



Evaluating the effects of continuous intravenous infusions of tramadol and tramadol-lidocaine on sevoflurane minimum alveolar concentration (MAC) and entropy values in dogs

Naris THENGCHAI SRI¹)* and Chulabhorn MAHIDOL¹)

¹)Department of Companion Animal Clinical Sciences, Faculty of Veterinary Medicine, Kasetsart University, Bangkok 10900, Thailand

ABSTRACT. The sparing effects of tramadol and tramadol-lidocaine infusion on the minimum alveolar concentration (MAC) of sevoflurane in dogs as well as the entropy indices were investigated. Anesthesia was induced in eight young, healthy German shepherds weighing 27.6 ± 3.2 kg (mean \pm SD) and maintained with sevoflurane. A standard tail-clamp technique was used to determine sevoflurane MAC during infusion with: sevoflurane alone to measure baseline MAC (MAC_B); tramadol (intravenous loading dose of 1.5 mg/kg and constant rate infusion [CRI] of 2.6 mg/kg/hr; MAC_T); and tramadol-lidocaine (tramadol CRI of 2.6 mg/kg/hr; and lidocaine intravenous loading dose of 1.0 mg/kg and CRI of 6 mg/kg/hr; MAC_{TL}). The state entropy (SE), response entropy (RE), and RE-SE difference were recorded 5 min prior to and during tail clamping. MAC_B was $2.4 \pm 0.2\%$. Tramadol and tramadol-lidocaine CRI decreased MAC to $2.2 \pm 0.3\%$ and $1.7 \pm 0.3\%$, respectively. The MAC-sparing effect of tramadol-lidocaine was greater than that of tramadol alone ($8.2 \pm 8.9\%$ vs. $30.1 \pm 10.7\%$; $P < 0.01$). SE and RE in all subjects, and RE-SE difference in most subjects, were increased (all $P < 0.05$) when they responded purposefully to noxious stimulation. A tramadol-lidocaine combination infusion can reduce anesthetic requirements to a higher degree than tramadol alone. Furthermore, MACentropy, MAC required to prevent increased entropy in response to a painful stimulation, and MAC of sevoflurane were similar in dogs.

KEY WORDS: tate and response entropy, lidocaine, minimum alveolar concentration, sevoflurane, tramadol

J. Vet. Med. Sci.

81(5): 682–688, 2019

doi: 10.1292/jvms.18-0448

Received: 1 August 2018

Accepted: 22 February 2019

Published online in J-STAGE:
15 March 2019

Pre-emptive analgesia helps lower the amount of anesthetic required, keeps patients under general anesthesia, and diminishes complications associated with anesthesia and surgery [37]. Continuous rate infusion (CRI) with opioids [28] and other classes of analgesics [9, 38] has been employed to reduce the amounts of inhalational agents required, as shown by reduction in the minimum alveolar concentration (MAC) of volatile anesthetics [9, 25, 38, 45]. Moreover, CRI assures a constant level of analgesia, avoiding intermittent peak plasma concentration associated with intermittent administration, and enables the use of smaller doses, leading to a reduction in side effects [19].

Systemic administration of lidocaine, a local anesthetic, is commonly used in dogs for the management of cardiac arrhythmias [40]. Studies have found that the intraoperative administration of lidocaine can significantly reduce the MAC of volatile anesthetic in rabbits, cats, and dogs [1], as well as in horses [13]. In addition, CRI of lidocaine alone [9], in combination with morphine [20], or in combination with ketamine and dexmedetomidine [21] has been shown to improve post-operative pain control in dogs.

Tramadol, a synthetic racemic mixture of the 4-phenylpiperidine analogue of codeine [52], has recently received widespread acceptance in veterinary medicine. In addition to a weak affinity to the μ -opioid receptor of tramadol, studies have identified an additional mechanism that is different from the pure μ -opioid agonist. Tramadol inhibits norepinephrine and serotonin reuptake in the central nervous system [22, 43], and administering it can lead to a reduction in the MAC of volatile anesthetics [45]. A study in a recent study demonstrated that tramadol can improve lidocaine efficacy when used in combination for pain management in patients undergoing a transrectal ultrasound-guided prostate biopsy [46]. Although tramadol is identified as a weak opioid agonist, it has been shown that a tramadol-morphine infusion has a synergistic effect on sevoflurane anesthesia [28]. Previous research has shown that

*Correspondence to: Thengchaisri, N.: ajnaris@yahoo.com

©2019 The Japanese Society of Veterinary Science



This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives (by-nc-nd) License. (CC-BY-NC-ND 4.0: <https://creativecommons.org/licenses/by-nc-nd/4.0/>)

epidural anesthesia with a lidocaine-tramadol combination provides analgesic efficacy comparable to that of a lidocaine-morphine combination in canine patients [2]. Lidocaine in combination with different drug classes for intravenous infusions leads to a greater reduction of isoflurane MAC [38] and better post-operative analgesia [21] than lidocaine infusion alone. Thus, addition of lidocaine to tramadol infusion may be able to increase the analgesic efficacy and the MAC-sparing effects on sevoflurane use in dogs.

