A DISSERTATION

FOR THE DEGREE OF MASTER

# Effect of Preservative Free Tafluprost on Intraocular Pressure, Pupil Diameter, and Anterior Segment Structures in Normal Canine Eyes

# 정상 개의 안구에서 무보존제 tafluprost가 안압, 동공크기 및 전안부 구조물에 미치는 영향

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# Effect of Preservative Free Tafluprost on Intraocular Pressure, Pupil Diameter, and Anterior Segment Structures in Normal Canine Eyes

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## ABSTRACT

The purpose of this study was to evaluate the changes in intraocular pressure (IOP), pupil diameter (PD), and anterior segment parameters using ultrasound biomicroscopy (UBM) after instillation of preservative-free (PF) tafluprost in normal dogs. Six beagle dogs were used. PF tafluprost was instilled in one randomly selected eye, and PF artificial tear was instilled in the other eye (control). IOP and PD were measured every 15 minutes for the first hour, every 2 hours for the next 17 hours, and at 24 hours and 36 hours post-instillation (PI). Anterior segment parameters including geometric iridocorneal angle (ICA), width of the entry of the ciliary cleft (CCW), width of the mid-part of the ciliary cleft, length of the ciliary cleft, area of the ciliary cleft, and depth of the anterior chamber were measured with

UBM before and after PF tafluprost instillation. Compared with the control group, IOP was significantly lower from 4 hours PI to 24 hours PI and PD was significantly smaller from 30 minutes PI to 18 hours PI ($P < 0.05$). Among UBM parameters, ICA and CCW significantly decreased and increased after PF tafluprost instillation, respectively ($P < 0.05$). Other parameters showed no significant changes. Instillation of PF tafluprost lowered IOP and induced miosis in normal canine eyes. Alterations in ICA and CCW occurred simultaneously, which probably affected the outflow of aqueous humor. PF tafluprost could be considered an alternative prostaglandin analog in the treatment of canine glaucoma.

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**Keywords: Tafluprost, Preservative, Glaucoma, Ultrasound biomicroscopy, Dog**

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# Introduction

Glaucoma is a group of diverse ocular diseases- characterized by high intraocular pressure (IOP) occurring because of an imbalance in the production and outflow of aqueous humor (Maślanka, 2015; Miller, 2012; Pizzirani, 2015). As glaucoma is a leading cause of impaired vision in dogs, many ocular hypotensive drugs have been introduced to lower the IOP and thus delay retinal damage (Bean *et al.,* 2008; Maślanka, 2015; Miller, 2015; Pizzirani, 2015; Slamovits *et al.*, 2002; Toris *et al.*,2008). Beta-blockers and topical prostaglandin analogs (PGAs) have been the most commonly used ocular hypotensive drugs in human medicine (Bean *et al.*, 2008; Maślanka, 2015; Slamovits *et al.*, 2002). Isopropyl unoprostone was first introduced in 1994, followed by latanoprost in 1996, travoprost and bimatoprost in 2001, and tafluprost in 2011 (Bean *et al.*, 2008; Maślanka, 2015). PGAs are known to reduce IOP by inducing changes in the ciliary muscles and consequently increasing uveoscleral outflow of aqueous humor (Toris *et al.*, 2008; Poyer *et al.*, 1995). Enhancement of the uveoscleral outflow facility is mainly related with the prostaglandin FP receptor, as was demonstrated by studies in FP-receptor-deficient mouse (Ota *et al.*, 2005). Currently, PGAs are widely used in small animal medicine, they not only are effective in lowering IOP but also have minimum side effects (Maślanka, 2015). Several PGAs, including latanoprost, travoprost, and bimatoprost, have been shown to significantly reduce IOP in normotensive and glaucomatous dogs (Gelatt *et al.*, 2001; 2002; 2004; Studer *et al.*, 2000).

