Postoperative Ocular Hypertension in Dogs Undergoing Phacoemulsification: Investigation of Risk Factors and Evaluation of Medical Prophylaxis

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ABSTRACT

Development of cataracts is a relatively frequent ocular disease of the dog and cataract extraction via phacoemulsification (PE) is commonly performed by veterinary ophthalmologists. Postoperative ocular hypertension (POH) describes the elevation of pressures within the eye during the acute postoperative period and can result in vision loss and poor surgical outcome. Relatively little is known about risk factors or efficacy of prophylactic treatment for POH, and current clinical practice with regard to pressure monitoring and medication administration are highly variable. The literature on POH prophylaxis in humans indicates that improved efficacy may be achieved with a multi-dose approach and that dorzolamide hydrochloride/timolol maleate (DHTM) may be more efficacious than other pressure lowering medications. The canine literature on POH prophylaxis is limited and DHTM has not yet been evaluated despite common use in the clinical setting. Our objectives, therefore, were to investigate risk factors for POH and to test the hypothesis that perioperative topical ophthalmic dorzolamide hydrochloride 2%/timolol maleate 0.5% (DHTM) reduces the prevalence and/or severity of postoperative ocular hypertension (POH) in dogs undergoing cataract extraction by phacoemulsification (PE). We employed a randomized double-masked placebo-controlled study and enrolled 103 dogs (180 eyes) presenting for unilateral or bilateral PE. Select historical, signalment, ophthalmic examination, and surgical data was collected. Dogs were treated with DHTM or Blink Contacts (BC) placebo at 14- and 2-h preoperatively and at conclusion of surgical closure. Intraocular pressures were assessed by rebound tonometry at 2, 4, 6, and 8 hours after surgery and at 8 am the following morning. POH was defined as IOP>25 mmHg and intervention consisted of latanoprost 0.005% if IOP rose to 26 mmHg - 45 mmHg or surgeon treatment of choice if >45 mmHg. Our investigation of risk factors yielded a statistically significant association only with surgeon and surgical time, which were also associated with one another. DHTM significantly reduced the prevalence of POH in comparison with BC (26% versus 49% of eyes, OR=0.36; 34% versus 62% of dogs, OR=0.32). There was also a trend toward reduction of POH severity in DHTM-treated eyes (POH value 37.17±10.47 mmHg with BC, 32.67±6.39 mmHg with DHTM). DHTM-treated eyes that developed POH were significantly more likely to respond favorably (1 hour post-treatment IOP <25 mmHg) to treatment with latanoprost than those in the BC group (76% versus 51%, OR=3.87). We conclude that multi-dose perioperative administration of DHTM may be recommended in dogs undergoing PE to reduce the risk of POH and improve responsiveness of POH to treatment with latanoprost.

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Table of Contents:

1. Introduction**:** Cataracts, Cataract Surgery, and Postoperative Ocular Hypertension (POH) in The Dog..……....1
    - Mechanisms of Postoperative Pressure Rise……..5
    - Investigations of Prevention and Prophylaxis……..10
    - Risk Factors for POH……...13
    - Treatment of POH… ……...15
    - Implications and Clinical Significance of POH……...16
2. Perioperative Administration of Topical Dorzolamide Hydrochloride/Timolol Maleate Reduces Postoperative Ocular Hypertension in Dogs Undergoing Cataract Surgery….18
    - Abstract……18
    - Introduction……..18
    - Materials and Methods…….19
    - Results……..23
    - Discussion……29
    - References……...35
3. Conclusions……40

References……...41

Appendix A: Annotated List of Figures…….....49

Figures:

1. Prevalence of POH in 103 dogs undergoing PE was significantly affected by surgeon (p=0.0080)……..25
2. Preoperative IOPs in 74 eyes of 39 dogs before and after administration of 1 dose of BC or DHTM 14 hours prior to planned time of surgical induction…….……..26
3. IOP values 2-8 hours post-phacoemulsification in 180 eyes of 103 dogs receiving DHTM or BC…….…..26
4. Prevalence of POH in 180 eyes of 103 dogs undergoing PE. POH was significantly (*) reduced by perioperative treatment with DHTM versus BC both by eye (p=0.0048) and by dog (p=0.0044)……..27
5. Prevalence of no POH, unilateral POH, and bilateral POH in 77 dogs undergoing bilateral PE surgery……..……....27
6. New cases of POH by eye over time for 66 eyes of 49 dogs undergoing PE.…….28
7. Cumulative frequency of POH in DHTM treated (24) and BC treated (42) eyes of dogs undergoing PE.……..……..28
8. Responsiveness of 60 eyes (25 DHTM treated; 35 BC treated) with POH in the range of 26-45 mmHg to treatment with 1 drop of topical ophthalmic 0.005% latanoprost.……...29

Abbreviations:
BC: Blink Contacts
CAI: Carbonic anhydrase inhibitor
DHTM: Dorzolamide hydrochloride 2%/Timolol maleate 0.5% Ophthalmic Solution
IOP: Intraocular Pressure
LOCF: Last outcome carried forward
PE: Phacoemulsification
POH: Postoperative ocular hypertension
TID: Three times daily
vI/A: Viscoelastic irrigation/aspiration time (s)
OR: Odds Ratio

1. Introduction:

Cataracts, Cataract Surgery, and Postoperative Ocular Hypertension (POH) in The Dog

The primary function of the crystalline ocular lens is to refract incoming light rays such that a focused image is generated on the retina. Disorders of the lens are generally limited to those of embryologic malformation, aberrant location, and loss of transparency. When imperfections in crystalline lens transparency arise, refraction of light is altered and the term cataract is used to describe the resultant opacity detected during clinical examination. Etiopathogeneses of canine cataracts are diverse, most commonly including embryologic or developmental anomalies, genetic defects, traumatic or inflammatory disturbances, changes associated with senility, and systemic metabolic derangements.[1] Of these, canine candidates for cataract surgery most commonly present with cataract secondary to senescence, genetic predisposition, or diabetes mellitus.[2-5] Senile cataracts are generally suspected in dogs presenting later in life with bilateral lens opacities, while cataracts are considered more likely to be hereditary in young to middle-aged patients with unilateral or bilateral lens opacities and no evidence of underlying metabolic or ocular disease. Although a genetic basis for cataractogenesis has been established in a number of dog breeds, the juvenile cataracts seen in many breeds are merely presumed to be inherited based on high incidence within the breed, age of onset, and, in some cases, the characteristic appearance of the cataract itself, which varies from breed to breed.[6] Cataract development is seen in approximately 80% of diabetic dogs within 16 months of diabetes diagnosis[7] and diabetic patients contribute significantly to the population of dogs undergoing cataract surgery, making up 20-33% of surgical candidates in some studies.[2,3,8]

Although the etiology of cataract is often noted during patient evaluation, classification by stage is of greater clinical significance, both from the standpoint of effect on vision and surgical decision-making. Cataract stages are often defined both by percentage of lens volume involved and by presence or absence of secondary degenerative changes. Incipient cataracts are those estimated to occupy less than 10-15% of lens volume, immature cataracts occupy 15-95%, and cataracts are considered mature when approximately 100% of the lens fibers are abnormal, thus obliterating all fundic reflection. A cataract is termed hypermature when there is evidence of significant proteolysis and subsequent loss of lens volume, dystrophic mineralization resulting in refractile foci within the lens or capsule, or lens capsule wrinkling associated with epithelial-mesenchymal transition of lens epithelial cells that cause contraction of the normally smooth lens capsule.[1] Staging of cataracts is important both because of the relative impact of cataract on vision and due to the fact that there has been association with more severe intraocular inflammation[9] and poorer surgical outcome with advancing stage of cataractogenesis.[10-13]

Regardless of stage or etiology, there is currently no medical treatment for cataracts. Surgical candidacy is determined based on the presence or impending development of clinically significant visual disturbance as well as the suitability of the animal for administration of anesthetic, antimicrobial, and anti-inflammatory medications.[12] Over time, surgical techniques have evolved and success rates have improved, leading clinicians to shift these criteria such that treatment is recommended at an earlier stage of disease. Canine cataract surgery was initially described in the late 1800s and early 1900s and involved dislocation of the opaque lens into the vitreous or extraction of the lens with or without the lens capsule (intracapsular lens extraction

(ICLE) or extracapsular lens extraction (ECLE)).[14] Up through the late 1950s, both physicians and veterinarians reported various techniques for ICLE and ECLE but success rates and postoperative vision remained extremely poor in canine subjects.[14] A critical turning point in modern cataract surgery was Dr. Kelman's development of the phacoemulsification procedure in the late 1960s, wherein a needle attached to an ultrasonic handpiece is inserted into the eye via a small incision and the lens is subsequently emulsified and aspirated without the need for large incision ICLE or ECLE procedures. This technique enables the surgeon to remove cataractous lens material from the eye while minimizing surgical factors that previously contributed to poor outcome, including trauma, size of corneal incision, degree and duration of eye collapse, and risk of vitreal prolapse into the anterior chamber, among others.[15]

With the advent and refinement of phacoemulsification and aspiration surgery (PE) in dogs, success rates improved. Startup reviewed his own surgical outcomes as well as those published by his contemporaries in the late 1950s – early 1960s and found failure rates to be consistently 50%, with good outcomes achieved in only 20% of cases.[16] In a 1985 retrospective study of dogs undergoing extracapsular cataract extraction at the university of Illinois, a short term success rate of 79% was seen at six weeks postoperatively.[17] Over a similar time period, Miller et al. demonstrated a short-term success rate of 94% utilizing phacofragmentation rather than ECLE and Davidson et al. showed good or excellent results in 90% of cases.[18,19] Klein reported vision retention in 90% of eyes with a median of 302 days of follow up in 2011[3] and Sigle et al. reported a failure rate of <10% up to three years postoperatively amongst 172 dogs or 290 operated eyes in 2005.[13] As surgical outcomes have improved, there has been a shift in surgical selection criteria. Historically, surgeons waited until cataractogenesis and associated blindness were complete or nearly so, altering the risk versus reward ratio such that surgical intervention was appropriate even with low success rates. Due to improvement in outcomes with phacoemulsification, waiting until the cataract reaches a stage of hypermaturity is considered contraindicated due to increased risk of complications and surgery is often recommended at earlier stages so long as some visual impairment is considered present or imminent.[11-13]

Benefits of cataract removal include restoration of vision and reduction of cataract-related complications, such as glaucoma and chronic uveitis.[11] Although this procedure is commonly performed by veterinary ophthalmologists and reported success rates vary between 79.4-95%,[3,11,13] postoperative complications are not infrequent and poor surgical outcomes may result. Potentially blinding postoperative complications include endophthalmitis, retinal detachment, glaucoma, endothelial degeneration, posterior lens capsule opacification, and postoperative ocular hypertension.[2,3,13,20-22] Of these, glaucoma is the complication that most commonly results in blindness, developing in up to 38% of dog eyes after cataract extraction surgery.[2,3,11,19]

In veterinary medicine, glaucoma is currently defined as a group of diseases manifesting with progressive degenerative optic neuropathy where the common risk factor is elevated intraocular pressure.[23] Increases in intraocular pressure signal dysfunction of aqueous humor dynamics, as balance of aqueous humor flow is the key determinant of pressure within the eye. Aqueous humor is produced by the nonpigmented ciliary epithelium, fills the posterior and anterior chambers of the anterior segment of the eye, and leaves the anterior chamber via pressure-dependent (conventional or corneoscleral trabecular meshwork) or pressure-independent (nonconventional or uveoscleral) outflow pathways. [24,25] In the dog, conventional outflow

accounts for the large majority of drainage, and disruption of flow due to hereditary abnormalities or acquired inflammatory or neoplastic diseases results in elevated intraocular pressure and secondary damage to retinal ganglion cells and the retina.[26,27]

In glaucomatous dogs, elevated intraocular pressure is associated with progressive optic nerve and retinal damage and, in most cases, the disease is eventually blinding despite therapy.[23] Cataract and cataract surgery are both documented risk factors for subsequent development of glaucoma. [11,20,27] Postoperative or aphakic/pseudophakic glaucoma is diagnosed in dogs that have undergone cataract surgery, when elevated intraocular pressures and subsequent optic nerve and retinal damage are detected in the postoperative period ranging from days to years after surgery.[22] In contrast to glaucoma, postoperative intraocular hypertension (POH) is a distinct clinical syndrome characterized by a transient elevation of intraocular pressure occurring within the acute post-cataract surgery period and not necessarily resulting in clinically detectable secondary intraocular pathology.

The human medical literature does not use the term POH but describes early ocular hypertension occurring within 3-8 hours of surgery, with a prevalence ranging from 0-59%,[28-30] including 25% prevalence of intraocular pressure (IOP) > 30 mmHg at 4-6 hours[30] or 3.6% prevalence of IOP >40 mmHg.[28] Peak incidence in humans has been reported to range from 2-12 hours postoperatively, [31-33] but pressures are frequently only recorded at 24 hours or later in the postoperative period. POH is defined by most veterinary researchers as an IOP of >25-27 mmHg occurring within the acute postoperative period[2,3,34-38] and may result in vision threatening damage to the retina, optic nerve, and corneal endothelium.[37,38] POH is a common occurrence in dogs undergoing routine phacoemulsification and aspiration (PE) of cataracts, reportedly affecting up to 75% of patients[2,3,34-40] with a reported peak incidence at two to five hours after surgery.[2,35,37,38] Review of the literature pertaining to POH in dogs reveals several limitations to our understanding of this condition. In particular, the large majority of studies are retrospective in nature and fail to adhere to common definitions or standardized monitoring or treatment protocols. However, general trends can be ascertained that are of utility in clinical practice and in planning future prospective work.