It is well known that anesthesia causes a reduction in neuronal activity [4, 30] and electroencephalographic activity in the brain [5, 47]. Entropy is a new technique involving electroencephalogram (EEG) signal processing that is used to monitor anesthetic depth in humans [7, 15, 50]. State entropy (SE) and response entropy (RE) are two parameters provided by spectral entropy. SE represents the frequency range dominated by the EEG (0.8–32 Hz), reflecting the cortical state of the patient [53]. RE represents the frequency range dominated by both EEG and electromyography (EMG) (0.8–42 Hz), partially reflecting facial EMG activation [53]. Although entropy indices were not correlated with the depth of anesthesia in dogs [36], recent studies reported the possible application of entropy indices as an objective measurement for predicting an awake response in human patients [39] as well as in anesthetized dogs [28, 29]. The objectives of the present study were to compare the effects of tramadol and tramadol-lidocaine infusions on the sevoflurane requirement and on hemodynamic alterations in dogs undergoing anesthesia. The effects of tramadol and tramadol-lidocaine infusion on spectral entropy were also evaluated to determine the effects of the anesthetic drugs used on the frontal brain electrical activity.

MATERIALS AND METHODS

Animals

Eight healthy, client-owned pet German Shepherd dogs (4 males and 4 females) were enrolled in the study. The dogs weighed 27.6 ± 3.2 kg (mean \pm SD) and ranged from 1 to 1.5 years of age. Food was withheld overnight for the study. This study was approved by the Kasetsart University Animal Care and Use Committee (ID: ACKU 03256) and informed owner consent was obtained for all dogs.

Experimental protocol

Anesthesia: Sevoflurane (Aesica Queenborough Ltd., Queenborough, Kent, U.K.) was used for anesthesia induction (by face mask) and maintenance in the eight dogs. Once anesthetized, the dogs were intubated with an endotracheal tube (internal diameter, 9–10 mm) to maintain anesthesia with sevoflurane. Oxygen (2 l/min) was delivered in a semi-closed breathing system and dogs were allowed to breathe spontaneously throughout the studies. A 20-gauge (5 cm) catheter (Becton Dickinson Infusion Therapy Systems Inc., Sandy, UT, U.S.A.) was placed in the cephalic vein for continuous infusion of Lactated Ringer's solution (A.N.B. Laboratories Co., Ltd., Bangkok, Thailand) (5 ml/kg/hr), tramadol, and tramadol-lidocaine. Respiratory rate, expired concentration of sevoflurane, and end-tidal CO₂ (ETCO₂) were monitored with an infrared gas analyzer (Dräger Medical, Lubeck, Germany). Gas samples were drawn at the level of trachea carina at a rate of 150 ml/min using a small catheter placed through an endotracheal tube. At the beginning of each test, the gas analyzer was calibrated using standard gases (1% sevoflurane in 5% CO₂ and 70% N₂O) supplied by the Air Liquide Healthcare America Corporation (Plumsteadville, PA, U.S.A.). A 20-gauge catheter was inserted into an intermediate auricular artery for direct arterial blood pressure monitoring. Other variables including heart rate, body temperature, and peripheral oxygen saturation (SpO₂) were continuously monitored using a Datex-Ohmeda CARESCAPE multifunctional anesthesia monitor (GE Healthcare Finland, Helsinki, Finland). A hot air blower (Breeze, Laboratorios Cair S.L., Coslada, Spain) and a circulating warm-water blanket (Soar Medical-Tech Co., Ltd., Taiwan) were applied to maintain body temperature within normal range (37.8–38.9°C).

MAC determination

MAC was determined using a standard tail-clamp technique [42]. A pair of Carmalt forceps covered with soft rubber was applied to the tail for up to 1 min (if the animal did not respond purposefully) until purposeful movement was observed [28, 29]. If purposeful movement occurred, the end-tidal sevoflurane was increased by 10% of the previous value for the following test; on the contrary, if no purposeful movement occurred, it was reduced by 10% for the following test. The tail clamp was then re-applied after a 15-min equilibration period. The MAC of sevoflurane was designated as the average of the highest end-tidal sevoflurane concentration at which purposeful movement occurred and the lowest concentration at which movement did not occur [42]. The determination of sevoflurane MAC was performed in triplicate and a single MAC value from each dog was used for statistical analysis.

The MAC determination protocol used in the present study is shown in Fig. 1. In short, MAC was determined at approximately 45 min after anesthesia induction for the baseline value (MAC_B). MAC_T was determined after the administration of tramadol (Harson Laboratories, Akota, Baroda, India) (loading dose: 1.5 mg/kg, intravenous injection), followed by a 2.6 mg/kg/hr CRI. While continuing the infusion of tramadol, lidocaine (L.B.S. Laboratory Ltd., Bangkok, Thailand) was administered intravenously (loading dose: 1.0 mg/kg intravenously; CRI: 6 mg/kg/hr) for MAC_{TL} determination.

An entropy sensor (Entropy Sensor, Datex-Ohmeda) with three electrodes was placed on a patch of shaved skin at the frontotemporal area [36]. The locations of the sensor were: Fp2 (primary lead), F4 (secondary lead), and T4 (ground lead) [36, 41]. Two entropy parameters, response entropy (RE) and spectral entropy (SE), were measured in the 8 dogs using the CARESCAPE monitor and recorded at 5 min prior to a noxious stimulation (tail clamping). The maximum values of the entropy indices during the noxious stimulation were recorded and the RE-SE differences were calculated. The RE, SE, and RE-SE difference at each

