Acta Scientiae Veterinariae, 2024. 52: 1972.

RESEARCH ARTICLE
Pub. 1972

ISSN 1679-9216

Effect of Xylazine, Midazolam and Dexmedetomidine Preanaesthetics on Changes in Intraocular Pressure in Rats

Kerem Yener, Ünal Yavuz, Ali Hayat, Kübra Dikmen İlginoğlu, Mehmet Salih Karadağ & Mehmet Sıdık Hurma

ABSTRACT

***Background*:** Intraocular pressure (IOP) is influenced by a variety of factors, including intraocular fluid volume, choroidal blood volume, and vitreous volume. Abnormal IOP can result in visual issues, with ocular hypotension potentially leading to retinal detachment and ocular hypertension, causing damage to the retina and optic nerve, which can lead to glaucoma. Anaesthetic agents and body position, such as the Trendelenburg position, can significantly affect IOP. While there is extensive research on IOP changes at various positions in humans, data on the effects of the prone and Trendelenburg positions in both human and veterinary medicine are limited. The Trendelenburg position, which involves tilting the head 15°-45° up or down, is commonly used in laparoscopic and bariatric surgeries and in veterinary procedures, such as ovariohysterectomy and castration. However, the impact of this position on IOP, particularly when combined with anaesthetics, has not been well documented. Preanaesthetic agents, such as xylazine (XYL) and dexmedetomidine (DEX), alpha-adrenoreceptor agonists, and midazolam (MID), a benzodiazepine, can influence intraocular pressure (IOP). This study evaluated the impact of these agents on IOP in Wistar albino rats positioned in reverse Trendelenburg (RTr), a common position in veterinary surgery, to assess their safe use.

***Materials, Methods & Results*:** The rats were randomly divided into 3 groups: DXM group [0.75 µg/kg, n=7], MID [5 mg/kg, n=7], and XYL [10 mg/kg, n = 7]. Intraperitoneal injections were administered, and IOP was measured using an Icare Tonovet Plus tonometer at baseline (T_0) and at intervals 5 (T_5), 10 (T_{10}), 15 (T_{15}), 30 (T_{30}), 45 (T_{45}), 60 (T_{60}), and 90 (T_{90}) min) post-anaesthesia. The rats were immobilized at a 15-degree angle for 90 min. Six consecutive IOP measurements were averaged for each time point. Sedation levels were assessed using a numerical rating scale. In-group measurements and statistical evaluations showed no significant differences at T0 between the DXM, MID, and XYL groups. A decrease in IOP was observed at T_{15}, T_{30}, T_{45}, T_{60}, and T_{90} in all groups ($P < 0.05$), with the lowest values at T_{45} in the XYL group and T_{60} in the DXM and MID groups. No significant differences were observed between the groups; however, sedation score (SS) increased significantly at T_{45} and T_{60}, correlating with the lowest IOP values compared to T0 ($P < 0.05$). The XYL group showed the fastest onset (2.44 ± 1.2 min) and longest duration (80.55 ± 6.56 min) of sedation, although these differences were not statistically significant. The findings of this study suggest that preanaesthetic administration of DXM, MID, and XYL can lead to significant decreases in IOP during deep sedation in the RTr position.

***Discussion*:** This is particularly important in veterinary medicine, where research on IOP is limited, particularly in relation to positioning during surgery. Previous studies in horses and cats have shown varying effects of surgical position on IOP, with significant increases in the dorsal and Trendelenburg positions. Human studies have indicated that RTr position can reduce IOP, especially with a greater head angle. This study found that the Tonovet Plus rebound tonometer provides reliable measurements, lending credence to its findings. Further research is required to understand the impact of anaesthetics on IOP across different species and surgical positions. This study suggests that DXM, MID, and XYL have minimal effects on IOP in the RTr position and can be safely utilized in procedures, such as ovariohysterectomy and castration, contributing to the development of strategies for preventing POVL in veterinary medicine and informing human surgical practices.

Keywords: intraocular pressure, reverse trendelenburg position, preanaesthesia.

DOI: 10.22456/1679-9216.141948

Received: 25 July 2024 Accepted: 26 October 2024 Published: 22 November 2024

Department of Surgery, Faculty of Veterinary Medicine, Harran University, Şanlıurfa, Turkey. CORRESPONDENCE: K. Yener [keremyener@harran.edu.tr]. Department of Surgery, Faculty of Veterinary Medicine, Harran University, Şanlıurfa, Turkey.

INTRODUCTION

Rabbits are frequently utilized in ophthalmologic research because their corneal thickness and anterior chamber depth are comparable to those of humans. However, differences in lens, lamina cribrosa (LC) and optic nerve structures limit their applicability in ocular disease studies [12,25,34,36]. In contrast, rats are preferred for intraocular pressure (IOP) studies, particularly in glaucoma research, because of their well-characterized ocular anatomy and suitability for controlled experiments [8,10,25,37,47,51].

IOP is crucial for ocular health, and elevated IOP is a significant risk factor for glaucoma, leading to optic nerve damage and vision loss [6, 20,22,23,35,39,44]. Although the effects of anesthetic agents and body position on IOP have been extensively studied in humans [2,7,13,16,24,27,30], veterinary data, particularly regarding the Reverse Trendelenburg (RTr) position, remain limited [9,14,46,48].

