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Sparing effect of tramadol, lidocaine, dexmedetomidine and their combination on the minimum alveolar concentration of sevoflurane in dogs

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ABSTRACT

Background: Problems associated with using inhalational anaesthesia are numerous in veterinary anaesthesia practice. Decreasing the amount of used inhalational anaesthetic agents and minimising of cardiorespiratory disorders are the standard goals of anaesthetists.

Objective: This experimental study was carried out to investigate the sparing effect of intravenous tramadol, lidocaine, dexmedetomidine and their combinations on the minimum alveolar concentration (MAC) of sevoflurane in healthy Beagle dogs.

Methods: This study was conducted on six beagle dogs. Sevoflurane MAC was determined by the tail clamp method on five separate occasions. The dogs received no treatment (control; CONT), tramadol (TRM: 1.5 mg kg⁻¹ intravenously followed by 1.3 mg kg⁻¹ h⁻¹), lidocaine (LID: 2 mg kg⁻¹ intravenously followed by 3 mg kg⁻¹ h⁻¹), dexmedetomidine (DEX: 2 µg kg⁻¹ intravenously followed by 2 µg kg⁻¹ h⁻¹), and their combination (COMB), respectively. Cardiorespiratory variables were recorded every five minutes and immediately before the application of a noxious stimulus.

Results: The COMB treatment had the greatest sevoflurane MAC-sparing effect (67.4 ± 13.9%) compared with the other treatments (5.1 ± 25.3, 12.7 ± 14.3, and 40.3 ± 15.1% for TRM, LID, and DEX treatment, respectively). The cardiopulmonary variables remained within the clinically acceptable range following COMB treatment, although the mean arterial pressure was higher and accompanied by bradycardia.

Conclusions: Tramadol-lidocaine-dexmedetomidine co-infusion produced a remarkable sevoflurane MAC-sparing effect in clinically healthy beagle dogs and could result in the alleviation of cardiorespiratory depression caused by sevoflurane. Cardiorespiratory variables should be monitored carefully to avoid undesirable side effects induced by dexmedetomidine.

Keywords: Dog; Tramadol; Lidocaine; Dexmedetomidine; Anaesthesia

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Conflict of Interest

The authors declare no conflicts of interest.

INTRODUCTION

Sevoflurane is a volatile anaesthetic widely used in veterinary practice, including in dogs [1,2]. It has a low blood/gas partition coefficient, resulting in rapid anaesthetic induction and recovery as compared with isoflurane [3]. However, similar to other volatile anaesthetics, sevoflurane may induce dose-dependent complications such as hypotension by causing vasodilation and impaired cardiac contractility in dogs [4,5]. Therefore, decreasing the amount of used inhalational anaesthetic agents and minimising of cardiorespiratory disorders are the standard goals of anaesthetists.

Minimum alveolar concentration (MAC) is defined as the partial pressure of a gas that produces immobility in 50% of individuals exposed to a supramaximal noxious stimulation. The MAC is the standard measure to evaluate inhaled anaesthetic potency [6]. MAC value may be related to the analgesic, sedative, and muscular relaxation effect of administered drugs, and can be used as a marker to assess the sparing effect of various drugs on inhaled anaesthetics.

Tramadol is an atypical opioid that exerts an analgesic effect by directly acting on opioid μ -receptors and a noradrenaline and serotonin reuptake inhibitory action in presynaptic neurons within the descending pain modulatory system [7-9]. Either a single intravenous (IV) dose or a constant rate infusion (CRI) of tramadol has been shown to reduce the required amount of inhaled anaesthetics in dogs [10,11]. Lidocaine is a sodium channel blocker that has been used as an IV analgesic during inhalation anaesthesia and is shown to decrease dose requirements for isoflurane [12,13] and sevoflurane [14,15] in dogs. Dexmedetomidine is a high-affinity agonist for α_2 -adrenergic receptors with strong pharmacological activities, including sedation, analgesia, and muscle relaxation [16]. Dexmedetomidine has been used as an IV analgesic to reduce inhalation anaesthetic requirements in dogs [6,9]; it has also been used as an adjunctive analgesic perioperatively and has demonstrated anaesthetic-sparing effects in dogs [17,18].