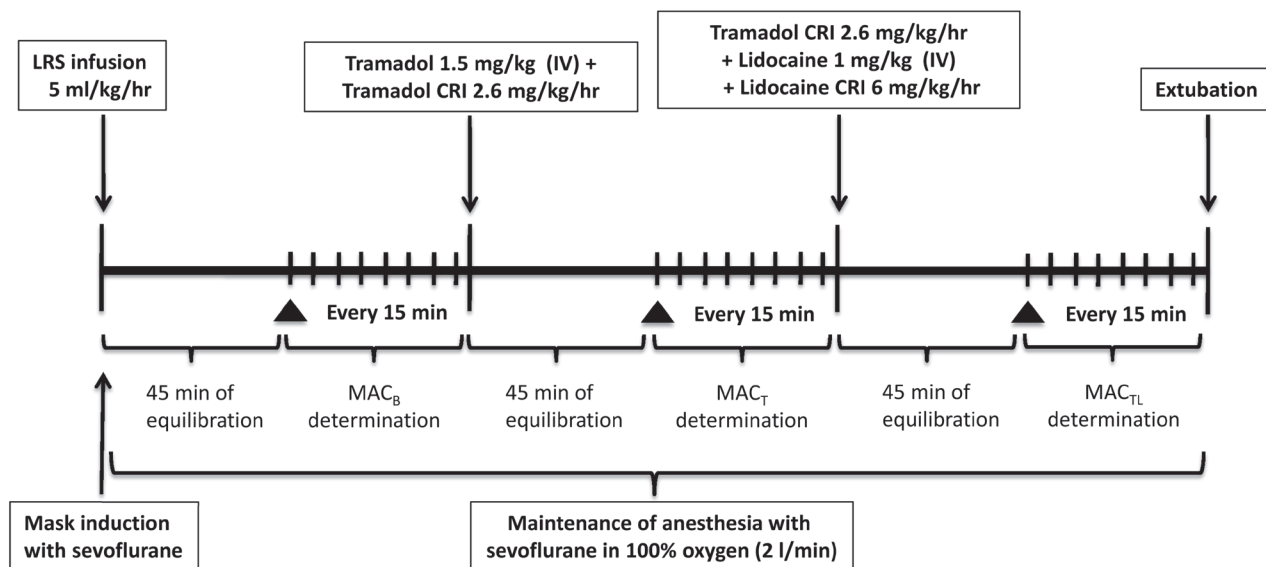


Fig. 1. Protocol used in the present study for determining the MAC of sevoflurane. ▲=start time for tail-clamping, MAC_B=MAC of sevoflurane at baseline during infusion of Lactated Ringer's solution (LRS), MAC_T=MAC of sevoflurane during tramadol infusion, and MAC_{TL}=MAC of sevoflurane during tramadol-lidocaine infusion.

Table 1. Effects of CRI of tramadol and CRI of tramadol with lidocaine on the MAC of sevoflurane (mean ± SD) at baseline (B) and during tramadol (T) and tramadol-lidocaine (TL) infusions in dogs (n=8)

Treatment	Sevoflurane (%)	Time to MACsevo (min)	% Change
B	2.4 ± 0.2	159 ± 19	-
T	2.2 ± 0.3 ^{a)}	178 ± 38	-8.2 ± 8.9
TL	1.7 ± 0.3 ^{b)}	167 ± 20	-30.1 ± 10.7

a) Significant difference compared to the corresponding MAC_B value; $P < 0.05$. b) Significant difference compared to MAC_T value; $P < 0.01$.

Table 2. Mean ± SD values for body temperature, heart rate, mean arterial pressure, SpO₂, respiratory rate, and ETCO₂ of eight German shepherd dogs at baseline and during tramadol and tramadol-lidocaine infusions

Parameters	Baseline	Tramadol	Tramadol-Lidocaine
Temperature (°C)	38.4 ± 0.3	38.7 ± 0.4	38.7 ± 0.4
Heart rate (beats/min)	95 ± 6	88 ± 8	89 ± 6
Mean arterial pressure (mmHg)	79 ± 17	87 ± 18	87 ± 12
SpO ₂ (%)	98 ± 0.9	97 ± 1.2	97 ± 1.3
Respiratory rate (breaths/min)	14 ± 3	21 ± 6 ^{a)}	22 ± 10 ^{a)}
ETCO ₂ (mmHg)	36 ± 4	38 ± 6	36 ± 5

The values are the average of all data obtained during each MAC determination period. a) Significant difference compared to the corresponding baseline value; $P < 0.05$.

timepoint of MAC determination were used for statistical analysis.

Statistical analysis

STATA12 (StataCorp, College Station, TX, U.S.A.) was used to estimate the required sample size for detecting a difference of 0.2% in sevoflurane MAC, using *t*-test for paired samples with a power of 80% and an alpha error of 0.05; this method determined that a minimum of eight dogs was needed for the present experiment. Data are summarized as mean ± SD using a statistical software (NCSS 2007, Kaysville, UT, U.S.A.). Repeated measures ANOVA was used for comparison of MAC, physiological parameters, and entropy. Pair-wise comparisons between parameters before and after 45-min infusion with either tramadol or tramadol-lidocaine infusions were examined using *t*-tests (Fig. 1). Residuals from ANOVA were approximately normal. A P -value < 0.05 was considered significant for all tests.

RESULTS

The duration of MAC determination in baseline, tramadol, and tramadol-lidocaine groups was 159 ± 19, 178 ± 38, and 167 ± 20 min, respectively. The MAC_B of sevoflurane was 2.4 ± 0.2%. Tramadol and tramadol-lidocaine decreased the MAC to 2.2 ± 0.3% and 1.7 ± 0.3%, respectively. MAC_B was decreased by 8.2 ± 8.9% ($P = 0.04$) following tramadol infusion. Additional lidocaine infusion decreased the MAC of sevoflurane from the baseline by 30.1 ± 10.7%, which was greater than tramadol alone (Table 1; $P < 0.01$).

