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RESEARCH ARTICLE

Effect of Tramadol on Medetomidine and Ketamine Anesthesia in Dogs

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ABSTRACT

The analgesic effects of three different doses of tramadol as a preanesthetic in medetomidine-ketamine anesthesia in dogs were compared. Twenty-eight healthy adult mongrel dogs were used. The dogs were divided into four groups at random; 1 ml kg^{-1} of normal saline, 1, 2 or 4mg kg^{-1} of tramadol premedication (group Control, TRA1, TRA2 and TRA4) was then administered intravenously followed by medetomidine and ketamine anesthesia. The behavioral changes, the duration of surgical anesthesia, blood gas parameters (pH, pO_2, and pCO_2), heart rate, and systolic/diastolic pressure were observed. Tramadol (4mg kg^{-1}) pretreatment significantly increased the degree of sedation when compared with the control, TRA1 and TRA2 groups at 15 min after tramadol administration ($P<0.05$). The duration of surgical anesthesia was significantly increased by tramadol (4mg kg^{-1}) pretreatment when compared with that of the control group ($P<0.05$). There were no significant differences in behavioral changes, blood gas parameters (pH, pO2 and pCO2), heart rate, and arterial pressure among the groups. Tramadol at 4mg kg^{-1} did not affect the cardiovascular system and recovery of anesthesia, but significantly increased the duration of surgical anesthesia with medetomidine and ketamine. This result suggests that intravenous tramadol at 4mg kg^{-1} is a useful preanesthetic agent for extending the surgical level of anesthesia in medetomidine-ketamine anesthesia in dogs.

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INTRODUCTION

Tramadol is a centrally acting analgesic agent with activity at μ-opioid, adrenergic and 5-hydroxytryptamine (5-HT) receptors. Its analgesic effect is a result of its dual mechanism of action, that is, as a re-uptake inhibitor of norepinephrine and serotonin and agonist of the μ-opioid receptor (Bamigbade *et al.*, 1997; Halfpenny *et al.*, 1999; Ide *et al.*, 2006). Tramadol has been in clinical use for the relief of mild to moderate pain in human and veterinary medicine (Buback *et al.*, 1996; Yaddanapudi *et al.*, 2000; Ozcengiz *et al.*, 2001; Mastrocinque and Fantoni, 2003; Pypendop and Ilkiw, 2008). Tramadol is also used perioperatively in veterinary anesthesia as it significantly reduces the requirements of volatile anesthetics and opioid agents (Wordliczek *et al.*, 2002; Seddighi *et al.*, 2009). Although tramadol has relatively effective analgesic effects, a higher tramadol infusion rate was needed to reduce sevoflurane requirements in dogs (Seddighi *et al*., (2009). Furthermore, recent results showed that tramadol exhibits different metabolic rates between species: tramadol is metabolized quickly to inactive metabolites in goats, horses and dogs (KuKanich and Papich, 2004; de Sousa *et al.*, 2008; Shilo *et al.*, 2008; Giorgi *et al.*, 2009b), in contrast with cats and camels (Elghazali *et al.*, 2008; Pypendop and Ilkiw, 2008).

A combination of medetomidine and ketamine is commonly used for animal anesthesia (Nevalainen *et al.*, 1989; Verstegen *et al.*, 1989; Jang *et al.*, 2009). To our knowledge, use of tramadol as a preanesthetic agent in veterinary medicine is uncommon; in particular, we found no reports of preemptive treatment in medetomidine and ketamine anesthesia in dogs. The purpose of this study was to determine the safety and efficacy of tramadol as a preanesthetic during medetomidine and ketamine anesthesia in dogs through evaluation of the behavioral changes, the duration of surgical anesthesia, blood gas parameters, heart rate, and arterial pressure.

MATERIALS AND METHODS

Animals

Twenty-eight adult mongrel dogs were used in the study. All animals were considered clinically healthy based on physical examination, complete blood count and serum biochemistry. The average weight of the dogs was

5.7 ± 1.4 kg (3.9 to 10.0 kg). Each dog was housed individually and fed commercially available dry pellet food and water *ad libitum*. The dogs were randomly divided into 4 groups administered normal saline, 1, 2 or 4mg kg^{-1} of tramadol, followed by medetomidine and ketamine anesthesia (Control, TRA1, TRA2 and TRA4, respectively); each group contained 7 dogs. This study was approved by the Kyungpook National University Institutional Animal Care and Use Committee.

