was also recorded. This was either a bolus of propofol or alfaxalone to allow for endotracheal intubation and/or isoflurane support during the surgery. The $ET_{Iso}$, start and end time of intervention was recorded.

3. Other rescue interventions, as described in "Anaesthetic Protocols" above were recorded on an individual basis. Volumes, times and intervention type with the reason for intervention were recorded.

The official data capture sheet has been included in the appendix for the reader's reference.

## Pain scoring

Two types of pain scoring systems were used in the present study. The pain scoring was done at 3, 4, 5, 6, 7, and 8 hours post injection. Two blinded co-investigators joined the primary investigator during the 5 hour pain scoring session to score the cat with the purpose of collecting inter-user variability of the two pain scoring systems.

The first pain scoring system was an interactive Visual Analogue Scale (VAS), which was done by marking a line where each end indicated an extreme of pain. The beginning of the line was indicated by a 0 which meant no pain detected, while the opposite end was indicated with a 10 which meant maximum pain imaginable for the patient. The user who was scoring the pain level had to interact with the cat and then mark along the line to indicate the observed pain level. Thus no pain was marked at the 0 end; mild pain was marked closer to the 0 end; severe pain was marked closer to the 10 end; and the most intractable pain was marked at the 10 end. The line on the study was exactly 100 mm long with no markings. The score was calculated as a percentage where the distance from the 0 end to the user's written mark to indicate pain level and expressed as a percentage. This pain scoring system has been well described in the veterinary literature (Hall et al. 2001, Tranquilli et al. 2007).

The second pain scoring system used was a multidimensional composite pain (MCP) scoring system first described by Brondani *et al.* in 2011. Due to the acute nature of the surgical injury, some of the factors were selectively excluded from the pain scoring system in this study, such as: the cat's appetite as it was starved for the operation; the systolic arterial blood pressure measured using the Doppler technique, due to lack of patient compliance in the first 5 cats proving a near impossible and tedious task resulting in uncertain data being captured. With the selective exclusions the total score was recalculated (total of 23) to allow for interpretation, where a score of 7 was considered to be 30% of the total score. The

more painful the cat the higher the overall score would be, while the more pain free the cat the lower the score with 0 indicating no pain detected. The two pain scoring data capture sheets are annexed for the reader's reference.

Pressure (mechanical nociception) pain threshold determination using a rigid tip (0.5 mm in diameter) Von Frey's device (Electronic von Frey Anesthesiometer 2390 series; IITC Inc. Life Science; CA, USA) was also captured during the study. This allowed a more objective data collection before and after the general anaesthesia. Paired pressure samples were taken from the right and left mid-lateral thoracic cage during each data collection time point. Two baseline data sets were captured before general anaesthetic induction and three post general anaesthetic data sets were captured at T4h, T6h and T8h (4, 6, and 8 hours after intramuscular injection) time points. The purpose was to determine if there was an increase in the pressure threshold after the intramuscular injection and whether there was a detectable difference between the three combinations. The primary investigator captured data on all cats enrolled in the study, while two co-investigators captured random baseline data for inter-user variability analysis from 10 of the cats.

All cats received a single dose of carprofen (4 mg $kg^{-1}$ SC; Rimadyl Injectable; Pfizer Laboratories Pty. Ltd.; Sandton, South Africa) at the end of the 8 hour pain score data collection time point. The following emergency rescue intervention was enforced during the study:

### Emergency rescue intervention for painful cats

The cats were closely monitored during the post surgical phase of the study to ensure that they did not experience unnecessary pain. Rescue analgesia was given if the cat's pain score in any of the 2 scales (interactive VAS or MCP) was > 30% of the total possible score at any given point in

time. The rescue analgesic was buprenorphine (15 µg $kg^{-1}$ IM; Temgesic; R & C Pharmaceuticals; Hertford, UK).

## Data collection

The primary investigator was responsible for manually collecting all data during the study. The written data was captured on various data capture sheets and filed within individual folders for each cat entering the study. These folders with all of their sheets will be stored for a period of 5 years in the OVAH, section of anaesthesiology. The captured data was stored electronically on a excel spreadsheet specifically designed for the study. A copy was stored on the primary and co-investigators computers for safe keeping and storage. Once the final data capture excel document was completed then copies were burnt onto 4 compact disks and distributed to all investigators of the section of anaesthesiology for safekeeping.

## Statistical analysis

The sample size was calculated based on an increase in heart rate of 10% over baseline during the surgical procedure, assuming a standard deviation of 10%, a power of 80%, and an alpha error of 5%. Thirty healthy intact male cats were enrolled for the study based on the sample size calculation of 10 cats required within each of the three treatment groups.

Data were assessed for normality by the evaluation of descriptive statistics, plotting of histograms, and performing the Anderson-Darling test for normality. All data were presented as median and interquartile ranges (IQR) if one or more variable appeared to violate the normality assumption. Categorical data were compared among groups using chi-square tests followed by multiple pairwise comparisons using Fisher exact tests with Bonferroni correction of p values. Quantitative data were compared using Kruskal-Wallis tests followed by multiple pairwise Mann-Whitney U tests with Bonferroni correction. A linear mixed model approach was used to estimate the effect of treatment, time, and surgery on

cardiorespiratory variables (HR, $f_R$, SABP, $PETCO_2$, $SpO_2$), including a random effect for cat that assumed a first-order autoregressive correlation structure among observations. Mixed models were adjusted for the cat's body temperature and whether or not oxygen or isoflurane rescue was administered. Wilcoxon signed rank tests were used to compare multidimensional composite pain scores pre- and post-sedation. Data were analyzed using commercially available software (SPSS version 20.0; SPSS Inc; Chicago, USA) and results interpreted at the 5% level of significance.

## Ethical consideration

The major ethical consideration in this study was the post-surgical analgesic management. The rescue analgesic protocol was followed precisely.

