UNIVERSITI PUTRA MALAYSIA

THE EFFECT OF PRE-EMPTIVE GABAPENTIN, TRAMADOL, AND MIDAZOLAM AS PRE-ANESTHETIC MEDICATIONS ON PROPOFOL INDUCTION DOSAGE AND RECOVERY TIME IN CATS

LOO JIE REN

The effect of pre-emptive gabapentin, tramadol, and midazolam as pre-anesthetic medications on propofol induction dosage and recovery time in cats

LOO JIE REN

A project paper submitted to the
Faculty of Veterinary Medicine, Universiti Putra Malaysia (UPM)

In partial fulfillment of the requirement for the
DEGREE OF DOCTOR OF VETERINARY MEDICINE
Universiti Putra Malaysia
Serdang, Selangor Darul Ehsan

DECEMBER 2023

CERTIFICATION

It is hereby certified that we have read this project paper entitled “The effect of pre-emptive gabapentin, tramadol, and midazolam as pre-anesthetic medications on propofol induction dosage and recovery time in cats”, by Loo Jie Ren and in our opinion, it is satisfactory in terms of scope, quality and presentation as partial fulfilment of the requirement for the course VPD4999 – Final Year Project.

DR. BENEDICT ONG HUAI ERN
DVM (UPM), MVM (UPM), PHD (MIYAZAKI)
Senior Lecturer,
Faculty of Veterinary Medicine,
Universiti Putra Malaysia.
(Supervisor)

DR. MICHELLE FONG WAI CHENG
DVM (UPM), PHD (UPM)
Senior Lecturer,
Faculty of Veterinary Medicine,
Universiti Putra Malaysia.
(Co-Supervisor)

DEDICATION

This study is wholeheartedly dedicated to my respected supervisor and co-supervisor, for being my guidance and motivators.

To my family who become my spiritual and emotional support.

ACKNOWLEDGEMENT

First and foremost, I would like to acknowledge and express my gratitude towards my supervisor, Dr. Benedict Ong Huai Ern for his continuous guidance and advice which carried me through all the stages of my project.

The same goes for my co-supervisor, Dr. Michelle Fong Wai Cheng for her assistance and motivation.

I want to thank my friends who always lend a helping hand and emotionally support me.

Finally, I would like to thank my family members who support and inspire me.

CONTENTS

LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS

ASA	= American Society of Anesthesiologists
et al.	= *et al* (abbr. Latin) *et alii* (and others)
GTM	= Gabapentin, Tramadol, Midazolam
HCM	= Hypertrophic Cardiomyopathy
IACUC	= Institutional Animal Care and Use Committees
IM	= Intramuscular
kg	= Kilogram
LVOT	= Left ventricular outflow tract
MAC	= Minimum alveolar concentration
MAOIs	= Monoamine oxidase inhibitors
mg	= Milligram
mins	= Minutes
ml	= Millilitre
n	= Sample size
NS	= Normal Saline
p	= Probability value
SAM	= Systolic anterior motion
SEM	= Standard error of mean
UPM	= Universiti Putra Malaysia
UVH	= University Veterinary Hospital Universiti Putra Malaysia

ABSTRAK

Abstrak kertas projek yang dikemukakan kepada Fakulti Perubatan Veterinar untuk memenuhi sebahagian daripada kursus VPD 4999 - Projek Tahun Akhir.

KESAN GABAPENTIN, TRAMADOL, DAN MIDAZOLAM SEBAGAI UBAT PRA-PEMBEDAHAN TERHADAP DOS INDUKSI PROPOFOL DAN MASA PEMULIHAN PADA KUCING

OLEH

LOO JIE REN

2023

Penyelia: Dr. Benedict Ong Huai Ern

Penyelia bersama: Dr. Michelle Fong Wai Cheng

Penggunaan ubat penenang yang optimum untuk mengurangkan keperluan anestesia am adalah penting dalam mengelakkan komplikasi yang memudaratkan seperti apnea, pemulihan yang berpanjangan, aritmia, bradikardia, dan kegagalan buah pinggang akut. Walaupun begitu, kesan ubat-ubatan sedatif yang biasa digunakan di Malaysia belum dikaji secara meluas. Gabapentin dan Tramadol adalah ubat-ubatan yang biasa digunakan dalam klinik swasta, sebagai pengurusan kesakitan yang berkesan, dan untuk mengurangkan keperluan anestesia am bagi kucing sihat yang menjalani ovariohisterektomi. Walaupun penggunaannya yang luas, terdapat maklumat terhad mengenai kesan premedikasi ubat-ubatan ini terhadap keperluan dos propofol untuk induksi dan masa pemulihan pada kucing. Oleh itu, kajian ini bertujuan untuk membandingkan kesan premedikasi gabapentin, tramadol, dan midazolam sebagai ubat pra-anestesia terhadap dos induksi propofol dan masa pemulihan pada kucing. Sejumlah enam ekor kucing yang memerlukan anestesia umum untuk pembedahan telah dipilih sebagai subjek kajian. Setiap pesakit telah diagihkan sebagai kumpulan kawalan negatif (normal saline sahaja sebagai plasebo) (n=3) atau kumpulan gabapentin, tramadol, dan midazolam (n=3). Jumlah dos propofol yang diperlukan untuk induksi yang berjaya dan masa dari induksi hingga gerakan pertama telah diukur. Keputusan menunjukkan bahawa purata dos propofol (mg/kg) yang diperlukan untuk pesakit yang disedasi dengan gabapentin, tramadol, dan midazolam adalah lebih rendah secara signifikan (p=0.001) berbanding kumpulan kawalan negatif. Walau bagaimanapun, tiada perbezaan yang signifikan (p=0.016) dalam masa pemulihan antara kumpulan gabapentin, tramadol, dan midazolam dan kumpulan kawalan negatif.Berbanding dengan kumpulan kawalan negatif yang menerima normal saline, penggunaan gabapentin, tramadol, dan midazolam sebagai ubat pra-anestesia memerlukan dos propofol yang lebih rendah secara keseluruhan untuk induksi, tetapi memerlukan masa pemulihan yang lagi lama. Kesimpulannya, pentadbiran sedasi sebelum induksi dapat mengurangkan keperluan propofol secara berkesan, dengan itu meningkatkan keselamatan kucing dalam kajian kami.

