Original Article

Effect of lidocaine, fentanyl, or dexmedetomidine on minimum infusion rate and cardiorespiratory variables in dogs undergoing ketofol total intravenous anesthesia

Khannejad, M.[1]; Keramat, M.[1]; Imani Rastabi, H.[2*]; Naddaf, H.[2] and Mosallanejad, B.[2]

[1]Graduated from Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran; [2]Department of Clinical Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran

[*]***Correspondence:*** *H. Imani Rastabi, Department of Clinical Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran. E-mail: h.imani@scu.ac.ir*

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Abstract

Background: It has been proposed that dose reduction via co-administration of other agents might ameliorate respiratory depression associated with ketofol. **Aims:** The present study was designed to evaluate the effects of adding lidocaine, fentanyl, or dexmedetomidine on the required dose and cardiorespiratory variables in dogs undergoing total intravenous anesthesia (TIVA) with ketofol. **Methods:** In phase I, twelve dogs (six per each treatment) were induced and maintained with two out of four anesthetic regimens of (1) ketofol (4 mg/kg and 0.3 mg/kg/min, respectively; KET), (2) ketofol and lidocaine (1.5 mg/kg and 0.25 mg/kg/min, respectively; KLD), (3) ketofol and fentanyl (5 µg/kg and 0.1 µg/kg/min, respectively; KFN), and (4) ketofol and dexmedetomidine (2 µg/kg and 2 mg/kg/h, respectively; KDX) with at least one-week interval. The minimum infusion rate (MIR) of ketofol was determined. In phase II, the other twelve dogs were given the same anesthetic regimens for 60 min with the determined infusion rate of ketofol, and cardiorespiratory variables were recorded. **Results:** Mean MIR of ketofol for KET, KLD, KFN, and KDX were 0.35, 0.23, 0.15, and 0.08 mg/kg/min, respectively. In phase II, the times of recovery events were shorter in KFN and KDX than KET and KLD. The heart rate was significantly higher than baseline in KET and KLD, which was also significantly lower than KFN and KDX at several time points. In all treatments, respiratory depression was detected. **Conclusion:** Despite the decrease in the dose of ketofol, none of the added drugs attenuated respiratory depression caused by this agent.

Key words: Canine, Recovery, Respiratory depression, Total intravenous anesthesia

Introduction

Total intravenous anesthesia (TIVA) can be a substitute for inhalation anesthesia, particularly in short-duration and minimally invasive procedures or diagnostic imaging (Kennedy and Smith, 2015). Unlike inhalation anesthesia, this technique does not require facilities for delivering and removing gases. Total intravenous anesthesia is becoming more popular, especially by the introduction of agents with short-acting and non-cumulative properties and modern technologies providing more efficient constant rate infusion (CRI) of drugs (Mannarino *et al*., 2012).

Propofol is the most widely used intravenous anesthetic for the induction and maintenance of anesthesia in small animals. This drug has a rapid onset, short duration, and slow recovery; however, it can be associated with dose-dependent respiratory depression and hypotension (Kennedy and Smith, 2015). Ketamine is another common anesthetic drug used for small animals. Anesthesia with ketamine may increase heart rate, blood pressure, and cardiac output. It may also lead to muscle stiffness, convulsion and eventful recovery (Kennedy and Smith, 2015).

Combinations of propofol and ketamine with various ratios are proposed for TIVA to reduce the doses required for each drug and subsequently more stable cardiorespiratory variables with less unpleasant consequences. Ketofol is a combination of 1:1 propofol and ketamine in a single syringe (Andolfatto and Willman, 2011). Human studies revealed that ketofol can increase hemodynamic stability (Smischney *et al*., 2012) and decreased complications associated with propofol or ketamine (Andolfatto and Willman, 2011; Alletag *et al*., 2012). In a study performed on dogs, TIVA with ketofol resulted in respiratory depression more pronounced than propofol (Kennedy and Smith, 2015). Respiratory depression has also been observed in dogs induced with ketofol alone or combined with diazepam or midazolam (Imani *et al*., 2016; Rastabi *et al*., 2018).

Various drugs have been combined with anesthetic agents to provide balanced anesthesia with the benefit of the reduced dose of the used drug(s) and, subsequently, to avoid unpleasant effects associated with each one. Lidocaine is an amino amide local anesthetic that reduces inhalant and injectable anesthetics without significant adverse effects (Valverde *et al*., 2004; Matsubara *et al*., 2009; Mannarino *et al*., 2012). Fentanyl is a pure μ opioid agonist with immediate and short-lived effects that reduces the minimum alveolar concentration of volatile anesthetics (Steagall *et al*., 2006; Ueyama *et al*., 2009; Reilly *et al*., 2013) as well as the dose of propofol and alfaxalone in dogs (Davis *et al*., 2017; Bennett *et al*., 2019). Dexmedetomidine (DEX) is a potent alpha-2 adrenergic agonist which has been shown to reduce the dose of anesthetic agents needed for the induction and maintenance of anesthesia in dogs (Vickery *et al*., 1988; Kuusela *et al*., 2001; Pascoe *et al*., 2006).

Due to scarce knowledge on the effect of CRI of ketofol with either lidocaine, fentanyl or DEX in dogs, the present study was designed to determine the MIR and the accompanied cardiovascular alterations in dogs receiving CRI of ketofol combined with lidocaine, fentanyl or DEX. We hypothesized that adding either employed drugs to ketofol via a significant reduction in the dose rate of ketofol would result in stable blood pressure and improved respiratory functions.