Preanesthetic agents, such as xylazine, dexmedetomidine, and midazolam, are commonly employed in veterinary practice [2,4,11], influencing IOP through their effects on the ocular sympathetic system [19,27,41]. Although generally reported to lower IOP, some studies suggest that these agents may elevate IOP under certain conditions [18,38,39,50], although literature on their effects in the RTr position is scarce [7,14,28,30,43,49].

This study aimed to evaluate the effect of RTr position, utilized in surgeries such as castration and ovariohysterectomy, on IOP in rats and to establish guidelines for the safe use of these preanesthetic agents.

MATERIALS AND METHODS

Animals

In this study, 21 male Wistar albino rats weighing between 180 and 250 g, obtained from Harran University Animal Experiment Application and Research Centre (HDAM), were utilized. Experimental procedures were conducted in accordance with the care and use protocols for laboratory animals, including maintaining it's a 12 h light-darkness cycle and temperature control at a temperature of 22 ± 2°C. This assessment included a comprehensive physical examination, a complete ophthalmic examination, and a basic blood profile. The ophthalmic examination included the evaluation of the blink reflex, pupillary light responses, direct ophthalmoscopy[1] (Ophthalmoscope), and rebound tonometer[2] (TONOVET Plus). In the study, only healthy rats free of ocular or systemic diseases were considered. All animals were acclimatised for 14 days to ensure the absence of corneal and conjunctival diseases. During the experimental treatments, rats were provided ad libitum access to standard commercial pellet feed and tap water.

Experimental groups

Twenty-one rats were randomly divided into 3 groups. The 1st group (n: 7) received 0.75 µg/kg dexmedetomidine[3] (DXM), the 2nd group (n: 7) 5 mg/kg midazolam[4] (MID)] and the 3rd group (n: 7) 10 mg/kg xylazine[5] (XYL) was administered intraperitoneally (IP). The use of rats and calibration of the tonometer were performed as described in the literature [16]. Lapin calibration was conducted using an IOP rebound tonometer (TONOVET Plus). At the commencement of each assessment, a novel probe was affixed for individual animals. The evaluations were exclusively administered by a singular researcher, ensuring uniform handling of the subjects throughout the entirety of the procedure. The researcher remained unaware of the method of drug administration and conducted all assessments impartially. No anaesthetic eye drops were used during measurements. IOP was assessed at T0 when the rats were in their normal stance and at RTr on a specially designed stand at a 15-degree angle following anesthesia. The rat's extremities were immobilized with a plaster cast to prevent them from slipping off the stand (as depicted in Figure 1A). The rats were kept on the stand in the determined position for 90 min (Figure 1B). The measurements of the rats were recorded at 5 (T5), 10 (T10), 15 (T15), 30 (T30), 45 (T45), 60 (T60) and 90 (T90) min at the same time of the day (9.00 to 10.30). The distance between the probe's tip and the cornea of the rat was consistently maintained within a range of 4 to 8 mm throughout the experiment. Six consecutive measurements were executed, and the resultant data were averaged to derive the final score at each designated time point. Each intraocular pressure (IOP) measurement was conducted by the same individual, with the left eye being consistently measured before the right eye. Since no significant differences were noted between the intraocular pressure (IOP) values of the left and right eyes, the right eye was chosen for all subsequent evaluations.

Figure 1. A- Image in the RTr on a specially designed stand. B- IOP measurements.

Rats were evaluated for sedation levels at specific time intervals (T_0, T_5, T_{10}, T_{15}, T_{30}, T_{45}, T_{60}, and T_{90}) using a customized numerical rating scale ranging from 0 to 19. The scoring criteria for assessing rat sedation include: Spontaneous activity/position: Scored from 0 to 3, Resistance when laid into lateral position: Scored from 0 to 4, Palpebral reflex: Scored from 0 to 3, Resistance to opening the mouth (tested only if the rat is in lateral recumbency, using the wooden part of a cotton-tipped applicator) is scored from 0 to 3. Response to noise (clicker activated near the tail base) is scored from 0 to 3. General appearance/attitude is scored from 0 to 3 [45]. The individual responsible for assessing sedation onset (characterized by the disappearance of reflexes) and sedation duration (defined as the period from T0 to the point of spontaneous recovery of reflexes) remained consistent throughout the study.

Statistical analysis

The data were evaluated using SPSS 22.1 (IBM Corporation, Armonk, NY, USA) statistical software. Shapiro-Wilk normality test was applied to determine whether all data were parametric. Due to the data not satisfying parametric test assumptions, differences among the experimental groups (DXM, MID, and XYL) in all measured quantitative characteristics were assessed using the Kruskal-Wallis and Mann-Whitney U tests. Differences between measurements repeated at different times on the same rat were determined by Freidman test for each experimental group separately. For the variables indicating significant differences in the Freidman test, pairwise comparisons were performed with the Wilcoxon test only on the differences between the baseline and other measurements. The results of the study are presented as mean +/- SD and median values. A value of $P < 0.05$ was deemed statistically significant in the statistical analysis.

