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Short-term vs. Long-term Effects of Topical administration of latanoprost on Schirmer Tear Test, Intraocular Pressure, and Pupil Size in Clinically Normal Dogs

Armin shokoohimand[1], Farnoosh Arfaee[1*], Ahmad Asghari[2], Ehsan khaksar[3]

1- Department of Clinical Science, Faculty of Specialized Veterinary Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran.

2- Department of Clinical Science, Faculty of Veterinary Medicine, Science and Research Branch, Islamic Azad University, Tehran, Iran.

3- Department of Clinical Science, Faculty of Veterinary Sciences, Garmsar Branch, Islamic Azad University, Garmsar, Iran.

Abstract

Background: Glaucoma poses significant challenges in veterinary medicine, necessitating effective management strategies to mitigate vision loss. Prostaglandin analogs like latanoprost offer promising avenues due to their ability to lower intraocular pressure (IOP). However, a comprehensive understanding of latanoprost's short-term and long-term effects on ocular parameters in dogs remains limited.

Objectives: This study aims to compare the effects of short-acting versus long-acting latanoprost on the Schirmer Tear Test (STT), intraocular pressure (IOP), and pupil size in clinically normal dogs, highlighting its potential applications in veterinary ophthalmology. By examining both short-term and long-term impacts, this study offers novel insights into the temporal pharmacological effects of latanoprost.

Methods: Twenty healthy adult male cross-bred dogs underwent thorough baseline assessments before receiving either latanoprost or saline drops in randomly chosen eyes over a three-week period. STT, IOP, and pupil size were measured at various intervals using standardized protocols. Statistical analysis was conducted to compare treated and untreated eyes.

Results: Short-term analysis revealed significant IOP reduction at 6 and 8 hours post-latanoprost instillation, with no significant changes in STT values. Pupil diameter showed significant differences between treated and untreated eyes. Long-term effects included sustained IOP reduction and pupil constriction after three weeks of latanoprost treatment.

Conclusions: Latanoprost demonstrates rapid and sustained efficacy in reducing IOP in dogs, with potential implications for glaucoma management. While it does not significantly affect tear production, it modulates pupil size, highlighting its multifaceted pharmacological effects. The study affirms latanoprost's safety profile and underscores its therapeutic potential in veterinary ophthalmology, urging further exploration into its mechanisms and applications.

Keywords: Dogs - Glaucoma - Intraocular pressure - latanoprost - Schirmer Tear Test

Introduction

Glaucoma is a multifactorial ocular disease characterized by elevated intraocular pressure (IOP), which if left uncontrolled, can lead to irreversible optic nerve damage and vision loss.(Graham et al., 2020) In veterinary medicine, glaucoma poses a significant clinical challenge, particularly in dogs, where primary and secondary forms of the condition are encountered. Effective management of glaucoma in dogs often involves the use of various ocular medications aimed at reducing IOP and preserving ocular integrity.(Ophthalmology & 2021, 2020)

Among the classes of antiglaucoma drugs, prostaglandin (PG) analogs have emerged as key therapeutic agents due to their ability to enhance uveoscleral outflow, thereby lowering IOP. (Plummer et al., 2021)Latanoprost, a member of this class, has been widely utilized in human and veterinary ophthalmology for its potent IOP-lowering effects.(Cordeiro et al., 2024) However, while the short-term efficacy of latanoprost in reducing IOP has been well-documented in dogs, this study uniquely addresses this gap by comparing latanoprost's short-acting versus long-acting effects, providing novel insights into its sustained pharmacological impact on canine ocular health.(Desai et al., 2022a) Understanding the effects of latanoprost on these parameters over both short-term and long-term durations is crucial for optimizing glaucoma management strategies and ensuring the overall ocular well-being of canine patients.

This study aims to compare the effects of short-acting versus long-acting latanoprost on the Schirmer tear test (STT), intraocular pressure (IOP), and pupil size in clinically normal dogs, for potential application in the management of glaucoma and other ocular conditions in veterinary practice.

Materials and methods:

The current investigation received approval from the ethics committee of the science and research branch of Islamic Azad University and adhered to the ARVO Statement guidelines for the ethical use of animals in ophthalmic and vision research.

