UNIVERSITY OF MODENA AND REGGIO EMILIA

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Quantitative analysis of intraocular inflammation after cataract surgery: a laser flare photometry study

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SUMMARY

Abbreviation

AC	Anterior Chamber
ARI	Aqueous-to-air Relative Intensity
AS-OCT	Anterior Segment Optical Coherence Tomography
BCVA	Best Corrected Visual Acuity
BVD	Bromfenac Versus Dexamethasone Study
CME	Cystoid Macular Edema
CMT	Central Macular Thickness
COX	Cyclo-oxigenase
ECCE	Extracapsular Cataract Extraction
ELISA	Enzyme-Linked Immunosorbent Assay
ESCRS	European Society of Cataract and Refractive Surgery
ICCE	Intracapsular Cataract Extraction
IOL	Intraocular Lens
IOP	Intraocular Pressure
LFCP	Laser Flare and Cell Photometry
LFP	Laser Flare Photometry
LOCS	Lens Opacities Classification System
MAR	Minimum Angle of Resolution
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
OCGA	Ocular Comfort Grading Assessment
OCT	Optical Coherence Tomography
PCME	Pseudophakic Cystoid Macular Edema
PEX	Pseudoexfoliatio
PG	Prostaglandin
PREMED	Prevention of Macular Edema After Cataract Surgery
QID	Four Times a Day
SD-OCT	Spectral Domain Optical Coherence Tomography
SUN	Standardize Uveitis Nomenclature
VEGF	Vascular Endothelial Growth Factor
VIT/RPE	Vitreous/Retinal Pigment Epithelium-relative intensity

Chapter 1

Abstract (English version)

Aims and scope

1. To review the literature for evidence of a correlation between quantitative analysis of AC inflammation and the risk of CME development after cataract surgery;
2. To adopt the laser flare photometry (LFP) to obtain a quantitative and non-invasive assessment of the anterior chamber inflammation;
3. To compare the effectiveness of single therapy with NSAIDs versus corticosteroids in controlling intraocular inflammation after uncomplicated cataract surgery.

Methods

Objective 1. We searched the PubMed database for peer-reviewed publications on AC inflammation after phacoemulsification. Keywords included: cataract surgery, cystoid macular edema, AC inflammation, laser flare and cells photometry, anterior segment optical coherence tomography (AS-OCT) and aqueous sample.

Objective 2, 3. A phase IV, single center, randomized, active-control, parallel design, open-label trial was conducted to compare a two-week therapy with topical Dexamethasone 0.1% (group 1) and Bromfenac 0.09% (group 2) after phacoemulsification. LFP was used to quantify AC inflammation and optical coherence tomography (OCT) to measure the central macular thickness (CMT) at 30 days. Subsequently, the follow-up was extended at 3 and 6 months to analyze the AC inflammation and the CMT in a long-term follow-up.

Results

Objective 1. 187 papers were identified. Inflammation was assessed by clinical grading 51%, by LFP in 42% and by aqueous humor sample in 4%. Sixteen (9%) studies investigated AC inflammation and macular changes by OCT (7%) or fluorescein angiography (2%), and a correlation between them was confirmed in 7 studies, not documented in 2 studies, and not examined in the other 7.

Objectives 2, 3. Seventy-six patients (37 in group 1; 39 in group 2) with only a senile cataract have been enrolled. Bromfenac was equivalent to dexamethasone to treat inflammation. LFP values increased the day after surgery and progressively decreased after starting the therapies, with no return at baseline and no statistically significant difference at all time points between the groups. The mean CMT was higher in group 1 at one month after surgery ($p = 0.0467$). The proportion of patients with CMT > 300 microns at day 30 did not differ between treatment groups.

LFP demonstrated persistent AC inflammation at days 90 and 180 in group 1, but not in group 2 that achieved a statistically significant reduction along with the follow-up ($p < 0.001$). The CMT increase

at days 90 and 180 was statistically significant in group 1 but not in group 2, where it decreased to levels similar to baseline. Dexamethasone showed a higher mean CMT compared to bromfenac along with the follow-up ($p < 0.001$). The proportion of patients that developed CME was 14% (n = 5) and 0% (n=0) in the Dexamethasone and Bromfenac group, respectively ($p = 0.02$). The bivariate analysis demonstrated a positive correlation between LFP and CMT in group 1 but not in group 2.

Conclusion

Objective 1. LFP can quantify shallow inflammation amount and correlates with the frequency of CME postoperatively. The adoption of LFP after phacoemulsification can potentially predict the risk of CME and may help to titrate duration and intensity of therapy properly.

Objectives 2, 3. Bromfenac and dexamethasone are equivalent in reducing inflammation measured by LFP, which revealed subtle aspects not clinically detectable. LFP values increase after surgery and significantly decreased after starting therapy in both groups, but did not recover to the baseline one month after surgery. Long-term LFP analysis showed a persistent inflammation from 30 days up to 3 months in a significant proportion of patients. This long-lasting reaction might explain the occurrence of CME several weeks after phacoemulsification probably because of a prolonged subclinical inflammation but clinically unremarkable.

Keywords: cataract surgery, inflammation, laser photometry, macular edema, anti-inflammatory

Abstract (Italian version)

Titolo in italiano:
ANALISI DELL'INFIAMMAZIONE INTRAOCULARE DOPO CHIRURGIA DELLA CATARATTA: UNO STUDIO CON LASER FLARE PHOTOMETRY

Scopo

1. Review della letteratura per identificare correlazione tra analisi quantitativa dell'infiammazione intraoculare e il rischio di sviluppare edema maculare dopo intervento di cataratta;

2. Adottare la fotometria laser flare (LFP) per ottenere una valutazione quantitativa e non invasiva dell'infiammazione in camera anteriore dopo chirurgia della cataratta;

3. confrontare l'efficacia della monoterapia con FANS rispetto ai corticosteroidi nel controllo dell'infiammazione dopo facoemulsificazione.

