

Clinical Anesthetic Evaluation of Pregabalin as Premedication for Ketamine-Induced General Anesthesia in Dogs and Cats

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Abstract

The current study aimed to evaluate the physiological and clinical anesthetic effects of perioperative single oral dose of pregabalin prior induction of anesthesia with ketamine in male dogs and cats. Twenty-four animals (12 dogs and 12 cats) were examined. No other preanesthetic sedative or analgesic were used to avoid masking. Animals were randomly and blindly divided into two groups. Ketamine only group and pregabalin/ ketamine group. Behavioral, anesthetic, and analgesic effects were estimated post administration of pregabalin. Onset, duration, and recovery from anesthesia were compared between the animal related groups. Results showed that pregabalin produces relevant perioperative sedation and analgesia in dogs and cats which was more relevant in cats. Good muscle relaxation in both animals was also noted. The onset of anesthesia was not significantly (≤ 0.05) different between the groups. Duration of anesthesia was prolonged in the pregabalin/ ketamine groups. Recovery was smooth and prolonged than ketamine only group in dogs and cats. Physiological parameters were not significantly (≤ 0.05) different in all groups than baseline measures. In conclusion, a single perioperative oral dose of pregabalin at 5 mg/kg is effective to produce preanesthetic sedation, preemptive analgesia and prolong induction time produced by intravenous ketamine in dogs and cats without significant physiological side effects.

Keywords: Anesthesia, Canine, Feline, Pregabalin, Ketamine.

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Introduction

Pregabalin (PG) is an analog of the neurotransmitter gamma-aminobutyric acid (GABA). Its action is due to reducing the release of glutamate, noradrenaline, and substance P neurotransmitters, so it possesses sympatholytic effects (White et al., 2015). It is structurally related to gabapentin, which has been shown to have an anticonvulsant effect on dogs. PG is commonly used for controlling pain (Singh et al., 2012), and it can be used to lower the postoperative morphine dose in dogs (Crocioli et al., 2015). PG blocks calcium channels, thereby lowering calcium influx, which is an active trigger of seizures in animals and convulsions, so it may be used for controlling idiopathic epilepsy and convulsions in cats and dogs (Bhatti et al., 2015). PG is tolerable, and its notable undesirable effects are restricted to mild sedation and pelvic limb ataxia (Govendir et al., 2005, Platt et al., 2006). It is used to alleviate anxiety and fear in cats and dogs (Lamminen et al., 2023). Ketamine HCl is a cyclohexylamine widely used dissociative anesthetic agent that is mostly used for chemical restraint, induction, and maintenance of anesthesia in several animal species. The sole use of ketamine as an anesthetic agent has several limitations, such as muscle hypertonicity, myoclonus, vicious recovery, and occasional convulsions (Yohannes, 2018, Muir et al., 2000, Lee et al., 2017). Ketamine may be combined with other medications, such as α_2 agonists or benzodiazepines, to enhance muscle relaxation, lower convulsion incidence, and increase analgesic effect and duration (Ibrahim, 2017, G. H. et al., 2017, Akhtar et al., 2019). Ketamine therapeutic doses may cause tachycardia, elevated arterial blood pressure (ABP) and transit

respiratory depression. Previous studies attributed this effect to the sympathomimetic effect of ketamine (Lee et al., 2017, Goddard et al., 2021). Cats with hypertension and a history of hypotrophic cardiomyopathy should be closely monitored during ketamine usage (Bell and Kalso, 2018). Postoperative pain is a common issue in most cases, Previous studies reported the used continuous rate infusions of ketamine to overcome pain and improve feed consumption in dogs (Wagner et al., 2002, Sarrau et al., 2007). Acknowledging the unmet need for evidence-based anesthetic recommendations, the primary aim of this study was to assess the efficacy and benefit-risk profile of PG premedication combined with ketamine induction anesthesia and its influence on normal physiological parameters. We hypothesize that the analgesic and sedative efficacy of PG will provide added value during ketamine anesthesia.