In 1987, Miller et al. reported acutely elevated postoperative intraocular pressures in 37.5% dogs undergoing cataract surgery, but specific values were not documented; in most of these cases, the pressure elevation resolved without treatment.[18] Smith et al. published a retrospective evaluation of 100 dogs undergoing cataract surgery by PE or ECLE in 1996, demonstrating a POH prevalence of 48.9% with a more rapid onset of elevated pressure in the PE group compared to the ECLE group (mean time to POH of 3.9 hours versus 8.4 hours).[36] Miller et al. performed a prospective study in normal beagle dogs to investigate possible mechanisms of POH. Intraocular pressures were measured hourly for eight hours, then at 12 h and 24 h after phacoemulsification. IOP reached a peak of >30 mmHg in all dogs by three hours (mean peak pressure 49.9 $\pm$ 5.0 mmHg, range 40-74 mmHg), but elevated pressure resolved by 24 hours in those dogs not euthanized earlier.[38] Stuhr et al. prospectively evaluated 32 healthy beagle dogs undergoing phacoemulsification with or without the use of intracameral carbachol or placement of an intraocular lens and measured intraocular pressures at three and six hours after surgery. POH, defined as IOP >27 mmHg, was detected in 75% of control dogs and in none of the dogs receiving intracameral carbachol. In the control group, three hour postoperative intraocular

pressure was 36.4 +/- 14 mmHg; no dog with a pressure <27 mmHg at 3 hours developed POH at the six hour time point. The overall prevalence of POH in the study was 37.5%.[39] In a retrospective study of 22 previously normotensive canine patients undergoing phacoemulsification, Lannek et al. reported treating six eyes for "large acute postoperative increases in IOP" and two eyes were treated with hypotensive medications due to a pressure that was considered "too high" for the degree of anterior uveitis detected on slit lamp biomicroscopy (flare). Although there is evidence that POH was occurring in this population, pressure and surgical protocols were poorly defined, which limits interpretation of these results.[34]

In a more standardized examination of POH, Chahory et al. prospectively compared 25 dogs undergoing manual extracapsular cataract extraction and 25 undergoing PE, monitoring intraocular pressure at 1, 3, 5, and 18 hours in the acute postoperative period. This study yielded POH prevalence of 16% and 20% for ECCE and PE, respectively, with no significant difference between surgical techniques. Time of POH was not specifically recorded, but there was a significant increase in IOP at three and five hours in comparison with baseline when both groups were combined. Antihypertensive treatment was instituted at or above 30 mmHg only and was required in 5 dogs; at 18 hours, only 1/50 dogs had an intraocular pressure measurement >25 mmHg.[35] In a retrospective study of dogs undergoing PE, Crasta et al. also demonstrated an early postoperative timeframe for POH. IOP was measured at two and four hours after surgery, as well as the following morning. Crasta defined POH as IOP >27 mmHg in one or both eyes and found a prevalence of 23.9% of eyes or 34.1% of dogs. In 94.7% of eyes experiencing POH, the pressure spike occurred by two hours after surgery; 64.3% of cases were unilateral and 35.7% were bilateral.[37] In a retrospective study by Klein et al., POH was defined as IOP >25 mm Hg extending out to a time period of two weeks after surgery with or without antihypertensive treatments; pressure was measured at 1, 5, and 20 hours, then weekly. POH was detected in 22.9% of eyes between 0 hours and 11 days after surgery, with the median time being less than 24 hours and the mean highest IOP being 40.8 ± 13.2 mmHg; the prevalence of POH at one and five hours was not specifically reported. Importantly, the eyes in this study received variable topical and systemic antihypertensive medications dependent on surgeon preference and intracameral carbachol was used in all cases,[3] likely biasing peak pressures, prevalence, and time to onset of POH. Despite this, results were consistent with previous papers with regard to early onset of POH and prevalence within the canine PE population.

In a retrospective study examining POH and glaucoma, Moeller et al. examined the effect of breed (Labrador retriever). POH was defined as a documented pressure of >25 mmHg occurring within the first 24 hours postoperatively, but pressure measurement intervals were not standardized due to the retrospective nature of the paper; additionally, dogs were variably treated with prophylactic antiglaucoma medications and intracameral carbachol. Data analysis yielded a POH prevalence of 28% in Labradors and 12% in non-Labradors in the first five hours after surgery, which increased to 33% and 18% by 24 hours.[2] Taking a prospective approach, Mclean et al. evaluated the effect of preoperative topical steroid administration on postoperative outcomes. Dogs were treated with topical 1% prednisolone acetate three times daily (TID) for either seven days or one day preoperatively and postoperative intraocular pressures were measured at four and eight hours after PE. Increased duration of preoperative steroid use was an apparent risk factor for POH in this study, as 60% of the dogs treated for seven days but only 18% of the dogs treated for one day developed pressures of >25 mmHg within the first 24 hours

after surgery.[40] Dogs with evidence of significant intraocular inflammation prior to surgery were excluded from this study, creating a significant bias and limiting the application of results to cases defined by the study parameters. Because some degree of lens induced uveitis is considered to occur at all stages of cataract,[9,41] the common practice of preoperative topical anti-inflammatory treatment is unlikely to be altered without corroborating evidence of an exacerbating effect on POH.

Clearly, the majority of these studies are retrospective in nature and thus an effective summary is limited by lack of standardization of surgical, medical, and statistical protocols between papers. Generally, however, it is possible to conclude that this body of literature implicates POH as a frequent and significant complication of canine cataract surgery in the acute postoperative period. Further prospective work is needed to refine our understanding of POH and create targeted, effective, and scientifically based monitoring and prophylactic treatment protocols.

Mechanisms of Postoperative Pressure Rise:
Despite the clinical implications of monitoring and hospitalization and the potential for negative sequelae related to POH, large gaps in information exist within the veterinary literature regarding mechanism, predisposing risk factors, and optimal treatment and prophylaxis strategies. Although the mechanism has not been precisely described, both patient and surgical factors are thought to play a role in the development of POH. Hypothesized mechanisms include decreased aqueous humor outflow facility[3,18,38,42] and increased intraocular fluid production.[31,38] In health, aqueous humor is produced by the epithelium of the ciliary body, flows through the posterior chamber and into the anterior chamber via the pupil, and then leaves the anterior chamber by either the corneoscleral trabecular meshwork or uveoscleral outflow pathway. [24,25,43] The rate of outflow equals the rate of production, such that intraocular pressure is maintained within a normal range.[44] Flow via the trabecular meshwork is regulated by the degree of resistance, which is determined by tissue of the trabecular meshwork as well as venous pressure in collecting vessels; outflow via this route is considered pressure dependent, as flow has been demonstrated to increase with increasing intraocular pressure.[43] Uveoscleral outflow is comprised of aqueous humor diffusion into the iris, ciliary body, and vitreous; this flow is generally considered independent of intraocular pressure, but does vary with hydrostatic pressure gradients and the amount of extracellular space present in the absorbing uveal tissue. For example, contraction of the ciliary body musculature decreases uveoscleral outflow and relaxation or cycloplegia secondary to atropine increases outflow via this route.[43]

Mechanisms of POH have largely been hypothesized based on presumed alterations in normal aqueous humor dynamics due to inflammatory, mechanical, or surgical factors. Although some authors have proposed increased aqueous humor production as a cause of POH, [31,38] the majority of both theoretical and scientifically demonstrated causes of elevated intraocular pressure are related to impaired aqueous humor outflow. The latter can be grouped into morphologic alterations of the drainage pathways versus blockage of drainage channels with endogenous or exogenous debris secondary to the surgical procedure.

In Miller's 1997 prospective study, unilateral phacoemulsification was performed in healthy research dogs and globes were evaluated both grossly and histopathologically after euthanasia at 0, 3, or 24 hours postoperatively. Control dogs underwent anterior chamber decompression

without PE. POH developed in all dogs by three hours with a mean maximal pressure of 49.9 ± 5.0 mmHg. Morphologic alterations potentially reducing aqueous humor outflow in this study included reduced ciliary cleft cross-sectional surface area and width at time 0 that did not occur in eyes undergoing anterior decompression without PE; however, pressure normalized by 24 hours despite the finding that cleft collapse became significantly worse.[38]

More recently, ultrasound biomicroscopy has been used to investigate angle and globe morphology before and after PE in humans and dogs. Rose et al. found that POH was more common in dogs with larger preoperative iridocorneal angle (ICA) and angle opening distance (AOD) measurements when measured prior to pupillary dilation. Odds of developing POH increased by 11% for each degree of increase in preoperative ICA greater than 13 degrees. The changes in the ICA and AOD after surgery were not significantly associated with POH. Interestingly, pre- and post-dilation values for ICA and AOD were not significantly different. The change between preoperative and postoperative values of ICA and AOD were also assessed as predictors for POH; no significant association was detected and postoperative changes in these measurements were markedly variable. Stage of cataract and diabetes mellitus were also not significantly associated with preoperative ICA or AOD measurements. There was a trend for increasing cataract maturity to be associated with decreasing ICA and AOD measurements preoperatively, which was thought to be related to a change in lens size.[45] Crumley et al. also utilized ultrasound biomicroscopy to investigate the use of preoperative angle opening distance to predict postoperative intraocular hypertension or glaucoma, setting their cut off for POH at >30 mmHg. They found only a weak association between angle opening distance prior to phacoemulsification surgery and IOP at one day postoperatively and no association could be derived when the relationships between AOD and IOP immediately postoperatively, at one week, or at one month were evaluated. This study utilized previously reported landmarks for AOD, and AOD was used to estimate the openness of the ICA at the anterior margin of the trabecular meshwork. [46]

In humans, ultrasound biomicroscopy has been used to evaluate the relationship between axial globe length, anterior chamber depth, and the prevalence of POH. Globes with larger axial length were found to be at higher risk of having intraocular pressures >25 mmHg both at one day and persisting for three weeks postoperatively, indicating the need for closer monitoring in these patients.[47] Axial globe length has not been assessed as a predictor of POH in dogs. Pre- and postoperative examination of the human ICA, anterior chamber depth (ACD), and IOP, revealed that phacoemulsification resulted in reduced IOP (first postoperative measurement occurred at one day, meaning that POH may have been missed), increased anterior chamber depth, and a wider ICA.[48] The authors of these papers hypothesize in many cases that removal of a cataractous lens could cause secondary changes in angle morphology that result in impaired aqueous humor outflow, but there is little evidence to explain the resolution of the intraocular hypertension whilst the angle morphology remains altered.

Cataract surgery requires the use of repeated topical applications of one or more cycloplegic agents to facilitate visualization of the lens via mydriasis.[12] Mydriasis is hypothesized to reduce aqueous humor outflow facility due to partial obstruction of the iridocorneal angle with iris tissue. However, others have also suggested that relaxation (or paralysis) of the ciliary body musculature increases uveoscleral outflow by increasing intercellular spaces and decreasing

tissue hydrostatic pressure.[43] An ultrasound biomicroscopy study evaluating 24 normal dogs undergoing unilateral pharmacologic mydriasis with 0.5% tropicamide revealed a secondary increase in iridocorneal angle and decrease in the opening width of the ciliary cleft, width of the mid ciliary cleft, and overall length of the ciliary cleft as well.[49] Evidence that pharmacologic mydriasis can cause an increase in pressure in eyes with pre-existing angle abnormalities does, however, exist in both humans and animals. Provocative mydriatic testing for angle closure glaucoma has been investigated in humans and dogs. Patel et al. found that none of the 4870 human patients administered topical mydriatics at a glaucoma screening center experienced acute angle closure glaucoma; dilation was not performed in 432 patients identified as having a shallow anterior chamber, a history of glaucoma, or blindness. Of all patients undergoing screening, 1770 were referred to the glaucoma specialty clinic where 38 were diagnosed with "potentially occludable" angles on gonioscopy; 24 of these 38 patients had previously undergone pharmacologic mydriasis with 0.5% tropicamide and none had experienced acute primary angle closure glaucoma. An increase of >5 mmHg was seen in one patient classified as having a potentially occludable angle. Patel concluded that there was minimal risk (less than 1/333) to the general patient population to undergo pharmacologic mydriasis for diagnostic purposes if prescreening was performed for shallow anterior chamber or history of glaucoma.[50] The results of this study, however, may not be directly applicable to canine medicine, as prevalence of angle closure glaucoma is significantly higher in dogs compared with humans. Provocative testing undertaken in 18 month old Basset Hounds with inherited primary angle-closure glaucoma and normal beagles demonstrated an abrupt rise in pressure in dogs with pre-existing angle abnormalities. At 30 minutes, tropicamide resulted in 35% elevation of intraocular pressure and addition of 1% atropine increased this elevation to 50% above baseline values by 12 hours. At that point, latanoprost 0.005% was administered and was able to reduce pressure by 69%, below baseline values, by four hours after treatment. No elevation or response was seen in normal beagles with the administration of tropicamide or atropine and thus no latanoprost was administered.[51] A study examining nonglaucomatous Cocker Spaniels, Golden Retrievers, and Siberian Huskies, found that 60% of dogs had a change in IOP of 5 mmHg or less in response to topical tropicamide administration at 30 minutes. Huskies had a higher average baseline IOP (17.2 ± 3.7 mmHg versus 14.2 ± 2.8 in Spaniels and 14 ± 1.9 in Retrievers) and two exceeded the 97.5% upper limit for IOP in this population (22 mmHg) at baseline. After tropicamide administration, only four animals had an intraocular pressure change >8 mmHg; these were all Huskies and ranged from 9-17 mmHg increase in response to mydriasis.[52] Prevalence of inherited predisposition to angle closure glaucoma in the population of dogs presenting for cataract surgery is currently unknown, and the use of mydriatic provocative testing as a screening test for development of POH and aphakic/pseudophakic glaucoma awaits investigation.

Gonioscopy is the practice of visually examining the iridocorneal angle, specifically the pectinate ligaments and anterior portion of the trabecular meshwork, employing a specially designed goniolens in conjunction with magnification. Gonioscopy is commonly employed in the diagnosis of primary glaucoma in the dog and is sometimes utilized as a means of screening patients for angle abnormalities that might predispose to reduced aqueous humor outflow after cataract surgery. Some veterinary ophthalmologists have anecdotally stated that gonioscopic findings may be predictive of POH and postoperative glaucoma. Numerous studies have documented an association between the presence of gonioscopic abnormalities and development

of primary glaucoma in a variety of breeds, so it is plausible that gonioscopy may predict postoperative glaucoma in dogs undergoing cataract surgery. [53-58] Moeller et al. performed gonioscopy at the surgeon's discretion in 32/42 Labradors and 152/199 non-Labradors and found no significant difference in prevalence of abnormalities between groups, indicating that gonioscopic results could not explain the increased risk of POH and postoperative glaucoma in the Labrador patient population. [2] However, there are no reports of postoperative outcomes of cataract surgery in dogs in which gonioscopy was routinely performed preoperatively in all patients; even in cases where gonioscopic examinations were performed, the extent and nature of gonioscopic abnormalities detected were not well described. Therefore, the relationship between gonioscopic findings and the prevalence of POH and postoperative glaucoma requires further investigation.

