

Topical use of injectable dexmedetomidine in combination with dorzolamide for the intraocular pressure reduction in dogs: a preliminary study

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Abstract – This study evaluated the efficacy of the isolated topical use of 2% dorzolamide eye drops three times a day compared with the combination of 100 µg/ml dexmedetomidine (initially formulated for injectable use and applied topically twice a day) associated with 2% dorzolamide in reducing intraocular pressure (IOP) in dogs with glaucoma. Twenty-nine dogs with IOP > 25 mmHg were selected based on specific clinical criteria and divided into two groups: Group 1 (DORZO) with 12 dogs treated only with dorzolamide every eight hours, and Group 2 (DEX DORZO) with 17 dogs receiving dorzolamide every eight hours combined with topical dexmedetomidine every 12 hours. IOP was measured on the first day and at 7 and 30 days after diagnosis. Vital parameters, including heart rate, respiratory rate, and systolic blood pressure, were assessed before and 30 minutes after the application of dexmedetomidine. Both treatments significantly reduced IOP, but the DEX DORZO group showed a greater decrease (35.99%, $p = 0.001$) compared with 20.32% in the DORZO group ($p = 0.6026$). No significant differences in vital parameters were observed, and no blepharospasm or hyperemia occurred. In conclusion, the topical combination of dexmedetomidine and dorzolamide significantly reduced IOP in glaucomatous dogs without causing ocular irritation or anterior uveitis. This combination proved more effective than dorzolamide alone. Although results are promising, further studies with larger samples and different dosing protocols are needed to confirm efficacy, optimize concentrations, and assess long-term safety in canine glaucoma management.

Keywords: alpha-2 agonist; ocular hypertension; ophthalmology; pharmacological repositioning.

1. Introduction

Glaucoma in dogs is a progressive and painful ocular disease characterized by a complex group of optic neuropathies that lead to vision loss, commonly associated with elevated intraocular pressure (IOP), which contributes to optic disc degeneration and retinal ganglion cell (RGC) death (Maggio & Bras, 2015; Komáromy et al., 2019). It is the leading cause of irreversible blindness in both humans and dogs (Gelatt & Mackay, 2004; Quigley & Bowman, 2006; Weinreb et al., 2014; Tham et al., 2014; Komáromy et al., 2019). The prevalence of primary and secondary glaucoma in dogs is estimated to be similar to that in humans, ranging between 1% and 2% (Plummer et al., 2013).

IOP is regulated by the balance between aqueous humor (AH) production and drainage. The primary mechanism of AH formation is active secretion by the ciliary processes, responsible for 80–90% of the total output (Goel et al., 2010). AH is primarily drained through the trabecular meshwork, with a smaller proportion exiting via the uveoscleral pathway (Komáromy et al., 2019). The ciliary muscle modulates uveoscleral outflow: relaxation increases flow, while contraction reduces it (Alm & Nilsson, 2009).

Disruption of physiological outflow pathways elevates IOP, which can stretch the lamina cribrosa and cause secondary axonal damage to RGCs (Flammer & Mozaffarieh, 2007). Medical and surgical treatments aim to lower IOP by decreasing AH production and/or enhancing its outflow, thus delaying vision loss (Webb, 2021). However, in many cases of canine glaucoma, vision continues to deteriorate despite intensive and costly treatment.

Two primary mechanisms can be employed to reduce IOP: suppressing aqueous production or enhancing aqueous outflow. Topical eye drops that decrease aqueous production include beta-blockers (β -blockers), carbonic anhydrase inhibitors (CAIs), and alpha-2 (α_2) agonists. The latter acts by simultaneously reducing aqueous production and increasing aqueous outflow (Reitsamer et al., 2005; Cantor, 2006).

Timolol, a nonselective beta-adrenergic antagonist that lowers IOP by decreasing production of aqueous humor, has been the historical topical first line against an increasing IOP in both humans and small animal patients. Bilateral miosis and relative bradycardia result from the systemic uptake of timolol and occur because of the inhibitory effects of the drug on the beta-adrenergic fibers in the canine iris sphincter muscle and on those within the cardiovascular system (Wilkie & Latimer, 1991; Zimmerman, 1993).

Dorzolamide and brinzolamide are two topical CAIs that are currently available to treat ocular hypertension and/or glaucoma. Dorzolamide is a very potent inhibitor of Carbonic Anhydrase-II (CA-II), and its site of action is local within the eye. Like oral CAIs, topically applied dorzolamide lowers IOP by decreasing the production of aqueous humor (Sugrue, 1999). Dorzolamide is available as a topical 2% ophthalmic preparation and has been evaluated in normotensive and glaucomatous dogs (Cawrse et al., 2001; Plummer et al., 2006). A 1% suspension of brinzolamide is comparable to 2% dorzolamide in lowering IOP, both drugs being administered three times daily (Whelan et al., 1999). Dorzolamide hydrochloride 2% ophthalmic solution was the first topical carbonic anhydrase inhibitor approved for the treatment of glaucoma in humans (Ingram & Brubaker, 1999).

Alpha-2 Adrenergic agonists decrease IOP in human and canine eyes via reduction of AH production and increased uveoscleral outflow facility (Arthur & Cantor, 2011; Plummer et al., 2013). Brimonidine tartrate is a highly selective A2-agonist labeled to reduce IOP in human patients with glaucoma (Plummer et al., 2013). Despite its effectiveness and low side-effect profile in humans, brimonidine appears to be less efficacious in canine patients. After single and multiple-drop applications of brimonidine in beagles

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affected with POAG, a trend of insignificant IOP reduction was observed. Side effects were mild and included reduced heart rate and miosis. Based on these results, brimonidine is not recommended as a sole agent to manage canine glaucoma (Gelatt & MacKay, 2002).

