



Research Article

Effect of Long-term Topical Application of 0.005% Latanoprost on Intraocular Pressure Uncontrolled by Multiple or Single Drug Therapy in Dogs with Secondary Glaucoma

Kumiko Kato^{1*} and Alexandra van der Woerdt²

Abstract

Purpose: To evaluate the effect of long-term topical application of 0.005% latanoprost on intraocular pressure (IOP) uncontrolled by multiple or single drug therapy in dogs with secondary glaucoma.

Animals Studied: Twenty-seven dogs with secondary glaucoma.

Procedure: Baseline IOP was measured before the start of 0.005% latanoprost therapy. The iridocorneal angle (ICA) was measured and graded as open, slightly narrow, narrow or closed. The effect of 0.005% latanoprost on IOP was followed for a minimum of two months. Dogs were classified as responders if IOP decreased with treatment or as non-responders if there was no change in IOP.

Results: IOP did not decrease in three dogs (11%). It decreased initially but subsequently increased over time in 21 dogs (78%). IOP remained <25 mmHg for more than 60 months in 3 dogs (11%). No correlation between ICA grade and IOP reduction from baseline was observed.

Conclusions: Topical application of 0.005% latanoprost resulted in long-term control of IOP in 11% of the dogs. The remaining dogs showed either no response or just a temporary decrease in IOP with topical 0.005% latanoprost treatment.

Keywords

Dog; Secondary glaucoma; Intraocular pressure; Latanoprost; Non-respond

Introduction

Glaucoma is a common eye disease that can cause irreversible blindness if left undiagnosed or untreated. It affects the ganglion cells of the optic nerve, eventually causing glaucomatous optic neuropathy (GON) and visual field loss. Although elevated IOP is not always present in glaucoma, it is a major risk factor in the development of GON.

Canine glaucoma can be etiologically classified as primary or secondary. Primary glaucoma may be defined as a breed-related

condition, in which dogs show increased IOP in the absence of other antecedent ophthalmic disorders. In secondary glaucoma, other intraocular disorders prevent aqueous humor flow within and from the eye, resulting in an elevation of IOP [1]. The most frequent causes of secondary glaucoma include lens displacement, acute or chronic anterior uveitis, lens-induced uveitis, intraocular cysts, hyphema, primary and secondary intraocular neoplasia, ocular melanosis, pseudophakic glaucoma and trauma [1-5].

Glaucoma is almost invariably the result of impaired aqueous humor outflow is characterized by increased IOP and subsequent death of retinal ganglion cells (RGCs), resulting in rapid loss of vision [6]. RGCs and the optic nerve are exceedingly sensitive to changes in IOP, vascular abnormalities, and movement of the posterior scleral lamina cribrosa [7,8]. Acute glaucoma represents an ophthalmic emergency and should promptly be addressed in order to preserve vision. Treatment for secondary glaucoma consists of resolving, whenever possible, the underlying ophthalmic disease and reduction of elevated IOP. The treatment goal for these patients is to lower the IOP to a level that will prevent progressive GON and visual field loss [9]. Medical treatment of glaucoma is aimed at controlling the increase in IOP by topical application of a variety of medications. Different categories of antiglaucomatous medications can be used in combination because of their complementary contribution to IOP reduction. In humans, initial therapy for glaucoma consists in either a topical β -blocker or a topical prostaglandin (PG) analog [9].

The use of PG analogs in patients with a history of active or previous uveitis is typically avoided [10]. With the increasing use of PG analogs, several studies have reported an association between the development of anterior uveitis or cystoid macular edema (CME) and PG analog therapy [11-15]. A definitive cause-effect relationship between PG analogs and these complications has not been established [14,15] and all reported human cases had, at least, one independent risk factor for the development of uveitis or CME, including previous intraocular surgery, pseudophakia or aphakia, posterior capsule rupture during surgery or uveitis [11-13,15].

