

# The Effects of Propofol-Sevoflurane, Midazolam-Sevoflurane and Medetomidine-Ketamine-Sevoflurane Anesthetic Combinations on Intraocular Pressure in Rabbits <sup>[1]</sup>

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## Abstract

Intraocular pressure (IOP) is dependent on equilibrium between the rate of formation and outflow humor aqueous in the eye. Determination of IOP is one of the most important points and a very useful parameter in ophthalmic surgery. The aim of this study was to compare the effects of propofol + sevoflurane, midazolam + sevoflurane, medetomidine + ketamine + sevoflurane anesthetic combinations on IOP, and to find out suitable anesthesia protocol in rabbits for ophthalmic surgery. For this purpose, a total of 40 healthy four months old New Zealand female rabbits (Mean weight  $2.34 \pm 0.67$  kg) were used as subjects. The animals were divided into four groups; propofol + sevoflurane (PS), midazolam + sevoflurane (MS), medetomidine + ketamine + sevoflurane (MKS), and control (C), each having 10 rabbits. The IOP was measured from the right eyes before injection of anesthetics (0. min), during sevoflurane anesthesia at 5<sup>th</sup>, 10<sup>th</sup>, 15<sup>th</sup>, 20<sup>th</sup>, 25<sup>th</sup> and 30<sup>th</sup> min, and post anesthesia at 10<sup>th</sup>, 20<sup>th</sup>, 30<sup>th</sup>, 60<sup>th</sup>, 120<sup>th</sup> min and 24 h in the study groups. In PS group; IOP values decreased during anesthesia between 5<sup>th</sup> and 25<sup>th</sup> min. In general, the measured IOP values of MS group were higher than 0<sup>th</sup> min, and the increases continued at 10<sup>th</sup> min in post anesthesia. The measured IOP values of MKS group during anesthesia were higher than other time points. As a result of this study PS anesthetic combination is an ideal anesthesia for ocular surgery in rabbits. The increase in IOP is undesirable in ocular surgery due to operative and postoperative complications. It was also concluded that investigating the effects of anesthetic combination on IOP should continue in more detailed researches including in different species.

**Keywords:** Propofol, Sevoflurane, Midazolam, Medetomidine, Ketamine, Anesthesia, Intraocular pressure, Rabbit

## Tavşanlarda Propofol-Sevofluran, Midazolam-Sevofluran ve Medetomidin-Ketamin-Sevofluran Anestezi Kombinasyonlarının Göz İçi Basıncına Etkileri

### Öz

Göz içi basıncı (GİB), humor aközün dengeli bir şekilde üretimi ve drenajına bağlı olarak şekillenmektedir. GİB, oftalmik cerrahide önemli ve yararlı parametreler arasında yer almaktadır. Bu çalışmanın amacı tavşanlarda propofol + sevofluran, midazolam + sevofluran ve medetomidine + ketamin + sevofluran anestezi kombinasyonlarının GİB üzerine etkilerinin karşılaştırılması, oftalmik cerrahi için optimal anestezi protokolünün araştırılmasıdır. Çalışmada 40 adet 4 aylık sağlıklı dişi (ortalama ağırlık  $2.34 \pm 0.67$  kg) Yeni Zelanda tavşanı kullanıldı. Hayvanlar; propofol + sevofluran (PS), midazolam + sevofluran (MS), medetomidine + ketamin + sevofluran (MKS) ve kontrol (K) grubu şeklinde her bir grupta 10 adet tavşan olmak üzere toplam dört gruba ayrıldı. GİB ölçümleri çalışma gruplarında sağ gözden anestezi öncesi (0. dk), sevofluran anestezi süresi boyunca 5, 10, 15, 20, 25 ve 30. dakikalarda ve anestezi sonrası 10, 20, 30, 60, 120. dakikalarda ve 24 saat sonra yapıldı. PS grubunda anestezi süresi boyunca 5 ve 25. dk'lar arasında GİB değerlerinde azalma görüldü. Genel olarak MS grubunun ölçülen GİB değerlerinin 0. dk'dan yüksek seyrettiği ve anestezi sonrası 10. dk'ya kadar artışın devam ettiği görüldü. MKS grubunun anestezi sırasında ölçülen GİB değerinin anestezi öncesi ve sonrası değerlerden yüksek olduğu tespit edildi. Bu çalışma sonunda PS kombinasyonunun göz cerrahisi için daha uygun bir anestezi kombinasyonu olduğu görüldü. Oküler cerrahide GİB değerinin artışı operatif ve postoperatif olarak istenmeyen bir durumdur. Özellikle GİB üzerine anestezi kombinasyonlarının etkileri daha ayrıntılı ve türlere özel olarak araştırılması gerekmektedir.