Experimental procedure

One day prior to the experiment, an arterial catheter was inserted about 5 cm into the right external carotid artery and forward toward the aorta of each dog under propofol and isoflurane anesthesia. The catheter was placed in a tunnel through the subcutis and brought out on the dorsal surface of the neck; it was then filled with heparin (50 IU mL^{-1}) diluted in saline. The arterial catheter was used for checking arterial blood pressure and heart rate and for collecting blood. The catheter was flushed with saline diluted in heparin two times a day to prevent coagulation of blood.

Food but not water was withheld for 12 h before the experiment. On the day of the experiment, the dogs were acclimatized to the experimental room for 1 h, and then the arterial catheter was connected to a Polygraph (Model 7P1, Grass Instrument Co., Quincy, MA). Following determination of baseline values in a sitting position, a 24-gauge cephalic vein catheter was placed for drug administration. Fifteen minutes after atropine (0.05 mg kg^{-1}, subcutaneously) injection, each dog was intravenously administered tramadol (Maritrol; Je Il Pharm. Co. Ltd., Daegu, Korea). Fifteen min later, medetomidine (Domitor; Orion Corporation ANIMAL HEALTH, Turku, Finland) (40μg kg^{-1}, intravenously [IV]) and ketamine (Ketamine; Yuhan Corp., Seoul, Korea) (10mg kg^{-1}, IV) were given with a 15-min interval.

Behavioral parameters

Degree of sedation: The degree of sedation was assessed by a numerical sedation score (NSS) (Valverde *et al.*, 2004). The NSS consists of a scale ranging from 0 to 3, with 0: no sedation; 1: mild sedation (less sedation but still active); 2: moderate sedation (drowsy, recumbent but can walk); and 3: intense sedation (very drowsy, unable to walk). NSS was evaluated at 30 and 15 min after ketamine injection (15 min after tramadol and medetomidine injection, respectively), and at 10 and 30 min after the dogs started showing head-up movement.

Duration of anesthesia: Arousal time after ketamine injection to the time the dog showed loss of righting reflex (loss of RR), head-up, positioning to a sternal recumbency position and walking movements were measured, and the mean values were presented (MHT, MST and MWT, respectively). The time difference between head-up movement and walking was defined as the recovery time.

Duration of surgical anesthesia: The duration of surgical anesthesia was determined by pedal withdrawal reflex. After ketamine administration, the period in which the dog showed negative response to toe-web pinching test was defined as surgical anesthesia. Each toe-web region in the forelimbs was alternatively pinched with mosquito forceps to the first ratchet-lock for 10 sec, and was evaluated at 5, 10, 15, 30, 40, 50, 60, 70, 80, 90 and 120 min from ketamine injection. Additional tests were stopped if the dog showed purposeful movement of the head and/or limbs.

Blood gas analysis (pH, PaO_2, $PaCO_2$)

Arterial blood sample was collected through the external carotid arterial catheter. Blood gas was analyzed with a portable blood gas analyzer (I- STAT® Analyzer MN300, Abbott Point of Care Inc., Abbott Park, IL) and test cartridges (I - STAT® G3+ Cartridge, Abbott Point of Care Inc., Abbott Park, IL). The blood sample (0.5 mL) was collected from the carotid arterial catheter, and the catheter was flushed with 0.5 ml of saline diluted heparin, following each sampling. The analysis was done within 10 sec after blood sampling.

Heart rate and mean arterial pressure

Heart rate and mean arterial blood pressure were measured with the polygraph (Model 7P3, Grass instrument Co., Quincy, MA). Values were calculated from 10-sec arterial pulse wave records in each recording time.

Statistical analysis

All data, except the behavioral parameters, were calculated as a percentage to the baseline values, and were expressed as mean ± standard deviation (SD). Mean arterial blood pressure, heart rate and blood gas values were statistically analyzed by two-factor ANOVA followed by a Bonferroni correction (SPSS 14.0K, Data solution, Seoul, Korea). One-way ANOVA followed by a Bonferroni correction were included to identify the statistical differences of behavioral changes (time to loss of righting reflex, mean head-up time, mean sternal-recumbency time, mean walking time and total recovery time), numerical sedation score and the duration of surgical anesthesia. Values of $P<0.05$ were considered significant.