The effects of PG analogs (as 0.005% latanoprost) on IOP have been evaluated in the normotensive eyes of dogs, cats, and horses [16,17]. In normotensive dogs and glaucomatous beagles, 0.005% latanoprost was shown to significantly reduce IOP [16,17]. Miosis and conjunctival hyperemia, without pain, were observed in latanoprost-treated normotensive eyes of research cats and dogs and glaucomatous beagles, although miosis is not a commonly reported side effect of latanoprost use in humans. Miosis is a well-known side effect of PG analogs in dogs and cats, it has observed severe intense miosis as like a pinhole in both glaucomatous and normotensive dog eyes treated with latanoprost. Therefore, cautious use of 0.005% latanoprost has been recommended in some disorders, such as lens luxation.

Several studies involving human patients have reported 15%-30% reduction in IOP from baseline with latanoprost but also a subset of patients who were unresponsive to latanoprost therapy [18-23]. These studies are often limited to patients with primary glaucoma and ocular hypertension. PG analog therapy for secondary glaucoma is still being debated [10,11,24-27]. To the best of our knowledge, no clinical studies have evaluated the effect of 0.005% latanoprost on the IOP of dogs with secondary glaucoma.

*Corresponding author: Kumiko Kato, Kumi Animal Hospital, Ophthalmology3-41-7 Cyuo, Misato-city, Saitama-Pref. 341-0038, Japan, Tel: +81 48 953 7755; Fax: + 81 48 952 3893; E-mail: 55kumi.k@gmail.com

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The purpose of the study was to assess the effect of long-term topical application of 0.005% latanoprost as a single agent or as a part of a multidrug regimen on IOP of dogs affected by secondary glaucoma. Patients were administered latanoprost for minimum two months duration.

Material and Methods

Medical records of all dogs that were referred to the Kumi Animal Hospital and the Veterinary Medical Center at the University of Tokyo for evaluation and treatment of glaucoma between January 1999 and December 2009 were reviewed. Ophthalmic examination was performed on all dogs, including slit lamp biomicroscopy, indirect ophthalmoscopy, gonioscopy, and applanation tonometry. IOP was measured using a Tono-pen XL (Mentor® O&O, Inc., Norwell, MA, USA). The morphological structures of the ICA were evaluated using gonioscopy (OLI-1 Layden Infant Lens, 11.5 mm; Koeppel, 17.0 mm; Sussman Four Mirror Hand Held Gonioscope; Ocular Instruments Inc., Bellevue, WA, USA) and were classified into open, slightly narrow, narrow and closed categories [28]. Gonioscopic and tonometric examinations were performed on conscious dogs after application of a topical anesthetic (0.4% oxybuprocaine hydrochloride; Santen, Osaka, Japan) to the corneal and conjunctival surfaces. The same veterinary ophthalmologist (KK) performed all examinations. Dogs were classified as having either primary or secondary glaucoma. Primary glaucoma was diagnosed if IOP was ≥ 25 mmHg, in the absence of preexisting contributory intraocular pathology. Other clinical signs such as cupping of the optic nerve head, decrease or loss of vision, conjunctival hyperemia, corneal striae, corneal edema, and buphthalmos were also recorded, whenever present. Secondary glaucoma was diagnosed when increased IOP was concomitant with the presence of at least one of the following intraocular abnormalities, including uveitis, intraocular hemorrhage, lens luxation, trauma, and neoplasia.

This study only included dogs with secondary glaucoma that were treated with 0.005% latanoprost either as a single agent or as a part of a multidrug regimen for, at least, two months. Medical records of 198 dogs were reviewed. Among these, 62 dogs were diagnosed with secondary glaucoma. Because latanoprost tends to cause miosis in dogs [16,29], those with active anterior uveitis or anterior lens luxation were excluded from this study. Twenty-seven dogs fulfilled all inclusion criteria and were added to this study. The baseline IOP was established before the start of treatment. One drop of 0.005% latanoprost was applied to the affected eye twice daily. IOPs were measured at baseline and then 1 to 2 weeks after starting therapy and at 1-3-month intervals, depending on the response to treatment.