Aside from morphologic changes to the conventional outflow pathway, blockage of collecting channels has also been implicated as a cause of reduced aqueous humor outflow facility and subsequent POH. Miller et al. detected plasmoid aqueous and refluxed blood in the collecting channels and spaces of the corneoscleral trabecular meshwork after PE surgery in normal eyes, but IOP normalized between 3 and 24 hours postoperatively despite worsening of intraocular protein and persistent presence of blood.[38] Inflammatory cells in these areas were rare or absent and it was noted that no lens fragments were detected in the trabecular meshwork or collecting channels. It should be noted, however, that the lenses undergoing PE in this study were noncataractous and therefore not representative of a clinical setting.[38] Using ultrasound biomicroscopy, Rose et al. documented the presence of echogenic material, presumably inflammatory debris, in the anterior chamber after cataract surgery, but found no effect of presence of this abnormality on the incidence of POH.[45] Tissue swelling resulting in blockage of channels within the trabecular meshwork has been proposed by many authors but not demonstrated scientifically in any studies.

Amongst proposed causes of aqueous humor outflow obstruction after cataract surgery, retained viscoelastic material has been the most thoroughly researched. Viscoelastic devices serve multiple crucial roles in cataract surgery, including corneal endothelial cell protection, chamber maintenance, tamponade of hemorrhage or vitreal prolapse, etc.[59] Thus, despite a known association with postoperative pressure rises, their use cannot be eliminated. The focus of investigation has been determination of which types of viscoelastic are most problematic and whether removal or breakdown of the substance can mitigate this effect. Both high molecular weight (cohesive) and low molecular weight (dispersive) viscoelastics have uses in cataract surgery and each has advantages and disadvantages with regard to postoperative intraocular pressures. While viscodispersive formulas are less likely to impair aqueous humor outflow, they are more difficult to remove from the eye; in contrast, viscocohesives are easily removed but significantly more likely to cause postoperative intraocular hypertension if retained.[59] Commonly available cohesive viscoelastics include a variety of products ranging from 1-3% Sodium Hyaluronate (NaHa) content, whilst dispersive viscoelastic products contain 2% hydroxypropylmethylcellulose (HPMC) or a combination of sodium hyaluronate (NaHa) and chondroitin sulfate (CDS).[59]

The association between elevated intraocular pressure after surgery and the use of intraocular viscoelastics prompted Gerding et al. to inject 1% NaHa 4% CDS, 2% HPMC, and balanced salt

solution into the anterior chamber of four groups of healthy research dogs and to assess post-injection intraocular pressures at two hours and then at 12 hour intervals until hour 168. The study found that pressures in all treatment groups were significantly elevated at two hours. The greatest increase occurred in the NaHa group with maximal IOP of 25.8 ± 19.1 mmHg (range 10 - 43.3 mmHg); by 12 hours, pressures in all groups were at or below baseline and no further spikes occured.[42] Multiple comparison studies between viscoelastic materials have also been carried out in the human literature. For example, Arshinoff used a fellow eye control model in 100 human patients undergoing cataract surgery to assess frequency and severity of postoperative pressure spikes. All patients received 1.4% NaHa (Healon GV) in one eye and were randomly assigned to receive either 2.3% NaHa (healon 5) or 1.0 % NaHa (Healon) in the other. Pressures were measured at five and 24 hours and seven days postoperatively. Postoperative pressures were elevated in comparison to preoperative pressures at five and 24 hours and decreased by seven days. Pressure requiring intervention was set at ≥ 30 mmHg and was seen in 11 eyes, of which three were later diagnosed with primary open angle glaucoma and four were considered glaucoma suspects at follow up. The study showed no significant difference in number or severity of spikes between viscoelastic treatment groups; additionally, most patients that experienced a pressure spike had similar presentation in both eyes. The author concluded that severe pressure spikes reported with these viscoelastic materials were likely the result of patient predisposition or inadequate removal at the completion of surgery. [60] In contrast, Schwenn et al. compared postoperative pressure rises in 48 eyes of 48 patients randomized to receive either 3.0% NaHa/4.0% CDS (Viscoat®) or 2.3% NaHa (Healon 5®) and found a stastically higher IOP at four and eight hours in the Viscoat ® group, along with increased laser flare values and no difference in endothelial cell loss between the two agents.[61] These results are somewhat unexpected, as Viscoat® is a dispersive viscoelastic and Healon5® combines both cohesive and dispersive properties and might therefore be expected to cause a more significant rise in postoperative pressure. [59,62]

Studies comparing the effect of various viscoelastic formulations on postoperative pressure in humans undergoing cataract surgery abound in the literature with various conclusions, as demonstrated by the sampling of papers above. The importance of these differences is somewhat tangential to clinical veterinary medicine, however, as the choice of viscoelastic is not only affected by performance, but also price per volume. Similar in composition to Healon® (14 mg/ml NaHa), Hylartin V® is a viscoelastic product containing 10 mg/ml NaHa. Hylartin V® is designed and approved for intra-articular injection in horses, but its lower cost and higher volume packaging (2 ml vials) have made it a frequent choice of veterinary ophthalmologists for use in intraocular surgery.[59,63]

In an in vitro study using post-mortem human eyes, Assia et al. determined relative time of complete removal of five viscoelastic agents using automated irrigation/aspiration to be the shortest for 1.0% NaHa (Healon®) and 1.4% NaHa (Healon GV®), at 20-25 seconds, in comparision with 1-2 minutes for 2.0% hydroxypropylmethylcellulose (OcuCoat®) and 3.5 minutes for 3.0% NaHa/4.0% CDS (Viscoat®). These findings follow the expected trend for easier removal of cohesive viscoelastic agents.[64] In vivo, Klein et al. demonstrated the importance of viscoelastic aspiration when the incidence of POH was reduced from 27% to 9.5% simply by enforcing an irrigation/aspiration (I/A) time of 60 seconds in eyes undergoing PE surgery using 1.0% NaHa (Hylartin V®).[3] Further study of the effect of I/A time is needed,

however, as this study did not document the duration of I/A prior to standardization and, while POH prevalence was reduced, it was not eliminated.

In addition to I/A studies, chemical breakdown of hyaluronic acid has been investigated as a means of reducing impedence of AH outflow. Harooni used a rabbit model to investigate intraocular pressures after anterior chamber injection of 1.0% NaHa (Healon), 1.4% NaHa (Healon GV), 3.0% NaHa/4.0% CDS (Viscoat), and 2.0% HPMC (OcuCoat) with and without the additional injection of hyaluronidase; in all except the group receiving OcuCoat, which is made of hydroxypropylmethylcellulose rather than hyaluronic acid, intraocular pressure was lower when viscoelastic and hyaluronidase were coinjected compared with viscoelastic alone. Intraocular pressures reached a peak between 4-8 hours and returned to baseline by 24 hours postoperatively. Hyaluronidase alone was also evaluated and resulted in a small reduction in IOP thought to be related to cleavage of endogenous NaHa in the trabecular meshwork and collecting channels.[65] Based on current veterinary and human literature regarding cataract surgery, the use of intracameral hyaluronidase does not appear to have gained favor for this purpose.

Investigations of Prevention and Prophylaxis:
Reduced aqueous humor outflow is considered the mechanism by which many of the factors described above lead to POH, and thus pharmacologic alteration of aqueous humor dynamics is a primary target for treatment and prophylaxis. Various intracameral, topical, and systemic antiglaucoma medications have been evaluated in both humans and dogs undergoing cataract surgery since the early 1990s, as potential agents for the reduction of incidence or severity of POH. Vuori et al. undertook a randomized double-blind placebo-controlled study to assess postoperative pressures in patients administered one topical drop of 0.5% betaxolol, 0.5% timolol, or placebo solution at the conclusion of surgery and measured pressures at five and 24 hours after surgery. A significant increase in intraocular pressure occurred in groups receiving the beta-1 selective adrenergic antagonist betaxolol (maximum 33.6 ± 8.0 mmHg) and placebo (maximum 34.9 ± 7.5mmHg) but not in those treated with timolol (maximum 18.2 ± 8.0 mmHg), indicating a potentially important role of beta-2 blockade in reducing aqueous humor formation.[66] In a 1996 study evaluating the effects of Healon® and Amvisc® viscoelastic agents with or without the use of one dose of postoperative timolol, Anmarkrud et al. also found that 0.5% timolol reduced intraocular pressure at 3-6 hours postoperatively in both groups, with no persistent effect at 24 hours. Overall, 45 patients experienced an IOP >30 mmHg at the 3-6 hour measurement, of which 7 had received 0.5% timolol and the remaining 38 had not.[67] Although 0.5% timolol alone appeared to be to some degree efficacious in reducing the severity of POH, its noncardioselective beta-blockade is cause for contraindication in patients with chronic obstructive airway disease or heart blockage, prompting investigators to seek alternate therapies.[68]

Miotics and carbonic anhydrase inhibitors have been investigated in the prevention of POH in humans. In 1998, Solomon et al. randomized 41 eyes of 41 patients to receive either placebo or intracameral 50:50 dilution of 0.01% carbachol intracamerally at the conclusion of cataract surgery. At six hours postoperatively, IOP in the carbachol-treated eyes was statistically significantly lower (15.9 mmHg) compared with the placebo group (20.4 mmHg) and this trend was persistent at day 1 measurements (15 versus 17.6 mmHg). Additionally, IOP was >30 mmHg in 5% of the carbachol treated group and 10% of the placebo group at six hours post

surgery.[69] In the same year, Scherer et al. evaluated the glaucoma medication latanoprost as a prophylactic for POH. In this case, 103 eyes were randomly assigned to receive 1 drop of 0.005% latanoprost or placebo at the conclusion of cataract surgery. In this study, postoperative pressures were not monitored until one day after surgery, but a significant effect was seen, with lower IOP of 16.4 ± 3.7 mmHg in the latanoprost treatment group compared with 18.2 ± 3.5 mmHg in the eyes receiving placebo. However, no information was available for the early postoperative time frame during which POH is most commonly detected and because many studies show a return to near baseline IOP by 24 hours without treatment, it is difficult to assess the effect of latanoprost on POH in this study.[70] However, in 1999, Rainer performed a randomized trial comparing efficacy of one drop of postoperatively administered topical dorzolamide 2%, latanoprost 0.005%, and no medication and measured intraocular pressures at six hours and 20-24 hours postoperatively. The smallest six hour IOP elevation was seen in the dorzolamide group (1.9 ± 3.9 mmHg), followed by latanoprost group (2.2 ± 3.0 mmHg) and the largest pressure rise was seen in the control group (4.8 ± 5.2 mmHg). By 24 hours, mean IOP continued to decrease in the dorzolamide group and had risen insignificantly in the latanoprost group when compared with control eyes. At six hours postoperatively, of the 34 patients in each group, pressures >30 mmHg were detected in four control eyes and in one eye of each of the dorzolamide and latanoprost treatment groups. Although both drugs were able to reduce the number of eyes experiencing a painful spike in IOP, neither drug entirely eliminated the problem.[71] Latanoprost was also compared with timolol gel for efficacy in preventing POH in a 2000 study by Lai et al. Postoperative pressures were evaluated at two, four, and 24 hours after surgery. The only significant differences between groups were seen where timolol gel treated eyes maintained a lower IOP at all three time points in comparison with control eyes. Latanoprost did not have a significant postoperative IOP reducing effect in this study.[72] Lai et al. subsequently compared topical latanoprost 0.005%, topical latanoprost 0.005% and intracameral acetylcholine, intracameral acetylcholine alone, and eyes receiving no medication. Eyes treated with latanoprost alone did not have a three hour IOP significantly lower than control eyes, but eyes treated with combination topical latanoprost/intracameral acetylcholine or intracameral acetylcholine alone had significantly lower IOP than control eyes at three hours. At 24 hours, no statistically significant differences were seen between groups.[68] Latanoprost was also shown to be ineffective at reducing intraocular pressure when administered two hours prior to surgery compared with unmedicated control eyes.[73]

During a similar time period, Rainer et al. prospectively compared the effect of one postoperative drop of fixed combination 2% dorzolamide hydrochloride/0.5% timolol maleate with 0.005% latanoprost in 60 eyes of 30 patients undergoing cataract surgery, using one medication in each eye of each patient. When comparing IOP at six hours after surgery with preoperative values, a 3.6 ± 3.5 mmHg increase was seen in latanoprost treated eyes while a mean decrease of 0.8 ± 3.2 mmHg was seen in the dorzolamide-timolol group. At 24 hours, IOP continued to rise in the latanoprost group and to fall in the dorzolamide-timolol group, with significant differences seen between groups at both the six and 24 hour time points.[74] Rainer subsequently evaluated the efficacy of one drop of postoperative dorzolamide-timolol in comparison with no treatment in the fellow eye of 38 patients and measured postoperative pressures at six and 20-24 hours. At six hours, the mean increase in IOP was 4.3 ± 5.6 mmHg in the dorzolamide-timolol group, which was significantly less than the rise of 8.4 ± 6.1 mmHg that occurred in the control group; this trend remained significant at 24 hours. IOP spikes greater than 30 mmHg occurred in two treated and nine control eyes, demonstrating that fixed dorzolamide-timolol was incapable of completely

preventing the development of intraocular pressures higher than 30 mmHg.[75]

Schwenn et al. adopted a broader scope and randomized patients into treatment groups receiving one postoperative dose of topical 0.25% timolol gel (Group 1), 2% dorzolamide (Group 2), fixed combination 0.5% timolol/2% dorzolamide (Group 3), 0.02% brominidine (Group 4), and control (Group 5) – IOPs were lower at all postoperative time points in eyes treated with fixed combination timolol-dorzolamide compared with all other groups with measurements obtained at three, six, nine, and 24 hours. Statistically significant differences were found between groups 1-3 versus 4 and 5 at three hours and group 3 was significantly lower than groups 4 and 5 at all time points except at 48 hours when no inter-group differences were detected. At several time points, group 3 was significantly lower than group 1 and or 2 as well. Overall, fixed combination dorzolamide-timolol showed the greatest ability to reduce intraocular pressure in the acute postoperative period.[76] Katsimpris et al. also investigated brominidine, but used a concentration of 0.2% rather than the 0.02% used in Schwenn's paper. Brominidine was administered in one eye twice daily the day before and the day of surgery in 40 patients. This concentration and treatment regimen appeared to be more effective than that used in Schwenn's study, as the treatment group IOPs were lower at every time point evaluated after surgery (four, six, and 24 hours). Postoperative pressure curves were consistent with previous studies, showing elevation at four hours that progressed further by six hours and returned to near baseline by 24 hours. The mean maximal IOP in the placebo group was 27.71 mmHg versus 21.45 mmHg in the treatment group at six hours. Twelve patients in the placebo group had a significant increase in IOP (ranging from 6-10 mmHg) at six hours and this persisted at 12 hours in two eyes; no eyes in the treatment group developed significant increases in pressure after surgery. Brominidine has a significantly better safety profile compared with timolol, making it a desirable treatment option for at risk patients.[77] A paper by Cetinkaya et al. in 2004 confirmed that single dose administration of brominidine may be inadequate in effectively reducing the incidence of POH, as results of a double-masked study using both eyes in 90 patients showed no significant difference in postoperative pressure rises in those receiving one drop of 1% brinzolamide, 1 drop of 0.2% brimonidine or placebo two hours prior to surgery. Pressures in all three groups were elevated three hours after surgery without a significant difference between groups and all three groups were again statistically the same at 16-20 hours. At three hours, intraocular pressures greater than 25 mmHg were seen in 6/30 brinzolamide treated eyes, 5/30 brimonidine treated eyes, and 7/30 placebo treated eyes, with no significant difference in incidence between groups.[78] In contrast, Erkin et al. found better efficacy of brinzolamide when administered either one time at the conclusion of surgery or every 12 hours starting when the eyelid speculum was removed, compared with control eyes. Intraocular pressures were significantly lower for both groups when measured at 4-6 hours after surgery and again at 18-24 hours. At the second time point, the group receiving twice daily brinzolamide postoperatively had significantly lower intraocular pressure compared with the group that received just one dose. Only one eye in the study, a control eye, had a postoperative pressure above 30 mmHg.[79] Unal et al. found in 2008 that one preoperative dose of 0.03% bimatoprost was able to significantly decrease IOP at 24 hours but not at three hours when compared with placebo treated eyes. Similarly, significantly fewer eyes in the treatment group experienced an IOP increase of >5 mmHg at 24 hours, but not at three hours.[80] Given that the majority of clinically significant pressure spikes occur closer to three than 24 hours after surgery in both humans and canines undergoing PE, [28-32,37,38] the clinical utility of this protocol may be limited.