Materiale e Metodi

Obiettivo 1. Ricerca nel database PubMed di pubblicazioni peer-reviewed sull'infiammazione dopo facoemulsificazione secondo le parole chiave: cataract surgery, cystoid macular edema, AC inflammation, laser flare and cells photometry, anterior segment optical coherence tomography and aqueous sample.

Obiettivo 2, 3. Condurre uno studio di fase IV, monocentrico, randomizzato, active-control, parallel design, open label, per confrontare una terapia di due settimane con desametasone topico 0.1% (gruppo 1) vs Bromfenac 0.09% (gruppo 2) dopo facoemulsificazione. A 30 giorni, l'infiammazione è stata analizzata con LFP e lo spessore maculare con OCT.

Successivamente, il follow-up è stato esteso a 3 e 6 mesi per analizzare l'infiammazione e il CMT a lungo termine.

Risultati

Obiettivo 1. Sono stati identificati 187 articoli. L'infiammazione è stata valutata mediante classificazione clinica nel 51%, LFP nel 42% e campione di umor acqueo nel 4%. Sedici studi (9%) hanno inoltre esaminato le alterazioni maculari mediante OCT (7%) o angiografia con fluoresceina (2%), ed una correlazione è stata confermata in 7 studi, non documentata in 2 studi e non esaminata negli altri 7.

Obiettivi 2, 3. Sono stati arruolati 76 pazienti (37 nel gruppo 1; 39 nel gruppo 2) candidati ad intervento di cataratta senile. Il bromfenac era equivalente al desametasone per ridurre l'infiammazione. I valori di LFP sono aumentati il giorno dopo l'intervento e sono progressivamente diminuiti dopo l'inizio delle terapie, senza ritorno al basale in assenza di differenze statisticamente significative nel follow-up. A 30 giorni, il CMT medio era maggiore nel gruppo 1 ($p = 0.0467$), ma la proporzione di pazienti con CMT > 300 micron non differiva tra i gruppi.

Il LFP ha dimostrato un'infiammazione persistente ai giorni 90 e 180 nel gruppo1, ma non nel gruppo2 che ha ottenuto una riduzione statisticamente significativa nel follow-up ($p < 0.001$). L'aumento della CMT ai giorni 90 e 180 è stato statisticamente significativo nel gruppo1 ma non nel gruppo2, dove è diminuito a livelli simili al basale. Il CMT medio era più alto nel gruppo1 rispetto al gruppo2 nel follow-up($p < 0.001$). La percentuale di pazienti che hanno sviluppato CMO è stata del 14% ($n = 5$) e dello 0% ($n = 0$) rispettivamente nel gruppo 1 e 2 ($p = 0.02$). L'analisi bivariata ha dimostrato una correlazione positiva tra LFP e CMT solo nel gruppo1.

Conclusione

Obiettivo 1. LFP consente un'analisi quantitativa dell'infiammazione intraoculare e correla con la frequenza di CMO dopo l'intervento. L'utilizzo di LFP dopo la facoemulsificazione permette di predire il rischio di CMO e consente di titolare adeguatamente durata e intensità della terapia antiinfiammatoria.

Obiettivi 2, 3. Bromfenac e desametasone sono equivalenti nel ridurre l'infiammazione misurata con LFP. I valori di LFP aumentano dopo l'intervento chirurgico e diminuiscono significativamente dopo l'inizio della terapia in entrambi i gruppi, ma non ritornano al valore basale un mese dopo l'intervento. L'analisi LFP a lungo termine ha evidenziato un'infiammazione persistente da 30 giorni fino a 3-6 mesi in una percentuale significativa di pazienti. Questa reazione di lunga durata potrebbe spiegare il verificarsi di CMO diverse settimane dopo la facoemulsificazione, probabilmente a causa di un'infiammazione subclinica prolungata ma clinicamente non rilevabile.

Parole chiave: cataratta, infiammazione, laser photometry , edema maculare, anti-infiammatori

Chapter 2

GENERAL INTRODUCTION

MODERN CATARACT SURGERY: CURRENT TRENDS

Cataract is the opacification of the crystalline lens of the eye and represents the world's leading cause of reversible blindness. It is a multifactorial disease associated with age, female sex, genetic predisposition, smoking, diabetes, drugs and environmental exposure to UVB radiation.[1]

Although 90% of cataracts in the world are reported in developing countries, its social, physical and economic impact is substantial also in the developed world.[2,3]

A cataract is a common cause of visual impairment in the elderly. Still, patients in their working-age may notice it at an early stage, and surgery is mandatory to restore normal vision.

Cataract surgery remains a major healthcare cost in Europe and other Western countries. [4] The progressive ageing of the European population is linked to the increase of incidence and prevalence of cataract. In the European Union, the proportion of elderly (> 65 years) is projected to increase from 20.3% (90.5 million) at the start of 2019 to 31.3% (130.2 million) by the end of 2100.[5] These numbers demonstrate that cataract extraction will continue to be one of the most commonly performed procedures in our increasingly ageing population, and demand for intervention will continuously increase with a challenge for proper management in the future.[6]

Through the years, cataract surgery has witnessed a constant evolution both for techniques and the equipment, becoming one of the most cost-effective procedures in medicine. Cataract surgery has evolved from an extremely invasive procedure (like ICCE, Intracapsular Cataract Extraction[7] and ECCE, Extracapsular Cataract Extraction[8]) with a high rate of complications, elevated hospitalization cost and poor visual outcomes to a minimally invasive procedure (phacoemulsification[9] with intraocular lens implantation) with fast recovery, excellent refractive and functional results, and reduced costs for the health care systems.[10]

Despite the extraordinary advances in surgical techniques and equipment of modern cataract surgery, preventing and managing postoperative ocular inflammation remain a challenge for ophthalmologists worldwide.

