Effects of Topical Latanoprost on Intraocular Pressure and Myopia Progression in Young Guinea Pigs

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PURPOSE. To determine whether latanoprost, a prostaglandin analog proven to be very effective in reducing intraocular pressure (IOP) in humans, can also slow myopia progression in the guinea pig form deprivation (FD) model.

METHODS. Two-week-old pigmented guinea pigs underwent monocular FD and daily topical latanoprost (0.005%, $n = 10$) or artificial tears (control, $n = 10$) starting 1 week after the initiation of FD, with all treatments continuing for a further 9 weeks. Tonometry, retinoscopy, and high-frequency A-scan ultrasonography were used to monitor IOP, refractive error, and ocular axial dimensions, respectively.

RESULTS. Latanoprost significantly reduced IOP and slowed myopia progression. Mean interocular IOP differences ($\pm$SEM) recorded at baseline and week 10 were -0.30 ± 0.51 and 1.80 ± 1.16 mm Hg ($P = 0.525$) for the control group and 0.07 ± 0.35 and -5.17 ± 0.96 mm Hg ($P < 0.001$) for the latanoprost group. Equivalent interocular differences for optical axial length at baseline and week 10 were 0.00 ± 0.015 and 0.29 ± 0.04 mm ($P < 0.001$; control) and 0.02 ± 0.02 and 0.06 ± 0.02 mm ($P = 0.202$; latanoprost), and for refractive error were $+0.025 \pm 0.36$ and -8.2 ± 0.71 diopter (D) ($P < 0.001$; control), and -0.15 ± 0.35 and -2.25 ± 0.54 D ($P = 0.03$; latanoprost).

CONCLUSIONS. In the FD guinea pig model, latanoprost significantly reduces the development of myopia. Although further investigations into underlying mechanisms are needed, the results open the exciting possibility of a new line of myopia control therapy.

Keywords: myopia, intraocular pressure, latanoprost, optical axial length, guinea pigs

Myopia (nearsightedness) is an increasingly common condition that typically results from a mismatch between the axial length of the eye (too long) and its optical power. The prevalence of myopia has been increasing in the United States[1] and even more so in Asian countries,[2] with one study recording a prevalence figure of 96.5% for young adult males.[3] While the focusing error in myopia can be corrected with glasses, contact lenses, and/or refractive surgery, these interventions do not prevent associated vision-threatening conditions such as retinal detachment, myopic maculopathy, and glaucoma.[4] Thus there is an urgent need for treatments that can either prevent myopia or slow its progression.

Intraocular pressure (IOP) exerts a stretching influence (tangential tension) on the outer scleral wall of the eye and is believed to play a modulatory role in ocular enlargement.[5] While in normal ocular development this inflationary force may play an important role in maintaining scleral integrity,[6] it may also contribute to accelerated eye elongation and thus myopia progression due to associated increased scleral remodeling. With myopia progression, the scleral walls become biomechanically weaker and thinner, these changes rendering them more vulnerable to the stretching influence of IOP. Eyes with higher than normal IOP are more vulnerable, as are already myopic eyes due to their larger size, as the tension exerted by IOP on the wall of the eye is proportionally increased.[7] It thus logically follows that a decrease in IOP, as may be achieved with ocular hypotensive drugs, could slow ocular elongation in eyes undergoing myopia progression.

A number of studies have linked human myopia with elevated IOPs, although a causal association remains the subject of debate.[8–13] It is of interest that altered diurnal IOP rhythms have been recorded in young adults with moderate to severe myopia (based on phase and amplitude) when compared to emmetropes and low myopes,[14] consistent with findings in an earlier study of form-deprived myopic chicks.[15] Altered diurnal IOP rhythms are also a reported feature of glaucoma.[16] Taken together, these findings lend further support for examining the efficacy of IOP-lowering drugs as myopia control treatments. These drugs may not only slow ocular elongation and thus myopia progression, but they could also offer prophylactic benefit by reducing the risk of glaucoma.

The notion of using ocular hypotensive drugs to control myopia progression is not new. Two previous studies have tested this idea in the form-deprived myopia chick model.[17,18] Nonetheless, the choice of drug in one case and delivery route in the second case were arguably poor. One of these studies tested the effect of the ocular hypotensive drug, timolol, a beta-blocker, which proved to have minimal protective effect against myopia in the chick model.[17] However, this outcome is perhaps not surprising given more recent human studies showing little effect of this drug on IOP at night,[19] when myopic growth occurs.[15] The effect of 0.25% timolol was also tested in children in a randomized clinical trial, which showed no significant difference in the progression of myopia when compared to single vision spectacles.[20] Other earlier studies likewise found timolol to have no significant effect on axial elongation, despite

FIGURE 1. Guinea pig with monocular detachable diffuser attached to induce FD myopia.

its ocular hypotensive action.[21,22] The second drug to be tested in chicks was latanoprost, a prostaglandin (PG) F2-alpha analog, which was also used in the study reported here. However, in this earlier study, latanoprost was delivered by intravitreal injection rather than applied topically.[18] Thus, while the study reported a positive benefit on myopia progression, the translatability of this result to the clinic is questionable given the drug delivery route. Moreover, the underlying scleral remodeling mechanism and role of IOP in eye enlargement are likely different in the chick, which has a bilayered sclera with a fibrous layer reinforced by an inner cartilaginous layer, compared to mammals and primates, both of which lack a scleral cartilaginous layer.