A total of twenty healthy adult castrated male cross-bred dogs were utilized in this study. Before commencement, all dogs were housed indoors for seven days under controlled environmental conditions, maintaining a constant temperature of 22 degrees Celsius and humidity levels between 40-45%. The lighting regimen followed a 12-hour light and 12-hour dark cycle.(Bódizs et al., n.d.) Dogs had access to food meeting their dietary requirements and were provided water ad libitum. Before inclusion in the study, each dog underwent a comprehensive physical examination, including a complete blood count and serum biochemical profile assessment, to ensure the baseline health status. Furthermore, a thorough ophthalmic examination, encompassing tests such as the Schirmer tear test, slit-lamp biomicroscopy, fluorescein staining, tonometry, and direct and indirect ophthalmoscopy, was conducted to confirm ocular health and ensure eligibility for participation in the study.

Baseline intraocular pressure (IOP) was assessed in dogs (T0). Subsequently, each dog was administered one drop of latanoprost (Latanapost®, Sinadarou Laboratories Company, Tehran, Iran) in a randomly chosen eye, while the other eye received one drop of normal saline as a control. These eye drops were administered every 12 hours for a consecutive duration of three weeks.

Each animal was gently restrained in a ventral recumbent position for the duration of the procedure. Intraocular pressure (IOP) was assessed using a rebound tonometer (TonoVet®, Jorgensen Laboratories, Loveland, CO, USA) calibrated to 'd'. Care was taken to avoid any stimulation to the head, neck, or eyelids during measurement to mitigate potential confounding factors.(Klein et al., 2011) For short-term assessment of IOP, Schirmer tear test (STT), and pupillary diameter (PD) IOP were measured at intervals of 30 minutes, 60 minutes, 90 minutes, 120 minutes, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours, and 36 hours. Additionally, for long-term evaluation, measurements were taken every Sunday for

three weeks at 2 hours, 4 hours, 6 hours, 8 hours, and 12 hours post-morning drug instillation. Pupillary diameter was recorded simultaneously using a Jameson caliper (Storz Ophthalmic, Bausch + Lomb, New York, NY, USA). All measurements and ocular examinations were conducted by a single examiner (AS) to ensure consistency and minimize inter-operator variability.

The statistical analysis was conducted utilizing SPSS statistical software (version 23.0, SPSS Inc., Chicago, IL, USA). All collected values were normalized using the one-sample Kolmogorov–Smirnov test ($p>0.3$). To compare the means of Schirmer tear test (STT), intraocular pressure (IOP), and pupillary diameter (PD) values between treated and untreated eyes, a repeated measures ANOVA with Bonferroni post hoc correction was employed. Statistical significance was defined as a P-value of <0.05.(Molazem et al., 2024; Mottaghian et al., 2022; Rassouli et al., 2021; Rezaey & Alizadeh, 2024)

Results:

Short-Term effects:

Significant differences in intraocular pressure were observed between treatment and non-treatment groups at 6- and 8-hours post-drop instillation ($p=0.008$, $p=0.014$, respectively), with a mean of 21±4.5 mmHg.

However, there were no significant differences in Schirmer test values between treated and untreated eyes across all time intervals (mean: 16.3±3.2 mm/min).

Notably, a significant difference in pupil diameter was noted between treated and untreated eyes at all time points, except baseline and 36 hours post-drop instillation ($p<0.001$; mean: 0.08 cm).

No significant differences were found in intraocular pressure, pupil diameter, or Schirmer test values between treated and untreated eyes at various time points ($p>0.05$).

Long-Term effects:

Baseline intraocular pressure values in the treated eyes were (16.6±2.8 mmHg) and a significant reduction in intraocular pressure was observed after 3 weeks of treatment.

Similarly, Schirmer test values were 0.6±0.1 cm, and no significant difference was observed after three weeks

Also, baseline pupil diameter values were 0.6±0.1 cm and 21.2±1.4 mm/min, and a significant reduction in pupil diameter was observed after 3 weeks of treatment respectively.

