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CATARACT

Effect of preoperative eyedrops on cytokine concentrations in aqueous humor of patients undergoing femtosecond laser–assisted cataract surgery

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Abstract

Purpose 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. Groups were administered 0.1% fluorometholone eyedrops, 0.45% ketorolac tromethamine eyedrops, both 0.1% fluorometholone and 0.45% ketorolac tromethamine eyedrops, or no eyedrops. Eyedrops were instilled 1 h, 20 min, and just before surgery. After anterior capsulotomy and nuclear fragmentation using a femtosecond laser, 0.1 cc aqueous humor was obtained using a needle and syringe. Cytokine and prostaglandin E_2 (PGE_2) concentrations were quantitatively determined.

Results The 120 patients included 59 men and 61 women, of mean age 65.02 years. The mean interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) concentrations after treatment did not differ significantly in the four groups. The average interleukin-8 (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 PGE_2 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).

Conclusion Preoperative fluorometholone instillation reduced IL-8, and ketorolac tromethamine instillation reduced IL-8 and PGE_2, in aqueous humor of patients undergoing femtosecond laser surgery, with the combination of both eyedrops being more effective than either alone.

Trial registration KCT0005717

Keywords Femtosecond laser–assisted cataract surgery · Postoperative inflammation · NSAID · Steroid

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Key messages

- Femtosecond laser-assisted cataract surgery has been reported to increase the intraocular concentrations of inflammatory cytokines and other inflammatory mediators.
- Eyedrops containing nonsteroidal anti-inflammatory drugs (NSAID) are widely used to reduce ocular inflammation in patients undergoing femtosecond laser-assisted cataract surgery; to our knowledge, however, steroid eyedrops have not been studied in patients with undergoing femtosecond laser-assisted cataract surgery.
- Preoperative instillation of steroid eyedrops reduced the concentrations of inflammatory cytokines in aqueous humor of patients undergoing femtosecond laser-assisted cataract surgery.
- Applying both steroid and NSAID eyedrops was more effective than either alone.

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, the ability of FLACS to concomitantly correct astigmatism has resulted in an increase in the number of patients undergoing this procedure.

To date, 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 of 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), fibroblast 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 steroids, on cytokine and PGE_2 concentrations in aqueous humor collected during FLACS.

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) and conformed to the tenets of the Declaration of Helsinki. All patients provided written informed consent. This study has been registered as a clinical trial (KCT0005717).

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. Before surgery, patients were administered no eyedrops (control group), fluorometholone 0.1% (Flumetholone, Santen Pharmaceutical), ketorolac tromethamine 0.45% (Acuvail, Allergan, Inc.) eyedrops, or both fluorometholone 0.1% and ketorolac tromethamine 0.45%. The respective eye drops were instilled 1 h, 20 min, and just before surgery. At the same time, all patients were preoperatively administered a combination of topical tropicamide 0.5% with phenylephrine 0.5% three times at 10-min intervals for mydriasis. All patients underwent capsulotomy, lens fragmentation, and astigmatic incision with the Catalys Laser System (Johnson & Johnson, Inc.). Five minutes later, a corneal incision of about 1 mm was made at 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.

The substances evaluated and compared included IL-6, IL-8, TNF-α, and PGE_2, as they have been evaluated in several previous studies of inflammatory mediators in aqueous humor. 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 for each chemokine/cytokine, and their concentrations in each sample were determined

Table 1 Demographic characteristics of study patients

	Control group	Fluorometholone group	Ketorolac tromethamine group	Fluorometholone + ketorolac tromethamine group	Total
Age (years)	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 Cytokine concentrations in anterior chamber aqueous humor of study patients

	Control group	Fluorometholone group	Ketorolac tromethamine group	Fluorometholone + ketorolac tromethamine group
IL-6 (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
IL-8 (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
TNF-α (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

*Compared with the control group by Student's *t*-test. Abbreviations: *IL-6*, interleukin-6; *IL-8*, interleukin-8; *TNF-α*, tumor necrosis factor-α; *SD*, standard deviation