Tafluprost (AFP-168) is a novel PGA commercially available as a preservative-free (PF) product. Like other PGAs, tafluprost lowers IOP mainly

through the prostanoid FP receptor, and partially through the EP3 receptor that is activated by the prostaglandin produced by the FP receptor (Ota *et al.*, 2007). Benefits of tafluprost over other PGAs, including retinal blood flow enhancement (Akaishi *et al.*, 2010), high potency of IOP reduction, and fewer side effects, have made tafluprost a highly recommended antiglaucoma medication in humans (Hommer *et al.*,2010; Konstas *et al.*, 2013; Liu *et al.*, 2013; Traverso *et al.*, 2010; Uusitalo *et al.*,2008; 2010). However, there are limited studies on its efficacy in dogs.

This study was designed to evaluate the effect of PF tafluprost after a single application in the normal canine eye. Changes in IOP and pupil diameter (PD) were measured and ultrasound biomicroscopy (UBM) was performed to detect structural changes in the anterior segment.

# Materials and Methods

## 1. Preparation of the animals

Six healthy male Beagle dogs were used in this study. All dogs were kept in an indoor laboratory animal facility under regulated illumination cycle and temperature. Before the experiment, the dogs were allowed to acclimatize for 2 days to get familiar with the procedures, namely, IOP and PD measurements and UBM. Slit-lamp biomicroscopy, indirect ophthalmoscopy, and rebound tonometry using Tonovet® (ICare Oy, Vantaa, Finland) were performed to confirm that all eyes are normal. This study was approved by the Institutional Animal Care and Use Committee of Seoul National University (SNU-150407-6).

## 2. Measurement of IOP and PD

One eye of each dog (n = 6) was randomly selected to receive PF tafluprost (Taflotan®-S; Santen Oy, Finland) at 6 a.m.. The opposite eye of each dog (n = 6) simultaneously received PF carboxymethylcellulose 0.5% (Refresh Plus®; Allergan, Irvine, CA, USA). IOP was measured with a rebound tonometer, and PD was measured with a digital infrared pupillometer (VIP™-200; NeuroOptics, Irvine, CA, USA) by the same investigator (JK). Values with standard deviation lower than 0.1 of IOP and 0.15 of PD were collected. IOP and PD were measured pre-instillation, every 15 minutes for the first hour, every 2 hours for the next 17 hours, and at 24 hours and 36 hours post-instillation (PI). IOP and PD were measured 3 times at all time points and the average values were used.

## 3. Ultrasound biomicroscopic examination

To evaluate the changes in the anterior segment after PF tafluprost administration, UBM with a 50 MHz probe (MD-320W; MEDA, Tianjin, China) was performed after instilling 0.5% proparacaine (Alcaine®; Alcon Laboratories, Fort worth, Texas, USA) with manual restraint. UBM was performed on the day before the drug instillation (4 p.m.) and 10 hours PI (4 p.m.). The 10 hours PI time point was selected to evaluate the effect of PF tafluprost at the same time. Each dog was positioned in sternal recumbency without sedation. Five parameters evaluated by the UBM software included: (1) geometric iridocorneal angle (ICA; formed by anterior plane of the iris root and inner cornea), (2) width of the ciliary cleft (CCW; perpendicular distance from anterior surface of the iris root to the inner sclera), (3) length of the ciliary cleft (CCL), (4) area of the ciliary cleft (CCA), and (5) depth of the anterior chamber (ACD). To evaluate parameters (1) through (4), a transducer was located at the 12 o'clock position of the eye to achieve the scan plane that is perpendicular to the dorsal limbus (Fig. 1a). Parameter (5) was measured in another view, locating the transducer at the center of cornea, perpendicular to the corneal surface (Fig. 1b). All procedures including tonometry, pupillometry and UBM were performed by the same investigator (JK) in the same room under the same light intensity.