Discussion

Glaucoma is a prevalent ocular disease in veterinary medicine, posing significant challenges due to its potential for irreversible vision loss.(Park & Komáromy, 2021) This study uniquely investigates the differential impacts of short-acting versus long-acting latanoprost on the Schirmer Tear Test (STT), intraocular pressure (IOP), and pupil size in clinically normal dogs. By providing a novel comparison of these formulations, our research sheds light on the temporal pharmacological dynamics of latanoprost. Our findings not only confirm the rapid IOP-lowering effects but also reveal the sustained efficacy and safety of long-term administration, which has been less frequently documented in veterinary literature. These results enhance our understanding of latanoprost's temporal effects and ocular tolerability, offering valuable insights for its clinical application in glaucoma management.

The short-term efficacy of latanoprost in reducing IOP in dogs has been previously established.(Studer et al., 2000) results corroborate these findings, demonstrating a significant reduction in IOP at 6 and 8 hours post-drop instillation. This rapid onset of action aligns with the pharmacokinetics of latanoprost, which acts by enhancing uveoscleral outflow.(NAKAGAWA et al., n.d.) However, despite its potent IOP-lowering effects, no significant changes in STT values were observed in our study, indicating that latanoprost may not directly influence tear production in clinically normal dogs. This finding is consistent with previous reports in the human and veterinary literature, suggesting that latanoprost primarily targets IOP regulation without affecting tear secretion.(Desai et al., 2022b)

Interestingly, this study revealed a significant difference in pupil diameter between treated and untreated eyes at various time points, suggesting a potential role of latanoprost in modulating pupillary dynamics. observation underscores the multifaceted pharmacological effects of latanoprost beyond its primary mechanism of IOP reduction.(Smith et al., 2010) Further investigations are warranted to elucidate the underlying mechanisms driving these changes in pupil size and their clinical implications.

In contrast to short-term effects, long-term analysis revealed a sustained reduction in IOP and pupil diameter following three weeks of latanoprost administration. These findings highlight the therapeutic durability of latanoprost and its potential for long-term glaucoma management in dogs. Importantly, this study also demonstrated the ocular safety profile of latanoprost, with no significant adverse effects on electrocardiography, blood cell counts, or biochemical profiles observed over both short and long-term intervals. This favorable safety profile further supports the use of latanoprost as a reliable therapeutic option for canine glaucoma.

These results are consistent with previous studies evaluating the effects of latanoprost in various animal models, including horses and cats.(McDonald et al., 2016; Willis et al., 2001) While ocular adverse effects have been reported in some species, this study provides reassurance regarding the ocular tolerability of latanoprost in dogs. Notably, the absence of significant changes in control eyes treated with saline reaffirms the specificity of latanoprost's effects on ocular parameters.

While this study sheds light on the short-term and long-term effects of latanoprost in dogs, limitations exist. These include a small sample size, a brief observation period of three weeks, and reliance on a fixed dosing regimen. Additionally, the study's focus on healthy dogs may limit generalizability, and the use of a single examiner could introduce bias. Not all relevant endpoints were assessed, and species-specific differences may impact applicability beyond dogs. Addressing these limitations in future research will enhance understanding of latanoprost's role in veterinary ophthalmology.

In conclusion, this study underscores the efficacy and safety of topical latanoprost in canine glaucoma management. By elucidating its short-term and long-term effects on STT, IOP, and pupil size, we provide valuable insights for optimizing treatment strategies and preserving ocular health in dogs affected by glaucoma. Future research should focus on further elucidating the mechanistic basis of latanoprost's effects on pupillary dynamics and exploring its potential therapeutic applications beyond glaucoma management.

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References

Bódizs, R., Kis, A., Gácsi, M., Sciences, J. T.-C. O. in B., & 2020, undefined. (n.d.). Sleep in the dog: comparative, behavioral and translational relevance. *Elsevier*. Retrieved April 20, 2024, from https://www.sciencedirect.com/science/article/pii/S2352154619301378

Cordeiro, M. F., Gandolfi, S., Gugleta, K., Normando, E. M., & Oddone, F. (2024). How latanoprost changed glaucoma management. *Acta Ophthalmologica*, *102*(2), e140–e155.

Desai, S. J., Pumphrey, S. A., & Koethe, B. (2022a). Comparative effects of latanoprost and latanoprostene bunod on intraocular pressure and pupil size in ophthalmologically normal Beagle dogs. *Veterinary Ophthalmology*, *25*(4), 282–290. https://doi.org/10.1111/VOP.12982

Desai, S. J., Pumphrey, S. A., & Koethe, B. (2022b). Comparative effects of latanoprost and latanoprostene bunod on intraocular pressure and pupil size in ophthalmologically normal Beagle dogs. *Veterinary Ophthalmology*, *25*(4), 282–290.