Kata kunci : gabapentin, kucing, midazolam, propofol, tramadol.

ABSTRACT

An abstract of the project paper presented to Faculty of Veterinary Medicine in partial fulfillment of the course VPD 4999 - Final Year Project.

THE EFFECT OF PRE-EMPTIVE GABAPENTIN, TRAMADOL, AND MIDAZOLAM AS PRE-ANESTHETIC MEDICATIONS ON PROPOFOL INDUCTION DOSAGE AND RECOVERY TIME IN CATS

By

LOO JIE REN

2023

Supervisor: Dr. Benedict Ong Huai Ern

Co-supervisor: Dr. Michelle Fong Wai Cheng

The appropriate usage of sedation to reduce the requirement for general anaesthesia is crucial in avoiding detrimental complications, such as apnea, prolonged recovery, arrhythmia, bradycardia, and acute kidney failure. However, the effects of common sedative drugs used in Malaysia have not been extensively studied. Gabapentin and tramadol are commonly used drugs in private clinic settings, providing effective pain management and reducing the general anaesthesia requirement for healthy cats undergoing ovariohysterectomy. Despite their widespread use, limited information exists on the pre-emptive effects of these medications on propofol dosage requirements for induction and recovery time in cats. Therefore, this study aimed to compare the effects of pre-emptive administration of gabapentin, tramadol, and midazolam as pre-anesthetic medications on propofol induction dosage and recovery time in cats. A total of six cats requiring general anaesthesia for surgery were recruited as study subjects. Each patient was assigned to either the negative control group (normal saline only for placebo) (n = 3) or the gabapentin, tramadol, and midazolam group (n = 3). The total propofol dosage needed for successful induction and the time from propofol cessation to the patient’s first swallowing reflex were measured. The results revealed that the average propofol dosage (3.77 ± 0.12 mg/kg) requirement for patients sedated with gabapentin, tramadol, and midazolam (GTM) was significantly lower ($p = 0.001$) than that of the negative control group (10.43 ± 0.81 mg/kg). The groups administered with GTM (11.67 ± 1.2 min) have significantly longer recovery time ($p = 0.016$) when compared to the negative control group (4.23 ± 1.4 min). Compared to the negative control group receiving normal saline, the use of gabapentin, tramadol, and midazolam as pre-anesthetic medications required a lesser propofol dosage for induction but resulted in a longer recovery time. In conclusion, administering GTM before induction can effectively reduce propofol requirements, thereby enhancing cats' safety in the present study.

Keywords : cats, gabapentin, midazolam, propofol, tramadol.

1.0 INTRODUCTION

Propofol is an anesthetic drug. It works by increasing the effects of a calming brain chemical called GABA and reducing brain activity (Berry, 2015). When administered, propofol can cause a significant drop in blood pressure (Berry, 2015). Propofol can also lead to temporary apnea after receiving the drug (Berry, 2015). This can increase the risks during surgery and may even be life-threatening if not managed carefully. Propofol also reduces intracranial and blood flow to the brain (Branson, 2007). It temporarily lowers blood pressure and heart function (Branson, 2007). Furthermore, propofol intensifies the arrhythmogenic impacts when combined with epinephrine (Branson, 2007). To ensure a cat's safety, it's crucial to give as little dose as possible to achieve jaw relaxation for intubation, as too high a dose can lead to these negative effects.

Based on the literature, midazolam given before surgery can reduce the amount of anesthetic needed for induction and maintenance (Robinson *et al*, 2015). Midazolam can decrease the necessary dose of propofol for endotracheal intubation when compared to using propofol with saline in cats (Robinson *et al*, 2015). When midazolam is administered before anesthesia, it lowers the amount of barbiturates and propofol needed for the initial anesthesia and reduces the concentration of isoflurane required to maintain anesthesia during surgery in dogs (Lemke, 2007).