**Anahtar sözcükler:** Propofol, Sevoflurane, Midazolam, Medetomidine, Ketamine, Anestezi, İntraküler basınç, Tavşan



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## INTRODUCTION

The rabbit is widely used at researches on ophthalmic surgery due to the large size of its eyes, docile character, easiness at handle and economy. The use of general anesthesia is very important in ocular surgery for central positioning of the globe, relaxation of the extra ocular muscle and maintenance of intraocular pressure<sup>[1]</sup>.

Intraocular pressure (IOP) is dependent on equilibrium between the rate of formation and outflow humor aqueous in the eye<sup>[2]</sup>. Determining IOP is one of the most important points and is a very useful parameter in ophthalmic surgery<sup>[3]</sup>. However, the use of certain drugs such as general anesthetics may cause an alteration in IOP. Alteration of IOP may cause complication after ophthalmic surgery. Because of this, investigations on an ideal anesthetic procedure for ophthalmic surgery were carried out by researchers<sup>[2,4,5]</sup>.

Ketamine and propofol are widely used as anesthetic agents in rabbits. But their effects on IOP are different. For instance, propofol reduces IOP while ketamine increases IOP<sup>[6,7]</sup>. Midazolam causes decrease in IOP and has been used in general with ketamine in ocular surgery<sup>[1,8]</sup>. Medetomidine produces sedation and hypertension depending on the administration routes in animals. The prior studies have been demonstrated that medetomidine lowers the IOP after topical application in normotensive cats and rabbits<sup>[9]</sup>. Sevoflurane is an inhalation anesthetic and used widely for the maintenance of general anesthesia. Induction and recovery of sevoflurane anesthesia are rapid and safe in comparison to injectable anesthetics<sup>[10]</sup>. Furthermore, potent inhalation anesthetics decrease IOP by lowering humor aqueous rate formation and increase the trabecular outflow facility<sup>[2]</sup>.

The aim of this study was to compare the effects of propofol + sevoflurane, midazolam + sevoflurane, medetomidine + ketamine + sevoflurane anesthetic combinations on IOP, and to find out suitable anesthesia protocol in rabbits for ophthalmic surgery.

## MATERIAL and METHODS

### Ethical Approval

Erciyes University Local Board of Ethics Committee for animal experiments has approved the study protocol of this research (EUHADYEK, decision no: 14/140).

### Animals

Forty healthy four months old New Zealand female rabbits (Mean weight  $2.34 \pm 0.67$  kg) were used as the study materials. Each of rabbits was kept in a separate, maintained on a 12 h light/dark cage, cycle,  $21 \pm 1^\circ\text{C}$  temperature in the Balıkesir University, Veterinary Faculty, Surgery

Department, before the study. The rabbits were fed with normal pellet diet and given water *ad libitum*. The animals were divided into four groups; as propofol + sevoflurane (PS), midazolam + sevoflurane (MS), medetomidine + ketamine + sevoflurane (MKS) and control (C) groups, each having 10 rabbits. Prior to anesthesia, the animals were transported to the examination table, and waited about 10 min to calm for accommodation to the environment conditions. Erol et al.<sup>[11]</sup> measured IOP with TonoVet from left and right eyes prior to anesthesia in healthy rabbits. They did not find significant differences between left and right eyes for IOP values. Therefore, we preferred the right eye for all the assessments. IOP was measured by TonoVet (RBT, I care Vet, Helsinki, Finland) with five repetitive measurements from right eyes (0. min) in all animals (Fig. 1). Mean values of repetitive measurements were recorded.

