Original Article

The effect of intranasal Medetomidine/Ketamine and Diazepam/Ketamine combinations on tear production and intraocular pressure in dogs

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Abstract

To determine the effect of intranasal medetomidine/ketamine and diazepam/ketamine combinations on tear production and intraocular pressure in dogs. The animal material included 28 dogs of different breeds, ages, weights and genders that were brought to the surgery department of the Adnan Menderes University, Faculty of Veterinary Medicine for simple anesthesia indications but were otherwise healthy ocularly. In a crossover design, the dogs were randomly assigned to 4 groups of 7 dogs. Animals in the first group were given 50 µg/kg of medetomidine and 10 mg/kg of ketamine intramuscularly (MEK-IM). The second group of animals was given 50 µg/kg of medetomidine and 10 mg/kg of ketamine intranasally (MEK-IN). The third group received 10 mg/kg of ketamine and 0.3 mg/kg of diazepam intramuscularly (DK-IM). The fourth group received 10 mg/kg of ketamine and 0.3 mg/kg of diazepam intanasally (DK-IN). Comparison of the data of more than two groups was done by ANOVA one-way test. The results of the study showed that MEK-IN and DK-IN combinations significantly decreased tear secretion and intraocular pressure in dogs. The decrease in tear secretion was more pronounced with the MEK-IN combination than with the DK-IN. The decrease in intraocular pressure was more pronounced with the MEK-IN combination than with the DK-IN. These results suggest that MEK-IN and DK-IN combinations can be used as pre-anesthetics in dogs to reduce tear secretion and intraocular pressure. Further studies are needed to evaluate the safety and efficacy of these combinations in clinical settings.

Keywords: anesthesia, canine, intramuscular, ophthalmology, schirmer tear test

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Received April 15, 2023
Accepted June 19, 2023
https://doi.org/10.14456/tjvm.2023.22

Introduction

General anesthesia is used not only for surgical procedures but also for various non-invasive diagnostic procedures such as radiography, wound care and endoscopy (Marjani *et al*., 2015; Vesal and Zare, 2006). The anesthesia technique to be used depends on the species of the animal, the purpose and duration of the procedure and the experience of the researcher (Mayer, 2007).

The advantages of injectable anesthetics are easy applicability, rapid induction of anesthesia, low cost, minimal equipment and they can be applied through subcutaneous (SC), intramuscular (IM), intravenous (IV) and intraosseous routes (Moghadam *et al*., 2009). However, IM and IV injectables have disadvantages such as pain and difficulty in administration (Bozkan *et al*., 2021).

In recent years, interest in the development of alternative drug delivery routes, such as IN drugs, has gained great momentum as alternative routes of administration (Grassin-Delyle *et al*., 2012). Drug delivery via IN administration is quick and painless. Mucosa with high blood flow rates allow for quick absorption of drugs into the bloodstream. It is possible to increase drug concentrations in the central nervous system (CNS) by directly transporting substances from the nose to the brain (bypassing the blood-brain barrier) using the olfactory nerve, trigeminal nerve and cerebrospinal fluid (CSF) pathways. (Jafarbeglou and Marjani, 2019). IN delivery of CNS acting medications can thus result is a quick onset of action and lessen systemic side effects. However, swallowing, drug inhalation, volume of liquid administered and animal position during drug application may limit absorption (Weiland *et al*., 2017).

In veterinary medicine, ketamine, a dissociative anesthetic, is frequently used to induce and maintain anesthesia. Typically, it is given SC, IM or IV (Bozkan *et al*., 2021). Pet animals have reportedly experienced IN ketamine's sedative and analgesic effects (Vermeire *et al*., 2009). Additionally, it has been noted that intranasal ketamine is used as a complementary therapy for the management of major depressive disorders in humans and a variety of behavioral disorders in dogs (Vlerick *et al*., 2020). Strong alpha-2 adrenergic receptor agonist medetomidine has sedative, analgesic and muscle relaxing properties. It is a good option for IN administration because of its low molecular weight, which improves drug absorption. Dexmedetomidine is reported to be more sedating to dogs when administered IM than when administered IV, and it also causes less bradycardia. (Jafarbeglou and Marjani, 2019). In dogs, it has been reported that IN diazepam administration is simple and well-tolerated (Platt *et al*., 2020).