Materials and Methods

Study Design

This study was designed as a randomized, double-blind, controlled trial to evaluate the efficacy of pregabalin and ketamine in providing sedation, analgesia, and anesthesia in dogs and cats undergoing surgical sterilization procedures.

Experimental Animals

A total of 24 healthy male dogs and cats (12 dogs and 12 cats) of local breed were included in the study. Power analysis was used to determine the appropriate sample size to ensure the detection of statistically significant differences between groups. Animals were excluded if they had pre-existing medical conditions that could interfere with study outcomes. The median

age of dogs was 1.5 years, with a mean weight of 17.5 ± 3.24 kg. The median age of cats was 3.6 years, with a mean weight of 3.26 ± 0.56 kg.

Drug Administration and Dosage

Animals were randomly assigned to group A (control): administered ketamine only at dose of 10 and 20 mg/kg (intravenously) in dogs and cats respectively (Green et al., 1981), or a group B (treatment): administered pregabalin at dose of 5mg/kg (orally) (Dewey et al., 2009, Lamminen et al., 2022) followed by ketamine 10 and 20 mg/kg (intravenously) in dogs and cats respectively.

Pain and Sedation Assessment

Pain and sedation were assessed after pregabalin administration but prior to ketamine induction, and during/after the anesthesia period. The Composite Measure Pain Scale (CMPS) (Reid et al., 2007) and the Ramsay Sedation Scale (Newton et al., 2013, 2004) were used. Additionally, a visual analog scale (VAS) with scores ranging from 0 (no pain) to 5 (severe pain) was used to assess analgesic quality (Hellyer, 2009). Anesthetic and surgical procedures were performed by the same surgeon while Assessors were blinded to the group assignment of the animals. The onset of anesthesia was defined as the time until the transition from consciousness to unconsciousness. Recovery was measured from the start when the animal maintained the first reflex. Full recovery is recognized when the animal is able to stand and attempt to prehend food or water.

Surgical procedures

Penile and scrotal orchiectomy procedures were performed in dogs and cats respectively under aseptic conditions.

After ketamine administration, the following were assessed and recorded: induction smoothness, muscle relaxation, duration of anesthesia, and any adverse events.

Prescrotal orchiectomy procedure:

Aseptic preparation of the caudal abdomen extending from the prepuce to the scrotum and encompassed the surrounding areas up to the medial thighs was performed. The surgical site was covered covered with a sterile fenestrated drape with the fenestrated opening positioned between the prepuce and the scrotum. With the non-dominant hand, pressure applied to the scrotum to displace one testicle cranially into the pre-scrotal area. A single decisive incision was made through the skin and subcutaneous tissue. The squeezed-out testicle was grasped gently, and the spermatic cord was then double ligated and severed. The same steps were repeated for the other testicle. The incision was opposed primarily with 2-0 vicryl sutures in subcuticular pattern.

Scrotal castration

The scrotum prepared for aseptic procedure. A sterile fenestrated drape enveloped scrotum, allowing visibility of the testes through the fenestration. A single incision was made on the ventral aspect of the testicle through the skin and subcutaneous tissue of the scrotum, positioned just lateral to the median raphe, approximately one third of the testicle's length. The undominant hand used to squeeze the testis outward. The testicle then grasped gently and the spermatic cord double ligated and severed. The scrotal incision left without suturing.

Postoperative Monitoring

Animals were monitored postoperatively for pain, recovery

smoothness and duration, motor function, and willingness to eat and drink. Preemptive analgesia using PG was administered following surgery. Full recovery was defined as the return of normal behavior and motor functions. Assessors remained blinded to the treatment groups.