Cats participating in the study that originated from welfare organisations or interest groups were not necessarily owned by anyone and were the property of the welfare organisation of origin. The welfare organisation may have already allowed the cat to be adopted by a person. The welfare organisation was not obligated to provide a cat that had already been adopted or owned by a third party person. The Informed Consent Form absolved the University and all its staff members from negligence, loss, death or any other unfortunate event the cat may have experience during the study. The welfare organisation should have obtained their own consent, or informed their own client if they opt to provide a cat that had an owner or potential adopter.

Private owners allowing their cat to participate in the study were informed about the procedures the cat would undergo and a consent form was signed before admission to the study.

In the event of disease, death or loss of the cat the primary investigator had to inform the welfare organisation or the owner within a short a time as reasonably possible. In the event of death during the study process a post-mortem examination was to be conducted to determine the cause of death.

People who assisted in the study were not obligated or forced. They participated by invitation only. The participants did not receive financial compensation.

None of the procedures or drugs used during the study was considered harmful to domestic cats or humans.

## Results

The estimated age of the cats, reported as median (IQR), was 1.0 (1-2) years for all treatment groups. The weight of the cats was 3.0 (2.2-3.7), 3.1 (2.3-3.6), and 2.8 (2.3-3.5) kilograms for MedK, MedKM, and MedKT treatment groups, respectively. Haematocrit and haemoglobin concentration were within clinically normal ranges in all cats. There were no significant differences in signalment or blood parameters among treatment groups.

## Induction phase

Induction was characterised as being rapid and excitement-free and event times did not vary among treatment groups (Table 2). Median (IQR) time for induction for all three treatment groups was 6.88 (4.90, 8.65) minutes. Increased agitation or activity before recumbency, and presence of nausea and emesis were not different among groups (Table 3).

**Table 2.** Descriptive statistics and comparisons among treatments for various time frames in minutes from time of injection (T0), except for recovery time, which was considered from the end of surgery to standing. Data reported as median (IQR).

| Time (min) | MedK | MedKM | MedKT | p Value |
|---|---|---|---|---|
| Induction time (Pedal reflex loss) | 5.6 (2.7-8.0) | 8.0 (5.8-14.9) | 7.4 (5.1-9.6) | 0.125 |
| Pedal reflex loss to start of surgery | 23.5 (20.0-26.1) | 20.5 (18.8-28.0) | 22.7 (16.6-30.0) | 0.798 |
| Extubation | 63.0 (61.8-64.2) | 62.8 (58.2-64.5) | 62.2 (61.0-64.0) | 0.688 |
| Pedal reflex gained | 69.9 (63.0-73.7) | 95.2 (67.8-107.8) | 81.5 (71.9-121.5) | 0.088 |
| Standing | 160.9 (131.7-169.6) | 177.9 (161.8-214.7) | 201.3 (155.3-235.1) | 0.074 |
| Recovery time (Head first lifted) | 128.5 (95.1-142.8) | 142.9 (123.4-180.2) | 166.4 (123.1-210.0) | 0.137 |

IQR = interquartile range.

**Table 3.** Clinical findings during the induction, maintenance, and recovery phases of general anaesthesia. Data reported as number of cats within treatment group, where 10 cats were assigned to each treatment group.

| Clinical parameter | MedK | MedKM | MedKT | p Value |
|---|---|---|---|---|
| Induction phase | | | | |
| Agitation | 3 | 6 | 5 | 0.392 |
| Nausea | 3 | 5 | 4 | 0.659 |
| Emesis | 1 | 1 | 1 | 1.0 |
| Maintenance phase | | | | |
| Alfaxalone rescue | 0 | 2 | 0 | 0.117 |
| Partial laryngospasm | 3 | 4 | 3 | 0.861 |
| $O_2$ rescue | 6 | 6 | 7 | 0.866 |
| Apneustic breathing pattern | 2 | 2 | 4 | 0.506 |
| 2° AV blocks | 6 | 4 | 2 | 0.189 |
| Surgery Phase | | | | |
| Isoflurane rescue | 3 | 3 | 4 | 0.861 |
| Recovery phase | | | | |
| Emesis | 3 | 0 | 0 | 0.036 |

2° AV blocks = second degree atrioventricular blocks.

## Maintenance phase

Alfaxalone administration during tracheal intubation, glottis activity during intubation, $SpO_2$ readings, isoflurane administration during surgery, as well as occurrence of apneustic breathing pattern and second-degree atrioventricular blocks were not significantly different among groups (Table 3).

All cats requiring oxygen rescue were due to a low $SpO_2$ reading except for one in MedKT group that had a low $PaO_2$ value despite having a normal $SpO_2$ reading. There were no significant differences among treatment groups for arterial blood gases, pH, $PETCO_2$, $SpO_2$, OE Ratio, and $P(A\text{-}a)O_2$ (Table 4). The $SpO_2$ reading increased by (mean ± SD) 3 ± 1.2% when the side-stream gas analyser sampling line was disconnected from the ET tube and returned to the previous value after reconnection.

During maintenance of anaesthesia (excluding times of surgical stimulation), cats in all treatment groups displayed similar cardiovascular (HR, SABP) and respiratory ($f_R$) parameters returning to normal physiological values after 25 minutes from T0 (Figure 1). Surgery had a significant ($p < 0.01$) effect on HR, SABP and $f_R$ causing an increase in these parameters in all treatment groups similarly (Table 5).