Agents that exclusively reduce IOP by increasing aqueous outflow include prostaglandin analogues (PGA), cholinergic agonists, and Rho Kinase Inhibitors (Jayanetti et al., 2020). PGA results in both short- and long-term increases in unconventional aqueous outflow (Oh et al., 2006; Stamer et al., 2010). Recent reports also suggest some increase in conventional outflow facility may occur as well (Richter et al., 2003; Plummer et al., 2013; Sambhara & Aref, 2014). PGAs (eg, Latanoprost) have very few systemic side effects and are considered first-line therapy in glaucoma and OHT (Holló, 2007). Latanoprost is one of the most commonly used topical medications for canine glaucoma and is available as a 0.005% topical solution. There have been extensive studies examining the IOP-lowering effects of latanoprost in both normotensive and glaucomatous dogs (Studer et al., 2000; Gelatt & MacKay, 2001).

Cholinergic agonists (e.g., Pilocarpine) increase conventional aqueous outflow; however, they are less commonly used than other classes due to their poorly tolerated side effect profile, including myopic shift, nyctalopia, and an increased risk of retinal tears and detachment (Plummer et al., 2013; Skaat et al., 2016). More recent developments have seen Rho kinase (ROCK) inhibitors such as Netarsudil (Rhopressa®) and Ripasudil approved for the treatment of glaucoma. This class offers dual benefits, including IOP-lowering and neuroprotection. The IOP-lowering effect of ROCK inhibitors is due to a decrease in outflow facility through the conventional pathway, which results from modification of the trabecular meshwork and Schlemm's canal cytoskeletons (Honjo et al., 2001; Rao et al., 2001). ROCK inhibitors are mostly used as adjunctive treatments because their IOP-lowering effect is modest compared with that of PGAs currently in use (Tanna & Johnson, 2018).

However, a critical need remains for more effective therapeutic strategies to manage glaucoma, driving the ongoing investigation of new drugs and therapeutic combinations that can reduce intraocular pressure (IOP) more efficiently and safely. Several emerging approaches are being studied, including Rho-kinase (ROCK) inhibitors, nitric oxide donors, gene therapies, stem cells, and sustained-release systems, all with the potential to enhance aqueous humor outflow or modulate its production. In this context, the present study aimed to evaluate the efficacy of topically administered injectable dexmedetomidine in combination with dorzolamide, compared with dorzolamide alone, for reducing intraocular pressure in dogs, contributing to the exploration of new therapeutic options in veterinary ophthalmology.

2. Materials and Methods

The project was approved by the Animal Use Ethics Committee of the Agricultural Sciences Sector at the Federal University of Paraná (UFPR), ensuring compliance with all applicable guidelines for animal welfare. Informed consent was obtained from all owners, who agreed to participate by signing a consent form.

The study included 29 dogs—16 females and 13 males—aged between six months and 14 years, presenting with unilateral glaucoma. The breeds represented were: 12 Shih Tzus, 3 mixed-breed dogs (MBD), 2 Siberian Huskies, 2 Lhasa Apsos, 2 Poodles, and 1 each of the following: American Bully, American Staffordshire Terrier, French Bulldog, Great Dane, Maltese, Pinscher, Pug, and German Spitz.

The dogs were enrolled between August 2023 and December 2024 at the ophthalmology service of REVET Veterinary Clinic, located in São Paulo, Brazil. Among the glaucoma cases, 15 were classified as primary, 12 as secondary, and two as congenital.

All animals underwent a comprehensive ophthalmic examination under controlled lighting conditions, including slit-lamp biomicroscopy (Keeler PSL One, Windsor, UK), indirect ophthalmoscopy (Welch Allyn 11820 Panoptic 3.5 V, New York, USA), rebound tonometry (TD-800, LanYuXuan, Beijing, China), and vital staining with fluorescein and rose Bengal (Drogavet, Curitiba, Brazil). General physical examination confirmed that all animals were otherwise healthy. Some ocular abnormalities were observed, but did not exclude animals from the study. These included Descemet's membrane rupture (Haab's striae), varying degrees of corneal edema, episcleral vessel congestion, fixed mydriasis, anterior or posterior synechiae, lens luxation or subluxation, and cataract.

The dexmedetomidine eye drop formulation was derived from intramuscular and intravenous ampoules at a concentration of 100 µg/mL (B. Braun Melsungen, Germany) and compounded into an ophthalmic solution by the veterinary pharmacy Drogavet (Curitiba, Brazil). The medication was diluted in saline solution for experimental use and administered topically twice daily, with a 12-hour interval between applications.

According to the manufacturer, each 2 mL ampoule contains less than 1 mmol (23 mg) of sodium, thus considered "sodium-free." Chemically, dexmedetomidine is described as the monohydrochloride of (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole, with a molecular weight of 236.7. It is water-soluble, with a pKa of 7.1, a pH range of 4.5 to 7.0, and an octanol:water partition coefficient of 2.89 at pH 7.4 (Chrysostomou & Schmitt, 2008).

