The effects of ketamine-midazolam anesthesia on intraocular pressure in clinically normal dogs

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Abstract
Objective To determine the effects of intravenous ketamine-midazolam anesthesia on intraocular pressure (IOP) in ocular normotensive dogs.

Animals Thirteen adult mixed-breed dogs.

Procedures Dogs were randomly assigned to treatment (n = 7) and control (n = 6) groups. Dogs in the treatment group received intravenous ketamine 15 mg/kg and midazolam 0.2 mg/kg and dogs in the control group received intravenous saline. The time of intravenous drug injection was recorded (T0). Measurements of IOP were then repeated 5 min (T5) and 20 min (T20) following the intravenous administration of ketamine-midazolam combination and saline in both groups.

Results Measurements showed normal IOP values in both groups. The mean ± SD baseline IOP values for treatment and control groups were 13.00 ± 1.47 and 10.33 ± 2.20, respectively. For baseline IOP values, there was no significant difference between treatment and control groups (P = 0.162). In the treatment group, the subsequent post-treatment mean ± SD values were 15.64 ± 2.17 (5 min), and 14.92 ± 1.98 (20 min). There was no evidence of statistical difference between baseline values and post-treatment values after treatment with ketamine-midazolam (P5 = 0.139; P20 = 0.442). In control eyes, the mean ± SD values at 5 and 20 min were 10.41 ± 2.01 and 10.16 ± 1.69, respectively. There was no significant difference between baseline values and post-treatment values in control group (P5 = 1.000; P20 = 1.000).

Conclusion Ketamine-midazolam combination has no clinically significant effect on IOP in the dog.

Key Words: dogs, intraocular pressure, ketamine, midazolam

INTRODUCTION
Glaucoma is defined as an abnormal increase in intraocular pressure (IOP) that is not compatible with ocular health.1

Anesthetic management should minimize changes, specifically an increase, in IOP over the entire anesthetic period.2 It has been documented in cats, dogs and rabbits that ketamine increases IOP when used as a sole agent for induction of anesthesia.3 A recent study reported that administration of ketamine-diazepam combination causes a significant elevation in IOP in eyes of normal dogs.3 Some studies have investigated possible effects of midazolam on IOP in humans, but the results were variable. Some authors reported a decrease in IOP,4 whereas others observed no changes in IOP.5

Combination of ketamine with midazolam for induction of anesthesia has not been investigated for its effects on IOP in dogs. The objective of this study was to determine the effects of anesthesia induction with ketamine-midazolam combination on IOP in clinically normal dogs.

MATERIAL AND METHODS
Thirteen adult mixed-breed intact dog, nine males and four females were evaluated. Dogs ranged in age from 2 to 4 years. Mean ± SD body weight was 22.38 ± 3.61 kg. Prior to the study, all dogs were determined to be free of disease by means of complete physical and complete ocular examinations, including biomicroscopy and indirect ophthalmoscopy.

During 12 days acclimatization period, dogs were restrained daily and IOPs measured by applanation

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tonometry (Tono-Pen Vet<sup>TM</sup>; Reichert, INC. USA) to reduce anxiety associated with the measurement procedure. Prior to each IOP measurement, one drop of 0.5% proparacaine hydrochloride ophthalmic solution (Falcon Pharmaceuticals, Ltd, TX, USA) was applied topically to each eye. Baseline IOP measurements were recorded immediately before administration of drugs in both groups.

Dogs were randomly assigned to treatment (n = 7) and control (n = 6) groups. Dogs in the treatment group received intravenous ketamine (15 mg/kg, Pantex Holland B. V.) and midazolam (0.2 mg/kg, Tehran Chemie) and dogs in the control group received intravenous saline (0.1 mL/kg, Tehran Chemie).

After induction of anesthesia, oxygen was administered by face mask at a flow rate of 0.5 L/min in the treatment group. Monitoring during the anesthesia included pulse oximetry and electrocardiography.

The time of intravenous drug injection was recorded as (T<sub>0</sub>). Measurements of IOP were then repeated 5 min (T<sub>5</sub>) and 20 min (T<sub>20</sub>) following the intravenous administration of ketamine-midazolam and saline in treatment and control groups, respectively.