Like after every surgical procedure, postoperative inflammation following phacoemulsification with IOL implantation is a common and expected occurrence. It is usually easily managed and of limited clinical impact. However, in a subset of patients, postoperative inflammation can be severe and prolonged, causing Cystoid Macula Edema (CME) with visual disability and requiring aggressive and, sometimes, extended therapy.

Moreover, no substantial evidence exists between the inflammation amount in the anterior chamber after uneventful phacoemulsification and the risk of CME. Besides, no widely accepted guideline on

the treatment of inflammation and prevention of CME have been published. Finally, shadows exist on the proper post-operative treatment after uncomplicated phacoemulsification.[11]

Inflammation and Cystoid Macular Edema (CME)

The exact pathogenesis of inflammation after cataract surgery is not well established. It is thought that it begins with tissue injury when the first surgical incision at the clear cornea is performed.

Surgical trauma and manipulation within the anterior chamber (Figure 1) lead to the release of arachidonic acid from uveal tissue, with the production of leukotrienes (via the lipoxygenase pathway) or prostaglandins (PGs) (via the cyclooxygenase (COX) pathway). These molecules disrupt the blood-aqueous barrier, resulting in the accumulation of PGs and other mediators of inflammation such as endotoxin, immune complex, and cytokines in the aqueous humor.[12]

Inflammatory mediators diffuse from the aqueous humor to the vitreous and reach the retina (Figure 1), where they trigger the disruption of the blood-retinal barrier. Thus, such mediators alter the permeability of retina capillaries and serum leaks from the blood vessels and pools in the retinal tissue. When the serum accumulates within the retinal layers with the formation of cysts, the condition can be identified as Pseudophakic Cystoid Macular Edema (PCME).[13]

PCME, also known as the Irvine-Gass syndrome, was first reported by Irvine in 1953 and discussed by Gass and Norton in 1966.[14,15] Although PCME was described many years ago, its pathogenesis remains uncertain and a multitude of mechanisms have been proposed such as inflammation, vascular instability, vitreomacular tractions, and light toxicity.[15–17] It is not clear why the fluid leaking from the perifoveal capillaries accumulates exclusively within the macula, despite the massive production and distribution of inflammatory cytokines throughout the retina. The reduced fluid reabsorption from the macula may be explained, at least in part, by the absence of blood vessels within the avascular zone combined with the high metabolic activity of the fovea.[18]

Patients with marked postoperative inflammation tend to develop PCME more frequently than others with a normal recovery after surgery.[17] This observation implies that the degree of inflammation may have a crucial role in determining the severity of PCME, which can range from very mild to clinically significant forms. Moreover, as postoperative inflammation is intrinsic to each phacoemulsification procedure, non-complicated cases also show a subclinical increase in central macular thickness (CMT).

Several studies reported a significant increase in CMT measured by Optical Coherence Tomography (OCT) between 1 and 6 months postoperatively and a progressive reduction to the baseline within the first 3 months. No consequences on visual acuity have been reported in the absence of cysts within the retinal layers. Moreover, the more complicated the surgery, the higher the CMT risk.[19–22] However, it is still obscure why patients developed intraretinal cysts with or without visual symptoms.

Cystic changes of the macula after cataract surgery are reported up to 70% in some studies with fluorescein angiography.[23,24] Subclinical pseudophakic CME (with no visual symptoms for the patients) ranges from 4% to 11% diagnosed by OCT[19,25,26]. Clinically significant CME (with a transient o permanent visual impairment) varies between 1% and 4% according to various studies.[24,25,27] It has been widely demonstrated that ocular and non-ocular conditions are associated with a greater pro-inflammatory state after cataract extraction with a consequent increased risk of developing CME. Systemic diseases (diabetes[23,24,28,29], hypertension[23]), intraoperative complications (posterior capsule rupture[24] with or without vitreous loss[23], iris trauma[30]), and pre-existing ocular comorbidities (uveitis[24,25], diabetic retinopathy[27], history of vein occlusion[27], macular epiretinal membranes[27], previous retinal detachment[24], pseudoexofliation[31]) show a greater incidence of pseudophakic CME development after phacoemulsification.

Despite the continuous improvement of cataract surgery with excellent visual outcomes for patients, PCME remains a challenge for the ophthalmologist. Moreover, according to the current knowledge, it is difficult to establish a direct correlation between the inflammation amount the risk of CME development.

