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## 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

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**ABSTRACT:** The objective of the present study was to compare the effects of propofol and ketofol on intraocular pressure, tear production and cardiorespiratory variables in dogs premedicated with midazolam. Six castrated adult mixed-breed dogs were used in a cross-over design with a one-week interval. Twenty minutes after premedication with midazolam (0.2 mg/kg), animals were assigned randomly to two groups and received either propofol (6 mg/kg) or ketofol (3 mg/kg; 1 : 1 mg/ml ratio) treatments intravenously. Intraocular pressure, tear production, heart rate, respiratory rate, rectal temperature and direct mean arterial blood pressure were measured at base (before induction), and at 5, 10, 15, 20 and 30 min after induction of anaesthesia. Blood gas samples were obtained at base (before induction), and at 5, 15 and 30 min after administration of treatments. Intraocular pressure showed significantly higher values at 5 min after induction in ketofol compared with propofol ( $16.1 \pm 4.5$  mm Hg vs  $8.2 \pm 1.2$  mm Hg, respectively). There were no significant changes in tear production in either group. Significantly higher heart rate and mean arterial blood pressure were detected in ketofol at several time points. Respiratory depression occurred in both groups with no significant differences between them. In conclusion, although ketofol improved heart rate and mean arterial blood pressure and did not elicit more pronounced respiratory depression than propofol, it resulted in significantly higher values of intraocular pressure at 5 min after administration in dogs. Despite the small number of dogs in this study, our results indicate that ketofol should not be recommended for ophthalmic surgical procedures in dogs. Appropriate oxygenation should be provided when propofol is used for ophthalmic surgeries.

**Keywords:** heart rate; respiratory rate; rectal temperature; direct mean arterial blood pressure; blood gases

In addition to acceptable general characteristics such as good quality of induction, minimal cardio-pulmonary depression and rapid recovery, a suitable anaesthetic protocol for ophthalmic surgical procedures should maintain or even decrease (but within normal range) intraocular pressure (IOP) during the perioperative period. Several pharmacological agents used for premedication and/or anaesthesia including medetomidin (Verbruggen et al. 2000; Wallin-Hakanson and Wallin-Hakanson 2001), dexmedetomidine (Artigas et al. 2012), thiopental (Hofmeister et al. 2008), ketamine (Hofmeister et al. 2006; Ghaffari et al. 2010), propofol (Hofmeister et al. 2008; Hofmeister et al. 2009;

Hasiuk et al. 2014), alfaxalon (Costa et al. 2014), isoflurane (Shepard et al. 2011) and sevoflurane and desflurane (Almeida et al. 2008) have been studied for their effects on ocular parameters. Since no anaesthetic agent or protocol has yet to satisfy all requirements for ophthalmologic procedures, research is ongoing to find an anaesthetic protocol with less pronounced adverse effects on haemodynamic as well as ophthalmologic parameters.

Propofol is commonly used for induction and maintenance of anaesthesia in different surgical procedures. It is characterised by smooth, rapid induction and recovery as well as lack of reliance on hepatic metabolism which makes propofol suit-

able in some special situations (Hofmeister et al. 2009). Propofol was reported to elicit a transient increase in IOP after administration of a single bolus in dogs (Hofmeister et al. 2008; Hofmeister et al. 2009; Costa et al. 2014). However, another study in dogs reported no changes in IOP after propofol administration (Batista et al. 2000). Propofol may be associated with some undesirable cardiorespiratory effects such as apnoea (Lerche et al. 2000), dose-dependent respiratory depression (Aguar et al. 2001; Henao-Guerrero and Ricco 2014; Kennedy and Smith 2015) and hypotension (Pagel and Warltier 1993) and reduction in cardiac output (Goodchild and Serrao 1989).

Ketofol is an admixture of propofol and a low dose of ketamine combined in a 1 : 1 ratio in a single syringe. The addition of ketamine to propofol reduces the dose of propofol administered which can provide for less pronounced cardiovascular depression and better haemodynamic stability. After induction and/or maintenance of anaesthesia with ketofol in comparison to propofol alone, higher heart rate (HR), improved mean arterial pressure (MAP), increased cardiac output and better oxygen delivery have been reported (Henao-Guerrero and Ricco 2014; Martinez-Taboada and Leece 2014; Kennedy and Smith 2015). Further, IOP did not increase after administration of ketofol in human patients (Frey et al. 1999). To the authors' knowledge, no previous study has evaluated the effects of ketofol on ocular variables in dogs.

