Effect of NSAIDs on Pupil Diameter and Expression of Aqueous Humor Cytokines in FLACS Versus Conventional Phacoemulsification

Natalia S. Anisimova, MD; Lisa B. Arbisser, MD; Goran Petrovski, MD, PhD; Svetlana V. Petrichuk, PhD; Nikolay P. Sobolev, MD, PhD; Beata Petrovski, PhD; Sergey A. Borsenok, MD, PhD; Yurii A. Komah, MD, PhD; Boris E. Malyugin, MD, PhD

ABSTRACT

PURPOSE: To compare the concentrations of interleukin (IL) (IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70), interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and TNF-β in the aqueous humor of patients undergoing femtosecond laser–assisted cataract surgery (FLACS) and corneal mechanical paracentesis treated with two different topical nonsteroidal anti-inflammatory drugs (NSAIDs): bromfenac and indomethacin.

METHODS: In this prospective, randomized controlled, single-center study, aqueous humor samples were obtained immediately after performing the femtosecond laser procedure or at the start of conventional phacoemulsification. Preoperatively, the FLACS groups were administered (once daily and four times daily, respectively) either topical bromfenac 0.09% (12 eyes) or indomethacin 0.1% (12 eyes). The corneal paracentesis bromfenac and indomethacin groups received the same regimen of instillation of NSAIDs, respectively. Quantitative analysis of the expressed cytokines in the aqueous humor was performed using FlowCytomix FC 500 Pro 3.0 Software (Bender MedSystems GmbH, Vienna, Austria).

RESULTS: The intraoperative pupil diameter was correlated with the expression of IL-6 after the femtosecond laser procedure in the FLACS indomethacin group ($r = -0.53$; $P = .07$). A significant difference in mean pupillary size was detected between the FLACS bromfenac and indomethacin groups at the aspiration/irrigation time point (0.53 ± 0.26 mm) and at the end of surgery (0.68 ± 0.37 mm). Progressive pupillary constriction was observed in the indomethacin and bromfenac groups.

CONCLUSIONS: A smaller expression of IL-6 to the overall cytokine network value was observed in cases receiving preoperative bromfenac 0.09%, explaining improved maintenance of intraoperative mydriasis.

[*J Refract Surg*. 2018;34(10):646-652.]

Since its introduction, femtosecond laser–assisted cataract surgery (FLACS) has proven to be a safe technology that provides a high rate of precision in both standard and complex cataract cases.[1] Despite its numerous advantages, the laser tissue interaction influences the cascade of inflammatory factors,[2-5] affecting the dynamics of the intraoperative pupil and causing miosis.[6] Once the pupil reaches a clinically significant small size, the surgery can become complicated even for the experienced surgeon.

A change in the variety of cytokines present can make a significant contribution to what is already complex machinery, from both a pro-inflammatory and defense mechanism perspective. The femtosecond laser technology has been known to cause an imbalance in the aqueous humor cytokine secretome.[2] Nonsteroidal anti-inflammatory drugs (NSAIDs) were first approved by the U.S. Food and Drug Administration to prevent surgically induced miosis, and were more recently shown to inhibit the array of intraocular pro-inflammatory factors,[7] providing maintenance of the pupil diameter.[8] Newer NSAIDs are being investigated to compare and validate their superiority in various clinical applications.[9-11] Additionally, the first generation NSAID indomethacin may show added potential when delivered in other formulations or devices.[12-14] Therefore, a comparative study between two different generations of NSAIDs—bromfenac 0.09% (once daily) and indomethacin 0.1% (four times daily)—was undertaken to evaluate their effects on cytokine concentrations in the aqueous humor and its correlation with intraoperative pupil maintenance.

From S. Fyodorov Eye Microsurgery State Institution, Moscow, Russia (NSA, NPS, SAB, YAK, BEM); John A. Moran Eye Center, University of Utah, Salt Lake City, Utah (LBA); Center for Eye Research, Department of Ophthalmology, Oslo University Hospital and University of Oslo, Oslo, Norway (GP); Scientific Center of Children Health, Moscow, Russia (SVP); Health Services Research Centre, Akershus University Hospital, Lørenskog, Norway (BP); and Faculty of Dentistry, University of Oslo, Oslo, Norway (BP).

Submitted: June 12, 2018; Accepted: August 13, 2018

Dr. Anisimova received a travel grant from Alcon Laboratories, Inc. The remaining authors have no financial or proprietary interest in the materials presented herein.

Correspondence: Natalia S. Anisimova, MD, Cataract and Implant Surgery Department, S. Fyodorov Eye Microsurgery State Institution, Beskudnikovsky Boulevard 59A, Moscow 127486, Russia. E-mail: mdnsanisimova@gmail.com

doi:10.3928/1081597X-20180814-02

Copyright © SLACK Incorporated

Both the defined biological agent concentration and the overall interaction with other molecules in the cytokine signaling pathway appear crucial.[15] Advances in network biology in conjunction with statistical analysis[16,17] define a new conceptual framework to demonstrate differences between various NSAID pretreatment regimens and their efficacy in the prevention of intraoperative iris diaphragm constriction.