Materials and Methods

The present investigation was designed as a blind, randomized (https://www.randomizer.org) prospective experimental study. Twenty-four mongrel male dogs weighing 19.1 ± 3.1 kg and aged 1.5-2.5 years old from a private shelter for stray dogs were transferred to the Veterinary Hospital at least one week before initiating the study. The animals were kept in separate cages, fed the same diet, and had free access to water. A thorough physical examination, complete blood count, and total protein measurements confirmed the dogs' health status. Only ASA-I dogs (according to the American Society of Anesthesiologists (ASA) physical status) were included in the study. Other exclusion criteria were aggressive behavior, and being extremely fat or slim. After that, the dogs fasted for 12 h, but they had free access to water for up to 2 h before the anesthesia session. All the procedures performed in the current study were approved by Ethical Committee of our university (EE/96.24.3. 85896/SCU.ac.ir).

The present study was conducted in two phases:

Phase I- Determination of MIR of ketofol

Twelve dogs were studied in this phase. On the experiment day, the animals were given a combination of acepromazine (0.025 mg/kg; Neurotranq® 10 mg/ml, Alfasan, Woerden, Holland) and morphine (0.25 mg/kg; Morphine Sulfate, Daru Pakhsh, Iran) intramuscularly. Thirty min later, the animals were transferred to a surgical table. Then, the cephalic veins of the forelimbs and the dorsal metatarsal artery of the left hind limb (for blood sample collection) were catheterized. The animals received 100% oxygen (2 L/min) with a mask for 5 min. Having passed 40 min from sedatives injection, the dogs received either of the following anesthesia regimens randomly:

1- KET: Induction by bolus injection of ketofol (Ketamine 10%, Alfasan, Woerden, Holland and Propofol-Lipuro 1%, B. Braun Medical; Melsungen, Germany, 4 mg/kg) followed by an IV bolus of 2 ml normal saline and the maintenance by CRI of ketofol (0.3 mg/kg/min) and NaCl 0.9% (0.0125 ml/kg/min).

2- KLD: Induction by bolus injection of ketofol (4 mg/kg) followed by an IV bolus of lidocaine (loading dose; 1.5 mg/kg; Lignodic® 2%, Caspian Tamin, Iran) and the maintenance by CRI of ketofol (0.3 mg/kg/min) and lidocaine (0.25 mg/kg/min).

3- KFN: Induction by bolus injection of ketofol (4 mg/kg) followed by an IV bolus of fentanyl (loading dose: 5 μg/kg; Fentanyl 0.005%, Caspian Tamin, Iran) and the maintenance by CRI of ketofol (0.3 mg/kg/min) and fentanyl (6 μg/kg/h).

4- KDX: Induction by bolus injection of ketofol (4 mg/kg) followed by an IV bolus of DEX (loading dose: 2 μg/kg; Precedex™ 100 μg/ml, Hospira, USA) and the maintenance by CRI of ketofol (0.3 mg/kg/min) and DEX (2 μg/kg/h).

Each dog received two out of four treatments with at least one-week intervals. The preparation process of ketofol was performed according to the study by Kennedy and Smith (2015). A syringe with 20 ml of propofol and 2 ml of ketamine was prepared to give the final concentration of 9.1 mg/ml propofol and 9.1 mg/ml ketamine. Infusions of ketofol and the accompanying drugs were performed using a syringe infusion device (Medifusion, DS-3000, South Korea) and a burette infusion micro-set (60 drops: 1 ml; Shanchuan Medical Instrument Co., China), respectively. Afterward, loading doses of lidocaine, fentanyl, and DEX were diluted to the final volume of 2 ml using NaCl 0.9%.

After the induction of anesthesia, the trachea was intubated using a proper-sized cuffed endotracheal tube, which was then connected to a rebreathing anesthetic system delivering oxygen at 2 L/min. The dogs were positioned in sternal recumbency and allowed to breathe spontaneously. All the animals received NaCl 0.9% at the dose rate of 10 ml/kg/h from the anesthesia induction until the complete removal of tracheal tube. It was attempted to maintain the dogs' rectal temperature at 37-38°C from anesthesia induction until the removal of the tracheal tube using a blanket and two warm-water bags placed over and at both sides of the animals, respectively.

To determine the MIR of ketofol, a noxious stimulus was applied between the animal's fingers using a hemostat forceps closed at the first ratchet for 2-3 s. If the dog had no purposeful movement, the infusion rate was reduced by 0.05 ml/kg/min. In contrast, if the dog had any purposeful movement, the infusion rate was increased by 0.05 ml/kg/min. Purposeful movement was

defined as noticeable movement of the head and trunk and/or limb withdrawal. Tremor and twitching were not considered as purposeful movements. The dog remained at the new rate for 10 min, and painful stimulation was applied again. MIR was calculated based on the arithmetic average of the two consecutive ketofol rates with the presence or absence of a purposeful movement (Mannarino *et al*., 2012).

Arterial blood sampling was done after 40 min from sedation (before the induction of anesthesia), 5 and 15 min after the induction of anesthesia, and then every 15 min until obtaining MIR. In this phase, no data were recorded except the infusion rate. The blood samples were discarded with no further analysis. Ketoprofen (2 mg/kg) was postoperatively administered to all dogs q 24 h for 2 days.

Phase 2- Determination of anesthesia scores, recovery times and cardiorespiratory effects

Twelve other dogs were used in this phase. Sedation, instrumentation, monitoring, and ketofol preparation were performed as described in phase 1. After that, dogs were randomly assigned to receive the two treatments of KET, KLD, KFN, or KDX with one week as washout period. The rate of ketofol was selected based on the results obtained from the first phase. Anesthesia was maintained for 60 min and then the infusion was stoppedwhile oxygen supplementation continued until extubation. The tracheal tube was removed once the swallowing reflex returned or tongue movement was observed.