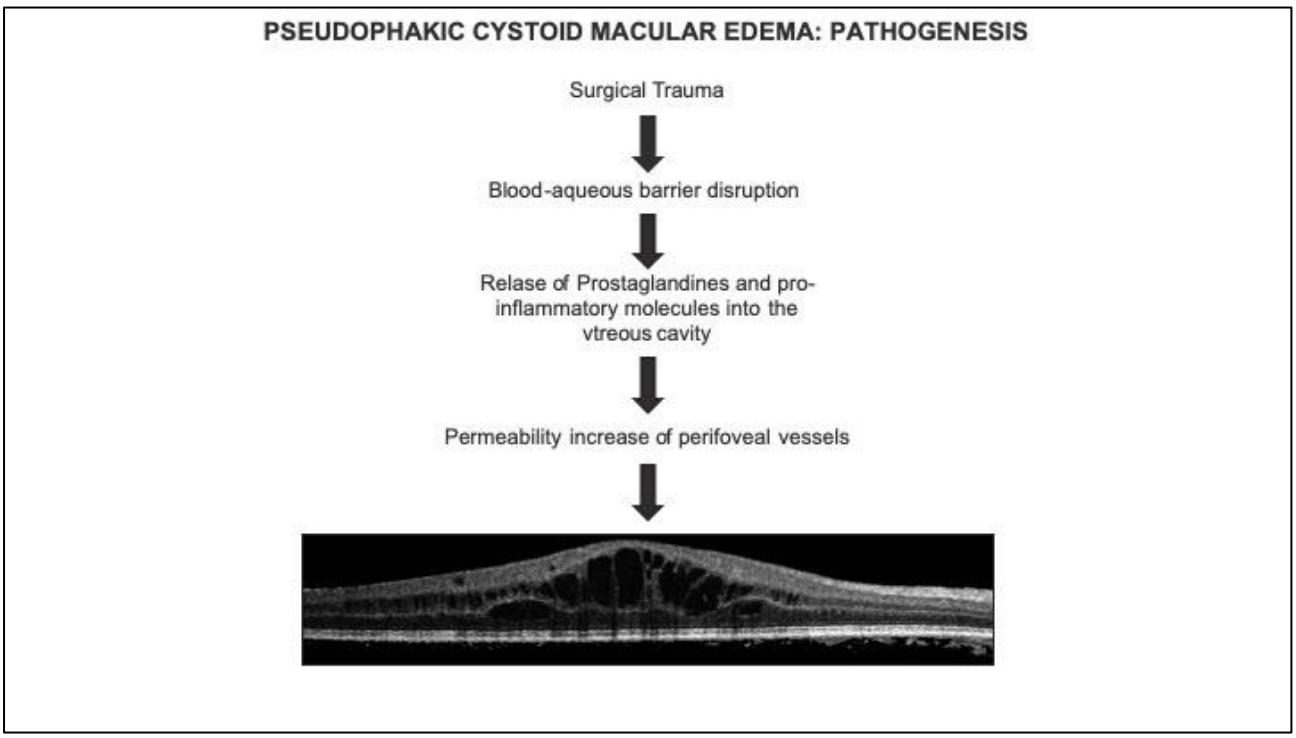

Figure 1. Pathogenesis of pseudophakic Cystoid Macular Edema

PSEUDOPHAKIC CYSTOID MACULAR EDEMA: PREVENTION AND TREATMENT

Treatment options of PCME reflect the various postulated mechanisms for macular edema formation. In general, corticosteroids and topical Non-Steroidal Anti-inflammatory Drugs (NSAIDs) (Table 1), either as single or combined therapy, are used as a first-line treatment approach. When ineffective, intravitreal/subtenonian injection of corticosteroids or intravitreal injection of anti-vascular endothelial growth factor agents represent the second line.[32–36]

Corticosteroids block the synthesis of PGs and leukotrienes by inhibiting phospholipase A2 in the arachidonic acid cascade. In addition, they also impede macrophage and neutrophil migration and decrease capillary permeability and vasodilation, facilitating the fluid reabsorption.[37] For years, ophthalmologists worldwide treated PCME with different formulations of corticosteroids.

NSAIDs act by inhibiting the COX2 enzymes that catalyze the biosynthesis of eicosanoids from arachidonic acid to produce PGs and thromboxanes.[37] COX-2 is an inducible isoform of COX enzymes, expressed primarily to inflammatory responses.[38]

Recently, topical non-steroidal anti-inflammatory drugs (NSAIDs) have received attention as possible adjuncts or substitutes of ophthalmic steroids[3], thanks to their better pharmacological profile than steroidal eye drops. Topical steroids are very well-known for their side effects: they can increase intraocular pressure, delay corneal healing and predispose to ocular infections or virus reactivation. [39,40] NSAIDs demonstrated to be useful to counterfeit the postoperative inflammation associated with cataract surgery with no relevant side effects. They are more successful than steroids at reestablishing the blood-aqueous barrier (BAB) and seems to be useful both to cure and prevent CME.[38]

Currently, ophthalmologists have two strategies after cataract surgery. Some prescribe only topical steroids in addition to the antibiotic eye drops. Others try to increase the efficacy of the postoperative treatment prescribing both steroids and NSAIDs. This strategy exposes patients not only to the potential side effects of the steroids (glaucoma, healing defects, and infections) but also to increased costs. The combination of three eye drops (antibiotic, steroidal and NSAIDs) very often causes very poor compliance and/or reduced efficacy. Patients may be unwilling of using so many eye drops, or they can miss some administrations along the day. When they put all the eye drops at the same time, there is a relevant “washing effect” with scarce penetration of the drugs into the ocular tissues. Finally, newer topical NSAIDs can be given only once or twice per day while steroids are usually recommended QID and then tapered.

It was argued that the greater therapeutic effect of NSAIDs plus corticosteroids is due to the additive rather than the synergistic effect of two anti-inflammatory drugs.[38] The latter subject is presently a topic of debate between those who advocate the standard use of NSAIDs in all cataract operations and those who support their use only in high-risk cases. However, since many PCME cases are mild

and resolve spontaneously, accurately estimating the therapeutic benefits of the available anti-inflammatory drugs is challenging. In the past, several studies investigated the prophylactic or therapeutic effect of steroids and NSAID, alone or in combination. However, discordant results have been found because of the differences in methodology about the diagnosis (clinical, fluorescein angiography, OCT) and classification of PCME (clinically significant, asymptomatic subclinical), treatment schedule (preoperative, postoperative), compared substances (different pharmacokinetic and pharmacodynamic properties) and preexisting comorbidities (uveitis, pseudoexfoliation, diabetes).[33,41–43]