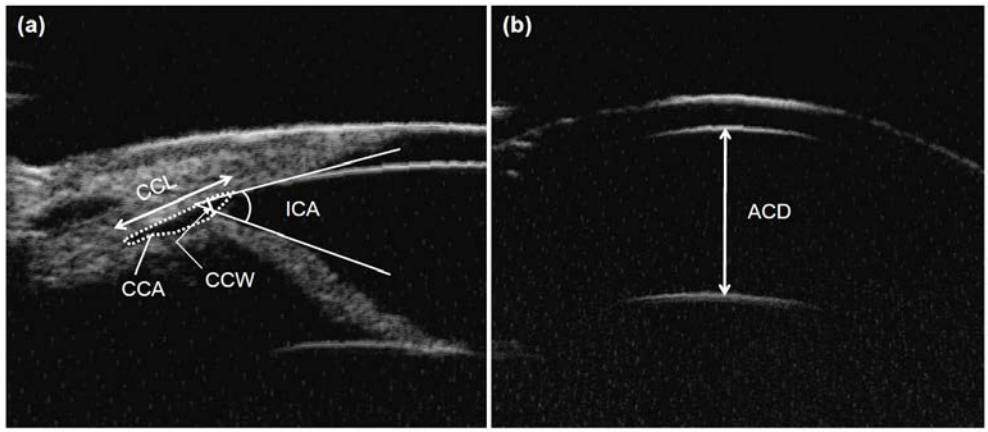


**Figure 1.** A representative UBM image in the normal dog showing the studied UBM parameters. Iridocorneal angle and ciliary cleft measurement were evaluated from (a) and the depth of anterior chamber was measured from (b). ICA, iridocorneal angle; CCW, width of the ciliary cleft; CCL, length of the ciliary cleft; CCA, area of the ciliary cleft; ACD, anterior chamber depth.

## 4. Slit-lamp biomicroscopic examination

To evaluate the abnormalities before and after PF tafluprost instillation, slit-lamp biomicroscopy was performed at 0, 4, 8, 12, 16, and 36 hours PI. The severity of conjunctival hyperemia, blepharospasm, and aqueous flare was evaluated and severity was scored on a scale of 0 to 3 (0=none, 1=mild, 2=moderate, and 3=severe).

## 5. Statistical analyses

All statistical analyses were conducted using SPSS Statistics 22 software (IBM SPSS Statistics®; IBM, Armonk, NY, USA). Analysis of variance for repeated measurements was used to compare the effect of drugs in IOP and PD. Changes in IOP and PD between the test group and control group over time were assessed using student's t-test with Bonferroni correction. To compare UBM parameters before and after drug instillation, paired t-test was used. In all analyses, $P < 0.05$ was considered significantly different.

# Results

## 1. Effect on intraocular pressure and pupil diameter

The mean ± SD IOP during the treatment period was 15.2 ± 1.0 mmHg in the control group and 12.2 ± 3.2 mmHg in the test group. For the control eyes, there was no significant changes in IOP during the study period ($P > 0.05$). PF tafluprost instilled eyes showed significant changes in IOP compared to the control eyes ($P = 0.031$). IOP was significantly lower in the test group from 4 hours PI to 24 hours PI when compared with the control group ($P < 0.05$). The difference in IOP before and after tafluprost instillation was up to 6 mmHg (39%), showing a peak effect at 8 hours PI (Fig. 2). The mean ± SD PD during treatment period was 9.82 ± 0.18 mm in the control group and 5.17 ± 3.60 mm in the test group. There was no significant changes in PD in the control group over time ($P > 0.05$). PF tafluprost eyes showed significant changes in PD compared to the control eyes ($P = 2.432e-10$). PD was significantly smaller in test group from 30 minutes PI to 18 hours PI ($P < 0.05$). The difference in PD before and after tafluprost instillation was up to 8.44 mm (85%), with a peak effect at 1 hour PI (Fig. 3).