The effects of ketamine and IN medetomidine and diazepam pre-anesthetics on dog tear secretion and intraocular pressure have not been studied. Therefore, the effects of MEK-IN and DEK-IN combinations on tear secretion and intraocular pressure were investigated in dogs.

Materials and Methods

This prospective, blinded, randomized clinical study was conducted in the Adnan Menderes University, Facult of Veterinary Medicine, Surgery Department, Aydin, Turkey. All procedures were approved by the Institutional Animal Care and Use Committee of Aydin Adnan Menderes University (Protocol No: 64583101/2021/138). All owners provided informed written consent prior to their dogs' participation in the study.

Animals: The animal material included 28 dogs of various breeds, ages, weights and genders that were brought Adnan Menderes University, Facult of Veterinary Medicine, Surgery Department for basic anesthesia endications (X ray, bandage, wound care) but were ophthalmologically healthy. Physical examination, thoracic X-ray, complete blood count and serum chemistry all indicated that the animals were healthy.

Instrumentation and study design: Twenty eight sexually intact mixed-breed dogs (14 males and 14 females) were included in the study. [SD] of 18.5 ± 10.2 months old and a mean body weight of 20.36 ± 6.37 kg were used in this study. Food was withheld for 12 hours prior to each trial and dogs were allowed free access to water during that period.

The dogs were randomly assigned to 4 groups of 7 in a crossover design. The first group received 10 mg/kg of ketamine and 50 µg/kg of medetomidine intramuscularly (MEK-IM). The second group received 10 mg/kg of ketamine and 50 µg/kg of medetomidine intranasally (MEK-IN). The third group received 0.3 mg/kg of diazepam and 10 mg/kg of ketamine intramuscularly (DK-IM). The fourth group received 0.3 mg/kg of diazepam and 10 mg/kg of ketamine intranasally (DK-IN). The intranasal application was performed by dripping the solution into the nose with the help of a syringe.

The purpose of this study was to confirm that the animals included were ophthalmologically healthy by carrying out reflex and direct ophthalmoscopy examinations. On the basis of direct and indirect ophthalmoscopy, both eyes of the animals were free of any indication of corneal and conjunctival pathologies.

The tear production was measured with the Schirmer Tear Test 1 (STT-I). This test was performed by placing the standard Schirmer paper in the lateral one-third of the lower eyelid of the dog and determining the tears volume that wet the paper after one minute. These measurements were made separately for the right and left eyes. Intraocular pressure was measured with the Tonovet rebound tonometry equipment, separately for the right and left eyes. The tear production and intraocular pressure were measured in the animals of each group before anesthesia (0 minutes) and 10, 20, 30, 45, 60 minutes after anesthesia application. All measurements were carried out by a single person.

Statistics: Differences between groups were analyzed using the GraphPad Prism 9.0 version (GraphPad Software, Inc, CA, USA). Data was given as mean

(Mean) ± standard deviation (SD) (minimum-maximum) values in each group. Graphical presentation and statistical analysis were presented using GraphPad Prism 8 software (Graphpad Software Inc., USA). Comparison of the data for both intraocular pressure and tear production performed using repeated measure ANOVA. $P<0.05$ values were considered statistically significant. A generic power analysis tool (G-Power 3.1.9.2. DE) was used for calculating each individuals within groups using effect size 0,5 and actual power 0,95.

Results

The animals accepted both delivery methods with no issues. With IM or IN administration, there were no anesthetic side effects noted.

There was a significant difference in intraocular pressure compared to baseline at the 20th and 30th minutes of MEK-IM and DK-IM administrations for both eyes ($p<0.05$). This distinction was especially apparent in MEK-IM applications (Fig. 1). There was no statistical difference between the groups in terms of intraocular pressure in the applications of MEK-IN and DK-IN ($p>0.05$). There was no statistically significant difference between the IN and IM applications of DK in terms of intraocular pressure in both eyes ($p>0.05$). However, there was a statistically significant difference between the IN and IM applications of MEK at 20 minutes ($p<0.05$) (Fig. 2).