The purpose of the present study was to compare the effects of propofol and ketofol on IOP and tear production and to assess haemodynamic changes following administration of a single dose in dogs. We hypothesised that ketofol, due to the lower dose of ketamine that is administered, would not elicit significant changes in ocular parameters in dogs while providing more haemodynamic stability than propofol.

## MATERIAL AND METHODS

Six castrated adult mixed-breed dogs weighing  $17.7 \pm 2.5$  kg (mean  $\pm$  SD) and aged 1.5–2.5 years old were used. No brachycephalic dogs were included in the present study. Animals were transferred to the Veterinary Hospital two weeks before the study to allow acclimatisation. Health status was confirmed by a thorough physical examination,

complete blood count (CBC), and total protein (TP) test. A general ophthalmic examination consisting of neuro-ophthalmology (menace response and pupillary light reflex), Schirmer tear test (STT-1; ERC, Turkey) and tonometry (Pulsair Intellipuff, Keeler, UK) was used to check for ocular abnormalities. Feeding was withdrawn overnight before the commencement of experiment, but the animals had free access to water. All experiments were performed in the morning to avoid any effect of time on data collection. All procedures in this study were approved by the Animal Care and Research Committee of Shahid Chamran University of Ahvaz.

On the day of the study, the dogs were allowed to rest for 30 min before any medication. Then, they were restrained on a surgery table and received midazolam (Midamax, 5 mg/ml, Tehran chemie, Iran) at a dose of 0.2 mg/kg *i.v.* Ten minutes later, two 20-gauge 2.5-cm catheters were placed in the left cephalic vein and the left pedal artery. For catheterisation of the pedal artery, 1 ml 1% lidocaine (Vetacaine, 20 mg/ml, Aburaihan, Iran) was infiltrated subcutaneously. The arterial catheter was connected to an aneroid manometer positioned at the level of the shoulder joint with the animal in sternal recumbency. Fifteen minutes after midazolam administration, animals received 100% oxygen via a face mask for 5 min.

Dogs were randomly assigned to one of two treatment groups and received either a single bolus injection of propofol (PF; 6 mg/kg) or ketofol (KF; 3 mg/kg; 1 : 1 mg/ml ratio) for induction of anaesthesia, *i.v.* Ketofol was prepared based on the study of Andolfatto and Willman (2010). In brief, 5% ketamine (Ketamine hydrochloride, Rotexmedica, Trittau, Germany; 50 mg/ml) was diluted to 1% ketamine (1 mg/ml) and combined with an equivalent volume of propofol (Anesia, Alleman, Germany; 10 mg/ml) in the same syringe (each ml ketofol contained 5 mg ketamine and 5 mg propofol). During the anaesthesia, the dogs received 100% oxygen at a rate of 100 ml/kg/min via a face mask as well as normal saline at a rate of 10 ml/kg/min via the cephalic vein. The animals were maintained in sternal recumbency and the head was positioned in a natural upright position at the same level as the shoulder joint and caution was taken not to compress the jugular vein. After midazolam administration, blankets were placed over the animals to prevent hypothermia ( $< 38$  °C). The interval between the two treatments was at least one-week for all dogs.

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IOP was recorded immediately before induction of anaesthesia (base) and at 5, 10, 20 and 30 min after induction. Attempts were made to avoid any head restraint and glob manipulation. The tonometer was self-calibrated and calculates the variation of the values with < 5% variance. STT-1 was used for evaluation of tear production at base and at 5, 15 and 30 min after induction. The strips of STT-1 were placed in the lateral third of the inferior conjunctival fornix. HR, respiratory rate (RR), rectal temperature (RT) and mean arterial pressure were recorded at base and at 5, 10, 20 and 30 min after induction. For arterial blood gas sample collection, 1 ml blood was first removed via the arterial catheter, a 0.5 ml test sample was collected anaerobically into a heparinised syringe and then the first 1 ml that was removed was flushed into the catheter together with 0.5 ml heparinised saline. pH, partial pressure of oxygen (PaO<sub>2</sub>), partial pressure of carbon dioxide (PaCO<sub>2</sub>), bicarbonate ion concentration (HCO<sub>3</sub><sup>-</sup>) and base excess (BE) of collected samples were measured using a calibrated gas analyser (Edan i15, Edan instrument Inc., China).