It can be concluded that no single prophylactic medication studied thus far consistently prevents postoperative spikes in intraocular pressure in humans undergoing cataract surgery. A similar lack of a definitive remedy is evident in the veterinary literature. The only prospective paper evaluating medical prophylaxis against POH in dogs undergoing PE examined the use of intracameral carbachol in 1998. In this study, Stuhr et al. compared 16 dogs receiving 0.5 ml of 0.01% intracameral carbachol to dogs receiving the same volume of balanced salt solution at the conclusion of surgery. Intraocular pressures were evaluated at three hours, six hours, and the morning following surgery. POH was defined as intraocular pressure >27 mmHg and was seen in 0/16 carbachol-treated dogs and 12/16 control dogs.[39] However, carbachol is known to cause "brow ache" in humans[39,69] and results in marked miosis in dogs, which may preclude posterior segment examination and predispose to the formation of posterior synechiae or fibrotic pupillary membranes. Crasta et al. also examined the use of carbachol in a retrospective paper comparing three protocols used sequentially over time. Treatment protocols for POH prophylaxis included one drop of topical 0.005% latanoprost, 0.3 ml 0.01% intracameral carbachol, or no adjunctive therapy at the conclusion of PE surgery. Pressures were measured at two hours, four hours, and the morning after surgery. The only significant difference in IOP between groups at any time point was a higher two-hour postoperative IOP in dogs treated with intracameral carbachol compared with dogs receiving no POH prophylaxis. Additionally, POH episodes (defined as >27 mmHg) occurred in 47% of carbachol-treated dogs, 29% of those receiving latanoprost, and 33% of dogs receiving no treatment for intraocular pressure; these differences were not significant, but there was a trend for a greater frequency of POH in the carbachol treated group. The conclusion of this study was that neither carbachol nor one postoperative dose of latanoprost was effective at reducing POH in dogs undergoing cataract surgery.[37] These results differ significantly from Stuhr's findings, and the influence of carbachol on prevalence of POH in dogs is further confused by findings in a retrospective by Moeller et al. where carbachol was associated with an increased frequency of POH in Labrador Retrievers and a decreased frequency of POH in the non-Labrador group. In that study, POH occurred in 45.7% of carbachol-treated Labradors and 16.7% of those not receiving the medication versus 13.8% of carbachol treated and 26.6% of non-treated dogs of other breeds. In humans, topical CAI or fixed-combination CAI –beta-blocker may be more effective than topical prostaglandin analogs at reducing prevalence and severity of POH. [71,74,75] However, to the author's knowledge, no study in the veterinary literature has evaluated the use of topical carbonic anhydrase inhibitors (CAI) or beta-blockers on POH in dogs.

Risk Factors for POH:

In the canine literature, the earliest clinical report of potential risk factors for POH was written by Smith et al. in 1996. In this retrospective examination of 100 dogs undergoing either phacoemulsification or extracapsular cataract extraction (ECCE) over a one year period, POH was defined as IOP >25 mmHg over 72 hours after surgery and the timing of IOP measurements was not standardized. The frequency of POH in this study was increased with longer PE times but overall was not affected by type of surgery. However, eyes undergoing PE developed POH significantly more rapidly than those undergoing ECCE, possibly due to a smaller, more watertight incision. Increasing age was associated with increasing risk of POH, which the authors postulate might relate to increased lens density and the resultant longer PE times and increased release of lens fragments into the trabecular meshwork; however, neither of these

hypotheses were verified. Sex was not associated with an altered risk of POH, nor was there an association between POH and preoperative lens induced uveitis (LIU) or mean preoperative IOP. Gonioscopic examination was performed on only four dogs in this study and thus angle morphology was not evaluated as a risk factor for POH. [36] Johnstone et al. retrospectively evaluated the prevalence and associated complications of posterior capsule disruption during PE surgery in 244 canine eyes from 1995-2002 and found that compromise of posterior capsular integrity did not increase the risk of POH in these patients.[81] In contrast to these veterinary studies, preoperative IOP and loss of posterior capsule integrity are considered risk factors for elevated postoperative IOP in humans undergoing PE surgery. [32,36]

In a 2011 retrospective evaluation of canine PE cases, Moeller et al. found no association between risk of POH and type of viscoelastic material used, surgeon experience (diplomate versus resident), patient age, gender, diabetes mellitus status, stage of cataract, abnormal gonioscopy findings, or the presence of preoperative lens induced uveitis. Neither preoperative IOP nor posterior lens capsule rupture were evaluated as potential risk factors in this population, since preoperative IOPs >25 mmHg and lens capsule rupture were used as exclusion criteria. [2] Although gonioscopy findings were not predictive of POH in this study, gonioscopic findings were available for only 184/241 patients and results appear to have been categorized merely as normal/abnormal. Gonioscopy has not been evaluated in any other clinical prospective or retrospective study of POH in dogs to the author's knowledge, although a wider iridocorneal angle is a risk factor for POH in humans.[82] The Moeller study was designed to assess a suspected breed predisposition of the Labrador retriever to postoperative glaucoma and this breed was indeed found to be at significantly higher risk than non-Labrador retrievers.[2] Breed was also a significant risk factor in a 2010 retrospective evaluation by Crasta et al., where the highest prevalence of POH was seen in Labrador retrievers and Boston terriers. Unlike the papers described above, hypermature cataracts were associated with decreased risk of POH in comparison with mature and immature cataracts in Crasta's patient population. In agreement with other findings, however, diabetes mellitus was not a risk factor for POH. [37] Klein et al. assessed Boston terrier and Miniature and Toy Poodle breeds as possible risk factors, but failed to find a statistically significant increase in risk of POH in these animals. This study also showed no increase in risk with phacoemulsification power, patient age, or the presence of preoperative lens induced uveitis.[3]

Rose et al. (2008) and Crumley et al. (2009) undertook prospective studies in which they attempted to document morphologic characteristics of the iridocorneal angle using ultrasound biomicroscopy rather than gonioscopy.
Due to the absence of previous UBM studies of the canine ICA, these studies attempted both to characterize anatomical features and postoperative changes in these parameters as well as to assess the effect of these variables on prevalence of POH. In the human literature, a postoperative increase in anterior chamber depth and iridocorneal angle opening distance have been documented with ultrasound biomicroscopy in patients undergoing PE[83] and wider preoperative iridocorneal angle has been associated with increased risk of POH[82]. Because these measurements have not been validated or standardized in the canine patient and normal values are unknown, it is important to examine not only the results of the following papers but also the methods by which they were achieved.

Rose et al. undertook a prospective clinical trial comparing ultrasound biomicroscopic (UBM – 50 mHz) measurements of the ICA and angle opening distance (AOD) in 23 dogs with bilaterally cataractous lenses and 56 dogs with noncataractous lenses between 2004-2005. Both ICA and AOD appeared to impact risk of POH: with each degree increase in pre-operative pre-dilation ICA the odds ratio of developing POH increased by 5.8% and with each 10 um increase in AOD at the same time point the odds ratio of developing POH increased by 3.9%; additionally, when the ICA was ≥13° there was a statistically significant association between increasing ICA and risk of POH. Neither post-dilation ICA and AOD nor pre-to-postoperative changes in ICA and AOD were associated with risk of POH.[45] In 2009, Crumley et al. published a retrospective study to investigate the potential correlation between pre- and postoperative UBM images and POH in 28 dogs undergoing cataract surgery between 1992-2007. In contrast with the positive correlation seen by Rose et al., statistical analysis in this study detected an inverse relationship between AOD and one day postoperative IOP. AOD and IOP were not associated at the remaining time points.[84] Interestingly, although Rose et al. demonstrated good inter-observer reliability,[45] the AOD values obtained by Rose et al. in cataractous dogs averaged 204.4 ±96.6 um, while those obtained by Crumley et al. were 400±172 um. The variability between values and results in these studies indicates that further study is needed before preoperative UBM imaging can reliably be used to predict POH in dogs undergoing PE.

In conclusion, ultrasound biomicroscopic and histopathologic studies of the iridocorneal angle following phacoemulsification as well as retrospective studies of risk factors for POH have produced conflicting results, suggesting a multifactorial etiopathogenesis of POH and the need for further investigation. Positive associations between POH and phacoemulsification time,[36] increasing age,[2,36] and use of carbachol instilled in the anterior chamber during surgery [2,37] have been demonstrated in some studies, while others have not found these associations[2,3,39] or found a reduction in POH with the use of intraoperative carbachol.[2,39] Various studies have been consistent in finding a lack of association between POH and gender, preoperative lens induced uveitis, placement of an intraocular lens, diabetes mellitus, and gonioscopy findings, while breed predispositions for Boston terriers and Labrador retrievers have been repeatedly confirmed.[2,36,37,39] In human studies, the single greatest predictor of postoperative intraocular pressure (IOP) is preoperative IOP; glaucoma patients and those with intraoperative posterior capsule rupture are at highest risk of developing POH.[32,33,85] Neither pre-operative IOP [36,39] nor lens capsule rupture have been associated with risk of POH in dogs.[81]

Treatment for POH:

Despite the fact that POH is a potentially sight-threatening complication that occurs in a significant portion of eyes[2,3,34-40] of dogs undergoing PE, there have been limited studies evaluating medical prophylaxis or interventional treatments for this condition. As a result, current medical protocols vary widely between institutions and surgeons. The goal of medical therapy of POH is to counteract the effect of reduced outflow capacity by altering aqueous humor dynamics. As IOP is the direct result of the balance between aqueous humor production and aqueous humor outflow, medical therapy for elevated IOP targets one or both of these processes and may be administered topically or orally. Currently employed topical aqueous humor suppressors include carbonic anhydrase inhibitors and beta-adrenergic antagonists, while prostaglandin analogs are thought to reduce intraocular pressure primarily by improving conventional and nonconventional outflow.[86] Prostaglandin analogs result in miosis and

breakdown of the blood-aqueous barrier (BAB) in normal dogs.[87] These side effects might be considered contraindications for use in cataract surgery patients with BAB breakdown as a result of the surgery itself;[88] however, the author is unaware of any literature describing the impact of prostaglandin analogs on BAB breakdown during the acute period after PE surgery in dogs and clinical experience has not demonstrated any grossly evident detrimental effects when this class of medication is used to treat POH. Orally administered carbonic anhydrase inhibitors may be utilized alone or in addition to topical medications, but are associated with increased risk of systemic side effects and may not offer a significant synergistic effect when topical CAIs are already in use.[89-91] In addition to medical therapy, drainage of fluid from the eye by needle aqueous paracentesis or inducing leakage of fluid from the corneal surgical incision is sometimes necessary when patients with POH are refractory to medical therapy. [92,93] These latter procedures incur additional risks, such as exacerbation of intraocular inflammation and potentially inducing trauma to the incision site during manual leakage or intraocular structures in the case of needle paracentesis.

Implications and Clinical Significance of POH:
The clinical significance of POH lies in the potential for resultant patient discomfort, poor surgical outcomes due to vision loss, and the economic impact of intense monitoring, hospitalization, and additional medications required to treat or prevent the condition. While POH is generally transient, responsive to treatment, and infrequently associated with permanent visual deficits, it does have the potential to cause blindness in dogs undergoing cataract surgery,[3] rendering the surgery a failure and resulting in poor client satisfaction.[18,33,36,46]

Primary literature examining POH-related retinal damage does not exist, leaving us to rely on clinical experience and reports by several investigators evaluating the effects of experimental short-term increases in intraocular pressure on the retina. In a prospective experimental setup, Grozdanic et al. used 14 healthy six-month old Beagle dogs to evaluate the effects of an acute, transient, marked rise in intraocular pressure on retinal thickness and function. Intraocular pressure in one eye of each patient was artificially elevated via cannulation of the anterior chamber under general anesthesia and maintained at a level equivalent to systolic blood pressure (ranging from 100-160 mmHg) for 60 minutes. On day one, dazzle reflexes, pupillary light reflexes (PLR), and menace response were present in only 10/14, 5/14 dogs, and 0/14 dogs, respectively; however, all dogs had recovered dazzle and PLR by day seven and menace by day 14.[94] Despite return of light reflexes and menace responses, slight but significant loss of ventrotemporal retinal thickness was detected at 15 and 30 days, with a similar but statistically insignificant decreased in thickness in the dorsotemporal retina.[94] Recovery of a menace is only a crude estimate of vision and by no means rules out some degree of vision loss; additionally, loss of retinal thickness likely implies loss of function. Although the artificial pressure rise created in this study was both significantly higher than that commonly experienced during POH and of short duration, the data are suggestive of the potential for retinal damage in dogs undergoing transient pressure spikes after cataract surgery.