Data analyses were performed using Microsoft® Excel 2007® for Windows 7 and Stata3 statistics software (OMS-publ., Saitama, Japan). Significance was set at $P < 0.05$. Student *t* test and F test were used for statistical analyses of the effects of age and sex. Chi-square for independence test and $m \times n$ contingency tables were used to evaluate the effect of breed, underlying ophthalmic disease and ICA grade on the decrease in IOP due to 0.005% latanoprost use. Multiple comparison tests for nonparametric data (Steel-Dwass) were used to evaluate the duration of IOP control by 0.005% latanoprost.

Results

Twenty-seven dogs were included in the study (Table 1). Nine dogs were male (six intact, three neutered) and 18 dogs were female

(nine intact, nine spayed). The median ages of male and female dogs were 6.5 ± 3.5 (range 1-12) and 7.4 ± 4.5 (range 1-15) years, respectively. The age distribution was uniform between sexes (F test, $P=0.47$), with no statistically significant differences (Student *t* test, $P=0.64$). Among the 27 dogs, three (11.1%) had a decreased IOP for more than two months (responder group); three (11.1%) did not exhibit any changes in IOP after treatment with 0.005% latanoprost (non-responder group); although temporary reductions in IOP were observed in 21 dogs (77.8%), these values returned to baseline after two months (temporary responder group). In summary, a total of twenty-four dogs (88.8%) had either no response or only a temporary response to 0.005% latanoprost.

A Kaplan-Meier analysis was used to compare survival times across groups (Figure 1). Ultimately, the cumulative survival time was significantly greater in the responder group (log-rank test, $P < 0.0001$). Differences in survival in the four subgroups of non-responders and temporary responders were estimated by Kaplan-Meier analysis (Figure 2). The cumulative survival rate in the high subgroup of temporary responders seemed to be longer than that in the non-responder group. However, there were no statistically significant differences in the cumulative survival rates (log-rank test, $P=0.23$). The duration of latanoprost use was compared across groups using the Kruskal-Wallis and multiple comparison tests for nonparametric data and the Steel-Dwass method (Figure 3). The non-responders had a significantly shorter treatment time compared to those in the high-reduction group ($P < 0.05$). The ICA grade was not correlated with the degree of IOP reduction from baseline (Kruskal-Wallis test, $P=0.33$).

The mean baseline IOP was 39.6 ± 12.9 mmHg (range 17-68 mmHg). The mean IOP of dogs treated with 0.005% latanoprost was 22.6 ± 11.9 mmHg (7-52 mmHg), which was measured one or two weeks after starting treatment. In the 3 responder patients, IOP was maintained at less than 20 mmHg throughout the study at an average of 71.8 ± 11.2 months (range 60-87 months; responder). The mean baseline IOP was 33.5 ± 17.3 mmHg (19-57 mmHg). The mean IOP after treatment with 0.005% latanoprost was 16.0 ± 4.0 mmHg (14-22 mmHg) and the decrease in the IOP ratio of the responder group was $40.6\% \pm 14.7\%$ (26.3%-61.1%). In the 3 non-responder patients, the IOP increased from an average of 41.5 ± 5.2 mmHg (35-47 mmHg) to an average IOP of 48.8 ± 3.0 mmHg (45-52 mmHg), the decrease in IOP ratio of the non-responder group was $-22.3\% \pm 21.7\%$ (-48.6-4.3%) and the IOP increased again to baseline values after an average of 0.8 ± 0.3 months (range 0.5-1.0 month). In the 21 temporary responder dogs, IOP increased to baseline values after an average of 7.3 ± 10