In our study, we aim to identify the effect of pre-emptive gabapentin, tramadol, and midazolam as preanesthetic medications on propofol induction dosage, and recovery time in cats. We employ a premedication protocol for sedation that consists of a combination of gabapentin, tramadol, and midazolam. Gabapentin and tramadol are commonly used drugs in clinical settings in Malaysia. We have chosen to use this combination of drugs in our project because when midazolam is administered alone, cats tend to exhibit excitatory side effects, becoming less sedate, and showing signs of excitement or agitation as the dosage increases (Rankin, 2015). Hence, we use the protocol because a combination of drugs has demonstrated better sedation and analgesia levels, as well as improved quality of recovery compared to using each drug alone, allowing for lower doses of individual drugs to be administered in cats (Simon, 2020). Utilizing multiple drugs that target different pathways in the central nervous system may produce a more balanced and synergistic sedative effect in humans (Brown *et al*, 2018).

The propofol dosage requirements and the recovery times will be determined in two separate groups: one with sedation (gabapentin, tramadol, midazolam) administration and the other without sedation (normal saline) administration.

The study hypothesises that the group receiving gabapentin, tramadol, and midazolam (GTM) will necessitate a lower amount of propofol for induction compared to the group with normal saline (NS). However, it is expected that the GTM group may experience a prolonged recovery period, while the NS group is anticipated to have a shorter recovery time.

1.1 RESEARCH FOCUS

The primary objective of this study is to investigate the effect of preanesthetic medications, the combination of gabapentin, tramadol, and midazolam (GTM), on propofol induction dosage and recovery time in cats undergoing anesthesia. The study aims to assess whether the administration of GTM results in a reduced requirement for propofol during induction compared to a control group receiving normal saline (NS). Furthermore, the research assesses the recovery times in both groups, hypothesizing that the GTM group may experience an extended recovery period while anticipating a shorter recovery time in the NS group.

2.0 LITERATURE REVIEW

2.1 SEDATION REDUCES THE GENERAL ANESTHESIA REQUIREMENTS

Cats are highly susceptible to stress, especially during physical examination, pre-surgery preparation, and rough handling. Stress can lead to tachycardia and the release of catecholamines. High levels of preoperative anxiety required a greater amount of propofol to maintain a clinically acceptable level of sedation. (Osborn *et al*., 2004).

In cats, oral administration of gabapentin two hours before starting minimal alveolar concentration (MAC) determination had a significant isoflurane MAC-sparing effect (Chen *et al*. 2023). Building upon this knowledge, our study aims to investigate whether adding gabapentin with tramadol and midazolam will also reduce the need for propofol dosage to achieve successful induction. When administering preanesthetic like morphine or medetomidine beforehand, a significant reduction in the induction dose of propofol can be achieved (Grimm *et al*., 2015).

2.1.1 PROPOFOL

Propofol induces depression by enhancing the effects of the inhibitory neurotransmitter GABA and decreasing the brain's metabolic activity (Grimm et al., 2015).

2.1.2 SIDE EFFECTS OF PROPOFOL

One of the most pronounced cardiovascular effects associated with the administration of propofol is a reduction in arterial blood pressure (Berry, 2015). Propofol inhibits the vasomotor mechanism in the dorsomedial and ventrolateral medulla to affect its hypotensive actions in cats (Yang *et al*., 1997). The myocardial depression and vasodilation appear to be dose (and plasma concentration) dependent (Berry, 2015). Following propofol induction, a brief period of apnea might ensue. In animals with spontaneous breathing, a temporary episode of hypercapnia can occur shortly after a rapid bolus injection of the drug (Berry, 2015). Apnea increases the likelihood of mortality. Thiopental and propofol can cause dose-dependent depression of ventilation and postinduction apnea with transient cyanosis occurring regularly (Berry, 2015). Propofol reduces both intracranial and cerebral perfusion pressures. It induces a momentary decline in arterial pressure and myocardial contractility, akin to the effects observed with ultra-short-acting thiobarbiturates. The occurrence of hypotension is predominantly attributed to the dilation of both arterial and venous blood vessels. Additionally, propofol intensifies the arrhythmogenic impacts caused by epinephrine. Thus, avoiding propofol overdose is crucial for the survival of cats.

2.1.3 METABOLISM OF PROPOFOL

The main metabolic process of propofol occurs within the liver, where it undergoes conjugation pathways to create inactive metabolites (Branson, 2007). These metabolites are subsequently eliminated from the body primarily through urine, with a minor portion also being excreted in bile (Branson, 2007). Cats exhibit extrahepatic metabolism of propofol in the pulmonary tissue. Even in cats with hepatic lipidosis, the use of propofol for anesthesia induction did not increase morbidity or mortality (Garcia-Pereira, 2015).