Among the various ocular hypotensive drugs available today as glaucoma therapies, PG analogs are the most widely used.[23] As a potential myopia control treatment, that they have proven to be effective in lowering IOP around the clock (24 hours) has considerable merit. However, their mode of action may be problematic. Specifically, PG analogs promote matrix metalloproteinase (MMP) activity and thus remodeling of the extracellular matrix (ECM) within the uveoscleral outflow pathway.[23] This group of drugs has also been reported to promote scleral ECM remodeling, an action that may exacerbate rather than slow myopia progression[24] given that myopia progression per se has also been linked to increased scleral remodeling.[25]

Because it is not possible to predict for the PG analogs the relative benefit of lowering IOP around the clock compared to the potential adverse effect of increased scleral ECM remodeling on myopia progression, we sought to directly assess their efficacy as myopia control therapies. For this purpose, we chose the well-established form deprivation (FD) guinea pig model of myopia[26] as a critical translational step before human clinical trial of the same. As our test drug, we selected topical latanoprost, which has a long positive track record as a therapy for primary open angle glaucoma in humans.[23] It has also been shown to lower IOP in otherwise untreated guinea pigs.[27] In brief, we confirmed that topical latanoprost lowers IOP around the clock in young guinea pigs. It is important that we also found latanoprost to significantly slow ocular elongation in the form-deprived eyes of our animal subjects, thus slowing myopia progression. Since first reporting our findings at the Association for Research in Vision and Ophthalmology (ARVO) annual meeting (El-Nimri and Wildsoet. *IOVS* 2017;58:ARVO E-Abstract 5469), a study investigating the efficacy of another topical ocular hypotensive drug, brimonidine, against lens-induced myopia in guinea pigs has been published. Brimonidine was found to be effective in inhibiting myopia progression,[28] lending further support to notion that lowering IOP can slow myopia progression, a topic revisited in the discussion.

MATERIALS AND METHODS

Animals

Pigmented guinea pigs were used in this study, with breeders obtained from the University of Auckland (Auckland, New Zealand). Study animals were bred on-site and housed in a temperature-controlled room with a 12-hour-light/12-hour-dark cycle (on at 9:30 AM, off at 9:30 PM). Pups were weaned at 5 days of age and housed as single-sex groups in 41 cm wide × 51 cm long transparent plastic wire-top cages. They had free access to water and vitamin C–supplemented food, with additional fresh fruit and vegetables given five times a week as diet enrichment. All animal care and treatments in this study conform to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Experimental protocols were approved by the Animal Care and Use Committee of the University of California, Berkeley.

A total of 20 animals were used in this study, composing two groups of 10 animals. All animals underwent monocular myopia-inducing FD, and the same eyes also underwent one of two topical ophthalmic treatments, as summarized below (see also Tables 1 and 2). Untreated contralateral eyes served as controls.

Form Deprivation

Detachable white plastic diffusers were fitted to 14-day-old guinea pigs and worn for 10 weeks. Animals were monitored hourly during the 12-hour-light period to ensure that the diffusers remained in place; they were also cleaned as necessary. The design of the diffusers and attachment protocol were adapted from those implemented in chicks.[29] In brief, the diffusers were made from sheets of white styrene (Midwest Products Co., Hobart, IN, USA), hot-molded into semicircular domes and mounted on hook Velcro ring supports. Opaque diffusers were used in this study. To attach the diffusers to the guinea pigs, rings of loop Velcro were cut in halves and the two segments symmetrically affixed to the fur surrounding one of the guinea pig's eyes using gel cyanoacrylate glue (SureHold Plastic Surgery, Chicago, IL, USA) (Fig. 1).

Topical Ophthalmic Drug Treatments

One group received 1 drop of latanoprost (0.005% ophthalmic solution; Akorn, Lake Forest, IL, USA), instilled daily into their FD eyes, starting 1 week after the initiation of diffuser wear and continuing throughout the rest of the 10-week treatment period. The FD eyes of the second (control) group received topical artificial tears daily. The animals were randomly assigned to one of these two treatment groups (latanoprost or artificial tears) at the end of the first week of the FD treatment.