PATIENTS AND METHODS

Patient inclusion criteria required the presence of age-related cataract of grades 2 to 4 on the Lens Opacities Classification System, version III (LOCS III).[18] Exclusion criteria were: any previous intraocular surgery, small rigid pupil, history of inflammatory or infectious eye disease, previous ocular surgery or trauma, glaucoma, exfoliation syndrome, diabetic retinopathy, age-related macular degeneration uveitis, or use of topical or systemic anti-inflammatory or anti-infectious agents. Patients with mechanical intraoperative iris instrument touch or damage were also excluded from the study.

According to our study protocol, the first two groups of patients received cataract surgery with the FLACS technique. The FLACS bromfenac group received topical bromfenac 0.09% once daily and the FLACS indomethacin group received indomethacin 0.1% four times a day 1 day prior to surgery and on the day of surgery 1 hour prior to laser docking. The corneal paracentesis groups had their cataract surgery in the conventional manner without laser pretreatment. The corneal paracentesis bromfenac group received the bromfenac and the corneal paracentesis indomethacin group received the indomethacin in the same dosage and timing prior to incision. Medical mydriasis was induced using topical tropicamide 0.8% and phenylephrine 5.0% as combined eye drops and instilled three times within 1 hour prior to surgery for all groups.

Following the tenets of the Declaration of Helsinki, an informed consent was signed by all participants before enrollment. The study was approved by the Ethical Committee of the Institutional Review Board of S. Fyodorov Eye Microsurgery State Institution, Moscow, Russia.

Sample Collection

All samples were harvested in the operating room by an experienced cataract surgeon under sterile conditions. The time between laser application and the start of cataract surgery was similar for both groups ($P > .05$). In all groups, the anterior chamber was entered with a disposable 30-gauge cannula through the side-port incision, and an undiluted aqueous humor specimen (70 to 100 µL) was collected into a 1-mL syringe and subsequently transferred to a sterile 1.5-mL Eppendorf plastic tube. The samples were stored immediately in a -80°C freezer known to stabilize cytokines for years until analyzed 1 week to 4 months later.

Measurement of Cytokines Using Multiplex Analysis

The following cytokines were measured in the aqueous humor samples: interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, interferon (IFN)-γ, tumor necrosis factor (TNF-α), and TNF-β. The aqueous humor was assayed to determine the concentrations of cytokines using the FlowCytomix human Th1/Th2 11-plex BMS810FF Kit, after minor modifications to the manufacturer's instructions (eBioscience; Bender MedSystems GmbH, Vienna, Austria). The kit allowed simultaneous quantification of 11 cytokines, including Th1 cytokines (IL-1β, IFN-γ, IL-2, TNF-α, and TNF-β), Th2 cytokines (IL-10, IL-4, IL-5, IL-6, and IL-8), and a Th22 cytokine (IL-12p70). Data were analyzed using FlowCytomics FC 500 Pro 3.0 Software (Bender MedSystems GmbH).

Surgical Technique

All manual and femtosecond laser surgeries were performed by the same experienced surgeon (NPS). The femtosecond laser procedure was performed using the LenSx (Alcon Laboratories, Inc., Fort Worth, TX) laser system (2.30 software) in the FLACS groups. Corneal applanation was performed using the SoftFit interface (Alcon Laboratories, Inc.). Laser adjustments were standard in all procedures and included capsulotomy diameter 5 mm (pulse energy: 5 µJ, tangential spot separation: 4 µm, layer separation: 4 µm), lens fragmentation diameter 4.8 mm (pulse energy: 10 µJ, tangential spot separation: 7 µm, layer separation: 7 µm), pattern of 7 cylindrical and 3 radial cuts, and primary and two side-port corneal incisions (pulse energy: 5 µJ, tangential spot separation: 4 µm, layer separation: 4 µm). A standardized lens fragmentation pattern (3 cross-sections with a chop diameter of 5.2 mm and 7 cylinders with a maximum cylinder diameter of 5.2 mm) was used. With regard to ultrasound use, there was no statistically significant difference of phacoemulsification time or power between the FLACS bromfenac and indomethacin groups.

Phacoemulsification was employed for all patients following hydrodissection using the Centurion machine (Alcon Laboratories, Inc.). The FLACS bromfenac and corneal paracentesis indomethacin groups had a bimanual phaco-chop technique employed. A single-piece AcrySof Natural SN60AT intraocular lens (Alcon Laboratories, Inc.) was implanted in the capsular bag in all groups.

Pupil Diameter Measurement

Screenshots from the surgical video files were used to calculate the pupil diameter at five different time points.