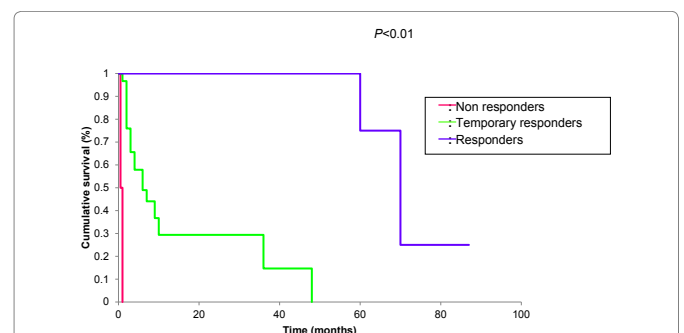
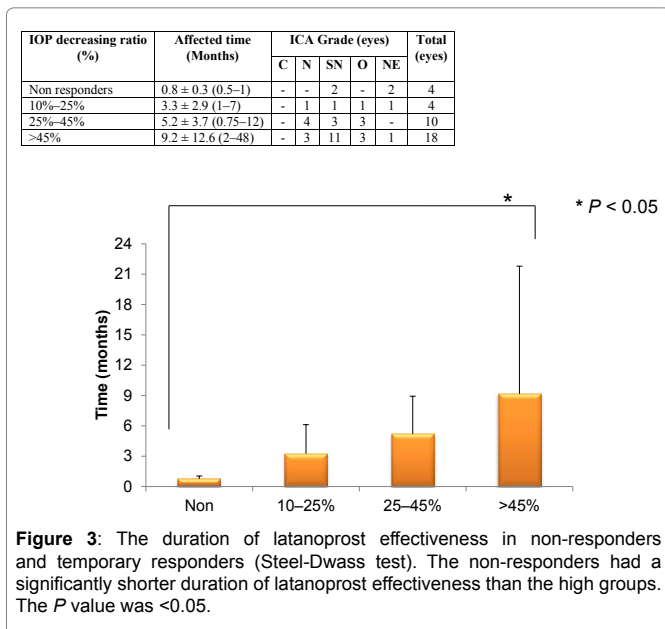
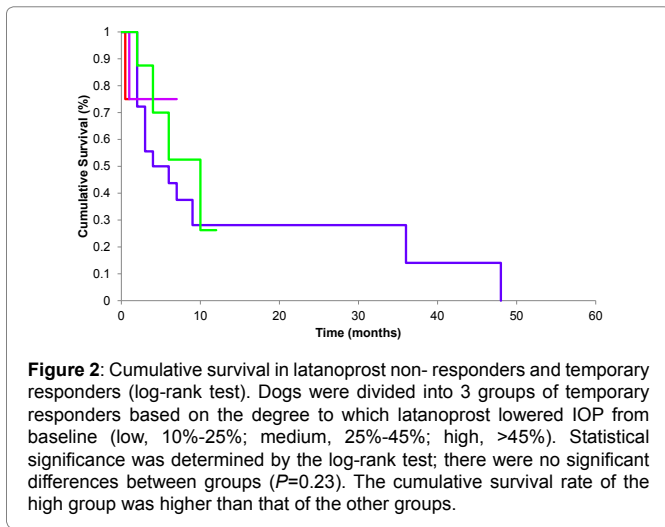


Figure 1: Cumulative survival in latanoprost non-responders, temporary responders, and responders (Kaplan-Meier analysis). Statistical significance was determined by log-rank test; survival was significantly reduced in the non-responders ($P < 0.01$).



months (range 0.75-48 months). The baseline IOP in the temporary responder group was 40.1 ± 13.1 mmHg (17-68 mmHg), which corresponds to a decrease in IOP of 20.1 ± 8.7 mmHg (7-46 mmHg) with 0.005% latanoprost. The decrease in IOP ratio was $46.8\% \pm 19.4\%$ (10.5%-88.7%). The mean decrease in IOP in 24 dogs (responder and temporary responders) was 19.7 ± 8.3 mmHg (7-46 mmHg), which corresponds to a decrease of 46.1 ± 18.9 mmHg (10.5-88.7 mmHg) in the IOP. There were no statistically significant differences in the baseline IOP and latanoprost following IOP between responder versus non-responder and temporary responder. The duration of 0.005% latanoprost efficacy was significantly different between all categories (multiple comparison test for parametric data; Steel-Dwass) when the following groups were compared: responder versus non-responder ($P<0.05$), responder versus temporary responder ($P<0.01$), and non-responder versus temporary responder ($P<0.01$).

In the responder group, ICA was slightly narrow in one dog, open in another, and not evaluated in the third. In the non-responder group, a slightly narrow ICA was observed in two dogs and one dog was not

evaluated. In the temporary responder group, narrow, slightly narrow and open angles were observed in six, eight, and six dogs, respectively. ICA was not evaluated in one dog from this last group. There were no statistically significant differences in the relative representations of the different ICA grades across the responder, non-responder, and temporary responder groups (chi-square for independence test; $m \times n$ contingency table, $P=0.36$) (Table 2).