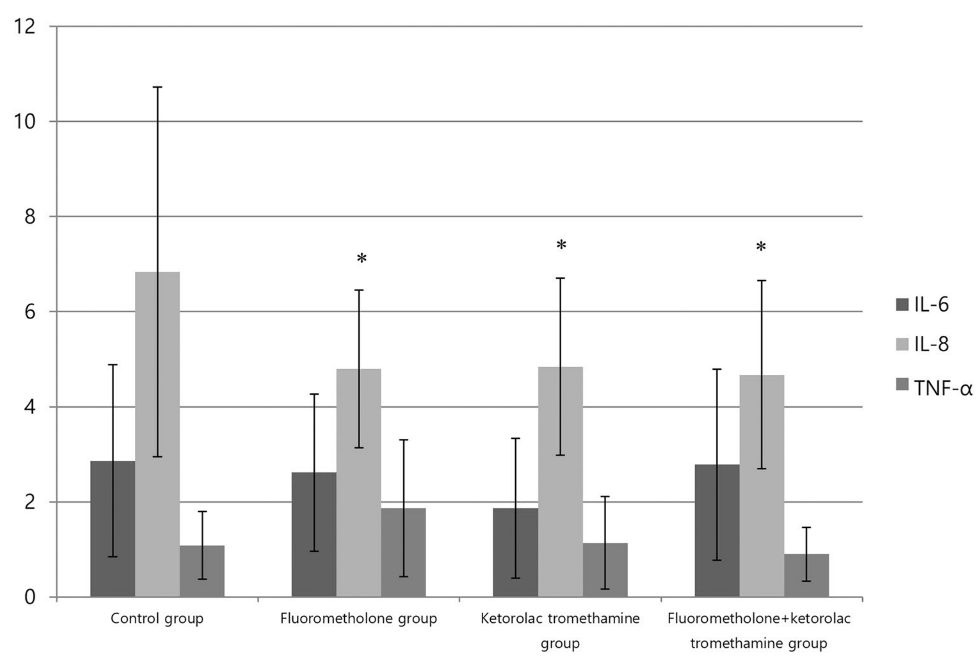

Figure 1 Cytokine concentrations in anterior chamber aqueous humor (pg/mL), *$p < 0.05$ compared with the control group by Student's *t*-test (IL-6 = interleukin-6; IL-8 = interleukin-8; TNF-α = tumor necrosis factor-α)

by curve-fitting. PGE_2 concentrations were determined using a commercially available PGE_2 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 2; Figure 1).

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 2; Figure 1). The average PGE_2 concentrations were significantly lower in the ketorolac tromethamine (270.04 ± 190.82 pg/mL) and fluorometholone + ketorolac tromethamine (239.00 ± 77.29

Table 3 PGE_2 concentrations in anterior chamber aqueous humor of study patients

	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

*Compared with the control group by Student's t-test. Abbreviations: PGE_2, prostaglandin E_2; SD, standard deviation

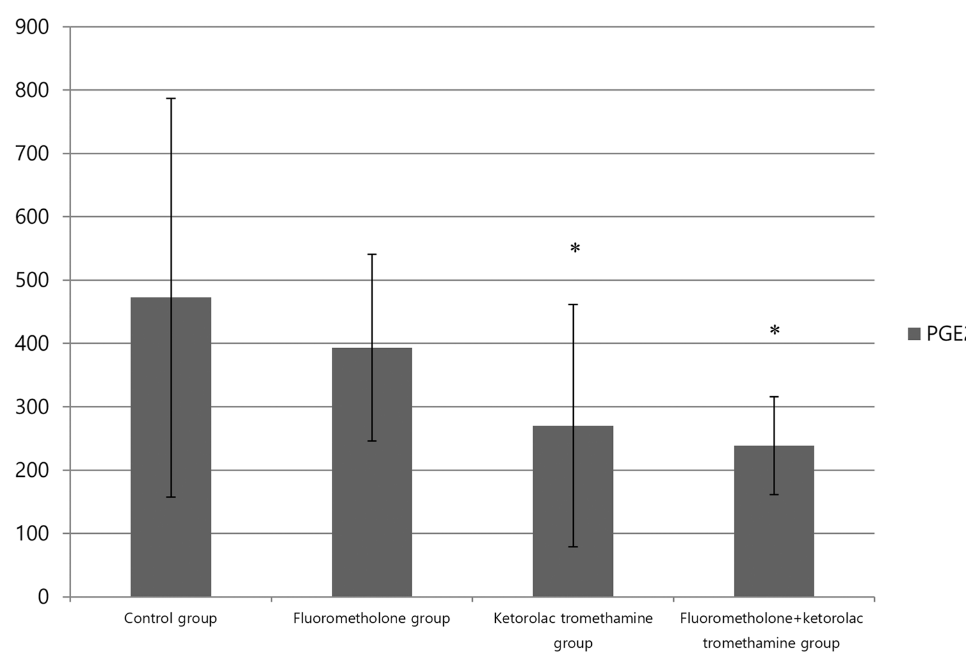

Figure 2 PGE_2 concentrations in anterior chamber aqueous humor (pg/mL), *$p < 0.05$ compared with the control group by Student's t-test (PGE_2 = prostaglandin E_2)

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 3; Figure 2).