TABLE 1

Demographic and Clinical Characteristics of the Study Population

Characteristic	FLACS Bromfenac (n = 12)	FLACS Indomethacin (n = 12)	CP Bromfenac (n = 12)	CP Indomethacin (n = 17)
Age (y), mean ± SD	68.3 ± 11.6	70.3 ± 12.0	62.1 ± 9.7	68.2 ± 10.1
Range (min/max)	43/83	52/86	51/74	52/80
Male/female sex	5/7	6/6	7/5	8/9
Current medical conditions, n (%)				
Hypertension	3 (21.4)	1 (8.3)	4 (33.3)	1 (5.9)
Gastric ulcer	0	1 (8.3)	0	0
Dietary allergy	0	2 (16.6)	1 (8.3)	0
Ophthalmological parameters				
Anterior chamber depth (mm), mean ± SD	3.1 ± 0.6	3.1 ± 0.4	3.3 ± 0.7	3.1 ± 0.4
Lens length (mm), mean ± SD	4.4 ± 0.6	4.8 ± 0.5	4.7 ± 0.5	4.8 ± 0.5
Axial length (mm), mean ± SD	24.2 ± 1.1	24.5 ± 1.6	23.9 ± 1.8	24.0 ± 2.0
Keratometry 1 (D), mean ± SD	43.70 ± 1.50	43.30 ± 1.10	43.10 ± 1.40	43.30 ± 1.10
Keratometry 2 (D), mean ± SD	44.30 ± 1.60	44.30 ± 1.60	44.00 ± 1.90	44.60 ± 1.30
Pachymetry (μm), mean ± SD	524.8 ± 41.8	516.6 ± 19.0	526.2 ± 14.6	545.5 ± 25.0
IOP (mm Hg), mean ± SD	16.7±2.8	16.5 ± 2.0	16.8 ± 3.8	17.0 ± 3.2
SE (D), mean ± SD	–3.00 ± 4.70	–5.20 ± 4.30	–3.50 ± 4.40	–2.50 ± 5.20
Peripheral chorioretinal dystrophy, n (%)	1 (7.1)	0	2 (16.6)	0
Dry eye medication use	1	1	0	1
Cataract grade (LOCS III), mean ± SD	2.6 ± 0.5	2.7 ± 0.7	2.4 ± 0.5	2.9 ± 1.1

FLACS = femtosecond laser–assisted cataract surgery; CP = corneal paracentesis; SD = standard deviation; D = diopters; IOP = intraocular pressure; SE = spherical equivalent; LOCS = Lens Opacities Classification System

Prior to femtolaser laser application (øpupil I), just before the start of the manual surgery (øpupil II), after ophthalmic viscosurgical device injection (øpupil III), during aspiration/irrigation of the lens cortex or at the middle of the procedure (øpupil IV), and after hydration of the clear corneal incisions (øpupil V). Proportional expressions were used to calculate pupil diameters.[6] Because no femtosecond laser step was performed in the corneal paracentesis groups, the pupil diameter was marked as øpupil II, III, IV, and V accordingly, to correspond to the time points used in the FLACS groups.

Statistical Analysis

Statistical processing of data was performed using StatPlus (version 6.2.2.0; AnalystSoft Inc., Walnut, CA) and Stata/SE version 11.0 (StataCorp, College Station, TX) software. Statistical significance of differences was determined by the Mann–Whitney *U* test, using the Holm–Bonferroni sequential correction when multiple comparisons were applied. The data are expressed as means ± standard deviation, and medians when appropriate. A *P* value of less than .05 was considered statistically significant. Spearman's correlation analysis was used to examine the relationship between the cytokine levels and the severity of miosis. Cytoscape version 3.5.1 (Cytoscape Consortium, Washington, DC) was used to verify the correlative interaction at the 0.5 and 0.7 Spearman's correlation coefficient threshold, whereas cluster analysis with the farthest neighbor method was used to identify the hierarchical structure and the difference in the cytokines' interactions. There was no statistically significant difference between groups for age, axial length, cataract grade ($P > .05$, *F* test), or gender distribution ($P > .50$, chi-square test).

RESULTS

The demographic and clinical characteristics of the study population are presented in **Table 1**. There were no differences between groups. There was no statistical difference in the intraoperative time parameters between the FLACS groups (**Table 2**).

The concentration of IL-6 ($P = .043$) was significantly higher in the FLACS bromfenac group compared to the corneal paracentesis bromfenac group (**Figure 1**).

Cluster analysis showed that IL-6 was included in the chain of cytokine interactions earlier in the FLACS

Copyright © SLACK Incorporated

TABLE 2

Intraoperative Femtosecond Laser and Time Parameters in the FLACS Groups

Parameter	FLACS Bromfenac	FLACS Indomethacin	*P*
Laser time (sec)	46.6 ± 5.1	48.0 ± 4.5	> .05
Suction time (sec)	142.8 ± 29.0	154.8 ± 16.0	> .05
Anterior capsule range (μm)	788.3 ± 111.6	859.9 ± 185.8	> .05
Lens thickness (μm)	3,267.1 ± 534.9	3,277.0 ± 454.4	> .05
Capsulotomy diameter (mm)	4.9 ± 0.2	4.9 ± 0.4	> .05
Lens diameter (mm)	5.0 ± 0.6	5.0 ± 0.6	> .05
Main tunnel length (μm)	1,692.1 ± 24.4	1,699.8 ± 0.9	> .05
Time between femto and phaco procedures (min)	20.9 ± 10.1	19.3 ± 9.9	> .05