During the anesthesia session, hypotension (mean arterial pressure (MAP) <60 mmHg) was treated by a Ringer's solution (15 ml/kg in about 10 min) and in a non-responsive situation by dopamine infusion (5 µg/kg/min). Bradycardia (Hear rate (HR) <40 beats/min) was treated with atropine (0.04 mg/kg) as needed. If end tidal carbon dioxide ($ETCO_2$) was >55 mmHg, intermittent positive pressure ventilation (IPPV) was performed manually to restore $ETCO_2$ within the normal range (i.e., 35-45 mmHg).

In this phase, sedation, anesthesia induction, and recovery qualities were scored in terms of the following scoring systems:

Sedation quality: 1- no sedation, 2- mild sedation, 3- moderate sedation, and 4- heavy sedation

Induction quality: 1- no sign of excitement, intubation within 60 s after the administration of ketofol, 2- mild symptoms of excitement, some struggle during intubation, and 3- hyperkinesia, restlessness, no intubation

Recovery quality: 1- no struggling, standing and walking with no difficulty, 2- some struggling, long-lasting sternal recumbency, and 3- severe struggling, inability to be in sternal recumbency or to walk

The times for tracheal intubation, the tracheal tube removal, uprising the head, sternal recumbency and ability to stand (at least for 10 s without assistance) were recorded. HR (via an oxygen saturation (SPO_2) probe connected to the tongue), blood pressure (by invasive arterial blood pressure measurement using a manometer attached to the catheter of the dorsal metatarsal artery), respiratory rate (via a capnograph, f_R), and rectal temperature (RT) (via a probe connected to the mucus of rectum with the same insertion length in all dogs) were recorded. HR, lead II electrocardiogram (EKG), f_R and RT were recorded using a multiparameter monitoring system (Vitapia 7000 KV, Trismed, South Korea). Variables were continuously measured but were recorded at 40 min after sedative administration (before induction of anesthesia), and also at 5, 15, 30, 45, and 60 min after the induction of anesthesia.

For blood gas analysis, 1 ml arterial blood sample was collected from the dorsal metatarsal artery catheter at each time point. For blood collection, 1 ml sample was collected in a syringe containing 0.1 ml heparin (Heparodic® 5000, Caspian Tamin, Iran). After that, the first collected blood plus 1 ml of normal saline was slowly injected into the artery. Blood gas analysis was performed using a calibrated gas analyzer (EDAN i15, China).

All the drug calculations and injections were done by one investigator (H.I.R). Two other investigators (M.K.N and M.K) who were unaware of the treatments scored sedation, intubation and recovery and measured and recorded data. Ketoprofen (2 mg/kg) was postoperatively administered intramuscularly to all dogs q 24 h for three days.

Statistical analysis

All statistical analyses were performed using SPSS software version 24 (IBM Corporation, USA). The normal distribution of data was assessed using the Kolmogorov-Smirnov test. For normally distributed data, repeated measures ANOVA (followed by Bonferroni's test as needed) was used to compare the changes between and within the treatments. The Friedman test was used to compare sedation quality, induction, and recovery data among the treatments. Parametric and non-parametric data were expressed as mean (standard deviation (SD)) and median (maximum-minimum), respectively. The statistical significance level was considered as $P<0.05$.

Results

Phase 1

There was no significant difference among the treatments concerning body weights (17.3 ± 2.7 kg, 17.1 ± 2.9 kg, 19.4 ± 3.5 kg, and 17.3 ± 2.2 kg in KET and KLD, KFN, and KDX treatments, respectively; $P>0.05$). In the case of MIR, adding lidocaine, fentanyl or DEX to ketofol reduced the MIR of ketofol by 37%, 50%, and 80%, respectively. The MIR of ketofol was 0.35 ± 0.04 mg/kg/min for KET, 0.23 ± 0.03 mg/kg/min for KLD, 0.15 ± 0.04 mg/kg/min for KFN, and 0.08 ± 0.02 mg/kg/min for KDX ($P=0.001$). The dose rates of 0.35, 0.23, 0.15, and 0.08 mg/kg/min were selected as the infusion rates of ketofol for KET, KLD, KFN, and KDX for phase 2, respectively.

Phase 2

Two dogs in the KLD, four dogs in KFN and four dogs in KDX treatments showed apnea immediately after the induction of anesthesia. Accordingly, these dogs required IPPV until the return of spontaneous breathing (30 and 50 min for KLD, 45 min for KFN and 30 and 45 min for KDX). The other dogs tolerated anesthesia well in all the treatments without any complications. The weights of dogs were 21.3 ± 3.3 kg (KET), 21.5 ± 3.0 kg (KLD), 16.1 ± 1.1 kg (KFN), and 18.4 ± 2.5 kg with no significant difference among the treatments (P>0.05).

The scores for sedation, induction, and recovery qualities are summarized in Table 1. Overall, sedation, induction, and recovery were acceptable in all the dogs and no noticeable complication was detected in any treatment. Although the induction and recovery scores gained higher quality in more dogs in KFN than KDX, no significant differences were observed (P>0.05). Table 2 shows the determined events in the recovery time. The head uprising and sternal recumbency times were significantly shorter in KFN than those of KLD (P=0.038 and P=0.003, respectively). Besides, the time of ability to stand was significantly lower in KFN and KDX than KLD P=0.016 and P=0.001, respectively).