RESULTS

In-group measurements and statistical evaluations of IOP and SS at all time intervals are presented in Table 1. IOP data are expressed in mmHg. No significant differences were noted in the values measured with the Tonovet Plus device during clinical observation. T0 mean values were 13 ± 1.11 mmHg in the DXM group, 13 ± 0.81 mmHg in the MID group and 12 ± 10 mmHg in the XYL group. There was no significant difference observed between the groups in the statistical evaluations. However, IOP was found to be statistically significant in all groups at T15, T30, T45, T60 and T90 ($P < 0.05$). IOP values decreased significantly in XYL (9 ± 2.94 mmHg) group at T45 and in DXM (9 ± 1.57 mmHg) and MID (9 ± 2.05 mmHg) groups at T60. The lowest IOP values were recorded at the T45 and T60 time points across all 3 groups. Although no statistically significant difference was observed between the groups, the SS exhibited a statistically significant increase at T45 and T60, corresponding to the time intervals when IOP values were lowest compared to T0 (baseline) ($P < 0.05$). The onset of sedation was earlier in the XYL group (2.44 ± 1.2 min) than in the DXM group (2.80 ± 0.8 min) and the MID group (3.22 ± 1.11 min). Sedation time was longer in the XYL group (80.55 ± 6.56 min) compared to the DXM group (74.44 ± 8.4 min) and the MID group (70.33 ± 1.68 min) [Table 2]. No statistically significant difference was observed between the groups.

Table 1. Effects of Dexmedetomidine (DXM) [0.75 µg/kg], Midazolam (MID) [5 mg/kg] and Xylazine (XYL) [10 mg/kg] on intraocular pressure (IOP, mmHg) and sedation score (SS) of Reverse trendelenburg position (RTr) in 21 wistar albino rats.

Variable	Group	T_0	T_5	T_{15}	T_{30}	T_{45}	T_{60}	T_{90}
IOP (mmHg)	DXM	13 ± 1.11 13	12 ± 1.46* 12	10 ± 1.67* 10	11 ± 2.76* 11	9 ± 2.60*# 9	9 ± 1.57*# 9	10 ± 1.67* 10
	MID	13 ± 0.81 13	14 ± 0.95* 14	11 ± 1.90* 11	12 ± 1.49* 12	10 ± 1.06*# 10	9 ± 2.05*# 9	10 ± 2.62* 10
	XYL	12 ± 1.10 12	12 ± 1.21* 12	10 ± 2.05* 10	10 ± 1.97* 10	9 ± 2.94*# 9	10 ± 1.71*# 10	11 ± 1.79* 11
SS	DXM	ND	15 ± 2.1 15	14 ± 0.6 14	15 ± 0.7 15	16 ± 1.44*# 16	16 ± 0.81*# 16	12 ± 1.51 12
	MID	ND	13 ± 1.02 13	13 ± 1.5 13	14 ± 1.9 14	15 ± 1.27*# 15	15 ± 0.16*# 15	11 ± 2.57 11
	XYL	ND	16 ± 1.10 16	15 ± 0.1 15	16 ± 2.05 16	17 ± 1.45*# 17	17 ± 1.03*# 17	10 ± 1.18 10

*Indicates significant differences within the groups ($P < 0.05$). #The time interval with the highest SS and the common time interval with the lowest IOP compared to T_0; Baseline value and at 5 min (T_5), 15 min (T_{15}), 30 min (T_{30}), 45 min (T_{45}), 60 min (T_{60}) and 90 min (T_{90}). ND: not determined.

Table 2. The effects of Dexmedetomidine (DXM), 0.75 µg/kg, Midazolam (MID) 5 mg/kg and Xylazine (XYL) 10 mg/kg on the onset time and duration of sedation in 21 wistar albino rats in the reverse trendelenburg position (RTr).

Group	Time to onset of sedation	Duration of sedation
DXM (min)	2.80 ± 0.8 3	74.44 ± 8.4 75
MID (min)	3.22 ± 1.11 3	70.33 ± 1.68 70
XYL (min)	2.44 ± 1.2 2.5	80.55 ± 6.56 80

DISCUSSION

In recent years, studies on IOP have been on the increase in human and veterinary medicine. These studies have focused more on the physiological parameters of IOP across species, especially in veterinary medicine, or how it changes with the effect of various anesthetic agents [29,31,33,41,42]. However, perioperative visual loss (POVL), which has been emphasized by human medicine since the mid - 90s, is a serious complication that can be observed in nonophthalmic surgical operations and has been associated with factors such as prolonged operations performed in surgical positions such as trendelenburg (Tr), reverse trendelenburg (RTr) and prone, significant blood loss and hypotension. It has also been emphasized that surgical positions (Tr, RTr) in procedures such as genital organ operations and bariatric surgery in men may cause POVL [7,19,31]. In veterinary medicine, there is a lack of literature data on both POVL and the effect of various surgical positions on IOP. This study aimed to examine the effects of RTr, a position used in surgical operations in both veterinary and human medicine, on IOP in rats using different types and current anesthetic agents, together with sedation scoring and duration data, including the length of operation time emphasized in POVL, with the aim of making a potential contribution to clinical practice and improving IOP management.

Research conducted on both rats and humans has underscored that the lamina cribrosa (LC) serves as the primary site of damage in glaucoma induced by high IOP [5,6,40]. Additionally, the literature

highlights that ischemic optic neuropathy (ION), a condition identified among the causes of perioperative visual loss (POVL), occurs due to compromised blood flow to the optic nerve associated with the localization of the LC [19]. Based on this information, some pioneering studies and scanning electron microscopic analyses indicate that changes in the structure of LC can be interpreted as a precursor of high IOP [6, 40]. Considering the LC structure in rat eyes, it is possible to use rats as a model for both IOP and POVL - related diseases. The experiments were carried out on rats. There was no statistical difference between the groups in terms of IOP and SS. However, although a slight decrease in IOP values was observed at most time intervals, the most significant decrease compared to T_0 was statistically significant at T_{45} and T_{60} time intervals both in IOP and SS. These findings suggest that since DXM, MID and XYL preanaesthetics may cause a greater decrease in IOP during deeper sedation in the RTr position, IOP values of the patients should be closely monitored during these time intervals.

