Comparison of required induction dose, induction and recovery characteristics, and cardiorespiratory effects of co-administration of ketofol with diazepam and midazolam in healthy dogs

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Abstract:

BACKGROUND: Co-administration of anesthetics has been employed to decrease potential unpleasant effects associated with single drug. **OBJECTIVES:** This study was designed to evaluate the effects of co-administration of ketofol with diazepam or midazolam in healthy dogs. **METHODS:** Six adult mix-breed male dogs were used. After sedation with acepromazine (0.1 mg/kg), anesthesia was induced with keteofol (KF; 1 ml contained 5 mg ketamine and 5 mg propofol), ketofol-diazepam (KFD), or ketofol-midazolam (KFM) (1 ml contained 5 mg KF and 2.5 mg diazepam or midazolam) randomly. All the dogs received the three treatments with at least one week interval. **RESULTS:** The total dose of ketofol used for induction of anesthesia in KF (4.2±0.44 mg/kg) was significantly higher than KFD (2.27±0.6 mg/kg) and KFM (1.68±0.25 mg/kg). The total dose of diazepam and midazolam used in KFD and KFM was 1.00±0.25 and 0.73±0.10 mg/kg, respectively ($p>0.05$). The time needed for sternal recumbency, standing position and normal walking was longer in KFD and KFM compared to KF ($p<0.05$). Heart rate (HR) showed significant increase in KF at several time points ($p<0.05$). Respiratory rate (fr) in KF showed a significant decrease during the anesthesia period compared to the base ($p<0.05$). HR and fr were more stable in KFD and KFM. Induction and recovery quality in the three treatments were acceptable. **CONCLUSIONS:** Co-administration of ketofol with diazepam and midazolam reduced the required induction dose and prolonged recovery in dogs. Diazepam and midazolam could attenuate the unfavorable effects of ketofol in some cardiorespiratory variables.

Introduction

General anesthesia is frequently used in dogs in various occasions from minimally invasive procedures to the most complicated surgeries. Induction as well as recovery of anesthesia are two critical conditions during general anesthesia due to the occurrence of certain life-threatening hazards in these stages. An optimum induction and recovery is calm and has fewer undesirable effects. Since no drug has been introduced without unfavorable effects, co-administration of various drugs is employed to reduce potential side effects and to produce

anesthesia with more satisfactory outcomes (Martinez-Taboada and Leece, 2014).

Propofol, an alkyl phenol, is a popular induction agent which is used widely in the anesthesia of dogs (Covey-Crump and Murison, 2008). The smooth induction with rapid and complete recovery have been proved as the most valuable characteristics of propofol in dogs (Watkins et al., 1987). The main complications associated with propofol are dose dependent respiratory and cardiovascular depression as well as hypotension (Kennedy and Smith, 2014). Ketamine, an NMDA antagonist, is another anesthetic that can be used for induction in dogs. In contrast to propofol, ketamine has some cardiovascular stimulatory effects which result in an increase in heart rate (HR) and cardiac output (Abbasivash et al., 2014). Ketamine can also be associated with muscle rigidity, convulsions, and violent recovery; it is therefore recommended that ketamine be used in conjunction with other drugs such as benzodiazepines (Kennedy and Smith, 2014). It has been suggested that ketamine may compensate the cardiovascular depression induced by propofol (Abbasivash et al., 2014). Co-administration of ketamine and propofol, used in separate syringes, has resulted in higher HR and less occurrence of apnea compared to propofol alone in dogs (Lerche et al., 2000). Ketofol, a mixture of propofol and low dose ketamine into the same syringe, has also been evaluated in dogs (Henao-Guerrero and Riccó, 2014; Kennedy and Smith, 2014; Martinez-Taboada and Leece, 2014). Ketofol is of interest as it requires administration of only a single infusion. In addition, ketofol may lead to more hemodynamic stability than other combinations of ketamine and propofol (Martinez-Taboada and Leece, 2014).

Benzodiazepines are commonly used as co-induction agents with conventional anesthetics. The three main benefits of these drugs are rapid onset of action, minimal negative cardiovascular effects, and anticonvulsant properties (Hopkins et al., 2014). It has also been shown that co-administration of diazepam and midazolam could reduce the induction dose of propofol in dogs (Braun et al., 2007; Fayyaz et al., 2009; Hopkins et al., 2014; Ko et al., 2006). Diazepam and midazolam have been used with ketamine as the co-induction agent mostly to reduce the central excitatory effects of ketamine (Ilkiw et al., 1996; White et al., 2001). To the best of the authors` knowledge, no study has yet evaluated the effects of co-administration of ketofol with diazepam or midazolam combined into the same syringe in dogs.