Physiological Parameters Measurement

Heart rate assessed via stethoscope and confirmed by pulse oximeter, respiratory rate observed visually, and rectal temperature measured with a digital thermometer were recorded at baseline, during the anesthesia period, and at regular intervals during the recovery phase. Blood pressure was determined indirectly using a digital sphygmomanometer, recording systolic and diastolic pressures to derive the mean arterial pressure (MAP) through the formula

$$MAP = DP + \frac{(SP-DP)}{3} \text{ (Karsli et al., 2022).}$$

Statistical Analysis

Data were analyzed using (SPSS Ver.29, IBM, USA) statistical software. Independent sample t-tests were used to compare physiological parameters between groups. Two-way ANOVA followed by T test was used to analyze pain and sedation scores, as well as other outcome measures.

Ethical approval

The study was approved by the Institutional Animal Care and Use Committee of Faculty of Veterinary Medicine, New Valley University and aligns with the ARRIVE guidelines.

Results

Behavioral Changes, sedation, and analgesia (after pregabalin only)

Dogs: Sternal recumbency and elevated heads were among the behavioral

changes that were observed an hour after oral pregabalin (PG) administration. Dogs remained responsive to auditory stimuli despite being in a state of moderate sedation that persisted for ninety minutes following PG. Based on the Ramsay Sedation Scale, the dogs' scores were 3–4 (awake but only react to commands to sleep and loud stimuli), while the CMPS and VAS pain scores were 2 (unwilling to interact), indicating mild to moderate analgesia.

Cats: Progressing from sternal recumbency with a depressed head to lateral recumbency with the head on the floor, cats showed signs of moderate sedation in a shorter amount of time. Sixty minutes after PG, there was noticeable ataxia. The cats scored 4 on the CMPS and 1 on the VAS (possibly nonresponsive, cries on painful stimulation), indicating moderate to severe analgesia, and 7 on the Ramsey sedation scale (animals asleep, non-purposeful reflex withdrawal to painful stimuli).

Anesthesia and Recovery

Dogs

Ketamine Only Group (Control group): the induction was quick and painless; the mean time for anesthesia to start was 3.52 seconds; mean duration time was 14.85 minutes; the jaw could not relax properly indicating poor muscle relaxation; the eyes stayed open with dilated central pupil during the procedure; and there was visible pain from twitch and paddling movements. Dogs start to show the first pedal reflex at 17.64 minutes. Attempts to restore sternal recumbency and head lifting were noted at 29.75 minutes. Smooth, steady recovery without abnormal behaviors was observed, with full recovery recorded at 38.54 minutes. Dogs were able

to stand with slight hind limb ataxia, eat, and drink.

Treatment Group: the induction onset in the pregabalin + ketamine treatment group did not differ significantly from that of ketamine alone. 3.176 minutes was the recorded mean onset time. Smooth, quick, and agitation-free induction took place. It was difficult to open the jaw, indicating a lack of muscle relaxation. With a recorded mean duration of 26.873 minutes, the mean duration of anesthesia increased significantly (≤ 0.05). The eyes stayed wide open. There were no convulsions, twitches, or tremors observed. The first reflex begins after 38.74 minutes. Attempts to restore the thoracic position and raise the head were noted after 43.55 minutes. A smooth, steady recovery with no abnormal behavior was observed, with complete recovery recorded at 47.58 minutes. Dogs were able to stand, eat, and drink. Dogs showed mild hindlimb ataxia.

Cats

Ketamine Only Group (Control group): the induction was quick and painless; the mean time for anesthesia to start was 2.582 minutes; fair muscle relaxation quality was demonstrated by the jaw opening with only a slight force and ataxia following the injection; the mean duration of anesthesia was 19.265 minutes; all cats showed mild to moderate peripheral analgesia, which was identified by the lack of a pedal reflex. The first reflex was recorded after 23.64 minutes. Attempts to restore the thoracic position and raise the head were noted after 35.46 minutes. A smooth, steady recovery with no abnormal behavior was observed, with complete recovery recorded at 47.43 minutes. cats were able to stand, but unwilling to eat, or drink or to move.