Measurements

IOP, spherical equivalent refractive errors (SEs), and optical axial lengths (ALs) were recorded for both eyes of each animal immediately before the initiation of the FD treatment (baseline), with follow-up measurements made at weekly intervals over the first month and every other week thereafter. Because of well-documented circadian rhythms in both IOP and eye elongation,[15] measurements were always taken around

TABLE 1. Summary of Mean Interocular Differences in IOP, SE, and AL (± SEM) and Summary Statistics for Monocularly FD Guinea Pigs Treated in Their Deprived Eyes With Either Topical Latanoprost or Artificial Tears (as a Control Treatment)

Parameter, Treatment Groups	Time of Measurement		Statistics, P Value
	Baseline	Week 10	
IOP, mm Hg			
FD + latanoprost	0.07 ± 0.35	−5.17 ± 0.96	<0.001
FD + artificial tears	−0.30 ± 0.51	1.80 ± 1.16	0.525
Spherical equivalent, D			
FD + latanoprost	−0.15 ± 0.35	−2.25 ± 0.54	0.03
FD + artificial tears	0.025 ± 0.36	−8.20 ± 0.71	<0.001
Optical axial length, mm			
FD + latanoprost	0.02 ± 0.02	0.06 ± 0.02	0.202
FD + artificial tears	0.00 ± 0.015	0.29 ± 0.04	<0.001

Statistics indicate significance of change over the treatment period.

TABLE 2. Summary of IOP, SE, and AL for FD and Fellow (Control) Eyes (± SEM) and Summary Statistics for Guinea Pigs Treated in Their Deprived Eyes With Either Topical Latanoprost or Artificial Tears (as a Control Treatment)

Parameter, Eye	Treatment	Baseline	Week 10	Statistics, P Value
IOP, mm Hg				
FD	Latanoprost	24.23 ± 0.87	23.4 ± 1.60	>0.999
Control	Latanoprost	24.17 ± 0.94	28.5 ± 1.60	0.01
FD	Artificial tears	22.23 ± 1.00	27.33 ± 1.50	0.009
Control	Artificial tears	22.53 ± 0.92	25.53 ± 1.17	0.083
Spherical equivalent, D				
FD	Latanoprost	2.08 ± 0.59	−1.32 ± 0.59	<0.001
Control	Latanoprost	2.22 ± 0.75	0.94 ± 0.34	0.15
FD	Artificial tears	2.33 ± 0.73	−6.9 ± 0.48	<0.001
Control	Artificial tears	2.30 ± 0.56	1.5 ± 0.37	0.55
Optical axial length, mm				
FD	Latanoprost	7.50 ± 0.05	8.5 ± 0.05	<0.001
Control	Latanoprost	7.50 ± 0.06	8.44 ± 0.03	<0.001
FD	Artificial tears	7.47 ± 0.03	8.64 ± 0.06	<0.001
Control	Artificial tears	7.47 ± 0.03	8.35 ± 0.02	<0.001

Statistics indicate signifcance of change over the treatment period.

the same time each day, early in the morning, after lights-on. Diurnal IOP rhythms were also recorded at monthly intervals.

All IOP measurements were conducted in awake animals prior to other procedures requiring anesthesia to avoid the possible confounding effects of the latter. A rebound tonometer (iCare; Tonolab, Helsinki, Finland) was used with the setting for rat eyes, for which this instrument has been calibrated; rat eyes are similar in size to those of guinea pigs. This instrument provides confidence interval information based on successive readings; only data with a confidence interval of 5% or less were used. Three measurements were taken on each eye and the average used in data analysis. To characterize diurnal rhythms in IOP, five measurements were made at approximately 6-hour intervals over 24 hours, including time points just after lights-on and just before lights-off. Measurements during the lights-off hours were taken under photographic dark light conditions to minimize the possible effect of brief exposures to light on circadian rhythms. Three measurements were taken on each eye at each time point and averaged for use in data analysis.

Refractive errors were measured using streak retinoscopy on awake animals 30 minutes after instillation of 1 drop of 1% cyclopentolate hydrochloride (Bausch & Lomb, Rochester, NY, USA) for cycloplegia. SEs (averages of results for the two principal meridians) were derived for use in data analysis.

Ocular axial dimensions were measured with a custom-built, high-frequency A-scan ultrasonography system, with an estimated resolution of approximately 10 μm.[15,29] For these measurements, animals were first placed under gaseous anesthesia (1.5%–2.5% isoflurane in oxygen), with eyelid retractors inserted to hold their eyes open. For each measurement, at least eight traces were captured per eye and analyzed off-line. Only optical ALs are reported here, derived as the sum of anterior chamber depth, axial lens thickness and vitreous chamber depth.