To obtain IOP values, the animals were placed in sternal recumbency with head in normal and upright position and the eyelids were not manipulated as measurements were taken. The IOP was measured by application tonometry (Tono-Pen Vet<sup>TM</sup>; Reichert, Inc., USA) in both eyes of all dogs. Prior to each IOP measurement, one drop of 0.5% proparacaine hydrochloride ophthalmic solution (Falcon Pharmaceuticals, Ltd, TX, USA) was applied topically to each eye. The tonometer was self-calibrated prior to data collection. With repeated measurements the Tono-Pen calculates the consistency of the values and in this investigation only IOP measurements with ≤5% variance were recorded.

**Statistical analysis**

Data were analyzed using the software package SPSS 15.0 for Microsoft windows. A one-way repeated measures ANOVA was used to compare data within the same group and to assess differences between groups. A P-value of less than 0.05 was considered statistically significant.

**RESULTS**

The mean values of IOP are depicted in Fig. 1. All data were expressed in mmHg. There were no statistically significant differences between the IOP mean values for the right and left eyes in both treatment and control groups (P-values, respectively, included 0.22 and 0.47). A mean IOP was calculated for each dog using the measuring value from the left eye and the right eye at each time point.

The mean ± SD baseline IOP values for treatment and control groups were 13.00 ± 1.47 and 10.33 ± 2.20, respectively. For baseline IOP values, there was no significant difference between treatment and control groups (P<sub>0</sub> = 0.162).

In the treatment group, the subsequent post-treatment mean ± SD values were 15.64 ± 2.17 (5 min), and 14.92 ± 1.98 (20 min). There was no evidence of statistical difference between baseline values and post-treatment values after treatment with Ketamine-midazolam (P<sub>5</sub> = 0.139; P<sub>20</sub> = 0.442).

In control eyes, the mean ± SD values at 5 and 20 min were 10.41 ± 2.01 and 10.16 ± 1.69, respectively. There was no significant difference between baseline values and post-treatment values in control group (P<sub>5</sub> = 1.000; P<sub>20</sub> = 1.000).

Statistical comparisons between post-treatment values of treatment and control groups indicated significant differences at 5 min (P<sub>5</sub> < 0.001) and 20 min (P<sub>20</sub> = 0.001).

**DISCUSSION**

The baseline values of IOP observed prior to treatment in the dogs presented in this study were similar to those reported in normal dogs.<sup>1</sup>

In the present investigation, we did not find a statistically significant effect of ketamine-midazolam combination on IOP; although there was a tendency towards an increasing effect (see Fig. 1). Our results were different from those in another study of ketamine and IOP in normal dogs, in which a statistically significant increasing effect was found.<sup>3</sup>

Ophthalmic surgical patients can be routinely anesthetized without complications if the surgeon has a thorough understanding of the effects of anesthetic agents on ocular physiology. The regulation of IOP is important for successful ophthalmic surgery and can be greatly affected by the anesthetic procedure.<sup>6</sup> In recent years, several studies have evaluated the effects of anesthetic drugs on IOP values in dogs. One study, for example, reported effects of propofol and thiopental on peri-induction IOPs in normal dogs. In the conclusion, the authors stated that propofol caused a significant increase in IOP compared to baseline and thiopental.<sup>7</sup> In another study, Almeida and co-workers discussed that sevoflurane and desflurane have no clinically significant effects on IOP in the dog.<sup>8</sup>

In contrast to previous reports in which ketamine alone or in combination with diazepam caused an increase in IOP,<sup>3</sup> in this study, no significant increase in IOP was detected.
Ketamine induces a dose-dependent CNS depression that leads to a dissociative state, characterized by profound analgesia and amnesia with maintained ocular, laryngeal, pharyngeal, pinnal and pedal reflexes. The suggested mechanism for increase of IOP after administration of certain drugs such as ketamine is due to contraction of the extraocular muscles.

In the study reported by Hofmeister, the authors stated that intravenous ketamine (10 mg/kg) and diazepam (0.5 mg/kg) combination increased IOP significantly after injection. In the present investigation, ketamine was administered intravenously at a dose of 15 mg/kg. The standard dosage range for intravenous ketamine in dogs is 5–15 mg/kg. The lack of significant IOP effect of ketamine-midazolam combination in the current study may be related to several factors, including higher dose of ketamine, the use of midazolam or small sample size.

In conclusion, ketamine-midazolam combination has no clinically significant effects on IOP in the dog.

REFERENCES