The data related to hemodynamic assessments are shown in Table 3. Comparison of HR among the treatments showed significantly lower values at anesthesia in KDX and KFN compared to those of KET (P≤0.022 and P≤0.049, respectively). At 45 min of anesthesia, HR in KLD was significantly higher than KET (P=0.029). In KET and KLD treatments, HR was significantly higher than baseline at all the time points during anesthesia (P≤0.029 for KET and P≤0.013 for KLD). HR was significantly lower in KDX treatment than baseline at several time points (P≤0.042). MAP was significantly higher in KDX than KLD and KFN at 5 min (P=0.022 and P=0.005, respectively) and KLD at 60 after induction (P=0.044). In KDX treatment, significantly higher MAP values were observed over time than baseline (P≤0.049). For f_R, there were significant differences between KET and KLD compared to KFN and KDX at 5, 15, and 30 min after induction (P≤0.049). Although f_R decreased in all the treatments over time, significant differences were detected only in KFN (P≤0.029) and KDX (P≤0.047). During the anesthesia session, the average RT values were calculated as 37.1, 37.0, 37.5, and 37.6°C for KET, KLD, KFN, and KDX, respectively, with no significant differences (P>0.05). EKG assessment occasionally revealed sinus arrhythmia

Table 1: Median (maximum-minimum) scores of sedation, induction, and recovery qualities in anesthetized dogs (n=6) received ketofol (KET), and ketofol plus lidocaine (KLD), fentanyl (KFN) or dexmedetomidine (KDX)

Treatment	Variable		
	Sedation	Induction	Recovery
KET	2 (1-3)	1 (1-2)	2 (1-2)
KLD	2 (1-3)	1 (1-3)	2 (1-3)
KFN	2 (1-2)	1 (1-2)	1 (1-3)
KDX	2 (1-2)	1 (1-1)	1 (1-2)

Table 2: Times (min) of recovery events (Mean±SD) in anesthetized dogs (n=6) received ketofol (KET), and ketofol plus lidocaine (KLD), fentanyl (KFN) or dexmedetomidine (KDX)

Treatments	Events			
	Extubation	Head uprising	Sternal recumbency	Ability to stand
KET	20.7 ± 9.6	32.2 ± 12.8	55.4 ± 31.5	74.8 ± 17.5
KLD	25.5 ± 11.5	52.3 ± 21.4	64.8 ± 20.2	88.0 ± 6.4
KFN	17.8 ± 11.8	24.4 ± 13.0 ^{A}	34.8 ± 17.0 ^{A}	47.2 ± 24.0 ^{A}
KDX	17.0 ± 4.6	28.6 ± 4.8	40.6 ± 4.4	50.6 ± 6.0 ^{A}

^{A} Significantly different from KLD (P<0.05)

Table 3: Mean±SD of heart rate (HR), mean arterial pressure (MAP), and respiratory rate (f_R) in anesthetized dogs (n=6) received ketofol (KET), and ketofol plus lidocaine (KLD), fentanyl (KFN) or dexmedetomidine (KDX)

Variable	Treatment	Time (min)					
		Baseline	5	15	30	45	60
HR (beats/min)	KET	59±10	110±24$^{A, a}$	119±29$^{A, a}$	106±14$^{A, a}$	100±18$^{A, a}$	107±16$^{A, a}$
	KLD	60±8	122±18$^{A, B, a}$	124±15$^{A, B, a}$	125±7$^{A, B, a}$	127±8$^{B, a}$	116±13$^{A, B, a}$
	KFN	75±14	62±13^{B}	56±19^{B}	57±19^{B}	51±8^{B}	58±8^{B}
	KDX	68±4	55±4$^{B, a}$	48±6^{B}	47±8$^{B, a}$	49±7$^{B, a}$	50±4$^{B, a}$
MAP (mmHg)	KET	87±7	95±25$^{A, B}$	96±29	99±33	100±32	96±21$^{A, B}$
	KLD	91±26	77±19^{B}	81±24	83±22	71±13	70±13^{B}
	KFN	101±4	92±4^{B}	95±6	94±3	89±1	90±2$^{A, B}$
	KDX	75±10	114±6$^{A, a}$	109±9^{a}	105±8^{a}	101±8^{a}	99±10$^{A, a}$
f_R (breaths/min)	KET	15±2	10±3^{A}	10±4^{A}	9±3^{A}	8±3	9±3
	KLD	12±4	11±7^{A}	10±5^{A}	7±1^{A}	6±1	6±1
	KFN	17±4	4±4^{a}	5±2^{a}	4±1^{a}	7±3^{a}	9±7
	KDX	15±3	5±1^{a}	4±1^{a}	5±2^{a}	6±3^{a}	7±3

Different uppercases indicate significant differences among treatments (P<0.05), and different lowercases indicate significant differences from baseline (P<0.05)

and S-T depression in KET and KLD. Second and third-degree atrioventricular heart blocks were observed in KFN and KDX in several cases.

The data related to the blood gas analysis are shown in Table 4. Partial pressure of CO_2 (PCO_2) in KLD treatment at 60 min after anesthesia was significantly higher than other treatments ($P \leq 0.038$). PCO_2 was significantly higher during anesthesia in KET and KLD compared to baseline ($P \leq 0.009$ for KET and $P \leq 0.035$ for KLD). PCO_2 also showed significantly higher values at 45 min in KFN ($P=0.001$) and 30, 45, and 60 min in KDX ($P \leq 0.012$) compared to baseline. Partial arterial pressure of oxygen (PO_2) was significantly higher in all the treatments throughout the anesthesia than baseline values ($P \leq 0.001$). pH at 5, 15, and 30 min after induction of anesthesia in KET treatment ($P=0.029$, $P=0.031$, and $P=0.006$, respectively), at 30, and 60 min after induction of anesthesia in KLD treatment ($P=0.029$ and $P=0.007$, respectively), and at 30, and 60 min in KDX ($P=0.001$ and $P=0.008$, respectively) was significantly lower than baseline Bicarbonate (HCO_3^-) was higher in the KET treatment at 5 and 15 min after induction of anesthesia compared to baseline ($P=0.026$ and $P=0.015$, respectively). Glucose level was significantly lower in KFN than other treatments ($P \leq 0.026$). Glucose level was significantly lower at 45 and 60 min in KFN ($P=0.047$ and $P=0.049$, respectively) and was significantly higher at 60 min of anesthesia in KDX ($P=0.026$) than the baseline values. There were no significant changes regarding lactate and base excess between treatments and over time ($P>0.05$).