Currently, the most recent update on treatment and prevention of PCME derive from the publication of the PREMED (Prevention of Macular Edema After Cataract Surgery) study. The European Society of Cataract and Refractive Surgeons funded a 2-year, multicenter, double-blind, randomized study, which started recruiting patients in 2013 and provided evidence-based results for PCME prevention and treatment after cataract surgery in patients without (report 1)[44] and with diabetes (report 2)[45]. The PREMED report 1 demonstrated that patients treated with a combination of topical bromfenac 0.09% and dexamethasone 0.1% had a lower risk for developing PCME after cataract surgery than patients treated with a single drug. Moreover, topical NSAIDs appear to be more effective than steroids in the prevention of macular edema after cataract extraction but failed to show differences between groups in terms of anterior segment inflammation.[44]

However, to date, no official approved strategy for PCME prevention after phacoemulsification with IOL implantation is available. The last Cochrane full systematic review[36] concluded that effect of NSAIDs in acute and chronic PCME remain unclear and need further investigation, aimed at highlighting a correlation between the impact of the molecule in reducing inflammation in the anterior chamber and the real risk of developing PCME in the follow-up.

Table 1. Ophthalmic corticosteroids and NSAID agents.

Ophthalmic Corticosteroid Agents	Ophthalmic NSAID* Agents
Prednisolone	Amfenac (Nepafenac)
Difluprednate	Ketorolac
Dexamethasone	Diclofenac
Fluorometholone	Bromfenac
Rimexolone	Flurbiprofen
Loteprednol	Indomethacin

*NSAID = Non-Steroidal Anti-inflammatory Drugs.

INFLAMMATION ASSESSMENT AFTER CATARACT SURGERY

Under normal conditions, the anterior chamber is an optically empty space. The optical clearness of the aqueous humor in the anterior chamber is preserved to allow optimal visual function. Under pathologic conditions or after any surgical procedure, the disruption of blood–ocular barriers leads to leakage of serum proteins into the anterior chamber as well as a spillover of inflammatory cells from the inflamed uveal tissues in the anterior segment. This phenomenon changes in the optical properties of the aqueous humor.

Slit-lamp biomicroscopy is traditionally used to evaluate the aqueous humor clearness. Cells in the aqueous humor appear as particles identified by backscattering light from the incoming beam. Increased protein content produces an optical phenomenon called flare or Tyndall effect, an optical phenomenon caused by the back-scattering of light by cloudy matters.[46]

Clinical Grading

Routinely, inflammation into di aqueous humor is evaluated by directly observing anterior chamber details at the slit lamp. Several classification systems based on the slit-lamp examination have been developed in an effort to standardize quantification of cells and flare in the anterior chamber by giving a numerical score based on the number of cells and cloudiness of flare observed.[47] In 2004, the First International Workshop on Standardization of Uveitis Nomenclature (Table 2) was held, and several terms were standardized to obtain objective and comparable data.[48]

Table 2. The SUN⁎ Working Group Grading Scheme for Anterior Chamber Cells[48]

Grade	Cells in Field†
0	<1
0.5+	1–5
1+	6–15
2+	16–25
3+	26–50
4+	>50
Grade	**Description of Flare**
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

⁎SUN = Standardization of uveitis nomenclature. †Field size is a 1 mm by 1 mm slit beam.

Whatever the standardization system is used based on slit-lamp examination, the evaluation of cells and flare remains subjective and imprecise. While grading of cells is semiquantitative, albeit short of defining a linear change, grading of flare is qualitative. The ability to interpret these parameters

depends on the experience of the examiner. Thus grading of flare based on this system is, in essence, qualitative, imprecise, and much more subject to intra- and interobserver variability. Confounding factors such as the intensity of slit beam (brightness of light) and darkness of the examination room may affect the interpretation of shallow grades of flare at the slit lamp, such as after uncomplicated phacoemulsification.

Laser Flare and Cell Photometry

Laser flare photometry (LFP) uses a laser beam that scans a measurement window projected into the anterior chamber. Light scattered by protein particles in the aqueous humor is detected by a photomultiplier and processed by a computer. The amount of back-scattered light is proportional to the concentration and size of proteins in the aqueous humor. The average of signals obtained from outside the measurement window (background signals) is subtracted from the signal coming from inside the measurement window, and the result is expressed in photon counts per millisecond (ph/ms). Current LFP adopts a semiconductor diode laser of 635 nm, a measurement window of the of 0.3 mm x 0.5 mm and a scanning time of 0.5 s. For cell count, two optical scanners operate in synchronization. A fixed volume (0.5 mm3) is scanned two-dimensionally by the laser beam. When the laser light passes across a large particle (an inflammatory cell, debris) a strong peak is produced, and the number of peaks in the fixed volume gives the number of cells. For both flare and cell count, usually, seven measurements are taken, the highest and lowest values are discarded, and the machine automatically calculates the mean and standard deviation of the remaining five readings. Patients do not complain of any discomfort during measurements. In eyes with central corneal opacity or very shallow anterior chamber, measurements cannot be done. Reliable measurements may not be obtained in eyes with extensive posterior synechiae or mature cataract due to increased background scattering of light. In laboratory studies, laser flare photometry values correlated well with protein concentrations in serial dilutions of protein solutions such as plasma or aqueous humor samples obtained from patients undergoing intraocular surgery.[49,50] Reproducibility and accuracy of laser flare and cell photometry measurements have been shown in several studies[49–54]. Coefficient of variation is less than 10%, and measurements are independent of the technician using the instrument.

Anterior Segment-OCT

Optical coherence tomography (OCT) is an imaging modality that allows high-resolution, cross-sectional imaging of the eye and that has revolutionized the diagnostics in ophthalmology of both anterior and posterior segment pathologies.

Recently, the necessity to obtain reliable and comparable data on inflammation, together with the refinement of anterior segment OCT hardware and software, has stimulated researchers to develop new systems of quantification of flare and cells into di anterior chamber.

