의학석사 학위논문

펨토초 레이저를 이용한 백내장 수술시 점안 약제에 따른 전방수내 사이토카인 농도 비교에 대한 관찰연구

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지도교수 차흥원

이 논문을 의학석사 학위 논문으로 제출함

2021년 2월

울산대학교 대학원

의학과

이재혁

이재혁의 의학석사학위 논문을 인준함

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국문 요약

연구 목표: 펨토초 레이저를 이용한 백내장 수술시 수술 전 약제의 점안에 따라 수술 중 채취한 전방수내 cytokine 농도 차이를 통해 항염작용을 비교해보고자 하였다.

연구 재료 및 방법: 펨토초 레이저를 이용한 백내장 수술을 받는 환자 총 120명을 무작위로 4군으로 배정하여 전향적으로 관찰하였다. 아무 약제도 점안하지 않은 대조군 30명, Fluorometholone 0.1% (Flumetholone®) 안약을 점안한 30명, Ketorolac tromethamine 0.45% (Acuvail®) 안약을 점안한 30명, 마지막으로 Fluorometholone 0.1% (Flumetholone®), Ketorolac tromethamine 0.45% (Acuvail®) 두 안약 모두 점안한 30명으로 구성하였다. 안약은 수술 1시간 전, 수술 20분 전, 수술 직전에 걸쳐 3회 점안하였다. 펨토초 레이저를 이용한 전낭절개와 핵조각 내기 후 26 gauge needle을 이용하여 약 0.1cc의 전방수를 1회 취득하였다. 이 검체를 이용하여 Cytokine과 PGE2 농도를 정량 분석하였다.

연구 결과: 총 120명의 환자가 연구에 포함되었으며 평균 연령은 65.02세였고, 남자는 59명이었다. IL-6와 TNF-α 평균 농도는 4군 간에 유의한 차이가 없었다. IL-8 평균 농도는 Fluorometholone 군에서 4.80pg/mL, Ketorolac tromethamine 군에서 평균 4.84pg/mL, Fluorometholone+Ketorolac tromethamine 군에서 평균 4.68pg/mL 이었으며, 대조군에서의 평균 농도 6.83pg/mL와 비교시 통계적으로 모두 유의한 차이를 보였다. 또한 PGE_2 농도는 Ketorolac tromethamine 군에서 평균 270.04pg/mL, Fluorometholone+Ketorolac tromethamine 군에서 평균 239.00pg/mL로 대조군에서의 평균 농도 472.36pg/mL 와 비교시 통계적으로 유의한 차이를 보였으나, Fluorometholone 군에서는 393.16pg/mL로 통계적으로 유의한 차이를 보이지 않았다.

결론: 펨토초 레이저를 이용한 백내장 수술 시 수술 전 fluorometholone 점안은 전방수내 IL-8 감소 효과, ketorolac tromethamine 점안은 전방수내 IL-8과 PGE_2 감소 효과를 보였으며, 두 약제를 함께 사용하는 경우 더 큰 효과를 보였다.

차례

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Introduction

Femtosecond laser-assisted cataract surgery (FLACS), first performed in 2009, has enabled capsulotomy with more precise position, shape, and size.(1) FLACS has also reduced the occurrence of intraocular lens tilt and the incidence of higher-order aberrations,(1) with less ultrasound energy being required.(2) Moreover, with the function of concomitant astigmatic correction, the number of patients undergoing FLACS is increasing.

However, the intraocular effects of FLACS have not been sufficiently evaluated. FLACS has been reported to increase the intraocular concentrations of inflammatory cytokines and other inflammatory mediators. For example, concentrations of interleukin (IL)-1β and IL-6,(3) as well as prostaglandin E_2 (PGE_2),(3),(4) have been reported to increase after FLACS. Other inflammatory mediators found to increase after FLACS include IL-1ra, IL-9, IL-18, tumor necrosis factor (TNF)α, TNFβ/leukotriene A (LTA), leukocyte inhibitory factor (LIF), eotaxin (CCL11), fibrosis growth factor (FGF)-2 (FGFbasic), and platelet derived growth factor (PDGF)-BB.(5)

Eyedrops containing nonsteroidal anti-inflammatory drugs (NSAID) are widely used to reduce ocular inflammation. For example, Ketorolac,(2, 6) Diclofenac,(7) and Nepafenac 0.1%(8) were found to decrease PGE_2, and Bromfenac 0.09% was found to reduce IL-6.(9) To our knowledge, however, no study to date has assessed the ability of preoperatively applied steroid eyedrops to reduce cytokine concentrations in aqueous humor of patients undergoing FLACS. The present study therefore compared the anti-inflammatory activities of preoperatively applied eyedrops including steroid on cytokine and PGE_2 concentrations in aqueous humor collected during FLACS.