2.2 HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a prevalent cardiac condition in feline patients. The pathophysiology of HCM involves idiopathic concentric hypertrophy of the left ventricle, leading to an elevated demand for oxygen by the heart muscle (Perkowski *et al*, 2015). The increased oxygen requirement can result in insufficient blood supply to the heart tissue, a condition known as myocardial ischemia (Perkowski *et al*, 2015). Additionally, HCM can lead to the development of an obstruction within the left ventricular outflow tract (LVOT) due to systolic anterior motion (SAM) of the mitral valve leaflets (Perkowski *et al*, 2015). The anesthesia approach for cats with HCM aims to improve diastolic filling. This is achieved by ensuring that heart rates are kept relatively low and by steering clear of medications that could enhance cardiac contractility (Perkowski *et al*, 2015). When venous access is available, midazolam or diazepam, both of which have minimal impact on the cardiovascular system, are frequently used (Perkowski *et al*, 2015).

2.3 GABAPENTIN

Gabapentin is a medication that is used in veterinary medicine to manage chronic pain, especially nerve-related pain, and to relieve anxiety associated with veterinary procedures, travel, and other fear-generating situations (Brooks, 2008). Although gabapentin is a structural analogue of the neurotransmitter gamma-aminobutyric acid (GABA), it appears not to interact with GABA receptors (Pypendop, 2012). Instead, it acts on the locus coeruleus (LC) by blocking voltage-gated calcium channels (VGCCs) and increasing extracellular glutamate, which can activate the descending noradrenergic system (Cesare *et al*, 2023). The most common side effect of gabapentin in cats is mild sedation or lethargy (Brooks, 2008). Other side effects may include vomiting, drooling, and diarrhea, but these side effects should resolve within 8 hours of receiving the medication (Brooks, 2008).

2.4 TRAMADOL

Tramadol is a synthetic compound derived from codeine and falls into the category of opioidergic/monoaminergic drugs (Lemke, 2007). Its mechanism of action involves the inhibition of norepinephrine and serotonin (5-hydroxytryptamine) reuptake in neuronal pathways (Lemke, 2007). These effects on central catecholaminergic pathways are believed to significantly contribute to the drug's efficacy in pain relief (Lemke, 2007). Both tramadol and its metabolite demonstrate agonistic properties toward the μ opioid receptor, concurrently supporting the descending serotonergic system, which plays a vital role in the body's inherent analgesic mechanism (Rankin, 2015).

Special caution is warranted regarding tramadol's influence on 5-hydroxytryptamine reuptake (Lemke, 2007). It is contraindicated for patients who have recently used monoamine oxidase inhibitors (MAOIs) such as selegiline or those with a recent history of seizures (Lemke, 2007).

2.5 MIDAZOLAM

Midazolam belongs to the benzodiazepine class, exerting most of its pharmacological effects by modulating GABA-mediated neurotransmission (Lemke, 2007). It is frequently administered to improve muscular relaxation and assist in the intubation process for dogs and cats, often alongside ketamine (Lemke, 2007). When given before anesthesia (at a dose of 0.1-0.2 mg/kg intravenously), it reduces the necessary amount of barbiturates and propofol during induction, as well as the required concentration of isoflurane for maintaining anesthesia during surgical procedures (Lemke, 2007). The cardiovascular effects of midazolam are minor in most cases (Rankin, 2015).

Cats tend to be less sedate, with excitement or agitation evident as doses increase (from 0.05 mg/kg to a non-clinical dose of 5.0 mg/kg) (Rankin, 2015).

2.5.1 SEDATION REDUCE INDUCTION DOSAGE

Midazolam will reduce the amount of propofol required for endotracheal intubation compared to the amount required when propofol is administered with saline (Robinson *et al*, 2015). To avoid the excitation caused by the administration of midazolam alone in cats, some sedative agents such as propofol will be administered with/before midazolam administration. After midazolam administration, the remaining propofol will be administered titered to effect. In that way, the administration of midazolam can reduce the induction dosage of propofol (Robinson *et al*, 2015).

3.0 MATERIALS AND METHOD

3.1 RESEARCH DESIGN

A prospective study was conducted to compare the effect of pre-emptive gabapentin, tramadol, and midazolam with normal saline as pre-anesthetic medications on propofol induction dosage in cats after obtaining approval from Institutional Animal Care and Use Committees (IACUC) of UPM (Reference Number: UPM/IACUC/AUP -U034/2023).

3.2 STUDY POPULATION

A total of six cat patients admitted into Universiti Veterinary Hospital, Universiti Putra Malaysia for surgeries in 2023 with the criteria of requiring general anesthesia and being classified as American Society of Anesthesiologists (ASA) class I to III were recruited into this study as our study subjects.

3.3 MATERIALS AND METHODS

3.3.1 TREATMENT GROUPS

The six cats were randomly assigned to two different sedation protocols, with three cats in each group. The first protocol involved administering a Gabapentin tablet (20 mg/kg) two hours before administering Tramadol and Midazolam. Subsequently, Tramadol at a dosage of 5 mg/kg and Midazolam at a dosage of 0.2 mg/kg were intravenously given 5 minutes before the induction with Propofol.

On the other hand, cats in the negative control group were subjected to the normal saline protocol. They did not receive anything two hours before the induction, but a placebo of normal saline at a dosage of 0.14 mL/kg was administered 5 minutes before the induction. The volume of normal saline is equivalent to the total volume of midazolam and tramadol injection. This is to blind the person who intubates and administers propofol injection to the treatment being administered.