Agrawal et al[55], in a prospective, nonrandomized, observational case series, evaluated the anterior chamber inflammatory reaction by anterior segment high-speed OCT in patients with uveitis. Hyperreflective spots suggesting the presence of cells in the AC from the OCT images were counted manually and by a custom made automated software using MATLAB (Mathworks, Natick, Massachusetts, USA) and correlated with clinical grading of anterior chamber cells using Standardization of Uveitis Nomenclature criteria. They demonstrated that anterior segment OCT can be used as an imaging modality in detecting AC inflammatory reaction in uveitis and also in eyes with decreased corneal clarity and compromised AC visualization, for example, attributable to corneal edema.

Similarly, Invernizzi et al[56] assessed the ability of swept-source OCT to measure anterior chamber inflammation (both flare and cells) objectively. Moreover, they compared OCT-derived inflammatory indices with standard techniques (LFP and clinical grading). Tomographic images were analyzed to count the AC cells and to calculate aqueous signal intensity in patients with uveitis. The absolute values were compared with the signal measured by the scan outside the eye, generating an optical density ratio (aqueous-to-air relative intensity [ARI] index). They demonstrated that patients with active uveitis had significantly higher ARI index compared with inactive uveitis and controls.

Additionally, the ARI index positively correlated with LFP measurement in the active uveitis subjects. Anterior chamber cell count and flare grading were more precise with OCT than clinical observation according to the SUN method. These findings demonstrate that Anterior segment SS-OCT could be used for a comprehensive assessment of AC inflammation, providing objective measurements of inflammatory cells and aqueous flare.

Despite the promising results, the adoption of anterior segment OCT to assess inflammation is still in its infancy since no approved software of analysis have been specifically designed, and no clinical trial in the field of cataract surgery have been published.

Aqueous Sample Analysis

The aqueous humor is a complex fluid and the number of known proteins that compose it is near to 900 different types.[57] It is well known that the proteome of the aqueous humor is of particular interest in eye diseases of the anterior chamber but, potentially, it may be altered in any ocular disease or after any surgical procedure. For example, aqueous humor proteins such as TGF-beta 1 and ceruloplasmin could distinguish between eyes with age-related macular degeneration and healthy controls.[58] A study that analyzed aqueous humor protein levels in patients following different types of glaucoma surgery found both a postoperative increase in overall protein concentration as well as differences in relative quantities of proteins depending on the type of glaucoma or surgery. Also, it

was postulated that differential changes in protein levels might explain the differences in risk of corneal decompensation following various glaucoma surgeries.[59]

As regard cataract surgery, the scenario is more complicated because, in regular patients, the aqueous humor is not inflamed. Murthy et al.[60] characterized the aqueous humor in 250 patients undergoing phacoemulsification, identifying a total of 763 proteins, of which 386 were newly discovered. They identified TGF-beta 2 and components of the complement pathway, angiogenic and anti-angiogenic proteins, and antioxidants such as glutathione and superoxide dismutase. High abundance proteins included enzymes involved in glycolysis, gluconeogenesis and pentose phosphate pathway, which most likely reflect the function of the aqueous to provide nourishment for the lens.[60] Even if fascinating findings, little is known about the actual protein composition of aqueous humor after cataract surgery.

Techniques of analysis include the enzyme-linked immunosorbent assay (ELISA) whose main limitation is the necessity 50-100 µl of aqueous humor for every single molecule to test. It is mandatory to specify that the maximum amount collectable with an aqueous sample is 0.15-0.20 ml, and it is not enough to examine a diverse number of molecules.[61] Alternative technologies allow the analysis of multiple proteins using a small amount of aqueous humor. Differently, multiplexed beads immunoassay[61] analyzes different mediators simultaneously in a single aqueous sample of 25-100 µl.[62–64] According to current knowledge, the concentration of IL-1β, IL-6, MCP-1, and VEGF are significantly higher in diabetic patients with CME, but the correlation has not yet been established in normal subjects.[65]

However, it is complicated to collect aqueous humor suitable for inflammation analysis after the surgical procedure. Generally, the aqueous sample is performed at the beginning of the surgery, before any other fluid is introduced in the anterior chamber. For this reason, the harvested fluid is not "inflamed" and not enriched with inflammatory mediators. To obtain fluid from the anterior chamber with a high expression and concentration of proinflammatory molecules, it would be necessary to perform an aqueous sample the day after surgery, and obviously, this is not free of risks and is unethical for the patients.

These technical problems have led to confusion in this field with no consistent results on the relevance of specific mediators in this definite condition.[62]

Chapter 3

RATIONALE AND OBJECTIVES

Despite the tremendous technological innovation and safety of modern phacoemulsification, it appears evident that the proper management of post-operative inflammation, from diagnosis to treatment, is still a topic of debate among ophthalmologist worldwide.

Inflammation after cataract surgery is difficult to assess because it is usually moderate and clinical observation with SUN grading is unsuitable for discriminating between minimum variation.

After cataract surgery, the necessity to adopt a quantitative method to assess postoperative inflammation seems to be mandatory to understand its complexity and how this phenomenon could influence the risk of post-operative complication.

To the best of current knowledge, uncontrolled inflammation after eye surgery increases the risk of postoperative complications, such as PCME. However, no evidence of a correlation has been published between the quantitative amount of inflammation after uncomplicated phacoemulsification and the risk of PCME development in the follow-up. Moreover, the current literature extensively evaluated macular changes depending on the type of post-operative therapy rather than effectively measure inflammation into the anterior chamber. Additionally, many papers presented a short follow-up from 1 to 3 months with no information on the natural course of the inflammatory response after cataract extraction in a long term follow-up.