RESULTS

Behavioral parameters

Degree of sedation: Tramadol (4mg kg^{-1}) treatment resulted in a significant increase of NSS ($P=0.001$, $P=0.042$ and $P=0.007$ when compared to control, TRA1 and TRA2 groups, respectively) at 15 min after tramadol administration. In contrast, one-way ANOVA did not reveal any significant differences between groups at other measurement times (Fig. 1).

Duration of anesthesia: One-way ANOVA revealed that no variables of behavioral changes during anesthesia were significantly affected by pretreatment with different doses of tramadol ($F=1.03$, $P=0.397$ in loss of RR; $F=1.46$, $P=0.250$ in MHT; $F=1.46$, $P=0.251$ in MST; $F=1.92$, $P=0.153$ in MWT; $F=1.95$, $P=0.149$ in total recovery time) (Fig. 2).

The duration of surgical anesthesia: One-way ANOVA revealed that treatments were significant ($F=4.04$,

P=0.019), and the Bonferroni test indicated that tramadol (4mg kg^{-1}) pretreatment significantly increased the duration of surgical anesthesia (P=0.023) when compared to the Control group (Fig. 3).

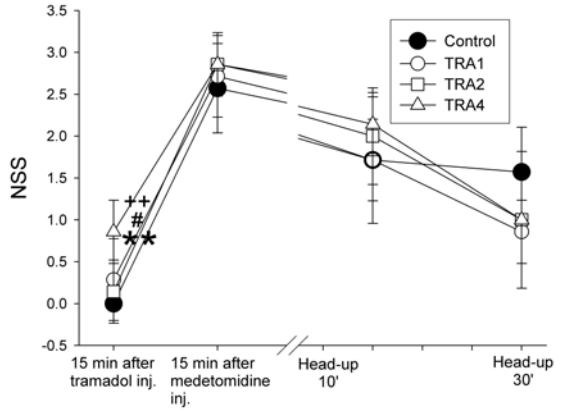

Fig. 1: Changes in the degree of sedation in dogs. The dogs were given saline, 1, 2 or 4mg kg^{-1} of tramadol (Control, TRA1, TRA2 and TRA4), followed by medetomidine and ketamine. The degree of sedation was measured by numerical sedation score (NSS) (0, no sedation; 5, severe sedation), and was recorded from 15 min after tramadol injection to 30 min after the dog showed head-up movement. NSS was not measured during anesthesia. TRA4 group exhibited a significant increase in NSS (**P=0.001, #P=0.042 and ++P=0.007 compared to Control, TRA1 and TRA2 groups, respectively) at 15 min after tramadol injection. Data were analyzed by one-way ANOVA and Bonferroni test.

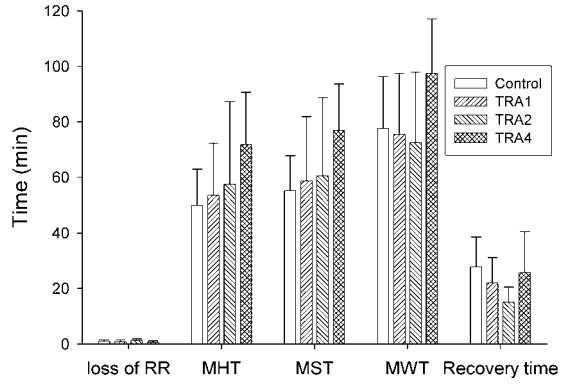

Fig. 2: Duration of anesthesia in dogs anesthetized with tramadol, medetomidine and ketamine. The dogs were given saline, 1, 2 or 4mg kg^{-1} of tramadol (Control, TRA1, TRA2 and TRA4), followed by medetomidine and ketamine. The behavioral changes after ketamine administration were measured; average time of latency to loss of righting reflex (RR), head-up movement (MHT), sternal recumbential position (MST) and walk (MWT) was measured. Additionally, total recovery time was determined as the time difference from head-up movement to walking-movement. None of the parameters showed any significant change by different doses of tramadol. Data were analyzed by one-way ANOVA and Bonferroni test.