Treatment group: the induction onset in the pregabalin + ketamine treatment group did not differ significantly from that of ketamine alone. The recorded mean onset time was 2.15 seconds. The induction proceeded quickly, painlessly, and without incident and lasted for 34.42 minutes. The jaws opened easily indicated good muscular relaxation. The first reflex begins after 35.64 minutes. Attempts to restore the thoracic position and raise the head were noted after 75.65 minutes. A smooth, slow recovery with sleepy behavior was observed, with complete recovery recorded at 193.24 minutes. Cats were able to stand with ataxic hind limbs, reluctant to move and unwilling to eat, or drink.

Physiological Parameters

Dogs

Heart rate (HR): At baseline recorded 182.5 bpm. During anesthesia, mean HR was 148.2 bpm in the control group which was non-significantly (≤ 0.05) different than recorded in the treatment group which had mean HR 141.9 bpm. Mean respiratory rate (RR) at baseline both groups were 41.6 bpm. During anesthesia the mean RR slightly decreased in the treatment group. In the control group it was 15.6 bpm while in the treatment group it was deep and shallow and recorded 14.4 bpm. The baseline rectal temperature (RT) in both groups recorded 39.4°C. During anesthesia there was no significant (≤ 0.05) difference between the control and treatment groups. The mean RT in the control group was 38.1 °C and 38.05 °C in the treatment group. Baseline mean arterial pressure (MAP) was 120.6. A significant (≤ 0.05) difference between the groups was recorded during anesthesia. The MAP in the control group was 73.5 while it was

86.6 in the treatment group. Non-significant changes in both groups during anesthesia from the baseline oxygen saturation (SPO₂) recording 95-97%

throughout the procedure. Changes in physiological parameters are illustrated in Figure 1.