Experimental studies have demonstrated the superior sparing effect of inhalational anaesthetics in dogs via the concomitant use of various analgesics [6,19-22]. However, to the best of our knowledge, the sparing effect of tramadol-lidocaine-dexmedetomidine co-infusion in sevoflurane anaesthetized dogs has not been studied previously. The purpose of this study was primarily to evaluate the sparing effect of IV infusion of tramadol, lidocaine, dexmedetomidine and their combinations on the MAC of sevoflurane in dogs, and secondly to observe the changes in cardiorespiratory parameter in these dogs. We hypothesised that IV co-infusion of these analgesics would further reduce the amount of sevoflurane requirement and cardiorespiratory parameters would be maintained within the reference ranges during anaesthesia.

MATERIALS AND METHODS**Animals and study design**

This study was performed as a randomised crossover design among six Beagle dogs (3 males and 3 females) weighing 10.4 [8.40-11.10] kg (median [range]). Food was withheld for 12 h and water was allowed for 30 min before the start of the experiment. All dogs were confirmed to be healthy through a physical examination, a complete blood count, a biochemistry panel, and thoracic X-ray examinations. The dogs were cared for according to the principles of the "Guide for the Care and Use of Laboratory Animals" prepared by Rakuno Gakuen University.

All procedures were approved by the Animal Care and Use Committee of Rakuno Gakuen University (approval no. VH15B3) and we strictly adhered to national and international laws and guidelines for animal ethics and welfare, including ARRIVE guidelines, in conducting this study. The dogs were assigned to receive one of five treatments on five different occasions at seven-day intervals (i.e., washout periods: all dogs received all five treatments in different orders) using an online randomisation system (<https://www.randomizer.org/>). The MAC for each dog was determined by NO, who was blinded to the type of injected analgesic agent.

Anaesthetic induction and instrumentation

Inhalational anaesthesia was induced using sevoflurane (Sevoflo, DS Pharma Animal Health Co., Ltd., Osaka, Japan) in 100% oxygen delivered via a face mask and orotracheally intubation. Intubation was performed using a suitable tracheal tube. Following induction, anaesthesia was maintained with an end-tidal concentration of sevoflurane ($Fe'Sevo$) at 2.5% while the dogs were positioned in left lateral recumbency, and volume-controlled mechanical ventilation was initiated with a tidal volume of 15 mL kg⁻¹, and a respiratory rate (f_R) of 12 breaths min⁻¹ using a time-cycled ventilator (Nuffield Anaesthesia Ventilator Series 200, Penlon, UK). The end-tidal carbon dioxide ($Pe'CO_2$) was maintained at 35–40 mmHg by adjusting the tidal volume. The oesophageal temperature (T) was measured using an electric thermometer probe placed orally into the thoracic oesophagus, and maintained at 37.5–38.5°C using a warm air blanket (FK-CL3, SANYO Electric Co., Ltd., Osaka, Japan). The following measurements were continuously monitored and recorded every five minutes using a veterinary patient monitoring system (BP-608V, Omron Colin Co., Ltd., Tokyo, Japan): T , heart rate (HR), electrocardiogram (lead 2), f_R , oxygen saturation using pulse oximetry (SpO_2), mean arterial pressure (MAP) measured by the oscillometric method, $Fe'Sevo$, and $Pe'CO_2$.

For measuring $Fe'Sevo$ and $Pe'CO_2$, exhaled gas was collected from an 8-Fr multipurpose tube (Atom Multi-Purpose Tube, Atom Medical Co., Ltd., Tokyo, Japan) with the tip placed at the proximal end of the endotracheal tube resting in the thoracic portion of the trachea. Side-stream capnography and anaesthetic agent monitor were used for measuring $Fe'Sevo$ and $Pe'CO_2$. The anaesthetic agent monitor was calibrated prior to each experiment.