Graham, K. L., McCowan, C. I., Caruso, K., Billson, F. M., Whittaker, C. J. G., & White, A. (2020). Optical coherence tomography of the retina, nerve fiber layer, and optic nerve head in dogs with glaucoma. *Veterinary Ophthalmology*, *23*(1), 97–112.

Klein, H. E., Krohne, S. G., Moore, G. E., Mohamed, A. S., & Stiles, J. (2011). Effect of eyelid manipulation and manual jugular compression on intraocular pressure measurement in dogs. *Journal of the American Veterinary Medical Association*, *238*(10), 1292–1295.

McDonald, J. E., Kiland, J. A., Kaufman, P. L., Bentley, E., Ellinwood, N. M., & McLellan, G. J. (2016). Effect of topical latanoprost 0.005% on intraocular pressure and pupil diameter in normal and glaucomatous cats. *Veterinary Ophthalmology*, *19*, 13–23.

Molazem, M., Amini, E., Salimi, A., Muhammadnejad, A., & Hasannejad, H. (2024). Magnetic Resonance Imaging Features of Olfactory Neuroendocrine Carcinoma in a Dog. *Iranian Journal of Veterinary Medicine*, *18*(3), 447–452.

Mottaghian, P., Raoofi, A., Madadgar, O., Badiei, A., & Tamai, I. A. (2022). A Study on Mycoplasmal and Viral Infections in Bovine Keratoconjunctivitis. *Iranian Journal of Veterinary Medicine*, *17*(4), 345–352.

NAKAGAWA, A., INOUE, A., SADAMOTO, K., KOUZAI, S., NEMOTO, S., KURATA, M., SAKAI, O., & TOKUSHIGE, H. (n.d.). *Evaluation of the utility of 0.005% latanoprost ophthalmic solution for lowering intraocular pressure: Efficacy, pharmacokinetics, and safety in dogs*.

Ophthalmology, T. W.-V., & 2021, undefined. (2020). A review of glaucoma surgical therapy. *Wiley Online Library*, *24*(S1), 34–38. https://doi.org/10.1111/vop.12852

Park, S. A., & Komáromy, A. M. (2021). Biomechanics of the optic nerve head and sclera in canine glaucoma: a brief review. *Veterinary Ophthalmology*, *24*(4), 316–325.

Plummer, C. E., Bras, D., Grozdanic, S., Komáromy, A. M., McLellan, G., Miller, P., Sapienza, J. S., Teixeira, L., & Webb, T. (2021). Prophylactic anti-glaucoma therapy in dogs with primary glaucoma: A practitioner survey of current medical protocols. *Veterinary Ophthalmology*, *24*(S1), 96–108. https://doi.org/10.1111/VOP.12820

Rassouli, A., Falahatipour, S. K., Ardakani, Y. H., Javar, H. A., & Kiani, K. (2021). Comparative Pharmacokinetics of Enrofloxacin After Subcutaneous Administration of a Novel in situ Gel Forming Preparation and a Conventional Product to Rabbits. *Iranian Journal of Veterinary Medicine*, *15*(1).

Rezaey, A., & Alizadeh, S. (2024). The Efficacy of Ultrasonographi Diagnosis in Assessing Causes of Ascites in Dogs. *Iranian Journal of Veterinary Medicine*, *18*(1), 141–150.

Smith, L. N., Miller, P. E., & Felchle, L. M. (2010). Effects of topical administration of latanoprost, timolol, or a combination of latanoprost and timolol on intraocular pressure, pupil size, and heart rate in clinically normal dogs. *American Journal of Veterinary Research*, *71*(9), 1055–1061.

Studer, M. E., Martin, C. L., & Stiles, J. (2000). Effects of 0.005% latanoprost solution on intraocular pressure in healthy dogs and cats. *American Journal of Veterinary Research*, *61*(10), 1220–1224.