The physiological parameters in the three different groups are presented in Table 2. There were no significant differences in

Table 3. Mean \pm SD response entropy (RE), state entropy (SE), and RE-SE difference of eight German shepherd dogs at 5 min before and during noxious stimulation (tail clamping) at baseline (B) and during tramadol (T) and tramadol-lidocaine (TL) infusions, according to the response to stimulation

		Positive response		Negative response	
		Before stimulation	During stimulation	Before stimulation	During stimulation
SE	B	50 \pm 12	74 \pm 10 ^{b)}	43 \pm 10	45 \pm 16
	T	47 \pm 13	69 \pm 13 ^{b)}	46 \pm 11	56 \pm 13
	TL	54 \pm 6	76 \pm 11 ^{b)}	50 \pm 7	60 \pm 13
RE	B	59 \pm 14	87 \pm 9 ^{b)}	51 \pm 10	56 \pm 22
	T	53 \pm 17	81 \pm 12 ^{b)}	54 \pm 14	68 \pm 13
	TL	60 \pm 9	90 \pm 8 ^{b)}	58 \pm 11	70 \pm 14
RE-SE	B	9 \pm 5	13 \pm 4	7 \pm 4	11 \pm 7
	T	7 \pm 5	12 \pm 4 ^{a)}	8 \pm 6	12 \pm 5
	TL	6 \pm 3	13 \pm 4 ^{b)}	7 \pm 4	10 \pm 3

a) Significant difference compared to the before stimulation value; $P < 0.05$. b) Significant difference compared to the before stimulation value; $P < 0.01$.

mean arterial blood pressure, SpO₂, and ETCO₂ in the baseline group compared to the tramadol and tramadol-lidocaine groups. Heart rate was slightly decreased after an infusion of tramadol (88 \pm 8 bpm) or tramadol-lidocaine (89 \pm 6 bpm) compared to the baseline (95 \pm 6 bpm), but this was not statistically significant. Respiratory rate in the tramadol (21 \pm 6 bpm, $P = 0.012$) and tramadol-lidocaine (22 \pm 10 bpm, $P = 0.031$) groups was significantly higher than that in the baseline group (14 \pm 3 bpm).

The average values of RE, SE, and RE-SE difference are given in Table 3. All of the RE and SE values, and most of the RE-SE differences increased ($P < 0.05$) when subjects responded purposefully to noxious stimulation compared to before stimulation. The entropy indices during noxious stimulation that produced a negative response were not significantly different from the same values before stimulation.

DISCUSSION

In the present study, the MAC-sparing effect of tramadol-lidocaine CRI was greater than that of tramadol infusion alone, indicating an interaction effect between tramadol and lidocaine on the reduction of the amount of anesthetic required to maintain general anesthesia. The MAC of sevoflurane in dogs prior to drug administration was 2.4%, which is in agreement with previous reports in unpremedicated dogs using the tail-clamp technique (MAC range: 2.10 to 2.36%) [14, 17, 26, 32, 54].

Tramadol is a non-selective opioid receptor agonist with weak binding to μ -opioid receptors. A single dose of 4 mg/kg of tramadol has been shown to reduce the sevoflurane MAC by 22% [23], while tramadol infusion at a rate of 1.3 or 2.6 mg/kg/hr can decrease the MAC of sevoflurane by 26 or 36%, respectively, using electric noxious stimulation [44]. The present study, which induced nociceptive challenge by tail clamping during MAC determination, revealed that a lidocaine-tramadol infusion can better reduce sevoflurane anesthesia requirements than a tramadol infusion alone.

An intravenous bolus injection of tramadol in dogs has been shown to be distributed following a two-compartment pharmacokinetic model [16]. Therefore, a bolus intravenous loading dose of tramadol followed by CRI was appropriate to produce a stable plasma anesthetic concentration. In the present study, the loading doses and infusion rates of tramadol were modified from those used in the previous study [45] to achieve an initial dosage of tramadol around 4 mg/kg with a total dosage around 8 mg/kg/day in each dog. The plasma concentration of tramadol should stay between 0.4–0.8 $\mu\text{g/ml}$, based on a pharmacokinetic study in dogs [45], a concentration which has been shown to provide significant reduction in sevoflurane MAC in dogs [23]. However, the present study did not measure the plasma concentration of tramadol, and the pharmacodynamic effects of tramadol on MAC_T and MAC_{TL} could not be analyzed.

The mechanism of the interaction effect between tramadol and lidocaine on volatile anesthesia remain obscure. Previous research reported that epidural anesthesia with lidocaine-tramadol provides analgesic efficacy comparable to that of lidocaine-morphine in canine patients [2]. Thus, it is possible that lidocaine-tramadol infusion enhances the anti-nociceptive effect in the present study. Possible mechanisms of the MAC-sparing effect of tramadol include the following: 1) tramadol inhibits norepinephrine and serotonin reuptake, enhancing descending inhibitory pathways in the central nervous system [6, 10, 12, 18, 22, 43]; and 2) tramadol and its active metabolite (*O*-desmethyltramadol) [24] that accumulate during drug infusion may bind to μ -opioid receptors, resulting in decreased responses to noxious stimulation. It is also possible that a tramadol has a sedative effect [35] that reduces anesthetic requirements during the determination of sevoflurane MAC [45]. The sevoflurane MAC-sparing effects of CRI administration of tramadol were also supported by the present study, although the MAC of sevoflurane was reduced only by 8.2 \pm

8.9%. Differences in tramadol dosage and in the types of noxious stimuli used to determine MAC do not allow direct comparisons between these results and previous findings [45]. Furthermore, differences in tramadol metabolism can lead to clinical variation in its analgesic efficacy among dogs [11].