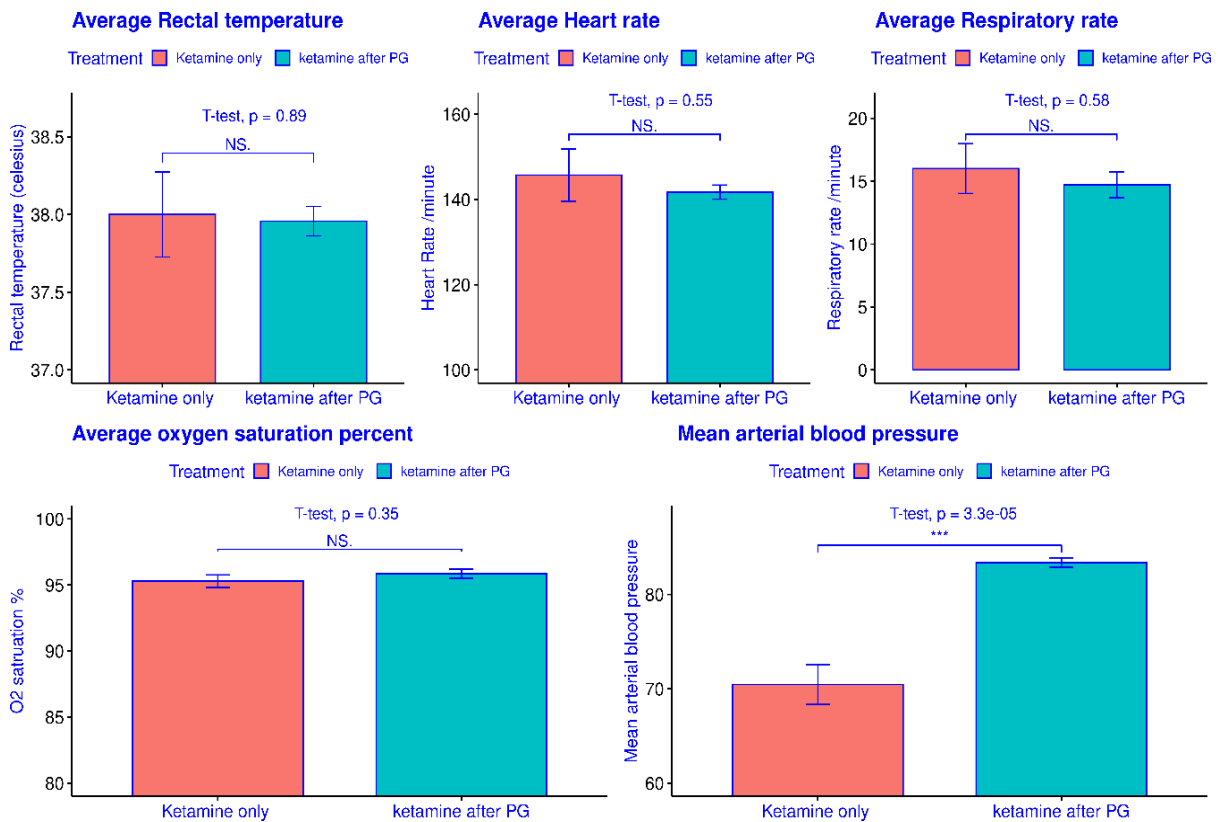


Figure 1. Changes in the physiological parameters among ketamine only and pregabalin/ketamine groups in dogs.

Cats:

Heart rate (HR): At baseline recorded 163.5 bpm. During anesthesia, mean HR was 148.4 bpm in the control group which was non-significantly (≤ 0.05) different than recorded in the treatment group which had mean HR 145.5 bpm. Mean respiratory rate (RR) at baseline was 27.6 bpm. During anesthesia the mean RR slightly decreased in the treatment group. In the control group it was 16.06 bpm while in the treatment group it was deep and shallow and recorded 14.13 bpm. The baseline rectal temperature (RT) in both groups recorded 38.06°C. During anesthesia there was no significant (≤ 0.05) difference between the

control and treatment groups. The mean RT in the control group was 39.1 °C and 38.5 °C in the treatment group. Baseline mean arterial pressure (MAP) was 98.6. A significant difference between the groups was recorded during anesthesia. The MAP in the control group was 82.05 while it was 83.65 in the treatment group, which was significantly higher. Non-significant changes in both groups during anesthesia from the baseline. oxygen saturation changes were non-significant, recording 95% throughout the procedure. Changes in physiological parameters are shown in Figure 2.