Determination of sevoflurane MAC

The MAC of sevoflurane was determined using the tail clamp method, as previously described [19]. After the dogs were allowed to equilibrate for 30 min at a $Fe'Sevo$ of 2.5%, a standard Backhaus towel clamp was placed around the tail and closed to the third ratchet. The clamp was kept closed in place for 60 seconds or until gross purposeful movement (i.e., substantial movement of the head or extremities that did not include coughing, chewing, swallowing, or increasing respiratory effort) was evident. When the dog showed positive movement, the $Fe'Sevo$ was increased by 10%, and the dog was retested after 20 min of sevoflurane re-equilibration. When the dog exhibited negative purposeful movement, the $Fe'Sevo$ was decreased by 10% and the dog was retested after 20 min of sevoflurane re-equilibration. The MAC of sevoflurane was determined as the mean of the $Fe'Sevo$ at which the dog did or did not demonstrate purposeful movement. The MAC for each dog was calculated as the mean of triplicate measurements. The time from the beginning of lateral recumbency until the end of triplicate MAC measurements was recorded. Cardiorespiratory variables (T , HR, MAP, SpO_2 , $Pe'CO_2$, f_R) were also recorded 1 min before the application of a noxious stimulus that produced changes in response to stimulation.

Experimental study procedure

The sevoflurane MAC for each dog was measured on each occasion when they received one of the following five treatments: control treatment (CONT; lactated Ringer's solution, Solulact, Terumo Corporation, Tokyo, Japan) administered at 5 mL kg⁻¹ hr⁻¹ through a 22 gauge catheter (Supercath, Medikit Co., Ltd., Tokyo, Japan) placed in the cephalic vein; tramadol (Tramal Injection, Nippon Shinyaku Co., Ltd., Kyoto, Japan) administered at a 1.5 mg kg⁻¹ as the loading dose followed by 1.3 mg kg⁻¹ hr⁻¹ CRI (TRM); lidocaine (Xylocaine 2% for IV injection, Aspen Japan K. K., Tokyo, Japan) administered at a 2 mg kg⁻¹ followed by 3 mg kg⁻¹ hr⁻¹ CRI (LID); dexmedetomidine (Precedex Injection, Pfizer Japan Inc., Tokyo, Japan) administered at a 2 µg kg⁻¹ loading dose followed by 2 µg kg⁻¹ hr⁻¹ CRI (DEX); and tramadol-lidocaine-dexmedetomidine co-infusion with the same doses as in the TRM, LID, and DEX treatments (COMB). Loading doses of each analgesic were administered through IV for over one minute. For CRI, each analgesic was added to lactated Ringer's solution, which was administered at 5 mL kg⁻¹ hr⁻¹. Loading dose and CRI were directly administered after anaesthetic induction and lateral recumbency.

The sevoflurane MAC-sparing rate for each dog was calculated using the following equation:

$$\text{sevoflurane MAC-sparing rate (\%)} = \frac{\text{MAC (CONT)} - \text{MAC (treatment)}}{\text{MAC (CONT)}} \times 100.$$

Statistical analysis

Statistical analyses were performed using Statcel 4 (OMS Publishing Inc., Tokyo, Japan). All data were analysed for normality using the Shapiro-Wilk test. Parametric values are expressed as mean ± standard deviation [SD], while nonparametric values are expressed as median (interquartile range [IQR]). Differences in MAC values and cardiorespiratory variables (T, HR, MAP, SpO₂, Pe'CO₂) among each treatment were analysed using the Quade test followed by the Wilcoxon signed-ranks test (conducted *post hoc*), which adjusted *p* values using Bonferroni correction. The time to MAC determination and the sparing rate of sevoflurane MAC among each treatment were analysed using a repeated-measures one-way analysis of variance (ANOVA) followed by a paired *t*-test (*post hoc*), which likewise adjusted *p* values using Bonferroni correction. For all analyses, the level of statistical significance was set at *p* < 0.05.

RESULTS

All dogs completed the experiment and recovered smoothly without any complications. The study was conducted over the course of 159 ± 33, 199 ± 31, 185 ± 40, 225 ± 46, and 269 ± 30 min for each treatment (CONT, TRM, LID, DEX, and COMB), respectively; there were the times necessary to obtain triplicate data for sevoflurane MAC in dogs (mean [SD]). The MAC decision time for COMB treatment was statistically significantly longer than for CONT (*p* < 0.001), TRM (*p* = 0.04), and LID (*p* = 0.01) treatments respectively.