In a pioneering study by Meekins *et al*. [27], a combination of xylazine- ketamine [1.1 mg/kg, IV - 2.2 mg/kg, IV] was started followed by midazolam [0. 05 mg/kg, IV], followed by continuous infusion guaifenesin 50 g/L, ketamine 4.4 mg/kg/L and xylazine 1.1 mg/kg/L at a rate of 999 mL/h. The effects of four different operating positions (Tr, RTr (15° head up), lateral and dorsal) on IOP in horses were examined and comparative inferences were drawn on POVL. In the study, horses were fully anesthetized approximately 5 - 7 min after anesthesia administration and IOP measurements were evaluated at 10 min intervals for a total of 60 min. At the end of the study, it was emphasized that IOP increased statistically significantly in all positions except the RTr position, especially in the dorsal position [27]. In the present study, the evaluation of the RTr position as 15° head - up and some of the anesthetic agents used are similar to this study. During the study, it was observed that rats administered DXM, MID and XYL became sedated in a shorter time. It was also statistically determined that all 3 anesthetic agents showed a slight decrease in the RTr position compared to T_0 at other time intervals. It is considered that these decreases may stem from high doses or species differences. Despite differences between species, high IOP could theoretically impair blood flow to the eye and lower ocular perfusion pressure, and humans and animals may be at risk of ION. This becomes even more important in view of the frequent occurrence of hypotension in surgical procedures performed with inhalation anesthetics. Therefore, it is possible to treat hypotension that may occur in anesthetized humans and animals with drugs such as vasopressors to reduce the risk of POVL in the future [30]. Another study on cats evaluated the effectiveness of left lateral, dorsal, and Trendelenburg (70° head down) positions on IOP with a combination of intramuscular administration of butorphanol [0.4 mg/kg], medetomidine [0.03 - 0.05 mg/kg] and ketamine [7 - 10 mg/kg]. Mean duration of anaesthesia in the study 9 ± 2.4 min and there was no statistically significant difference between the groups. In the cat study, it was reported that the IOP value increased in all positions but increased more in the Tr position [9]. In addition, compared to the horse study (Tr 15° head down), the Tr (70° head down) position yielded higher IOP values than the dorsal position, suggesting that the degree of angle at which the head is positioned may have a more elevating effect on IOP. Thus, greater care is required when positioning the head during operative procedures, especially in patients with glaucoma. In contrast to the cat study, the current study exhibited a shorter sedation onset time. However, similar to the findings of the cat study, no statistically significant difference was observed between the groups.

While the number of studies evaluating the effect of RTr position on IOP in veterinary medicine is limited, more studies have been conducted on humans [1,15]. In some of the pioneering studies in which the RTr position was evaluated in humans, Van Wicklin *et al*. [50] emphasized that the IOP value increased in the prone position under general anesthesia, but when the RTr was moved to 5° upside down and 10° upside down positions and measured again, a decrease in the IOP value was observed, especially this decrease was more significant in the 10° upside down position [50]. Another study by Carey *et al*. [3] compared the efficacy of RTr 5° upside down and RTr 10° upside down positions on IOP following prone position with local anesthesia. In the study, it was emphasized that the increased IOP value after prone position in operations lasting less than 120 min was safer by performing a superior mitigating effect with the RTr 10° upside down position [3]. Considering the available study data, it could be suggested that there may be a further

lowering effect on IOP with an increase in the angle at which the head is positioned in the RTr position. Accordingly, considering the findings of the present study and other studies, it could be concluded that the RTr position may reduce the risk of glaucoma, retinal detachment and POVL, especially with its mild IOP lowering effect in surgical operations where the RTr position is indicated in comparison with the application of various anesthetic agents or different positions.

A search of the Web of Science and Scopus databases, covering a period from 1980 to 2024, points to a pioneering study in which preanaesthetic agents such as DXM, MID and XYL were used to evaluate IOP in rats in the RTr position using a modern and more reliable device, the Tonovet Plus. The literature suggests that the Tonovet Plus rebound tonometer used in this article gives higher IOP values compared to the applanation tonometer. However, in an exemplary study, researchers found no statistically significant difference between these 2 tonometers when comparing the IOP values in normal rat eyes. In this respect, it is considered that our study results could be evaluated jointly with the studies using rebound tonometry [6].