As part of the experimental protocol, intraocular pressure (IOP) was measured in all animals to determine baseline values at the time of glaucoma diagnosis (Time 0 – T0), using rebound tonometry with a Portable Tonometer. After diagnosis, the animals were allocated into two treatment groups: Group 1 DORZO, consisting of 12 dogs treated with one drop of 2% dorzolamide every 8 hours, and Group 2 DEX DORZO, composed of 17 dogs treated with one drop of 2% dorzolamide every 8 hours combined with one drop of 100 µg/mL dexmedetomidine every 12 hours. A second IOP measurement (Time 7 – T7) was performed seven days after initiating the treatment protocol, along with an evaluation of potential adverse effects. A third tonometry (Time 30 – T30) was performed 30 days after treatment initiation to monitor response. To measure IOP, the examiner manually restrained animals, and three consecutive readings were taken per eye. A variance of less than 5% between readings was accepted, and the mean value was calculated for each time point.

Vital parameters were evaluated by measuring heart and respiratory rates via stethoscopic auscultation, and systolic blood pressure was measured using a vascular Doppler device, both before and 30 minutes after topical dexmedetomidine application.

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Blepharospasm and conjunctival hyperemia were recorded as either present or absent throughout the study. Changes in IOP, heart rate, respiratory rate, and systolic blood pressure over the treatment period were analyzed using comparative statistical methods. Normality of all variables was assessed using the D'Agostino-Pearson test (MedCalc Statistical Software version 20.305, MedCalc Software Ltd, Ostend, Belgium).

For variables following a normal distribution, IOP changes were analyzed using a parametric model with repeated measures (ANOVA), and results were reported as mean \pm standard deviation. In contrast, non-normally distributed variables (heart rate, respiratory rate, systolic blood pressure) were analyzed using the nonparametric Friedman test. The results were expressed as medians and interquartile ranges (IQRs). A p -value < 0.05 was considered statistically significant.

To ensure adequate statistical power, a sample size calculation was performed using a two-sample t -test power analysis as described by Cohen (1988). The study was based on the mean difference in IOP between time points and the pooled standard deviation, used to calculate Cohen's d (effect size). The power analysis was conducted with a significance level of 5% ($\alpha = 0.05$) and a power of 80% ($1 - \beta = 0.8$), assuming a normal distribution of the data. When considering the groups as a single sample, the estimated minimum required sample size was nine, confirming that the actual sample exceeded the threshold for statistical validity. This calculation was performed using the `solve_power` function from the `statsmodels.stats.power—TTestIndPower` module in Python (Python Language Reference, version 2.7; available at <http://python.org>).

3. Results

The results were presented graphically, with measures of central tendency and variability displayed in separate figures: Figure 1 for the DORZO group, Figure 2 for the DEX DORZO group, and Figure 3 providing a direct comparison between the two groups.

A comparative analysis between the DORZO and DEX DORZO groups revealed substantial differences in IOP progression over the evaluated time points. In the DORZO group, the reduction from Time 0 to Time 7 was 8.08 ± 12.88 mmHg ($p = 0.7878$). In contrast, the DEX DORZO group showed a decrease of 8.53 ± 8.05 mmHg during the same period ($p = 0.0230$), although this result did not reach statistical significance. Between Time 7 and Time 30, the DORZO group exhibited a negligible change of 0.08 ± 4.68 mmHg ($p = 1.000$), while the DEX DORZO group demonstrated a further reduction of 6.12 ± 9.62 mmHg ($p = 0.5706$). When comparing treatment efficacy from Time 0 to Time 30, the DORZO group showed a decrease of 8.17 ± 13.40 mmHg ($p = 0.6026$). In contrast, the DEX DORZO group exhibited a significantly greater reduction of 14.65 ± 9.29 mmHg ($p = 0.0012$), indicating a statistically significant treatment effect in the latter group.

Regarding heart rate, the median in the DORZO group was 114 (IQR: 19) beats per minute (bpm) at Time 0, with a slight decrease to 112 (12) bpm after 30 minutes of 2% dorzolamide instillation. In the DEX DORZO group, the median heart rate was 111 (24) bpm at Time 0, decreasing to 104 (19.5) bpm after dexmedetomidine administration. However, the difference between groups was not statistically significant ($p = 0.71393$), suggesting that any observed variation was likely due to chance rather than a pharmacological effect.

The median respiratory rate in the DORZO group was 28 (9) breaths per minute at Time 0, remaining nearly unchanged at 26 (9) bpm after treatment. In the DEX DORZO group, the rate decreased from 33.5 (16) bpm at Time 0 to 29.5 (12) bpm post-treatment. Statistical analysis revealed a significant difference between groups and time points ($p = 0.02466$), indicating that dexmedetomidine had a more pronounced effect on respiratory rate than dorzolamide.

Animal	Sex	Breed	Glaucoma	IOP (mmHg) time 0	IOP (mmHg) time 7	IOP (mmHg) time 30
1	Male	Shih tzu	Secondary	30	18	25
2	Female	Poodle	Primary	39	40	38
3	Male	Shih Tzu	Primary	48	30	38
4	Male	American Bully	Secondary	27	24	22
5	Male	Lhasa Apso	Secondary	40	32	28
6	Female	German Spitz	Primary	52	30	36
7	Female	Shih Tzu	Primary	36	34	33
8	Male	Maltese	Secondary	68	38	33
9	Female	Mixed Breed	Secondary	48	32	28
10	Female	Mixed Breed	Secondary	25	45	40
11	Male	French Bulldog	Secondary	39	35	36
12	Male	Shih Tzu	Primary	30	27	27

Table 1 – Signalment and demographic characteristics of the animals in the DORZO group, along with intraocular pressure (IOP) measurements recorded at baseline (T0), day 7 (T7), and day 30 (T30) of the study.