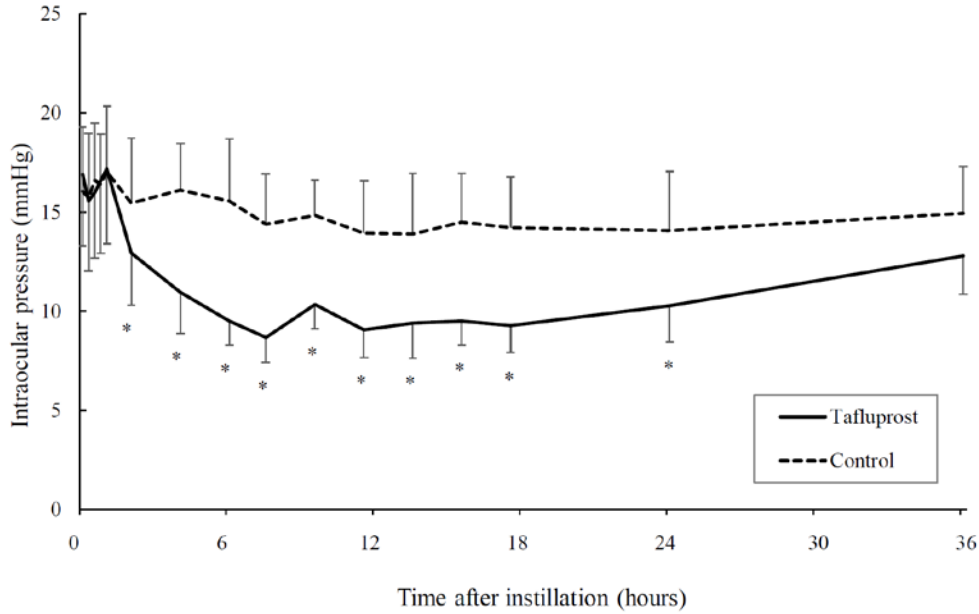


**Figure 2.** Effect of PF tafluprost on Mean ± SD intraocular pressure in normal dogs. *P < 0.05

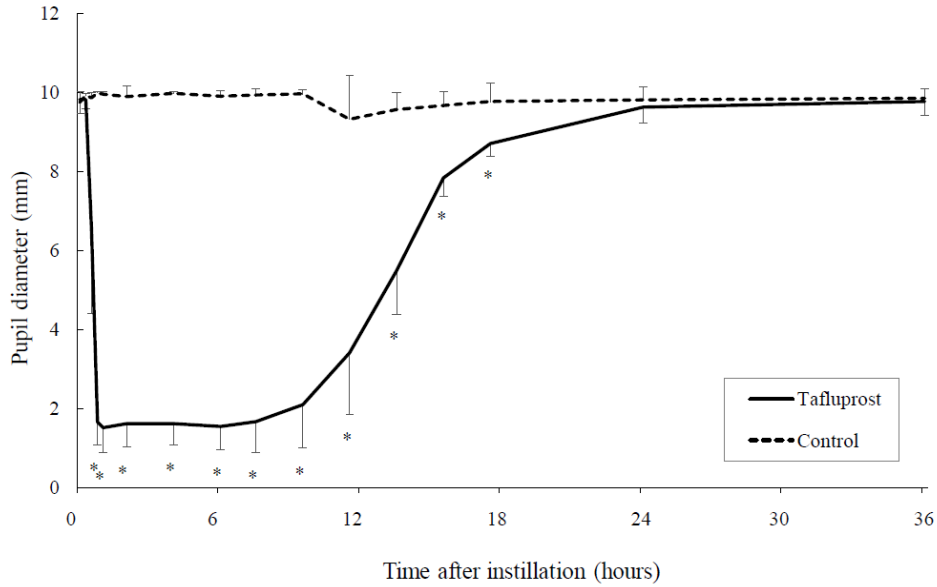


**Figure 3.** Effect of PF tafluprost on Mean ± SD pupil diameter in normal dogs.

*P < 0.05

## 2. Structural changes in the anterior ocular segment

The values of UBM parameters, ICA and CCW, revealed structural changes in the anterior segment after PF tafluprost instillation (Fig. 4). The ICA significantly decreased after instillation from 39.02 ± 6.63 ° before the instillation to 22.76 ± 5.07 ° after ($P$ = 0.001). The CCW significantly increased after instillation from 0.37 ± 0.06 mm before the instillation to 0.49 ± 0.09 mm after ($P$ = 0.017). Other parameters including the CCL, CCA, and ACD showed no significant changes ($P$ = 0.429, 0.165, and 0.232, respectively) over time during the observation period (Table 1).