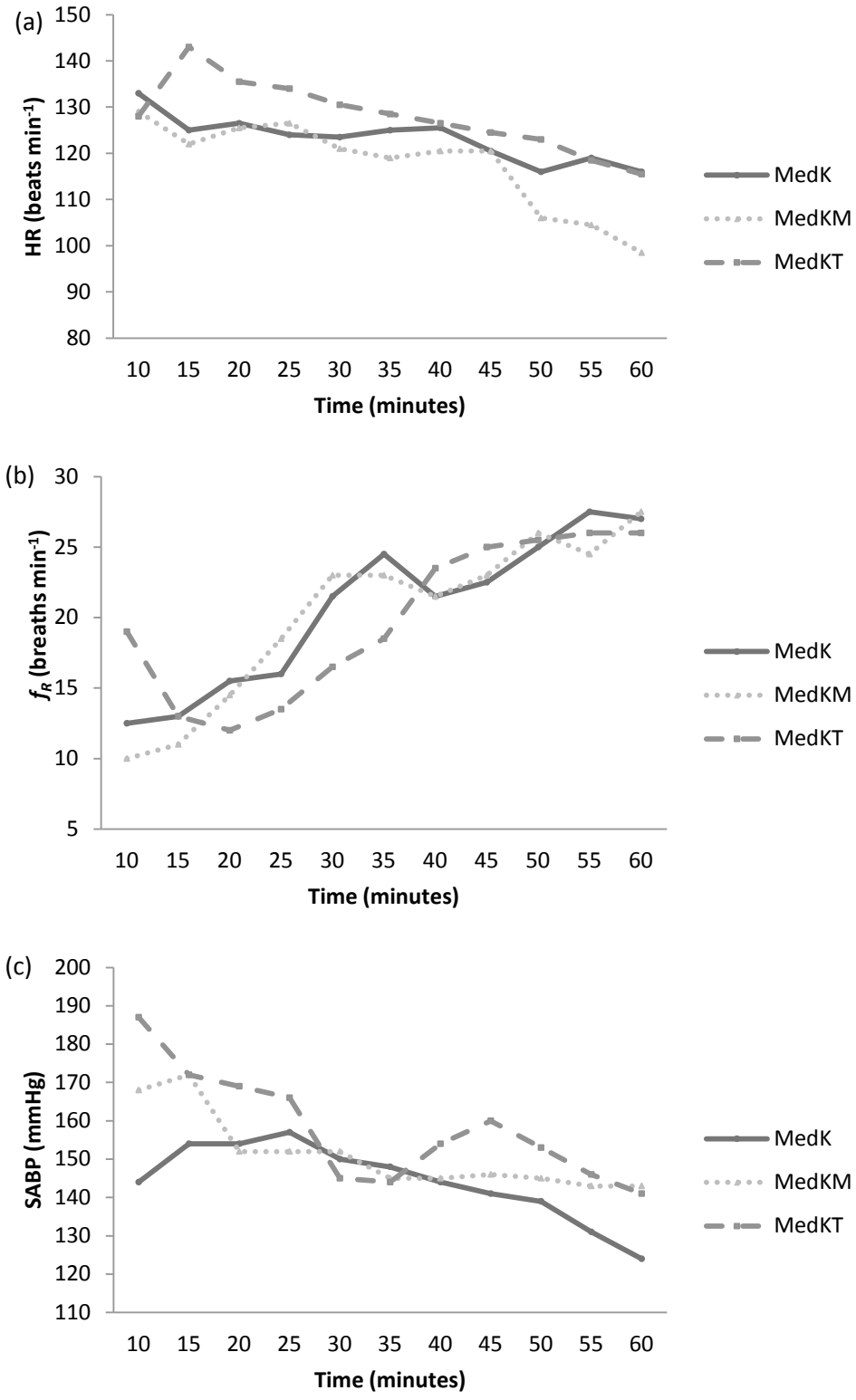


**Figure 1.** Descriptive statistics and comparison among treatments for median values over time (min) for heart rate (a), respiratory rate (b), and systolic arterial blood pressure (c) from 10 to 60 min after T0.

**Table 4.** Descriptive statistics and comparison among treatments for blood gas values, $PETCO_2$, $SpO_2$, OE ratio, and $P(A\text{-}a)O_2$. Data reported as median (IQR).

| Variable | | MedK | | MedKM | | MedKT | | p Value |
|---|---|---|---|---|---|---|---|---|
| $PaO_2$ | (mmHg) | 68.1 | (58.2-73.6) | 65.0 | (60.2-71.7) | 65.5 | (54.9-68.0) | 0.560 |
| | (kPa) | 9.1 | (7.8-9.9) | 8.7 | (8.0-9.6) | 8.7 | (7.3-9.1) | |
| $PaCO_2$ | (mmHg) | 35.9 | (32.7-37.4) | 34.8 | (32.8-36.9) | 36.0 | (35.2-37.3) | 0.628 |
| | (kPa) | 4.8 | (4.4-5.0) | 4.6 | (4.4-4.9) | 4.8 | (4.7-5.0) | |
| pH | | 7.326 | (7.32-7.34) | 7.325 | (7.32-7.34) | 7.344 | (7.31-7.37) | |
| $PETCO_2$ | (mmHg) | 40.5 | (38.5-43.5) | 42.5 | (41.5-47.3) | 40.5 | (38.8-45.3) | 0.334 |
| | (kPa) | 5.4 | (5.1-5.8) | 5.7 | (5.5-6.3) | 5.4 | (5.2-6.0) | |
| $SpO_2$ | (%) | 88.0 | (85.5-93.0) | 89.0 | (87.5-91.3) | 88.0 | (84.8-91.0) | 0.627 |
| OE Ratio | (%) | 38 | (28-40) | 33 | (28-36) | 37 | (32-40) | |
| $P(A\text{-}a)O_2$ | (mmHg) | 14.3 | (13.6-21.6) | 20.7 | (15.1-21.5) | 17.5 | (16.1-27.1) | 0.717 |

IQR = interquartile range; $PaO_2$ = arterial partial pressure of oxygen; $PaCO_2$ = arterial partial pressure of carbon dioxide; $PETCO_2$ = end-tidal carbon dioxide; $SpO_2$ = oxygen haemoglobin saturation; OE Ratio = oxygen extraction ratio; $P(A\text{-}a)O_2$ = alveolar-arterial oxygen gradient.