Similar experimental studies evaluating retinal damage in rats after acute and transient elevations in IOP have varied significantly in study design and yielded mixed results. Abbot et al. documented retinal nerve fiber layer thickness (RNFLT) and axonal transport after subjecting rat

eyes to an intraocular pressure of 50 mmHg for eight hours and found no persistent alteration in axonal transport, RNFLT, or retinal ganglion cell loss at six weeks.[95] To the contrary, Suzuki et al. found electroretinographic and histologic evidence of inner nuclear layer apoptosis and dysfunction after rat eyes sustained an artificially elevated pressure of 110 mmHg for 40 minutes.[96] More data is necessary to distinguish the role played by the degree of pressure, duration of pressure rise, and different criteria evaluated in creating the contradictory outcomes of these two papers.

Generally, investigators in human medicine have concluded that pressure spikes are of more concern in eyes with pre-existing glaucoma or increased susceptibility to optic nerve damage and that treatment may not be necessary in healthy eyes; however, there remains the concern that high postoperative pressures lasting hours to days could cause significant damage despite the lack of documentation of this effect.[28-30] Despite lack of scientific documentation of the rate of complications due to POH in dogs, clinical experience with both POH and glaucoma leads veterinary ophthalmologists to follow a conservative course of action with regard to intraocular pressures after cataract surgery. Many veterinary clinicians routinely hospitalize dogs postoperatively to facilitate monitoring and intervention for POH and occurrence of POH may further prolong the hospital stay and cost. Additionally, anti-glaucoma medications are routinely prescribed by 35% of veterinary ophthalmologists for all surgical cases and by an additional 41% of ophthalmologists for all cases that experience POH.[97] This puts the patient at risk of negative medication side effects, incurs greater cost to the owner, increases the complexity of postoperative medication regimens, and has not been examined for efficacy.

The primary aims of this investigation, therefore, were to improve our understanding of risk factors for POH and to establish a scientific basis for the implementation of perioperative antiglaucoma medications to patients undergoing cataract surgery, specifically evaluating the prophylactic use of a fixed-combination carbonic anhydrase inhibitor-beta blocker for the first time in dogs. Additionally, long term follow up of the study population will allow further investigation of the suspected association between development of POH and subsequent development of glaucoma in affected eyes after cataract surgery.[2,34]

2. Perioperative Administration of Topical Dorzolamide Hydrochloride/Timolol Maleate Reduces Postoperative Ocular Hypertension in Dogs Undergoing Cataract Surgery

Abstract

Objective: To test the hypothesis that perioperative topical ophthalmic dorzolamide hydrochloride 2%/timolol maleate 0.5% (DHTM) reduces the prevalence and/or severity of postoperative ocular hypertension (POH) in dogs undergoing cataract extraction by phacoemulsification (PE).
Design: Randomized double-masked placebo-controlled study.
Animals: 103 dogs (180 eyes) presenting for unilateral or bilateral PE.
Procedures: Select historical, signalment, ophthalmic examination, and surgical data was collected. Dogs were treated with DHTM or Blink Contacts (BC) placebo at 14- and 2-h preoperatively and at conclusion of surgical closure. Intraocular pressures were assessed by rebound tonometry at 2, 4, 6, and 8 hours after surgery and at 8 am the following morning. POH was defined as IOP>25 mmHg and intervention consisted of latanoprost 0.005% if IOP rose to 26 mmHg - 45 mmHg or surgeon treatment of choice if >45 mmHg.
Results: DHTM significantly reduced the prevalence of POH in comparison with BC (26% versus 49% of eyes, OR=0.36; 34% versus 62% of dogs, OR=0.32). There was also a trend toward reduction of POH severity in DHTM-treated eyes (POH value 37.17±10.47 mmHg with BC, 32.67±6.39 mmHg with DHTM). DHTM-treated eyes that developed POH were significantly more likely to respond favorably (1 hour post-treatment IOP <25 mmHg) to treatment with latanoprost than those in the BC group (76% versus 51%, OR=3.87).
Conclusions and Clinical Relevance: Multi-dose perioperative administration of DHTM may be recommended in dogs undergoing PE to reduce the risk of POH and improve responsiveness of POH to treatment with latanoprost.

Introduction:
Phacoemulsification and aspiration surgery (PE) for cataract extraction in dogs is an elective procedure commonly performed by veterinary ophthalmologists. Benefits include restoration of vision and reduction of cataract-related complications, such as glaucoma and chronic uveitis.[1] Reported success rates of the surgery vary from 79.4-95%.[1-3] Postoperative complications are not infrequent, however, and poor outcomes may result. Potentially blinding postoperative complications include retinal detachment, glaucoma, endophthalmitis, corneal endothelial degeneration, posterior lens capsule opacification, and postoperative ocular hypertension (POH).[2-7]

In contrast to glaucoma, which in dogs is associated with a persistent pathologic IOP elevation, POH is a distinct clinical syndrome characterized by a transient but sometimes severe elevation of IOP after cataract extraction surgery. In dogs, POH is generally defined as an IOP of >25-27 mmHg occurring within the acute postoperative period[2,4,8-12] It is a common occurrence in dogs undergoing routine PE for cataracts, affecting up to 75% of patients[2,4,8-14] with a reported peak incidence at two to five hours after surgery.[4,9,11,12] While POH is generally transient and is infrequently associated with permanent clinically detected visual deficits, it does have the potential to cause blindness in dogs undergoing cataract surgery, rendering the surgery a failure and resulting in poor client satisfaction.[10,15-17] As a result, clinicians may hospitalize dogs

postoperatively to facilitate monitoring and intervention for POH and hospital stays may be further prolonged if POH does occur. Additionally, due to the high prevalence of POH, postoperative anti-glaucoma medications are routinely prescribed by 35% of veterinary ophthalmologists for all surgical cases and by an additional 41% of ophthalmologists for all cases that experience POH.[a] This puts the patient at risk of negative medication side effects, incurs greater cost to the owner, and increases the complexity of postoperative medication regimens. Lastly, POH may be associated with subsequent development of glaucoma in affected eyes.[4,8]

Prior studies evaluating risk factors for POH have produced conflicting results, suggesting a multifactorial etiopathogenesis. Increasing age and phacoemulsification time, for example, have been associated with higher risk of POH in some studies, but not in others.[2,4,10,13] There has been a consistent lack of statistical relationship between POH and gender, preoperative lens induced uveitis, placement of an intraocular lens, diabetes mellitus, and gonioscopy findings, while breed predispositions in Boston terriers and Labrador retrievers have been repeatedly confirmed.[4,10,11,13] Gonioscopic examination of the iridocorneal angle has not been routinely performed in any study of POH to date and, when it has been reported, it generally was recorded for only a small percentage of the patient population.[18-23] In human studies, the single greatest predictor of postoperative IOP is preoperative IOP; glaucoma patients and those with intraoperative posterior capsule rupture are at highest risk of developing POH.[15,24,25] Preoperative IOP has not yet been investigated as a risk factor for POH in dogs.

Reduced aqueous humor outflow is considered the most likely mechanism of POH,[12,16,17] and the main pharmacologic target for treatment and prophylaxis is alteration of aqueous humor dynamics. Various intracameral, topical, and systemic antiglaucoma medications have been evaluated in humans undergoing cataract surgery as potential prophylactic agents against POH, but the veterinary literature addressing this subject is limited to just two prospective studies[9,13] and one retrospective[11] report. Interestingly, while pharmacologic intervention has the potential to ameliorate POH, preoperative anti-glaucoma medications are routinely employed by only 10% of veterinary ophthalmologists when performing phacoemulsification.[a]

Topical carbonic anhydrase inhibitor (CAI) and fixed-combination CAI–beta-blocker medications reduce aqueous humor production and are routinely used for treatment of glaucoma in dogs.[26-28] In humans, they may be more effective than topical prostaglandin analogs at reducing prevalence and severity of POH. [29-31] However, to the author's knowledge, no study in the veterinary literature has evaluated the use of topical CAIs, beta-blockers, or combination products on POH in dogs. The primary aims of this investigation, therefore, were to improve our understanding of risk factors for POH and establish a scientific basis for the implementation of perioperative antiglaucoma medications to combat POH in canine patients undergoing cataract surgery, specifically evaluating the prophylactic use of a fixed-combination CAI-beta-blocker, dorzolamide hydrochloride 2%/timolol maleate 0.5%[b] (DHTM).

Materials and Methods:
A prospective double-masked randomized placebo-controlled clinical trial design was employed and patients were enrolled during the period of March 2013-July 2014. The study protocol was

approved by the Virginia Tech Institutional Animal Care and Use Committee and owner consent was obtained for all study dogs.

Patient Eligibility and Enrollment

Canine patients presenting to the Virginia-Maryland College of Veterinary Medicine Veterinary Teaching Hospital for PE were considered candidates for enrollment in the study. All study candidates had been previously evaluated and found to have an acceptable prognosis for surgery. This included dogs presenting with unilateral or bilateral juvenile or senile cataracts, as well as cataracts secondary to diabetes mellitus. Dogs with cataracts and associated conditions that precluded the likelihood of a successful surgical outcome (e.g. retinal degeneration or retinal detachment) were not considered study candidates. Eligible study candidates were subsequently excluded only when significant deviation from the study protocol was necessary for optimal patient care or when clients declined to participate. Patient care factors precluding study enrollment included preexisting glaucoma requiring medical therapy and severe lens induced uveitis requiring additional preoperative cycloplegic medication.

Study dogs were assigned to the treatment or control group based on a computer-generated random numbers table. The test medication DHTM and placebo solution Blink Contacts (BC)[c] were of similar physical appearance and viscosity and were dispensed in identical bottles by pharmacy staff. Clients, clinicians, students, and staff were masked to the treatment solution for the duration of the study.

Historical Data Collection and Patient Evaluation

Standard preoperative evaluation on study dogs involved collection of pertinent historical information and ophthalmic examination, which included evaluation of white light pupillary light and dazzle reflexes and slit lamp biomicroscopy. Indirect ophthalmoscopy was performed where possible based upon the completeness of cataract. Ocular ultrasonography and flash electroretinography were performed when the fundus could not be visualized adequately to rule out retinal detachment and retinal degeneration. Historical data collected included signalment, diabetes mellitus status, and previous cataract-related treatments. Ophthalmic examination was performed by one of two board-certified ophthalmologists or one of two ophthalmology residents. Prior to pupillary dilation with 1% tropicamide, direct gonioscopy was performed using a Layden or Koeppe goniolens and a slit lamp biomicroscope to provide magnification, with attempted visualization of approximately 270 degrees of the iridocorneal angle (dorsal quadrant excluded). Angles were first scored as either open/normal or abnormal. Abnormal angles were further categorized by estimated percent of visualized region that was affected by narrowing, closure, or pectinate ligament dysplasia/dysgenesis. Those angles judged to be <10% affected by one or more abnormality were judged mildly affected; those with 10-50% involvement of one or more abnormality were called moderately affected; and those with >50% involvement of one or more abnormalities were deemed severely affected. Additional examination data recorded for purposes of statistical evaluation included diabetic status, eye(s) to be operated, presence of biomicroscopically evident anterior uveitis at time of evaluation or drop off appointment (aqueous flare, keratic precipitates, or synechiae) and stage of cataract (incipient, immature, mature, hypermature).

All study dogs underwent routine physical examination. Preoperative laboratory evaluation was determined at clinician discretion based upon perceived clinical need, ranging from minimal (packed cell volume, serum total solids, estimate of blood urea nitrogen, blood glucose and urine specific gravity) to more comprehensive (complete blood count, serum biochemistry panel, urinalysis and urine bacterial culture). Topical corticosteroids were routinely employed prior to surgery, with the duration of treatment determined primarily by clinician preference, the timing of surgery relative to preoperative evaluation appointment and the presence of clinical lens-induced uveitis.

Study Treatment Protocol

In order to standardize total applied dosage and account for any potential ocular effects related to systemic absorption, study treatments were applied to both eyes regardless of whether unilateral of bilateral surgery was performed. One drop of DHTM or BC was administered to both eyes at three perioperative time points: 14 and 2 hours prior to planned anesthetic induction and at the time of surgical corneal wound closure.

Intraocular Pressure Measurement

IOPs were measured and recorded at several specified time points in each study animal, including before and one hour after application of topical ophthalmic 1% tropicamide on the day prior to surgery; at the conclusion of corneal closure; at two, four, six, and eight hours postoperatively; and between 7:30-8:00 am (16-20 hours postoperatively) on the morning following surgery. If POH was detected and rescue medications were administered, IOP in affected eyes was measured 1 hour following rescue treatment. Additional measurements were performed at clinician discretion, as dictated by clinical need. Measurements in awake animals were obtained in sternal recumbency or in a seated or standing position with a designated handheld rebound tonometer[d] by students, technicians, and clinicians trained in its appropriate use. Due to intraoperative patient positioning limitations precluding use of a rebound tonometer, IOP was assessed at the completion of corneal closure using a hand held applanation tonometer[e] by an ophthalmology surgical technician trained in its use. IOP measurements were performed in triplicate at all time points and the first three values obtained with low or no error were recorded and averaged. In a subset of patients, IOP was measured preoperatively at 0, 6, and 11 hours after administration of the first dose of treatment solution to evaluate the effect of the test treatment versus placebo on preoperative IOP in cataractous eyes.

Within 24 hours of surgery, all eyes to be operated were treated TID with topical ophthalmic prednisolone acetate 1% suspension and neomycin-polymyxin-gramicidin. A standardized topical ophthalmic preoperative medication regimen was used the morning of surgery, as follows: 1% tropicamide was applied to operated eyes three hours prior to induction to facilitate a dilated morning examination, and then every 30 minutes starting at two hours prior to induction. Diclofenac sodium 0.1%, prednisolone acetate 1%, and neomycin-polymyxin-gramicidin were applied to operated eyes every 30 minutes beginning two hours prior to induction and one dose of topical 10% phenylephrine was applied 30 minutes prior to induction.

The anesthetic protocol was standardized to include intramuscular acepromazine and hydromorphone (doses at discretion of the attending anesthesiologist), induction with intravenous propofol to effect, and anesthetic maintenance with isoflurane in 100% oxygen.

Neuromuscular blockade was achieved with rocuronium at a 0.2 mg/kg loading dose followed by 0.8 mg/kg/hr constant rate. All dogs received one dose of postoperative buprenorphine intravenously.

Systemic medications were administered based upon surgeon preference and diabetic status: preoperatively, dogs received oral or injectable anti-inflammatories (nonsteroidal anti-inflammatories if diabetic, prednisone or prednisolone if non-diabetic); most dogs received intravenous cefazolin (22 mg/kg) every 90 minutes intraoperatively, while some received preoperative oral antibiotics instead.