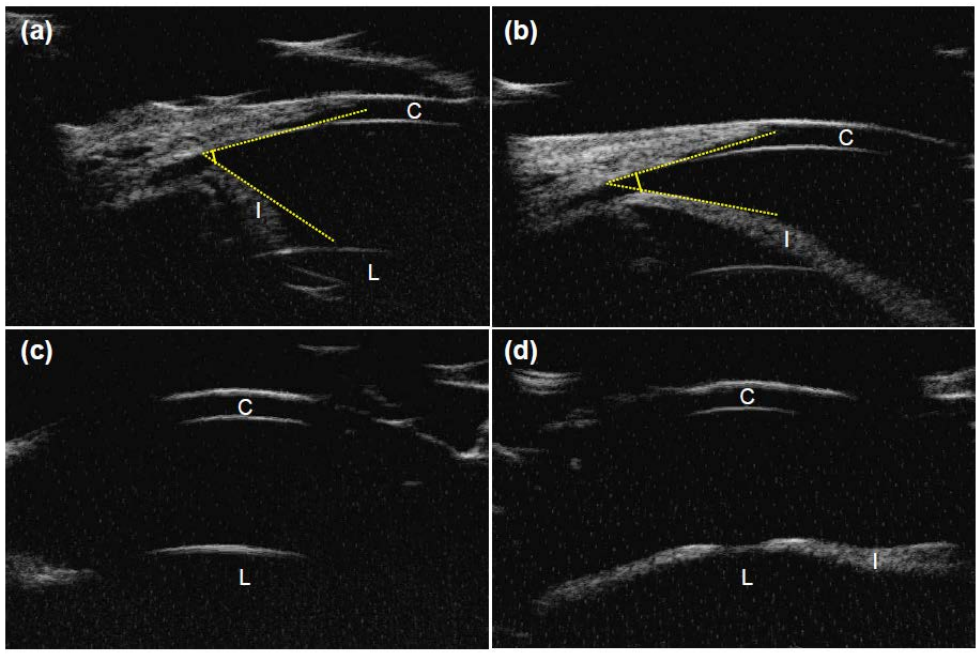


**Figure 4.** Representative UBM images in the normal dog. (a) and (c); UBM images taken before the instillation. (b) and (d); UBM images taken 10 hours post-instillation. Dotted lines indicate measurement of the iridocorneal angle and full lines indicate measurement of width of the ciliary cleft. C, cornea; I, iris; L, lens

**Table 1.** Mean ± SD values of anterior segment parameter before and after instillation of PF tafluprost in normal dogs (n = 6)

| **Parameter** | **Pre-instillation** | **Post-instillation**[†] | ***P* value** |
|---|---|---|---|
| ICA (°) | 39.02 ± 6.63 | 22.76 ± 5.07[*] | 0.001 |
| CCW (mm) | 0.37 ± 0.06 | 0.49 ± 0.09[*] | 0.017 |
| CCL (mm) | 2.64 ± 0.17 | 2.60 ± 0.09 | 0.429 |
| CCA ($mm^2$) | 0.79 ± 0.09 | 0.85 ± 0.15 | 0.165 |
| ACD (mm) | 3.34 ± 0.18 | 3.39 ± 0.12 | 0.232 |

[*]Significantly different. [†]10 hours post-instillation. ICA, iridocorneal angle; CCW, width of the ciliary cleft; CCL, length of the ciliary cleft, CCA, area of the ciliary cleft; ACD, anterior chamber depth.

## 3. Slit-lamp biomicroscopic examination

Mild conjunctival hyperemia was seen in all eyes in the test group (mean score = 0.48), but in only one eye in the control group. No other ocular signs including blepharospasm and aqueous flare were observed in both groups.

# Discussion

In the present study, PF tafluprost instillation in normal canine eyes caused a significant reduction in IOP and PD. Compared with the control eyes, a mean maximum IOP reduction of 6 mmHg (39%) was observed after drug administration, which is consistent with that of 3 mmHg (24.5%) previosly reported with latanoprost in normal dogs (Studer *et al.*, 2000). No evidence of ocular irritation except very mild conjunctival hyperemia was observed. As several studies have reported a decline in IOP after PGA instillation in both normotensive and glaucomatous dogs, PF tafluprost was considered to also induce a rapid decline in IOP in glaucomatous dogs (Gelatt *et al.*, 2001; 2002; 2004; Miller *et al.*, 2003; Studer *et al.*, 2000). IOP reduction was accompanied by strong miosis. The mean maximum PD reduction was 8.44 mm (85%) after PF tafluprost administration. The use of a digital infrared pupillometer in the same light condition allowed precise measurement of PD and, in turn, the duration of PD reduction that was present for approximately 18 hours.