Statistical Analysis

Data analysis made use of statistical analysis software (Prism 6; GraphPad Software, La Jolla, CA, USA). Data for treated and control eyes, as well as derived interocular differences (treated eye versus control eye), are reported as mean ± SEM. For diurnal IOP data, the timing of peak IOPs was analyzed, as was rhythm amplitudes, derived as the difference between the highest and lowest IOP recorded during the 24-hour period, regardless of time of day. Two-way repeated measures ANOVA with a Bonferroni post hoc test were applied to longitudinal data. P values from post hoc testing are reported in the Results

section and are summarized in Tables 1 and 2. A 2-tailed paired t-test was applied to compare the IOP rhythm amplitudes of treated and control eyes. By way of indirectly evaluating the influence of IOP on myopic growth, the relationship between latanoprost-induced reductions in IOP at week 10, relative to baseline, and the ratio of changes in optical AL of FD eyes to changes in fellow eyes over the same time period was examined by regression analysis.

RESULTS

Daily topical latanoprost was effective in lowering IOP and slowing myopia progression in FD myopic eyes. These trends are evident in the graphical plots of interocular differences in IOP, SEs, and optical ALs across time in Figures 2 and 3 and they are described in more detail below for each treatment group.

Effects of Latanoprost on SE and Ocular Dimensions

As expected, the control group showed significant ocular elongation of their FD eyes and myopic shifts in SE, as reflected in the changes in interocular differences and in FD eyes over the 10-week treatment period. In contrast, the latanoprost group showed much smaller changes in these parameters over the same time period. Relevant mean baseline and week-10 interocular SE and AL difference data for both groups are summarized in Table 1; equivalent data for treated eyes and their fellows are also provided (Table 2).

Over the first week of the FD treatment, before the initiation of drug treatments, FD eyes elongated faster than their fellows and showed myopic shifts in their SEs. For the two groups combined, the mean interocular differences in SE and AL at the end of this 1-week treatment period reflect these changes (i.e., −2.9 ± 0.35 diopter [D] and 0.05 ± 0.02 mm). However, over the following drug treatment period, results for the latanoprost and control groups diverged, with the FD eyes of former group showing much smaller increases in AL and smaller myopic shifts in SE. These trends are shown graphically in Figures 2A and 2B. By the end of study period, interocular differences in AL and SE had changed minimally from baseline for the latanoprost group (i.e., 0.02 ± 0.02 vs. 0.06 ± 0.02
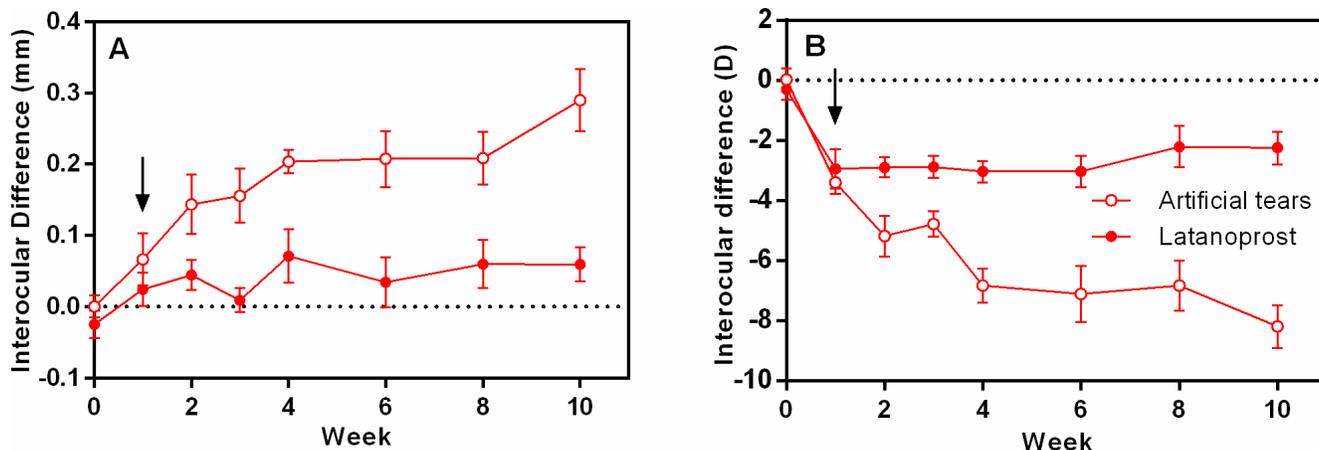
FIGURE 2. (A) Mean (±SEM) interocular differences in optical ALs (distance from front surface of cornea to inner retina [mm]) and (B) SE (diopters) in guinea pigs that were monocularly form-deprived for 10 weeks and treated in their FD eye with topical latanoprost or artificial tears from week 1. The *arrows* indicate the start of the topical treatments (latanoprost or artificial tears).