Bradycardia or respiratory depression can occur as a result of opioid [28] or lidocaine use [3]. In the present study, tramadol and tramadol-lidocaine infusions led to a slight reduction in heart rate without affecting mean arterial blood pressure (Table 2). Since mean arterial blood pressure is a result of cardiac output and total peripheral resistance, it is possible that an increase in stroke volume compensates for a slower heart rate, and cardiac output is thus minimally affected by the infusions. It is also possible that an increase in systemic vascular resistance after tramadol infusion [25] may counteract the effect of a reduced cardiac output and help maintain the mean arterial blood pressure. Furthermore, the possibility of cardiac output being affected by sevoflurane cannot be ruled out. Since cardiac output was not measured in the present study, this cannot be confirmed, and blood pressure should be continuously monitored during infusion with tramadol or tramadol-lidocaine. After dogs received tramadol and tramadol-lidocaine infusions, respiratory rate increased significantly (Table 2). In spontaneous breathing dogs, an increase respiratory rate can lead to a significant decrease in end-tidal CO₂. However, the end-tidal CO₂ did not significantly change after tramadol and tramadol-lidocaine infusions. This phenomenon may be partly due to a shallow breathing pattern combined with increased dead space ventilation [34].

The relatively high dose of lidocaine was used in the present study to achieve a reduction of tramadol-lidocaine infusion on sevoflurane MAC comparable to that of morphine infusion [28]. Toxic effects of high dose lidocaine were not detected in the present study. Thus, our data suggested that 6 mg/kg/hr of lidocaine infusion can be used up to 150–183 min. Nonetheless, high dose lidocaine can lead to cardiotoxicity [3] and continuous monitoring is thus essential to ensure patient safety during the use of lidocaine infusion.

Monitoring entropy indicated significant elevation of both SE and RE values ($P < 0.05$) when subjects had a positive response to tail clamping. In contrast, none of the entropy indices changed throughout the 1-min stimulation when subjects had a negative response to tail clamping. This shows the potential of using spectral entropy, especially the measurement of SE and RE, to monitor real-time changes in the cortical EEG of dogs in an awake-unresponsive transition when responding to painful stimulation during anesthesia. Consequently, monitoring entropy may provide an avenue for determining the MAC of volatile anesthetics that prevents cortical excitability in dogs after noxious stimulation. Previous studies have shown that entropy indices were inversely correlated with the end-tidal concentration of inhalant anesthetics [27, 48]. Interestingly, in the present study, the entropy indices during tramadol and tramadol-lidocaine infusion remained comparable to the baseline values despite a significant reduction in sevoflurane concentration. It is possible that the tramadol-lidocaine infusion modulated the cerebral response to noxious stimulation during the determination of MAC. The concurrent alteration of electroencephalographic responses in dogs with purposeful movements during MAC determination was detected in the present study using entropy indices. Thus, our results suggested that MACentropy (MAC required to prevent increased RE or SE in response to a painful stimulation) and MAC is similar in dogs anesthetized with sevoflurane.

The MAC required to suppress cerebral activity can be determined using the bispectral index (BIS), an algorithm based on EEG measurements [8]. This MAC (MAC_{BIS}) is a reliable index to indicate anesthesia depth in humans [33, 49] and has also been studied in cats [31]. Spectral entropy, a newer model for EEG analysis, has been reported to have a better correlation with expired sevoflurane than BIS at high concentrations [44]. Entropy monitoring also has been shown to be a useful tool for monitoring patient awareness during anesthesia [51]. Moreover, our findings in a recent study indicated that entropy indices are good predictors of positive responses to noxious stimulation during MAC determination [29]. Nonetheless, in a previous study involving beagle dogs, no differences in RE and SE prior to, between, or after noxious stimulations at 1 MAC were observed [36]. It is possible that the varying results can be attributed to differences in study design, particularly the duration of pre- and post-stimulus periods used for recording data. It should be noted that values of SE over 65 and values of RE over 75 are good predictors for patient awareness during noxious stimulation [29]. Moreover, entropy indices were significantly elevated in dogs with purposeful movement in response to noxious stimulation in the presence of tramadol- and tramadol-lidocaine infusions, suggesting that entropy indices could be useful for determining the AC-sparing effects of various analgesic drugs. Due to its subjective nature, outcomes when evaluating response by detecting the purposeful movement of animals in reaction to supramaximal pain stimuli during determination of MAC for volatile anesthetic agents can vary widely. Entropy indices measured during MAC determination in the present study were significantly different during the awake and sleep stages. The objective measurement of entropy indices or MACentropy may, therefore, improve the consistency of anesthetic MAC determination in dogs.

In conclusion, a tramadol-lidocaine infusion produces a better anesthetic sparing effect than a tramadol infusion alone when using sevoflurane in dogs, without significant cardiovascular side effects. Furthermore, entropy indices change in accordance with nociceptive responses in dogs undergoing anesthesia, suggesting that determination of brain electrical activity using entropy indices may be applicable in the determination of the potency of inhaled anesthetics in dogs. Moreover, MACentropy and MAC of sevoflurane were found to be similar in dogs.

ACKNOWLEDGMENTS. The authors would like to thank Dr. Nattika Koatsang, Dr. Jakarin Satthatum, and Dr. Ketkaew Wasanasuk for their technical support.