**Table 5.** Descriptive statistics and comparison among treatments for variables associated with autonomic responses to surgical stimulation: heart rate (HR), respiration rate ($f_R$) and systolic arterial blood pressure (SABP) for baseline and five critical time points during surgery reported as median (IQR).

| Variable | Group | Baseline | HP | SC1 | TP1 | SC2 | TP2 |
|---|---|---|---|---|---|---|---|
| HR | MedK | 126 | 127 | 125 | 123 | 128 | 136 |
| (beats min$^{-1}$) | | (116-132) | (116-134) | (113-130) | (112-131) | (115-136) | (117-142) |
| | MedKM | 119 | 124 | 115 | 127 | 125 | 132 |
| | | (99-133) | (103-131) | (95-133) | (102-135) | (110-133) | (128-137) |
| | MedKT | 128 | 132 | 129 | 128 | 131 | 130 |
| | | (125-140) | (118-143) | (121-140) | (124-142) | (123-141) | (127-140) |
| $f_R$ | MedK | 18 | 16 | 20 | 23 | 25 | 22 |
| (breaths min$^{-1}$) | | (10-25) | (9-23) | (11-25) | (14-28) | (16-29) | (16-29) |
| | MedKM | 19 | 21 | 19 | 22 | 19 | 21 |
| | | (15-24) | (11-22) | (15-26) | (16-25) | (15-26) | (15-28) |
| | MedKT | 16 | 15 | 17 | 19 | 17 | 20 |
| | | (11-22) | (10-18) | (12-24) | (10-25) | (10-21) | (11-22) |
| SABP | MedK | 151 | 157 | 152 | 152 | 151 | 157 |
| (mmHg) | | (122-161) | (136-167) | (128-161) | (126-164) | (124-168) | (125-174) |
| | MedKM | 149 | 155 | 148 | 151 | 154 | 154 |
| | | (135-153) | (139-160) | (136-154) | (140-159) | (144-160) | (144-174) |
| | MedKT | 162 | 165 | 167 | 165 | 163 | 163 |
| | | (142-171) | (143-177) | (133-175) | (138-178) | (138-170) | (139-174) |

IQR = interquartile range; Baseline = time point just before surgery; HP = scrotal hair pluck; SC1 = first scrotal skin cut; TP1 = first spermatic cord ligation; SC2 = second scrotal skin cut; TP2 = second spermatic cord ligation

## Recovery phase

Recovery was characterised as being long and excitement-free. None of the cats required emergency reversal of any drugs. Three cats in MedK group had emesis during recovery compared to no cats in the other treatment groups ($p = 0.03$). Duration of euphoria was longer in the MedKM ($p = 0.003$) and MedKT ($p = 0.006$) groups compared to MedK group. Proportion of cats with mydriasis was different among groups ($p = 0.046$). MedKM and MedKT treated cats had mydriatic pupils up to 8 hours post-injection compared to 4 hours in MedK cats.

## Pain scoring

Multidimensional composite pain scores and VAS scores did not vary among groups (Table 6). The VAS scores recorded were 0 in almost all cats, except in two cats assigned to MedK and MedKM groups and one assigned to the MedKT group that obtained a score of less than 30%. Cats had a significantly higher multidimensional composite pain score when they were sedated compared to when they were non-sedated ($p < 0.001$). Sedation was noticed in 9 cats from each treatment group 4 hours after T0; in 5 cats from the MedKM, 5 cats from the MedKT and 1 cat from the MedK groups 6 hours after T0; and in 2 cats from the MedKT group 8 hours after T0 ($p = 0.190$). Mechanical threshold measurements also did not vary among groups; however, they varied over time differently by treatment ($p < 0.001$). Mechanical threshold values within the MedK group returned to baseline more rapidly than in MedKM and MedKT groups (Figure 2).

**Table 6.** Descriptive statistics and comparisons among treatments for multidimensional composite pain scores evaluated at different time points during recovery, expressed as time after injection of the drugs (T0). Data reported as median (IQR).

| Time (Hour) | MedK | MedKM | MedKT | p Value |
|---|---|---|---|---|
| 3 | 4.0 (3.0, 5.0) | 4.5 (3.5, 5.3) | 4.5 (3.8, 5.3) | 0.644 |
| 4 | 2.0 (1.0, 4.0) | 2.5 (1.8, 4.0) | 3.5 (1.8, 5.0) | 0.375 |
| 5 | 2.0 (1.0, 2.3) | 2.0 (1.0, 2.5) | 2.0 (0.8, 3.0) | 0.982 |
| 6 | 1.0 (0, 1.3) | 1.0 (0, 1.3) | 1.0 (0, 2.3) | 0.809 |
| 7 | 0 (0, 1.3) | 0 (0, 1.3) | 0.5 (0, 1.3) | 0.730 |
| 8 | 0 (0, 1.3) | 0 (0, 0.3) | 0 (0, 0.3) | 0.782 |

IQR = interquartile range.

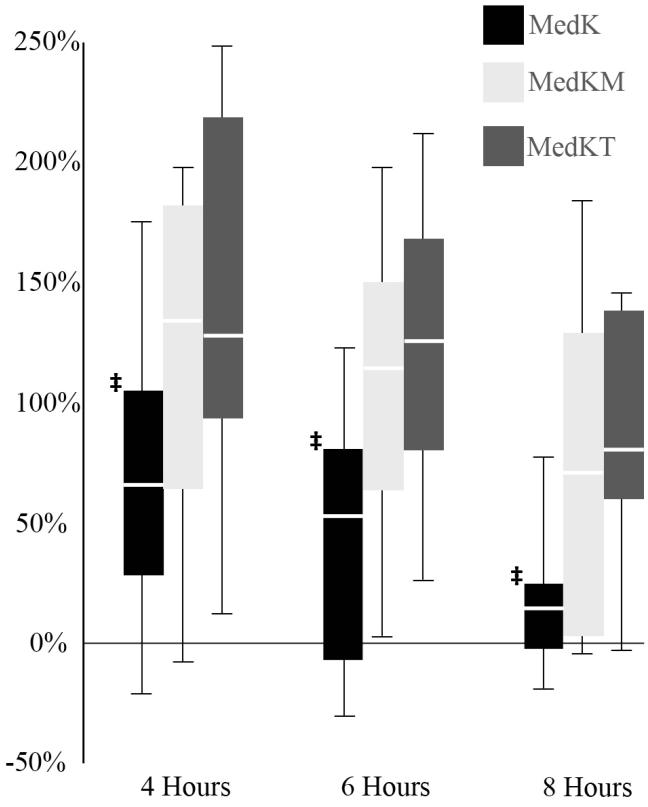


**Figure 2.** Descriptive statistics and comparison among treatments for percent (%) change from baseline (0%) von Frey values over time (hours) from T0. ‡Statistically significant finding where MedK return to baseline values faster compared to MedKM and MedKT.