Blood gas analysis (pH, pO_2, pCO_2)

Repeated measures ANOVA revealed that time course (F=1.00, P=0.415), interaction (F=0.99, P=0.472)

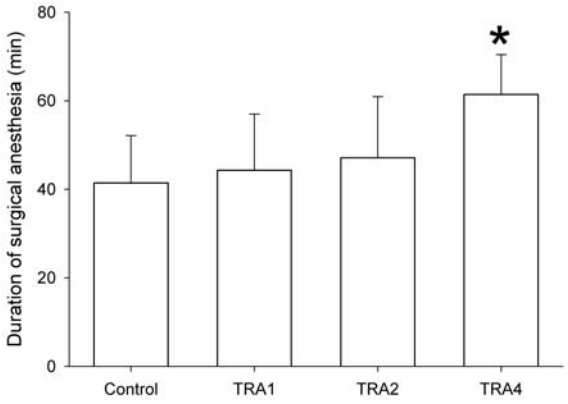

Fig. 3: Duration of surgical anesthesia was determined by pedal withdrawal reflex in dogs anesthetized with tramadol, medetomidine and ketamine. The dogs were given saline, 1, 2 or 4mg kg^{-1} of tramadol (Control, TRA1, TRA2 and TRA4), followed by medetomidine and ketamine. After ketamine administration, the period in which the dog showed negative response to the toe-web pinching test was defined as the surgical anesthesia. The duration of surgical anesthesia in the TRA4 group was significantly increased compared with Control (*P<0.05, one-way ANOVA and Bonferroni test).

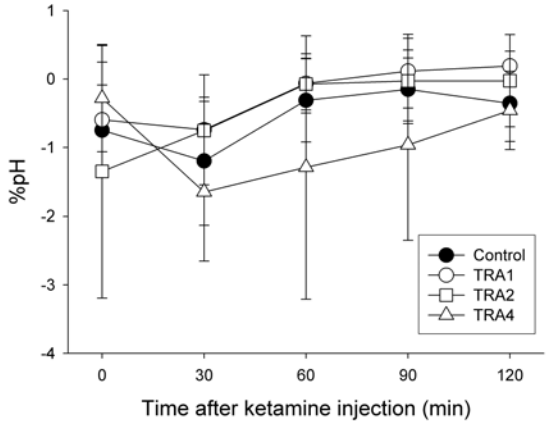

Fig. 4: Changes of blood pH in dogs anesthetized with tramadol, medetomidine and ketamine. The dogs were given saline, 1, 2 or 4mg kg^{-1} of tramadol (Control, TRA1, TRA2 and TRA4), followed by medetomidine and ketamine. Data were analyzed by two-factor repeated measures ANOVA and Bonferroni test, and variables were not significant.

and treatment (F=0.80, P=0.511) were not significant in pH variables. Variables of pCO_2 and pO_2 were significantly affected by time course (F=19.43, P<0.001 at pCO_2, and F=15.35, P<0.001 at pO_2), but not interaction (F=0.44, P=0.94 at pCO_2, and F=0.79, P=0.654 at pO_2) or treatment (F=0.68, P=0.575 at pCO_2, and F=0.31, P=0.815 at pO_2) (Fig. 4-6).

Hemodynamic values

Heart rate: Repeated measures ANOVA revealed that time course was significant (F=35.05, P<0.001), but interaction (F=0.50, P=0.993) and treatment (F=0.07, P=0.976) were not significant for heart rate (Fig. 7).

Mean arterial blood pressure: Repeated measures ANOVA revealed that time course was significant

(F=11.27, P<0.001), but interaction (F=1.16, P=0.265) and treatment (F=0.56, P=0.648) were not significant for arterial blood pressure (Fig. 8).

DISCUSSION

The present results show that premedication with 4mg kg^{-1} of tramadol significantly increased the duration of surgical anesthesia of medetomidine and ketamine without affecting the hemodynamic parameters or delaying the recovery. However, pretreatment with 1 or 2mg kg^{-1} of tramadol failed to extend the expected duration of surgical anesthesia.