Breeds included Shih Tzu (ten dogs), American Cocker Spaniel (four dogs), Mixed Breeds (three dogs), Miniature Dachshund (three dogs), and one of each of the following breeds: Akita, Boston terrier, Chihuahua, Golden Retriever, Labrador Retriever, Pekingese, and Yorkshire Terrier. The underlying etiologies of secondary glaucoma included previous anterior uveitis (total of 18 eyes; Miniature Dachshund: six eyes, cross breeds: six eyes, Akita: two eyes, Labrador Retriever: two eyes, Shih Tzu: two eyes, Chihuahua: one eye, Pekingese: one eye), retinal detachment (nine eyes, all Shih Tzu dogs), cataract (total of seven eyes; American Cocker Spaniel: five eyes, Boston Terrier: two eyes), trauma (two eyes: Shih Tzu), intraocular neoplasia (total of two eyes; Golden Retriever: one eye, Cross Breeds: one eye), and lens luxation (one eye, Yorkshire Terrier; presented initially with an anterior lens luxation, which changed into a posterior lens luxation after a week). There were statistically significant differences in the incidence of underlying etiologies among the various breeds (chi-square for independence test; $m \times n$ contingency tables, $P<0.01$).

All glaucoma medications administered before the starting of latanoprost treatment are listed in Table 3. Two eyes were not previously treated with antiglaucomatous medications. The remaining 39 eyes were already being treated with antiglaucomatous medications before 0.005% latanoprost administration.

Discussion

Latanoprost is a prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analog that is widely used in the management of glaucoma. The mechanism by which latanoprost reduces IOP involves an increase in uveoscleral outflow by remodeling the extracellular matrix (ECM) and/or relaxation of the ciliary muscle bundles [30-33]. In addition, a reduction in aqueous humor production has also been shown in healthy dogs [34]. Although latanoprost has a high affinity for prostaglandin F (FP) receptors, which is one of the PG receptor subtypes present in the eye, previous studies have revealed that latanoprost induces endogenous PGs production, including PGE_2 , which influence ECM metabolism [35,36]. It is believed that latanoprost reduce IOP by direct signal transduction through the FP receptor or by inducing endogenous PG production [37].

In human clinical trials, latanoprost was evaluated mostly in patients with primary open-angle glaucoma or ocular hypertension [20-23,38,39]. Several information exists on the use of latanoprost to treat secondary glaucoma, and uveitic glaucoma [10,26,27,40,41]. However, several concerns exist regarding the use of latanoprost in patients with uveitis. First, because latanoprost is a PG analog, it could worsen inflammation in patients with uveitis or in those who are predisposed to uveitis. Second, latanoprost works by increasing uveoscleral outflow, which may be obstructed in the presence of an inflamed iris [42,43]. Therefore, there is significant debate regarding the use of latanoprost for secondary glaucoma treatment [10,11,24-27,44-47]. $FP_{2\alpha}$ stimulates the release of PGE_2 , which stimulates arachidonic acid release via activation of phospholipase II [35]. Increased release of arachidonic acid will enhance the production

Table 1: Comparison of characteristics of treatment responders and non-responders among dogs with secondary glaucoma.