### Anesthesia Protocol

In PS group; 7 mg/kg Propofol (Propofol 10 mg/mL, PROPOFOL ABBOTT, Abbott Laboratories, USA) was applied intravenously (IV) from right *vena auricularis*. In MS group 0.3 mg/kg midazolam (Demizolam, DEM, Turkey) and in MKS group 0.3 mg/kg medetomidine (Domitor, Zoetis, Turkey) were applied intramuscularly (IM). After 5 min, 30 mg/kg ketamine (Ketasol 10%, Interhas, Turkey) was applied IM in MKS group. Group C received no anesthetic.

For endotracheal intubation of animals, the head and neck were held in atlantooccipital extension to displace the epiglottis to provide a straight passage for the endotracheal tube. The mouth was opened and local anesthetic, 2% lidocaine HCl, was sprayed into larynx. The neonatal intubation tube (2.5 mm diameter) was placed into trachea. After intubation the tube was connected to anesthetic machine (Non-breathing system, Magill circuit) and anesthesia was maintained 4% sevoflurane during 30 min in all study groups. At the end of anesthesia, the anesthetic machine was shut down and the system was washed with oxygen, then oxygen support was carried out for 2 min. The animals were followed until chewing reflex returned, then extubated.



Fig 1. IOP measurement before anesthesia

### IOP Measurement

All animals were placed on the operation table dorso-ventrally and fixed with hypoallergenic patch. The immobilization of animals was achieved by fixation, and the tightly fixing was avoided for the IOP measurement (Fig. 2). The IOP was measured from right eyes before injectable anesthesia (0. min), during sevoflurane anesthesia at 5<sup>th</sup>, 10<sup>th</sup>, 15<sup>th</sup>, 20<sup>th</sup>, 25<sup>th</sup> and 30. min, and post anesthesia (after extubation) at 10<sup>th</sup>, 20<sup>th</sup>, 30<sup>th</sup>, 60<sup>th</sup>, 120. min and 24 h after in study groups. In group C, at the same time intervals IOP were also measured.

### Statistical Analysis

The obtained data were statistically evaluated with IBM SPSS Statistics 21.0 (USA) program. Shapiro-Wilk test was used for normality. One-way ANOVA was used to compare values between groups; Student-Newman-Keuls test was used for multiple comparisons. The differences between repeated measurements were analyzed by repeated measure variance analysis and Bonferroni test.  $P < 0.05$  was



Fig 2. IOP measurement during anesthesia

accepted statistical significance and results are presented as Mean  $\pm$  Standard error (SE).

## RESULTS

In-group measurements and statistical evaluations of IOP are presented in Table 1. In PS group IOP values decreased during anesthesia between 5 and 25 min. The decreases between 0 and at 5<sup>th</sup>, 10<sup>th</sup> and 25<sup>th</sup> min during anesthesia were significant ( $P < 0.05$ ). In post anesthesia time intervals; significant alterations were recorded between 30 and 120<sup>th</sup> min ( $P < 0.05$ ). The measured value of IOP at 120<sup>th</sup> min was higher than the values measured at 30<sup>th</sup> min.

In general, the measured IOP values obtained from MS group were higher than the values obtained at 0 time, and the increase continued at 10<sup>th</sup> min during post anesthesia, which was statistically significant ( $P < 0.05$ ). At 30<sup>th</sup> min in post anesthesia the value of IOP approached to normal. Furthermore, the recorded values between 5<sup>th</sup> min during anesthesia and post anesthetic 30<sup>th</sup> min were higher than 0 time. The alteration in IOP were detected in MKS group. During anesthesia the measured values of IOP were higher than 0 time which were statistically different during anesthesia (between 5<sup>th</sup>, 10<sup>th</sup> and 15<sup>th</sup>, 20<sup>th</sup>, 30<sup>th</sup>) ( $P < 0.05$ ). In group C, there were some decreases and increases detected between measurements, but they were not significant.