Animal	Sex	Breed	Glaucoma	IOP (mmHg) time 0	IOP (mmHg) time 7	IOP (mmHg) time 30
1	Female	Siberian Husky	Congenital	34	28	26
2	Male	Shih Tzu	Congenital	38	32	32
3	Female	American Staffordshire	Secondary	54	47	25
4	Female	Pug	Secondary	34	30	26
5	Female	Siberian Husky	Primary	38	28	20
6	Male	Great Dane	Primary	35	26	24
7	Female	Poodle	Primary	40	38	20
8	Male	Shih Tzu	Secondary	40	31	24
9	Female	Shih Tzu	Primary	34	24	30
10	Female	Pinscher	Primary	30	34	24
11	Male	Shih Tzu	Secondary	38	15	15
12	Female	Lhasa Apso	Primary	54	38	39
13	Female	Shih Tzu	Primary	41	31	33
14	Female	Mixed Breed	Primary	48	30	20
15	Male	Shih Tzu	Secondary	33	36	29
16	Male	Shih Tzu	Secondary	46	29	25
17	Female	Shih Tzu	Primary	55	50	21

Table 2 – Signalment and demographic characteristics of the animals in the DEX DORZO group, along with intraocular pressure (IOP) measurements recorded at baseline (T0), day 7 (T7), and day 30 (T30) of the study.

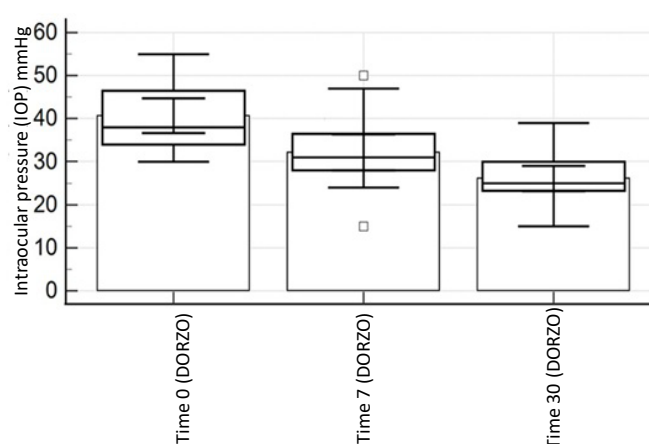


Figure 1 – Boxplot showing the distribution of intraocular pressure (IOP) values in the DORZO group at baseline (T0), day 7 (T7), and day 30 (T30). The boxplot represents descriptive statistics for a non-Gaussian variable, including median, interquartile range, and outliers.

Systolic blood pressure (SBP) was the third physiological parameter evaluated. In the DORZO group, the median SBP remained stable at 120 (15) mmHg at Time 0 and 120 (10) mmHg after 30 minutes. The DEX DORZO group also showed no relevant change, with a median of 120 (15) mmHg at Time 0 and 120 (25) mmHg post-treatment. Friedman test results indicated no statistically significant differences in SBP between groups or over time ($p > 0.05$), suggesting no cardiovascular impact from either treatment.

Throughout the 30-day follow-up, no signs of ocular discomfort or marked conjunctival hyperemia were reported in any of the dogs. However, a transient vasoconstrictive effect on the conjunctival vessels was observed immediately following dexmedetomidine instillation, followed by a gradual return to baseline vascular appearance.

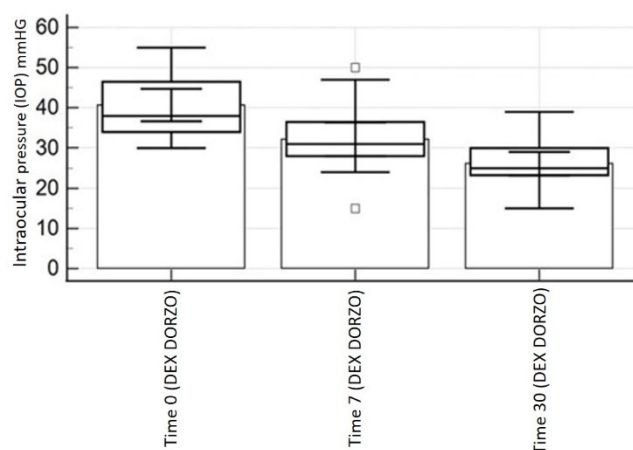


Figure 2 – Boxplot showing the distribution of intraocular pressure (IOP) values in the DEX DORZO group at baseline (T0), day 7 (T7), and day 30 (T30). The boxplot presents descriptive statistics for a non-Gaussian variable, including median, interquartile range, and outliers.

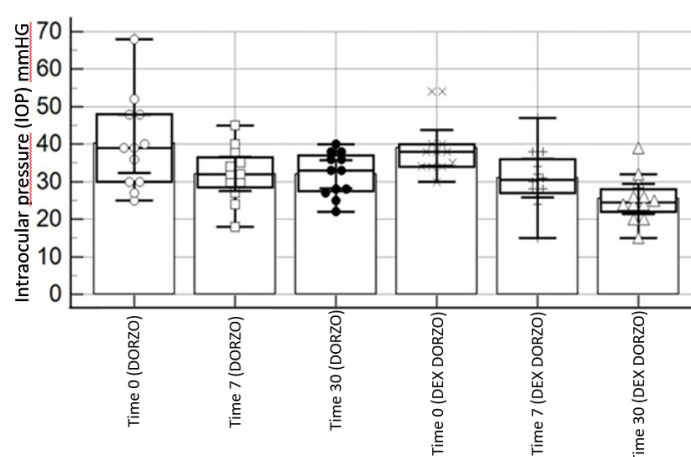


Figure 3 – Boxplot comparing the distribution of intraocular pressure (IOP) values between the DORZO and DEX DORZO groups at baseline (T0), day 7 (T7), and day 30 (T30). The boxplot displays descriptive statistics for non-Gaussian variables, including the median, interquartile range, and outliers.