Discussion

In the present study, adding lidocaine to ketofol reduced the MIR of ketofol by 37% (0.35 ± 0.04 mg/kg/min for KET vs. 0.23 ± 0.03 mg/kg/min for KLD). Mannarino *et al*. (2012) reported that adding an intravenous infusion of lidocaine leads to a decrease of 18% in the MIR of propofol in dogs, nevertheless, this difference was not statistically significant. The authors also reported that simultaneous infusion of ketamine and lidocaine reduces the MIR of propofol by 37%. Co-administration of lidocaine to animals undergoing inhalation anesthesia has reduced the minimum alveolar concentration by 10 to 45% (Himes *et al*., 1977; Valverde *et al*., 2004; Wilson *et al*., 2008; Matsubara *et al*., 2009). The mechanism by which lidocaine reduces the amount of anesthetics has not been well elucidated

Table 4: Mean±SD of blood gas variables in anesthetized dogs (n=6) received ketofol (KET), and ketofol plus lidocaine (KLD), fentanyl (KFN) or dexmedetomidine (KDX)

Variable	Treatment	Time (min)				
		Baseline	5	15	30	60
pH	KET	7.35±0.02	7.28±0.01[a]	7.26±0.04[a]	7.26±0.02[a]	7.27±0.03
	KLD	7.34±0.03	7.30±0.01	7.24±0.04	7.24±0.03[a]	7.23±0.01[a]
	KFN	7.36±0.3	7.34±0.04	7.32±0.3	7.33±0.05	7.29±0.04
	KDX	7.33±0.02	7.29±0.04	7.27±0.05	7.25±0.01[A]	7.24±0.03[a]
PO_2 (mmHg)	KET	97±3	486±87[a]	566±99[a]	528±87[a]	549±59[a]
	KLD	95±4	452±104[a]	492±86[a]	530±49[a]	492±50[a]
	KFN	93±5	584±50[a]	541±54[a]	566±46[a]	590±60[a]
	KDX	91±4	566±37[a]	543±44[a]	536±62[a]	545±14[a]
PCO_2 (mmHg)	KET	34±5.9	47.8±6.1[a]	49.5±5.7[a]	53.1±4.6[a]	52.1±7.3[a]
	KLD	36.8±4.4	45.0±5.6[a]	51.6±5.9[a]	56.5±3.7[a]	59.3±3.5[A, a]
	KFN	37.5±3.9	41.8±6.9	46.1±6.2	51.9±5.9[a]	44.05±9.9
	KDX	35.2±4.8	41.4±3.6	48.8±4.6[a]	46.9±6.9[a]	51.0±3.1[a]
HCO_3^- (mmol/L)	KET	19.4±2.7	23.8±2.3[a]	23.9±1.5[a]	23.5±1.5	22.2±1.7
	KLD	18.4±3.4	22.0±0.6	22.8±1.1	22.7±1.9	25.1±2.3
	KFN	20.9±2.2	22.1±2.6	20.9±3.8	21.9±2.7	21.6±3.2
	KDX	17.4±3.6	18.6±2.7	18.2±4.4	19.2±2.9	20.3±3.2
Base excess	KET	-6.1±2.6	-2.4±2.4	-3.4±1.5	-4.3±2.6	-5.3±3.1
	KLD	-6.7±2.2	-4.6±0.7	-5.0±2.1	-5.4±2.0	-4.6±3.5
	KFN	-4.5±2.4	-3.6±2.5	-5.5±3.8	-4.3±2.5	-5.1±2.5
	KDX	-6.7±2.9	-6.3±1.2	-5.6±4.4	-7.6±2.9	-6.7±3.4
Glucose (mmol/L)	KET	82±11	90±14	86±6	85±10	79±7
	KLD	89±8	77±8	89±8	92±11	94±10
	KFN	89±12	86±12	78±6	70±8[a]	66±3[A, a]
	KDX	75±6	81±5	88±11	81±6	102±13[a]
Lactate (mmol/L)	KET	4.5±2.3	5.3±2.4	5.1±1.2	4.5±3.0	4.3±1.0
	KLD	4.7±2.1	4.0±0.9	3.8±1.3	3.8±1.2	4.4±2.4
	KFN	6.2±0.9	5.2±0.8	6.0±1.5	5.5±0.3	6.0±1.1
	KDX	4.9±1.5	6.1±1.3	3.8±0.4	4.1±1.2	3.4±0.7

Different uppercases indicate significant differences among treatments ($P<0.05$), and different lower cases indicate significant differences from baseline ($P<0.05$)

yet, although both sedative (Murrell *et al*., 2005) and analgesic properties (Smith *et al*., 2004) of lidocaine might be important in this regard.

In the present study, fentanyl decreased the MIR of ketofol by 50%. Although this was expected, the magnitude of the decrease was very interesting. Several reports in dogs indicate the effect of fentanyl on decreasing minimum alveolar concentration (MAC) of volatile anesthetics (in a range of 35-66%) (Steagall *et al*., 2006; Ueyama *et al*., 2009; Reilly *et al*., 2013). It has been proposed that the co-administration of propofol and fentanyl would be more effective in reducing anesthetic dose than the combined use of an inhaled drug and fentanyl. In addition, fentanyl has reduced propofol requirement for the prevention of movement by about 51 and 63% following the application of low (0.1 µg/kg/min) and high (0.2 µg/kg/min) doses, respectively (Davis *et al*., 2017). By comparing fentanyl and lidocaine, it appeared that fentanyl could decrease the MIR of ketofol more efficiently than lidocaine. This finding is in accordance with the study by Steagal *et al*. (2006), who reported a more considerable sparing effect of fentanyl on dogs anesthetized with isoflurane than lidocaine.