Discussion

Despite the many advantages of FLACS, intraoperative miosis is not infrequent [10, 11]. Smaller pupils can make cataract surgery more difficult and are associated with 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 treatment before FLACS. To our knowledge, this is the first study to evaluate the anti-inflammatory effects of both steroid and nonsteroid medications in patients undergoing FLACS. Both of the agents used in this study had anti-inflammatory effects and are therefore likely 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], but the need for NSAIDs has significantly decreased with the development of new technologies and the shortened duration of surgery. Pupillary miosis, however, may recur after FLACS. 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, which are responsible for chemotaxis, and of arachidonic acid, which is converted to prostaglandins by cyclooxygenases [17]. Due to these properties, steroids have been widely used as anti-inflammatory agents in patients undergoing manual cataract surgery [18, 19]. 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 [20]. This inflammation can also induce the expression of vascular endothelial growth factor (VEGF), promoting vascular permeability and angiogenesis [21]. IL-6 concentrations were found to be significantly higher in ocular fluids obtained from patients with than without refractory or chronic uveitis [22]. IL-8 is a strong chemoattractant involved in the activation of both neutrophils and T-lymphocytes, indicating that it has both immune and vascular functions. IL-8 was also reported to be increased in the aqueous humor of patients with uveitis and glaucoma [23], and vitreous gel levels of IL-8 were higher in patients with than without proliferative diabetic retinopathy [24]. TNF-α, a macrophage/monocyte-derived pluripotent cytokine, has been associated with ischemic tissue damage and remodeling of neurons [25]. TNF-α was shown to be associated with the development of posterior capsular opacification [26] and may induce postoperative inflammation and lens epithelial cell proliferation [27]. Prostaglandins, which are synthesized in the iris and ciliary body following trauma [28], are highly potent regulators of inflammation, with various effects on the conjunctiva, cornea, iris, ciliary body, choroid, and retina [29]. PGE_2 was thought to be released from uveal tissue due to an increase in temperature, vibrations, or shockwaves during FLACS when laser spots pass through the aqueous humor [30]. 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 varied according to study settings. Therefore, the cytokine concentrations reported in different studies could not be compared directly. 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, IL-6 and TNF-α are likely similar to other inflammatory cytokines, anti-inflammatory agents more potent than ketorolac tromethamine 0.45% and fluorometholone 0.1% might achieve greater reductions in the concentrations of pro-inflammatory cytokines. Additional studies are needed, however, to confirm this hypothesis.

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 (IOP) [31], impaired wound healing [32], and a greater risk of infection [33]. Topical NSAIDs have been associated with corneal melts [34], as well as with ocular discomfort [35]. 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. Fluorometholone 0.1% is regarded as the weakest steroid agent available, with little effect on IOP [31], which may explain its weaker anti-inflammatory effect than NSAID in this study. Patients without definite risk factors associated with the side effects described above and/or prone to increased inflammation after FLACS may benefit from simultaneous instillation of both agents.

Increased PGE_2 concentration is also thought to be responsible for intraoperative miosis in FLACS, although the precise mechanism remains unclear [3, 4, 36]. Preoperative instillation of ketorolac tromethamine reduced PGE_2 concentration, with the combination of this agent with fluorometholone being more effective in this study. Therefore, treatment with both agents can likely reduce the incidence of intraoperative miosis. Moreover, reducing the concentrations of inflammatory cytokines may result in lower rates of postoperative inflammation, including uveitis, secondary glaucoma, and pseudophakic cystoid macular edema.

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 previous studies. Moreover, extracting more aqueous humor may be dangerous for patients due to shrinkage of the intraocular space. 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 PGE_2, in the aqueous humor of patients undergoing FLACS. Moreover, application of both eyedrops was more effective than either alone.