4. Discussion

In this study, dexmedetomidine (DEX) was administered topically at a concentration of 100 µg/mL—matching the commercially available injectable formulation—to evaluate its ocular hypotensive efficacy. The combination of DEX with dorzolamide (DORZO) produced a more sustained and pronounced reduction in intraocular pressure (IOP) compared to DORZO alone. While IOP stabilization occurred in the DORZO group after the first week, the DEX DORZO group continued to show a gradual decrease throughout the evaluation period, suggesting an additive effect between the two agents.

Dorzolamide, a carbonic anhydrase inhibitor, is widely recognized for its efficacy and safety in the management of canine glaucoma (Sugrue, 1996; Sugrue, 2000; Cawrse et al., 2001). In this study, its use as monotherapy and in combination with DEX allowed the assessment of both its isolated and combined effects. The enhanced IOP reduction in the combination group indicates complementary mechanisms involving reduced aqueous humor production and alpha-2 adrenergic-mediated vascular modulation.

The IOP-lowering effect observed in the DEX DORZO group may be explained by complementary pharmacological actions rather than a proven synergism. Dorzolamide reduces aqueous humor formation by inhibiting carbonic anhydrase activity in the ciliary epithelium (Sugrue, 2000), whereas dexmedetomidine is believed to modulate aqueous humor dynamics through α_2 -adrenergic receptor-mediated vasoconstriction and enhancement of uveoscleral outflow (Reitsamer & Kiel, 2003; Fakhoury et al., 2021). Although these mechanisms act on distinct pathways, their combined use could plausibly result in an additive or, potentially, even a synergistic reduction of IOP, as each targets different components of intraocular fluid regulation. However, further studies are required to confirm whether this interaction represents true pharmacologic synergism or simple additivity.

Dexmedetomidine is a highly selective alpha-2 adrenergic agonist commonly used as a pre-anesthetic due to its sedative and analgesic properties (Gertler et al., 2001; Villela & Nascimento Jr, 2003). In ophthalmology, DEX has been shown to attenuate IOP spikes during anesthesia and surgical procedures. Its IOP-lowering action has been attributed to vasoconstriction of the ciliary body and consequent reduction in aqueous humor formation (Jaakola et al., 1992; Mowafi et al., 2008; Pal et al., 2011; Banga et al., 2015; Abdelhamid et al., 2016; Pegu et al., 2020; Senthil et al., 2020).

Previous investigations have demonstrated similar effects across species and routes of administration. Fakhoury et al. (2021) reported a modest IOP decrease after topical DEX instillation without ocular irritation, while Abdelhamid et al. (2016) observed greater IOP reduction in peribulbar blocks containing DEX. Vartiainen et al. (1992) found a marked decrease in IOP in rabbits with laser-induced glaucoma, and Artigas et al. (2012) described similar results in dogs after intravenous administration. These findings collectively support the ocular hypotensive potential of DEX and are consistent with the present observations.

The underlying cause of glaucoma may influence variability in IOP response. In this study, one dog with secondary glaucoma due to uveitis (ehrlichiosis-associated) exhibited a poor response to treatment, likely due to inflammatory interference with aqueous outflow, as previously described by Leiva et al. (2005) and Komnenou et al. (2007). The limited response observed in secondary glaucoma associated with uveitis reinforces that inflammatory mediators may alter aqueous humor outflow and pharmacologic responsiveness. Cytokine-induced damage to the trabecular meshwork and breakdown of the blood–aqueous barrier could reduce drug efficacy in such cases (Vohra et al., 2012; Bencurova et al., 2023).

Regarding safety, no systemic side effects were observed. MacDonald et al. (1993) reported that topical DEX achieved detectable plasma concentrations without cardiovascular alterations, which aligns with the current findings. Although DEX can induce emesis when administered systemically (Sinclair, 2003; Brioschi et al., 2018), no signs of nausea or vomiting were observed following topical application, suggesting limited systemic absorption and favorable tolerability.

In addition to established topical therapies such as dexmedetomidine, several novel experimental pharmacotherapies show promise for lowering IOP or providing neuroprotection in glaucoma. They may hold future relevance for veterinary ophthalmology. Firstly, selective modulators of the adenosine A₃ receptor, such as HL3501 (an A₃AR antagonist), have produced significant IOP reductions in rabbit and mouse models of ocular hypertension (Kim et al., 2022). Secondly, agonists of the A₁ adenosine receptor, such as Trabodenson, have demonstrated IOP-lowering effects in human and rodent trials, acting by enhancing trabecular meshwork outflow (Li et al., 2018; Waters et al., 2019). Thirdly, ATP-sensitive potassium channel openers such as CKLP1 showed significant IOP reduction in canine, primate, and murine models (Roy Chowdhury et al., 2021; Roy Chowdhury et al., 2022). Fourthly, inhibitors of the Rho-kinase (ROCK) pathway have shown efficacy in lowering IOP by increasing trabecular outflow and reducing episcleral venous pressure, with early preclinical and clinical evidence (Honjo et al., 2015). Fifthly, blockers of the renin–angiotensin system such as Losartan have demonstrated not only modulation of IOP but also neuroprotection and scleral remodeling effects in experimental glaucoma models (Quigley et al., 2015). Given these experimental developments, future veterinary studies should evaluate the cross-species pharmacokinetics, long-term safety, and efficacy of these agents, aiming to integrate them into combination protocols for canine glaucoma management (Kim et al., 2022; Roy Chowdhury et al., 2021).