In veterinary medicine, there are studies examining the effects of DXM, MID and XYL preanaesthetics on IOP in different species without the use of operating positions such as Tr, RTr, prone or dorsal [26,35,38]. As an example of studies examining the effects of DXM alone or in combination with different anesthetics on IOP, Kusolphat *et al*. [21] reported that management of DXM alone [dose of 5 µg/kg- intravenous (IV)] was associated with a slight but significant IOP reduction at T10 and T20 compared to T_0 in dogs [21]. However, Monk et al. [32] reported that the intravenous a combination of dexmedetomidine [0.3 mg m-2] and butorphanol [6 mg m-2] in dogs resulted in a significant increase in intraocular pressure (IOP) at T_{10} compared to T_0, followed by a significant decrease at T_{30} and T_{40} [32]. In the present study, DXM [0.75 µg/kg] in rats at lower doses than in the 1st study had similar findings with the RTr position, suggesting that low dose DXM and RTr position can be used in genital organs and lower abdominal region operations in dogs. The difference between the findings of the present study and the other study may be a result of the effect of butorphanol on choroidal vasodilation [7]. Therefore, it is our belief that further scientific research is needed to further elucidate the effects of anesthetics used in surgical procedures on IOP in order to obtain more comprehensive information about the different effects of various combinations of preanaesthetic agents on IOP. In a study conducted in 18 horses, XYL was administered to the horses as a premedication and IOP values were measured until they were placed on the operating table, and IOP value at the time of placement on the operating table (20 ± 7.1 mmHg) showed a statistically significant increase compared to T_0 (18 ± 2.5 mmHg) [32]. In this study, similar to the current study, different IOP results were obtained as the head position changed. In a study in which XYL was administered IM at 5 dosages [0.5, 1, 2, 4 and 8 mg/kg-1] in dogs, it was reported that XYL administration caused a slight decrease in IOP values at all doses and no risky findings were obtained, while in the current study, similarly, rats in the RTr position were given XYL at a dose of 10 mg/kg compared to T_0 and a slight decrease in IOP values was observed over time compared to T_0, but this decrease was not at risky levels [17]. In exemplary studies in which MID was evaluated, no statistically significant difference was found in IOP values in midazolam [0.2 mg/kg] - ketamine [15 mg/kg] combination in dogs and it was emphasized that this may be due to the much higher dose of ketamine [38]. Another study conducted on monkeys found that combinations of xylazine [0.5 mg/kg] with ketamine [15 mg/kg], midazolam [0.5 mg/kg] with ketamine [15 mg/kg], and dexmedetomidine [0.005 mg/kg] with ketamine [15 mg/kg] resulted in a statistically significant increase in intraocular pressure (IOP) values. It was also reported that sedation times were longer in dexmedetomidine and midazolam combinations, but sedation was not effective enough in xylazine group [11]. Ketamine can cause central nervous system depression and dissociative anesthesia. Its effect on intraocular pressure (IOP) is primarily due to increased tone in the extraocular muscles [10]. The observed increase in IOP values in the present study aligns with these findings. However, the differences observed with the sedation findings in the XYL group in the present study may be considered as a reason for the use of xylazine at a much lower dose in the other study. In the present study, it is predicted that preanaesthetic agents that slightly lower IOP values in the RTr position may provide a balanced IOP value at appropriate doses if used in combination with the elevating effect of ketamine. This could be considered as an important finding in terms of providing a safe general anesthesia in operations performed in the RTr position.

CONCLUSION

As a result, this study evaluated the effects of preanaesthetic medications, namely dexmedetomidine (DXM), midazolam (MID), and xylazine (XYL), on intraocular pressure (IOP) during the Trendelenburg position in rats. According to the results obtained, these preanaesthetic drugs had similar and minimal effects on IOP, suggesting that they can be safely used in procedures such as ovariohysterectomy and castration. Furthermore, these findings may shed light on future studies in human surgery, such as those focusing on procedures in the lower body and obesity surgery. This study contributes to the development of strategies to prevent postoperative vision loss (POVL) in veterinary medicine and may assist in making informed decisions regarding anesthesia and surgical positioning in clinical practice.

MANUFACTURERS

[1]Gowllands. Croydon, United Kingdom.

[2]Icare. Madison, WI, USA.

[3]Haver Farma. Istanbul, Turkey.

[4]VEM Ilaç. Istanbul, Turkey.

[5]Alfasan International B.V. Woerden, Netherlands.

***Ethical approval*.** This study was completed in accordance with the procedures and principles of Harran University Animal Experiments Local Ethics Committee (Session Number: 2023/002/10 Decision Number:01-17 Date/Time: 10.05.2023 / 15.00).

***Declaration of interest*.** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of paper.

REFERENCES

1 **Adisa A.O., Onakpoya O.H., Adenekan A.T. & Awe O.O. 2016.** Intraocular pressure changes with positioning during laparoscopy. *Journal of the Society of Laparoendoscopic Surgeons*. 20(4). DOI: 10.4293/JSLS.2016.00078

2 **Alling C.R., Cremer J., Liu C.C., Lewin A.C., Camacho-Luna P. & Carter R.T. 2021.** Effect of multiple head positions on intraocular pressure in healthy, anesthetized horses during hoisting. *Veterinary Ophthalmology*. 24(1): 71-79. DOI: 10.1111/vop.12849

3 **Carey T.W., Shaw K.A., Weber M.L. & DeVine J.G. 2014.** Effect of the degree of reverse Trendelenburg position on intraocular pressure during prone spine surgery: a randomized controlled trial. *The Spine Journal*. 14(9): 2118-2126. DOI: 10.1016/j.spinee.2013.12.025

4 **Chandra A., Ranjan R., Kumar J., Vohra A. & Thakur V.K. 2016.** The effects of intravenous dexmedetomidine premedication on intraocular pressure and pressor response to laryngoscopy and intubation. *Journal of Anaesthesiology Clinical Pharmacology*. 32(2): 198-202. DOI: 10.4103/0970-9185.173354