The present investigation was designed to evaluate required induction dose, induction and recovery characteristics, and cardiorespiratory variables in dogs sedated with acepromazine and induced with a single infusion of ketofol with diazepam and midazolam.

Materials and Methods

Six adult mix-breed male dogs, weighing 20 ± 1 kg and aged 22 ± 3 months were used. The animals were transferred to Veterinary Hospital of Shahid Chamran University of Ahvaz at least two weeks prior to the beginning of study. Health status was established based on a complete blood count (CBC), total protein (TP), and thorough physical examination. The animals were housed in individual cages with free access to water and feeding twice a day. The dogs were fasted 12 hours prior to any experiment. They had no access to water for two hours before any experiment. All procedures in this study were approved by the Animal Care and Research Committee of Shahid Chamran University of Ahvaz.

In the present study, the dogs received one of the three treatments of keteofol (KF), ketofol-diazepam (KFD), and ketofol-midazolam (KFM), randomly in each session. All the animals received all three treatments with at least one week interval (6 dogs per group). Prepa-

ration of ketofol in this study was based on the study of Andofatto and Willman (2010). In brief, ketamine 5% (Ketamine hydrochloride, Rotexmedica, Trittau, Germany; 50 mg/mL) was attenuated to ketamine 1% (1 mg/mL) by normal saline. Then, an equivalent volume of ketamine and propofol (Anesia, Alleman, Germany; 10 mg/mL) was combined into the same syringe (each mL ketofol contained 5 mg ketamine and 5 mg propofol). The syringe of ketofol admixture was kept for maximum 6 hours after preparation. For preparing KFD and KFM, diazepam (Zepadic, Caspian Tamin, Iran; 5 mg/mL) or midazolam (Midamax, Tehran Chemie, Iran; 5 mg/mL) were added to previously prepared ketofol admixture in the ratio of 1:1 (each mL KFD and KFM contained 5 mg ketofol and 2.5 mg diazepam or midazolam). The time of KFD and KFM preparation was immediately prior to injection.

To conduct the experiment, the animals were transferred to the place of the study. Thirty min was given to allow animals to acclimatize to the environment. After recording the temperament of the animals and recording heart rate (HR), respiratory rate (*f*r), and rectal temperature (RT), acepromazine (Neurotranq, Alfasan, Netherland; 10 mg/mL) at 0.1 mg/kg was administered intramuscularly (IM). Thirty min later and after scoring the quality of sedation (Appendix), and recording HR, *f*r and RT, the animals were transferred onto a surgery table and positioned in sternal recumbency. A 20 gauge catheter was placed into the left cephalic vein and normal saline was administered at the rate of 10 mL/kg/hr for five minutes. To induce anesthesia, treatments were injected via a syringe connected to the cephalic catheter at a rate of about 0.2 mL/kg/min. All injections were performed via hand and the person who applied injections was unaware of the treatments. Nonetheless, the color of KF and KFM was milky and the color of KFD was yellowish. Another researcher was responsible for placement of the tracheal tube, concomitantly. The dogs were intubated when chewing and licking were stopped. After ensuring the correct placement of the tracheal tube, the administration of the drugs was discontinued immediately. The animals were allowed to breathe the room air, spontaneously. At this time, induction quality was scored (Appendix).

After induction of anesthesia, the animals were positioned in the right lateral recumbency and immediately connected to a multiparameter monitoring system (Burtons, Guardian Industrial Estate, UK) for measurement of hemoglobin oxygen saturation (SPO2), noninvasive systolic, diastolic and mean arterial blood pressure (SAP, DAP, and MAP, respectively), end-tidal carbon dioxide tension (ETCO2), HR, *f*r, and RT. All data were recorded one minute after intubation, then at every three minutes, and at just before extubation. Extubation was done when the animal was chewing continuously and could not tolerate tracheal tube any more. The animal received normal saline intravenously (IV) at the rate of 10 mL/kg/hr, until the extubation was done. After extubation, HR, *f*r, and RT were recorded every five min till 30 min post induction and then every 10 min till the full recovery of the animal. During the recovery period, the times of head upraising, sternal recumbency, standing position and normal walking were recorded. Full recovery was defined as when the dogs started walking normally. Recovery was scored at this time (Appendix). All the scores for sedation, intubation and recovery were given by the same researcher who was not aware of the treatments.