Materials & Methods

The design of this prospective comparative study, including the collection of aqueous humor from patients, was approved by the Institutional Review Board of Asan Medical Center (2020-0056), registered as a clinical trial (KCT0005717), and conformed with the tenets of the Declaration of Helsinki. All patients provided written informed consent.

This study enrolled patients with uncomplicated senile cataract undergoing unilateral FLACS between September and October 2020. Patients with accompanying serious eye diseases, a history of inflammatory ocular diseases, previous eye trauma or surgery, corneal opacity, age-related macular degeneration, retinopathy associated with diabetes or hypertension, glaucomatous eyes, pseudoexfoliation, or poorly dilated pupils were excluded. Patients aged <20 years, pregnant women, and patients who had used NSAIDs or steroids within 6 months were also excluded.

The 120 enrolled patients were randomly assigned to four groups of 30 patients each. Patients were administered no eyedrops (control group), fluorometholone 0.1% (Flumetholone®, Santen Pharmaceutical, Osaka, Japan), ketorolac tromethamine 0.45% (Acuvail®, Allergan, Inc, Irvine, CA, USA) eyedrops, or both fluorometholone 0.1% and ketorolac tromethamine 0.45% before surgery. The respective eye drops were instilled 1 hour, 20 minutes, and just before surgery. At the same time, all patients were preoperatively administered a combination of topical tropicamide 0.5% with phenylephrine 0.5% for mydriasis. All patients underwent capsulotomy, lens fragmentation, and astigmatic incision with the Catalys Laser System (Johnson & Johnson, Inc., Santa Ana, CA, USA). Five minutes later, a corneal incision of about 1 mm was made in the 2 o'clock position, and a 0.1 cc specimen of aqueous humor was obtained using a 1 cc syringe and a 26-gauge needle. An equal volume of balanced salt solution (BSS) was injected intraocularly. The collected aqueous

humor was placed in a 1.5 mL Eppendorf tube and immediately stored in a -80 C freezer. The lens was phacoemulsified and aspirated, followed by intraocular lens implantation.

Concentrations of cytokines and chemokines in aqueous humor were measured using Magnetic Luminex® Performance Assay multiplex kits (Luminex®MAGPIX® CCD Imager, R&D Systems, Minneapolis, MN, USA). Concentration standards were run in parallel on each plate tested, representing the average concentration of triplicate standard dilutions of each chemokine/cytokine. A standard curve was drawn, and the concentrations of chemokines/cytokines in each sample were determined by curve-fitting. PGE2 concentrations were determined using a commercially available PGE2 Parameter Assay Kit (cat no. KGE004B; R&D Systems, Minneapolis, MN, USA). Concentrations were measured on a microplate reader (Clariostar Monochromator Microplate Reader; BMG LABTECH, Ortenberg, Germany). All assays were performed by an experienced technician who was blinded to the nature of the samples.

Comparisons between pairs of groups were performed using Student's t-tests. All statistical analyses were performed using SPSS statistical software (version 22; IBM Software), with a p-value ≤ 0.05 considered statistically significant.

Results

The study enrolled 120 eyes of 120 patients, randomized into 30 eyes per group. Table 1 shows the demographic characteristics of these patients. The 120 patients were of mean age 65.02±9.85 years, with no significant differences in age, gender or laterality of the eyes among the four groups ($p>0.05$ each)

The mean IL-6 concentrations in the fluorometholone (2.62±1.65 pg/mL, ketorolac tromethamine (1.86±1.47 pg/mL), and fluorometholone+ketorolac tromethamine (2.78±2.01 pg/mL) groups were similar to those in the control group (2.86±2.02 pg/mL) ($p>0.05$ each; Table 2; Figure 1). By contrast, the average IL-8 concentrations were significantly lower in the fluorometholone (4.80±1.66 pg/mL), ketorolac tromethamine (4.84±1.86 pg/mL), and fluorometholone+ketorolac tromethamine (4.68±1.98 pg/mL) groups than in the control group (6.84±3.89 pg/mL) ($p<0.05$ each; Table 3; Figure 2).