FLACS = femtosecond laser–assisted cataract surgery

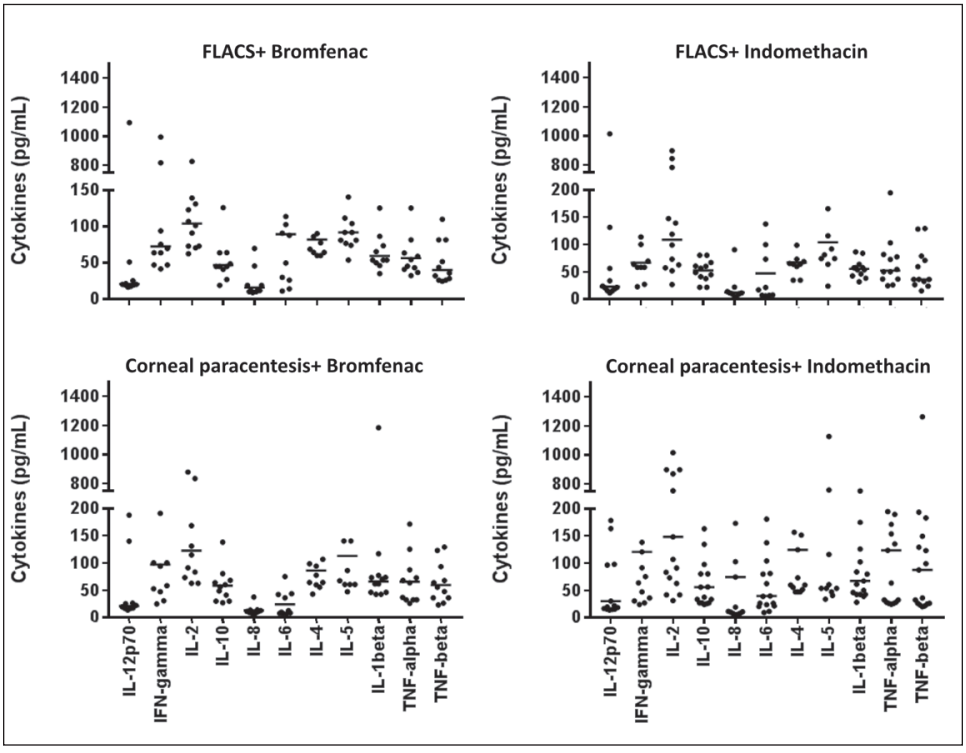

Figure 1. Concentration of cytokines in the aqueous humor of the femtosecond laser–assisted cataract surgery bromfenac and indomethacin groups, and the corneal paracentesis bromfenac and indomethacin groups after mechanical side-port corneal incision with the nonsteroidal anti-inflammatory drugs included in the preoperative treatment. Data are expressed as the medians (horizontal lines). There were no significant differences in the concentrations of the other mediators between the femtosecond laser and conventional phacoemulsification groups. IL = interleukin; IFN = interferon, TNF = tumor necrosis factor

indomethacin group compared to the other groups (**Figure 2**).

Correlation networks of 11 cytokines with a 0.5 and 0.7 threshold correlation coefficient showed less binding to the chain for IL-6 in the FLACS bromfenac group compared to the FLACS indomethacin group (**Figures A-B**, available in the online version of this article). Among the corneal paracentesis groups, a difference was found only in the corneal paracentesis bromfenac group with a 0.5 threshold correlation coefficient, where IL-6 showed 3 bindings in comparison to the corneal paracentesis indomethacnin group, where 9 IL-6 bindings were observed.

A negative correlation was found between the intraoperative pupil diameter (øpupil II) and the concentration of IL-6 in the FLACS indomethacin group (r = -0.53; P = .07). The pupil dynamics revealed better intraoperative mydriasis maintenance in the group treated with bromfenac 0.09% once daily. Furthermore, a significant difference in the mean pupillary size between the FLACS groups was detected at the aspiration/irrigation time point (øpupil IV) by 0.53 ± 0.26 mm and at the end of the surgery by 0.68 ± 0.37 mm. No significant difference was observed at the various stages of surgery between the corneal paracentesis groups. During the second part of the surgical proce-