## Discussion

The present study demonstrated that medetomidine and ketamine administered in combination intramuscularly, or further combination with morphine or tramadol induced a similar, rapid and stable general anaesthetic associated with arousal requiring isoflurane rescue during surgery. All combinations provided adequate analgesia for orchiectomy in domestic cats. Clinically significant findings included a moderate hypoxemia detected on arterial blood gas analysis and $SpO_2$ in all treatment groups; and an increased mechanical stimulus threshold for a longer duration within the MedKM and MedKT treatment groups despite having a descriptively higher multidimensional composite pain score when compared to the MedK treatment group. Other clinically relevant findings included the need for alfaxalone rescue to allow endotracheal intubation in 2 cats from the MedKM treatment group and emesis during the recovery phase of 3 cats from the MedK treatment group.

Ketamine has been previously used with success for induction and maintenance of general anaesthesia in cats at doses of 10 mg $kg^{-1}$ (Harrison et al. 2011) and 5 mg $kg^{-1}$ (Wiese et al. 2007). Medetomidine has a wide published dose range, recent publications report doses of 100 µg $kg^{-1}$ (Harrison et al. 2011) and 60 µg $kg^{-1}$ (Wiese et al. 2007) administered with ketamine and an opioid in combination. Morphine administered at 0.2 mg $kg^{-1}$ in combination with ketamine and medetomidine has been studied in cats using noxious stimulation by applying a Pean intestinal clamp to the metatarsus and tail base (Wiese et al. 2007). Tramadol administered alone at 2 mg $kg^{-1}$ either subcutaneously (Brondani et al. 2009) or intravenously (Cagnardi et al. 2011) was considered cardiovascularly safe and provided adequate analgesia for gonadectomy in domestic cats.

Low lingual $SpO_2$ readings have been recorded in studies using combinations of ketamine (10 mg $kg^{-1}$), medetomidine (100 µg $kg^{-1}$) and buprenorphine (10 µg $kg^{-1}$) (Harrison et al. 2011) or

tiletamine/zolazepam (4 mg $kg^{-1}$), ketamine (6.5 mg $kg^{-1}$) and xylazine (1.65 mg $kg^{-1}$) (Cistola et al. 2004) in cats. These studies postulated hypoxemia as the cause of the low $SpO_2$ readings, but did not perform arterial blood gas analysis to confirm the low $PaO_2$. It has also been postulated that intense peripheral vasoconstriction due to medetomidine and xylazine could have influenced the accuracy of the lingual $SpO_2$ readings (Cistola et al. 2004, Harrison et al. 2011). A reading of 88% on the pulse oximeter used in the present study was associated with a $PaO_2$ of 66.8 mmHg, which is consistent with studies of feline oxygen haemoglobin saturation (Cambier et al. 2004). This finding suggests that the pulse oximeter was able to accurately detect low oxygen haemoglobin saturation despite the intense peripheral vasoconstriction. This means that the pulse oximeter used in this study may be a reliable tool to use clinically to estimate the peripheral oxygen haemoglobin saturation in cats anaesthetised using these drugs. The present study observed a clinically significant increase in the $SpO_2$ reading once the side-stream sampling line was removed from the endotracheal tube. This could suggest that a sampling rate of 200 mL $min^{-1}$ was high enough to alter the inspired alveolar gas mixture. The mean calculated minute volume for the 30 cats was 609 mL $min^{-1}$, which means the sampling line was extracting 33% of the minute volume of gases for analysis. Retrospectively, the sampling rate should have been adjusted to 50 mL $min^{-1}$ to lessen the effects on the pulse oximeter reading and perhaps the arterial blood gas results.

The $PaO_2$ of 66.8 mmHg was lower than expected based on predicted $PaO_2$ levels. The predicted $P_AO_2$ based on the altitude and ambient temperature in theatre was (mean ± SD) 84.7 ± 4.3 mmHg. The expected $PaO_2$ levels may be slightly lower than this value, often in the order of 3.75 to 15 mmHg less due to physiological right-to-left shunting (Baylis et al. 2009). Unfortunately, no arterial blood gas samples were analysed in awake, non-sedated cats before anaesthesia to determine the normal $PaO_2$ range. The possible causes for the low $PaO_2$ values detected within the present study include: 1) the side-stream sampling rate being excessively high thus decreasing the minute volume of gases within the

lung; 2) an increase in oxygen extraction ratio (normal range: 20 to 30%) (McLellan et al. 2004) probably caused by the increased transit time of blood within the systemic circulation (Cullen 1996); 3) the P(A-a)$O_2$ gradient was slightly higher compared to the normal expected range of 3.75 to 15 mmHg (Baylis et al. 2009), which suggests a ventilation-perfusion (V/Q) mismatch. Another possible cause suspected to have contributed to the low $PaO_2$ values is the cardiovascular effects of medetomidine, which include: decreased cardiac output, decreased transit time of blood through the alveolar capillary bed hindering equilibration of gases during diffusion and increased right-to-left shunting fraction (Sinclair 2003).

The $PaCO_2$ and $PETCO_2$ values were within expected physiological range and did not suggest respiratory depression, as observed in previous studies (Wiese et al. 2007, Cistola et al. 2004, Harrison et al. 2011) using similar drug combinations. Therefore, respiratory depression was unlikely to have contributed to the decreased $PaO_2$ values reported.