Some limitations must be acknowledged. The sample size, while sufficient for preliminary evaluation, should be expanded in future studies to better represent biological variability. Inclusion of other drug classes—such as prostaglandin analogues and beta-blockers—would allow broader therapeutic comparison. Moreover, a longer follow-up would help determine long-term efficacy and safety. Despite these limitations, the results contribute to veterinary ophthalmology by demonstrating that the topical co-administration of dexmedetomidine and dorzolamide enhances IOP reduction without systemic adverse effects. This combination may represent a safe and effective adjunctive therapy for canine glaucoma and warrants further clinical evaluation.

5. Conclusion

Topical administration of dexmedetomidine (100 µg/mL) every 12 hours, combined with 2% dorzolamide every 8 hours, effectively reduced intraocular pressure (IOP) without inducing adverse effects, such as ocular irritation or anterior uveitis, in dogs with various forms of glaucoma. This combination demonstrated greater efficacy compared to dorzolamide monotherapy. While these preliminary results are promising, further studies are warranted to compare this protocol with other combinations of antiglaucoma agents and to evaluate different concentrations and dosing regimens of dexmedetomidine. Additionally, investigations involving larger cohorts are needed to understand better the therapeutic potential and long-term safety of this approach in canine glaucoma management.

Ethics Committee Approval – This study was approved by the Ethics Committee on Animal Use of the Federal University of Paraná (CEUA/UFPR) under protocol number 022/2023, in accordance with national and international ethical standards for animal experimentation.

6. References

- Abdelhamid AM, Mahmoud AAA, Abdelhaq MM, et al. Dexmedetomidine as an additive to local anesthetics compared with intravenous dexmedetomidine in peribulbar block for cataract surgery. *Saudi Journal of Anesthesia*, 10(1);50-54, 2016.
- Alm A, Nilsson SFE. Uveoscleral outflow – A review. *Experimental Eye Research*. 88(4);760-768, 2009.
- Arthur S, Cantor LB. Update on the Role of Alpha-Agonists in Glaucoma Management. *Experimental Eye Research*, 93;271-283, 2011.
- Artigas C, Redondo JI, López-Murcia M. Effects of intravenous administration of dexmedetomidine on intraocular pressure and pupil size in clinically normal dogs. *Veterinary Ophthalmology*, 15(1);79-82, 2012.
- Banga PK, Singh DK, Dadu S, et al. A comparative evaluation of the effect of intravenous dexmedetomidine and clonidine on intraocular pressure after suxamethonium and intubation. *Saudi Journal of Anesthesia*, 9(2);179-183, 2015.
- Bencurova DM, Vyborny P, Dankova P. Comparative analysis of tear cytokines in patients with glaucoma, ocular hypertension, and healthy controls. *International Ophthalmology*, 43;3559-3568, 2023.