Intravenous and epidural administration of tramadol (2mg kg^{-1}) in dogs undergoing soft tissue and orthopedic surgery provided effective post-operative analgesia (Vettorato *et al*., 2010), and 2mg kg^{-1} of tramadol had an analgesic potency comparable to that of 0.2mg kg^{-1} of morphine (Mastrocinque and Fantoni, 2003). In addition, constant rate infusion of tramadol also had MAC-reducing effects in dogs (Seddighi *et al*., 2009). In contrast, some results have indicated that pretreatment with a single bolus of tramadol for anesthesia was insufficient to obtain a significant level of enhanced surgical general anesthesia (Kongara *et al*., 2010).

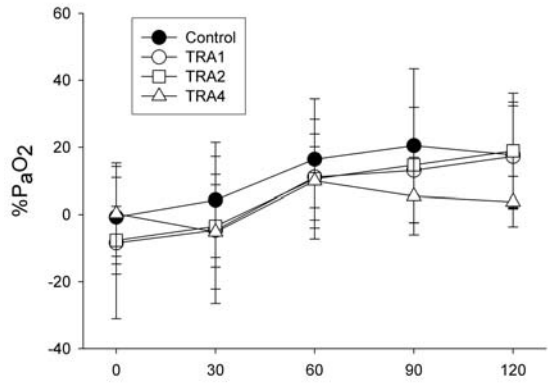

Fig. 5: Changes in P_aO_2 in dogs anesthetized with tramadol, medetomidine and ketamine. The dogs were given saline, 1, 2 or 4mg kg^{-1} of tramadol (Control, TRA1, TRA2 and TRA4), followed by medetomidine and ketamine. Data were analyzed by two-factor repeated measures ANOVA and Bonferroni test. Time course was significant (P<0.05), but interaction and treatment were not significant.

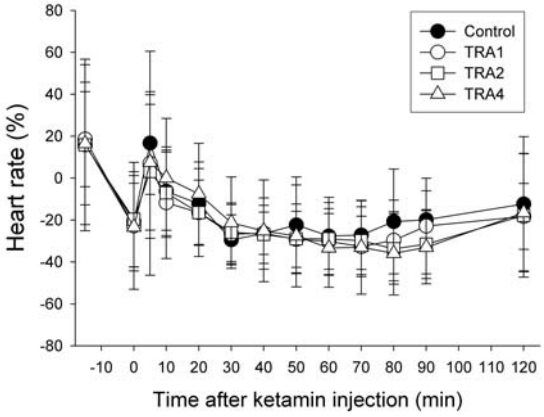

Fig. 7: Changes in heart rates in dogs anesthetized with tramadol, medetomidine and ketamine. The dogs were given saline, 1, 2 or 4mg kg^{-1} of tramadol (Control, TRA1, TRA2 and TRA4), followed by medetomidine and ketamine. Data were analyzed by two-factor repeated measures ANOVA and Bonferroni test. Time course was significant (P<0.05), but interaction and treatment were not significant.

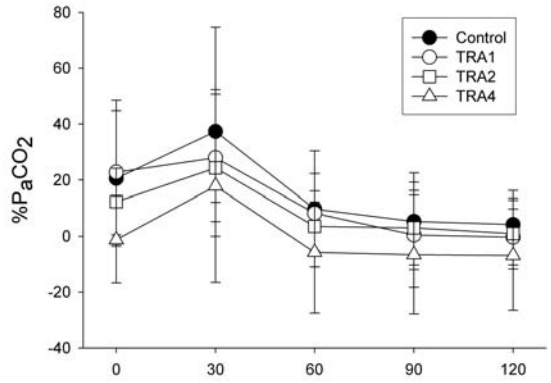

Fig. 6: Changes in P_aCO_2 in dogs anesthetized with tramadol, medetomidine and ketamine. The dogs were given saline, 1, 2 or 4mg kg^{-1} of tramadol (Control, TRA1, TRA2 and TRA4), followed by medetomidine and ketamine. Data were analyzed by two-factor repeated measures ANOVA and Bonferroni test. Time course was significant (P<0.05), but interaction and treatment were not significant.