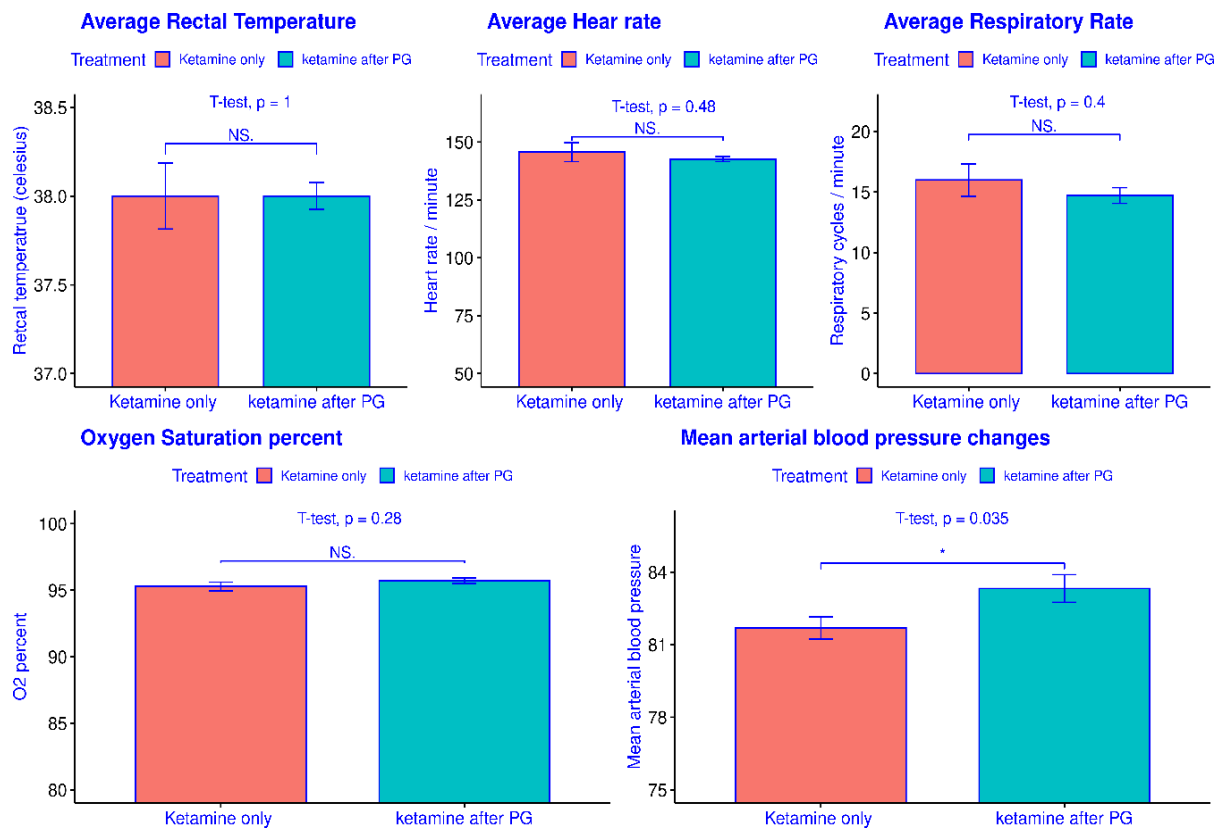


Figure 2. Changes in the physiological parameters among ketamine only and pregabalin/ketamine groups in cats.

Discussion

The current study evaluated the effect of using a single oral dose of pregabalin at 5mg/kg as premedication prior induction of anesthesia with ketamine in dogs and cats. The evaluation criteria focused on the behavioral changes after administration of pregabalin, physiological parameters differences between ketamine only and pregabalin/ ketamine group including the rectal temperature, respiratory rate, heart rate, oxygen saturation, and clinical anesthetic parameters including the degree of sedation and analgesia, onset of anesthesia, duration of anesthesia, and recovery. Other recognized sedative premedications were not used to avoid masking effect. The rationale for using pregabalin prior surgery to achieve primitive analgesia and evaluate its sedative side effect (Sebastian et al., 2016, Kaur et al., 2023, Karube et al., 2017,

Hosokawa et al., 2018). No previous reports in dogs evaluated pregabalin premedication prior induction anesthesia with intravenous ketamine. In cats pregabalin recently was evaluated preoperatively in cats generally anesthetized with typical inhalation protocol (Madan et al., 2024). The results of the present study showed that ketamine is a good anesthetic agent for dogs and cats, although it may be accompanied by muscle rigidity, convulsions, and poor analgesic effects, which is congruent with the findings of (Irwin et al., 2023). Pregabalin is commonly used as a pain killer in dogs (Singh et al., 2012) and used for controlling convulsions and epilepsy in dogs and cats (Bhatti et al., 2015). Results of the current study, although tonic or colonic convulsions were not recorded in ketamine only group in both dogs and cats, complete absence of convulsions were also