3.3.2 PRE-OXYGENATION BEFORE INDUCTION

After administering the sedation, pre-oxygenation was provided using an oxygen mask for 5 minutes to increase the oxygen reserve in the body and thus delay the desaturation of arterial blood haemoglobin if the patient is apneic after induction. *(Refer to Image 1 on page 25)*

3.3.3 DETERMINATION OF PROPOFOL DOSAGE REQUIREMENT FOR SEDATION

Propofol was administered after 5 minutes of pre-oxygenation. A syringe pump was used to administer propofol intravenously at a constant rate at a rate of 3 mg/kg/minute. Lidocaine was sprayed on the larynx when the cat's jaw relaxed, and subsequent attempts at intubation using an endotracheal tube were performed. Once successful intubation was achieved, the propofol administration was immediately stopped, and the total amount of propofol required for induction until successful intubation was calculated. *(Refer to Image 2 on page 25)*

3.3.4 MEASUREMENT OF RECOVERY TIME FROM SEDATION

The duration from propofol cessation until the cat's tongue starts to move (swallowing reflex), is recorded to measure the duration of sedation. This recorded time is considered as the recovery period from sedation.

3.4 STATISTICAL ANALYSIS

The data was inserted into and analyzed using IBM SPSS Statistical Software 27.0 (IBM SPSS® Statistics, United States of America). Normality test was done on Propofol dosage and Recovery time. Their normality was determined using Shapiro-Wilk’s test. The propofol dosage used in each group is analyzed using Independent T-test to determine whether there is any significant difference between them. Meanwhile, the recovery time of each group is analyzed using Independent T-test to determine whether there is any significant difference between them.

Figure 1: Timeline of methodology

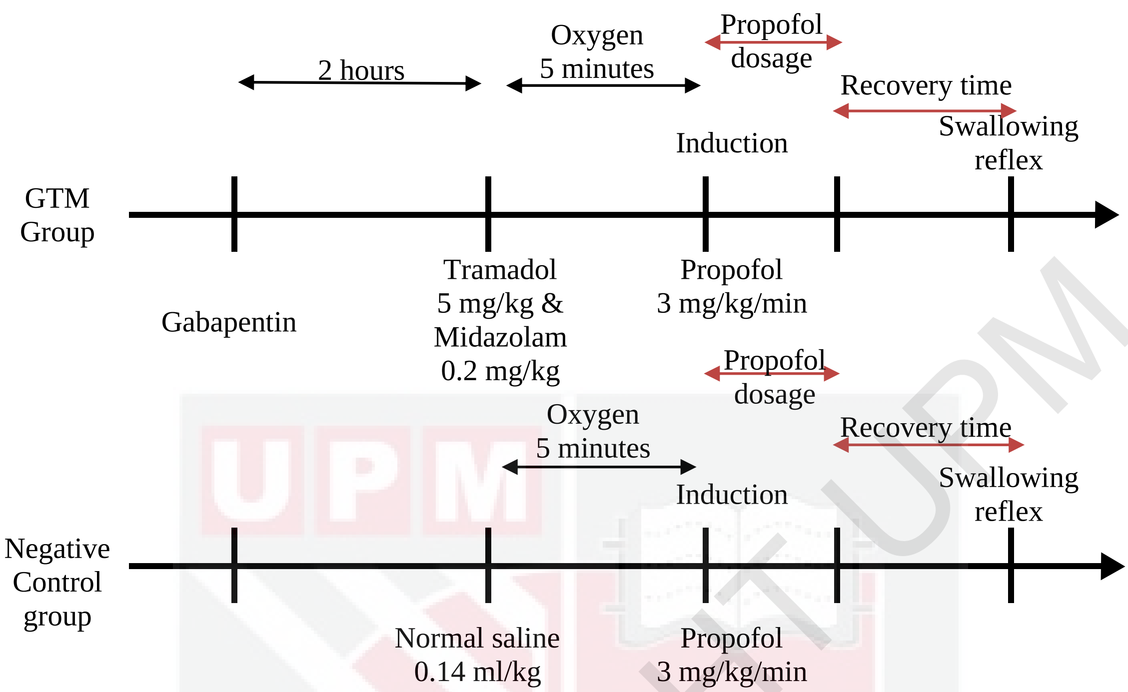


Image 1: Cat receiving pre-oxygenation

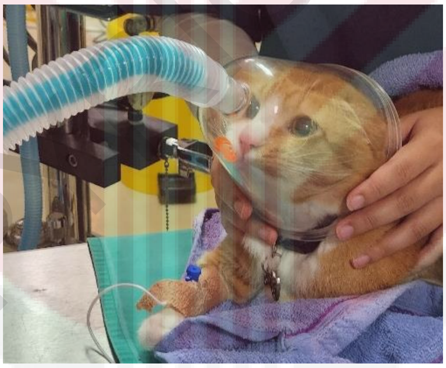
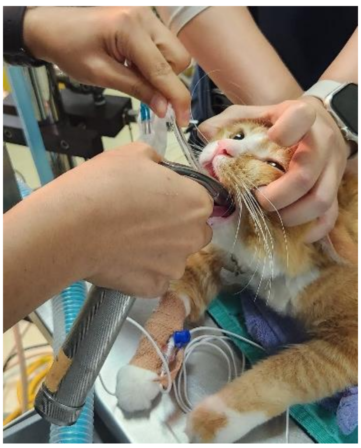