In the current study, DEX reduced the MIR of ketofol more strongly (i.e., 80%) compared to lidocaine (i.e., 37%) and fentanyl (i.e., 50%). DEX dose-dependently has decreased MAC of halothane and isoflurane in dogs up to 90% and 60%, respectively (Vickery *et al*., 1988; Pascoe *et al*., 2006). Two other studies have also reported a reduction in MAC of isoflurane by 86% (Weitz *et al*., 1991) and 89% (Bloor *et al*., 1992). Therefore, DEX appears to be superior to lidocaine and fentanyl with regard to MIR reduction of ketofol. Consistent with the current study results, in a study conducted on pigs, the combination of ketamine-propofol-DEX showed higher analgesic properties than when fentanyl was substituted with DEX (Lervik *et al*., 2018).

In the current study, the recovery events generally took longer times to occur in KLD treatment. Mannarino *et al*. (2012) have also reported a prolonged recovery period in dogs anesthetized with propofol and lidocaine compared to propofol alone. The prolonged time to extubation and standing have also been reported in dogs anesthetized with sevoflurane and high doses of lidocaine (Matsubara *et al*., 2009). Although the cause of this observation was not investigated in dogs, lidocaine-induced sedation as a reason for the prolonged recovery and lidocaine-induced muscle relaxation as a cause of poor quality of recovery has been proposed in horses (Valverde *et al*., 2005). A similar mechanism might also play a role in the dogs.

In the present experiment, HR significantly increased in both KET and KLD treatments over time compared to baseline. Furthermore, MAP was clinically stable during anesthesia compared to baseline in both treatments. These results are consistent with those of previous studies in which co-administration of ketamine and propofol or using ketofol hasled to an increased heart rate and improved blood pressure in dogs compared to the administration of propofol alone (Seliskar *et al*., 2007; Henao-Guerrero and Riccó, 2014; Kennedy and Smith, 2015). The observed result can be attributed to the cardiovascular effects of ketamine, which results in higher HR and MAP through catecholamine release (Changmin *et al*., 2010).

Heart rate and MAP in KFN treatment remained clinically stable during anesthesia, near the baseline values. Even though fentanyl has been proposed to decrease HR dose-dependently (Kukanich and Clark, 2012) and to provide stable MAP (Hogue *et al*., 1996), we did not expect this strong effect of fentanyl on ketofol when compared to the results obtained from the KET and KLD treatments. It seems that fentanyl has blunted the potential benefit of ketamine on HR in KFN. The same scenario has just happened for KDX. Those dogs treated with ketofol and DEX showed a mild decrease in HR and an increase in MAP during anesthesia sessions compared to baseline. DEX is associated with bradycardia and hypertension in dogs through its parasympathetic activity and vasoconstrictive properties, respectively (Murrell and Hellebrekers, 2005). We predicted that ketamine can prevent the decrease in HR following the DEX administration, but it appeared that DEX effects were predominant over ketamine. The results regarding HR in KFN and KLD are highly likely to be due to the tremendous decrease of MIR of ketofol in these treatments, which resulted in a significant reduction in the magnitude of ketamine to a level that was not effective enough to affect cardiovascular alterations significantly.

In the present study, the respiratory rate was lower in all treatments during anesthesia compared to baseline. Additionally, there was a significant decrease in pH and a significant increase in PCO_2 during anesthesia compared to the baseline in four treatments. The decreased respiratory rate and pH and the increased PCO_2 are indicators of respiratory depression. The depressant effect of the propofol and ketamine combination on the respiratory system has been documented in previous studies (Seliskar *et al*., 2007; Mair *et al*., 2009; Kennedy and Smith, 2015). It seems that ketamine and propofol, when used concurrently, have an additive depressant effect on respiration (Kennedy and Smith, 2015). Propofol decreases the ventilatory response to CO_2 and arterial hypoxemia by affecting central chemoreceptors (Blouin *et al*., 1993). Ketamine also affects the ventilatory response to CO_2 depending on the concentration of the drug in the central nervous system (Craven, 2007). In addition, effects of ketamine on µ opioid receptors can lead to respiratory depression (Lamont and Mathews, 2007).

Respiratory depression was not ameliorated by ketofol dose reduction in the KLD, KFN, and KDX treatments. Besides, respiratory depression tended to be more severe in dogs that received lidocaine. Intravenous lidocaine infusion in the dogs anesthetized with isoflurane has not changed the respiratory rate and other related parameters (Steagall *et al*., 2006; Gutierrez-

Blanco *et al*., 2013). The reason for the lidocaine depressant effect on ketofol is still unclear to the authors and needs to be investigated in future studies. Respiratory depression was also detected in KFN and KDX. Respiratory depression has been reported in dogs receiving fentanyl and isoflurane anesthesia (Bufalari *et al*., 2007; Keating *et al*., 2013). Opioids have been shown to affect hypoxia and hypercapnia responses in the brainstem which results in respiratory depression due to almost all opioids (Pattinson, 2008). Although like other alpha-2 agonists, DEX may be considered free of respiratory effects, its combination with other sedative and anesthetic agents has resulted in respiratory depression (Rankin, 2015), as seen in the current study.

In conclusion, adding lidocaine, fentanyl, or DEX at doses used in the current study, reduces the MIR of TIVA with ketofol in dogs. The magnitude of this reduction was greatest for DEX and lowest for lidocaine. The dogs that received lidocaine showed better preservation on HR than those that were administered fentanyl and DEX. Notably, all three added drugs resulted in respiratory depression during anesthesia. A reduction in the dose of ketofol, even as much higher as DEX, could not attenuate respiratory depression induced by ketofol.

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Conflict of interest

The authors of this manuscript have no conflict of interest to declare.