Table 1 shows the sevoflurane MAC values and the sevoflurane MAC-sparing rate among the treatments. Compared with the CONT treatment, the MAC was statistically significantly lower within the DEX (*p* < 0.001) and COMB treatments (*p* < 0.001). There were also statistically significant differences in sevoflurane MAC between the DEX and TRM treatments (*p* < 0.001), DEX and LID treatments (*p* < 0.001), DEX and COMB treatments (*p* < 0.001), TRM and COMB treatments (*p* < 0.001), and LID and COMB treatments (*p* < 0.001).

Table 1. MAC values (%) and degree of sparing effect (%) in control (CONT), tramadol (TRM), lidocaine (LID), dexmedetomidine (DEX), combination (COMB) treatment

Variables	MAC value (%)	Sparing effect (%)
CONT	2.24 (2.15–2.34) ^{a,b}	N/A
TRM	2.44 (1.90–2.59) ^{a,b}	5.1 ± 25.3 ^{a,b}
LID	2.23 (1.69–2.35) ^{a,b}	12.7 ± 14.3 ^{a,b}
DEX	1.23 (1.13–1.39) ^{b,c,d,e}	40.3 ± 15.1 ^{b,d,e}
COMB	0.62 (0.51–0.98) ^{a,c,d,e}	67.4 ± 13.9 ^{a,d,e}

Data shows the median (interquartile range) for MAC value and mean ± SD for the degree of sparing effect. Data were obtained from 6 dogs in each treatment.

^aStatistically different from the DEX ($p < 0.05$); ^bStatistically different from the COMB ($p < 0.05$); ^cStatistically different from the CONT ($p < 0.05$); ^dStatistically different from the TRM ($p < 0.05$); ^eStatistically different from the LID ($p < 0.05$).

N/A, not available.

The sevoflurane MAC-sparing effect of the COMB treatment was statistically significantly larger than that of the DEX ($p < 0.001$), TRM ($p < 0.001$), and LID ($p < 0.001$) treatments, respectively. The sevoflurane MAC-sparing effect of the DEX treatment was statistically significantly larger than that of the LID ($p < 0.001$) and TRM ($p < 0.001$) treatments. However, there was no statistically significant difference in the sevoflurane MAC-sparing effect between the TRM and LID treatments ($p = 0.107$).

Table 2 shows the cardiorespiratory variables that were collected one minute before the application of the noxious stimulus. Compared to CONT, SpO₂ was statistically significantly lower in dogs receiving DEX ($p < 0.001$) and COMB ($p < 0.001$). Pe'CO₂ was statistically significantly lower in the DEX ($p < 0.001$) and COMB ($p < 0.001$) treatments. MAP was statistically significantly higher in dogs receiving COMB treatment ($p < 0.001$). HR was significantly decreased in the TRM ($p < 0.001$), LID ($p < 0.001$), DEX ($p < 0.001$), and COMB treatments ($p < 0.001$); in particular, HR statistically significantly decreased in dogs receiving DEX and COMB treatments. Second-degree atrioventricular block was observed in one dog receiving COMB treatment and in two dogs treated with DEX. Escaped rhythm was observed in one dog receiving DEX treatment.

DISCUSSION

The present study investigated the sparing effect of tramadol, lidocaine, dexmedetomidine and their combination on MAC following treatment with sevoflurane in dogs. As expected, the sevoflurane MAC-sparing effect of this combination treatment (designated COMB) was much greater than that of the other treatments. The cardiorespiratory variables in the COMB

Table 2. Cardiorespiratory variables in control (CONT), tramadol (TRM), lidocaine (LID), dexmedetomidine (DEX), combination (COMB) treatment