The normality of data was tested using Kolmogorov-Smirnov test. All data were expressed as means ± standard deviation (SD). A paired sample *t*-test was employed for comparison of variable between groups at each time point. A repeated measure ANOVA followed by Bonferroni test was used for the comparison of variables within each group over time. Pearson's correlation coefficient was employed to detect any correlation between IOP and cardiorespiratory and blood gas variables. Statistical analysis was undertaken using IBM SPSS Statistics for Windows Version 22 (IBM Corporation, USA). Significant level was set at *P* < 0.05.

## RESULTS

There were no significant differences with respect to the body weights between the two groups (17.6 ± 2.42 kg vs 17.6 ± 2.73 kg in PF vs KF, respectively). All dogs completed the study, and induction and recovery were satisfactory in both groups without any sequelae. There were no significant differences in the first head movement between groups (14 ± 4 min vs 13 ± 5 min in PF vs KF, respectively).

No significant differences in IOP were observed between the right and left eyes at any time point (*P* > 0.05). IOP showed significantly higher values

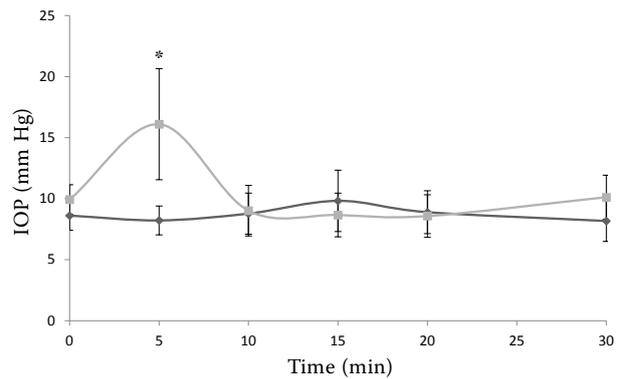


Figure 1. Mean (SD) intraocular pressure (IOP) in propofol (—◆—) and ketofol (—■—) groups (*n* = 6) at each time point

\*Significantly different between groups (*P* < 0.05)

at T5 in KF compared with PF (*P* < 0.05; Figure 1). No significant change in IOP was observed within groups over time (*P* > 0.05). A moderate correlation was found between IOP and pH (*r* = -0.428; *P* = 0.007) as well as IOP and PCO<sub>2</sub> (*r* = 0.514; *P* = 0.001). No correlation between IOP and cardiorespiratory and other blood gas variables was found. There were no significant changes between and within the two groups in tear production (*P* > 0.05), however; with the exception of T5, STT-1 was higher in KF than in P at the time points evaluated (Figure 2).

Data related to HR, RR, RT and MAP are summarised in Table 1. HR was significantly higher at T15, T20 and T30 in KF when compared with PF (*P* < 0.05). Comparison of HR with base value in PF did not show significant differences (*P* > 0.05). HR in KF was significantly higher at all time points in comparison to base (*P* < 0.05). Apnoea occurred after induction of anaesthesia in two dogs from PF

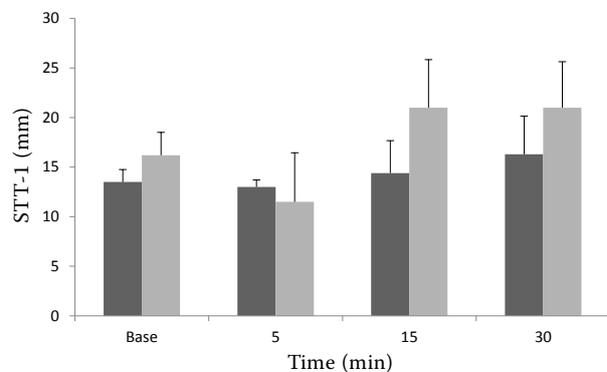


Figure 2. Mean (SD) Schirmer tear test 1 (STT-1) in propofol (■) and ketofol (■) groups (*n* = 6) at each time point

<https://doi.org/10.17221/18/2017-VETMED>Table 1. Mean (SD) values for heart rate, respiratory rate, rectal temperature and mean arterial blood pressure in propofol (PF) and ketofol (KF) groups ( $n = 6$ ) at each time point