Routine PE cataract extraction surgery was performed on all study dogs. Sterile irrigation solution[f] was supplemented with 5,000 units of heparin per 500 mL bottle. Upon anterior chamber entry, 0.3 ml dilute 1:10,000 injectable epinephrine was routinely administered intracamerally. Sodium hyaluronate viscoelastic[g] was used intraocularly, as needed, and removal was performed at the completion of surgery via irrigation/aspiration; the duration of the viscoelastic removal via irrigation/aspiration (vI/A) was documented but was not standardized. Phacoemulsification time was recorded for each eye. Foldable acrylic lenses[h] were placed within the capsule in all cases, except when the surgeon deemed it contraindicated due to factors such as severe lens capsular instability and lens capsular tears. Clear corneal wound closure was accomplished via either a simple continuous symmetrical sawtooth pattern (3 surgeons) or five simple interrupted sutures (1 surgeon), according to surgeon preference. Suture materials included 8-0 polyglactin 910, 8-0 PGA, or 9-0 polyglactin 910. Hydroxypropyl methylcellulose was applied five minutes after application of the study solution (DHTM or BC) following completion of corneal closure to provide ocular lubrication and protection from desiccation during the remainder of surgery and recovery from anesthesia.

Placement of intraocular lenses, capsular tension rings, and tarsorrhaphy sutures was documented and any surgical complications were noted and described. In rare instances where the surgeon elected to administer intracameral carbachol 0.01% to address vitreous prolapse or capsular instability with resultant capsule/IOL subluxation, the study protocol was arrested and the patient was removed from the study.

Definition and Treatment of POH

Postoperative ocular hypertension was defined as any postoperative intraocular pressure measurement >25 mmHg occurring at the predetermined IOP measurement time points. Rescue protocols were regimented as follows: eyes with a pressure of ≤ 25 mmHg were considered normal and monitored at the described IOP measurement intervals; eyes with IOP measurements of 26-45 mmHg were treated with one drop of latanoprost 0.005% and rechecked in one hour (positive response defined as IOP <25 mmHg); eyes not responding to latanoprost and eyes with IOP of >45 mmHg at any time point were treated according to surgeon preference, including some combination of topical latanoprost 0.005%, topical or oral carbonic anhydrase inhibitors, topical beta-blockers, aqueous paracentesis, or manual leakage of fluid via the corneal incision.

Statistical Analysis

A two-eye model was employed for this study, requiring that statistical analysis take into account correlation between eyes of the same individual. Additionally, this method was employed to

account for the fact that although the majority of study subjects provided data from two eyes, those undergoing unilateral surgery provided data from only one. Methods of statistical analysis of data from two-eye models have been recommended in the human[32,33] and veterinary[11,34] literature and such an approach was taken here.

The primary exposure was treatment group, while the primary outcome was POH. Prognostic factors evaluated included sex, diabetes mellitus status, surgeon, breed, age, gonioscopy scores, use of preoperative topical steroids, evidence of lens induce uveitis, baseline IOP, provocative testing result, vI/A, phacoemulsification time, closure IOP, cataract stage, age, and surgical time (cut to close for each eye), as described in more detail above. Normal probability plots were employed to confirm the normal distribution of age, vI/A, phacoemulsification time, surgical time, and all IOP measurements (baseline, closure, 2-8 hours postoperatively). Associations between treatment group and each of the prognostic factors were assessed using chi-square (treatment group, sex, diabetes mellitus, surgeon, breed) (these were dog level factors); binary logistic generalized estimating equations (normal vs abnormal gonioscopy, preoperative topical steroid use, lens induced uveitis, provocative test results); ordinal logistic generalized estimating equations (gonioscopy grade, cataract stage); mixed-model ANOVA (baseline IOP, vI/A, phacoemulsification time, closure IOP); and 2-sample tests (age, surgical time).

Associations between each of the prognostic factors and the outcome (POH) were assessed using chi-squares (treatment group, sex, diabetes mellitus, surgeon, breed)(dog level POH was used for these factors) and binary logistic generalized estimating equations (age, normal vs abnormal gonioscopy, preoperative use of topical steroids, lens induced uveitis, gonioscopy grade, baseline IOP, provocative test results, vI/A, phacoemulsification time, closure IOP, surgical time, cataract stage). Effects of abnormal vs. normal gonioscopy and gonioscopy grade on POH value were assessed using mixed model ANOVAs. Between treatments (DHTM vs. BC), comparison of intraocular pressures as a continuous variable was performed using a mixed model ANOVA, while logistic generalized estimating equations were used to assess the effect of treatment group on development of POH as a categorical variable (yes or no). Effect of age on phacoemulsification time was assessed using mixed model linear regression. Association between treatment group and dog level POH designated as unilateral or bilateral was tested using a chi-square. All mixed-model ANOVA/regression and generalized estimating equations models specified dog as a blocking factor to account for correlation between eyes of dogs undergoing bilateral surgery. Tests for associations between pairs of prognostic factors and multivariable analyses were performed on an ad hoc basis to further investigate any potentially spurious associations observed. Statistical significance was set to $p < 0.05$. All analyses were performed using statistical software.[i]

Results:

Study population

During the study period of March 2013-July 2014, 223 eyes of 130 dogs were presented to the ophthalmology service at the VTH for PE, having previously been screened and deemed acceptable candidates for surgery. In total, 180 eyes of 103 dogs completed the protocol and were included in data analysis. The remaining eyes were excluded or enrolled and subsequently removed from the study for a variety of reasons, as follows: severe lens induced uveitis or miosis requiring additional preoperative treatment with mydriatics (10 eyes of 7 dogs); scheduling

conflicts with preoperative medication protocol (6 eyes of 3 dogs); preoperative diagnosis of glaucoma or treatment with antiglaucoma medications (6 eyes of 4 dogs); post-provocative test IOP >30 mmHg requiring topical antiglaucoma therapy in at least one eye (5 eyes of 3 dogs); lack of client consent (4 eyes of 3 dogs); intraoperative administration of carbachol (4 eyes of 3 dogs); cardiomyopathy-related anesthetic death prior to surgery (2 eyes of 1 dog); Cairn Terrier with ocular melanosis treated with additional mydriatics (2 eyes of 1 dog); lack of 2-hour postoperative IOP data (2 eyes of 1 dog); and early discharge from hospital due to excessively anxious behavior (2 eyes of 1 dog). Of the 180 eyes completing the study, 94 eyes of 53 dogs received DHTM and 86 eyes of 50 dogs were treated with BC. All risk factors evaluated for association with POH were statistically balanced between treatment groups.

The study population of 103 dogs included 49 spayed females, 46 neutered males, and four each of intact males and females. Mean age of presentation was 8.3 ± 3.2 years, with a range of 1-16 years. Breeds represented by ≥3 individuals included Yorkshire terriers (11), miniature schnauzers (7), Boston terriers (5), pugs (5), cocker spaniels (5), toy poodles (4), miniature pinschers (4), Jack Russell terriers (4), miniature dachshunds (3), bichon frise (3), miniature poodles (3), and rat terriers (3). The remainder of the population included 23 dogs of breeds represented by fewer than three individuals and 23 mixed breed dogs. Diabetes mellitus was present in 53% (55/103) of cases. No significant association to POH was detected for signalment factors or diabetes mellitus ($p>0.05$).

Of the 180 eyes undergoing surgery, 154 were treated with twice-daily topical steroids preoperatively, with the majority receiving treatment for 1-3 weeks in advance of surgery (mean 17.4 ± 13.0 days, median 14 days, range 1-90 days). For the remaining 26 eyes, topical treatment was not initiated prior to surgery due to failure of owner compliance or the decision to perform surgery the day following evaluation to account for scheduling limitations or marked lenticular intumescence prompting urgent surgical intervention. Preoperative topical steroid treatment was not associated with development of POH ($p>0.05$).

Preoperative Ophthalmic Factors

Cataracts were most commonly categorized as mature (46% or 82/180 eyes), followed by immature (32% or 58/180) and hypermature (22% or 40/180). Biomicroscopically detectible evidence of quiescent or active LIU at evaluation or drop off for surgery (flare, keratic precipitates, posterior synechia) was present in only 13/180 eyes enrolled in the study. Neither cataract stage nor LIU were predictors of POH ($p>0.05$).

Average baseline IOP was 11.9 ± 3.8 mmHg, with a range of 5.3-24 mmHg. Tropicamide mydriatic provocative testing data was available for 176 eyes, of which 3 eyes had positive results (IOP > 25 mmHg at 1 h). In total, only 29 (16%) eyes showed an increase of ≥ 5 mmHg at the 1-hour time point. Preoperative baseline IOP and provocative mydriatic test results were not significantly associated with development of POH ($p>0.05$).

Gonioscopy findings were available for 175/180 eyes; gonioscopy data was not available for 5 eyes due to failure of record keeping or clinician failure to perform the examination. The iridocorneal angle was considered normal/open in 51% (90/175) of eyes evaluated; of the remaining eyes, grades of mild, moderate, and severe were assigned to 10% (17/175), 19%

(34/175), and 19% (34/175) of eyes, respectively. The relationship between gonioscopic findings and POH was explored statistically in four ways: gonioscopy findings were grouped first as normal versus abnormal and second as grades normal, mild, moderate, or severe; effect was measured both as prevalence and severity of POH for each grouping. Regardless of the parameters evaluated, no association was seen between gonioscopy findings and the occurrence or severity of POH ($p>0.05$).

Surgical Factors

Surgical factors evaluated in this study included surgeon, vI/A, surgical time by eye, phacoemulsification time, and IOP at completion of corneal closure. Surgeon was a significant predictor of POH ($p=0.0080$) and was examined at a dog level rather than an eye level, as no dog had more than one surgeon. Rates of POH varied from 36% to 78% for individual surgeons (Figure 1). Longer surgical time (cut to close, per eye) was also associated with increased risk of POH ($p=0.0203$), although this data was only available for 82/180 eyes (29 with POH and 53 without, including 37 BC treated and 45 DHTM treated eyes) due to the retrospective decision to evaluate this factor and variability in recording on the anesthesia sheet. Although surgical time and surgeon were each statistically significant predictors of POH when evaluated individually, further analysis using mixed-model ANOVA showed that there was a significant association between the two ($p=0.0014$) and the statistical significance of surgical time was reduced to an non-significant trend after adjusting for surgeon in a multivariable logistic generalized estimating equations model ($p=0.0743$). Similarly, a statistically significant relationship was initially detected between increased vI/A and development of POH ($p=0.0292$), but mixed-model ANOVA showed that vI/A was significantly associated with surgeon ($p<0.0001$) and significance of vI/A was lost after adjusting for surgeon in a multivariable logistic generalized estimating equations model ($p=0.8040$).

Phacoemulsification time was positively associated with dog age, with an increase of 26.23 s (95% CI 17.64-34.81 s) for each additional year ($p<0.0001$). No significant difference was present between phacoemulsification times for eyes with and without POH ($p>0.05$). Similarly, closure IOP was not statistically related to likelihood of developing POH ($p=0.05$), with a combined average of 6.88±4.24 mmHg and respective means for eyes with and without POH of 7.12±5.49 and 6.74± 3.40 mmHg.

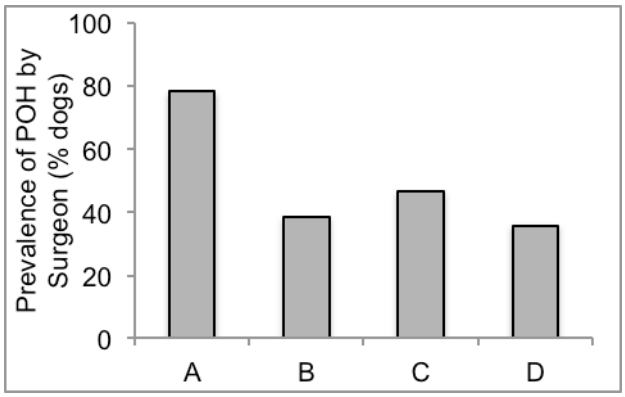

Figure 1. Prevalence of POH in 103 dogs undergoing PE was significantly affected by surgeon ($p=0.0080$). Total number of cases varied by surgeon, but each surgeon's cases were statistically balanced between treatment groups.

Treatment Effects

Preoperative response of IOP to treatment with DHTM versus BC was assessed in a subset of 74 eyes (36 DHTM, 38 BC) at 6 and 11 hours post-treatment. IOP was not different between groups at baseline (DHTM 11.75±3.22 mmHg, BC 12.23±4.77 mmHg, p=0.6722) or 6 hours (DHTM 11.37±2.94 mmHg, BC 12.64±3.90 mmHg, p=0.2304); however, by 11 hours, DHTM treated eyes had a significantly lower IOP than those receiving BC (DHTM 10.27±2.72 mmHg, BC 12.57±3.56 mmHg, p=0.0292). DHTM also resulted in a significantly lower IOP at 11 hours versus baseline (p=0.0248), whereas BC did not (p=0.8245) (Figure 2). Similarly, mean IOP of all DHTM treated eyes remained significantly lower (p=0.0007) than that of BC treated eyes at all contiguous postoperative time points using the last outcome carried forward method (LOCF) to account for drop out when POH occurred (Figure 3).

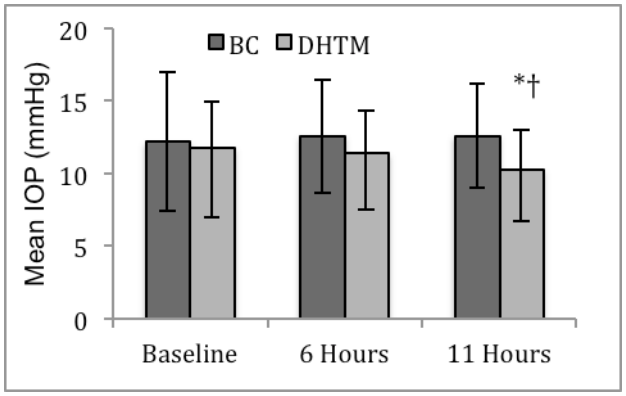

Figure 2. Preoperative IOPs in 74 eyes of 39 dogs before and after administration of 1 dose of BC or DHTM 14 hours prior to planned time of surgical induction. Intraocular pressures were measured at baseline (just before treatment application), then at 6 and 11 hours. At 11 hours, mean IOP of DHTM-treated eyes was significantly reduced compared with baseline (*) and with BC treated eyes (†).