When values obtain from different groups evaluated (Table 2), MS and MKS values were higher and statistically different than PS group ( $P < 0.05$ ). Furthermore, increases in IOP were higher in MS than MKS group. In post anesthesia intervals the lowest values were recorded in PS group. Generally, IOP values approached to normal values at 60<sup>th</sup> min post anesthesia in MS and MKS groups. At the same time, it was also low in PS group.

Table 1. Ingroup comparison of IOP measurements (Mean $\pm$ SE)

Groups	0 <sup>th</sup> min	5 <sup>th</sup> min	10 <sup>th</sup> min	15 <sup>th</sup> min	20 <sup>th</sup> min	25 <sup>th</sup> min	30 <sup>th</sup> min	PA 10 <sup>th</sup> min	PA 20 <sup>th</sup> min	PA 30 <sup>th</sup> min	PA 60 <sup>th</sup> min	PA 120 <sup>th</sup> min	PA 24 <sup>h</sup>
PS	13.1 $\pm$ 2.18	10.6 $\pm$ 0.96 <sup>b</sup>	10.4 $\pm$ 0.84 <sup>b</sup>	9.7 $\pm$ 1.41 <sup>ab</sup>	9.3 $\pm$ 1.33 <sup>ab</sup>	8.6 $\pm$ 1.34 <sup>a</sup>	9.2 $\pm$ 2.2 <sup>ab</sup>	8.6 $\pm$ 2.06 <sup>a</sup>	9.1 $\pm$ 2.51 <sup>ab</sup>	8.7 $\pm$ 1.25 <sup>a</sup>	8.8 $\pm$ 2.78 <sup>a</sup>	10.4 $\pm$ 2.06 <sup>b</sup>	14.1 $\pm$ 1.91
MS	11.2 $\pm$ 2.82	22.5 $\pm$ 5.60 <sup>a</sup>	21.2 $\pm$ 6.01 <sup>a</sup>	18.9 $\pm$ 5.38 <sup>a</sup>	17.8 $\pm$ 5.18 <sup>a</sup>	18.1 $\pm$ 5.30 <sup>a</sup>	19.2 $\pm$ 5.41 <sup>a</sup>	13.0 $\pm$ 2.40 <sup>b</sup>	12.1 $\pm$ 2.51	11.4 $\pm$ 2.98	11.1 $\pm$ 2.46	11.7 $\pm$ 1.82	11.9 $\pm$ 2.13
MKS	13.1 $\pm$ 2.07	19.1 $\pm$ 4.58 <sup>a</sup>	18.6 $\pm$ 5.66 <sup>a</sup>	17.9 $\pm$ 6.04 <sup>b</sup>	17.3 $\pm$ 5.16 <sup>b</sup>	17.1 $\pm$ 5.46 <sup>b</sup>	17.8 $\pm$ 5.61 <sup>b</sup>	11.2 $\pm$ 2.14	11.2 $\pm$ 3.15	11.7 $\pm$ 2.71	12.4 $\pm$ 2.75	12.3 $\pm$ 3.02	11.1 $\pm$ 2.60
C	13.2 $\pm$ 1.68	13.6 $\pm$ 1.57	14.3 $\pm$ 2.26	14.3 $\pm$ 2.71	13.8 $\pm$ 1.98	14.0 $\pm$ 1.63	14.6 $\pm$ 1.89	14.6 $\pm$ 1.34	14.3 $\pm$ 1.41	14.10 $\pm$ 2.18	13.4 $\pm$ 1.83	12.9 $\pm$ 2.07	13.3 $\pm$ 2.21

PS: Propofol + Sevoflurane, MS: Midazolam + Sevoflurane, MKS: Medetomidine + Ketamine + Sevoflurane, PA: Post anesthesia, <sup>ab</sup> in same line is statistically significant ( $P < 0.05$ )

Table 2. Between groups comparison of IOP measurements (Mean $\pm$ SE)