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Author contribution JHL: study supervision, concept and study design, data collection, data interpretation, data analysis and statistics, drafting, revision and final approval of manuscript

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Data availability The data used to support the findings of this study are available from the corresponding author upon request.

Code availability Not applicable.

Declarations

Ethics approval This study adhered to the tenets of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Asan Medical Center (Seoul, Republic of Korea).

Consent to participate Written informed consent forms were signed by all study participants prior to the procedure.

Consent for publication Written informed consent forms for publication of the research were signed by all study participants prior to the procedure.

Competing interests The authors declare no competing interests.

References

1. Day AC, Burr JM, Bennett K, Dore CJ, Bunce C, Hunter R, Nanavaty MA, Balaggan KS, Wilkins MR, FACT trial group, (2020) Femtosecond laser-assisted cataract surgery compared with phacoemulsification cataract surgery: randomized noninferiority trial with 1-year outcomes. J Cataract Refract Surg 46:1360–1367
2. Jun JH, Yoo YS, Lim SA, Joo CK (2017) Effects of topical ketorolac tromethamine 0.45% on intraoperative miosis and prostaglandin E2 release during femtosecond laser-assisted cataract surgery. J Cataract Refract Surg 43:492–497
3. Wang L, Zhang Z, Koch DD, Jia Y, Cao W, Zhang S (2016) Anterior chamber interleukin 1 β, interleukin 6 and prostaglandin E2 in patients undergoing femtosecond laser-assisted cataract surgery. Br J Ophthalmol 100:579–582
4. Schultz T, Joachim SC, Kuehn M, Dick HB (2013) Changes in prostaglandin levels in patients undergoing femtosecond laser-assisted cataract surgery. J Refract Surg 29:742–747
5. Chen H, Lin H, Zheng D, Liu Y, Chen W, Liu Y (2015) Expression of cytokines, chemokines and growth factors in patients undergoing cataract surgery with femtosecond laser pretreatment. PLoS One 10:e0137227
6. Diakonis VF, Anagnostopoulos AG, Moutsiopoulou A, Yesilirmak N, Cabot F, Waren DP, O'Brien TP, Yoo SH, Weinstock RJ, Donaldson KE (2018) The effect of NSAID pretreatment on aqueous humor prostaglandin E2 concentration in eyes undergoing femtosecond laser-assisted capsulotomy. J Ophthalmol 2018:1891249
7. Schultz T, Joachim SC, Szuler M, Stellbogen M, Dick HB (2015) NSAID pretreatment inhibits prostaglandin release in femtosecond laser-assisted cataract surgery. J Refract Surg 31:791–794
8. Kiss HJ, Takacs AI, Kranitz K, Sandor GL, Toth G, Gilanyi B, Nagy ZZ (2016) One-day use of preoperative topical nonsteroidal anti-inflammatory drug prevents intraoperative prostaglandin level elevation during femtosecond laser-assisted cataract surgery. Curr Eye Res 41:1064–1067