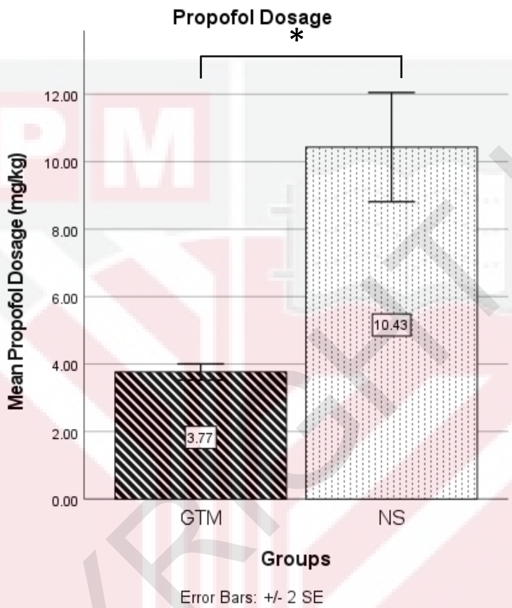
Image 2: Intubation of endotracheal tube in the cat



4.0 RESULTS

4.1 REDUCTION IN PROPOFOL DOSAGE FOR INDUCTION AFTER SEDATION

Figure 2: The propofol dosage needed for induction



*= significant difference

The GTM group received sedation with an oral dose of 20 mg/kg Gabapentin administered 2 hours before surgery, followed by an intravenous administration of 5 mg/kg Tramadol and 0.2 mg/kg Midazolam 5 minutes before the initiation of propofol induction. In this context, the patients necessitated an average propofol dosage of 3.77 ± 0.12 mg/kg to achieve successful induction.

In contrast, the group that did not receive any sedation and were administered only 0.14 ml/kg of normal saline as a placebo exhibited a markedly different outcome. Their requirement for achieving successful endotracheal intubation was notably higher, with an average propofol dosage of 10.43 ± 0.81 mg/kg.

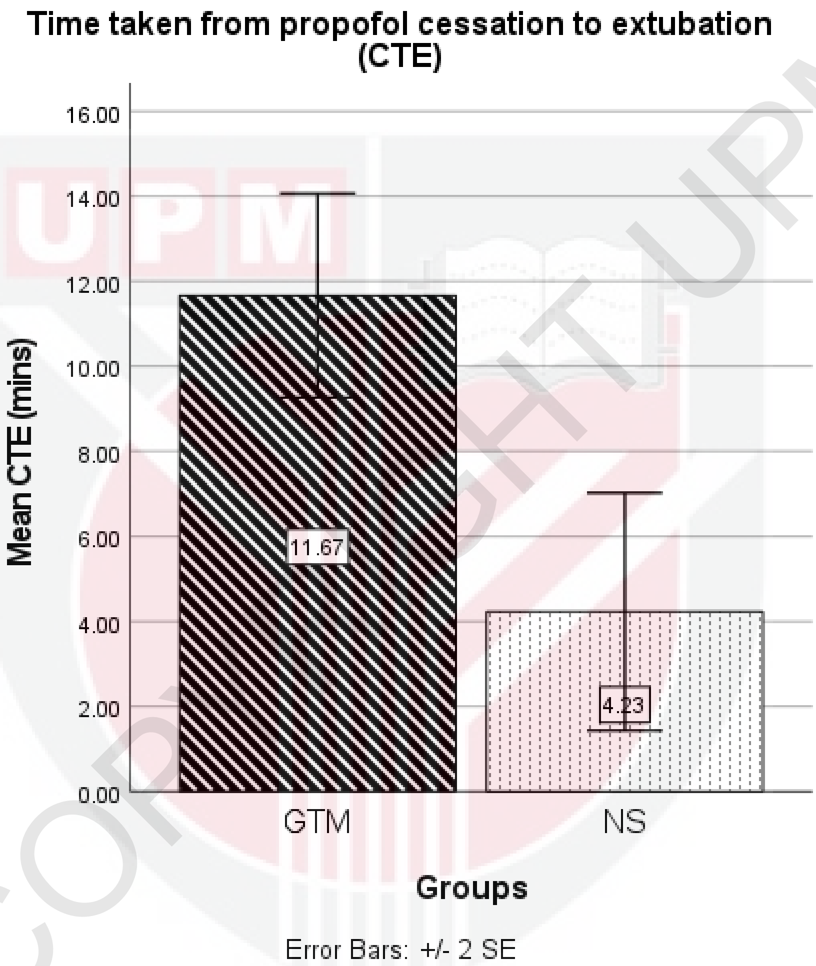
There is a significant difference in both groups' propofol dosage requirements for induction. These findings underscore the significance of pre-anesthetic medications, specifically Gabapentin, Tramadol, and Midazolam, in substantially reducing the propofol dosage required for effective induction, as demonstrated by the GTM group.