mm, $P = 0.202$, and -0.15 ± 0.35 vs. -2.25 ± 0.54 D, $P = 0.03$) compared to the changes in the control group, which recorded significantly increased interocular differences (i.e., 0.00 ± 0.015 vs. 0.29 ± 0.04 mm, $P < 0.001$, and 0.025 ± 0.36 vs. -8.2 ± 0.71 D, $P < 0.001$). There were also statistically significant differences between the two groups in interocular differences in SE and AL at week 10 ($P < 0.001$, $P < 0.001$; repeated measures 2-way ANOVA with a Bonferroni's post hoc analysis, respectively). The above patterns are mirrored in the patterns of change in treated compared to fellow eyes across the 10-week treatment period (Table 2). For the treated and fellow eyes of the latanoprost group, the changes in AL were not significantly different ($P = 0.215$), while they were for the control group ($P < 0.001$). On the other hand, the AL changes in the fellow eyes of the two groups were not significantly different from each other ($P = 0.275$), implying that latanoprost had no contralateral effect.

Latanoprost Treatment–Induced Effects on IOP

The morning IOP measurements provide convincing evidence of the effectiveness of daily topical latanoprost in lowering
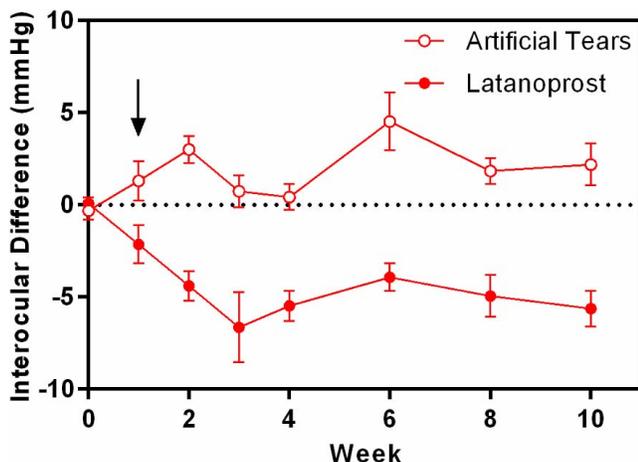

FIGURE 3. Interocular differences in IOP (mean ± SEM, mm Hg) in guinea pigs treated in their FD eyes with topical latanoprost or artificial tears from week 1 of a 10-week FD treatment period. The *arrow* indicates the start of the topical treatments (latanoprost or artificial tears).

IOP. Specifically, the mean interocular differences in IOP changed from 0.07 ± 0.35 mm Hg at baseline to -5.17 ± 0.96 mm Hg after 10 weeks of latanoprost treatment ($P < 0.001$). In contrast, interocular differences in IOP for the control group did not change significantly over the study period ($P = 0.53$), with the difference at the week 10 time point being slightly, but not significantly, higher than the baseline value (i.e., 1.80 ± 1.16 vs. -0.30 ± 0.51 mm Hg) (Fig. 3). Both eyes of control animals and the fellow (control) eyes of latanoprost-treated animals recorded higher IOPs at week 10 compared to baseline values. In contrast, the FD eyes treated with latanoprost showed relatively stable IOP over the treatment period (i.e., 24.23 ± 0.87 mm Hg vs. 23.4 ± 1.6 mm Hg) (Table 2). In comparing the changes in the two groups, it is of note that the mean increase in IOP for the FD eyes of the control group was also larger in absolute terms than the reduction in IOP for the FD eyes of the latanoprost group.

Diurnal IOP Rhythms and Effects of Latanoprost

The diurnal data offer a further perspective on the ocular hypotensive profile of latanoprost in guinea pigs. Figures 4A and 4B show the average diurnal rhythm in IOP for FD and fellow eyes derived from measurements made at 6-hour intervals over 24 hours for both groups. As in humans,[30] latanoprost induced a sustained drop in IOP across 24 hours. Thus, there were significant differences between the latanoprost and control groups in the IOPs of FD eyes, recorded in both the dark period ($P = 0.02$) and morning ($P = 0.005$), with differences in IOPs recorded just before lights-off being borderline significant ($P = 0.051$). The timing of peak IOP was similar for the FD eyes of both latanoprost and control groups, as well as for their fellows, around 9:35 AM, just after lights-on. However, control FD eyes recorded a larger rhythm amplitude than their fellow eyes (8.1 vs. 5.9 mm Hg, $P = 0.045$), while in contrast, latanoprost-treated FD eyes and their fellows recorded similar amplitudes (5.7 vs. 5.23 mm Hg, $P = 0.94$). There was no statistically significant difference between the amplitudes of the fellow eyes of each group.