Statistical analysis: Statistical analysis was performed using SPSS software version 22 for windows (IBM SPSS statistic, IBM Corporation, NY, USA). Values of HR, *f*r, and RT were expressed at seven sections including base (prior to premedication), sedation (30 minutes after premedication), after induction, anesthesia period (the mean values during the anesthesia till extubation), before extubation,

recovery period (the mean values during the recovery till normal walking), and recovery point (when the dog was able to walk normally). Data related to SPO2, SAP, DAP, MAP, and ETCO2 were reported at three sections including after induction, anesthesia period (the mean values during the anesthesia till extubation), and before extubation. The normality of data was analyzed using Kolmogrov-Smirnov test. All normally distributed data were expressed as mean ± standard deviation (SD) and nonparametric data were reported as median (range). A repeated measure ANOVA followed by Bonferoni test was used for the comparison of sequences during recovery, and variables of HR, *f*r, RT, SPO2, SAP, DAP, MAP, and ETCO2. Friedman tests were employed for the comparison of sedation score, induction score, and recovery score. $p<0.05$ was considered statistically significant.

Results

There were no differences in the temperaments of the dogs and all the dogs were seemingly normal prior to beginning the study. The sedation score following administration of acepromazine did not show any significant differences among the three groups ($p>0.05$; Table 1).

The induction time in KFM (1.63±0.10 min) was significantly faster in comparison to KF (2.14±0.11 min) and KFD (2.25±0.23 min) ($p<0.05$). The total dose of ketofol used for induction of anesthesia in KF (4.2±0.44 mg/kg) was significantly greater than KFD (2.27±0.6 mg/kg) and KFM (1.68±0.25 mg/kg) ($p<0.05$). The total dose of ketofol was significantly higher in KFD versus KFM ($p<0.05$). The total dose of diazepam and midazolam used in KFD and KFM was 1.00±0.25 and 0.73±0.10 mg/kg, respectively, with no significant differences between them ($p>0.05$). The time needed for chronological sequences of events in the recovery period is presented in Table 2. Significant swallow reflex was seen later in KFD compared to KF and KFM ($p<0.05$). The time to the sternal recumbency, standing position and normal walking was longer in KFD and KFM compared to KF ($p<0.05$).

Table 1. Median (upper-lower range) of scores that were given for quality of sedation, induction, and recovery in dogs (n = 6) that received KF (ketofol), KFD (ketofol-diazepam), and KFM (ketofol-midazolam).

	Sedation score	Induction Score	Recovery score
KF	1 (1-2)	1 (1-1)	1 (1-1)
KFD	1 (0-2)	1 (1-1)	1 (1-2)
KFM	1 (1-2)	1 (1-2)	2 (1-2)

HR, *f*r, and RT values were presented in Table 3. Comparison of HR among the groups showed significant lower values in KFD compared to KF at anesthesia period, before extubation, and recovery period ($p<0.05$). HR in KFM before extubation was significantly higher than KFD ($p<0.01$). HR in KFM in the recovery period was significantly lower in comparison to KF ($p<0.05$). HR within KF showed a significant increase during the entire evaluation period compared to the base ($p<0.05$). HR in KFD was significantly higher at normal walking than the base ($p<0.01$). HR in KFM was significantly higher at recovery period compared to the base ($p<0.05$). *f*r was significantly higher in KFM compared to KF at anesthesia period ($p<0.05$). *f*r Showed a significant difference at normal walking in KF compared to KFD ($p<0.05$) and KFM ($p<0.01$). The comparison of *f*r in KF showed a significant decrease after induction and anesthesia period compared to the base ($p<0.05$).

Values related to SPO2, SAP, DAP, MAP, and ETCO2 were presented in Table 4. SPO2 in KFM was significantly higher in anesthesia period and before extubation in comparison to after induction ($p<0.05$). SPO2 before extubation was significantly higher than in anesthesia period in this group ($p<0.05$). SAP in KFM showed a significant decrease before extubation compared to after induction ($p<0.05$).

Table 2. Time (min) needed for various chronological sequences of recovery events in dogs (n = 6) that received KF (ketofol), KFD (ketofol-diazepam), and KFM (ketofol-midazolam). * Significantly different from KF values (p<0.05).