References

Aguiar, AJ; Luna, SP; Oliva, VN; Eugênio, FR and Castro, GB (2001). Continuous infusion of propofol in dogs premedicated with methotrimeprazine. Vet. Anaesth. Analg., 28: 220-224.

Alletag, MJ; Auerbach, MA and Baum, CR (2012). Ketamine, propofol, and ketofol use for pediatric sedation. Pediatr. Emerg. Care. 28: 1391-1395.

Andolfatto, G and Willman, E (2011). A prospective case series of single-syringe ketamine-propofol (Ketofol) for emergency department procedural sedation and analgesia in adults. Acad. Emerg. Med., 18: 237-245.

Bennett, KJ; Seddighi, R; Moorhead, KA; Messenger, K; Cox, SK; Sun, X; Pasloske, K; Pypendop, BH and Doherty, TJ (2019). Effect of fentanyl on the induction dose and minimum infusion rate of alfaxalone preventing movement in dogs. Vet. Anaesth. Analg., 46: 173-181.

Bloor, BC; Frankland, M; Alper, G; Raybould, D; Weitz, J and Shurtliff, M (1992). Hemodynamic and sedative effects of dexmedetomidine in dog. J. Pharmacol. Exp. Ther., 263: 690-697.

Blouin, RT; Seifert, HA; Babenco, HD; Conard, PF and Gross, JB (1993). Propofol depresses the hypoxic ventilatory response during conscious sedation and isohypercapnia. Anesthesiology. 79: 1177-1182.

Bufalari, A; Di Meo, A; Nannarone, S; Padua, S and Adami, C (2007). Fentanyl or sufentanil continuous infusion during isoflurane anaesthesia in dogs: clinical experiences. Vet. Res. Commun., 31: 277-280.

Changmin, H; Jianguo, C; Dongming, L; Guohong, L and Mingxing, D (2010). Effects of xylazole alone and in combination with ketamine on the metabolic and neurohumoral responses in healthy dogs. Vet. Anesth. Analg., 37: 322-328.

Craven, R (2007). Ketamine. Anaesthesia. 62: 48-53.

Davis, CA; Seddighi, R; Cox, SK; Sun, X; Egger, CM and Doherty, TJ (2017). Effect of fentanyl on the induction dose and minimum infusion rate of propofol preventing movement in dogs. Vet. Anaesth. Analg., 44: 727-737.

Ebner, LS; Lerche, P; Bednarski, RM and Hubbell, JA (2013). Effect of dexmedetomidine, morphine-lidocaine-ketamine, and dexmedetomidine-morphine-lidocaine-ketamine constant rate infusions on the minimum alveolar concentration of isoflurane and bispectral index in dogs. Am. J. Vet. Res., 74: 963-970.

Gutierrez-Blanco, E; Victoria-Mora, JM; Ibancovichi-Camarillo, JA; Sauri-Arceo, CH; Bolio-González, ME; Acevedo-Arcique, CM; Marin-Cano, G and Steagall, PV (2013). Evaluation of the isoflurane-sparing effects of fentanyl, lidocaine, ketamine, dexmedetomidine, or the combination lidocaine-ketamine-dexmedetomidine during ovariohysterectomy in dogs. Vet. Anaesth. Analg., 40: 599-609.

Gutierrez-Blanco, E; Victoria-Mora, JM; Ibancovichi-Camarillo, JA; Sauri-Arceo, CH; Bolio-González, ME; Acevedo-Arcique, CM; Marin-Cano, G and Steagall, PV (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.

Henao-Guerrero, N and Riccó, CH (2014). Comparison of the cardiorespiratory effects of a combination of ketamine and propofol, propofol alone, or a combination of ketamine and diazepam before and after induction of anesthesia in dogs sedated with acepromazine and oxymorphone. Am. J. Vet. Res., 75: 231-239.

Himes, JR; DiFazio, CA and Burney, RG (1977). Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. Anesthesiology. 47: 437-440.

Hogue, CW; Bowdle, TA; O'Leary, C; Duncalf, D; Miguel, R; Pitts, M; Streisand, J; Kirvassilis, G; Jamerson, B and McNeal, S (1996). A multicenter evaluation of total intravenous anesthesia with remifentanil and propofol for elective inpatient surgery. Anesth. Analg., 83: 279-285.

Imani, H; Baniadam, A; Mosallanejad, B and Shabani, S (2016). Comparison of required induction dose, induction and recovery characteristics, and cardiorespiratory effects of co-administration of ketofol with diazepam and midazolam in healthy dogs. Iran. J. Vet. Med., 10: 181-190.

Keating, SC; Kerr, CL; Valverde, A; Johnson, RJ and McDonell, WN (2013). Cardiopulmonary effects of intravenous fentanyl infusion in dogs during isoflurane anesthesia and with concurrent acepromazine or dexmedetomidine administration during anesthetic recovery. Am. J. Vet. Res., 74: 672-682.

Kennedy, MJ and Smith, LJ (2015). A comparison of cardiopulmonary function, recovery quality, and total

dosages required for induction and total intravenous anesthesia with propofol versus a propofol-ketamine combination in healthy Beagle dogs. Vet. Anaesth. Analg., 42: 350-359.

Kukanich, B and Clark, T (2012). The history and pharmacology of fentanyl: relevance to a novel, long-acting transdermal fentanyl solution newly approved for use in dogs. J. Vet. Pharmacol. Ther., 35: 3-19.

Kuusela, E; Raekallio, M; Väisänen, M; Mykkänen, K; Ropponen, H and Vainio, O (2001). Comparison of medetomidine and dexmedetomidine as premedicants in dogs undergoing propofol-isoflurane anesthesia. Am. J. Vet. Res., 62: 1073-1080.

Lamont, LA and Mathews, KS (2007). Opioids, nonsteriodal antiinflammatories, and analgesic adjuvants. In: Tranquilli, WJ; Thurmon, JC and Grimm, KA (Eds.), *Lumb & Jones' veterinary anesthesia and analgesia*. (4th Edn.), Ames, USA, Blackwell. PP: 241-271.