<https://doi.org/10.5380/avs.v30i4.99797>

- Brioschi FA, Gioeni D, Jacchetti A, et al. Effect of metoclopramide on nausea and emesis in dogs premedicated with morphine and dexmedetomidine. *Veterinary Anaesthesia and Analgesia*, 45(2);190-194, 2018.
- Cantor LB. Brimonidine in the treatment of glaucoma and ocular hypertension. *Therapeutics and Clinical Risk Management*, 2(4);337-343, 2006.
- Cawrse MA, Ward DA, Hendrix DVH. Effects of topical application of a 2% solution of dorzolamide on intraocular pressure and aqueous humor flow rate in clinically normal dogs. *American Journal of Veterinary Research*, 62(6);859-863, 2001.
- Chrysostomou C, Schmitt CG. Dexmedetomidine: sedation, analgesia and beyond. *Expert Opinion on Drug Metabolism & Toxicology*, 4;619-627, 2008.
- Cohen J. Statistical power analysis for the behavioral sciences (2nd ed.). Lawrence Erlbaum Associates, 1988.
- Fakhoury H, Abdelmassih Y, El-Khoury S, et al. Effect of Topical Dexmedetomidine (0.0055%) on Intraocular Pressure in Healthy Eyes: A Randomized Controlled Trial. *Journal of Current Glaucoma Practice*, 15(2);58-63, 2021.
- Flammer J, Mozaffarieh M. What Is the Present Pathogenetic Concept of Glaucomatous Optic Neuropathy? *Survey of Ophthalmology*, 52, Suppl. 2; S162-S173, 2007.
- Gelatt KN, MacKay E.O. Effect of different dose schedules of latanoprost on intraocular pressure and pupil size in the glaucomatous Beagle. *Veterinary Ophthalmology*, 4(4);283-288, 2001.
- Gelatt KN, MacKay EO. Effect of single and multiple doses of 0.2% brimonidine tartrate in the glaucomatous Beagle. *Veterinary Ophthalmology*, 5(4);253-262, 2002.
- Gelatt KN, Mackay EO. Prevalence of the breed-related glaucomas in pure-bred dogs in North America. *Veterinary Ophthalmology*, 7(2);97-111, 2004.
- Gertler R, Brown C, Mitchell DH, et al. Dexmedetomidine: a novel sedative-analgesic agent. *Baylor University Medical Center Proceedings*, 14;13-21, 2001.
- Goel M, Picciani RG, Lee RK, et al. Aqueous humor dynamics: a review. *The open ophthalmology journal*, 4;52-59, 2010.
- Holló G. The side effects of the prostaglandin analogues. *Expert Opinion on Drug Safety*, 6(1);45-52, 2007.
- Honjo M, Inatani M, Kido N, et al. Effects of protein kinase inhibitor, HA1077, on intraocular pressure and outflow facility in rabbit eyes. *Archives of Ophthalmology*, 119(8);1171-1178, 2001.
- Honjo M, Tanihara H, Inoue T, et al. Rho-kinase inhibitors as emerging targets for glaucoma therapy. *Ophthalmology*, 122(8); 1830-1838, 2015.
- Ingram CJ, Brubaker RF. Effect of brinzolamide and dorzolamide on aqueous humor flow in human eyes. *American Journal of Ophthalmology*, 128(3);292-296, 1999.
- Jaakola ML, Melkkilä TA, Kanto J, et al. Dexmedetomidine reduces intraocular pressure, intubation responses, and anaesthetic requirements in patients undergoing ophthalmic surgery. *British Journal of Anaesthesia*, 68;570-575, 1992.
- Jayanetti V, Sandhu S, Lusthaus JA. The Latest Drugs in Development That Reduce Intraocular Pressure in Ocular Hypertension and Glaucoma. *Journal of Experimental Pharmacology*, 12;539-548, 2020.
- Kim Y, Lee H, Park J, et al. HL3501, a novel selective A3 adenosine receptor antagonist, lowers intraocular pressure in animal glaucoma models. *Investigative Ophthalmology & Visual Science*, 63(13); 5731-5742, 2022.
- Komáromy AM, Bras D, Esson DW, et al. The future of canine glaucoma therapy. *Veterinary Ophthalmology*, 22(5);726-740, 2019.
- Konnenou AA, Mylonakis ME, Kouti V, et al. Ocular manifestations of natural Canine Monocytic Ehrlichiosis (*Ehrlichia canis*): a retrospective study of 90 cases. *Veterinary Ophthalmology*, 10(3);137-142, 2007.
- Leiva M, Naranjo C, Peña MT. Ocular signs of Canine Monocytic Ehrlichiosis: A retrospective study in dogs from Barcelona, Spain. *Veterinary Ophthalmology*, 8(6); 387-393, 2005.
- Li G, Zhang L, Wu X, et al. Trabodendoson, an adenosine mimetic with A₁ receptor selectivity, lowers intraocular pressure by increasing conventional outflow facility in mice. *Investigative Ophthalmology & Visual Science*, 59(1); 383-392, 2018.
- MacDonald E, Vartiainen J, Jasberg K. Systemic absorption and systemic effects of ocularly administered dexmedetomidine in rabbits. *Current Eye Research*, 12(5);451-460, 1993.
- Maggio F, Bras D. Surgical treatment of canine glaucoma: Filtering and End-Stage Glaucoma Procedures. *Veterinary Clinics of North America: Small Animal Practice*, 45;1261-1282, 2015.
- Mattos-Junior E, Pypendop BH, Cabrini TM, et al. Effects of dexmedetomidine alone or in combination with opioids on intraocular pressure in healthy Beagle dogs. *Veterinary Anaesthesia and Analgesia*, 48(4);541-544, 2021.
- Mowafi HA, Aldossary N, Ismail AS, et al. Effect of dexmedetomidine premedication on the intraocular pressure changes after succinylcholine and intubation. *British Journal of Anaesthesia*, 100(4);485-489, 2008.
- Oh DJ, Martin JL, Williams AJ, et al. Analysis of expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human ciliary body after latanoprost. *Investigative Ophthalmology & Visual Science*, 47(3);953-963, 2006.
- Pal CK, Ray M, Sen A, et al. Changes in intraocular pressure following administration of suxamethonium and endotracheal intubation: Influence of dexmedetomidine premedication. *Indian Journal of Anesthesia*, 55(6);573-577, 2011.
- Pegu J, Purang AK, Dubery S, et al. Effect of dexmedetomidine on intraocular pressure as an additive in peribulbar block during glaucoma surgery. *Indian Journal of Ophthalmology*, 69 (6), 612-616, 2020.
- Plummer CE, MacKay EO, Gelatt KN. Comparison of the effects of topical administration of a fixed combination of dorzolamide-timolol to monotherapy with timolol or dorzolamide on IOP, pupil size, and heart rate in glaucomatous dogs. *Veterinary Ophthalmology*, 9(4);245-9, 2006.