	Swallow reflex (Extubation)	Head upraising	Sternal recumbency	Standing position	Normal walking
KF	8.67 ± 2.50	13.00 ± 3.74	13.83 ± 3.65	18.00 ± 7.51	27.00 ± 7.01
KFD	15.17 ± 4.83 *	19.50 ± 7.17	22.00 ± 7.26 *	27.50 ± 8.16 *	42.00 ± 11.11 *
KFM	12.33 ± 5.42	16.17 ± 7.33	19.83 ± 4.44 *	31.17 ± 8.56 *	46.83 ± 8.83 *

Table 3. Mean ± SD of HR (beats/min), *fr* (breaths/min), and RT (°C) in dogs (n = 6) that received KF (ketofol), KFD (ketofol-diazepam), and KFM (ketofol-midazolam). HR: heart rate, fr: respiratory rate, RT: rectal temperature. * Significantly different from KF values (p<0.05). † Significantly different from KFD values (p<0.05). a Significantly different from base values (p<0.05).

	Base	Sedation	After induction	Anesthesia period	Before extubation	Recovery period	Normal walking
KF							
HR	94 ± 7	93 ± 16	128 ± 29 a	122 ± 22 a	120 ± 18 a	133 ± 18 a	135 ± 13 a
fr	24 ± 7	19 ± 6	11 ± 5 a	11 ± 3 a	24 ± 11	24 ± 7	23 ± 7
RT	38.8 ± 0.3	38.4 ± 0.4	36.8 ± 0.9 a	37.3 ± 0.9	37.5 ± 0.8	38 ± 0.5	37.9 ± 0.7
KFD							
HR	99 ± 13	78 ± 15	108 ± 9	91 ± 7 *	92 ± 8 *	112 ± 11 *	132 ± 9 a
fr	24 ± 7	18 ± 5	15 ± 8	17 ± 6	23 ± 11	25 ± 7	27 ± 7 *
RT	38.7 ± 0.5	38.3 ± 0.5	37.4 ± 0.2	37.5 ± 0.8	37.3 ± 0.8	37.4 ± 0.5	37.4 ± 0.6
KFM							
HR	88 ± 16	86 ± 14	117 ± 18	101 ± 21	105 ± 9 †	114 ± 13 * , a	125 ± 26 a
fr	23 ± 9	22 ± 7	18 ± 7	22 ± 5 *	27 ± 10	31 ± 8	28 ± 8 *
RT	38.7 ± 0.4	38.3 ± 0.4	37.5 ± 0.6	37.6 ± 0.5	37.5 ± 0.6	37.5 ± 0.8	37.4 ± 0.9

Table 4. Mean ± SD of SPO2 (%), SAP (mmHg), DAP (mmHg), MAP (mmHg), and ETCO2 (mmHg), in dogs (n = 6) that received KF (ketofol), KFD (ketofol-diazepam), and KFM (ketofol-midazolam) treatments. SPO2: hemoglobin oxygen saturation, SAP: systolic arterial pressure, DAP: diastolic arterial pressure, MAP: mean arterial pressure. ETCO2: end-tidal carbon dioxide tension. a significantly different from after induction (p < 0.05).

	After induction	Anesthesia period	Before extubation
KF			
SPO2	90 ± 6	92 ± 3	95 ± 2
SAP	125 ± 14	126 ± 15	123 ± 18
DAP	76 ± 8	77 ± 12	81 ± 12
MAP	91 ± 12	93 ± 13	91 ± 16
ETCO2	26 ± 10	29 ± 6	30 ± 7
KFD			
SPO2	89 ± 5	92 ± 4	94 ± 4
SAP	137 ± 10	135 ± 17	136 ± 34
DAP	90 ± 18	81 ± 13	79 ± 9
MAP	107 ± 16	95 ± 16	94 ± 14
ETCO2	30 ± 9	31 ± 5	28 ± 6
KFM			
SPO2	88 ± 3	93 ± 1 a	96 ± 2 a
SAP	125 ± 10	127 ± 15	122 ± 13
DAP	80 ± 5	73 ± 8	72 ± 4 a
MAP	98 ± 11	91 ± 10	85 ± 5
ETCO2	30 ± 8	31 ± 5	27 ± 5

Table 5. Appendix. Description of scoring system used to categorize sedation and quality of induction and recovery in dogs (n = 6) that received KF (ketofol), KFD (ketofol-diazepam), and KFM (ketofol-midazolam). * Source: Adapted from Mair A.R., Pawson P., Courcier E., Flaherty D.: 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 Anesth Analg 2009, 36, 532-538. †Source: Adapted from Muir W., Gadawski J.: Respiratory depression and apnea induced by propofol in dogs. Am J of Vet Res 1998, 59, 157-161.