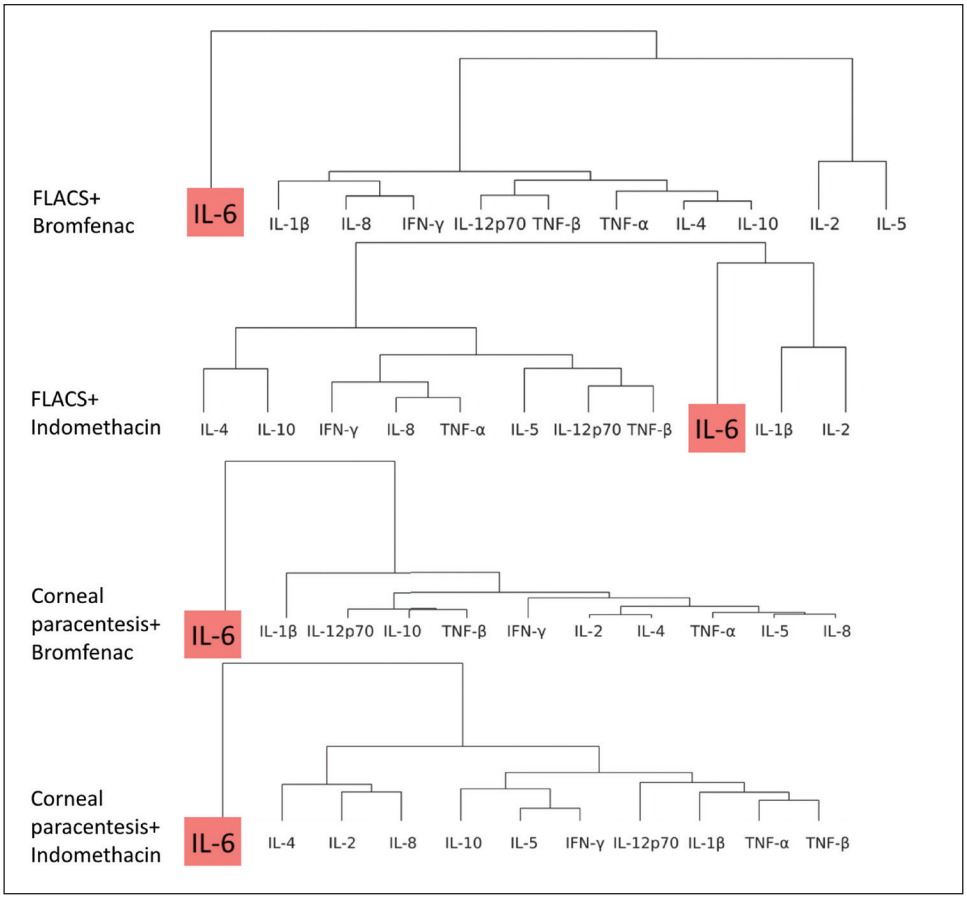

Figure 2. Cluster analysis of the cytokines' interaction. Interleukin (IL)-6 (red boxes) is included in the chain of cytokines' interaction earlier in the femtosecond laser–assisted cataract surgery (FLACS) indomethacin group in comparison to the other groups. IFN = interferon, TNF = tumor necrosis factor

TABLE 3

Intraoperative Pupil Diameter in Groups With Different NSAID Pretreatment

Group	øpupil I	øpupil II	øpupil III	øpupil IV	øpupil V
FLACS bromfenac (mm) (n = 12)					
Mean ± SD	7.0 ± 0.8	6.9 ± 0.6	7.2 ± 0.5	6.9 ± 0.4	6.4 ± 0.7
Range	5.9 to 8.4	6.3 to 8.0	6.4 to 8.2	6.1 to 7.4	4.7 to 7.2
øpupil ≤ 5	0	0	0	0	1
FLACS indomethacin (mm) (n = 12)					
Mean ± SD	7.3 ± 0.9	6.8 ± 0.9	6.8 ± 1.1	6.4 ± 0.8	5.7 ± 1.1
Range	6.4 to 9.0	4.2 to 7.6	4.5 to 7.7	4.7 to 7.3	4.0 to 7.1
øpupil ≤ 5	0	1	2	2	4
CP bromfenac (mm) (n = 12)					
Mean ± SD	–	7.0 ± 0.7	7.3 ± 0.6	6.8 ± 0.7	5.9 ± 0.9
Range	–	5.7 to 8.1	5.8 to 8.2	5.6 to 8.0	4.5 to 7.1
øpupil ≤ 5	–	0	0	0	3
CP indomethacin (mm) (n = 17)					
Mean ± SD	–	7.3 ± 0.7	7.5 ± 0.5	6.5 ± 0.8	5.8 ± 0.9
Range	–	6.3 to 8.7	6.8 to 8.5	4.6 to 8.0	4.5 to 7.0
øpupil ≤ 5	–	0	0	1	6

NSAID = nonsteroidal anti-inflammatory drug; FLACS = femtosecond laser–assisted cataract surgery; SD = standard deviation; CP = corneal paracentesis

Copyright © SLACK Incorporated

dure, pupillary constriction (defined as 5 mm or less) was observed in the FLACS and corneal paracentesis indomethacin groups compared to the FLACS and corneal paracentesis bromfenac groups (**Table 3**).

DISCUSSION

Maintenance of pupil dilation at all stages of cataract surgery is crucial for safe, successful outcomes. NSAIDs are known to be inhibitors of COX-1 and COX-2 enzyme activity, thereby rapidly diminishing the expression of different cytokines, chemokines, and growth factors in the aqueous humor following surgical intervention. Decades ago, NSAIDs were considered to be a routine treatment regimen for inhibition of surgically induced pupillary miosis.[19,20] Recently, with the development of new technologies and shortened surgical time, the need for NSAIDs has significantly decreased. However, the concern has been revisited with the introduction of FLACS.[8,21]

Elevated prostaglandin levels after FLACS is a known phenomenon[3] and NSAIDs inhibit prostaglandin levels.[22,23] Elevated cytokine levels are attributed to breakdown of the blood–aqueous barrier and may correlate with iris damage.[24] Others have shown that concentrations of IL-1β, IL-6, and PGE2 in aqueous humor increase during FLACS compared to controls.[5] To our knowledge, to date, no studies have compared the effectiveness of different NSAIDs (bromfenac and indomethacin) for FLACS correlating intraoperative pupil dynamics to aqueous humor cytokine levels.

All currently available, topical ophthalmic NSAIDs (eg, ketoralac, bromfenac, nepafenac, diclofenac, and indomethacin) reduce levels of prostaglandin E2, a significant component of ocular inflammation.[25] Indomethacin has a unique effect on COX-2 compared to bromfenac and amfenac, resulting in less retinal vascular leakage,[26] but their effects during FLACS have not been studied.

It remains unknown which type of NSAID best inhibits intraoperative iris smooth muscle contraction, causing clinically significant miosis. Use of the two different generation NSAIDs (bromfenac 0.09% and indomethacin 0.1%) is standard preoperative care in our institute in the regimens used for this study.

There is interest in exploring underlying biological mechanisms of various processes potentiated by therapeutic agents and surgical interventions.[27] Multiple analysis of simultaneous measurements of many clinically relevant samples, despite limited volume, critically contribute to our understanding of disease processes and drug interaction. The methods employed in this study quantified 11 cytokines: pro-inflammatory, anti-inflammatory, and immunomodulatory factors from the anterior chamber aqueous humor samples. Besides the correlation network, a cluster analysis elucidated the hierarchy of the correlative interactions between the studied cytokines and defined the differences in metabolic interactions. IL-6 appears to be the most prominent cytokine detected in our analysis; it can be viewed as a biomarker for the cytokine imbalance caused by the surgical intervention.