5 **Chidlow G., Ebneter A., Wood J.P. & Casson R.J. 2011.** The optic nerve head is the site of axonal transport disruption, axonal cytoskeleton damage and putative axonal regeneration failure in a rat model of glaucoma. *Acta Neuropathologica*. 121(6): 737-751. DOI: 10.1007/s00401-011-0807-1

6 **Choy Y. & Choi J.H. 2021.** Comparison of intraocular pressure in Spargue-Dawley rats using two types of tonometers. *Exploratory Animal & Medical Research*. 11(2): 152-156. DOI: 10.52635/eamr/11.2.152-156

7 **Corona D., Ranninger E., Jörger F., Goldinger E., Stefan A., Torgerson P.R. & Bettschart-Wolfensberger R. 2020.** Cats undergoing spay with medetomidine, ketamine and butorphanol develop arterial oxygen desaturation independent of surgical positioning and increased intraocular pressure in Trendelenburg position. *Schweizer Archiv für Tierheilkunde*. 162(9): 539-550. DOI: 10.17236/sat00271

8 **El Basty A., Gaber R., Elmaria A., Sabry M. & Hussein T.R. 2021.** Correlation between changes in lamina cribrosa structure and visual field in primary open-angle glaucoma. *Clinical Ophthalmology*. 15: 4715-4722. DOI: 10.2147/OPTH.S343019

9 **Emery S.E., Daffner S.D., France J.C., Ellison M., Grose B.W., Hobbs G.R. & Clovis N.B. 2015.** Effect of head position on intraocular pressure during lumbar spine fusion: a randomized, prospective study. *The Journal of Bone & Joint Surgery*. 97(22): 1817-1823. DOI: 10.2106/JBJS.O.00091

10 **Erol M., Erol H., Atalan G., Ceylan C. & Yönez M.K. 2020.** The effects of propofol-sevoflurane, midazolam-sevoflurane and medetomidine-ketamine-sevoflurane anesthetic combinations on intraocular pressure in rabbits. *Kafkas Üniversitesi Veteriner Fakültesi Dergisi*. 26(4): 477-481. DOI: 10.9775/kvfd.2019.23557

11 **Ghaffari M.S., Rezaei M.A., Mirani A.H. & Khorami N. 2010.** The effects of ketamine-midazolam anesthesia on intraocular pressure in clinically normal dogs. *Veterinary Ophthalmology*. 13(2): 91-93. DOI: 10.1111/j.1463-5224.2010.00762.x

12 **Gloe S., Rothering A., Kiland J.A. & McLellan G.J. 2019.** Validation of the Icare® TONOVET plus rebound tonometer in normal rabbit eyes. *Experimental Eye Research*. 185: 107698. DOI: 10.1016/j.exer.2019.107698

13 **Goel N., Chowdhury I., Dubey J., Mittal A. & Pathak S. 2020.** Quantitative rise in intraocular pressure in patients undergoing robotic surgery in steep Trendelenburg position: a prospective observational study. *Journal of Anaesthesiology Clinical Pharmacology*. 36(4): 546-551. DOI: 10.4103/joacp.JOACP_96_20

14 **Grant G.P., Szirth B.C., Bennett H.L., Huang S.S., Thaker R.S., Heary R.F. & Turbin R.E. 2010.** Effects of prone and reverse Trendelenburg positioning on ocular parameters. *The Journal of the American Society of Anesthesiologists*. 112(1): 57-65. DOI: 10.1097/ALN.0b013e3181c294e1

15 **Hwang J.W., Oh A.Y., Hwang D.W., Jeon Y.T., Kim Y.B. & Park S.H. 2013.** Does intraocular pressure increase during laparoscopic surgeries? It depends on anesthetic drugs and the surgical position. *Surgical Laparoscopy Endoscopy & Percutaneous Techniques*. 23(2): 229-232. DOI: 10.1097/SLE.0b013e31828a0bba

16 **Joo J., Koh H., Lee K. & Lee J. 2016.** Effects of systemic administration of dexmedetomidine on intraocular pressure and ocular perfusion pressure during laparoscopic surgery in a steep Trendelenburg position: prospective, randomized, double-blinded study. *Journal of Korean Medical Science*. 31(6): 989-996. DOI: 10.3346/jkms.2016.31.6.989

17 **Kanda T., Iguchi A., Yoshioka C., Nomura H., Higashi K., Kaya M., Yamamoto R., Kuramoto T. & Furukawa T. 2015.** Effects of medetomidine and xylazine on intraocular pressure and pupil size in healthy Beagle dogs. *Veterinary Anaesthesia and Analgesia*. 42(6): 623-628. DOI: 10.1111/vaa.12249

18 **Kaur G., Sharma M., Kalra P., Purohit S. & Chauhan K. 2018.** Intraocular pressure changes during laparoscopic surgery in Trendelenburg position in patients anesthetized with propofol-based total intravenous anesthesia compared to sevoflurane anesthesia: a comparative study. *Anesthesia Essays and Researches*. 12(1): 67-72. DOI: 10.4103/aer.AER_177_17