recorded in the treatment groups. This result supports the claim of pregabalin anticonvulsant effect in dogs and cats (Bhatti et al., 2015). The absence of epileptic effect did not accompany muscle relaxation in dogs. Meanwhile in cats muscle relaxation was evident. Similar results were obtained in humans (Park et al., 2018) and rats (Naidu and Rani, 2019). In both treatment groups in dogs and cats, negative myoclonus and ataxic movement was recorded. Similar results reported in humans received large doses of pregabalin (Park et al., 2018, Kim et al., 2017). Ketamine only causes no significant changes in physiological parameters which is congruent with the findings of Yohannes (2018), however, ketamine causes an increase in MAP, and this effect assures better blood supply and tissue perfusion during surgery. This finding is consistent with the findings of Zhou et al. (2022). In the same context, pregabalin ketamine-treated animals showed significant increases in the MAP, which may be due to the negative effect of pregabalin on the level of circulating nitric oxide that possesses a vasodilator effect. This finding matches those presented by Amany and Heba (2013). The vasoconstriction accompanying the PG may be beneficial, as it may decrease oozing during surgery and may provide a clear surgical theatre and maintaining elevated MAP during anesthesia may assure better tissue perfusion for vital organs. In contrast, some authors reported no significant changes in blood parameters with pregabalin usage, even though most parameters were in the lower limit of their normal ranges (Rahat Dahmardeh et al., 2018, White et al., 2015, Gupta et al., 2011). Further reports in humans, reported to decrease the MAP on a single dose

administer prior surgery (Reddy and Murari, 2019). In the current study, sedation was mild to moderate after pregabalin administration in dogs, while in cats it was moderate to severe. Similar results were reported in cats received a single dose with evident ataxic effect (Lamminen et al., 2021). Physiological parameters were relatively under the reference range during the recovery period. Abnormal dissociation behavior, hypersomnia, ataxia and coordination during movement, and long-lasting loss of appetite were recorded at and after recovery was recorded in cats. The length of the recovery period with the prementioned oral dose of PG in both dog and cat patients may be related to the elimination half-lives ranging from 6 to 11 hours in these animal species; these findings are consistent with those of Salazar et al. (2009) and Esteban et al. (2018) (Ravasio et al., 2012). In the present experiment, the recovery period in cats exhibited a notable delay compared to dogs. Further investigation is warranted to explore the progression of PG plasma concentration over time in dogs and cats. In this study, a single oral dose of PG at 5mg/kg was adequate to obtain a sedative and preemptive analgesic effect. The dose was constant with that reported in previous reports (Ravasio et al., 2012, Lamminen et al., 2021, Salazar et al., 2009). Pregabalin may have a dose-dependent sedative, analgesic, and muscle relaxant effect that may be valuable for use as a premedication with ketamine alone or with other premedication drugs in canines and felines. This conclusion was reported in humans (White et al., 2009). PG has been reported to exhibit potent anticonvulsant, analgesic, and anxiolytic effects in a range of animal models (Ben-Menachem, 2004). The

outcomes of this study showed that PG achieved analgesic effect prior and after surgery in both canine and feline patients. This observation is consistent with the findings of Taylor et al. (1993) and Vartanian et al. (2006). Perioperative use of pregabalin may be helpful to produce preemptive analgesia which may decrease the need for postoperative analgesia (Wagner et al., 2002, Sarrau et al., 2007). In cats, PG resulted in smooth but delayed recovery, longer than the same relative periods after ketamine alone and that recorded in related group in dogs. This result was constant with recent reports (Madan et al., 2024, Lamminen et al., 2021). Limitations of the study encompasses the small experimental sample and using male animals only. Further studies are to evaluate the effect of using a single oral dose on typical inhalation anesthesia protocol for elective surgical procedures in both sexes of dogs and cats.

Conclusions

Perioperative administration of a single oral dose of pregabalin at 5 mg/kg was tolerable in dogs and cats and resulted in significant sedation and analgesia and in cats resulted in a relatively negative myoclonus effect and a prolonged duration of anesthesia while maintaining physiological parameters.

Conflict of Interest

Authors declare no conflict of Interest.

Funding

Not applicable.

Author Contributions

MWE, Data curation, investigation, methodology, validation, visualization, writing original draft, writing, review and editing final manuscript. MAM, Data

curation, formal analysis, investigation, validation, visualization, writing the original draft.

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