Furthermore, the majority of the published studies analyzed the anti-inflammatory effect of ophthalmic steroids and NSAIDs to prevent or treat CME, principally measuring macular changes after surgery, more than quantitatively assessing the AC inflammatory response to the different types of therapy.

Finally, despite a large number of published papers on this topic, no widely accepted guidelines for the post-operative use of anti-inflammatory drugs have been published, and more evidence is needed to define the better therapeutic regimen to increase post-operative outcomes and reduce the risk of CME.

This thesis aims to shed light upon the current knowledge about the possible link between inflammation amount quantitatively measured by LFP and the risk of PCME analyzed with OCT. It proposes the adoption of LFP to measure the anti-inflammatory effect of a single therapy with NSAID or steroid after uncomplicated cataract surgery and to test the risk of CME in the long term follow-up depending on the type of drugs adopted.

The main objectives are summarized as follow:

1. To review the current literature for evidence of a correlation between quantitative analysis of AC inflammation and the risk of CME development after cataract surgery;
2. To adopt the laser flare photometry (LFP) to obtain a quantitative and non-invasive assessment of the anterior chamber inflammation;
3. To compare the effectiveness of single therapy with NSAIDs versus corticosteroids in controlling intraocular inflammation after uncomplicated cataract surgery and prevent the risk of PCME.

Chapter 4

Letter - J Cataract Refract Surg. 2018 Sep;44(9):1164.

Quantitative evaluation of anterior chamber inflammation after phacoemulsification in clinical trials

De Maria Michele, Coassin Marco, Mastrofilippo Valentina, Fontana Luigi

We read with interest the report from the European Society of Cataract and Refractive Surgeons (ESCRS) PREvention of Macular EDema after cataract surgery (PREMED) study by Wielders et al.[44] This large multicenter clinical trial clearly showed that the combination of topical bromfenac 0.09% and dexamethasone 0.1% lowered the risk for developing macular edema after cataract surgery in non-diabetic patients when compared to the same 2 drugs administered separately.

We noted that anterior chamber inflammation was not enlisted among the secondary outcomes in the methods section of the manuscript. Changes in inflammatory signs were reported in the Adverse Events paragraph in the results section. Postoperative inflammation was evaluated subjectively at the slitlamp by measuring aqueous flare and cells in the anterior chamber at 6 and 12 weeks according to the Standardization of Uveitis Nomenclature (SUN) classification.[48] The authors registered very low levels of inflammation in all treatment groups at all timepoints. We believe that although the SUN is a well-established and practical method to evaluate inflammation in uveitis, it might have a limitation in assessing the modest inflammatory response that usually follows uneventful phacoemulsification surgery.

An objective and precise measurement of anterior chamber flare would have been preferable in the evaluation of inflammation after cataract surgery. Laser flare photometry evaluates, by means of a diode laser, the light scattering from aqueous proteins and gives a quantitative measure of inflammation as photon counts per milliseconds. A highly significant linear relationship between laser flare intensity and protein concentration in the anterior chamber of the eye has been shown.[44] After ocular surgery, proteins and other molecules are released in the anterior chamber as result of blood–aqueous barrier breakdown.

We recently used laser flare photometry to evaluate ocular inflammation after cataract surgery in eyes with pseudoexfoliation syndrome.[31] In this clinical trial, we compared the effect of dexamethasone 0.1% eyedrops alone with that of combined treatment using bromfenac 0.09% and dexamethasone 0.1% for reducing postoperative inflammation. We found that compared with the single drug, the combined therapy was more effective in decreasing anterior chamber flare (by 31% at 3 days and by 43% at 7 days). Even if our study were not powered to measure the risk for developing postoperative macular edema, patients treated with bromfenac 0.09% and dexamethasone 0.1% had a significant

lower central macular thickness 1 month after cataract surgery than patients in the single therapy group. These findings seem to be confirmed by the outcomes in the ESCRS PREMED study.

The results in the PREMED study represent a huge step forward for the formulation of the most effective therapeutic regimen after cataract surgery. A more precise assessment of the effect of topical treatment on anterior chamber inflammation is advisable in future clinical trials. Further studies are warranted to show the link between postoperative anterior chamber inflammation and the risk for developing cystoid macular edema (CME) after cataract surgery.

Chapter 5

Literature Review - Clin Ophthalmol. 2020 Jan 9;14:41-52.

Measuring anterior chamber inflammation after cataract surgery: a review of the literature focusing on the correlation with cystoid macular edema.

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ABSTRACT

Cystoid macular edema (CME) is an infrequent, though potentially visually impairing, complication after uneventful cataract surgery. Rupture of the blood-aqueous barrier, with leakage of serum proteins into the aqueous humour, is the main pathogenic factor. However, only a few studies investigated the potential correlation between anterior chamber (AC) inflammation and the risk of cystoid macular changes occurring after surgery. This review aims to identify evidence of a correlation between AC inflammation and the risk of pseudophakic CME.

One hundred eighty-seven prospective trials investigating AC inflammation after uncomplicated cataract surgery were identified. Methods of analysis of AC inflammation and the frequency of macular changes were recorded. In the majority (51%) of the studies, inflammation was assessed by clinical grading, followed by laser flare and cell photometry (LFCP) (42%) and aqueous humour sample (4%). Few studies (4%) adopted a combined LFCP and aqueous sample or clinical grading analysis. Sixteen (9%) studies investigated AC inflammation and macular changes by OCT (7%) or fluorescein angiography (2%). Correlation between the amount of postoperative AC inflammation and frequency of CME was documented in 7 studies, not confirmed in 2 studies, and not examined in the other 7. LFCP, more than the other methods of analysis, correlated with the frequency of CME postoperatively.