Like other PGAs, PF tafluprost exerts its miotic effect via PGF2α, which induces direct contraction of canine iris sphincter muscle (Yoshitomi *et al.*, 1988). Comparing the onset time and duration of IOP and PD reduction with previous studies (Gelatt *et al.*, 2001; 2002; 2004), IOP reduction by PGA would coincide with PD reduction. As the PD reduction effect of PF tafluprost lasted for approximately 18 hours to 24 hours in this study, the duration of IOP reduction is presumed to be longer with tafluprost than with other PGAs. Thus, PF tafluprost could be administered once or twice daily in dogs. Considering the circadian rhythm of IOP in dogs, in which the highest values are observed in the morning, our findings

suggest that instillation of tafluprost could be recommended at night in the once-daily schedule (Gelatt *et al.*, 1981; Giannetto *et al.*, 2009).

Although we demonstrated the ocular hypotensive effect of PF tafluprost alone in this study, previous studies studies in man have suggested that this drug has higher IOP lowering effect and fewer side effects than other PGAs. (Hommer *et al.*, 2010; Konstas *et al.*, 2013; Liu *et al.*, 2013; Takagi *et al.*, 2004; Traverso *et al.*, 2010; Uusitalo *et al.*, 2008; Uusitalo *et al.*, 2010). In normotensive mouse and monkey, tafluprost was found to reduce IOP more efficiently than unoprostone, latanoprost, and travoprost (Ota *et al.*, 2005; Takagi *et al.*, 2004). When tafluprost was instilled once daily in normotensive monkeys, the duration of IOP reduction effect of tafluprost lasted for over 24 hours which was significantly longer than that observed after latanoprost instillation. The finding of the current study is also coherent with previous results in mouse showing a longer pharmacological effect of tafluprost compared with those of latanoprost and unoprostone (Ota *et al.*, 2005). The high IOP-lowering efficacy of tafluprost is attributed to its high binding affinity for the prostanoid FP receptor, which is 12 times stronger than that of latanoprost and 1700 times stronger than that of isopropyl unoprostone (Takagi *et al.*, 2004). The present study focused on the efficacy of PF tafluprost alone; therefore advanced studies will be needed to compare the efficacy of tafluprost with other PGAs in dogs.

The use of PF tafluprost resulted in structural alterations in the anterior segment. In the present study, UBM was used to quantitatively assess the changes in the anterior segment (Gibson *et al.*, 1998). Instillation of PF tafluprost decreased ICA and increased CCW simultaneously with IOP reduction. In canine eyes, trabecular meshwork is located within the recess of the ciliary cleft, different from

the human eyes where the trabecular meshwork is posteriorly bound by scleral spur and anteriorly by the cornea (Dulaurent *et al.*, 2012). Therefore aqueous outflow through the trabecular meshwork in dogs may not be influenced by ICA narrowing, and CCW may be a more meaningful parameter to assess the ciliary cleft functionality in dogs (Bedford *et al.*, 1986; Dulaurent *et al.*, 2012). Widening of the ciliary cleft after PF tafluprost instillation might have increased the aqueous outflow through the trabecular meshwork and contributed to the IOP reduction effect, although there is no compelling evidence. Pre-existing PGAs are known to enhance the uveoscleral outflow by remodeling the extracellular matrix filling spaces between the ciliary muscles (Ocklind *et al.*, 1998) and reducing anterior chamber depth (Gutiérrez-Ortiz *et al.*, 2006) when used for a long-term period.