Variable		T0	T5	T10	T15	T20	T30
Heart rate	PF	75 ± 11	77 ± 26	84 ± 22	81 ± 20	79 ± 16	76 ± 19
	KF	78 ± 9	112 ± 22 <sup>†</sup>	104 ± 18 <sup>†</sup>	123 ± 12 <sup>*†</sup>	113 ± 18 <sup>*†</sup>	110 ± 21 <sup>*†</sup>
Respiratory rate	PF	24 ± 11	11 ± 4	29 ± 5	28 ± 7	33 ± 10	30 ± 7
	KF	25 ± 7	11 ± 8 <sup>†</sup>	22 ± 6	30 ± 4	24 ± 7	29 ± 7
Rectal temperature	PF	38.9 ± 0.6	38.6 ± 0.7	38.7 ± 0.8	38.5 ± 0.7	38.5 ± 0.9	38.5 ± 0.7
	KF	38.7 ± 0.3	38.5 ± 0.4	38.2 ± 0.3 <sup>†</sup>	38.1 ± 0.3 <sup>†</sup>	38.2 ± 0.4 <sup>†</sup>	38.2 ± 0.4 <sup>†</sup>
Mean arterial blood pressure	PF	95 ± 7	88 ± 5 <sup>†</sup>	95 ± 10	98 ± 13	103 ± 10	99 ± 10
	KF	97 ± 10	108 ± 11 <sup>*</sup>	113 ± 13 <sup>*†</sup>	112 ± 9 <sup>†</sup>	112 ± 12 <sup>†</sup>	118 ± 10 <sup>†</sup>

\*Significantly different from values of propofol at that time point ( $P < 0.05$ )<sup>†</sup>Significantly different from base in each group ( $P < 0.05$ )

and three dogs from KF; all cases resolved within 1–2 min without any further intervention. RR did not show any significant differences between the two groups and within PF ( $P > 0.05$ ). A significantly lower value of RR was detected in KF at T5 when compared with base ( $P < 0.05$ ). Mean RT was higher than 38 °C at all time points evaluated in two groups. MAP was significantly higher at T5 and T10 in KF when compared with PF ( $P < 0.01$  and  $P < 0.05$ , respectively). A significantly lower value of MAP was detected in PF at T5 compared with the baseline value ( $P < 0.05$ ). MAP in KF did not change significantly over time ( $P > 0.05$ ).

Table 2 shows the results of blood gas analysis. pH did not show significant differences between the two groups at the time points evaluated ( $P > 0.05$ ). In both groups, pH decreased significantly at T5 when compared with base ( $P < 0.05$ ). Comparison of PaO<sub>2</sub> between the two groups did not reveal sig-

nificant differences ( $P > 0.05$ ), while PaO<sub>2</sub> was significantly higher at T5, T15 and T30 in comparison to base in both groups ( $P < 0.05$ ). No significant differences in PCO<sub>2</sub> between groups were detected at any time point ( $P > 0.05$ ). PCO<sub>2</sub> was significantly higher in both groups at T5 compared with base ( $P < 0.05$ ). HCO<sub>3</sub><sup>-</sup> and BE did not show any significant changes between and within the two groups ( $P > 0.05$ ).

## DISCUSSION

The equilibrium between the formation and drainage of aqueous humour results in a relatively constant IOP (Miller 2013). Any abrupt increase in IOP should be minimised or prevented, especially in near-perforating corneal lesions or glaucoma as it may lead to lens luxation, vitreous hernia

Table 2. Mean (SD) values for blood gas variables in propofol (PF) and ketofol (KF) groups ( $n = 6$ ) at each time point