Groups	0 <sup>th</sup> min	5 <sup>th</sup> min	10 <sup>th</sup> min	15 <sup>th</sup> min	20 <sup>th</sup> min	25 <sup>th</sup> min	30 <sup>th</sup> min	PA 10 <sup>th</sup> min	PA 20 <sup>th</sup> min	PA 30 <sup>th</sup> min	PA 60 <sup>th</sup> min	PA 120 <sup>th</sup> min	PA 24 <sup>h</sup>
PS	13.1 $\pm$ 2.18	10.6 $\pm$ 0.96	10.4 $\pm$ 0.84	9.7 $\pm$ 1.41	9.3 $\pm$ 1.33	8.6 $\pm$ 1.34	9.2 $\pm$ 2.2	8.6 $\pm$ 2.06	9.1 $\pm$ 2.51	8.7 $\pm$ 1.25	8.8 $\pm$ 2.78	10.4 $\pm$ 2.06	14.1 $\pm$ 1.91
MS	11.2 $\pm$ 2.82	22.5 $\pm$ 5.60 <sup>*</sup>	21.2 $\pm$ 6.01 <sup>*</sup>	18.9 $\pm$ 5.38 <sup>*</sup>	17.8 $\pm$ 5.18 <sup>*</sup>	18.1 $\pm$ 5.30 <sup>*</sup>	19.2 $\pm$ 5.41 <sup>*</sup>	13.0 $\pm$ 2.40	12.1 $\pm$ 2.51	11.4 $\pm$ 2.98	11.1 $\pm$ 2.46	11.7 $\pm$ 1.82	11.9 $\pm$ 2.13
MKS	13.1 $\pm$ 2.07	19.1 $\pm$ 4.58 <sup>*</sup>	18.6 $\pm$ 5.66 <sup>*</sup>	17.9 $\pm$ 6.04 <sup>*</sup>	17.3 $\pm$ 5.16 <sup>*</sup>	17.1 $\pm$ 5.46 <sup>*</sup>	17.8 $\pm$ 5.61 <sup>*</sup>	11.2 $\pm$ 2.14	11.2 $\pm$ 3.15	11.7 $\pm$ 2.71	12.4 $\pm$ 2.75	12.3 $\pm$ 3.02	11.1 $\pm$ 2.60
C	13.2 $\pm$ 1.68	13.6 $\pm$ 1.57	14.3 $\pm$ 2.26	14.3 $\pm$ 2.71	13.8 $\pm$ 1.98	14.0 $\pm$ 1.63	14.6 $\pm$ 1.89	14.6 $\pm$ 1.34	14.3 $\pm$ 1.41	14.10 $\pm$ 2.18	13.4 $\pm$ 1.83	12.9 $\pm$ 2.07	13.3 $\pm$ 2.21

PS: Propofol + Sevoflurane, MS: Midazolam + Sevoflurane, MKS: Medetomidine + Ketamine + Sevoflurane, PA: Post anesthesia, <sup>\*</sup> in same column is statistically significant ( $P < 0.05$ )

## DISCUSSION

Intraocular pressure is defined as the pressure of eye ball and its components, and the pressure against to the surrounding tunica fibrosa. It is affected by humor aqueous, choroid blood volume, volume of corpus vitreum, scleral flexibility, muscle tone surrounding the eye ball and external pressure<sup>[11]</sup>. At the same time, the laying position of the patient may cause the alteration in IOP. In the present study, the measurements of animals were done in sterno abdominal position by the same person (ME) to minimize the alterations in IOP. Blood pressure, diurnal cycle, posture and blood biochemistry may cause short time alteration in IOP. On the other hand, species, sex, age, season and weight may also affect the IOP in long time period<sup>[12-14]</sup>. In this study, same sex and species of animals were used, and the anesthesia was planned to coincide in the same hours during the day. In this way, the conditions that can cause intraocular pressure changes were minimized.