Sedation *	0	No sedation
	1	Mild sedation (i.e. quieter, but still bright and active)
	2	Moderate sedation (i.e. quiet, reluctant to move, possibly ataxic but still able to walk)
	3	Profound sedation (i.e. unable to walk)
Induction †	1	No outward sign of excitement, rapidly assumes lateral recumbency, good muscular relaxation, easily intubated within 60 seconds of finishing dosing
	2	Mild signs of excitement, some struggling, may or may not be intubated within 60 seconds of finishing dosing
	3	Hyperkinesis, obvious signs of excitement, vocalization, defecation or urination, cannot be intubated
Recovery †	1	Assumes sternal recumbency with little or no struggling, and attempts to stand and walk with little or no difficulty
	2	Some struggling, requires assistance with sternal recumbency or standing, responsive to external stimuli, becomes quiet in sternal recumbency
	3	Prolonged struggling, unable to assume sternal recumbency or difficulty in maintaining sternal or standing position, becomes hyperkinetic when assisted, prolonged paddling and swimming motion

Median (upper-lower range) of scores for induction and recovery was shown in Table 1. There were no significant differences in induction scores as well as recovery scores among the three treatments ($p>0.05$). Overall, induction and recovery were smooth in all of the dogs, except for the two dogs in KFD that showed some twitching in the recovery period. Although it was not measured, imbalance in walking was more apparent in KF than KFD and KFM.

Discussion

In this study the total dose of ketofol required for tracheal intubation was smaller in KFD and KFM compared to KF. Ketofol was introduced to anesthesiologists in an attempt to reduce the doses of ketamine and propofol to avoid or lessen the unfavorable effects associated with the use of each of these two drugs. Previous studies in dogs have shown a significant reduction in the amount of ketamine and propofol when used together, and necessary for induction and/or maintenance of anesthesia compared to propofol alone (Henao-Guerrero and Riccó, 2014; Kennedy and Smith, 2014; Lerche et al., 2000; Mannarino et al., 2012; Seliskar et al., 2007). Similar findings have been observed when ketofol was employed for induction of anesthesia in humans (Andolfatto and Willman, 2010; Erdogan et al., 2013). The total dose of ketofol used for induction of anesthesia in the current study was 4.2±0.44 mg/kg in KF, which is comparable to 4.0±1.0 mg/kg and 3.6±1.8 mg/kg in dogs reported by Kennedy and Smith (2014) and Martinez-Taboada and Leece (2014), respectively. Addition of diazepam and midazolam to ketofol in the current study showed an approximately 46% and 60% reduction in the dose of ketofol, respectively (2.27±0.6 mg/kg and 1.68±0.25 mg/kg, respectively). Co-administration of various anesthetics with benzodiazepines with the aim of reducing the dose of anesthetics and employing cardiovascular benefits of benzodiazepines has already been reported in dogs (Covey-Crump and Murison, 2008; Henao-Guerrero and Riccó, 2014; Hopkins et al., 2014; Riccó and Henao-Guerrero, 2014). The clinical efficacy of co-induction of propofol-ketamine-midazolam in humans has also been shown by Abbasivash et al. (2014). To the best of the authors` knowledge, the

current study is the first experimental investigation aimed at evaluation of combination of diazepam and midazolam with ketofol into the same syringe, as the co-administration agents.

Diazepam is a poorly water soluble drug and therefore requires being prepared in a solution of an organic solvent such as propylene glycol and ethanol (Rankin, 2015). In the current study, diazepam was added to previously prepared ketofol. Because of the possible unwanted interaction of drugs, we prepared the admixture immediately prior to injection. Addition of diazepam to ketofol into the same syringe resulted in changing the color of the admixture from white to yellowish; nevertheless, no precipitation or biphasic state was observed prior to or during the injection period.

The results of the present study showed the prolongation of recovery period in KFD and KFM compared to KF. Although benzodiazepines have been used in dogs to ameliorate the central excitatory effects, reduce the dose, and to minimize hemodynamic changes associated with anesthetics (Rankin, 2015), these drugs have also been used to prolong anesthesia in horses (Brock and Hildebrand, 1990; Butera et al., 1978).