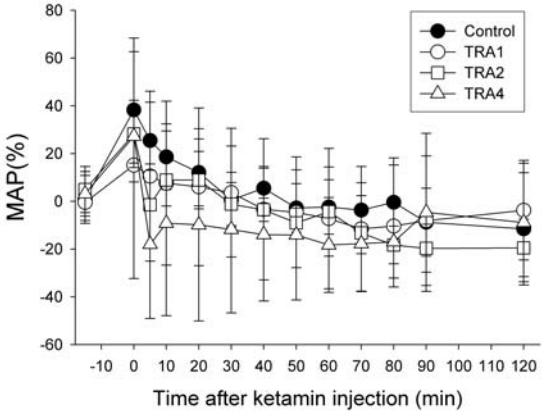

Fig. 8: Changes in mean arterial pressure (MAP) in dogs anesthetized with tramadol, medetomidine and ketamine. The dogs were given saline, 1, 2 or 4mg kg^{-1} of tramadol (Control, TRA1, TRA2 and TRA4), followed by medetomidine and ketamine. Data were analyzed by two-factor repeated measures ANOVA and Bonferroni test. Time course was significant (P<0.05), but interaction and treatment were not significant.

Recent pharmacokinetics results of tramadol in beagles suggested that lower M1 plasma concentration levels were detected in dogs, and the M1 metabolite is an important analgesic contributor of tramadol (McMillan *et al.*, 2008; Giorgi *et al.*, 2009a). Prior to our experiment, we anticipated that the 2mg kg^{-1} dose of tramadol could significantly extend the duration of surgical anesthesia and that 4mg kg^{-1} of tramadol would extend not only the period of surgical anesthesia but also the recovery duration. We also surmised that this prolonged recovery would be the main reason to select 2mg kg^{-1} of tramadol for the pretreatment dose. However, 1 and 2mg kg^{-1} doses of tramadol pretreatment were ineffective in enhancing the duration of surgical anesthesia in the present study. Effective enhancement only at the higher dose of tramadol could be related to the low level of M1 metabolites in dogs as mentioned earlier. Furthermore, a rapid elimination rate of tramadol in dogs cannot be ruled out (McMillan *et al.*, 2008). The higher dose of tramadol resulted in higher and more sustained tramadol plasma concentration (McMillan *et al.*, 2008), and tramadol itself seemed to have an analgesic effect in dogs (Giorgi *et al.*, 2009a). In the present study, tramadol was injected 30 min before ketamine administration, and a relatively long time passed in order to differentiate the duration of surgical anesthesia and compare it to the control group. That is, in the early period of anesthesia, the effect of tramadol could be masked by medetomidine and ketamine, but as the anesthetic time passed, the efficacy of tramadol as well as medetomidine and ketamine could be attenuated. In this situation, the higher tramadol plasma concentration would contribute to the enhancement of anesthetic depth.

In the present study, only treatment with 4mg kg^{-1} of tramadol induced a sedative effect at 15 min after tramadol administration. Previous results about the sedative effect of tramadol were controversial; one described a dose-dependent sedative effect of tramadol (Mastrocinque and Fantoni, 2003; Turker *et al.*, 2005; McMillan *et al.*, 2008), but another study reported no marked sedation (Seddighi *et al.*, 2009). However, significant sedation was induced with 4mg kg^{-1} of tramadol in the present study, but none of the doses of tramadol tested affected the anesthetic induction (no significant difference in loss of RR) or behavioral changes during recovery, and the sedative effect of tramadol did not persist for long.

Tramadol premedication did not cause a clinically important sedation in dogs during the recovery period (Seddighi *et al.*, 2009). In the present study, variables of behavioral changes were not significantly affected by different doses of tramadol, although a dose-dependent delay was observed. That is, tramadol premedication did not affect the recovery time, and the higher dose of tramadol in the present study prolonged the surgical anesthesia without hangover.

Previous results demonstrated that tramadol premedication has minimal effects on hemodynamics and respiratory function during anesthesia (Mastrocinque and Fantoni, 2003; McMillan *et al.*, 2008; Seddighi *et al.*, 2009). Dogs given tramadol premedication showed no significant changes in blood pressure, heart rate, arterial blood gases and pH during isoflurane anesthesia (Mastrocinque and Fantoni, 2003). The results of our study were consistent with the previously published results.

In conclusion, tramadol premedication at a dose of 4mg kg^{-1} can significantly increase the duration of surgical anesthesia with medetomidine and ketamine in dogs, without imparting significant changes to the cardiovascular system or recovery from anesthesia. Therefore, this study suggests that 4mg kg^{-1} of tramadol may be a useful preanesthetic agent for sustaining the level of surgical anesthesia longer in medetomidine and ketamine anesthesia in dogs.

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