		Secondary glaucoma (27)		
		Responder	Nonresponder	Temporary Responder
Dogs (n) (Male/Female)		3 (1/2)	3 (2/1)	21 (6/15)
Ratio (%)		3/27 (11.1)	3/27 (11.1)	21/27 (77.8)
Age (years)		7.0 ± 3.5 (5-11)	3.0 ± 1.7 (1-4)	7.7 ± 4.21 (1-15)
Baseline IOP (range) (mmHg)		33.5 ± 17.3 (19-57)	41.5 ± 5.2 (35-47)	40.1 ± 13.1 (17-68)
Latanoprost following IOP (range) (mm Hg)		16.0 ± 4.0 (14-22)	48.8 ± 3.0 (45-52)	20.1 ± 8.7 (7-46)
Decrease in IOP ratio (range) (%)		40.6 ± 14.7 (26.3-61.1)	-22.3 ± 21.7 (-48.6-4.3)	46.8 ± 19.4 (10.5-88.7)
Month with use latanoprost (range)		71.8 ± 11.2 (60.0-87.0)	0.8 ± 0.3 (0.5-1.0)	7.3 ± 10.0 (0.75-48.0)
ICA grading (n dogs)	Closed	-	-	-
	Narrow	-	-	6
	Slightly Narrow	1	2	8
	Open	1	-	6
	Not evaluated	1	1	1
Affected eyes (n dogs)	OD	-	-	10
	OD to OU	-	-	-
	OS	-	-	5
	OS to OU	-	1	2
	OU	3 {1}	2 {1}	4 {0}

Values are expressed as numbers of dogs (n) or mean ± SD (range in parenthesis).

Total nonresponders: 24/27 (88.9%); responders: 3/27 (11.1%) + temporary responders: 21/27 (77.8%); OD, right eye; OS, left eye; OU, both eyes; {#}, Buphthalmos dogs

Table 2: Comparison of dog breeds, lesion distribution across groups, and causes of secondary glaucoma.

	Secondary glaucoma						
	Responder		Nonresponder		Temporary Responder		Total eyes
	Affected eyes	Cause	Affected eyes	Cause	Affected eyes	Cause	
Akita	-	-	1 (SN)	1: AU	1 (SN)	1: AU	2
American Cocker Spaniel	-	-	-	-	5 (N)	5: Cat	5
Cross Breeds (Mix)	2 (NE)	2: AU	2 (NE)	2: AU	3 (O:1, NE:2)	1: IN; melanoma, 2: AU	7
Miniature Dachshund	2 (SN)	2: AU	1 (SN)	1: AU	3(SN)	3: AU	6
Shih Tzu	1 (O)	1: RD	-	-	12 (N:3, SN:4, O:4, NE:1)	8: RD, 2: Tra, 2: AU	13
Other dog breeds	-	-	-	-	Boston Terrier; 2 (SN): Cat Chihuahua; 1 (O): AU Golden Retriever; 1 (O): IN; lymphoma Labrador Retriever; 2 (SN): AU Pekingese; 1 (SN): AU Yorkshire Terrier; 1 (SN): LL	8	
Total eyes	5		4		32		41

ICA grading in parentheses: C, closed angle; N, narrow angle; SN, slightly narrow angle; O, open angle; NE, not evaluated

AU, anterior uveitis of unknown cause; Cat, cataract; IN, intraocular neoplasia; LL, lens luxation; RD, retinal detachment; Tra, trauma

of proinflammatory eicosanoids. Therefore, PG analogs may not be suitable for long-term therapy in some patients because they

may induce ocular inflammation by further enhancement of proinflammatory prostanoïd release within the eye [11].

Table 3: Comparison of the distribution of dogs according to the different IOP-lowering medications at the start of latanoprost, their causes of secondary glaucoma, and distribution of ICA grades by gonioscopy in each group.