Variable		T0	T5	T15	T30	Reference range <sup>15</sup>
pH	PF	7.37 ± 0.03	7.32 ± 0.02 <sup>†</sup>	7.34 ± 0.04	7.36 ± 0.04	7.35–7.46
	KF	7.38 ± 0.03	7.30 ± 0.05 <sup>†</sup>	7.34 ± 0.04	7.36 ± 0.05	
PO <sub>2</sub> (mm Hg)	PF	95 ± 1	200 ± 44 <sup>†</sup>	244 ± 24 <sup>†</sup>	234 ± 70 <sup>†</sup>	80–110 (it will increase with oxygenation)
	KF	95 ± 3	260 ± 57 <sup>†</sup>	284 ± 93 <sup>†</sup>	277 ± 59 <sup>†</sup>	
PCO <sub>2</sub> (mm Hg)	PF	35 ± 8	39 ± 3 <sup>†</sup>	33 ± 7	33 ± 5	32–43
	KF	33 ± 5	37 ± 3 <sup>†</sup>	35 ± 5	32 ± 4	
HCO <sub>3</sub> <sup>-</sup> (mmol/l)	PF	19.4 ± 4.6	19.8 ± 2.7	20.2 ± 2.3	18.8 ± 2.6	18–26
	KF	18.4 ± 2.7	19.6 ± 3.8	19.4 ± 3.6	19.4 ± 4.4	
Base excess (mmol/l)	PF	-6 ± 2	-6 ± 3	-6 ± 2	-7 ± 2	-8 to +2
	KF	-7 ± 2	-8 ± 3	-6 ± 3	-6 ± 3	

<sup>†</sup>Significantly different from base in each group ( $P < 0.05$ )

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(Cunningham and Barry 1986; Hofmeister et al. 2009) and permanent electrophysiological effects on the retina (Hamor et al. 2000). IOP is mainly regulated by the central nervous system; however, it may be also affected by some external factors including external pressure, scleral rigidity and topical or systemic effects of drugs (Cunningham and Barry 1986; Hofmeister et al. 2009; Miller 2013). Several studies have evaluated the effects of drugs used for premedication, induction and/or maintenance of anaesthesia on IOP in dogs.

Most anaesthetic agents were described to decrease IOP; however, the effects of propofol and ketamine on IOP are controversial. While some studies have shown an increase in IOP after propofol and ketamine administration (Hofmeister et al. 2006; Hofmeister et al. 2008; Hofmeister et al. 2009; Kovalcuka et al. 2013; Costa et al. 2014), others have not detected any changes in IOP (Batista et al. 2000; Ghaffari et al. 2010). In a study in humans, IOP did not increase in any of patients and decreased after administration of hypnotic doses of propofol and ketofol (Frey et al. 1999). In the present study, an increase in IOP at T5 after ketofol administration was observed (in normal range; Gelatt and MacKay 1998); however, IOP returned to the base values again at T10. IOP did not show any significant changes after propofol administration and remained relatively constant during the evaluation period. Therefore, it is reasonable to attribute the increase in IOP in the KF group to the ketamine component of ketofol. Although the exact mechanism underlying the ketamine-elicited increase in IOP is not clear, some authors have postulated that direct effect of ketamine on ocular structures and contraction of extraocular muscle may play a role (Thomson 2007). It needs to be noted that the lack of increase in IOP after propofol administration in the present study is in contrast to several previous studies in dogs which have detected higher values of IOP after induction of anaesthesia with propofol (Hofmeister et al. 2008; Hofmeister et al. 2009; Costa et al. 2014). Propofol has been suggested to change IOP through direct effects on ocular structures (Hofmeister et al. 2009). The differing results can be attributed to the fact that IOP was measured immediately after induction of anaesthesia in previous studies, while IOP was recorded at 5 min after induction in the study reported here. Thus, a potential increase in IOP immediately after the administration of drugs, and which also might have

occurred in the current study, cannot be ruled out. It is also necessary to mention that base values of IOP in the present study were taken 20 min after midazolam administration. It has been showed that midazolam decreases IOP in halothane-anaesthetised dogs (Artru 1991). Therefore, the potential effect of midazolam should also be considered, particularly when relatively lower values of IOP have been detected during the assessment period.

Changes in IOP, in the current study, correlated with changes in pH and  $PCO_2$ , but not blood pressure. These findings are in contrast to two previous studies which stated that changes in IOP cannot be attributed to hypercarbia; however, as with their results, IOP did not vary with changes in blood pressure (Cunningham and Barry 1986; Hofmeister et al. 2009). Therefore, it seems that propofol and ketamine can affect IOP not only via direct mechanisms but also in indirect ways; nevertheless, the involved parameters and exact mechanism remained to be investigated in further studies.