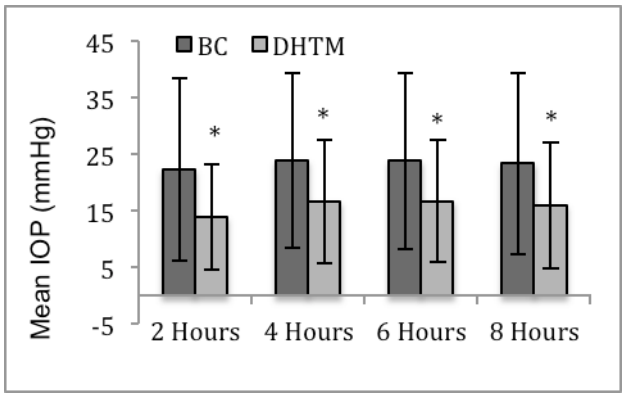

Figure 3. IOP values 2-8 hours post-phacoemulsification in 180 eyes of 103 dogs receiving DHTM or BC. Using the LOCF method to reduce dropout bias due to POH, IOPs remained significantly different (*) at all time points, with lower IOP in DHTM treated eyes (p<0.0001 at each time point, p=0.0007 for effect of treatment group over time).

Forty-nine percent (42/86) of BC- and 26% (24/94) of DHTM-treated eyes developed POH at one of the standardized postoperative IOP measurement time points (Figure 4), with an overall prevalence of 37% (66/180) for POH in the study population. This corresponds to a POH prevalence of 62% (31/50) and 34% (18/53) for BC and DHTM-treated dogs (Figure 4), with a combined prevalence of 48% (49/103). Analysis revealed a significant reduction in prevalence and odds of POH in the DHTM treatment group versus the BC control, both by eye and by dog (p=0.0048, odds ratio (OR)=0.36 by eye; p=0.0044, OR=0.32 by dog). The significance of the treatment effect was strengthened after adjusting for surgeon (p=0.0007, OR=0.19) in a multivariable logistic generalized estimating equations model. Treatment effect was also analyzed specifically for the 77 subjects undergoing bilateral surgery, and DHTM significantly reduced the prevalence of both unilateral and bilateral POH (p=0.0293): amongst BC treated dogs, 33% (12/36) had no POH, 36% (13/36) had unilateral POH, and 31% (11/36) had bilateral POH; in contrast, 63% (26/41) of DHTM treated dogs had no POH, 22% (9/41) had unilateral POH, and 15% (6/41) had bilateral POH (Figure 5).

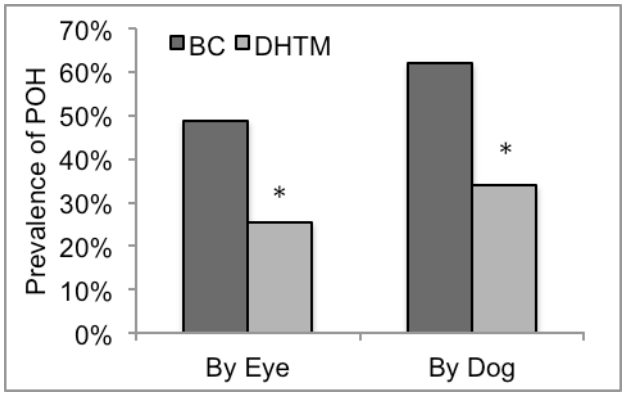

Figure 4. Prevalence of POH in 180 eyes of 103 dogs undergoing PE. POH was significantly (*) reduced by perioperative treatment with DHTM versus BC both by eye (p=0.0048) and by dog (p=0.0044).

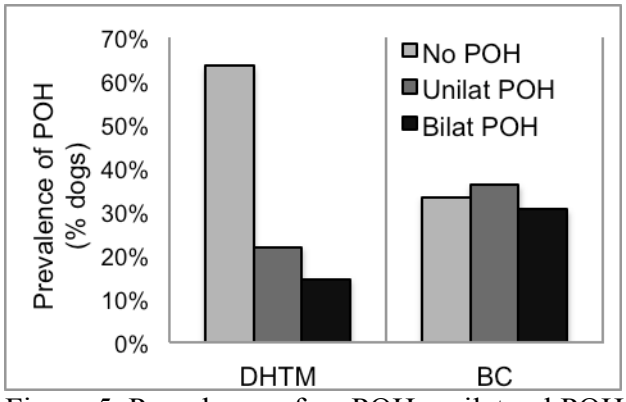

Figure 5. Prevalence of no POH, unilateral POH, and bilateral POH in 77 dogs undergoing bilateral PE surgery. DHTM was associated with a significant reduction in prevalence of unilateral and bilateral POH (p=0.0293). Note that the percentage of DHTM-treated dogs that did not develop POH in either eye was nearly double that of the BC group.

Examining the incidence of POH over time revealed that the large majority (91%) of cases occurred by the four-hour time point, with the greatest detected incidence (61%) at two hours (Figure 6). To compare incidence of POH between treatment groups over time, cumulative frequencies (LOCF) were used to avoid drop out bias. Using this method, incidence of POH was significantly lower at 2, 4, 6, and 8 hours postoperatively in DHTM versus BC treated eyes (p=0.0004, p=0.0015, p=0.0023, and p=0.0034, respectively) (Figure 7). The 8 am time point was not contiguous and therefore not included in the LOCF analysis of POH; since only one eye (DHTM group) was diagnosed with POH at 8 am, statistical analysis was not possible.

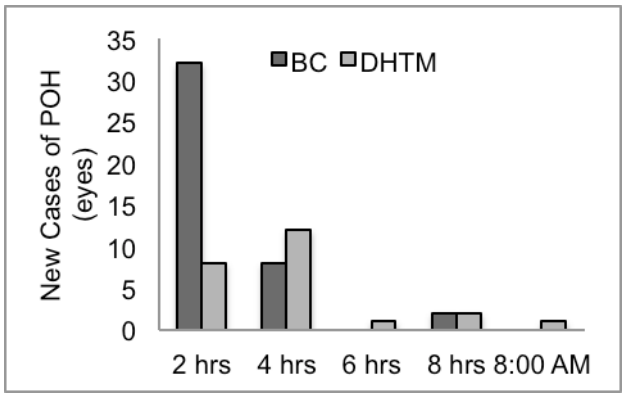

Figure 6. New cases of POH by eye over time for 66 eyes of 49 dogs undergoing PE. The highest incidence of POH occurred at 2 h and the vast majority (91%) of POH cases were diagnosed by 4 h.

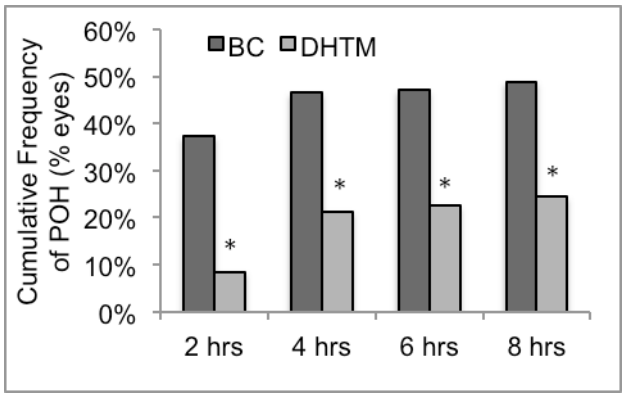

Figure 7. Cumulative frequency of POH in DHTM treated (24) and BC treated (42) eyes of dogs undergoing PE. Using the LOCF method, cumulative frequency of POH remained significantly lower in DHTM treated eyes at all time points (2 hrs, p=0.0004; 4 hrs, p=0.0015; 6 hrs, p=0.0023; 8 hrs, p=0.0034). The cumulative prevalence of POH by 8 hours postoperatively was 24% and 49% for DHTM and BC treated eyes, respectively.

In addition to reducing the incidence of POH at each time point and the overall prevalence of POH in the population, there was a strong trend indicating that DHTM also ameliorated the severity of POH (p=0.0692): IOP at time of POH detection was 32.67±6.39 mmHg (range 25.33-51.67) for DHTM treated eyes and 37.17±10.47 mmHg (range 25.33-66.67) for those treated with BC. For the 60 eyes initially treated for POH with one drop of latanoprost (POH value 26-

45mmHg), the odds of an acceptable response to treatment (IOP<25 mmHg at one hour) in the DHTM group were 3.87 times the odds of an acceptable response to treatment in the control group (DHTM 19/25 or 76%; BC 18/35 or 51%; odds ratio 3.87, 95% CI 1.03 - 14.51; p=0.0451) (Figure 8). Absolute IOP one hour after latanoprost administration was not significantly different between groups, but there was a trend indicative of lower IOP in DHTM treated eyes (DHTM 21.41±7.89 mmHg, BC 27.49±14.67 mmHg; p=0.0895).

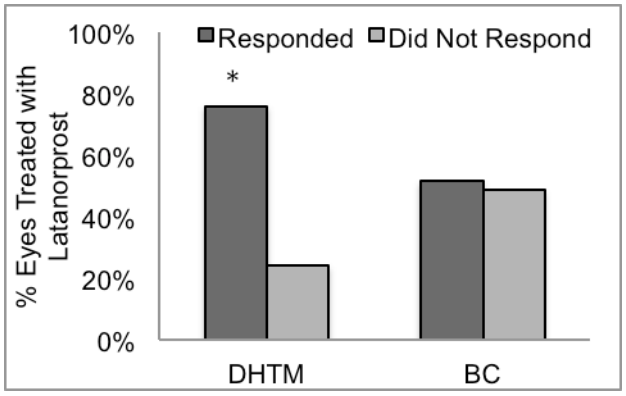

Figure 8-Responsiveness of 60 eyes (25 DHTM treated; 35 BC treated) with POH in the range of 26-45 mmHg to treatment with 1 drop of topical ophthalmic 0.005% latanoprost. Acceptable response was defined as IOP ≤25 mmHg at 1 h following application of latanoprost. DHTM treated eyes were significantly more likely to exhibit an acceptable response (p=0.0451, OR=3.87).

Discussion:

This is the first masked, placebo controlled prospective investigation of prophylactic treatment for POH in dogs using DHTM. Perioperative administration of DHTM to dogs undergoing PE successfully reduced the prevalence of POH in this study when compared with the placebo solution. Overall, POH occurred in 37% of eyes and 52% of dogs, fitting within previously published prevalence ranges (20-100% of eyes and 18-60% of dogs).[2,4,9-14,35] DHTM-treated cases fell near the lower end of both ranges, with 26% of eyes and 34% of dogs experiencing POH, whereas 48% of eyes and 62% of dogs receiving control solution experienced POH. Additionally, a significantly greater percentage of dogs undergoing bilateral surgery and receiving DHTM failed to develop POH in either eye compared with those receiving BC (63% vs. 33%). The DHTM multi-dose approach we employed was based on a review of the human literature, which indicated that single pre- or post-operative dosing may be less effective than multi-dose prophylaxis regimens.[36-38]

Prior studies evaluating the effect of prophylactic medications on POH in dog have been limited to topical latanoprost and intracameral carbachol, producing mixed results. In a retrospective study, Crasta et al. examined the effect of routine postoperative administration of latanoprost and found no significant effect on prevalence of POH (29% with latanoprost, 33% in untreated dogs).[11] Stuhr et al. prospectively evaluated the use of intracameral carbachol in a small sample using one eye of 32 dogs undergoing elective cataract surgery and detected POH in 12/16 of untreated control and 0/16 treated eyes.[13] Conversely, Crasta et al. found a trend toward higher IOP and increased frequency of POH in carbachol treated eyes,[11] and Moeller et al. found that carbachol was associated with increased risk of POH in Labrador Retrievers and decreased risk

in dogs of other breeds.[4] Additionally, carbachol is known to cause "brow ache" in humans[13,39] and both carbachol and latanoprost result in a marked miosis that precludes postoperative examination of the posterior segment, both of which are undesirable traits in an ideal pharmacologic agent for POH amelioration.

The highest incidence of POH in this study was at 2 h, accounting for 61% of total POH cases, with 91% of POH cases occurring by 4 h after surgery. This early onset conforms to the findings of several previous studies, including: Crasta et al, where 36/38 cases occurred at 2 h;[11] Chahory et al, where 7/14 cases occurred by 3 h and 13/14 by 5 h;[9] and Miller et al, where 17/17 cases had IOP>30 mmHg by 3 h postoperatively.[12] However, it is impossible to rule out the occurrence of POH at unmonitored time points. The former two studies[9,11] failed to measure pressures between 4 h and the following morning and 5 h to18 h postoperatively, respectively, and another review by Smith et al. had a mean incidence at 4.9 h, indicating the presence of later onset cases.[10] Our study limited IOP monitoring to 2, 4, 6, 8 h postoperatively and 8 am the morning after surgery, and at least three cases manifested POH outside of these time points. In one case, the clinician inadvertently performed a 10 h postoperative IOP measurement on a DHTM-treated dog and diagnosed bilateral POH; this dog was not included in the POH group as the pressure spike did not occur at one of the standardized study time points, but IOPs were excluded from the 8 am calculations since antiglaucoma medications had been administered. Additionally, one Boston Terrier in the BC group and one Jack Russell Terrier in the DHTM group developed and were treated for POH *after* 8 am the morning following surgery, prior to discharge from the hospital; these dogs also were not counted as developing POH in the analysis.

It is difficult to determine whether any residual pharmacologic effects of DHTM remained at or after the 8 am time point the day following surgery. To the author's knowledge, neither the duration of action nor point of maximal efficacy of DHTM on IOP reduction have been specifically evaluated in the human or veterinary literature. Additionally, we administered three doses of DHTM during our treatment protocol (14- and 2-h pre-op, at time of closure) and TID dosing has not been specifically evaluated in dogs. However, Moisseiev et al. demonstrated the safety and improved IOP reduction of this protocol in humans,[40] and we commonly employ TID DHTM in treatment of canine glaucoma cases without complication. It seems likely that the treatment effect in our study would have been reduced by the morning following surgery, given that the final study dose was administered minimally by 16 hours but more commonly around 20 hours prior to the 8 am IOP measurement. However, further study of three times daily dosing of DHTM in dogs would be required before we could state the duration of efficacy of our protocol for POH prophylaxis.