Similar to IL-6, the mean TNF-α concentrations in the fluorometholone (1.86±1.44 pg/mL), ketorolac tromethamine (1.14±0.97 pg/mL), and fluorometholone+ketorolac tromethamine (0.90±0.57 pg/mL) groups did not differ significantly from those in the control group (1.08±0.71 pg/mL) ($p>0.05$ each; Table 4; Figure 3). The average PGE2 concentrations were significantly lower in the ketorolac tromethamine (270.04±190.82 pg/mL) and fluorometholone+ketorolac tromethamine (239.00±77.29 pg/mL) groups, but not in the fluorometholone (393.16±147.34 pg/mL) group, than in the control group (472.36±314.81 pg/mL) (Table 5; Figure 4)

Discussion

Despite the many advantages of FLACS, intraoperative miosis is not infrequent.(10, 11) A smaller pupil can make cataract surgery harder and is associated higher rates of intraoperative complication.(12) Moreover, anterior segment flare, macular thickness change, and cystoid macular edema have also been reported following FLACS,(13, 14), suggesting the need for preventive anti-inflammatory medication before FLACS. To our knowledge, this is the first study to evaluate the anti-inflammatory effects of both steroid and non-steroid medications in patients undergoing

FLACS. Both of the agents used in this study had anti-inflammatory effects and thus, they are expected to alleviate the complications mentioned above.

Prostaglandins are highly active mediators of inflammation and pain. Prostaglandins are synthesized from arachidonic acid by the enzymes cyclooxygenases 1 and 2, both of which are inhibited by NSAIDs.(15) NSAIDs were once considered routine treatment for surgically induced pupillary miosis inhibition,(16, 17) but the need for NSAIDs has significantly decreased with the development of new technologies and the shortened duration of surgery. However, after performing FLACS, pupillary miosis recurred and the present study found that preoperative instillation of ketorolac tromethamine 0.45% eyedrops reduced the concentrations of IL-8 and PGE_2 in aqueous humor.

Steroids act primarily by inhibiting phospholipase A_2, reducing the concentrations of leukotrienes responsible for chemotaxis and arachidonic acid, which is converted to prostaglandins by cyclooxygenases.(18) Due to these properties, steroids have been widely used as anti-inflammatory agents in patients undergoing manual cataract surgery.(19, 20) The present study found that preoperative administration of the steroid fluorometholone 0.1% effectively reduced IL-8 concentrations in aqueous humor of patients undergoing FLACS.

The serum concentrations of the pro-inflammatory cytokine IL-6 can be increased by noninfectious inflammation, including burns and traumatic injuries.(21) This inflammation can also induce the expression of vascular endothelial growth factor (VEGF), promoting vascular permeability and angiogenesis.(22) IL-8 is a strong chemo-attractant involved in the activation of both neutrophils and T-lymphocytes, thereby having both immune and vascular functions. IL-8 was also reported to be increased in the aqueous humor of patients with uveitis and

glaucoma.(23) TNF-α, a macrophage/monocyte-derived pluripotent cytokine, has been associated with ischemic tissue damage and remodeling of neurons.(24) Prostaglandins are synthesized in the iris and ciliary body following trauma.(25) These molecules are highly potent regulators of inflammation, with various effects on the conjunctiva, cornea, iris, ciliary body, choroid, and retina.(26) The different characteristics of each cytokine might express various tendency of concentration decrease in this study. The findings of this study suggest that cytokine balance is disturbed in eyes following FLACS. Moreover, differences in laser platforms, parameters used, and measurement methods may alter the concentrations of individual cytokines. In addition, the time interval between femtosecond laser pretreatment and aqueous humor collection varies according to study settings; therefore, a direct comparison of the cytokine concentrations reported in different studies is not possible. Nevertheless, our results showed that pretreatment with a steroid and/or an NSAID reduced the concentrations of the pro-inflammatory cytokines evaluated in this study, with some of the differences being statistically significant. Also, because there are no reasons why IL-6 and TNF-α should have tendencies different from those of other inflammatory cytokines, other more potent anti-inflammatory agents might achieve greater reductions in concentrations of the pro-inflammatory cytokines than ketorolac tromethamine 0.45% and fluorometholone 0.1%, but this will need to be confirmed in a future study.