To define the functional difference between the preoperative NSAIDs' effects, pupillary size was evaluated at various time points. Greater progressive pupillary constriction was observed in the indomethacin treatment groups correlating with observed cytokine imbalance.

Our study demonstrates an increase in the indicators reflecting IL-6 content alone among the cytokines tested, thus showing NSAIDs' potential to neutralize prostaglandin inflammatory mediators activated by femtosecond laser application.[22,23] Of the two NSAIDs tested, bromfenac proved more potent in maintaining mydriasis, presumably due to superior efficacy in excluding IL-6 from the correlation network of cytokines.

We conclude that indomethacin and bromfenac effectively neutralize the release of pro-inflammatory cytokines and the disruption of the balance between pro-inflammatory and anti-inflammatory cytokines. However, indomethacin is not effective in completely neutralizing the activation of IL-6 and its correlation to intraoperative pupil size.

Our study of correlation networks reveals that, compared to indomethacin, bromfenac preoperative treatment is a more potent neutralizer of pro-inflammatory factors. This is associated with a reduction in correlation dependence of IL-6 to the cytokine network and results in better maintenance of intraoperative mydriasis. The higher the IL-6 concentration measured in the aqueous humor, the smaller the intraoperative pupil size.

There is currently no consensus on which NSAIDs, especially those with mostly similar chemical structures, most effectively prevent progressive intraoperative miosis during cataract surgery. Many studies show the relative effectiveness of some NSAIDs over others,[28] whereas other studies contradict those same claims.[29] Intraocular availability and interindividual variability of NSAIDs' pharmacokinetics play a key role in drug effectiveness. Moreover, the complete mechanism of NSAIDs' interaction with the metabolic system is undefined. The interactions in key biologic agents potentiating the miotic effect of surgical intervention have yet to be discovered.

There are limitations to this study. Aqueous humor was obtained at a different time point in the FLACS and corneal paracentesis groups. This was unavoidable due to the need to inject an ophthalmic viscosurgical device prior to opening the anterior capsule in the corneal paracentesis groups.

The cytokine data dispersion may be due to errors in material storage, drying, or sublimation of intraocular fluid samples. Reaction of the cytokine system to surgical trauma is highly variable in the population. There may be other unknown factors.

A key challenge remains, aided by novel approaches and correlation network analysis, to further define the inflammatory response and the impact of single factors on anterior segment parameters in FLACS. We highlight the variable points in the cytokine networks known to have an impact on iris constriction.

AUTHOR CONTRIBUTIONS

Study concept and design (NSA, LBA, BP, SAB, BEM); data collection (NSA, SVP, NPS, YAK); analysis and interpretation of data (NSA, GP); writing the manuscript (NSA); critical revision of the manuscript (NSA, LBA, GP, SVP, NPS, BP, SAB, YAK, BEM); statistical expertise (NSA, BP)