When POH did occur in our study population, those eyes having previously been treated with DHTM were significantly more likely to respond to 1 drop of latanoprost 0.005% than placebo treated eyes. Latanoprost was chosen based on the desire to apply a novel class of antihypertensive medication to any eye with elevated postoperative IOP in light of the fact that the double masked study design precluded us from knowing which eyes had already been treated with DHTM. Additionally, latanoprost has been shown to have a relatively short time to maximal efficacy in glaucomatous research beagles (reduction of IOP by 6.3±0.3 mmHg at 4 h)[41] and is known to effect a rapid and marked drop in IOP in glaucomatous canine patients.[42,j] Some researchers and clinicians have expressed concern over the use of latanoprost in the presence of

uveitis, as the prostaglandin activity may exacerbate such inflammation.[26,43] However, latanoprost has been shown to be safe for use in uveitic glaucoma in humans.[44] Although latanoprost may induce mild blood-aqueous-barrier breakdown,[43] this seems unlikely to cause a substantial difference in eyes with considerable pre-existing breakdown related to the cataract surgery itself. Additionally, in the short term, control of elevated IOP is arguably a more important goal than control of inflammation. No overt complications were noted during our study, although markers of uveitis were not directly compared between those eyes that did and did not receive latanoprost treatment.

We found no association between POH risk and the signalment factors evaluated (breed, age, sex). Previous studies have demonstrated increased risk in Labrador Retrievers,[4,11] while Boston terriers have been associated with higher risk of POH in some studies[11] but not in others.[2] We had low numbers of both of these breeds in our study. Six eyes of 4 Boston terriers in our study were treated with BC and 2 eyes of 1 Boston terrier were treated with DHTM. Three of 6 eyes (2/4 dogs) in the BC group developed POH. Both eyes of the Boston terrier in the DHTM group developed elevated pressures only after the study protocol had been completed and the effects of that treatment were likely abolished, and were therefore not counted as developing POH. Only two Labrador retrievers were enrolled in our study, with one in each treatment group. Both dogs developed bilateral POH, but, again, the numbers were too small to have any statistical meaning. Like Klein et al, we did not see elevated risk in miniature or toy Poodles.[2] Age was associated with POH in the study by Smith et al,[10] but not in ours or those by Moeller or Klein.[2,4] Also, like previous studies, we found no relationship between POH and diabetic status[4,11] or sex.[4,10]

Our findings with regard to the relationship of ophthalmologic factors and POH were generally in agreement with the preexisting literature. Lens-induced uveitis failed to show an association with risk of POH in our data, consistent with three previous reports.[2,4,10] However, it should be acknowledged that fluorophotometric studies have demonstrated loss of blood-aqueous-barrier stability indicative of inflammation in eyes with all stages of cataract, despite lack of clinical evidence in some cases,[45] making LIU a difficult risk factor to assess effectively. Additionally, eyes with marked intraocular inflammation were often excluded from our study due to treatment with confounding medications, leaving only13 eyes in the study with evidence of significant historic or ongoing LIU (presence of keratic precipitates, aqueous flare, posterior synechia) and potentially limiting the strength of our conclusions on the lack of association between LIU and POH. Cataract stage was also not associated with risk of POH in our study, confirming the results of Smith et al and Moeller et al.[4,10] We did not see a protective effect of cataract hypermaturity against development of POH as was reported by Crasta et al,[11] in which the authors hypothesized that the effect may have been related to their exclusion of cases with LIU. Ours is only the second study to evaluate preoperative baseline IOP as a risk factor for POH in dogs and our finding of a lack of association was in agreement with previous results.[10] However, we excluded patients with pre-existing ocular hypertension or treatment with antiglaucoma medications. This may explain the difference between our results and those in human medicine, where many eyes undergoing PE have pre-existing glaucoma, and higher baseline IOP and preoperative glaucoma are predictors of POH. [24,46,47]

At first analysis of surgical factors, surgeon, vI/A, and total surgical time reached statistical significance; however, further analysis revealed that surgeon was likely the underlying factor for

the other two and that vI/A was not significant. One surgeon in the study (surgeon A) was statistically more likely to have patients experience POH compared with the remaining three. A strong interaction between total surgical time and surgeon prevented us from determining the relative importance of these two factors, as both lost significance in the multivariate analysis. Several surgical technique factors were not controlled in this study but were generally very similar between surgeons B-D, with surgeon A employing several methods not performed by the other 3, including: endocapsular phacoemulsification, a 2-minute intracapsular incubation of sterile water to facilitate visualization and removal of lens epithelial cells, performing vI/A prior to suture placement for corneal closure, and closing the incision with an interrupted rather than a continuous suture pattern. As these technique differences were specific to the POH-overrepresented surgeon, they could not be evaluated separately as risk factors for development of POH.

Surgical time and corneal suture pattern are both plausible factors in the surgeon specific POH rate in this study. It is generally accepted that "time is trauma" during intraocular surgery and postulated mechanisms of POH in dogs include tissue swelling and altered anatomy at the iridocorneal angle/ciliary cleft,[12,16,48] but to the author's knowledge, total surgical time has not been previously evaluated as a risk factor for POH in humans or veterinary species. As surgeon A had both the longest surgical times and highest prevalence of POH, it is plausible that increased duration of surgery exacerbated tissue swelling at the drainage angle and predisposed such eyes to development of POH. However, the clinical relevance of this association is unclear, given the overlapping and broad ranges of surgical time in each group (30-110 minutes for eyes with POH and 25-90 minutes for eyes without). Watertight wound closure has also been postulated to contribute to the development of POH in humans.[49] While is possible that a simple interrupted suture pattern is more watertight, potentially leading to a greater risk of POH, no data is available on relative wound leakage of the simple interrupted versus continuous symmetrical sawtooth patterns employed to close the bi-planar incisions employed in this study. Further evaluation of surgical time and various closure techniques would be required for more definitive conclusions.

Intracameral use of viscoelastics is known to be associated with POH in dogs and removal by irrigation/aspiration is recommended.[50-52] Experimental studies have demonstrated complete removal of a similar viscoelastic from human eyes by 20-25 seconds.[53] Although this has not been specifically evaluated in dogs, a reduced rate of POH was documented in one canine study where vI/A was standardized to ≥1 minute in dogs undergoing cataract surgery.[2] In our study, we found no correlation between vI/A time and POH once the statistical analysis was adjusted for surgeon.

None of the remaining surgical factors evaluated were significant predictors of POH. In a 1996 study by Smith et al,[10] increased phacoemulsification time was associated with increased risk of POH. However, in our study phacoemulsification time was not related to risk of POH. Klein et al[2] found no significant effect of phacoemulsification power on incidence of POH, but phacoemulsification duration was not evaluated in that study. The relationship between age and phacoemulsification time has not been previously investigated to the author's knowledge. A positive correlation between phacoemulsification time and age confirmed statistically in this study and is likely explained by the increase in lens density that occurs throughout life. Since age

was not a predictor of POH, the lack of association between phacoemulsification time and POH is not surprising. Lastly, IOP at time of incisional closure was also not a predictor of POH.

Several weaknesses exist in this study. Four clinicians, including two board-certified ophthalmologists and two residents in veterinary ophthalmology, performed ophthalmic examinations, gonioscopy, and surgery on enrolled patients. Frequently, both a board-certified and resident clinician performed ophthalmic examination and gonioscopy on a given dog. In such cases agreement on gonioscopy findings, while not analyzed statistically, was subjectively strong. The intent of the gonioscopy grading scheme was to create a mechanism of scoring that would be indicative of the severity of abnormalities in each patient whilst also being adequately time-efficient to fit into our standard cataract evaluation appointment. This meant that we could not adhere to previously published schemata requiring sedation, anesthesia, or gonioscopic photography.[20,23,54] To account for the relatively subjective nature of clinical gonioscopy, our desire to grade both PLD and narrowing/closure, the small number of cases in each group, and the variability of definitions of gonioscopic abnormalities within the literature, we grouped together all eyes with minimally affected (<10%), moderately affected (10-50%), or markedly affected (>50%) angles in any of the three categories (PLD, narrowing, closure) for statistical purposes. Statistical significance was not achieved when abnormalities were grouped in this manner, nor was gonioscopy predictive of POH when eyes with normal/open angles were compared to those with any level of gonioscopic abnormality.

Tonometry was another potential source of variability in this project and specific steps were taken to minimize this source of error. Applanation IOP measurements obtained just after corneal closure were taken by one of three trained veterinary technicians from the ophthalmology service using the TonoPen XL and three readings of low or no error were averaged. Postoperative pressures were measured at time points during which the surgeon and ophthalmology technicians were not consistently available. We therefore employed the TonoVet rebound tonometer for all IOP measurements in awake animals, as results obtained by inexperienced and experienced users have been well correlated in previous studies using this instrument.[55,56] Additionally, instructions and training were provided to all users and three low- or no-error readings were required and averaged for each time point. In order to avoid error related to topical agents on the cornea (e.g. ointment), a water-soluble topical lubricant (hydroxypropyl methylcellulose 2.5%) that could be easily rinsed from the eye prior to tonometry was used as a protectant from anesthesia induced reduction of tear production.

Limitations in this study were mainly related to patient factor variability and the involvement of multiple clinicians and tonometrists. Conversely, these very factors may broaden the applicability of our results to the clinical practice of veterinary ophthalmology across diverse patient populations and surgical techniques. The exclusion of dogs with complications that precluded adhesion to the study protocol is certainly a source of bias, but was ethically unavoidable. Comparatively few patients fell into this category, with a total exclusion of 22 eyes of 15 dogs. In four cases, the surgeon detected significant lens subluxation with vitreal prolapse and felt the use of intracameral carbachol was indicated for optimal surgical outcome. Twelve eyes of 8 dogs were excluded from the study based on the presence of marked LIU necessitating additional preoperative cycloplegic medications. Similarly, the exclusion of cases with pre-

existing glaucoma or IOP >30 mmHg 1 hour after pharmacologic mydriasis was unavoidable but prevented us from establishing efficacy of the treatment protocol for such cases.

Conclusions:
Multi-dose prophylactic perioperative treatment with topical DHTM significantly reduced the prevalence of POH in this study. Additionally, eyes pre-treated with DHTM were more likely to respond to rescue administration of topical latanoprost if POH did arise. This study indicates that monitoring IOPs for 4 h postoperatively will allow clinicians to detect >90% but not all cases of POH, which is relevant to clinicians performing outpatient surgery. Future research might evaluate the potential of routine postoperative administration of latanoprost in combination with our DHTM protocol to further reduce or eliminate POH.

Footnotes:
[a] Herring IP, Dorbandt D. Canine Cataract Surgery – A survey of surgical techniques and management protocols employed by ACVO Diplomates. 43rd Annual Scientific Meeting of the ACVO. October 17-21, 2012. Portland, OR.; 2012.
[b] Hi-Tech Pharmacal Co., Inc., Amityville, NY
[c] Abbot Medical Optics Inc, Santa Ana, CA
[d] TonoVet, Icare Finland Ov, Helsinki, Finland/Jorgensen Laboratories, Loveland, Co
[e] Tono-Pen XL, Reichert Technologies, Depew, NY/Dan Scott and Associates, Westerville, OH
[f] BSS, Alcon Laboratories, Fort Worth, TX
[g] Hylartin-V, Pfizer Animal Health, New York, NY, USA
[h] 60V, S&V Technologies GmbH, Acrivet Inc., Salt Lake City, UT
[i] SAS version 9.4, Cary, NC, USA
[j] Miller, PE, Bentley, E, Diehl, KA, et al. High resolution ultrasound imaging of the anterior segment of dogs with primary glaucoma prior to and following the topical application of 0.005% latanoprost. Abstracts: 34th Annual Meeting of the American College of Veterinary Ophthalmologists, Coeur D'Alene, ID, USA. October 22–25, 2003. 2003:1–16.

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3. Conclusions:

Postoperative ocular hypertension is a common occurrence in dogs undergoing cataract surgery. Perioperative treatment with DHTM reduces the prevalence of POH, improves responsiveness to treatment when POH occurs, and may reduce the severity of POH as well. Perioperative use of DHTM is therefore a scientifically founded prophylactic treatment for POH and may be indicated in dogs undergoing cataract surgery.

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Appendix A: Annotated List of Figures

1. Prevalence of POH in 103 dogs undergoing PE was significantly affected by surgeon ($p=0.0080$). Total number of cases varied by surgeon, but each surgeon's cases were statistically balanced between treatment groups.
2. Preoperative IOPs in 74 eyes of 39 dogs before and after administration of 1 dose of BC or DHTM 14 hours prior to planned time of surgical induction. Intraocular pressures were measured at baseline (just before treatment application), then at 6 and 11 hours. At 11 hours, mean IOP of DHTM-treated eyes was significantly reduced compared with baseline (*) and with BC treated eyes (†).
3. IOP values 2-8 hours post-phacoemulsification in 180 eyes of 103 dogs receiving DHTM or BC. Using the LOCF method to reduce dropout bias due to POH, IOPs remained significantly different (*) at all time points, with lower IOP in DHTM treated eyes ($p<0.0001$ at each time point, $p=0.0007$ for effect of treatment group over time).
4. Prevalence of POH in 180 eyes of 103 dogs undergoing PE. POH was significantly (*) reduced by perioperative treatment with DHTM versus BC both by eye ($p=0.0048$) and by dog ($p=0.0044$).
5. Prevalence of no POH, unilateral POH, and bilateral POH in 77 dogs undergoing bilateral PE surgery. DHTM was associated with a significant reduction in prevalence of unilateral and bilateral POH ($p=0.0293$). Note that the percentage of DHTM-treated dogs that did not develop POH in either eye was nearly double that of the BC group.
6. New cases of POH by eye over time for 66 eyes of 49 dogs undergoing PE. The highest incidence of POH occurred at 2 h and the vast majority (91%) of POH cases were diagnosed by 4 h.
7. Cumulative frequency of POH in DHTM treated (24) and BC treated (42) eyes of dogs undergoing PE. Using the LOCF method, cumulative frequency of POH remained significantly lower in DHTM treated eyes at all time points (2 hrs, $p=0.0004$; 4 hrs, $p=0.0015$; 6 hrs, $p=0.0023$; 8 hrs, $p=0.0034$). The cumulative prevalence of POH by 8 hours postoperatively was 24% and 49% for DHTM and BC treated eyes, respectively.
8. Responsiveness of 60 eyes (25 DHTM treated; 35 BC treated) with POH in the range of 26-45 mmHg to treatment with 1 drop of topical ophthalmic 0.005% latanoprost. Acceptable response was defined as IOP $\leq$25 mmHg at 1 h following application of latanoprost. DHTM treated eyes were significantly more likely to exhibit an acceptable response ($p=0.0451$, OR=3.87).