Instillation of eyedrops significantly reduced the concentrations of both IL-8 and PGE_2, with minimum concentrations observed in eyes instilled with both an NSAID and a steroid, suggesting a synergistic effect. However, topical steroids have adverse effects, including increased intraocular pressure,(27) wound healing impairment,(28) and greater risk of infection.(29) Topical NSAIDs have been associated with corneal melts,(30) as well as with ocular discomfort.(31) These possible adverse events should be considered before applying either or both types of eyedrops. However,

these side effects rarely occur with less-potent agents such as ketorolac tromethamine 0.45% and fluorometholone (0.1%), which were used in this study. Especially, fluorometholone 0.1% is regarded as the weakest steroid agent available, which might explain why it had a weaker anti-inflammatory effect than NSAID in this study. If there are no definite risk factors associated with the side effects described above, and if the patient is prone to more inflammation after FLACS, the use of both agents simultaneously is recommended, depending on the clinician's judgement.

One limitation of this study was the small volume of aqueous humor obtained from each patient, which may have affected the results of the enzyme-linked assays. However, this volume was comparable to that in other previous studies, and extracting more aqueous could have been dangerous because of intraocular space shrinkage. Another limitation was the relatively small number of patients in each group. Further larger studies are warranted to determine the exact role of these inflammatory cytokines in patients undergoing FLACS.

In conclusion, preoperative application of fluorometholone decreased IL-8, and preoperative ketorolac tromethamine instillation decreased IL-8 and PGE2, in the aqueous humor of patients undergoing FLACS. Moreover, application of both eyedrops was more effective than either alone.

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Abstract

Purpose: The purpose of this study was to compare the anti-inflammatory activity of preoperatively applied eyedrops, as determined by cytokine concentrations in aqueous humor collected during surgery in patients undergoing femtosecond laser-assisted cataract surgery.

Methods: A total of 120 patients undergoing femtosecond laser-assisted cataract surgery were randomly assigned to four groups of 30 patients each who were administered no eyedrops, fluorometholone 0.1% (Flumetholone®) eyedrops, ketorolac tromethamine 0.45% (ACUVAIL®) eyedrops, and both 0.1% fluorometholone and 0.45% ketorolac tromethamine. Eyedrops were instilled 1 hour, 20 minutes, and just before surgery. After anterior capsulotomy and nuclear fragmentation using femtosecond laser, about 0.1 cc aqueous humor was obtained using a 1 cc syringe and a 26-gauge needle. Cytokine and PGE2 concentrations were quantitatively determined.

Results: The 120 patients consisted of 59 men and 61 women, of mean age 65.02 years. The mean IL-6 and TNF-α concentrations did not differ significantly in the four groups. The average IL-8 concentrations were significantly lower in the fluorometholone (4.80 pg/mL), ketorolac tromethamine (4.84 pg/mL), and fluorometholone+ketorolac tromethamine (4.68 pg/mL) groups than in the control group (6.83 pg/mL). Furthermore, the average PGE2 concentrations were significantly lower in the ketorolac tromethamine (270.04 pg/mL) and fluorometholone+ketorolac tromethamine (239.00 pg/mL) groups, but not in the fluorometholone (393.16 pg/mL) group, than in the control group (472.36 pg/mL).

Conclusions: Preoperative fluorometholone instillation reduced IL-8, and ketorolac tromethamine instillation reduced IL-8 and PGE2, in aqueous humor of patients undergoing femtosecond laser surgery, with both eyedrops being more effective than either alone.

Table 1. Patient Demographics

	Control group	Fluorometholone group	Ketorolac tromethamine group	Fluorometholone+ ketorolac tromethamine group	Total
Age, yr	63.16±11.20	64.44±10.34	65.00±7.01	67.38±10.42	65.02±9.85
Gender (male : female)	16 : 14	14 : 16	13 : 17	16 : 14	59 : 61
Eye laterality (right : left)	14 : 16	14 : 16	13 : 17	15 : 15	56 : 64

Table 2. IL-6 concentrations in anterior chamber aqueous humor

	Control group	Fluorometholone group	Ketorolac tromethamine group	Fluorometholone+ketorolac tromethamine group
Mean±SD, pg/mL	2.86±2.02	2.62±1.65	1.86±1.47	2.78±2.01
p-value		.672	.101	.900

*p<0.05 compared with the control group by Student's t-test.

Table 3. IL-8 concentrations in anterior chamber aqueous humor

	Control group	Fluorometholone group	Ketorolac tromethamine group	Fluorometholone+ketorolac tromethamine group
Mean±SD, pg/mL	6.84±3.89	4.80±1.66	4.84±1.86	4.68±1.98
p-value		.025*	.026*	.021*

*p<0.05 compared with the control group by Student's t-test.