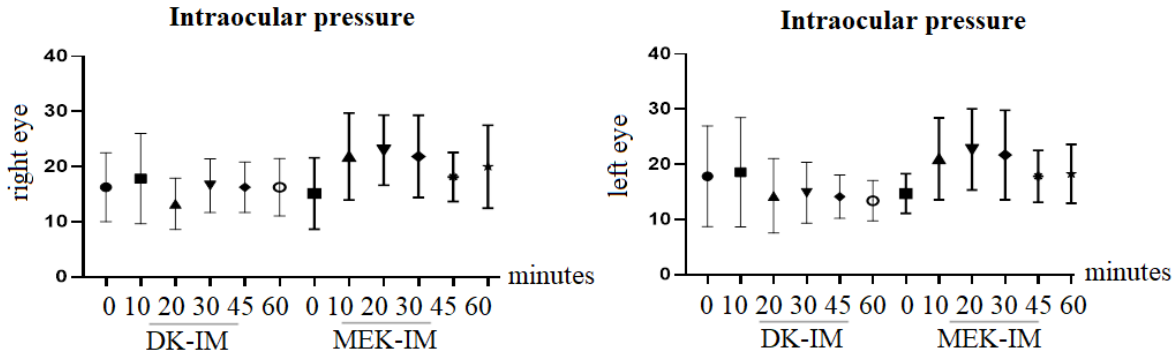

Figure 1 The effects of intramuscular applications of drugs on intraocular pressure in both eyes.

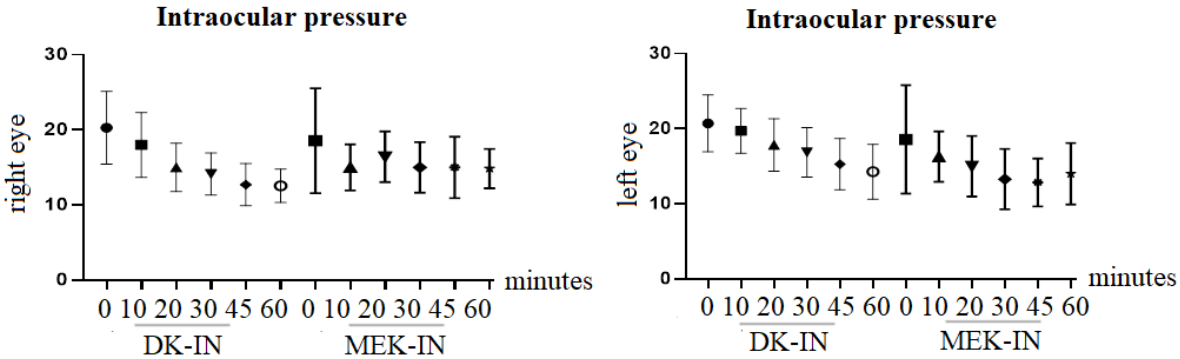

Figure 2 The effects of intranasal applications of drugs on intraocular pressure in both eyes.

Administration of MEK-IM and DK-IM showed a statistically significant difference in tear secretion in the first 30 minutes ($p<0.05$). The MEK-IM significantly reduces tear production compared to the basal level. While both groups showed a significant decrease in tear production compared to the basal level, the MEK group exhibited a higher reduction in tear production. There were no appreciable differences in STT-I values between the right and left eyes (Fig. 3).

Administration of MEK-IN and DK-IN did not show any change in tear secretion at the time of application but a statistically significant difference was found between the groups at 10 and 20 minutes ($p<0.05$). At these minutes, the MEK-IN showed a decrease in tear secretion compared to the DK-IN. Administration of DK-IN and DK-IM did not show any statistical difference in tear secretion ($p>0.05$), while there was a statistically significant difference in MEK ($p<0.05$) (Fig. 4).