REFERENCES

1. Acevedo-Arcique, C. M., Ibancovich, J. A., Chavez, J. R., Gutierrez-Blanco, E., Moran-Muñoz, R., Victoria-Mora, J. M., Tendillo-Cortijo, F., Santos-González, M. and Sanchez-Aparicio, P. 2014. Lidocaine, dexmedetomidine and their combination reduce isoflurane minimum alveolar concentration in dogs. *PLoS One* **9**: e106620. [Medline] [CrossRef]
2. Almeida, R. M., Escobar, A. and Maguilnik, S. 2010. Comparison of analgesia provided by lidocaine, lidocaine-morphine or lidocaine-tramadol delivered epidurally in dogs following orchiectomy. *Vet. Anaesth. Analg.* **37**: 542–549. [Medline] [CrossRef]
3. Anderson, K. P., Walker, R., Lux, R. L., Ershler, P. R., Menlove, R., Williams, M. R., Krall, R. and Moddrelle, D. 1990. Conduction velocity depression and drug-induced ventricular tachyarrhythmias. Effects of lidocaine in the intact canine heart. *Circulation* **81**: 1024–1038. [Medline] [CrossRef]
4. Antognini, J. F., Buonocore, M. H., Disbrow, E. A. and Carstens, E. 1997. Isoflurane anesthesia blunts cerebral responses to noxious and innocuous stimuli: a fMRI study. *Life Sci.* **61**: 349–354. [Medline] [CrossRef]
5. Antognini, J. F. and Carstens, E. 1999. Isoflurane blunts electroencephalographic and thalamic-reticular formation responses to noxious stimulation in goats. *Anesthesiology* **91**: 1770–1779. [Medline] [CrossRef]
6. Baraka, A., Siddik, S. and Assaf, B. 1998. Supplementation of general anaesthesia with tramadol or fentanyl in parturients undergoing elective caesarean section. *Can. J. Anaesth.* **45**: 631–634. [Medline] [CrossRef]
7. Bein, B. 2006. Entropy. *Best Pract. Res. Clin. Anaesthesiol.* **20**: 101–109. [Medline] [CrossRef]
8. Campagnol, D., Teixeira Neto, F. J., Monteiro, E. R., Beier, S. L. and Aguiar, A. J. 2007. Use of bispectral index to monitor depth of anesthesia in isoflurane-anesthetized dogs. *Am. J. Vet. Res.* **68**: 1300–1307. [Medline] [CrossRef]
9. Columbano, N., Secci, F., Careddu, G. M., Sotgiu, G., Rossi, G. and Driessen, B. 2012. Effects of lidocaine constant rate infusion on sevoflurane requirement, autonomic responses, and postoperative analgesia in dogs undergoing ovariectomy under opioid-based balanced anesthesia. *Vet. J.* **193**: 448–455. [Medline] [CrossRef]
10. Dayer, P., Desmeules, J. and Collart, L. 1997. [Pharmacology of tramadol]. *Drugs* **53** Suppl 2: 18–24 (in French). [Medline] [CrossRef]
11. Delgado, C., Bentley, E., Hetzel, S. and Smith, L. J. 2014. Comparison of carprofen and tramadol for postoperative analgesia in dogs undergoing enucleation. *J. Am. Vet. Med. Assoc.* **245**: 1375–1381. [Medline] [CrossRef]
12. Desmeules, J. A., Pigué, V., Collart, L. and Dayer, P. 1996. Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br. J. Clin. Pharmacol.* **41**: 7–12. [Medline] [CrossRef]
13. Doherty, T. J. and Seddighi, M. R. 2010. Local anesthetics as pain therapy in horses. *Vet. Clin. North Am. Equine Pract.* **26**: 533–549. [Medline] [CrossRef]
14. Galloway, D. S., Ko, J. C., Reaugh, H. F., Mandsager, R. E., Payton, M. E., Inoue, T. and Portillo, E. 2004. Anesthetic indices of sevoflurane and isoflurane in unmedicated dogs. *J. Am. Vet. Med. Assoc.* **225**: 700–704. [Medline] [CrossRef]
15. Gao, J. D., Zhao, Y. J., Xu, C. S., Zhao, J., Huang, Y. G., Wang, T. L., Pei, L., Wang, J., Yao, L. N., Ding, Q., Tan, Z. M., Zhu, Z. R. and Yue, Y. 2012. Evaluation of entropy for monitoring the depth of anesthesia compared with bispectral index: a multicenter clinical trial. *Chin. Med. J. (Engl.)* **125**: 1389–1392. [Medline]
16. Giorgi, M., Del Carlo, S., Saccomanni, G., Lebkowska-Wieruszewska, B. and Kowalski, C. J. 2009. Pharmacokinetics of tramadol and its major metabolites following rectal and intravenous administration in dogs. *N. Z. Vet. J.* **57**: 146–152. [Medline] [CrossRef]
