

Effects of Systemically Used Midazolam, Ketamine and Isoflurane Anesthetic Agents on Intraocular Pressure and Tear Production in Rabbits

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Abstract: The aim of this study was to determine of the effects of midazolam, ketamine and isoflurane anesthetic agents on tear production and intraocular pressure in rabbits. In this study twenty healthy (n=20) male white New Zealand rabbits (mean weight 2.20 ± 0.50 kg, age 16 weeks) were used. Anesthesia was performed intramuscular (IM) midazolam 3 mg/kg, and ketamine 30 mg/kg in group I. In second group (Group II), after midazolam and ketamine injections isoflurane 2% was used for general anesthesia. After anesthesia means intraocular pressure (IOP) decreased in both groups. Intraocular pressure in first group (Group I) was 10.3 ± 0.85 mmHg (right eyes), 11.4 ± 0.95 mmHg (left eyes) while it was 8.5 ± 0.85 mmHg (right eyes), 8.3 ± 0.85 mmHg (left eyes) n group II. The result of this study show that systemically used midazolam, ketamine and isoflurane anesthetic agents decrease IOP and tear secretion in rabbits.

Keywords: Anesthesia, Intraocular pressure, Rabbit, Tear production.

Tavşanlarda Sistemik Olarak Kullanılan Midazolam, Ketamin ve İsofluranın Gözyaşı Üretimi ve Göziçi Basıncı Üzerine Olan Etkilerinin Deneysel Olarak Araştırılması

Özet: Bu çalışmanın amacı; tavşanlarda midazolam, ketamin ve isofluran anestezi ajanlarının gözyaşı üretimi ve göziçi basıncı üzerine olan etkilerini belirlemektir. Bu çalışmada yirmi adet (n = 20) sağlıklı, (ortalama ağırlıkları 2.20 ± 0.50 kg, yaşları 16 hafta) erkek Yeni Zelanda tavşanı kullanıldı. Birinci grupta intramuskuler (İM) midazolam 3mg/kg, ve ketamine İM 30 mg/ kg uygulanarak anestezi sağlandı. İkinci grupta (Grup 2), midazolam ve ketamine enjeksiyonundan sonra genel anestezi için %2'lik İsofluran uygulandı. Anesteziden sonra her iki grupta da intraoküler basınç değerlerinde düşüşler görüldü. Birinci grupta (Grup I) göz içi basıncı sağ gözde 10.3 ± 0.85 mmHg ölçülürken, sol gözde 11.4 ± 0.95 mmHg olarak ölçüldü. İkinci grupta (Grup II) göziçi basıncı sağ gözde 8.5 ± 0.85 mmHg ölçülürken, sol gözde 8.3 ± 0.85 mmHg (sol göz) vardı. Bu çalışmanın sonucunda tavşanlarda sistemik olarak kullanılan midazolam, ketamin ve isofluran gibi anestezi ajanlarının GİB ve gözyaşı salgısını azalttığı görüldü.

Anahtar Kelimeler: Anestezi, Göz içi basıncı, Tavşan, Gözyaşı üretimi.

Introduction

Intraocular pressure (IOP) is defined as equilibrium production and drainage of humor aqueous in the ciliary processes of the eye. But the control and regulating mechanism of IOP are not fully understood (Ofri et al., 2008; Reitsamer et al., 2004). The conventional (iridocorneal angle) and unconventional (uveoscleral) pathways have an active role in drainage of humor aqueous. It is necessary to nourishment of the avascular intraocular tissues which named cornea and lens (Meekins et al., 2016). The Schirmer tear test (STT) is generally used to evaluate basal and reflex tear production. Since the introduction of applanation tonometer, the measurements of IOP and STT have become common procedure in routine ocular

examinations. Because the ocular diseases can cause significant alterations both IOP and tear production (Gianetto et al., 2009; Swinger et al., 2009). Except these reasons, day time, drugs, age, ocular inflammation, blood circulating and anesthesia can cause to alteration of IOP and tear production (Ofri et al., 2008; Pintor et al., 2001).

In veterinary medicine ketamine hydrochloride and benzodiazepine combinations are usually used for general anesthesia. Ketamine hydrochloride induces increase in cerebral blood flow, intracranial pressure and IOP as a result of cerebral vasodilatation. Benzodiazepines decrease the systemic arterial blood pressure, cerebral blood flow, cerebral pressure and IOP (Hazra et al., 2011;

Kovaljuva and Birgele, 2011). Potent inhalation anesthetics are used widely for maintenance of general anesthesia because of their ease of administration and practicable intraoperative and recovery characteristics. But they decrease IOP by lowering humor aqueous rate formation and increasing the trabecular outflow facility (Sator et al., 1998; Sator- Katzenschlager et al., 2002).

The use of anesthetic agents may cause to change in intraocular pressure (IOP) and tear production (TP) values. In animals chemical restraint is usually required to reduce stress, pain, motion and the other manipulations (Santangelo et al., 2002). The sedatives, tranquilizers and anesthetic drugs can cause lowered IOP. They reduce extra ocular and adnexal muscle tone (Pintor et al., 2001). The aim of this study was to determine of the effects of midazolam, ketamine and isoflurane anesthetic agents on tear secretion and intraocular pressure in normal laboratory New Zealand white rabbits.