Usage of propofol for induction of anesthesia is known to reduce the intraocular pressure<sup>[6,15,16]</sup>. Sator-Katzenschlager et al.<sup>[15]</sup> emphasized that using sevoflurane and propofol anesthetic combination in humans decreases the IOP in non-ophthalmic surgery. They related this decrease to the potential effects of anesthetic agents on IOP.

Benzodiazepines such as midazolam are widely used with ketamine in laboratory animals' anesthesia. It decreases systemic arterial blood pressure, cerebral blood flow, cerebral pressure and IOP<sup>[2]</sup>. In general, benzodiazepines relax the extraocular muscles and increase outflow of humor aqueous. Thus, the relaxing and the other effects of benzodiazepines decrease the IOP. In ocular surgery, one of the essential aims of anesthetic management is to prevent the increase of IOP during anesthesia. The anesthesia related practices (Laryngoscopy, endotracheal intubation and extubation) cause increase in IOP through the stimulation of sympathetic nervous system. Additionally, hypoxia and hypercarbia also induce an increase in choroidal blood volume<sup>[17,18]</sup>. However, in the present study IOP values in MS group were higher than other groups during anesthesia. Statistically significant differences were detected among MS, PS and C groups. It has been thought that the rises in IOP at MS group might occur due to the tracheal intubation. Because benzodiazepines cause loss in airway muscle tone and results an increase in airway resistance<sup>[19]</sup>. In the present study, the intubation in MS group animals were more difficult than others. At the end of anesthesia, animals in all study groups were supported with oxygen to eliminate hypoxia and hypercarbia.

Alpha-2 adrenergic agonist such as medetomidine can affect IOP by several mechanisms. It decreases IOP by suppressing sympathetic neuronal function in rabbits<sup>[7]</sup>. Ketamine induces a dose dependent central nervous system depression that leads to a dissociative anesthesia. It increases cerebral blood volume, intracranial pressure

and cerebrospinal fluid pressure. For all these reasons, the increase in IOP is a side effect of ketamine<sup>[8]</sup>. Hofmeister et al.<sup>[20]</sup> used ketamine alone in dogs for anesthesia, and investigated alteration in the IOP. They found that ketamine increases the IOP in dogs and suggested not to use alone in patients with glaucoma risk. Furthermore, Kılıç<sup>[21]</sup> investigated the clinical effects of medetomidine + ketamine and xylazine + ketamine anesthetic combinations in rabbits. He found that the heart rate and venous partial oxygen pressure of medetomidine + ketamine groups were lower than that of xylazine + ketamine group during anesthesia. He explained this difference as the effects of medetomidine + ketamine on cardiovascular system in rabbits. The injection of ketamine (30-90 mg/kg, IM) increases 6 mmHg in IOP of rabbits that last for 2-4 h<sup>[4]</sup>. In the present study, 30 mg/kg ketamine injected IM to MKS group's animals, and the IOP increased about 6 mmHg during anesthesia. However, the increase did not continue for 2 h. In fact, the measured value at 10<sup>th</sup> min post anesthesia was lower than 0 time in MKS group. This situation showed that medetomidine causes suppression on sympathetic neuronal function in humor aqueous production and ciliary vasoconstriction in a short time period. Furthermore, reduction in IOP value at MS group at 10<sup>th</sup> min post anesthesia can be explained by the relaxing effect of midazolam on extraocular muscles and its increasing outflow effect of humor aqueous.

At the same time, sevoflurane causes dose dependent decrease in IOP<sup>[22]</sup>. In the present study, same dose sevoflurane was used in all study groups during 30 min anesthesia. The increase in IOP in MS and MKS groups supported above-mentioned literature<sup>[22]</sup>. There were no decreases recorded during sevoflurane anesthesia in MS and MKS groups. The decreases were detected only in PS group. These decreases can be explained by the effects of propofol on IOP.

As a result of this study, PS anesthetic combination is an ideal anesthesia for ocular surgery in rabbits. The increase in IOP is undesirable in ocular surgery due to operative and postoperative complications. It was also concluded that investigating the effects of anesthetic combination on IOP should continue in more detailed researches including in different species.

## CONFLICT OF INTEREST

None

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