An adequate and efficient tear film should cover the cornea in order to provide lubrication between the lids and ocular surface, to protect the eye against microbial protein sources and to facilitate drainage of debris and exfoliated cells (Gross and Pablo 2015). Generally, tear production decreases during general anaesthesia; however, STT-1 showed no statistically significant changes following administration of propofol, but not alfaxalone, in dogs (Costa et al. 2014). In the present study, STT-1 did not show significant changes between and within the two groups, which is consistent with the results of Costa et al. (2014) who evaluated the effect of propofol on tear production in dogs.

HR and MAP were relatively constant in group propofol compared with the base, except for MAP at T5, which was significantly lower than base value. HR and MAP in group KF showed significantly higher values at several time points in comparison to the base. Thus, ketofol increased HR and improved MAP in the current study, results which are in accordance with previous investigations in dogs (Hena-Guerrero and Ricco 2014; Martinez-Taboada and Leece 2014; Kennedy and Smith 2015). Similar to IOP, the relatively lower base values of HR and MAP in the current study are attributable to midazolam administration, which has also been reported by other studies (Rankin 2015).

Blood gas analysis showed a distinct respiratory acidosis in both groups which is indicated by stable

BE, reduction of RR, decrease in pH and increase in  $\text{PCO}_2$  at T5. Respiratory depression is a common finding after propofol administration in dogs (Aguiar et al. 2001; Henao-Guerrero and Ricco 2014; Kennedy and Smith 2015). Exacerbated respiratory depression has been reported after total intravenous anaesthesia with ketofol in healthy Beagle dogs (Kennedy and Smith 2015), but respiratory depression induced with ketofol was described to not exceed that induced by propofol in dogs (Henao-Guerrero and Ricco 2014). The results of the study reported here are in accordance with the latter study; however, it is in contrast to the expected advantage of the addition of low doses of ketamine to propofol and the subsequent reduction in the dose of propofol, which would result in less respiratory depression than propofol alone. The higher values of  $\text{PO}_2$  in the present study showed that despite hypoventilation and respiratory depression, adequate oxygenation has been provided via the face mask. Administration of supplemental oxygen has been recommended for dogs anaesthetized with propofol and ketofol (Henao-Guerrero and Ricco 2014).

In the current study, a Keeler Pulsair Intellipuff was employed for determination of IOP in dogs. This device is a non-contact self-calibrated pneumotonometer which employs a puff of air to measure IOP. The major advantages of pneumotometry over other methods are avoidance of contamination of eyes and lack of need for topical anaesthesia which could affect IOP. To the authors' knowledge, no study has yet employed this device in dogs; however, the Pulsair Intellipuff has been reported as a highly reliable and acceptable tool for IOP determination in both normotensive and hypertensive humans (Hubanova et al. 2015).

The present study has some limitations. Firstly, a small sample size and no defined breed of dogs were used. Increasing the number of dogs in each group and using a single defined breed would probably lead to more accurate results. Secondly, base values were recorded after premedication with midazolam. Administration of midazolam resulted in mild to moderate sedation and more comfort for the animals and also facilitated restraint and catheterisation and minimised excitement-induced changes in data. However, the possible effects of midazolam and probable interaction of midazolam with propofol and ketofol should also be considered. Thirdly, in the current study, just a single dose of propofol and ketofol was administered, which

differs markedly from practical situations in which an appropriate stable regimen of anaesthesia must be provided; however, the protocol of the study reported here was the same as other investigations which evaluated the effects of different protocols of anaesthesia on ocular parameters using just a single dose (Hofmeister et al. 2006; Ghaffari et al. 2010; Costa et al. 2014; Jang et al. 2015). Despite these limitations, we were able to achieve the goals of our study, which were the comparison of IOP, tear production and haemodynamic variables in dogs premedicated with midazolam and induced with either propofol or ketofol.

In conclusion, although the addition of a low dose of ketamine to propofol (ketofol) improved HR and MAP and did not result in more pronounced respiratory depression than propofol alone, it resulted in significantly higher values of IOP at 5 min after administration in dogs premedicated with midazolam. Propofol did not change IOP during the 30-min evaluation period. Neither propofol nor ketofol changed tear production significantly. Therefore, ketofol is not recommended for ophthalmic surgical procedures, especially for cases at risks of any abrupt increase in IOP. It seems that propofol can be used more safely in the aforementioned situations; however, appropriate oxygenation, via supplemental oxygenation and/or assisted ventilation, is warranted.

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