Variables	CONT	TRM	LID	DEX	COMB
T (°C)	38.0 (38.0–38.0)	37.9 (37.9–38.0)	38.0 (37.9–38.1)	38.2 (38.0–38.3)	38.2 (38.2–38.3)
HR (beats minute ⁻¹)	113 (110–119)	93 (83–102) ^a	102 (89–110) ^a	47 (46–60) ^a	56 (50–62) ^a
MAP (mmHg)	78 (75–80)	67 (62–75)	74 (63–82)	81 (77–84)	106 (95–116) ^a
SpO ₂ (%)	99 (98–99)	100 (99–100)	99 (98–99)	96 (95–97) ^a	98 (92–99) ^a
Pe'CO ₂ (mmHg)	37 (37–38)	37 (36–37)	36 (36–37)	35 (35–35) ^a	36 (35–37) ^a
f _R (breaths minute ⁻¹)	12	12	12	12	12

Data shows median (interquartile range) of the cardiorespiratory variables in control (CONT), tramadol (TRM), lidocaine (LID), dexmedetomidine (DEX) and combination (COMB) treatment at MAC determination before 1 min applying noxious stimulus. The median and interquartile range are calculated from a total of 18 data in 6 dogs.

T, oesophageal temperature; HR, heart rate; MAP, mean arterial pressure; SpO₂, oxygen saturation using pulse oximetry; Pe'CO₂, end-tidal carbon dioxide; f_R, respiratory rate.

^aStatistically different from CONT ($p < 0.05$).

treatment remained within the clinically acceptable range, although MAP was maintained at a higher level than in other treatments and was accompanied by lower HR and SpO₂.

In the present study, the MAC for the CONT treatment is very close to those of previous studies, in which the mean sevoflurane MAC ranged between 2.1% and 2.4% [14,19,22,23].

The loading dose and infusion rates for the TRM, LID, and DEX treatments used in this study were based on those used in previous studies in dogs [6,11,15]. In these previous studies, the observed sevoflurane MAC-sparing effects were approximately 26% for tramadol [11], 15% for lidocaine [15], and 44% for dexmedetomidine [6]. In the present study, the sevoflurane MAC-sparing effects (%) were 5.1 ± 25.3 , 12.7 ± 14.3 , and 40.3 ± 15.1 for TRM, LID, and DEX infusions, respectively (mean [SD]). These results for the LID and DEX treatments were similar to those reported previously [6,15]. From clinical point of view, CRI administration of lidocaine or dexmedetomidine will reduce the dose of inhalant anaesthetic agents and so decrease the cardiorespiratory depressant effect [5].

In contrast, TRM treatment did not produce a meaningful sevoflurane MAC-sparing effect in our study compared to the aforementioned report [11]. It has been reported that sevoflurane MAC-sparing effect of approximately 8% for tramadol administered at 1.5 mg kg^{-1} as a loading dose followed by $2.6 \text{ mg kg}^{-1} \text{ hr}^{-1}$ CRI; this previous study [22] used twice the dose of tramadol CRI as compared with the present study. Previous pharmacokinetic studies of tramadol have demonstrated differences in tramadol metabolism among different populations of dogs [24-26]. It has also been reported that differences in tramadol metabolism can lead to clinical variation in its efficacy among dogs [27]. Therefore, the lower efficacy of tramadol on the sevoflurane MAC-sparing effect observed in the present study may be attributed to differences in metabolism.

In the current study, the COMB treatment resulted in the greatest reduction in sevoflurane requirement among all the investigated treatments. Dexmedetomidine alone likewise produced a superior sevoflurane-sparing effect on MAC [9,17,18,28]. In addition, it has been reported that approximately 54% of sevoflurane MAC-sparing effects are produced by dexmedetomidine ($2 \mu\text{g kg}^{-1}$ followed by $2 \mu\text{g kg}^{-1} \text{ hr}^{-1}$ [CRI]) and lidocaine (2 mg kg^{-1} followed by $6 \text{ mg kg}^{-1} \text{ hr}^{-1}$ [CRI]) co-infusion [6]. The results for the COMB treatment evaluated in the current study showed greater sevoflurane MAC-sparing effect as compared with the results of previous studies. In a multimodal analgesic approach such as COMB treatment, the sevoflurane MAC-sparing effect is considered to be enhanced by the interactions of each analgesic (which have different mechanisms of action for sedation, muscle relaxation, and analgesia) as compared to when these drugs are used alone. It may therefore be considered that the reduction effect of sevoflurane produced by COMB treatment observed in the current study may provide dogs with clinical benefits, especially with respect to the cardiovascular depression induced by sevoflurane. However, the cardiovascular effects of COMB treatment need to be considered, as increased systemic vascular resistance (SVR) and decreased cardiac output (CO) have been previously reported for dexmedetomidine CRI [29,30]. A previous prospective randomized crossover study showed that systemic vascular resistance index (SVRI) increased approximately 1.9-fold and cardiac index (CI) decreased approximately 42% when dexmedetomidine was administered at a $2 \mu\text{g kg}^{-1}$ loading dose followed by $2 \mu\text{g kg}^{-1} \text{ hr}^{-1}$ CRI [30].