Willis, A. M., Diehl, K. A., Hoshaw-Woodard, S., Kobayashi, I., Vitucci, M. P., & Schmall, L. M. (2001). Effects of topical administration of 0.005% latanoprost solution on eyes of clinically normal horses. *American Journal of Veterinary Research*, *62*(12), 1945–1951.

تأثیرهای کوتاه‌مدت و بلندمدت مصرف لاتانوپروست به‌صورت موضعی بر آزمون شیرمر، فشار داخل چشم و اندازه مردمک در سگ‌های سالم

آرمین شکوهی‌مند[۱]، فرنوش ارفعی[۱]*، احمد اصغری[۲]، احسان خاکسار[۳]

۱ -دانشکده علوم بالینی، دانشکده علوم دامی تخصصی، دانشگاه علوم و تحقیقات، واحد علوم و تحقیقات، دانشگاه آزاد اسلامی، تهران، ایران.

۲ -دانشکده علوم بالینی، دانشکده دامپزشکی، دانشگاه علوم و تحقیقات، واحد علوم و تحقیقات، دانشگاه آزاد اسلامی، تهران، ایران.

۳ -دانشکده علوم بالینی، دانشکده دامپزشکی، واحد گرمسار، دانشگاه آزاد اسلامی، گرمسار، ایران.

چکیده

زمینه مطالعه: گلوکوم چالش‌های مهمی در دامپزشکی ایجاد می‌کند و نیاز به مدیریت مؤثری برای کاهش از دست دادن بینایی دارد. آنالوگ های پروستاگلاندین مانند لاتانوپروست به دلیل توانایی آنها در کاهش فشار داخل چشمی (IOP) راه های امیدوارکننده ای را ارائه می دهند. با این حال، درک جامع از اثرات کوتاه مدت و بلند مدت لاتانوپروست بر پارامترهای چشمی در سگ ها محدود است.

هدف: این مطالعه با هدف مقایسه اثرات کوتاه مدت و بلندمدت لاتانوپروست بر تست اشک شرمر(STT) ، IOPو اندازه مردمک در سگ‌های سالم انجام شد و کاربردهای بالقوه آن در چشم پزشکی دامپزشکی را مشخص می کند.

روش کار: بیست سگ نر بالغ سالم قبل از دریافت قطره‌های لاتانوپروست یا سالین در چشم‌هایی که به‌طور تصادفی انتخاب شده بودند. در طی یک دوره سه هفته‌ای ارزیابی‌های کاملی را انجام دادند و STT ،. IOP، و اندازه مردمک در فواصل مختلف با استفاده از پروتکل های استاندارد اندازه گیری شد. تجزیه و تحلیل آماری برای مقایسه چشم های درمان شده و درمان نشده انجام شد.

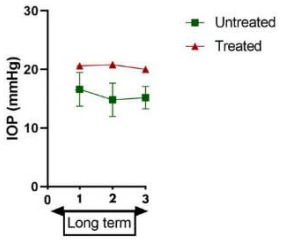
نتایج: آنالیز کوتاه‌مدت کاهش چشمگیر IOP را در 6 و 8 ساعت پس از استفاده لاتانوپروست را نشان داد، بدون اینکه تغییر معنی‌داری در مقادیر STT مشاهده شود.همچنین قطر مردمک بین چشم های درمان شده و درمان نشده تفاوت معنی داری نشان داد. اثرات طولانی مدت شامل کاهش مداوم IOP و تنگ شدن مردمک پس از سه هفته درمان با لاتانوپروست بود.

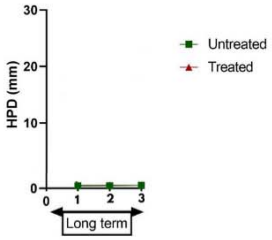
نتیجه‌گیری نهایی: لاتانوپروست اثربخشی سریع و پایداری را در کاهش فشار داخل چشم در سگ‌ها نشان می‌دهد که نتایج بالقوه‌ای برای مدیریت گلوکوم دارد. در حالی که به طور قابل توجهی بر تولید اشک تأثیر نمی گذارد، اندازه مردمک را تعدیل می کند و اثرات دارویی چند وجهی آن را برجسته می کند. این مطالعه استفاده ایمن از لاتانوپروست را تأیید می‌کند و بر پتانسیل درمانی آن در چشم پزشکی دامپزشکی تأکید می‌کند و به بررسی بیشتر مکانیسم‌ها و کاربردهای آن می‌پردازد.

