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



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Vol. 30 No. 4 (2025)

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

Submitted: 27/03/2025
Accepted: 04/11/2025

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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 α_2 -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

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



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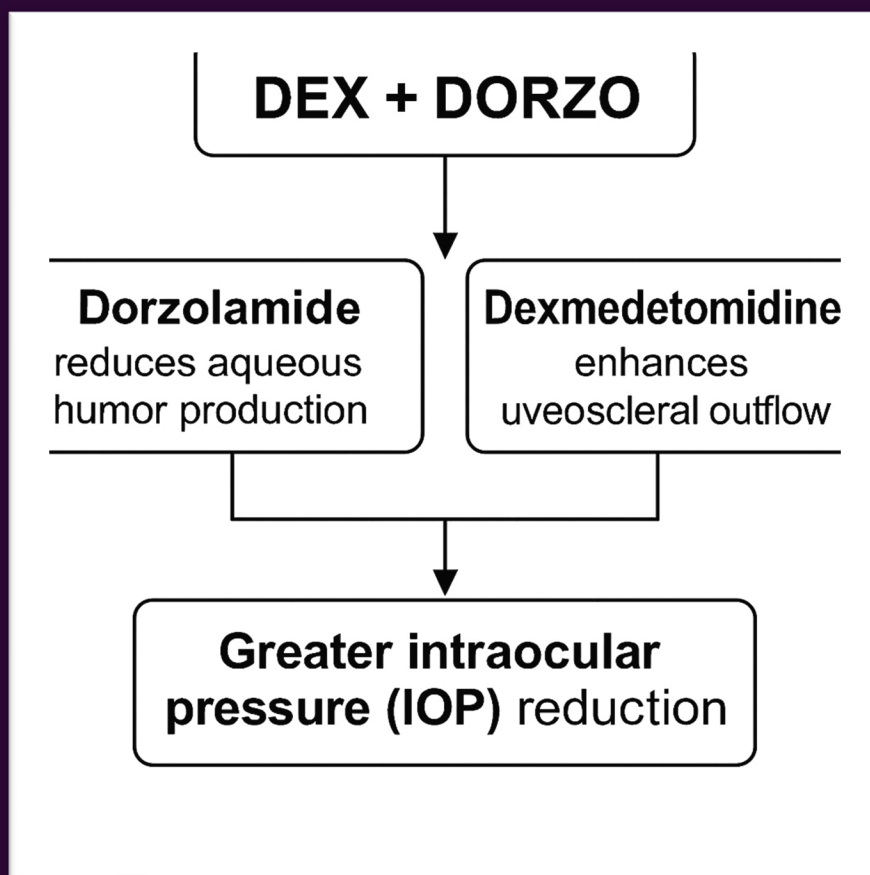
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GRAPHICAL ABSTRACT



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