HR showed a trend to increase one minute post administration of all three treatments; however, it was not statistically significant in KFD and KFM. Ketofol has been associated with higher HR values compared to baseline in dogs (Henao-Guerrero and Riccó, 2014; Kennedy and Smith, 2014; Martinez-Taboada and Leece, 2014). Similar results have been observed when ketamine and propofol, in separate syringes, were employed for induction of anesthesia in dogs (Lerche et al., 2000; Seliskar et al., 2007). Ketamine could indirectly stimulate the cardiovascular system and subsequently increase HR and MAP (Tweed et al., 1972; Wong and Jenkins, 1974). Furthermore, it is speculated that addition of ketamine to propofol could attenuate dose-dependent depression of sympathetic tone produced by propofol (Martinez-Taboada and Leece, 2014). Higher values of HR during anesthesia in KF could be explained by the stimulating effects of ketamine on the cardiovascular system (Henao-Guerrero and Riccó, 2014; Riccó and Henao-Guerrero, 2014). HR showed greater decrease in KFD and KFM compared to KF at several time points. Use of diazepam has been associated with decreasing myocardial contractility, systemic blood pressure, and HR in anesthetized cats (Chai and Wang, 1966). It has also been reported that administration of diazepam prior to ketamine minimizing the cardiovascular stimulation produced by ketamine (Haskins et al., 1986). It is likely that decreases in HR in KFD and KFM could be produced by diazepam and midazolam via the same mechanism.

Combination of ketamine and propofol has attenuated the decrease of MAP associated with administration of propofol alone in dogs (Henao-Guerrero and Riccó, 2014; Kennedy and Smith, 2014; Lerche et al., 2000; Martinez-Taboada and Leece, 2014). In the present study MAP did not show any significant differences among groups and all values were in the second half of the normal range reported in dogs (Haskins et al., 2005). MAP was also not statistically different in the evaluation period in all three treatments; nevertheless, MAP tended to decrease over time in KFD and KFM. As mentioned above, this trend could be explained by the effects of benzodiazepines on stimulatory effects of ketamine.

Propofol is known as a dose-dependent respiratory depressant in humans and dogs (Muir and Gadawski, 1998; Smith et al., 1994; Smith et al., 1993). It has been reported that ketamine in clinically applicable or sub-anesthetic doses can cause respiratory depression in dogs (Haskins et al., 1985). Respiratory depression is also a relatively common finding in studies that evaluated the respiratory effects of ketofol or ketamine and propofol combination in dogs (Kennedy and Smith, 2014; Lerche et al.,

2000; Mair et al., 2009; Martinez-Taboada and Leece, 2014; Seliskar et al., 2007). It seems that ketamine could exacerbate respiratory depression produced by propofol (Lerche et al., 2000; Seliskar et al., 2007). In the present study *fr* in KF showed a significant decrease after induction and anesthesia period in comparison with base. *fr* decreased after induction in KFD and KFM, however, in contrast to KF this decrease was not significant. SPO2 in all the treatments showed a trend to increase over time; nonetheless, the differences were not significant. The decrease of fr and lower values of SPO2 after induction could be interpreted as the occurrence of respiratory depression after the treatments. In the study reported here, in all the three treatments, ETCO2 was lower than the normal range for dogs (Haskins, 2015). Oxygen supplementation and/or assisted ventilation to resolve respiratory depression have been recommended in dogs anesthetized with ketofol (Kennedy and Smith, 2014).

Selisker et al. (2015) reported stiffness as well as some excitement and disorientation in dogs that received propofol/ketamine. In contrast, recovery has obtained a better score in ketofol treatments in comparison with propofol alone in the study of Kennedy and Smith 2014; still, the difference was not significant. In the current study, all recoveries were quiet and satisfactory, except for the two dogs in KFD that showed some twitching. Both dogs eventually recovered without any sequelae. However, it was not recorded, imbalance in walking was more common in KF than KFD and KFM.

Conclusion: Co-administration of ketofol with diazepam and midazolam reduced the required induction dose and prolonged recovery in dogs. Induction and recovery quality in the three treatments were acceptable; however, more attention is needed for recovery in using the combination of ketofol and midazolam. In the present study, diazepam and midazolam attenuated unfavorable effects of ketofol in HR and *fr*. Oxygen supplementation in dogs receiving ketofol with or without diazepam and midazolam is recommended.

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References

1. Abbasivash, R., Aghdashi, M.M., Sinaei, B., Kheradmand, F. (2014) The effects of propofol-midazolam-ketamine co-induction on hemodynamic changes and catecholamine response. J Clin Anesth. 26: 628-633.
2. Andolfatto, G., Willman, E. (2010) A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe ketamine-propofol combination (Ketofol). Acad Emerg Med. 17: 194-201.
3. Braun, C., Hofmeister, E.H., Lockwood, A.A., Parfitt, S.L. (2007) Effects of diazepam or lidocaine premedication on propofol induction and cardiovascular parameters in dogs. J Am Anim Hosp Assoc. 43: 8-12.
4. Brock, N., Hildebrand, S. (1990) A comparison of xylazine-diazepam-ketamine and xylazine-guaifenesin-ketamine in equine anesthesia. Vet Surg. 19: 468-474.
5. Butera, T., Moore, J., Garner, H., Amend, J., Clarke, L., Hatfield, D. (1978) Diazepam/xylazine/ketamine combination for short-term anesthesia in the horse. Vet Med Small Anim Clin. 73: 490,495-496,499.
6. Chai, C., Wang, S. (1966) Cardiovascular actions of diazepam in the cat. J Pharmacol Exp Ther. 154: 271-280.
7. Covey-Crump, G.L., Murison, P.J. (2008) Fentanyl or midazolam for co-induction of anaesthesia with propofol in dogs. Vet Anesth An-