Table 4. TNF-α concentrations in anterior chamber aqueous humor

	Control group	Fluorometholone group	Ketorolac tromethamine group	Fluorometholone+ketorolac tromethamine group
Mean±SD, pg/mL	1.08±0.71	1.86±1.44	1.14±0.97	0.90±0.57
p-value		.062	.858	.612

*p<0.05 compared with the control group by Student's t-test.

Table 5. PGE_2 concentrations in anterior chamber aqueous humor

	Control group	Fluorometholone group	Ketorolac tromethamine group	Fluorometholone+ketorolac tromethamine group
Mean±SD, pg/mL	472.36±314.81	393.16±147.34	270.04±190.82	239.00±77.29
p-value		.303	.030*	.005*

*p<0.05 compared with the control group by Student's t-test.

Figure Legends

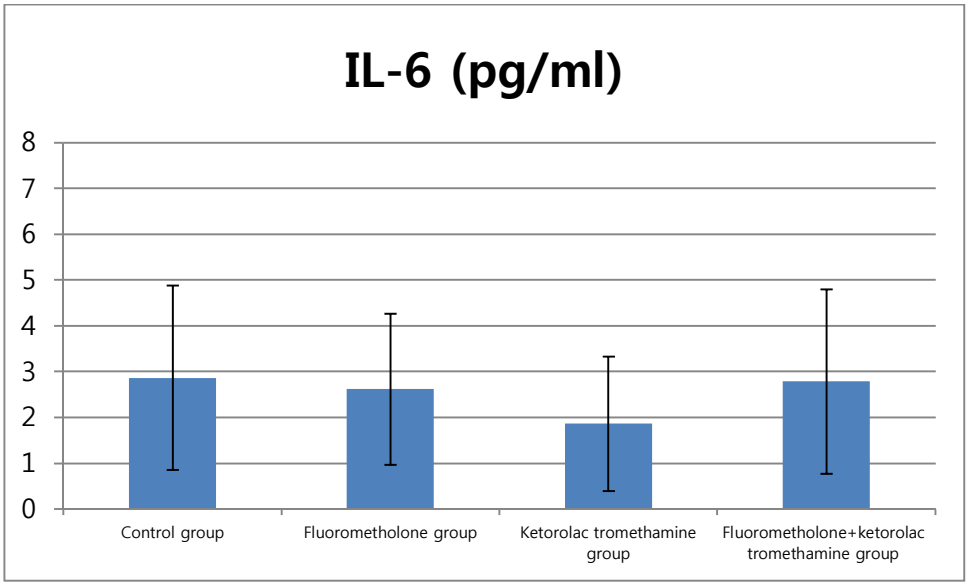

Figure 1. IL-6 concentrations in anterior chamber aqueous humor.

*p<0.05 compared with the control group by Student's t-test.

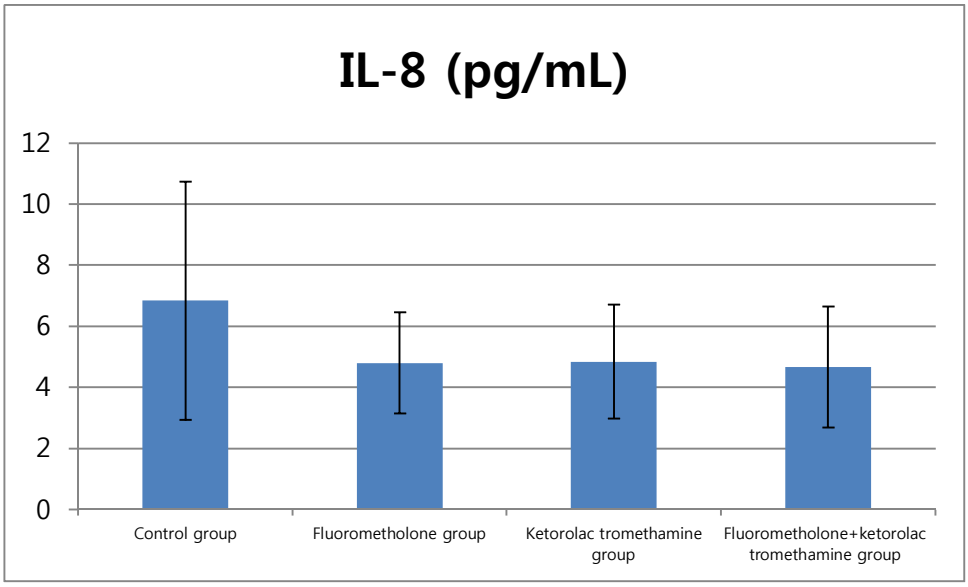

Figure 2. IL-8 concentrations in anterior chamber aqueous humor.