To further analyze the effects of the latanoprost treatment on diurnal IOP rhythms, interocular difference patterns for latanoprost and control groups were compared. These data are shown in Figure 4C. The interocular difference was highest in the morning, just after lights-on (-6.6 ± 1.2 mm Hg), for the latanoprost group, while for the control group, the largest
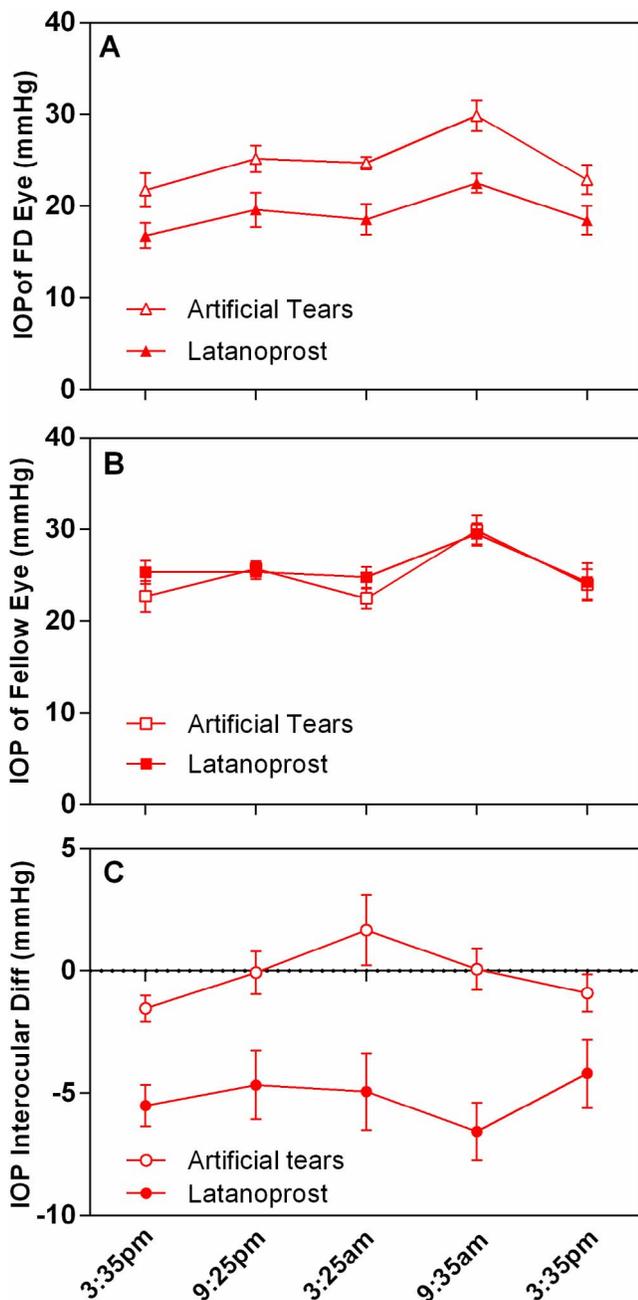
FIGURE 4. Mean IOPs (±SEM) measured at 6-hour intervals over 24 hours for (A) the form-deprived eyes of guinea pigs treated daily with either topical latanoprost or artificial tears, (B) the fellow eyes for both groups, and (C) mean interocular (treated-control) differences (±SEM) for the same animals. In all cases, IOPs were recorded at the end of the 10-week treatment period and both topical treatments were initiated 1 week after the start of the FD treatment.

difference was recorded in the dark phase, at approximately 3:35 AM and was small (1.67 ± 1.45 mm Hg). Interocular differences for the two groups were also significantly different at 9:25 PM, 3:25 AM, and 9:35 AM (P values: 0.03, 0.004, and 0.004, respectively) (Fig. 4C).

IOP Versus AL Interactions

To examine the potential influence of IOP on myopia development for individual animals of both groups, the ratios
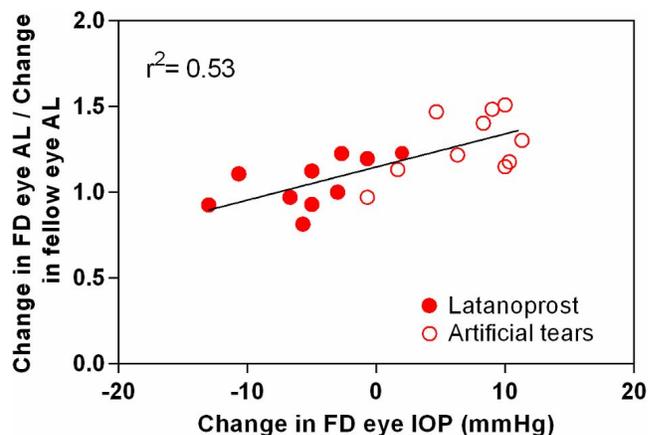

FIGURE 5. Ratio of changes over the 10-week treatment period in optical ALs of FD eyes to their fellow eyes plotted against changes in IOP for both latanoprost and control (artificial tears) groups.

of changes over the 10-week treatment period in the ALs of FD to fellow eyes were plotted against the changes in IOP over the same period (Fig. 5). A regresson analysis undertaken on these data revealed a significant linear correlation ($r^2 = 0.53$, $P = 0.003$), providing indirect evidence for a role of IOP as an inflationnary force in myopia development, as discussed further below.