9. Anisimova NS, Arbisser LB, Petrovski G, Petrichuk SV, Sobolev NP, Petrovski B, Borsenok SA, Komah YA, Malyugin BE (2018) Effect of NSAIDs on pupil diameter and expression of aqueous humor cytokines in FLACS versus conventional phacoemulsification. J Refract Surg 34:646–652
10. Bali SJ, Hodge C, Lawless M, Roberts TV, Sutton G (2012) Early experience with the femtosecond laser for cataract surgery. Ophthalmology 119:891–899
11. Hashemi H, Seyedian MA, Mohammadpour M (2015) Small pupil and cataract surgery. Curr Opin Ophthalmol 26:3–9
12. Joseph J, Wang HS (1993) Phacoemulsification with poorly dilated pupils. J Cataract Refract Surg 19:551–556
13. Conrad-Hengerer I, Hengerer FH, Al Juburi M, Schultz T, Dick HB (2014) Femtosecond laser-induced macular changes and anterior segment inflammation in cataract surgery. J Refract Surg 30:222–226
14. Levitz L, Reich J, Roberts TV, Lawless M (2015) Incidence of cystoid macular edema: femtosecond laser-assisted cataract surgery versus manual cataract surgery. J Cataract Refract Surg 41:683–686
15. Vane JR, Botting RM (1998) Mechanism of action of nonsteroidal anti-inflammatory drugs. Am J Med 104:2S-8S (**discussion 21S-22S**)
16. Keulen-de Vos HC, van Rij G, Renardel de Lavalette JC, Jansen JT (1983) Effect of indomethacin in preventing surgically induced miosis. Br J Ophthalmol 67:94–96
17. Li Q, Luyo D, Matteson DM, Chan CC (1998) Suppressive effect of antiflammin-2 on compound 48/80-induced conjunctivitis. Role of phospholipase A2s and inducible nitric oxide synthase. Ocul Immunol Inflamm 6:65–73
18. McColgin AZ, Heier JS (2000) Control of intraocular inflammation associated with cataract surgery. Curr Opin Ophthalmol 11:3–6
19. El-Harazi SM, Feldman RM (2001) Control of intra-ocular inflammation associated with cataract surgery. Curr Opin Ophthalmol 12:4–8
20. Matzinger P (2002) The danger model: a renewed sense of self. Science 296:301–305
21. Chu L, Wang B, Xu B, Dong N (2013) Aqueous cytokines as predictors of macular edema in non-diabetic patients following uncomplicated phacoemulsification cataract surgery. Mol Vis 19:2418–2425
22. Mesquida M, Leszczynska A, Llorenç V, Adán A (2014) Interleukin-6 blockade in ocular inflammatory diseases. Clin Exp Immunol 176:301–309
23. Gu R, Zhou M, Jiang C, Yu J, Xu G (2016) Elevated concentration of cytokines in aqueous in post-vitrectomy eyes. Clin Exp Ophthalmol 44:128–134
24. Hernandez C, Segura RM, Fonollosa A, Carrasco E, Francisco G, Simo R (2005) Interleukin-8, monocyte chemoattractant protein-1 and IL-10 in the vitreous fluid of patients with proliferative diabetic retinopathy. Diabet Med 22:719–722
25. Balaiya S, Edwards J, Tillis T, Khetpal V, Chalam KV (2011) Tumor necrosis factor-alpha (TNF-α) levels in aqueous humor of primary open angle glaucoma. Clin Ophthalmol 5:553–556
26. Meacock WR, Spalton DJ, Stanford MR (2000) Role of cytokines in the pathogenesis of posterior capsule opacification. Br J Ophthalmol 84:332–336
27. Prada J, Ngo-Tu T, Baatz H, Hartmann C, Pleyer U (2000) Detection of tumor necrosis factor alpha and interleukin 1 alpha gene expression in human lens epithelial cells. J Cataract Refract Surg 26:114–117
28. Ambache NP, Brummer HC (1968) A simple chemical procedure for distinguishing E from F prostaglandins, with application to tissue extracts. Br J Pharmacol Chemother 33:162–170
29. Hall DW, Bonta IL (1977) Prostaglandins and ocular inflammation. Doc Ophthalmol 44:421–434
30. Schultz T, Joachim SC, Stellbogen M, Dick HB (2015) Prostaglandin release during femtosecond laser-assisted cataract surgery: main inducer. J Refract Surg 31:78–81
31. Musleh MG, Bokre D, Dahlmann-Noor AH (2020) Risk of intraocular pressure elevation after topical steroids in children and adults: a systematic review. Eur J Ophthalmol 30:856–866
32. Beck LS, Deguzman L, Lee WP, Xu Y, McFatridge LA, Amento EP (1991) TGF-beta 1 accelerates wound healing: reversal of steroid-impaired healing in rats and rabbits. Growth Factors 5:295–304
33. Wu YT, Truong TN, Tam C, Mendoza MN, Zhu L, Evans DJ, Fleiszig SMJ (2019) Impact of topical corticosteroid pretreatment on susceptibility of the injured murine cornea to Pseudomonas aeruginosa colonization and infection. Exp Eye Res 179:1–7
34. Rigas B, Huang W, Honkanen R (2020) NSAID-induced corneal melt: clinical importance, pathogenesis, and risk mitigation. Surv Ophthalmol 65:1–11
35. Aragona P, Stilo A, Ferreri F, Mobrici M (2005) Effects of the topical treatment with NSAIDs on corneal sensitivity and ocular surface of Sjögren's syndrome patients. Eye (Lond) 19:535–539
36. Chen H, Lin H, Chen W, Zhang B, Xiang W, Li J, Chen W (2017) Topical 0.1% bromfenac sodium for intraoperative miosis prevention and prostaglandin E2 inhibition in femtosecond laser-assisted cataract surgery. J Ocul Pharmacol Ther 33:193–201