کلمات کلیدی: سگ - گلوکوم - فشار داخل چشم - لاتانوپروست - تست اشک شیرمر

Table 1. Mean and standard deviation of measured pupillary diameter, intraocular pressure, and Schirmer tear test post-instillation of latanoprost in 20 healthy adult castrated male dogs during 3 weeks.

Groups/time points	*0hr*	*0.5hr*	*1.5hr*	*2hr*	*4hr*	*8hr*	*12hr*	*24hr*	*36hr*	*Week one*	*Week two*	*Week three*
Pupillary diameter												
Untreated eyes	0.8 ±00	0.8 ±00	0.76 ±0.05	0.76 ±0.05	0.83 ±0.05	0.73 ±0.05	0.73 ±0.05	0.7 ±0.1	0.71 ±0.11	0.76 ±0.05	0.74 ±0.05	0.78 ±0.04
Treated eyes	0.8 ±00	0.3 ±0.1	0.26 ±0.05	0.2 ±0.1	0.3 ±0.17	0.2 ±0.1	0.66 ±0.11	0.63 ±0.05	0.65 ±0.02	0.7 ±0.12	0.68 ±0.17	0.68 ±0.1
Intraocular pressure												
Untreated eyes	21 ±4.58	20.33 ±4.72	16.66 ±3.51	16 ±1	17.3 ±3.21	17.66 ±2.51	19 ±5.1	21.33 ±5.68	20.43 ±2.44	20.6 ±2.7	20.3 ±1.49	19.77 ±2.22
Treated eyes	19.66 ±4.5	19 ±4.58	17.1 ±1.1	12 ±1	12.33 ±1.52	10.1 ±1.1	17.33 ±8.09	16.1 ±1.1	16.5 ±1.2	16.6 ±2.88	14.57 ±1.58	15.57 ±2.64
Schirmer tear test												
Untreated eyes	16.33 ±3.21	15.66 ±3.05	24.66 ±6.8	24.66 ±6.8	24.66 ±6.8	19.33 ±5.13	23.33 ±5.5	23 ±5.29	23.1 ±4.09	22.4 ±1.34	21 ±1.87	21.6 ±1.94
Treated eyes	19.33 ±7.57	19.66 ±6.42	22.66 ±8.08	22.66 ±8.08	22.66 ±8.08	20.33 ±8.5	25.66 ±7.09	19.33 ±7.57	20.32 ±5.55	20.8 ±2.04	20.6 ±1.51	20.8 ±1.64





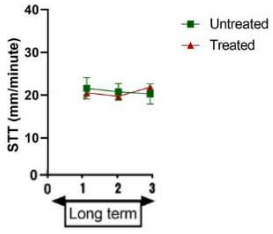


Figure 1. Mean intraocular pressure (IOP), pupillary diameter (PD), and Schirmer tear test (STT) of treated (T) and untreated eyes (UT), post-instillation of latanoprost in dogs during three weeks.

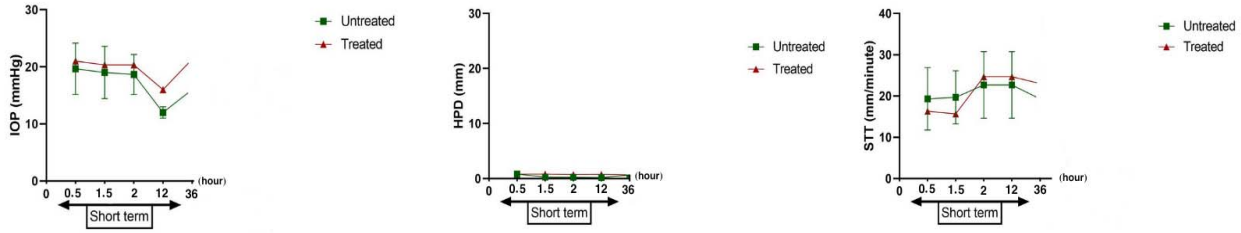


Figure 2. Mean intraocular pressure (IOP), pupillary diameter (PD), and Schirmer tear test (STT) of treated (T) and untreated eyes (UT), post-instillation of latanoprost in dogs during first 36 hr.