alg. 35: 463-472.
8. Erdogan, M.A., Begec, Z., Aydogan, M.S., Ozgul, U., Yucel, A., Colak, C., Durmus, M. (2013) Comparison of effects of propofol and ketamine-propofol mixture (ketofol) on laryngeal mask airway insertion conditions and hemodynamics in elderly patients: a randomized, prospective, double-blind trial. J Anesth. 27: 12-17.
9. Fayyaz, S., Kerr, C.L., Dyson, D.H., Mirakhur, K.K. (2009) The cardiopulmonary effects of anesthetic induction with isoflurane, ketamine-diazepam or propofol-diazepam in the hypovolemic dog. Vet Anesth Analg. 36: 110-123.
10. Haskins, S., Farver, T., Patz, J. (1986) Cardiovascular changes in dogs given diazepam and diazepam-ketamine. Am J Vet Res. 47: 795-798.
11. Haskins, S., Pascoe, P.J., Ilkiw, J.E., Fudge, J., Hopper, K., Aldrich, J. (2005) Reference cardiopulmonary values in normal dogs. Comp Med. 55: 156-161.
12. Haskins, S.C. (2015) Monitoring Anesthetized Patients, In: Veterinary Anesthesia and Analgesia. The Fifth Edition of Lumb and Jones. Grimm, K.A., Lamont, L.A., Tranquilli, W.J., Greene, S.A., Robertson, S.A. (eds.). John Wiley & Sons, Pondicherry, India, p. 86-113.
13. Haskins, S.C., Farver, T.B., Patz, J.D. (1985) Ketamine in dogs. Am J Vet Res. 46: 1855-1860.
14. Henao-Guerrero, N., Riccó, C.H. (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.
15. Hopkins, A., Giuffrida, M., Larenza, M.P. (2014) Midazolam, as a co-induction agent, has propofol sparing effects but also decreases systolic blood pressure in healthy dogs. Vet Anesth Analg. 41: 64-72.
16. Ilkiw, J., Suter, C., McNeal, D., Farver, T., Steffey, E. (1996) The effect of intravenous administration of variable-dose midazolam after fixed-dose ketamine in healthy awake cats. J Vet Pharmacol Ther. 19: 217-224.
17. Kennedy, M.J., Smith, L.J. (2014) 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 Anesth Analg. 42: 350-359.
18. Ko, J.C., Payton, M.E., White, A.G., Galloway, D.S., Inoue, T. (2006) Effects of intravenous diazepam or microdose medetomidine on propofol-induced sedation in dogs. J Am Anim Hosp Assoc. 42: 18-27.
19. Lerche, P., Nolan, A., Reid, J. (2000) Comparative study of propofol or propofol. Vet Rec. 146: 571-574.
20. Mair, A.R., Pawson, P., Courcier, E., 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 Anesth Analg. 36: 532-538.
21. Mannarino, R., Luna, S.P., Monteiro, E.R., Beier, S.L., Castro, V.B. (2012) Minimum infusion rate and hemodynamic effects of propofol, propofol-lidocaine and propofol-lidocaine-ketamine in dogs. Vet Anesth Analg. 39: 160-173.
22. Martinez-Taboada, F., Leece, E.A. (2014) Comparison of propofol with ketofol, a propofol-ketamine admixture, for induction of anaesthesia in healthy dogs. Vet Anesth Analg. 41: 575-582.
23. Muir, W., Gadawski, J. (1998) Respiratory depression and apnea induced by propofol in dogs. Am J Vet Res. 59: 157-161.
24. Rankin, D.C. (2015) Sedatives and Tranquilizers, In: Veterinary Anesthesia and Analgesia. The Fifth Edition of Lumb and Jones. Grimm, K.A., Lamont, L.A., Tranquilli, W.J., Greene, S.A., Robertson, S.A. (eds.). John Wiley & Sons, Pondicherry, India, p. 196-207.