Surgical stimulation significantly increased the HR, SABP and $f_R$ which suggests that the plane of anaesthesia was allowing autonomic responses to occur in response to surgery. Isoflurane rescue was needed in some cats, which is similar to findings of previous studies using similar combinations (Wiese et al. 2007, Cistola et al. 2004, Harrison et al. 2011). The long time frame from induction to start of surgery (mean ± SD: 22.2 ± 1.6 min) was suspected to have contributed to arousal during surgery due to waning of the clinical effects of the drugs (Cagnardi et al. 2011, Pypendop et al. 2008, Hanna et al. 1988, Salonen 1989, Taylor et al. 2001). This was also the time when the monitored parameters (HR, SABP and $f_R$) returned to normal expected values, which supports this hypothesis. Alfaxalone rescue was required for intubation in 2 cats within the MedKM group, which has been described in a previous study using the same combination at a different ketamine dose (5 mg $kg^{-1}$) (Wiese et al. 2007). These findings suggest that not all cats may be induced into a deep enough surgical plane of anaesthesia with the doses

administered in the present study and that a rescue induction and maintenance anaesthetic agent should be administered when required.

The recovery phase was long and excitement-free with all combinations. There is lack of data in the literature describing quality of recovery where medetomidine had not been antagonised with atipamezole. A potential clinical concern of not antagonising the combination is the high incidence of emesis during the early recovery phase as observed in the MedK group which may lead to aspiration pneumonia if consciousness has not been fully recovered. On the other hand, a concern of routine antagonisation of medetomidine in these protocols is the reversal of the analgesia, potentially rendering the animals painful if no other analgesic drugs are administered. Thus it is imperative to provide appropriate analgesia for the anticipated level of pain prior to antagonising the effects of medetomidine.

Various methods have been used to detect mechanical (Brondani et al. 2009, Castro et al. 2009, Steagall et al. 2008) and thermal (Pypendop et al. 2009) analgesic properties of drugs in cats. In the present study, a rigid tip von Frey mechanical threshold device was applied to the mid-thorax as opposed to a tension bracelet (Steagall et al. 2008, Steagall et al. 2007) applied to the distal limb used in previous studies. A rigid tip von Frey device, as used in the present study, has been successfully used to evaluate the antinociceptive effects of morphine in a pharmacodynamic modelling study in dogs (KuKanich et al. 2005). The baseline readings were aimed at gauging the cats' natural responses to this type of stimulation and to determine the individual end-points for the cats. The pre-determined end-point was then used for that individual cat throughout all measurements post-injection. The von Frey device was found to be useful to assess length of analgesia to mechanical stimulation in this study. Cats in the MedKM and MedKT groups had higher mechanical thresholds for longer compared with the MedK

group, which was probably due to the analgesic effects of the opioids used within the combinations. No statistically significant relationship was found between the level of sedation and the increased mechanical thresholds among the treatment groups. A previous study in dogs using the von Frey device was able to detect a difference in mechanical nociception threshold between sedated and un-sedated dogs (KuKanich et al. 2005). A potential additional use of the von Frey device is that it could be applied around a surgical site to determine sensitivity to mechanical stimulation to detect changes in peripheral sensitisation (Brondani et al. 2009). This was not performed in the present study due to the difficulty in applying the device around the peri-scrotal area to obtain accurate baseline readings to compare to the post operative readings. The mid-lateral thorax proved to be an anatomical area that most cats tolerated well allowing a steady application of pressure required by the device to detect mechanical stimulation thresholds.

The multidimensional composite scores were higher during the first few hours and gradually decreased over time, which is contrary to the anticipated results. It was anticipated that as the analgesic effects of the drugs wore off then the score would increase due to the pain. Rather the scoring system tended to penalise sedated cats due to their quieter nature (Brondani et al. 2011), making it difficult to evaluate true pain in sedated cats using this scale. None of the pain scoring systems used in the study could detect any difference between treatment groups, which suggests that the systems are not sensitive enough to detect pain or that the pain was not severe enough to allow detection.

Limitations of the study include a small sample size for some analysed parameters (e.g. pain scoring systems, sedation scores) unrelated to the sample size calculation, the high side-stream sampling rate of the gas analyser, orchiectomy not being painful enough to detect the analgesic effects of the combinations or to detect significant pain using the pain scoring systems, or that indeed there were no

differences between the combinations used. The delay between induction and start of surgery due to instrumentation and base line sample collection may have negatively influenced the efficacy of the combinations to provide adequate surgical anaesthesia as the effects may have been waning.

## Conclusion

In conclusion, the three drug combinations used in the present study provided similar anaesthetic, analgesic and cardiorespiratory effects in cats undergoing orchiectomy. Rescue induction and maintenance agents should be readily available when these drug combinations are used for surgical anaesthesia in cats. Hypoxaemia is a concern with all the studied combinations and oxygen supplementation is recommended**.**

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# Addendum

## Contents

# Informed Consent (Form A-1)

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

## Brief Overview of Study

Many South African veterinary practices make use of intramuscular injected drug combinations to induce surgical anaesthesia in cats for routine sterilisation. Many of these combinations do not incorporate an effective analgesic (pain killer). This has many ethical repercussions. The Department of Anaesthesiology is conducting a clinical trial to compare three new drug combinations that are based on sound surgical anaesthetic and analgesic properties. In order to conduct this study we need to source young, healthy, un-sterilised male domestic cats and are asking for you facility's assistance.

## Brief Overview of the Procedure

Cats will arrive at Onderstepoort Veterinary Academic Hospital and be booked into the clinical trial. The first stage is an acclimatisation phase where the cats will be allowed to settle into their enclosure. A basic clinical examination, blood and parasite tests will be conducted. These are not painful to the cat. If they are relaxed and healthy they will enter the procedure stage of the clinical trial. The cats will be assigned randomly to one of three groups. On the day of the sterilisation they will be starved, as per standard pre-anaesthesia requirements. They will be induced into a surgical plane of anaesthetic and a bilateral orchiectomy will be done. There will be additional blood tests and an arterial catheter will be placed to monitor blood pressure during the surgery. These additional tests are not harmful to the cat and potential complications are not expected during the study.

## Timeframe and Schedule for Cats

- **Day one:** arrive at Onderstepoort Veterinary Academic Hospital, basic clinical examination, begin acclimatisation phase
- **Day three:** Pre-procedure examination, blood and parasite test
- **Day four:** Procedure
- **Day five to seven:** monitoring analgesic effect of combination
- **Day seven:** discharged from study in the afternoon after the final data collection.