Material and Method

Erciyes University local board of ethics committee for animal experiments has approved the study protocol of this research (EUHADYEK decision no: 17/047). In this study twenty healthy male white New Zealand rabbits (Mean weight 2.20 ± 0.50 kg, age 16 weeks) were used. The animals were housed as separate standard cages with no bedding, maintained on a 12-hours light/dark cycle (light from 6 a.m. to 6 p.m.), 21 ± 1 °C temperature in Erciyes University Veterinary Faculty Clinic. The rabbits were fed normal pellet diet and given water ad libitum. Before the application of anesthetic agents the rabbits were randomly separated into two groups of ten. The general health condition, direct and indirect ocular examinations were done prior to IOP (TONOVET, RBT, IcareVet, Helsinki, Finland) and STT I (Vet Eickemeyer, Schimer Strip, Ophthalmic strips) measurements.

Anesthesia was performed intramuscular (IM) Midazolam (3 mg/kg, IM, Demizolam 5 mg/5mL, DEM, TURKEY) and ketamine Hcl (30 mg/kg, IM, 10% Ketasol, Interhas, Turkey) in first group. In second group, after midazolam (3 mg/kg, IM) and ketamine (30 mg/kg, IM) injections ear pinching, palpebral, corneal and pedal reflexes were controlled. Absence of these reflex responses the head and neck was held in atlantooccipital extension to displace the epiglottis for endotracheal intubation. Local anesthetic lidocaine Hcl (Vemcaine 10% pump spray, VEM ilaç, Turkey) was sprayed into to larynx than the mouth was opened. Neonatal endotracheal tube (Internal 2.5 mm

diameter, Chilecom, China) was placed into the larynx with the help of an otoscope (Gowllands Croydon, UK). After that the tube was connected to inhalation anesthetic machine (SMS 2000, Turkey). Isoflurane 2% (Forane, 250 mL, Baxter, USA) was used for general anesthesia. Heart rate, respiratory rate and body temperature were measured manually during anesthesia. After thirty minutes of ketamine injection in first group and isoflurane anesthesia in second group, IOP and STT measured again.

The Measurement: The measurements of IOP and STT were done by the same examiner for each group. All animals were restrained in standing position. During restraint no pressure was applied on neck, head, throat and eyelids. The STTs were placed in the central aspect of ventral conjunctival sacs for one minute. TP as indicated on the strip was recorded in mm/minute immediately up on removal from the sacs. Following removal of strips calibrated Tono Vet (P mode) was performed on each eye. Tono Vet measures IOP by an original method as impact-multiplication (31). Local anesthesia is not necessary before use. The 50 mm stainless steel probe includes 2 coaxial magnet systems with a diameter of 1x1.4 mm. The measurement is made by keeping the tip of the probe at 4-8 mm away from the cornea. During measurement, the voltage is detected by the sensor and converted into a digital signal. This voltage occurs in the magnetic system resulting of contact the probe to the cornea. In this way, the measurement is completed by reading from the screen (Ollivier et al., 2008, Sarıcaoğlu, 2010). The measurements were repeated if the instrument indicated an unacceptable standard deviation as described in the manual. Anesthetic eye drop was not used before the measurements. They were recorded at the same time of day (09.00-10.00).

Statistical Analysis: The obtained datas were statistically evaluated. They were analyzed using Shapiro wilk test for normality than two-way repeated measure ANOVA followed by Tukey or Bonferroni's significant difference tests used to compare intragroup and between group's values. Statistical significance was accepted $p < 0.05$. All analyses were performed using IBM SPSS statistics 21 program. Results are presented as Mean \pm Standart error (SE).

Results

Before anesthetic application, mean IOP values of first group was 14.2 ± 0.75 mmHg (right eyes)

and 14 ± 0.80 mmHg for the left eyes and, 12.0 ± 0.75 mmHg for the right eyes and 12.2 ± 0.80 mmHg the left eyes in the second group. In both groups there was no significant difference obtained in IOP between left and right eyes. The baseline values (preanesthetic measurement) of first group were higher than second group. After anesthesia

mean IOP decreased in both groups. In first group there were 10.3 ± 0.85 mmHg (right eyes), 11.4 ± 0.95 mmHg (left eyes). In second group there were 8.5 ± 0.85 mmHg (right eyes), 8.3 ± 0.85 mmHg (left eyes). The measured differences of values in both groups were statically significant ($p < 0.05$) (Table 1).

Table 1. Preanesthetic and postanesthetic measurements of IOP and TP.