*p<0.05 compared with the control group by Student's t-test.

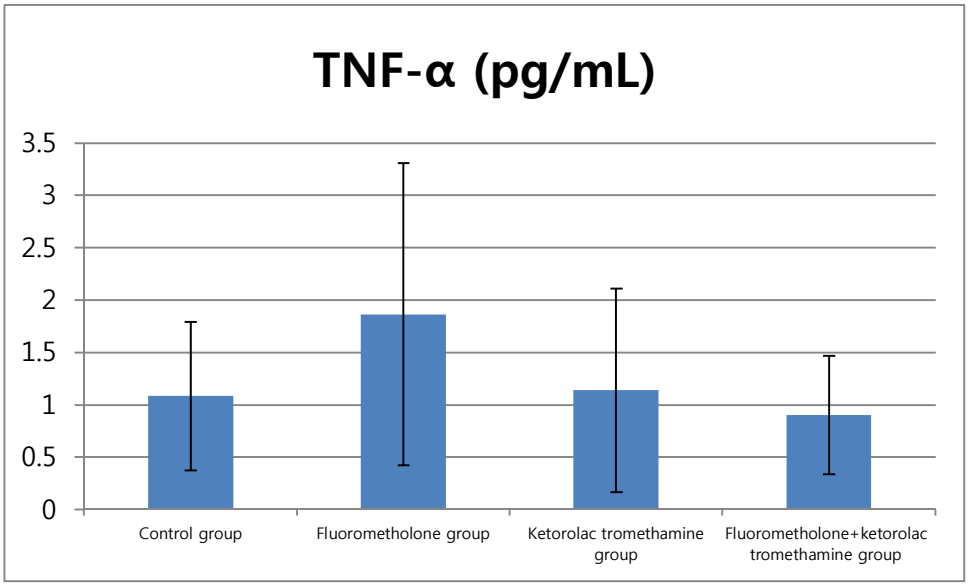

Figure 3. TNF-α concentrations in anterior chamber aqueous humor.

*p<0.05 compared with the control group by Student's t-test.

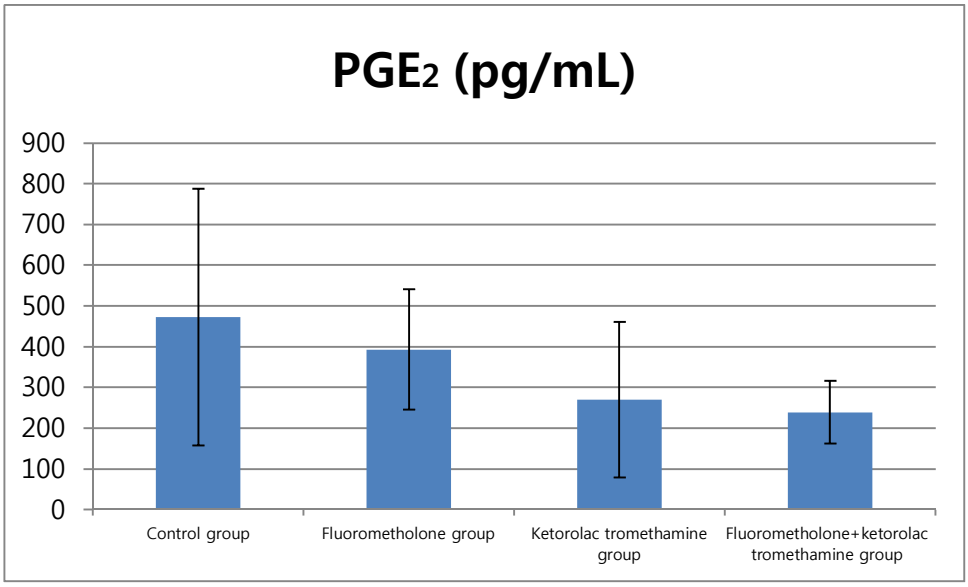

Figure 4. PGE_2 concentrations in anterior chamber aqueous humor.

*p<0.05 compared with the control group by Student's t-test.