This is a typical time schedule for a cat moving through the stages of the study. Cats are expected to have a variation in the acclimatisation phase which may prolong the stay at the Hospital. A good line of communication will be established if the cats need to be returned to the facility at a later date than expected.

## Informed Consent to Provide Cats for the study

I/We _____

of the _____

Facility give permission and informed consent to provide friendly, young (6 months to 4 years old), unsterilized, healthy male domestic cats, with normal body condition (not skinny nor obese) to participate in the Department of Anaesthesiology Clinical Study with the following conditions:

1. Once the cats 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 7

day timeframe as described in the "Timeframe and Schedule for Cats" 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 cats to and from your facility at our costs.
3. Cats enrolled in the clinical study will undergo a standard, routine bilateral orchiectomy.
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 cats.
6. The cats will be kept in an indoor enclosure facility to provide a warm, quite and friendly environment throughout their stay. They will be attended to several times per day to ensure their comfort and wellbeing.
7. If the cats experience pain post-surgery a rescue analgesic (pain killer) will be administered to ensure pain relief.
8. The cats will be shaved on their ventral abdomen and at least two legs to allow intravenous and intra-arterial catheter placement. The hair is expected to grow back within 6 weeks post study.
9. All cats will be dewormed after the data collection phase of the study.
10. All cats will be fed Hills Feline of Royal Canine cat food during their stay at our facility.
11. Your facility may opt to have the cats returned to your facility post study, or donate them to our facility so we may attempt to find owners for the cats, or insist on euthanasia. This information must be indicated on Form A2 "Admission Information" for each cat leaving the facility.
12. If euthanasia is elected your facility may insist on having the carcasses returned to your facility for disposal or allow our facility to dispose of the carcases.
13. If the cats have owners, it is your duty to inform them of the study and the potential time delay in getting their cat back from the surgery. The cats will not, under any circumstances be released from the study at an earlier stage.
14. Aggressive cats, feral cats that cannot be safely handled may not be included in the study.
15. In the very unlikely event of a death during the cat'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 cat needs to be returned to your facility and a comprehensive report will be issued.
16. 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 cat's stay at our facility.
17. 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.
18. Our facility will make every effort to provide the best care and attention for the cats during their stay at the Onderstepoort Veterinary Academic Hospital.
19. Your facility will not be charged (billed, invoiced) for any of the work conducted on the cats during their enrolment in the trial, this includes deworming, the surgery, the food and boarding.
20. The veterinarians conducting the study have a right to exclude any cat obtained from your facility that do not conform to the requirements (friendly, healthy, good body condition score, young, unsterilised, male) of the study participants.
21. The cats cannot be vaccinated during the study due to a possible change in the study variables. We will allow micro-chipping at your cost while the cats are under general anaesthetic if required by your facility's adoption protocol.

22. Cats may not be vaccinated within 14 days before the study. It is your obligation to inform us if the cat has been vaccinated 14 days or less before the study. These cats will be excluded from the study due to potential variables that may alter the results of the study.

If your facility consents to assisting our important clinical study that is not harmful to the cats then please indicate the number of cats you will be willing to assist with:

☐ 5 Cats ☐ 10 Cats ☐ 15 Cats ☐ **20 Cats** ☐ 30 Cats ☐ 50 Cats

*Indicating the number here is an obligation to provide the cats within a 16 week period.*

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: _____

# General Anaesthetic Data Capture Form Cat Study (Form C4)

## Log Information:

Person Capturing Data: _____

Cat's Study Log Number: _____

Cat's Cage Number: _____

Signature: _____

**Induction**

| Parameter | Time after T0 |
|---|---|
| Head drops | |
| Lateral Recumbency | |
| Legs Relaxed | |
| Loss of Pedal Reflex | |
| Lateral Recumbency | ☐ Assisted<br>☐ On Own |
| Vomiting | ☐ Yes<br>☐ No<br>☐ Retching |

**Recovery**

| Parameter | Time after T0 |
|---|---|
| Ear Flick (Extubation) | |
| Regain Pedal Reflex | |
| Conscious | |
| Head Lift | |
| Ambulatory | |
| Vomiting | ☐ Yes<br>☐ No<br>☐ Retching |
| Excitement | ☐ Yes<br>☐ No |

Surgery

| Time | Heart Rate | Resp Rate | SABP | MABP | DABP | Doppler BP | ETCO2 | SpO2 |
|---|---|---|---|---|---|---|---|---|
| 0 | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| 5 | | | | | | | | |
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| 10 | | | | | | | | |
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| 15 | | | | | | | | |
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| 60 | | | | | | | | |
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| 65 | | | | | | | | |
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| 70 | | | | | | | | |
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| | | | | | | | | |
| 75 | | | | | | | | |
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| | | | | | | | | |

Surgery Time Points

Record hair pluck in right boarder margin.

| | 1st Skin Cut | 1st Tes | 2nd Skin cut | 2nd Tes |
|---|---|---|---|---|
| HR | | | | |
| RR | | | | |
| SAPB | | | | |
| MABP | | | | |
| DABP | | | | |
| Dop BP | | | | |
| | | | | |
| | | | | |
| ETCO2 | | | | |
| SpO2 | | | | |

# Multidimensional Composite Scale Score Sheet (Form D-2)

## Log Information:

Date of Post-Anaesthetic Evaluation: _____:_____:20____
Person Capturing Data: _____
Cat's Study Log Number: _____
Cat's Cage Number: _____
Signature: _____