REFERENCES

1. Popovic M, Campos-Möller X, Schlenker MB, Ahmed IIK. Efficacy and safety of femtosecond laser-assisted cataract surgery compared with manual cataract surgery: a meta-analysis of 14 567 eyes. *Ophthalmology*. 2016;123:2113-2126.
2. Chen H, Lin H, Zheng D, Liu Y, Chen W, Liu Y. Expression of cytokines, chemokines and growth factors in patients undergoing cataract surgery with femtosecond laser pretreatment. *PloS One*. 2015;10:e0137227.
3. Schultz T, Joachim SC, Kuehn M, Dick HB. Changes in prostaglandin levels in patients undergoing femtosecond laser-assisted cataract surgery. *J Refract Surg*. 2013;29:742-747.
4. Schultz T, Joachim SC, Stellbogen M, Dick HB. Prostaglandin release during femtosecond laser-assisted cataract surgery: main inducer. *J Refract Surg*. 2015;31:78-81.
5. Wang L, Zhang Z, Koch DD, Jia Y, Cao W, Zhang S. Anterior chamber interleukin 1β, interleukin 6 and prostaglandin E2 in patients undergoing femtosecond laser-assisted cataract surgery. *Br J Ophthalmol*. 2016;100:579-582.
6. Jun JH, Hwang KY, Chang SD, Joo CK. Pupil-size alterations induced by photodisruption during femtosecond laser–assisted cataract surgery. *J Cataract Refract Surg*. 2015;41:278-285.
7. Schoenberger SD, Kim SJ, Sheng J, Calcutt MW. Reduction of vitreous prostaglandin E2 levels after topical administration of ketorolac 0.45%. *JAMA Ophthalmol*. 2014;132:150-154.
8. Jun JH, Yoo YS, Lim SA, Joo CK. Effects of topical ketorolac tromethamine 0.45% on intraoperative miosis and prostaglandin E_2 release during femtosecond laser–assisted cataract surgery. *J Cataract Refract Surg*. 2017;43:492-497.
9. Jha R, Sur V, Bhattacharjee A, Ghosh T, Kumar V, Konar A, Hazra S. Intracameral use of nepafenac: safety and efficacy study. *Curr Eye Res*. 2017;43:630-638.
10. Rodríguez-García A, Hernández-Camarena JC, López-Jaime GR, Nava-García JA. Effect of topical nonsteroidal anti-inflammatory drugs on pupillary size during uncomplicated cataract surgery. *J Refract Surg*. 2017;33:236-242.
11. Wielders LH, Schouten JS, Aberle MR, et al. Treatment of cystoid macular edema after cataract surgery. *J Cataract Refract Surg*. 2017;43:276-284.
12. Balguri SP, Adelli GR, Majumdar S. Topical ophthalmic lipid nanoparticle formulations (SLN, NLC) of indomethacin for delivery to the posterior segment ocular tissues. *Eur J Pharm Biopharm*. 2016;109:224-235.
13. Bertens CJF, Gijs M, Nuijts RMMA, van den Biggelaar FJHM. Topical drug delivery devices: a review. *Exp Eye Res*. 2018;168:149-160.
14. Nagai N, Ito Y, Okamoto N, Shimomura Y. A nanoparticle formulation reduces the corneal toxicity of indomethacin eye drops and enhances its corneal permeability. *Toxicology*. 2014;319:53-62.
15. Dinarello CA. Proinflammatory cytokines. *Chest*. 2000;118:503-508
16. Barabasi AL, Oltvai ZN. Network biology: understanding the cell's functional organization. *Nat Rev Genet*. 2004;5:101-113.
17. Bastos MS, Coelho-Oos-Reis JG, Zauli DAG, et al. Divergent cerebrospinal fluid cytokine network induced by non-viral and different viral infections on the central nervous system. *BMC Infect Dis*. 2015;15:345.
18. Chylack LT Jr, Wolfe JK, Singer DM, et al. The lens opacities classification system III: the longitudinal study of Cataract Study Group. *Arch Ophthalmol*. 1993;111:831-836.
19. Duffin RM, Camras CB, Gardner SK, Pettit TH. Inhibitors of surgically induced miosis. *Ophthalmology*. 1982;89:966-979.
20. Keulen-de Vos HCJ, Van Rij G, Renardel de Lavalette JCG, Jansen JTG. Effect of indomethacin in preventing surgically induced miosis. *Br J Ophthalmol*. 1983;67:94-96.
21. Diakonis VF, Yesilirmak N, Sayed-Ahmed IO, et al. Effects of femtosecond laser-assisted cataract pretreatment on pupil diameter: a comparison between three laser platforms. *J Refract Surg*. 2016;32:84-88.
22. Kiss HJ, Takacs AI, Kranitz K, et al. One-day use of preoperative topical nonsteroidal anti-inflammatory drug prevents intraoperative prostaglandin level elevation during femtosecond laser-assisted cataract surgery. *Curr Eye Res*. 2016;41:1064-1067.
23. Schultz T, Joachim SC, Szuler M, Stellbogen M, Dick HB. NSAID pretreatment inhibits prostaglandin release in femtosecond laser-assisted cataract surgery. *J Refract Surg*. 2015;31:791-794.
24. Aketa N, Yamaguchi T, Suzuki T, Higa K, et al. Iris damage is associated with elevated cytokine levels in aqueous humor. *Invest Ophthalmol Vis Sci*. 2017;58:42-51.
25. Hoffman RS, Braga-Mele R, Donaldson K, et al. Cataract surgery and nonsteroidal antiinflammatory drugs. *J Cataract Refract Surg*. 2016;42:1368-1379.
26. Bucolo C, Marrazzo G, Platania CB, Romano GL, Drago F, Salomone S. Effects of topical indomethacin, bromfenac and nepafenac on lipopolysaccharide-induced ocular inflammation. *J Pharm Pharmacol*. 2014;66:954-960.
27. Bastarache JA, Koyama T, Wickersham NE, Mitchell DB, Mernaugh RL, Ware LB. Accuracy and reproducibility of a multiplex immunoassay platform: a validation study. *J Immunol Methods*. 2011;367:33-39.
28. Psilas K, Kalogeropoulos C, Loucatzicos E, Asproudis I, Petroutsos G. The effect of indomethacin, diclofenac and flurbiprofen on the maintenance of mydriasis during extracapsular cataract extraction. *Doc Ophthalmol*. 1992;81:293-300.
29. Dimitrakos SA, Topouzidis C, Panidou-Kyriakidou I. Prevention of peroperative miosis: comparison between prostaglandin inhibitors: sodium diclofenac and indomethacin in local application [article in French]. *J Fr Ophtalmol*. 1992;15:5-8.