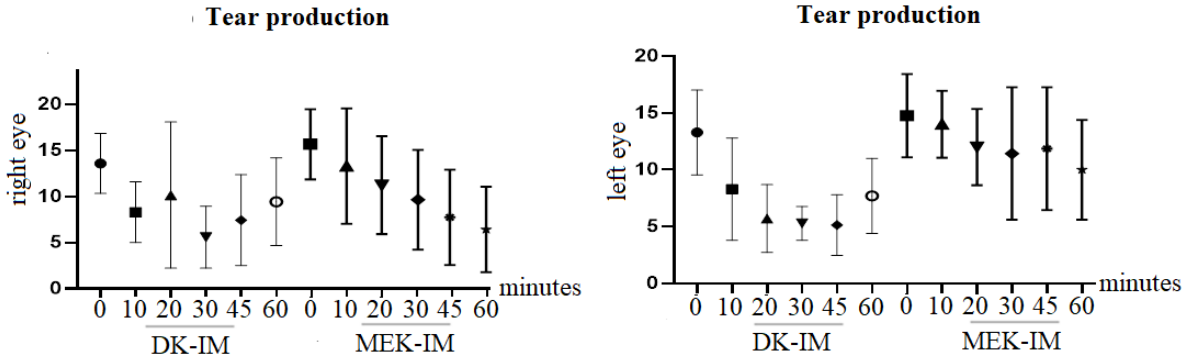

Figure 3 The effects of intramusculer applications of drugs on tears volume in both eyes.

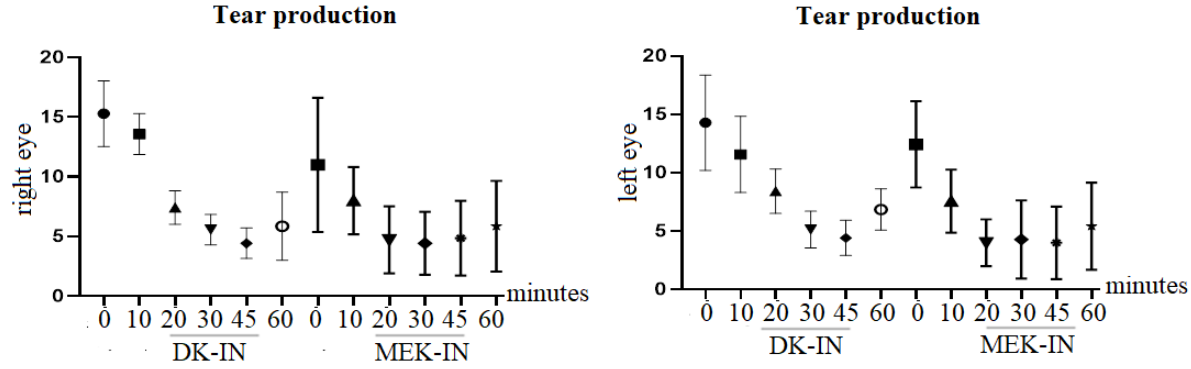

Figure 4 The effects of intranasal applications of drugs on tears volume in bot.

Discussion

Dogs tolerated the administration of the MEK and DK combinations with ease. The administration method had no impact on the anesthetic parameters. However, when the drug combination was given IN, recovery was noticeably quicker. This might be because the nasal mucosa has good vascularization, resulting in the drugs being absorbed quickly (Grassin *et al*., 2012).

The lack of comparison of the degree of anesthesia when the MEK and DK combinations were administered by the IN and IM routes was one of the study's limitations. There is a need for further research on the IN administration of these drug combination and its impact on intraocular pressure and tear production.

In dogs, intraocular pressure and corneal health are closely related. The cornea is the transparent outermost layer of the eye that plays a crucial role in maintaining the structural integrity and optical clarity of the eye. Changes in IOP can have significant implications for corneal health (Bozkan *et al*. 2022). Regarding the measurement time of intraocular pressure, it is essential to consider that it can vary throughout the day in dogs. Diurnal fluctuations in intraocular pressure have been observed in both healthy dogs and those with ocular diseases. The highest intraocular pressure values are typically observed during the daytime, while lower values are seen at night (Almeida *et al*. 2013). The results of this study showed that the mean baseline intraocular pressure was 15.71 (±1.52) mmHg in IM applications and 19.42 (±2.02) mmHg in İN applications. Especially in MEK-IM applications, significant changes were observed compared to baseline. Thus, MEK was determined to increase intraocular pressure in IM applications. Kibar *et al*., (2022) also found similar findings. Bozkan *et al*., (2022) determined that the IM application of MEK in buzzards resulted in a decrease in intraocular pressure values. Mrazova *et al*. (2018), reported that only the administration of MEK reduced intraocular pressure in dogs. The increase in intraocular pressure is due to ketamine, as stated in the literature (Kovalcuka *et al*., 2012). In DEK-IM applications, although significant changes were observed in the first 20-30 minutes relative to the baseline, it was observed that they returned to baseline values in the following minutes. Kovalcuka *et al*., (2012) reported that intraocular pressure increased 10 minutes after diazepam injection but returned to baseline values after 45 minutes in dogs. Smith *et al*., (2019) found that intraocular pressure increased immediately after DEK-IM applications. Similar to ketamine, diazepam has been demonstrated to elevate canine short-term intraocular pressure. There was no difference between IM applications for the right and left eyes.