19 **Kitamura S., Takechi K., Nishihara T., Konishi A., Takasaki Y. & Yorozuya T. 2018.** Effect of dexmedetomidine on intraocular pressure in patients undergoing robot-assisted laparoscopic radical prostatectomy under total intravenous anesthesia: a randomized, double-blinded placebo-controlled clinical trial. *Journal of Clinical Anesthesia*. 49: 30-35. DOI: 10.1016/j.jclinane.2018.06.006

20 **Komáromy A.M., Garg C.D., Ying G.S. & Liu C. 2006.** Effect of head position on intraocular pressure in horses. *American Journal of Veterinary Research.* 67(7): 1232-1235. DOI: 10.2460/ajvr.67.7.1232

21 **Kusolphat P., Soimala T. & Sunghan J. 2022.** Intraocular pressure and cardiovascular effects of dexmedetomidine premedication and tiletamine-zolazepam for anesthetic induction in dogs. *Veterinary World*. 15(12): 2929-2936. DOI: 10.14202/vetworld.2022.2929-2936

22 **Ling Y.T.T., Pease M.E., Jefferys J.L., Kimball E.C., Quigley H.A. & Nguyen T.D. 2020.** Pressure-induced changes in astrocyte GFAP, actin, and nuclear morphology in mouse optic nerve. *Investigative Ophthalmology & Visual Science*. 61(11): 14. DOI: 10.1167/iovs.61.14.27

23 **Martínez-Águila A., Fonseca B., Bergua A. & Pintor J. 2013.** Melatonin analogue agomelatine reduces rabbit's intraocular pressure in normotensive and hypertensive conditions. *European Journal of Pharmacology*. 701(1-3): 213-217. DOI: 10.1016/j.ejphar.2012.12.009

24 **Mathew D.J., Greene R.A., Mahsood Y.J., Hallaji N., Vargas A.M.B., Jin Y.P., Finelli A., Parotto M., Belkin A., Trope G.E. & Buys Y.M. 2018.** Preoperative brimonidine tartrate 0.2% does not prevent an intraocular pressure rise during prostatectomy in steep Trendelenburg position. *Journal of Glaucoma*. 27(11): 965-970. DOI: 10.1097/IJG.0000000000001047

25 **May C.A. 2008.** Comparative anatomy of the optic nerve head and inner retina in non-primate animal models used for glaucoma research. *The Open Ophthalmology Journal.* 2: 94-101. DOI: 10.2174/1874364100802010094

26 **Mayordomo-Febrer A., Rubio M., Martínez-Gassent M. & López-Murcia M.M. 2017.** Effects of morphine-alfaxalone-midazolam premedication, alfaxalone induction and sevoflurane maintenance on intraocular pressure and tear production in dogs. *Veterinary Record*. 180(19): 474. DOI: 10.1136/vr.104040

27 **Meekins J.M., McMurphy R.M. & Roush J.K. 2020.** The effect of body position on intraocular pressure in anesthetized horses. *Veterinary Ophthalmology*. 23(4): 668-673. DOI: 10.1111/vop.12769

28 Micieli F., Chiavaccini L., Lamagna B., Vesce G. & Santangelo B. 2018. Comparison of intraocular pressure and pupil diameter after sedation with either acepromazine or dexmedetomidine in healthy dogs. *Veterinary Anaesthesia and Analgesia*. 45(5): 667-672. DOI: 10.1016/j.vaa.2018.05.003

29 Mizumoto K., Gosho M., Iwaki M. & Zako M. 2017. Ocular parameters before and after steep Trendelenburg positioning for robotic-assisted laparoscopic radical prostatectomy. *Clinical Ophthalmology*. 11: 1643-1650. DOI: 10.2147/OPTH.S139874

30 Molloy B. & Watson C. 2012. A comparative assessment of intraocular pressure in prolonged steep Trendelenburg position versus level supine position intervention. J*ournal of Anesthesiology & Clinical Science*. 1(1): 9. DOI: 10.7243/2049-9752-1-9

31 Molloy B. & Cong X. 2014. Perioperative dorzolamide-timolol intervention for rising intraocular pressure during steep Trendelenburg positioned surgery. *Journal of the American Association of Nurse Anesthesiology*. 82(3): 203-211. PMID: 25109158.

32 Monk C.S., Brooks D.E., Granone T., Garcia-Pereira F.L., Melesko A. & Plummer C.E. 2017. Measurement of intraocular pressure in healthy anesthetized horses during hoisting. *Veterinary Anaesthesia and Analgesia.* 44(3): 502-508. DOI: 10.1016/j.vaa.2016.10.001

33 Mowafi H.A., Aldossary N., Ismail S.A. & Alqahtani J. 2008. Effect of dexmedetomidine premedication on the intraocular pressure changes after succinylcholine and intubation. *British Journal of Anaesthesia*. 100(4): 485-489. DOI: 10.1093/bja/aen020

34 Murillo J., Robledo S., Montaño J. & Acevedo S.P. 2021. Variation of intraocular pressure comparing rebound (TONOVET Plus®) and applanation (TONO-PEN VET®) tonometry in New Zealand rabbits treated with Amlodipine®. *CES Medicina Veterinaria y Zootecnia*. 16(3): 10-27. DOI: 10.21615/cesmvz.6319

35 Nicou C.M., Pillai A. & Passaglia C.L. 2021. Effects of acute stress, general anesthetics, tonometry, and temperature on intraocular pressure in rats. *Experimental Eye Research*. 210: 108727. DOI: 10.1016/j.exer.2021.108727