Table 1: Propofol Dosage for induction in GTM group and negative control group (mg/kg).

Groups	Propofol Dosage (mg/kg)
GTM	3.6
	3.7
	4
NS	12
	10
	9.3

4.2 CHANGES IN TIME FROM PROPOFOL CESSATION TO EXTUBATION

Figure 3: The average time taken from propofol cessation to extubation (CTE)



Following successful induction confirmed by the appropriate endotracheal tube intubation, patients were subjected to observation for swallowing reflex, to note the time for extubation. Notably, the average CTE time within the GTM sedation group is significantly longer than the NS group (p = 0.05)

Within the GTM sedation group, the average CTE time was 11.67 minutes. However, the average recovery time for the NS group is 4.23 minutes. These findings emphasize the trend towards extended recovery times in the presence of GTM sedation.

Table 2: Recovery time in GTM group and negative control group (mins).

Groups	Recovery time (mins)
GTM	14
	11
	10
Ns	2.29
	7
	3.22

5.0 DISCUSSION

5.1 REDUCTION OF PROPOFOL DOSAGE INDUCTION REQUIREMENT AFTER ADMINISTRATION OF SEDATION

Comparing both groups, the average amount of propofol needed to induce anesthesia was significantly lower in the group that received sedation (gabapentin, tramadol, midazolam) compared to the group without sedation (negative control). In human cases where preoperative anxiety levels are high, a greater amount of propofol may be required to maintain a clinically acceptable level of sedation (Osborn *et al*., 2004). This suggests that sedation reduces anxiety hence successfully reducing the requirement for general anesthesia. Stress triggers sympathetic discharge, leading to the release of hormones such as epinephrine (adrenaline), norepinephrine (noradrenaline), and cortisol. Consequently, norepinephrine is released by nerve endings, causing elevations in heart rate (HR), respiratory rate (RR), systolic blood pressure (SBP), and rectal temperature. The heightened stress levels can then lead to an increased need for general anesthesia during induction. Consequently, this elevates the risk of experiencing side effects associated with propofol, such as apnea, hypotension, and decreased respiratory rate (Branson, 2007). Such risks can be especially concerning in high-risk patient groups, such as geriatric cats, pediatric patients, animals undergoing high ASA class surgeries, or those with impaired heart, kidney, or liver function. It is essential to carefully administer sedation and anesthesia and to tailor treatment plans to each patient's specific needs. Proper monitoring and individualized care are crucial to ensuring the safety and well-being of patients during surgical procedures.

5.2 Difference in recovery time and importance

Recovery rate is a critical concern in our study as sedation may reduce the propofol requirement but could potentially result in prolonged sedation in animals, leading to extended recovery times. Previous studies have indicated that a combination of sevoflurane and midazolam does not cause a prolonged recovery effect, while the combination of propofol and midazolam does in human patients (Kim *et al*., 2020), which aligns with our study's protocol. Our study also found there were significant differences in the recovery rate when using gabapentin, midazolam, and tramadol as premedication compared to non-sedated cats.

Both midazolam and propofol exert their effects on GABA receptors, which can contribute to prolonged recovery times from anesthesia. Midazolam is a benzodiazepine that acts as a positive allosteric modulator of GABA receptors in a similar manner to propofol (Baez *et al*, 2020). Both midazolam and propofol enhance GABAergic neurotransmission and contribute to the overall depth of anesthesia, the presence of these drugs in the body can prolong the time it takes for the effects to wear off and for the patient to fully regain consciousness and cognitive function.

In a veterinary clinical setting, manpower is often limited (Yuen, 2018), and there may not be sufficient medical personnel available to closely monitor animals until they fully recover. Hence, if animals can quickly wake up and be safely discharged, it would be advantageous for both their well-being and the clinic's efficiency. Providing sedation to cats may potentially decrease the amount of propofol needed during surgery, thereby enhancing the safety of the procedure for the cats. However, this comes at the cost of extended post-surgery recovery and monitoring periods.

6.0 CONCLUSION

In summary, giving patients Gabapentin, Tramadol, and Midazolam (GTM) before anesthesia can lower the amount of propofol needed for sedation. At the same time, it results in longer recovery time when compared to situations where such pre-anesthetic medications are not used.

7.0 RECOMMENDATIONS

A significant limitation of this study pertains to the constrained sample size. Our subject pool was exclusively drawn from UVH patients, with a primary emphasis on ensuring the safety of these patients during the clinical trial process. It is emphasizing that this study serves as a preliminary study. Future research endeavours are expected to encompass a larger sample size, particularly when involving experimental animals which are acclimatized to the environment and personnel. It is recommended to follow a crossover methodology, adhering to established regulatory guidelines and the principles outlined in the 3R framework for animal testing (Replacement, Reduction, Refinement).

8.0 REFERENCES

Baez, A., Van Brunt, T., Moody, G., Wollmuth, L.P. and Hsieh, H. (2020). Voltage dependent allosteric modulation of IPSCs by benzodiazepines. Brain Res. J. 1;1736:146699.