Lervik, A; Raszplewicz, J; Ranheim, B; Solbak, S; Toverud, SF and Haga, HA (2018). Dexmedetomidine or fentanyl? Cardiovascular stability and analgesia during propofol-ketamine total intravenous anaesthesia in experimental pigs. Vet. Anaesth. Analg., 45: 295-308.

Mair, AR; Pawson, P; Courcier, E and Flaherty, D (2009). A comparison of the effects of two different doses of ketamine used for co-induction of anaesthesia with a target-controlled infusion of propofol in dogs. Vet. Anaesth. Analg., 36: 532-538.

Mannarino, R; Luna, SP; Monteiro, ER; Beier, SL and Castro, VB (2012). Minimum infusion rate and hemodynamic effects of propofol, propofol-lidocaine and propofol-lidocaine-ketamine in dogs. Vet. Anaesth. Analg., 39: 160-173.

Matsubara, LM; Oliva, VN; Gabas, DT; Oliveira, GC and Cassetari, ML (2009). Effect of lidocaine on the minimum alveolar concentration of sevoflurane in dogs. Vet. Anaesth. Analg., 36: 407-413.

Murrell, JC and Hellebrekers, LJ (2005). Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog. Vet. Anaesth. Analg., 32: 117-127.

Murrell, JC; White, KL; Johnson, CB; Taylor, PM; Doherty, TJ and Waterman-Pearson, AE (2005). Investigation of the EEG effects of intravenous lidocaine during halothane anaesthesia in ponies. Vet. Anaesth. Analg., 32: 212-221.

Nagashima, Y; Furukawa, Y and Chiba, S (2000). Propofol decreases contractility of isolated blood-perfused left ventricular muscle in the dog. J. Anesth., 14: 45-47.

Nagashima, Y; Furukawa, Y; Hirose, M and Chiba, S (1999). Cardiac effects of propofol and its interaction with autonomic nervous system in isolated, cross-circulated canine atria. J. Anesth., 13: 34-39.

Pagel, PS and Warltier, DC (1993). Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. Anesthesiology. 78: 100-108.

Pascoe, PJ; Raekallio, M; Kuusela, E; McKusick, B and Granholm, M (2006). Changes in the minimum alveolar concentration of isoflurane and some cardiopulmonary measurements during three continuous infusion rates of dexmedetomidine in dogs. Vet. Anaesth. Analg., 33: 97-103.

Pattinson, KT (2008). Opioids and the control of respiration. Br. J. Anaesth., 100: 747-758.

Rankin, DC (2015). Sedatives and tranquilizers. In: Grimm, KA; Lamont, LA; Tranquilli, WJ; Green, SA and Robertson, SA (Eds.), *Veterinary anesthesia and analgesia, The Fifth Edition of Lumb and Jones*. Pondichery, India, Wiley Blackwell. PP: 196-206.

Rastabi, HI; Baniadam, A; Ronagh, A; Khajeh, A and Kamyabnia, M (2018). Comparison of intraocular pressure, tear production and cardiorespiratory variables before and after induction of anaesthesia with either propofol or ketofol in dogs premedicated with midazolam. Vet. Med., 63: 271-278.

Reilly, S; Seddighi, R; Egger, CM; Rohrbach, BW; Doherty, TJ; Qu, W and Johnson, JR (2013). The effect of fentanyl on the end-tidal sevoflurane concentration needed to prevent motor movement in dogs. Vet. Anaesth. Analg., 40: 290-296.

Seliskar, A; Nemec, A; Roskar, T and Butinar, J (2007). Total intravenous anaesthesia with propofol or propofol/ ketamine in spontaneously breathing dogs premedicated with medetomidine. Vet. Rec., 160: 85-91.

Smischney, NJ; Beach, ML; Loftus, RW; Dodds, TM and Koff, MD (2012). Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: a randomized, controlled trial. J. Trauma. Acute. Care Surg., 73: 94-101.

Smith, LJ; Bentley, E; Shih, A and Miller, PE (2004). Systemic lidocaine infusion as an analgesic for intraocular surgery in dogs: a pilot study. Vet. Anaesth. Analg., 31: 53-63.

Steagall, PV; Neto, FJT; Minto, BW; Campagnol, D and Corrêa, MA (2006). Evaluation of the isoflurane-sparing effects of lidocaine and fentanyl during surgery in dogs. J. Am. Vet. Med. Assoc., 229: 522-527.

Ueyama, Y; Lerche, P; Eppler, CM and Muir, III WW (2009). Effects of intravenous administration of perzinfotel, fentanyl, and a combination of both drugs on the minimum alveolar concentration of isoflurane in dogs. Am. J. Vet. Res., 70: 1459-1464.

Valverde, A; Doherty, TJ; Hernández, J and Davies, W (2004). Effect of lidocaine on the minimum alveolar concentration of isoflurane in dogs. Vet. Anaesth. Analg., 31: 264-271.

Vickery, RG; Sheridan, BC; Segal, IS and Maze, M (1988). Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an alpha 2-adrenergic agonist, in halothane-anesthetized dogs. Anesth. Analg., 67: 611-615.

Weitz, JD; Foster, S; Waugaman, W; Katz, R and Bloor, B (1991). Anesthetic and hemodynamic effects of dexmedetomidine during isoflurane anesthesia in a canine model. Nurse. Anesth., 2: 19-27.

Wilson, J; Doherty, TJ; Egger, CM; Fidler, A; Cox, S and Rohrbach, B (2008). Effects of intravenous lidocaine, ketamine, and the combination on the minimum alveolar concentration of sevoflurane in dogs. Vet. Anaesth. Analg., 35: 289-296.