Copyright © SLACK Incorporated

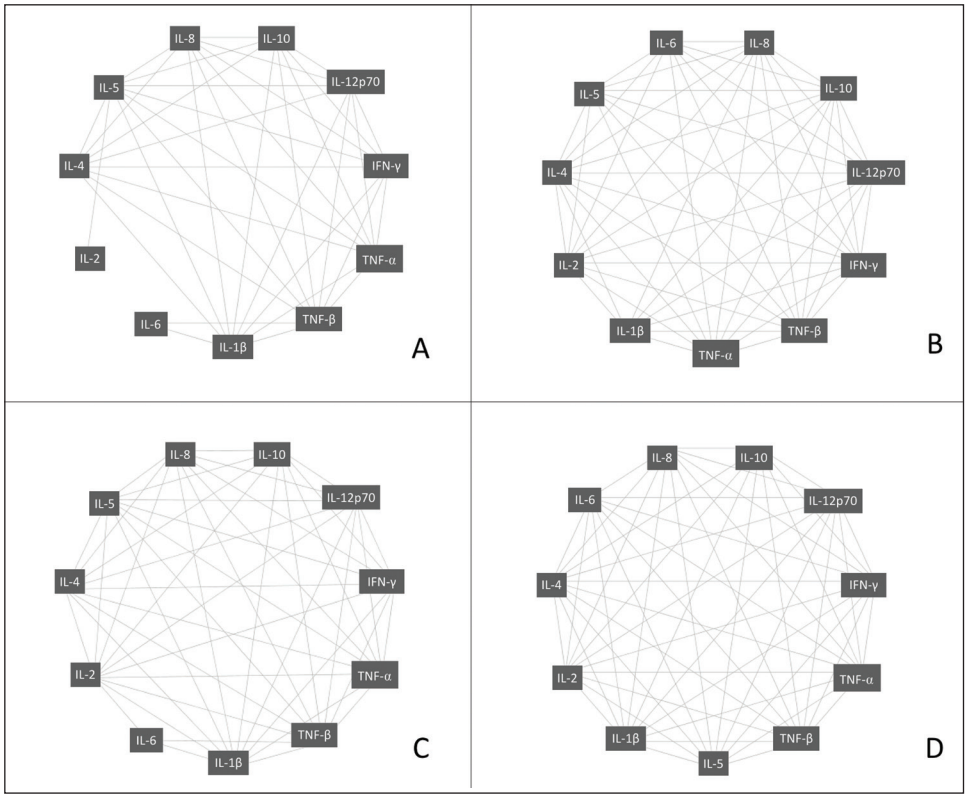

Figure A. Correlation networks of various cytokines using a > 0.5 Spearman correlation coefficient. (A) Femtosecond laser–assisted cataract surgery (FLACS) procedure using bromfenac 0.09% preoperatively. (B) FLACS procedure using indomethacin 0.1% preoperatively. (C) Corneal mechanical paracentesis procedure using bromfenac 0.09% preoperatively. (D) Corneal mechanical paracentesis procedure using indomethacin 0.1% preoperatively. IL = interleukin; IFN = interferon, TNF = tumor necrosis factor

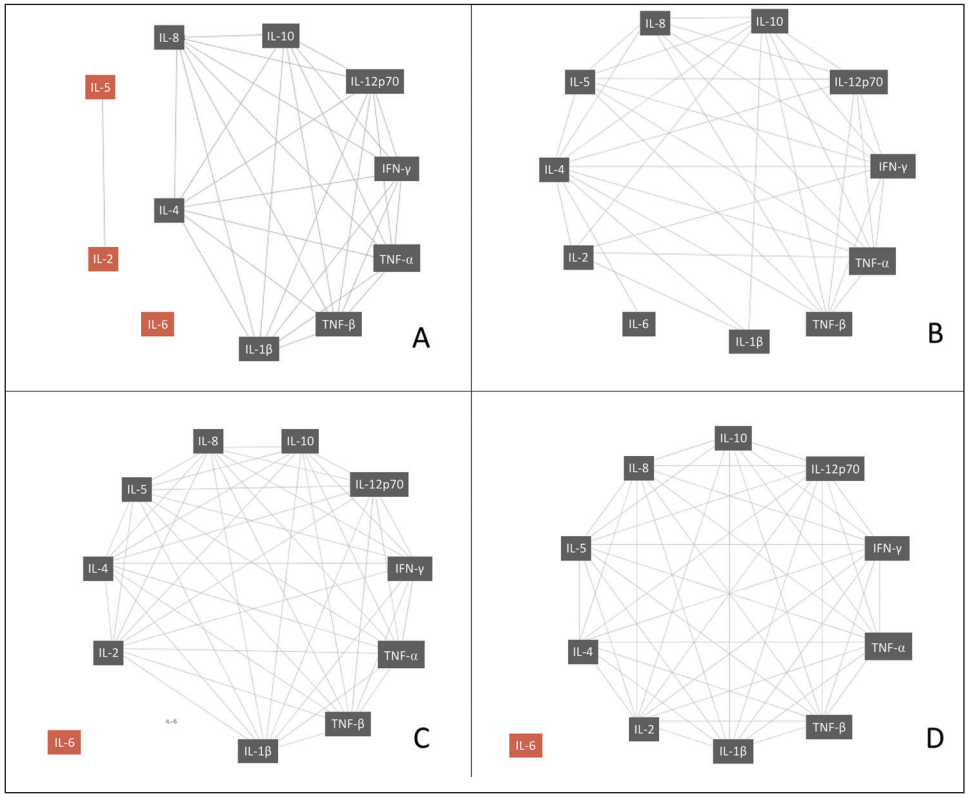

Figure B. Correlation networks of various cytokines using a > 0.7 Spearman correlation coefficient. Red boxes show cytokines that are out of the correlation network. (A) Femtosecond laser–assisted cataract surgery (FLACS) procedure using bromfenac 0.09% preoperatively. (B) FLACS procedure using indomethacin 0.1% preoperatively. (C) Corneal mechanical paracentesis procedure using bromfenac 0.09% preoperatively. (D) Corneal mechanical paracentesis procedure using indomethacin 0.1% preoperatively. IL = interleukin; IFN = interferon, TNF = tumor necrosis factor