	Secondary glaucomatous eyes (41)															Total eyes
	Responder (5)					Non-responder (4)					Temporary responder (32)					
	C	N	SN	O	NE	C	N	SN	O	NE	C	N	SN	O	NE	
No previous treatment	-	-	-	-	-	-	-	-	-	-	-	-	1:UI	-	1:UI	2
Nonselective β-receptor blockers	-	-	-	-	-	-	-	-	-	-	-	1:Cat	1:UI	1:IN, 1:Tra	-	4
Nonselective β- & α-receptor blockers (Nipradilol; Hypadil)	-	-	-	-	-	-	-	-	-	-	-	1:RD	-	-	-	1
Nonselective β- & α1-receptor blockers (Levobunolol hydrochloride; Mirol)	-	-	-	-	-	-	-	-	-	-	-	1:RD	1:UI, 2:Cat	-	-	4
Topical CAI	-	-	-	-	-	-	-	-	-	-	-	1:Cat	1:UI, 1:LL	1:RD, 1:Cat	-	5
Nonselective β-receptor blockers + Topical CAI	-	-	-	-	-	-	-	-	-	-	-	3:Cat	1:RD	1:Tra, 1:IN	1:UI	7
Nonselective β-receptor blockers + α1-receptor blocker (Bunazosin hydrochloride; Detantol) + Topical CAI	-	-	-	1:RD	-	-	-	-	-	-	-	-	-	1:RD	-	2
Nonselective β- & α1-receptor blockers + Topical CAI	-	-	-	-	2:UI	-	-	2:UI	-	2:UI	-	-	2:UI	-	1:UI	9
Nonselective β- & α1-receptor blockers + α1-receptor blocker + Topical CAI	-	-	2:UI	-	-	-	-	-	-	-	-	1:RD	-	-	-	3
Nonselective β- & α-receptor blockers + Topical CAI	-	-	-	-	-	-	-	-	-	-	-	-	2:RD 2:UI	-	-	4
Total eyes	0	0	2	1	2	0	0	2	0	2	0	8	14	7	3	41

Although miosis is not induced by PG analogs in humans, PG analogs induce miosis in dogs [29,46-51], cats [46] and horses [17]; it may also induce posterior synechiae and exacerbate glaucomatous conditions [10,11,24-27,44,45]. Other studies have suggested that PG analogs are not associated with an increased rate of inflammatory relapse [10,26,27,52,53]. However, patients with active uveitis and anterior lens luxation were excluded in these studies, because the authors were afraid of induced inflammation or exacerbation of ocular conditions by latanoprost. As the patients receiving latanoprost therapy were cautiously selected for fear of intense miosis, it is believed that this careful selection of cases is a reason for the successful long-term effects (3dogs of responder group; 71.8 ± 11.2 months, 21 dogs of temporary responder group; 7.3 ± 10.0 months), especially in the responder group.

The most common ocular abnormalities associated with secondary glaucoma in the present study were previous anterior uveitis of unknown cause, retinal detachment and cataracts, which are consistent with previous studies [54-56]. A breed predisposition toward retinal detachment in the Shih Tzu dog (69.2%, 9/13 eyes) and anterior uveitis (48.8%) in Akitas and Miniature Dachshunds appears to be present in this study [57].

Latanoprost was effective in lowering IOP when used in combination with other antiglaucomatous medications in few dogs with secondary glaucoma. IOP was still controlled until study completion in three dogs that had previously anterior uveitis was present in two dogs and retinal detachment in one dog. IOP was lowered but returned to baseline IOP in 21 dogs. Underlying ophthalmic diseases included cataracts in six dogs, retinal detachments in five dogs, previous anterior uveitis of unknown causes in five dogs, trauma in two dogs, intraocular neoplasia (melanoma and lymphoma) in two

dogs, and lens luxation in one dog. Although there were no recurrent cases of inflammation or exacerbation of ocular conditions after using 0.005% latanoprost, these cases had previously uveitis and they did not respond to latanoprost. The use of 0.005% latanoprost resulted in an increase in IOP in three dogs, which were affected by anterior uveitis of unknown cause in two dogs and uveodermatologic uveitis in one dog. In a previous study, 40% of uveitic glaucoma patients receiving latanoprost did not achieve $\geq 20\%$ IOP reduction [27]. The lack of response in patients with uveitic glaucoma was believed to be secondary to a decrease in uveoscleral outflow by the inflamed uveal tract [42].

In conclusion, topical application of 0.005% latanoprost may help decrease IOP in some dogs with secondary glaucoma. Although latanoprost therapy showed some effects in lowering IOP in dogs with secondary glaucoma, this IOP-lowering effect decreased over time in most dogs. As PG analogs are particularly known for causing miosis in dogs, the use of topical 0.005% latanoprost should be avoided in dogs with glaucoma secondary to active anterior uveitis or anterior lens luxation in order to prevent posterior synechiae.

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Author Affiliation

[Top](#)

¹Kumi Animal Hospital, Department of Ophthalmology, Saitama-ken, Japan
²The Animal Medical Center, New York, USA

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