The findings of this study demonstrated that the mean baseline intraocular pressure was 19.42 (±2.02) mmHg in IN applications. There is no statistical difference between the groups in terms of intraocular pressure in the applications of DEK-IN and MEK-IN (p>0.05). Yanmaz *et al*. (2016) in their study on intraocular pressure of cats showed that IN combinations of zolazepam and tiletamine did not make a significant difference compared to IM administrations. For both eyes there was no difference between IN and IM administrations of DEK (p>0.05).

The MEK-IM group was found an increase, whereas the IN group saw a decrease in comparison to baseline for both eyes. Despite the fact that ketamine raises intraocular pressure, the drop from baseline in MEK-IN administration is regarded as significant.

Tear production is important for maintaining the health of the eyes and preventing dryness and irritation. In general, tear production tends to be highest during a dog's younger years and gradually decreases with age. Puppies typically have well-developed tear glands and produce an adequate amount of tears. It's important to note that not all geriatric dogs will develop decreased tear production or dry eye. Tear production can vary among different breeds (Sanchez *et al*. 2006). Based on the information provided, the average age of the animals in our study is 18.5 ± 10.2 months old, and they are identified as twenty eight sexually intact mixed-breed dogs. There were no appreciable differences in tear production and age of the dogs in the study.

Aqueous tear production is frequently assessed using STT strips. The STT-I meaasures both reflex tearing brought on by contact between the paper strip and the ocular surface and basal lacrimal production. After applying topical anesthetic to the ocular surface and using a cotton swab to dry the lower conjunctival fornix, the STT II is done to ascertain basal values for tear formation (Sanchez *et al*. 2006). There is a range of results reported for adult canine STT-I values including 21.3 ± 3.8 mm/min (Wyman *et al*., 1995) 18.89 ± 2.62 mm/min (Saito and Kotani 2001) and 18.64 ± 4.471 mm/min (Hirsh and Raswan 1995).

It is known that ketamine increases the STT-I compared to the basal value (Abdelhakiem *et al*., 2019). However, in the study conducted by Dipietro *et al*., (2015), it was observed that when used in combination with medetomidine, ketamine did not increase STT-I as it did when used alone but rather decreased it. These results suggest that the use of medetomidine and ketamine together can inhibit tear production. In a similar study conducted by Sanchez *et al*., (2006), they reported that medetomidine decreased the STT-I after IM in dogs. Several drug combinations, including acepromazine - oxymorphone, diazepam - butorphanol, and xylazine - butorphanol, were found to significantly lower STT-I values from baseline in a study by Dodam *et al*., (1998). However Ghaffari *et al*., (2009) reported that, there were no significant changes in the STT values observed in the rabbits treated with diazepam. In the study, for any treatment, there were no appreciable differences in STT-I values between the right and left eyes. Additionally, a reduction in tear production was observed in the MEK-IM group in our study, which is consistent with literature data. A similar decrease was observed in the DEK-IM group as well. However, the reduction was not as dominant as in the MEK-IM and IN group. In the application of drugs via the IN route, no statistical difference is observed between the right and left eye and there is also no statistical difference between them in IM applications. Both drugs have caused a decrease in tear production in IN applications. However, in the first 20 minutes, the DEK has been less effective than the MEK in reducing tear production.

In conclusion, this study looked at the effects of intranasal medetomidine and diazepam combined with ketamine on tear production and intraocular pressure in dogs. Dogs received the drug combination through intranasal or intramuscular injections. The results showed that the IN administration was quicker and caused less pain in the dogs. The drug combination caused an increase in intraocular pressure in IM applications but not in IN applications. The combination also caused a decrease in tear production, especially in IM applications. The researchers concluded that IN administration of the drugs was quicker and had fewer side effects.

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