	Preanaesthesia			Postanaesthesia	
	Eye	IOP	STT	IOP	STT
Group 1	L	$14 \pm 0.80^*$	$12.12 \pm 0.70^{*,a}$	$11.4 \pm 0.95^{*,a}$	$7.62 \pm 0.85^*$
	R	$14.2 \pm 0.75^*$	$13.25 \pm 0.70^{*,a}$	$10.3 \pm 0.85^*$	$9.87 \pm 0.67^{*,a}$
Group 2	L	$12.2 \pm 0.80^*$	$8.12 \pm 0.70^{*,a}$	$8.3 \pm 0.85^{*,a}$	$5.37 \pm 0.85^*$
	R	$12 \pm 0.75^*$	$7.75 \pm 0.70^{*,a}$	$8.5 \pm 0.85^*$	$5.62 \pm 0.70^{*,a}$

IOP: intraocular pressure, STT: schirmer test strips, L: left, R: right, *: $P < 0.05$, a: significantly differences between groups ($P < 0.05$).

The mean value of STT before anesthesia in first group was 13.25 ± 0.70 mL/minute for the right eyes, 12.25 ± 0.70 mL/minute for the left eyes, and, 7.75 ± 0.70 mL/minute for the right eyes and 8.12 ± 0.70 mL/minute for the left eyes in the second group. In both group there was significant difference in STT measurements between left and right eyes ($p < 0.05$). In first group baseline values (preanesthetic measurement) are higher than second group ($p < 0.05$). After anesthesia mean STT measurement decreased in both group and this was statically significant ($p < 0.05$) (Table 1). There was no complication detected and additional injection required in anesthesia.

Discussions

Most anesthetic and hypnotic agents including volatile agents, α -2 adrenoreceptor agonists, ketamine and benzodiazepines have been reported to decrease IOP in humans and domestics (Holve et al., 2013; Sator et al., 1998). The rabbits are docile, easy handle and economical in comparison than the other domestics. In addition, the large size of rabbits eye is ideal and suitable for testing of new technologies in ophthalmic surgery (Hazra et al., 2011). In the present study sedative and general anesthetics were performed to rabbits for investigation of their effects on IOP and TP. The appropriate measurement rebound tonometric method was preferred for IOP in rabbits. To decrease the error values when measuring IOP and TP, the measurements were done with same position and by person. STT is a common method of tear measurement in domestics. It is considered gold standard in veterinary medicine for determining qualitative TP than the other methods

(Ofri et al., 2001; Swinger et al., 2009). We used the STT I test for determining qualitative TP in our study. It has been reported that the normal intraocular pressure measurements using Tonovet in rabbits are ranged between 9.51 ± 2.62 mm Hg (Hazra et al., 2011). In this study, the mean intraocular pressures of baseline values for all rabbits were lower than 9.51 ± 2.62 mm Hg. The preanesthetic measurements values of IOP and TP in left and right eyes were different in groups. Previous studies demonstrated that IOP and TP are affected by the daily time, light cycle and sex in domestics (Alkan et al., 2004; Gianetto et al., 2009). This difference was thought to be due to changes in intraocular pressures and tear secretion during the day time and it supported the previous studies. In ophthalmic surgery general anesthetics are commonly used for central position of the globe, relaxation of the extra ocular muscles, and maintenance of intraocular pressure. In rabbits several anesthetic combinations are used. Xylazine-ketamine anesthetic combination is the popular anesthetics used in rabbit general anesthesia and ocular surgery because of increasing IOP (Dogan et al., 2016; Hazra et al., 2011). In the present study ketamine-midazolam and isoflurane combinations were performed and compared the measurements of IOP and TP.

Holve et al. (2013), reported that intravenous and intramuscular xylazine-ketamine anesthetic combinations significantly decreased IOP from baseline at 10 min after administration. This effect was maintained 25 min after intravenous administration and for at least 45 min after intramuscular administration. The anesthetic effects on IOP and TP investigations are continuing in animals. Inhalation anesthetics such as halothane

and isoflurane decrease IOP by lowering the formation rate of humor aqueous and increasing the trabecular outflow facility (Grundon et al., 2011; Riberio et al., 2010; Sator et al., 1998; Sator-Katzenschlager et al., 2002). The values of IOP and TP were compared and postanesthetic values were significantly lower than baselines in the current study. This assessment showed that midazolam-ketamine and isoflurane combinations decrease the IOP and TP, the effects maintained 30 min during anesthesia. Most anesthetics reduce IOP via their central depressive effects on central nervous system (Schäfer et al., 2002). Ketamine has been shown to increase IOP in cats, dogs and rabbits when used a sole agent for induction of anesthesia (Ghaffari and Moghaddassi, 2010). IOP is determined by the rate of production of humor aqueous, vitreous volume and external pressure. In our study, the anesthetic agents decreased the IOP and TP. The decreases of IOP and TP are more in second group than first group. This was thought due to more powerful effect of isoflurane on central nervous system. Our study supported the using ketamine with the other anesthetics IOP and TP production not increase.

The result of this study show that systemically used midazolam, ketamine and isoflurane anesthetic agents decrease IOP and tear production in rabbits. The anesthesia and anesthetic agents' choice of the animals with eye problems should be careful. Because the increases and decreases of IOP and TP are very important in ophthalmic surgery. Our results suggest that midazolam-ketamine and isoflurane are ideal and safe anesthetic agent for ophthalmic surgery in animals.

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