Branson, K.R. (2007). Injectable and Alternative Anesthetics Techniques. In: Veterinary Anesthesia and Analgesia. Tranquilli, W.J., Thurman, J.C., & Grimm K.A. (Eds) 4th ed., Blackwell Publishing, USA. pp. 291-292.

Brown, E.N., Pavone K.J. and Naranjo, M. (2018). Multimodal General Anesthesia: Theory and Practice. Anesth Analg. 127(5):1246-1258.

Berry, S.H. (2015). Injectable Anesthetics. In: Veterinary Anesthesia and Analgesia. Grimm K.A., Lamont, L.A., Tranquilli, W.J., Greene, S.A., and Robertson, S.A. (Eds) 5th ed., John Wiley & Sons, Inc, USA. pp. 280-283.

Brodbelt, D.C., Flaherty, D. and Pettifer, G.R. (2015). Anesthetic Risk and Informed Consent. In: Veterinary Anesthesia and Analgesia. Grimm K.A., Lamont, L.A., Tranquilli, W.J., Greene, S.A., and Robertson, S.A. (Eds) 5th ed., John Wiley & Sons, Inc, USA. pp. 16.

Chen, H., Yang, H., Li, M., Peng, H., Guo, W. and Li, M. (2023). Effect of oral administration of gabapentin on the minimum alveolar concentration of isoflurane in cats. Front. Vet. Sci. 10:1117313.

Garcia-Pereira, F. (2015). Physiology, Pathophysiology, and Anesthetic Management of Patients with Hepatic Disease. In: Veterinary Anesthesia and Analgesia. 5th ed., Grimm K.A., Lamont, L.A., Tranquilli, W.J., Greene, S.A., and Robertson, S.A. (Eds), John Wiley & Sons, Inc, USA. pp. 630-631.

Grubb, T., Sager, J., Gaynor, J.S., Montgomery, E., Parker, J.A., Shafford, H. and Tearney, C. (2020). AAHA Anesthesia and Monitoring Guidelines for Dogs and Cats. J Am Anim Hosp Assoc. 56(2): 59-82.

Kim, H., Park, S.S. and Shim, J. (2020). Differences in midazolam premedication effects on recovery after short-duration ambulatory anesthesia with propofol or sevoflurane for gynecologic surgery in young patients. A randomized controlled trial. Medicine (Baltimore). 20;99(47):e23194.

Lemke, K.A. (2007). Anticholinergics and Sedatives. In: Veterinary Anesthesia and Analgesia. Tranquilli, W.J., Thurman, J.C., & Grimm K.A. (Eds) 4th ed., Blackwell Publishing, USA. pp. 229-230.

Perkowski, S.Z. and Oyama, M.A. (2015). Pathophysiology and Anesthetic Management of Patients with Cardiovascular Disease. In: Veterinary Anesthesia and Analgesia. Grimm K.A., Lamont, L.A., Tranquilli, W.J., Greene, S.A., and Robertson, S.A. (Eds) 5th ed., John Wiley & Sons, Inc, USA. pp. 504-505.

Rabbani, A. H., Ullah, Q., Naseer, O., Gardezi, F. H., Shahid, M., Hussain, K., Saleem, T., Ali, A., Khan, H. and Waheed, A. (2021). Comparative Multimodal Palliative efficacy of gabapentin and tramadol By Using Two Pain Scoring Systems in Cats Undergoing Ovariohysterectomy. Acta Vet. 71(4): 417-434.

Rankin, D.C. (2015). Sedatives and Tranquilizers. In: Veterinary Anesthesia and Analgesia. Grimm K.A., Lamont, L.A., Tranquilli, W.J., Greene, S.A., and Robertson, S.A. (Eds) 5th ed., John Wiley & Sons, Inc, USA. pp. 198-199.

Robinson, R. and Borer-Weir, K. (2015). The effects of diazepam or midazolam on the dose of propofol required to induce anaesthesia in cats. Veterinary Anesthesia and Analgesia. 42(5): 493-501.

Robertson, S.A., Gogolski, S.M., Pascoe, P., Shafford, H.L., Sager, J. and Griffenhagen, G.M. (2018). AAFP Feline Anesthesia Guidelines. Journal of Feline Medicine and Surgery. 20(7): 602-634.

Simon, B.T. and Steagall, P.V. (2020). Feline procedural sedation and analgesia: When, why and how. J. Feline Med. Surg. 22(11): 1029-1045.

Osborn, T.M. and Sandler, N.A. (2004). The effects of preoperative anxiety on intravenous sedation. Anesth. Prog. 51(2): 46-51.

Pypendop, B.H., Ilkiw, J.E. (2012). Anesthesia and Perioperative Care. In: The Cat. Little, S.E. (Ed), Saunders, W.B. pp. 112-150.

Yang, C.Y., Luk, H.N., Chen, S.Y., Wu, W.C. and Chai, C.Y. (1997). Propofol inhibits medullary pressor mechanisms in cats. Can J Anaesth. 44: 775-781.

Yuen, M. (2018). Animal Doctors Needed. The Star. https://www.thestar.com.my/news/nation/2018/05/06/animal-doctors-needed/