## Questions Needing Answers

| Factor | Item | Description | Score |
|---|---|---|---|
| Psychomotor Change | Posture | Cat is in any usual posture for the species; cat looks comfortable and relaxed.<br>Cat is lying in lateral recumbency; pelvic limbs are extended or partially extended and muscles are tense.<br>Cat is in sternal recumbency with arched back and head held low; cat may be in any position, but it has tense muscles and is reluctant to move.<br>Cat adopts different postures in an attempt to find a comfortable position. | 0<br>1<br>2<br>3 |
| | Comfort | Cat is awake or asleep; when stimulated, it is interested in its surroundings.<br>Cat is quiet and dissociated of its environment; when stimulated, it is not interested in its surroundings.<br>Cat may be sitting in the back of the cage or facing the back of the cage.<br>Cat is uncomfortable, agitated, and restless; it lies down and stands up continuously. | 0<br>1<br>2 |
| | Activity | Cat moves in a normal manner.<br>Cat is quieter than usual.<br>Cat is reluctant to move.<br>Cat frequently changes its body position. | 0<br>1<br>2<br>3 |
| | Mental Status | Observation of mental status A.<br>Observation of 1 of mental status B, C, D, or E.<br>Observation of 2 of mental status B, C, D, or E.<br>Observation of 3 or 4 of mental status B, C, D, or E. | 0<br>1<br>2<br>3 |
| Categories were as follows: A = Satisfied (cat is alert and interested in its surroundings; it is friendly and interacts with the observer), B = Uninterested (cat does not interact with the observer), C = Indifferent (cat is not interested in its surroundings), D = Anxious (cat is nervous or frightened and attempts to hide or escape), and E = Aggressive (cat is aggressive and tries to bite or scratch the observer after the slightest manipulation). | | | |

| | | | |
|---|---|---|---|
| | Miscellaneous behaviours | Observation of none of the listed behaviours.<br>Observation of 1 of the listed behaviours.<br>Observation of 2 of the listed behaviours.<br>Observation of 3 or 4 of the listed behaviours. | 0<br><br>1<br>2<br>3 |
| The 4 behaviours were as follows: the cat wags its tail excessively, contracts and extends its pelvic limbs or contracts the abdominal muscles, has partially closed eyes (ie, squinted eyes), or frequently licks or chews the wound area. | | | |
| | | Partial score | |
| Protection of wound area | Reaction to palpation of the surgical site | Cat does not react when the surgical wound is touched or pressed, or response to palpation is similar to that during preoperative evaluation (if preoperative value surgical wound was recorded).<br>Cat does not react when the surgical wound is touched but flinches and may vocalize when surgical wound is pressed.<br>Cat flinches and may vocalize when the surgical wound is touched; cat withdraws and turns its head toward the wound and may vocalize or try to bite when surgical wound is pressed.<br>Cat withdraws with fast and intense head movement toward the wound and may vocalize or try to bite when surgical wound is touched or pressed.<br>Cat vocalizes or tries to bite when the observer approaches and does not permit touching of the surgical wound. | 0<br><br>1<br><br>2<br><br><br>3<br><br>4 |
| | Reaction to palpation of the abdomen and flank | Cat does not react when abdomen and flank are palpated or there is no change from preoperative palpation response (if preoperative value was recorded); abdomen is not tense.<br>Cat vocalizes or tries to bite when abdomen and flank are palpated; abdomen is tense.<br>Cat vocalizes or tries to bite when the observer approaches; cat does not permit any touching of the abdomen or flank. | 0<br><br><br>1<br><br>2 |
| Vocal expression of pain | Vocalization | Cat purrs when touched or meows and interacts with observer, but it does not groan, hiss, or growl.<br>Cat vocalizes (groan, hiss, or growl) when observer approaches, but it calms down when touched.<br>Cat vocalizes (groan, hiss, or growl) when observer approaches, and it does not calm down when touched. | 0<br><br>1<br><br>2 |

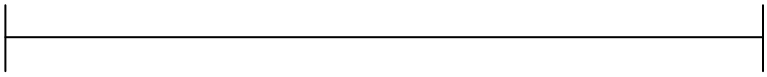
| | | | |
|---|---|---|---|
| | | Cat vocalizes (groan, hiss, or growl) spontaneously. | 3 |
| | | Partial score | |
| | | Total score | |
| Rescue analgesia needed: □ Yes □ No | | | |
| Guidelines for use of the composite pain scale—The observer should choose only 1 value within each item that best fits the cat's condition. Initially, the cat's behaviour may be assessed from outside the cage. Observe whether the cat is at rest or moving, interested or not interested in its surroundings, and silent or vocalizing. Then assess specific behaviours (miscellaneous behaviours). Open the door of the cage and call the cat's name to encourage it to approach to allow assessment of evoked behaviours and interaction with the observer. Assess its reaction (friendly, aggressive, scared, indifferent, or vocal). Touch the cat and interact with it while observing whether it is receptive. If the cat is resting, encourage it to move by placing it in a standing position. Observe whether the cat moves spontaneously or is reluctant to move. When possible, the cat should be removed from the cage to assess activity. Observe the cat's response after stimulating its interest in its surroundings by playing with it, offering it food, or talking to it. Gently place the cat in lateral or ventral recumbency and measure SABP. Finally, assess the cat's reaction when the area around the surgical wound is touched and then gently pressed; perform the same procedure with the abdomen and flank, if appropriate. | | | |

(Brondani et al. 2011)

## VAS Score

0 is no pain seen
10 is maximum pain
Place a cross over the line where you think the cat's level of pain fits in.
Assign VAS score before Composite Score.

0 10



# Presentations and publication arising from study

The outcome of the study achieved its objective of contributing to the literature. The following presentations and publication were compiled from the study.

## Presentations

| Event | Venue | Date | Title | Type |
|---|---|---|---|---|
| **Faculty Day** | Faculty of Veterinary Science, Onderstepoort | 6 September 2012 | Anaesthetic, analgesic and cardiorespiratory effects of intramuscular medetomidine and ketamine alone or in combination with morphine or tramadol for orchiectomy in cats. | Abstract presentation |
| **World Congress of Veterinary Anaesthesiology 2012** | Cape Town International Convention Centre | 25 September 2012 | Anaesthetic, analgesic and cardiorespiratory effects of intramuscular medetomidine and ketamine alone or in combination with morphine or tramadol for orchiectomy in cats. | Abstract presentation |

## Publication

**Zeiler GE, Dzikiti BT, Fosgate GT, Stegmann FG, Venter FJ, Rioja E**. Anaesthetic, analgesic and cardiorespiratory effects of intramuscular medetomidine-ketamine combination alone or with morphine or tramadol for orchiectomy in cats. *Veterinary Anaesthesia and Analgesia (in press).*