25. Riccó, C.H., Henao-Guerrero, N. (2014) Cardiovascular effects of orotracheal intubation following anesthetic induction with propofol, ketamine-propofol, or ketamine-diazepam in premedicated dogs. J Am Vet Med Assoc. 244: 934-939.
26. Seliskar, A., Nemec, A., Roskar, T., Butinar, J. (2007) Total intravenous anaesthesia with propofol or propofol/ketamine in spontaneously breathing dogs premedicated with medetomidine. Vet Rec. 160: 85-91.
27. Smith, I., White, P.F., Nathanson, M., Gouldson, R. (1994) Propofol. An update on its clinical use. Anesthesiology. 81: 1005.
28. Smith, J., Gaynor, J., Bednarski, R., Muir, W. (1993) Adverse effects of administration of propofol with various preanesthetic regimens in dogs. J Am Vet Med Assoc. 202: 1111-1115.
29. Tweed, W., Minuck, M., Mymin, D. (1972) Circulatory responses to ketamine anesthesia. Anesthesiology, 37: 613-619.
30. Watkins, S., Hall, L., Clarke, K. (1987) Propofol as an intravenous anaesthetic agent in dogs. Vet Rec. 120: 326-329.
31. White, K.L., Shelton, K., Taylor, P.M. (2001) Comparison of diazepam-ketamine and thiopentone for induction of anaesthesia in healthy dogs. Vet Anesth Analg. 28: 42-48.
32. Wong, D.H., Jenkins, L.C. (1974) An experimental study of the mechanism of action of ketamine on the central nervous system. Can Anesth Soc J. 21: 57-67.

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مقایسه دوز مورد نیاز القا، خصوصیات القا و برگشت از بیهوشی و تأثیرات قلبی-تنفسی تجویز همزمان کتوفول با دیازپام و میدازولام در سگ‌های سالم

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چکیده

زمینه مطالعه: تجویز همزمان داروهای بیهوشی به منظور کاهش اثرات ناخواسته هر یک از این داروها انجام می‌شود. **هدف:** این مطالعه به منظور بررسی اثرات تجویز همزمان کتوفول با دیازپام و میدازولام در سگ‌های سالم طراحی شد. **روش کار:** تعداد شش قلاده سگ بالغ نژاد مخلوط مورد استفاده قرار گرفتند. پس از آرام‌بخشی با داروی آسپرومازین (۰/۱ mg/kg)، بیهوشی با یکی از سه درمان کتوفول (KF، هر میلی‌لیتر شـامل ۵mg کتامین و ۵mg پروپوفول)، کتوفول-دیازپام (KFD) و کتوفول-میدازولام (KFM) (هر میلی‌لیتر شامل ۵mg کتوفول و ۲/۵mg دیازپام یا میدازولام) به صورت تصادفی القا شد. همه سگ‌ها هر سه درمان را به فاصله حداقل یک هفته دریافت نمودند. **نتایج:** دوز مورد نیاز برای القای بیهوشـی در KF (۴/۲±۰/۴۴ mg/kg) بالاتر از KFD (۲/۲۷±۰/۶ mg/kg) و KFM (۱/۶۸±۰/۲۵ mg/kg) تعیین شد ($p<0/05$). دوز نهایی دیازپام و میدازولام در KFD و KFM به ترتیب mg/kg ۱/۰۰±۰/۲۵ و mg/kg ۰/۷۳±۰/۱۰ بود ($p>0/05$). زمان مورد نیاز برای نشستن روی جناغ، ایستادن و راه رفتن طبیعی در گروه KFD و KFM طولانی‌تر از KF بود ($p<0/05$). تعداد ضربان قلب در KF در چندین نقطه زمانی افزایش یافت ($p<0/05$). تعداد تنفس در KF یک کاهش معنی‌داری را در زمان بیهوشی در مقایسه با زمان پایه نشان داد. ضربان قلب و تعداد تنفس در KFD و KFM ثبات بیشتری را نشان داد. کیفیت القا و برگشت از بیهوشی در هر سه درمان قابل قبول بود. **نتیجه‌گیری نهایی:** تجویز همزمان کتوفول با دیازپام و کتامین مقدار داروی مورد نیاز برای القا را کاهش داد و برگشت از بیهوشی را طولانی ساخت. دیازپام و میدازولام توانستند برخی اثرات جانبی قلبی-تنفسی کتوفول را کاهش دهند.

واژه‌های کلیدی: تجویز همزمان، دیازپام، سگ، کتوفول، میدازولام

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