36 Okur S., Yanmaz L.E., Senocak M.G., Ersöz U., Gölgeli A., Turgut F., Orhun O.T. & Kocaman Y. 2023. Comparison of intraocular pressure in New Zealand White rabbits measured using rebound and applanation tonometers and four different methods of physical restraint. *New Zealand Veterinary Journal*. 71(5): 251-258. DOI: 10.1080/00480169.2023.2224277

37 Omodaka K., Horii T., Takahashi S., Kikawa T., Matsumoto A., Shiga Y., Maruyama K., Yuasa T., Akiba M. & Nakazawa T. 2015. 3D evaluation of the lamina cribrosa with swept-source optical coherence tomography in normal tension glaucoma. *PLoS One*. 10(4): e0122347. DOI: 10.1371/journal.pone.0122347

38 Pal C.K., Ray M., Sen A., Hajra B., Mukherjee D. & Ghanta A.K. 2011. Changes in intraocular pressure following administration of suxamethonium and endotracheal intubation: influence of dexmedetomidine premedication. *Indian Journal of Anaesthesia*. 55(6): 573-577. DOI: 10.4103/0019-5049.90611

39 Qiu Y., Yang H. & Lei B. 2014. Effects of three commonly used anesthetics on intraocular pressure in mouse. *Current Eye Research*. 39(4): 365-369. DOI: 10.3109/02713683.2013.845224

40 Quigley H.A., Addicks E.M., Green W.R. & Maumenee A.E. 1981. Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. *Archives of Ophthalmology*. 99(4): 635-649. DOI: 10.1001/archopht.1981.03930010635009

41 Raposo A.C., Ofri R., Schaffer D.P., Gomes Júnior D.C., Libório F.A., Martins Filho E.F. & Oriá A.P. 2015. Evaluation of ophthalmic and hemodynamic parameters in capuchin monkeys (*Sapajus* sp.) submitted to dissociative anesthetic protocols. *Journal of Medical Primatology*. 44(6): 381-389. DOI: 10.1111/jmp.12200

42 Rauser P., Mrazova M. & Zapletalova J. 2016. Influence of dexmedetomidine-propofol-isoflurane and medetomidine-propofol-isoflurane on intraocular pressure and pupil size in healthy dogs. *Veterinarni Medicina*. 61(11): 635-642. DOI: 10.17221/115/2016-VETMED

43 Rauser P., Mrazova M., Crha M., Urbanova L. & Vychodilova M. 2017. Influence of capnoperitoneum on intraocular pressure in spontaneously breathing dogs undergoing ovariectomy. *Veterinarni Medicina*. 62(12): 661-667. DOI: 10.17221/89/2017-VETMED

44 Ripa M., Schipa C., Kopsacheilis N., Nomikarios M., Perrotta G., De Rosa C., Aceto P., Sollazzi L., De Rosa P. & Motta L. 2022. The impact of steep Trendelenburg position on intraocular pressure. *Journal of Clinical Medicine*. 11(10): 2844. DOI: 10.3390/jcm11102844

45 Rondeau A., Langlois I., Pang D.S. & Leung V.S.Y. 2020. Development of a sedation assessment scale for comparing the sedative effects of alfaxalone-hydromorphone and ketamine-midazolam-hydromorphone for intravenous catheterization in the domestic rat (*Rattus norvegicus*). *Journal of Exotic Pet Medicine*. 35: 117-122. DOI: 10.1053/j.jepm.2020.09.004

46 Shanmugham V. & Subban R. 2022. Capsanthin from *Capsicum annum* fruits exerts anti-glaucoma, antioxidant, anti-inflammatory activity, and corneal pro-inflammatory cytokine gene expression in a benzalkonium chloride-induced rat dry eye model. *Journal of Food Biochemistry*. 46(10): e14352. DOI: 10.1111/jfbc.14352

47 Smith L., Weng H.Y. & Park S.A. 2023. Positional variance of intraocular pressure in conscious New Zealand White rabbits. *SSRN*. 4417901. Available from: http://dx.doi.org/10.2139/ssrn.4417901.

48 Souza A.T., Garcia D.O., Nishimura L.T., Magalhães M.L., Mattos-Junior E., Paulino-Junior D., Jorge A.T. & Honsho C.S. 2019. Effects of pneumoperitoneum and Trendelenburg position on intraocular pressure (IOP) in isofluorane-anesthetised cats. *Biosci Journal*. 35(6): 1899-1906. DOI: 10.1093/bja/aew356

49 Tucker L., Almeida D., Wendt-Hornickle E., Baldo C.F., Allweiler S. & Guedes A.G.P. 2022. Effect of 15° reverse Trendelenburg position on arterial oxygen tension during isoflurane anesthesia in horses. *Animals (Basel)*. 12(3): 353. DOI: 10.3390/ani12030353

50 Van Wicklin S.A. 2020. Systematic review and meta-analysis of prone position on intraocular pressure in adults undergoing surgery. *International Journal of Spine Surgery*. 14(2): 195-208. DOI: 10.14444/7029

51 Zernii E.Y., Baksheeva V.E., Iomdina E.N., Averina O.A., Permyakov S.E., Philippov P.P., Zamyatnin A.A. & Senin I.I. 2016. Rabbit models of ocular diseases: new relevance for classical approaches. *CNS Neurol Disord Drug Targets*. 15(3): 267-291. DOI: 10.2174/1871527315666151110124957