17. Greene, S. A., Benson, G. J., Tranquilli, W. J. and Grimm, K. A. 2002. Relationship of canine bispectral index to multiples of sevoflurane minimal alveolar concentration, using patch or subdermal electrodes. *Comp. Med.* **52**: 424–428. [Medline]
18. Grond, S. and Sablotzki, A. 2004. Clinical pharmacology of tramadol. *Clin. Pharmacokinet.* **43**: 879–923. [Medline] [CrossRef]
19. Gudes, A. G. P. 2012. Pain Management: constant-rate infusion. *Clinician's Brief*. March 2012: 29–33.
20. Guimarães Alves, I. P., Montoro Nicácio, G., Diniz, M. S., Alves Rocha, T. L., Prada Kanashiro, G. and Navarro Cassu, R. 2014. Analgesic comparison of systemic lidocaine, morphine or lidocaine plus morphine infusion in dogs undergoing fracture repair. *Acta Cir. Bras.* **29**: 245–251. [Medline] [CrossRef]
21. Gutierrez-Blanco, E., Victoria-Mora, J. M., Ibancovich-Camarillo, J. A., Sauri-Arceo, C. H., Bolio-González, M. E., Acevedo-Arcique, C. M., Marin-Cano, G. and Steagall, P. V. 2015. Postoperative analgesic effects of either a constant rate infusion of fentanyl, lidocaine, ketamine, dexmedetomidine, or the combination lidocaine-ketamine-dexmedetomidine after ovariohysterectomy in dogs. *Vet. Anaesth. Analg.* **42**: 309–318. [Medline] [CrossRef]
22. Hennies, H. H., Friderichs, E. and Schneider, J. 1988. Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. *Arzneimittelforschung* **38**: 877–880. [Medline]
23. Itami, T., Kawase, K., Tamaru, N., Ishizuka, T., Tamura, J., Miyoshi, K., Umar, M. A., Inoue, H. and Yamashita, K. 2013. Effects of a single bolus intravenous dose of tramadol on minimum alveolar concentration (MAC) of sevoflurane in dogs. *J. Vet. Med. Sci.* **75**: 613–618. [Medline] [CrossRef]
24. Itami, T., Saito, Y., Ishizuka, T., Tamura, J., Umar, M. A., Inoue, H., Miyoshi, K. and Yamashita, K. 2016. Comparison of pharmacokinetics of tramadol between young and middle-aged dogs. *J. Vet. Med. Sci.* **78**: 1031–1034. [Medline] [CrossRef]
25. Itami, T., Tamaru, N., Kawase, K., Ishizuka, T., Tamura, J., Miyoshi, K., Umar, M. A., Inoue, H. and Yamashita, K. 2011. Cardiovascular effects of tramadol in dogs anesthetized with sevoflurane. *J. Vet. Med. Sci.* **73**: 1603–1609. [Medline] [CrossRef]
26. Kazama, T. and Ikeda, K. 1988. Comparison of MAC and the rate of rise of alveolar concentration of sevoflurane with halothane and isoflurane in the dog. *Anesthesiology* **68**: 435–437. [Medline] [CrossRef]
27. Klockars, J. G., Hiller, A., Ranta, S., Talja, P., van Gils, M. J. and Taivainen, T. 2006. Spectral entropy as a measure of hypnosis in children. *Anesthesiology* **104**: 708–717. [Medline] [CrossRef]
28. Mahidol, C., Niyom, S., Thitiyanaporn, C., Suprasert, A. and Thengchaisri, N. 2015. Effects of continuous intravenous infusion of morphine and morphine-tramadol on the minimum alveolar concentration of sevoflurane and electroencephalographic entropy indices in dogs. *Vet. Anaesth. Analg.* **42**: 182–186. [Medline] [CrossRef]
29. Mahidol, C. and Thengchaisri, N. 2015. Optimal cutoff points of entropy indices for use in predicting responses elicited during determination of minimum alveolar concentration of sevoflurane in dogs. *Am. J. Vet. Res.* **76**: 500–506. [Medline] [CrossRef]
30. March, P. A. and Muir, W. W. 2005. Bispectral analysis of the electroencephalogram: a review of its development and use in anesthesia. *Vet. Anaesth. Analg.* **32**: 241–255. [Medline] [CrossRef]
31. March, P. A. and Muir, W. W. 3rd. 2003. Minimum alveolar concentration measures of central nervous system activation in cats anesthetized with isoflurane. *Am. J. Vet. Res.* **64**: 1528–1533. [Medline] [CrossRef]
32. Matsubara, L. M., Oliva, V. N., Gabas, D. T., Oliveira, G. C. and Cassetari, M. L. 2009. Effect of lidocaine on the minimum alveolar concentration