- Plummer CE, Regnier A, Gelatt KN. The canine glaucomas. In: Gelatt KN, Gilger BC, Kern TJ, eds. *Veterinary Ophthalmology*, vol 2, 5th edition. Ames, IA: John Wiley Inc;1050-1145, 2013.
- Quigley HA, Bowman AT. The number of people with glaucoma worldwide in 2010 and 2020. *British Journal of Ophthalmology*, 90;262-267, 2006.
- Quigley HA, Pitha I, Welsbie DS, et al. Losartan treatment protects retinal ganglion cells and alters scleral remodeling in experimental glaucoma. *Investigative Ophthalmology & Visual Science*, 56(7); 4149-4161, 2015.
- Rao PV, Deng P, Kumar, J, et al. Modulation of aqueous humor outflow facility by the Rho kinase-specific inhibitor Y-27632. *Investigative Ophthalmology & Visual Science*, 42(5);1029-1037, 2001.
- Reitsamer HA, Kiel JW. Relationship between ciliary blood flow and aqueous production in rabbits. *Investigative Ophthalmology & Visual Science*, 44(9);3967-3971, 2003.
- Reitsamer HA, Posey M, Kiel JW. Effects of a topical alpha2 adrenergic agonist on ciliary blood flow and aqueous production in rabbits. *Experimental Eye Research*, 82(3);405-415, 2005.
- Richter M, Krauss AH, Woodward DF, et al. Morphological changes in the anterior eye segment after long-term treatment with different receptor selective prostaglandin agonists and a prostamide. *Investigative Ophthalmology and Visual Science*, 44(10);4419-26, 2003.
- Roy Chowdhury U, Brackett D, Hong H, et al. Pharmacological profile and ocular hypotensive effects of Cromakalim Prodrug 1 (CKLP1), a novel ATP-sensitive potassium channel opener, in normotensive dogs and non-human primates. *Journal of Ocular Pharmacology and Therapeutics*, 37(5);251-260, 2021.
- Roy Chowdhury U, Brackett D, Hong H, et al. Effect of ATP-sensitive potassium channel openers on intraocular pressure in ocular hypertensive animal models. *Investigative Ophthalmology & Visual Science*, 63(2);15, 2022.
- Sambhara D, Aref AA. Glaucoma management: relative value and place in therapy of available drug treatments. *Therapeutic Advances in Chronic Disease*, 5(1);30-43, 2014.
- Senthil S, Burugupally K, Rout U, et al. Effect of Intravenous Dexmedetomidine on Intraocular Pressure in Patients Undergoing Glaucoma Surgery Under Local Anesthesia: A Pilot Study. *Journal of Glaucoma*, 29(10);846-850, 2020.
- Sinclair MD. A review of the physiological effects of alpha2-agonists related to the clinical use of medetomidine in small practice. *The Canadian Veterinary Journal*, 44(11);885-897, 2003.
- Skaat, A, Rosman, MS, Chien JL. Effect of pilocarpine hydrochloride on the Schlemm canal in healthy eyes and eyes with open-angle glaucoma. *Journal of the American Medical Association Ophthalmology*, 134(9);976-981, 2016.
- Stamer WD, Piwnica D, Jolas T, et al. Cellular basis for bimatoprost effects on human conventional outflow. *Investigative Ophthalmology & Visual Science*, 51(10);5176-5181, 2010.
- Studer ME, Martin CL, Stiles J. Effects of 0.005% latanoprost solution on intraocular pressure in healthy dogs and cats. *American Journal of Veterinary Research*, 61(10);1220-1224, 2000.
- Sugrue MF. The preclinical pharmacology of dorzolamide hydrochloride, a topical carbonic anhydrase inhibitor. *Journal of Ocular Pharmacology and Therapeutics*, 12(3);363-376, 1996.
- Sugrue MF. Pharmacological and ocular hypotensive properties of topical carbonic anhydrase inhibitors. *Progress in Retinal and Eye Research*, 19(1);87-112, 2000.
- Tanna AP, Johnson MR. Rho kinase inhibitors as a novel treatment for glaucoma and ocular hypertension. *Ophthalmology*, 125(11);1741-1756, 2018.
- Tham YC, Li X, Wong TY, et al. Global Prevalence of glaucoma and projections of glaucoma burden through 2040. *Ophthalmology*, 121(11);2081-2090, 2014.
- Vartiainen J, MacDonald E, Urtti A, et al. Dexmedetomidine-Induced Ocular Hypotension in Rabbits with Normal or Elevated Intraocular Pressures. *Investigative Ophthalmology & Visual Science*, 33(6);2019-2023, 1992.
- Villela NR, Nascimento JR P. Uso de dexmedetomidina em anestesiologia. *Revista. Brasileira de Anestesiologia*, 53;97-113, 2003.
- Vohra R, Tsai JC, Kolko M. The role of inflammation in the pathogenesis of glaucoma. *Survey of Ophthalmology*, 58(4);311-320, 2012.
- Waters, H., Johnson, A., Smith, R., et al. Topical trabodenoson is neuroprotective in a rodent model of anterior ischemic optic neuropathy. *Translational Vision Science & Technology*, 8(6); 47, 2019.
- Webb TER. A review of glaucoma surgical therapy. *Veterinary Ophthalmology*, 24(S1);34-38, 2021.
- Weinreb RN, Aung T, Medeiros FA. The Pathophysiology and Treatment of Glaucoma: A Review. *Journal of the American Medical Association*, 311(18);1901-1911, 2014.
- Whelan NC, Welch P, Pace A, et al. A comparison of the efficacy of topical brinzolamide and dorzolamide alone and in combination with oral methazolamide in decreasing normal canine intraocular pressure. 30th Annual Meeting of the American College of Veterinary Ophthalmologists. Chicago (IL), October 1999.
- Wilkie DA, Latimer CA. Effects of topical administration of timolol maleate on intraocular pressure and pupil size in dogs. *American Journal of Veterinary Research*, 52(3);432-435, 1991.
- Zimmerman, T.J. Topical ophthalmic beta blockers: a comparative review. *Journal of Ocular Pharmacology and Therapeutics*, 9(4);373-384, 1993.