DISCUSSION

This study aimed to reexamine the possibility of using ocular hypotensive drugs as myopia control therapies, specifically addressing the question of whether myopia progression can be inhibited through an appropriate sustained reduction in IOP. To this end, we examined the efficacy of topical latanoprost as a representative PG analog for controlling myopia progression in a form-deprived guinea pig model of myopia. We found that topically applied latanoprost was effective in both lowering IOP and slowing myopia progression in this model.

As noted in the introduction, to-date there has been three studies investigating the effects of intervention with ocular hypotensive drugs on myopia progression in animal models. Two of the studies involved form-deprived chicks, and one of them also involved latanoprost delivered by intravitreal injection.[18] The latter study also reported attenuation of eye elongation. Intravitreal injection of 100 ng latanoprost acid twice for a duration of one week approximately halved the mean interocular difference compared to that recorded from chicks injected with isotonic saline (i.e., 0.17 ± 0.12 vs. 0.30 ± 0.04 mm). Nevertheless, intravitreal injection of latanoprost in chicks was less effective than our longer-term topical latanoprost treatment in guinea pigs (0.06 ± 0.02 mm latanoprost vs. 0.29 ± 0.04 mm control at week 10). This is possibly because the chick sclera has an inner cartilage layer in addition to the more commonly found fibrous layer. Thus, the underlying scleral "growth" mechanism(s) and the role of IOP in eye enlargement in the chick may be different from those in mammals and humans. The other earlier study in chicks tested timolol, a beta-blocker, which proved to have minimal effect on the development of FD myopia, even though it was found to lower IOP by approximately 18% in myopic eyes.[17] It is interesting that timolol is the only ocular hypotensive drug to have been evaluated clinically, and while a correlation between reductions in IOP and the rate of myopia progression was reported in the earliest of two studies,[21] the latter effect was reported to be small, even though timolol apparently lowered

IOP by approximately 3 mm Hg.[21,22] Finally, recent study tested the efficacy of brimonidine, another ocular hypotensive drug, against lens-induced myopia in guinea pigs.[28] Brimonidine belongs to a drug class different from that of both latanoprost and timolol, being an alpha-2 adrenergic agonist, with effects on both aqueous inflow and uveoscleral outflow. Nevertheless, it also proved effective in stabilizing myopia progression.

In our study, the FD eyes of control (artificial tears–treated) animals showed a trend toward IOP elevation. Although this trend was not statistically significant, the brimonidine study also reported an increase in IOP in lens-induced myopic eyes receiving 0.9% saline by the end of the study.[28] These findings also fit with isolated reports in humans of higher IOPs in myopes compared to emmetropes.[7,9] Nevertheless, even without significant IOP elevation, for eyes with fibrous scleras, biomechanically weakening of the sclera due to increased ECM during myopia progression will arguably render them more vulnerable to the stretching (inflationary) influence of IOP. In this context, the results of our study (i.e., that latanoprost lowered IOP and slowed axial elongation in treated FD eyes relative to control FD eyes) are predictable. The possibility that structural changes in myopic (FD) eyes can lead to IOP elevation as a further adverse complication is the subject of ongoing investigations.

Why did latanoprost prove so effective relative to timolol in slowing myopia progression in our study? Apart from the differences in animal models used to test their efficacy, guinea pig versus chicks, the ocular hypotensive action of timolol is largely limited to daytime hours in comparison to latanoprost, which has an enduring (24 hours) ocular hypotensive effect.[19] Overall, the PG analogs also tend to be more effective in lowering IOP than beta blockers, such as timolol.[31] These features of latanoprost's profile contributed to its selection for our study, along with other data showing robust ocular hypotensive effects in a variety of species, including monkeys[32] and dogs.[33] The study reported here allows the guinea pig to be added to this list. The only previous study involving the use of topical latanoprost in guinea pigs was short term (24 hours), and the animals studied were normal and older than those used in the current study.[27] Nevertheless, a reduction in IOP in response to latanoprost was also reported, as 2.1 ± 1.3 mm Hg after 1 hour.