The tafluprost used in this study was free of benzalkonium chloride (BAK), and a preservative-free drug is known to be more beneficial than preservative-containing ones. BAK has been widely used in many antiglaucoma eye drops to prevent contamination, although many recent studies have shown toxic effects of BAK on ocular structures (Baudouin *et al.*, 2012; Boimer *et al.*, 2013; Brasnu *et al.*, 2008; Liang *et al.*, 2008; Kahook *et al.*, 2011). Repeated instillation of BAK in the eye labilizes the pre-corneal teal film and enhances apoptosis and oxidative stress on the cornea and conjunctiva (Baudouin *et al.*, 2007; Brasnu *et al.*, 2008; Liang *et al.*, 2008). In one study on the ocular Draize test in normal rabbit eyes, BAK-containing drug groups showed significantly higher clinical scores compared with the PF tafluprost group (Liang *et al.*, 2008). Human studies have also shown that increased preoperative exposure to BAK could increase the risk of failure of glaucoma surgery including Ahmed gonioimplantation (Boimer *et al.*, 2013). Long-term use of BAK

has a negative effect on the trabecular meshwork: BAK degenerates the trabecular meshwork by inducing trabecular apoptosis and inflammation (Baudouin *et al.*, 2012; Kahook *et al.*, 2011). Therefore long-term use of BAK-containing eye drops could reduce the effect of ocular hypotensive agents and thereby shorten the period of management by antiglaucoma medication alone (Baudouin *et al.*, 2012; Geffen *et al.*, 2014).

Some limitations of this study include the use of only a single drop in normotensive dogs and a small group size. Therefore, advanced large-scale studies with long-term instillation schedules are needed to investigate the long-term tolerance and efficacy of PF tafluprost. Drug efficacy should also be evaluated in glaucomatous dogs and then compared with the results of other ocular hypotensive drugs.

# Conclusions

PF tafluprost use led to considerable IOP reduction and strong miosis in normotensive dogs with few side effects. Alteration in the iridocorneal angle and ciliary cleft entry after PF tafluprost instillation might be related to its hypotensive effect. Considering that glaucoma needs life-long treatment and that PF tafluprost had a potent IOP reduction effect in this study, PF tafluprost may be a viable medical option for the treatment of canine glaucoma.

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# 국 문 초 록

# 정상 개의 안구에서 무보존제 tafluprost가 안압, 동공크기 및 전안부 구조물에 미치는 영향

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본 연구에서는 정상 개의 안구에서 무보존제 tafluprost의 효과를 확인하고자 하였다. 총 6마리의 건강한 비글견을 사용하였으며 무작위로 한쪽 눈에는 무보존제 Tafluprost, 반대쪽 눈에는 무보존제 인공눈물을 점안 후 안압, 동공크기, 전안부 구조물의 변화를 관찰하였다. 안압과 동공크기는 점안 후 1시간동안 15분 간격으로, 이후 점안 17시간 후까지는 2시간 간격으로 측정하였다. 이후 점안 24시간 후 그리고 36시간 후에 2회 더 측정 후 시간에 따른 안압과 동공크기 변화를 분석하였다. 전안부 구조물은 초음파생체현미경(ultrasound

biomicroscopy)을 이용해 검사했으며 무보존제 tafluprost 점안 전후의 홍채각막각, 모양체틈새의 너비와 길이 및 면적, 전안방의 깊이가 측정하였다. 무보존제 tafluprost를 점안한 눈은 점안 후 4시간에서 24시간까지 유의적으로 감소하였으며, 동공 크기는 점안 후 30분부터 18시간까지 유의적으로 감소하였다 ($P < 0.05$). 초음파생체현미경을 이용한 전안부 구조물의 검사 및 측정결과 홍채각막각은 유의적으로 감소했으며 모양체틈새의 너비는 유의적으로 증가하였다. 본 연구 결과 정상 개에서 무보존제 tafluprost의 효과적인 안압하강작용이 확인되었으며 추후 추가적인 연구를 통해 개 녹내장 환자에서 새로운 prostaglandin 유사체 약물의 선택지로 적용 가능할 것으로 판단된다.

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주요어: Tafluprost, 보존제, 녹내장, 초음파생체현미경, 개

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