MAP was statistically significantly higher in dogs receiving COMB treatment than in those receiving other treatments, including DEX. It was demonstrated that IV lidocaine infusion

significantly improved the haemodynamics of dogs administered with an IV bolus dose of dexmedetomidine by increasing HR, decreasing SVRI, and improving CI [31]. In another study, dexmedetomidine ($2 \mu\text{g kg}^{-1} \text{hr}^{-1}$ followed by $2 \mu\text{g kg}^{-1} \text{hr}^{-1}$ [CRI]) and lidocaine (2mg kg^{-1} followed by $6 \text{mg kg}^{-1} \text{hr}^{-1}$ [CRI]) administration in dogs anaesthetized with sevoflurane significantly increased MAP compared to dexmedetomidine infusion alone [6]. Therefore, we believe that the MAP value observed in COMB treatment could be attributed to improving haemodynamics provided by lidocaine co-infusion in dogs.

In the present study, HR was considerably lower in the DEX and COMB treatments; α_2 -adrenergic agonists, including dexmedetomidine, bind to α_2 -adrenergic receptors in the central nervous system (CNS) and centrally reduce HR by decreasing sympathetic output from the CNS [16]. Meanwhile, α_2 -adrenergic agonists also bind to α_2 -receptors on the vascular endothelium and produce contraction of peripheral blood vessels and increase SVR [16]. Such vasoconstriction causes a transient increase in blood pressure in animals with normal cardiac function and peripherally reduces HR via the baroreceptor reflex. These central and peripheral effects could have contributed to the lower HR readings in the dogs receiving DEX and COMB treatments in the present study.

Compared to the CONT treatment, decreased SpO_2 was observed in the DEX and COMB treatments, although this value was within the clinically acceptable range. A previous study regarding effects on cardiorespiratory function due to administering dexmedetomidine to isoflurane-anaesthetized dogs reported that the arterial partial pressure of oxygen (PaO_2) remained within the reference range ($\text{PaO}_2 > 500 \text{ mmHg}$) when dexmedetomidine was administered at a $3 \mu\text{g kg}^{-1}$ loading dose followed by $3 \mu\text{g kg}^{-1} \text{hr}^{-1}$ CRI [29]. As mentioned above, dexmedetomidine induces the contraction of peripheral blood vessels, leading to decreased peripheral blood flow [16]. Therefore, we believe that the vasoconstriction induced by dexmedetomidine could have affected the results of SpO_2 measurement in the current study.

There are some limitations to the present study. First, detailed cardiovascular parameters such as CO, SVR, and invasive arterial pressure were not measured; therefore, the cardiovascular effect of tramadol-lidocaine-dexmedetomidine co-infusion in dogs anaesthetized with sevoflurane could not be evaluated comprehensively. Second, there were some individual variations in the present study because of the small number of experimental dogs. However, it was clear that tramadol-lidocaine-dexmedetomidine co-infusion showed an excellent sevoflurane MAC-sparing effect in the present study, despite the above limitations.

In the current study, we demonstrated that tramadol-lidocaine-dexmedetomidine co-infusion produces a remarkable sevoflurane MAC-sparing effect and maintains MAP in clinically healthy beagle dogs. Hence, these results may provide clinical benefit to dogs. However, as the cardiovascular effects of COMB treatment have not been detailed, careful monitoring is needed with respect to the cardiovascular effects induced by dexmedetomidine, although these effects may be tolerable for clinically healthy dogs. Further research is warranted to clarify these limitations, confirm the findings of the present study, and inform clinical guidelines.

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