Ophthalmic research into the actions of latanoprost and closely related PG analogs has largely been directed toward understanding their ocular hypotensive action. In this context, they are known to increase MMP activity and thus remodeling of the ECM within the uveoscleral outflow pathway.[34] Our finding that treatment efficacy (i.e., inhibition of FD myopia was directly related to the extent to which IOP was reduced; Fig. 5) supports a biomechanical explanation (i.e., that the reduced rate of ocular elongation reflects the reduced tension on the scleral wall achieved by lowering IOP). However, alternative explanations cannot be ruled out, including the possibility that increased uveoscleral outflow may have contributed to the observed myopia control effect in other ways, for example, by increasing the clearance of scleral-directed myopiagenic growth factors released by the retinal pigment epithelium[35] and/or thickening the choroid, which has been linked to inhibited eye elongation in a variety of animal models (see Refs. 12 and 15). As noted in the introduction, latanoprost has also been reported to increase scleral remodeling,[7] which might exacerbate rather than inhibit myopia progression; although such effects cannot be ruled out in the current study, they clearly did not dominate in terms of the treatment outcome. Nevertheless, further investigation of the scleral and choroidal effects of latanoprost at the molecular, cellular, and biomechanical levels would seem warranted to better understand its myopia control effect.

Diurnal rhythms in IOP have been documented in many species, including chicks,[15] rats,[36,37] rabbits,[38] monkeys,[39] and humans,[34] with species differences in the phase and amplitude of IOP rhythms apparent (e.g., lower in rhesus monkey eyes [5 mm Hg],[39] than in rat eyes[36,37] and rabbit eyes [10 mm Hg]).[38] For our guinea pigs, the highest IOP was recorded at the first morning time point, just after lights-on, with IOP decreasing throughout the day. These results agree with our already published diurnal IOP patterns for normal guinea pigs.[40] While all eyes showed daily rhythms in IOP in the current study, it is interesting that the IOP rhythm amplitude for myopic eyes treated with artificial tears was increased to approximately 8 mm Hg compared to fellow eyes. However, while the latter value is comparable to the amplitude reported for FD myopic chick eyes,[15] amplitude was reported to be not significantly affected, but the phase of the rhythm was more variable in the latter study (e.g., trough does not consistently occur at night), pointing to a possible species difference. It is noteworthy that latanoprost reduced the IOP rhythm amplitude for FD myopic eyes to a level similar to that of untreated fellow eyes (approximately 5 mm Hg), comparable to data from normal monkeys.[39] Thus, in addition to reducing IOP overall, latanoprost appears to normalize IOP rhythms in myopic eyes. In keeping with a biomechanical explanation for the slowed myopia progression with latanoprost, could the normalization of the IOP rhythm amplitude in the FD myopic eyes of the guinea pigs underlie the slowed myopia progression observed? Alternatively, it is possible that the sustained ocular hypotensive action of latanoprost, that is, around the clock, was responsible.

Limitations

Below we summarize key weaknesses in our study. As mentioned, guinea pigs wore diffusers affixed over one of their eyes via Velcro rings. While this method successfully induced myopia, the long-term nature of these experiments carried a significant risk of the diffusers becoming detached. However, in cases of diffuser detachment, temporary intervention using masks with diffusers attached limited the disruption to the FD treatment. Also, there were no clear treatment-related biases (i.e., latanoprost versus artificial tears in detachment events). On average, diffusers of each animal were detached once or twice a week for no longer than 1 hour each time. Accurate measurement of IOP is also critical to this study. While we did not undertake calibration measurements for the iCare rebound tonometer used in our study, it has been calibrated for rat eyes, which are similar in size to guinea pig eyes. Central corneal thickness is also known to influence IOP readings but was not measured in our study and it is not possible to rule out an effect of latanoprost via remodeling of the ECM of the corneal stroma, as there are to our knowledge no relevant published studies. Our analyses were also largely based on interocular differences by way of reducing the effects of interanimal variability. Lending validity to this approach, we also report no significant differences between the fellow eyes of the latanoprost and control groups; nevertheless, subtle changes in the fellow eyes to form-deprived eyes have been reported in a number of past studies involving other animal models.[41,42] Finally, we did not test the effect of latanoprost on normal (non–form-deprived) eyes, leaving open the question of its effect on normal eye growth. However, data collected from older (3-month-old) animals are encouraging; monocular latanoprost significantly reduced IOP in otherwise untreated eyes after 2 weeks (mean interocular IOP differences ± SEM:

–0.44 ± 0.48 mm Hg at baseline, –2.89 ± 1.13 mm Hg, $P = 0.05$), while neither SEs nor ALs were affected.

In summary, our study appears to be, to our knowledge, the first longitudinal investigation into the effects of latanoprost on myopic eye growth, here using the guinea pig as an animal model for myopia. The results provide convincing evidence that daily topical latanoprost can slow myopia progression in young guinea pigs, presumably linked to its ocular hypotensive action. While there is much more to learn about underlying mechanisms, our results represent an exciting advance, given the very limited therapeutic options for myopia control today.

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