- of sevoflurane in dogs. *Vet. Anaesth. Analg.* **36**: 407–413. [[Medline](#)] [[CrossRef](#)]
33. Matsuura, T., Oda, Y., Tanaka, K., Mori, T., Nishikawa, K. and Asada, A. 2009. Advance of age decreases the minimum alveolar concentrations of isoflurane and sevoflurane for maintaining bispectral index below 50. *Br. J. Anaesth.* **102**: 331–335. [[Medline](#)] [[CrossRef](#)]
 34. Meyer, M., Hahn, G., Buess, C., Mesch, U. and Piiper, J. 1989. Pulmonary gas exchange in panting dogs. *J. Appl. Physiol.* **66**: 1258–1263. [[Medline](#)] [[CrossRef](#)]
 35. Monteiro, E. R., Junior, A. R., Assis, H. M., Campagnol, D. and Quitzan, J. G. 2009. Comparative study on the sedative effects of morphine, methadone, butorphanol or tramadol, in combination with acepromazine, in dogs. *Vet. Anaesth. Analg.* **36**: 25–33. [[Medline](#)] [[CrossRef](#)]
 36. Morgaz, J., Granados, M. M., Domínguez, J. M., Navarrete, R., Fernández, A., Galán, A., Muñoz, P. and Gómez-Villamandos, R. J. 2011. Evaluation of spectral entropy to measure anaesthetic depth and antinociception in sevoflurane-anaesthetised Beagle dogs. *Vet. J.* **188**: 352–355. [[Medline](#)] [[CrossRef](#)]
 37. Muir, W. W. 3rd. 2002. Physiology and pathophysiology of pain. pp. 13–41. *In: Handbook of Veterinary Pain Management*, 2nd ed. (Gaynor, J. S. and Muir, W. W. 3rd. eds.), Mosby, St. Louis.
 38. Muir, W. W. 3rd., Wiese, A. J. and March, P. A. 2003. Effects of morphine, lidocaine, ketamine, and morphine-lidocaine-ketamine drug combination on minimum alveolar concentration in dogs anesthetized with isoflurane. *Am. J. Vet. Res.* **64**: 1155–1160. [[Medline](#)] [[CrossRef](#)]
 39. Paloheimo, M., Edmonds, H. L. Jr., Wirtavuori, K. and Tammisto, T. 1989. Assessment of anaesthetic adequacy with upper facial and abdominal wall EMG. *Eur. J. Anaesthesiol.* **6**: 111–119. [[Medline](#)]
 40. Pariaut, R., Moïse, N. S., Koetje, B. D., Flanders, J. A., Hemsley, S. A., Farver, T. B., Gilmour, R. F. Jr., Gelzer, A. R., Kraus, M. S. and Otani, N. F. 2008. Lidocaine converts acute vagally associated atrial fibrillation to sinus rhythm in German Shepherd dogs with inherited arrhythmias. *J. Vet. Intern. Med.* **22**: 1274–1282. [[Medline](#)] [[CrossRef](#)]
 41. Pellegrino, F. C. and Sica, R. E. 2004. Canine electroencephalographic recording technique: findings in normal and epileptic dogs. *Clin. Neurophysiol.* **115**: 477–487. [[Medline](#)] [[CrossRef](#)]
 42. Quasha, A. L., Eger, E. I. 2nd. and Tinker, J. H. 1980. Determination and applications of MAC. *Anesthesiology* **53**: 315–334. [[Medline](#)] [[CrossRef](#)]
 43. Raffa, R. B., Friderichs, E., Reimann, W., Shank, R. P., Codd, E. E. and Vaught, J. L. 1992. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an ‘atypical’ opioid analgesic. *J. Pharmacol. Exp. Ther.* **260**: 275–285. [[Medline](#)]
 44. Rinaldi, S., Consales, G. and De Gaudio, A. R. 2007. State entropy and bispectral index: correlation with end tidal sevoflurane concentrations. *Minerva Anesthesiol.* **73**: 39–48. [[Medline](#)]
 45. Seddighi, M. R., Egger, C. M., Rohrbach, B. W., Cox, S. K. and Doherty, T. J. 2009. Effects of tramadol on the minimum alveolar concentration of sevoflurane in dogs. *Vet. Anaesth. Analg.* **36**: 334–340. [[Medline](#)] [[CrossRef](#)]
 46. Sen, H., Seckiner, I., Bayrak, O., Sen, E., Erturhan, S. and Yagci, F. 2015. Combination of Tramadol and Lidocaine for Pain Control During Transrectal Ultrasound-guided Prostate Biopsy: A Randomized Double-blinded Study. *Urology* **85**: 1247–1251. [[Medline](#)] [[CrossRef](#)]
 47. Steriade, M., Amzica, F. and Contreras, D. 1994. Cortical and thalamic cellular correlates of electroencephalographic burst-suppression. *Electroencephalogr. Clin. Neurophysiol.* **90**: 1–16. [[Medline](#)] [[CrossRef](#)]
 48. Takamatsu, I., Ozaki, M. and Kazama, T. 2006. Entropy indices vs the bispectral index for estimating nociception during sevoflurane anaesthesia. *Br. J. Anaesth.* **96**: 620–626. [[Medline](#)] [[CrossRef](#)]
 49. Tsuruta, S., Satsumae, T., Mizutani, T., Inomata, S., Shimizu, T., Takahashi, S. and Tanaka, M. 2011. Minimum alveolar concentrations of sevoflurane for maintaining bispectral index below 50 in children. *Paediatr. Anaesth.* **21**: 1124–1127. [[Medline](#)] [[CrossRef](#)]
 50. Vakkuri, A., Yli-Hankala, A., Talja, P., Mustola, S., Tolvanen-Laakso, H., Sampson, T. and Viertiö-Oja, H. 2004. Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. *Acta Anaesthesiol. Scand.* **48**: 145–153. [[Medline](#)] [[CrossRef](#)]
 51. Vanluchene, A. L., Struys, M. M., Heyse, B. E. and Mortier, E. P. 2004. Spectral entropy measurement of patient responsiveness during propofol and remifentanyl. A comparison with the bispectral index. *Br. J. Anaesth.* **93**: 645–654. [[Medline](#)] [[CrossRef](#)]
 52. Vettorato, E., Zonca, A., Isola, M., Villa, R., Gallo, M., Ravasio, G., Beccaglia, M., Montesissa, C. and Cagnardi, P. 2010. Pharmacokinetics and efficacy of intravenous and extradural tramadol in dogs. *Vet. J.* **183**: 310–315. [[Medline](#)] [[CrossRef](#)]
 53. Viertiö-Oja, H., Maja, V., Särkelä, M., Talja, P., Tenkanen, N., Tolvanen-Laakso, H., Paloheimo, M., Vakkuri, A., Yli-Hankala, A. and Meriläinen, P. 2004. Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. *Acta Anaesthesiol. Scand.* **48**: 154–161. [[Medline](#)] [[CrossRef](#)]
 54. Yamashita, K., Iwasaki, Y., Umar, M. A. and Itami, T. 2009. Effect of age on minimum alveolar concentration (MAC) of sevoflurane in dogs. *J. Vet. Med. Sci.* **71**: 1509–1512. [[Medline](#)] [[CrossRef](#)]