Investigation of the relationship between AC inflammation and the risk of CME changes requires the adoption of quantitative methods of analysis of the inflammatory response after surgery. For this purpose, due to the low level of inflammation in the AC after uncomplicated cataract surgery, LFCP, more than subjective clinical grading, seems a more sensitive and reproducible method of measurement.

Inflammation assessment after cataract surgery has a potential role in predicting the risk of CME development and may help to titrate the duration and intensity of treatment in relation to the surgical inflammatory response.

Keywords: anterior chamber inflammation, cataract surgery, clinical grading, laser flare photometry, anterior segment optical coherence tomography, aqueous humour sample, cystoid macular edema

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INTRODUCTION

Cataract surgery is the most frequently performed procedure in many developed countries. The technique is continuously evolving to meet the goals of patients and surgeons, having reached a level of refinement to be considered one of the most successful treatments in medicine.[66] Despite the high level of safety of modern phacoemulsification, pseudophakic cystoid macular edema (CME) remains a frequent cause of unfavourable visual outcomes that may occur after uncomplicated surgery.[33,67] By definition, CME is a thickening of the macula due to leakage and accumulation of fluid in the intracellular spaces, causing blurred or decreased vision. Systemic diseases (diabetes[23,24,28,29], hypertension[23]), intraoperative complications (posterior capsule rupture[24] with or without vitreous loss[23], iris trauma[30]), and pre-existing ocular conditions (uveitis[24,25], diabetic retinopathy[27], history of vein occlusion[27], macular epiretinal

membranes[27], previous retinal detachment[24], pseudoexofliation[31]) increase the risk of pseudophakic CME development. Alongside these predisposing factors, angiographic signs of CME after cataract surgery are reported up to 70% in some studies.[23,24] More specifically, the incidence of subclinical pseudophakic CME, diagnosed by optical coherence tomography (OCT), varies between 4 and 10.9%[19,25,26], while clinically significant CME, with transient or permanent visual impairment, ranges from 1% to 4% according to various studies.[24,25,27]

The exact pathogenesis of CME after cataract surgery remains unclear. Surgical trauma causes blood-aqueous barrier disruption with leakage of pro-inflammatory molecules and cells in the anterior chamber (AC).[68] Prostaglandins and other pro-inflammatory mediators, released by the anterior uvea, diffuse into the vitreous and increase the permeability of perifoveal capillaries, resulting in the intraretinal fluid accumulation with cystoid changes of the retinal layers.[12]

To date, the risk of CME, based on the amount of post-surgical inflammation, remains uncertain, as only a few studies in the literature have attempted to correlate the degree of intraocular inflammation to the risk of CME development after cataract surgery. The majority of the studies focused on the anti-inflammatory effect of ophthalmic steroids and non-steroidal anti-inflammatory drugs for preventing or treating of CME, principally measuring macular changes after surgery, more than accurately assessing the AC inflammatory response.

Routinely, clinicians evaluate the level of AC inflammation by grading cells and flare at the slit lamp according to the Standardized Uveitis Nomenclature (SUN).[48] Compared to uveitis, inflammation after uncomplicated cataract surgery is generally low. Therefore, SUN grading may present some limitations due to its qualitative assessment. Lately, new technologies have been developed to quantify AC inflammation objectively. Laser flare and cell photometry (LFCP)[49] and, more recently, anterior segment optical coherence tomography (AS-OCT)[20,21], have arisen popularity and consensus among specialists in order to quantitatively define inflammation and to obtain objective measurements on its course and therapy response. Moreover, molecular biology and modern methods of aqueous humour samples analysis[62] allow clinicians to titrate inflammatory mediators involved in this process.

This literature review focuses on the results of studies that evaluated AC inflammation after uneventful cataract surgery, aiming to identify evidence of a correlation between quantitative measurements of AC inflammation and the risk of CME development. Strengths and weaknesses of each technique used to evaluate AC inflammation will be discussed. Finally, the rationale of their choice and use in the field of research and routine clinical practice will be further addressed.

METHOD OF LITERATURE SEARCH

We searched the PubMed database (1949-2019) and Ovid Medline (1946-2018) for peer-reviewed publications relevant to the topic of AC inflammation after cataract surgery starting from 1989. The year 1989 was chosen as it is when the first generation of an LFCP was commercialized. Keywords included: cataract surgery, cystoid macular edema, AC inflammation, laser flare and cells photometry, anterior segment optical coherence tomography (AS-OCT) and aqueous sample. We did not use any language restriction in the electronic searches. Data were extracted from the full-texts of the articles considered. For non-English articles, the provided English abstracts were examined in advance for eligibility before to extrapolate data from the full paper. The last electronic search was conducted in September 2019. We selected only prospective studies on uneventful cataract surgery by using the dedicated research tool on the PubMed web site. Experimental animal models, in vitro studies, reviews, and case reports or case series were excluded. Only papers in which one of the primary or secondary outcomes were the assessment of AC inflammation were included.

Data from the included studies were compiled in a Microsoft Excel Database (Version 16.16.14, 2018 Microsoft, Washington, USA). Information extracted and analyzed were:

- The title, authors, publication years, journal;
- Sample size;
- Research Field;
- Follow-up;
- The test used to assess AC inflammation: clinical grading (SUN), LFCP, AS-OCT, aqueous sample analysis;
- The examination used to assess CME: fluorescein angiography or OCT;
- Correlation between AC inflammation and CME, if present.

RESULTS

The literature search retrieved 187 titles of full-length articles. The full-text of the papers was reviewed by two authors (MDM and LF) to check for adherence to the topic under investigation. We identified ninety-five papers (51%) that measured inflammation by clinical grading, 78 (42%) that used LFCP, and 7 (3%) that analyzed aqueous samples. We found no studies that employed AS-OCT to assess inflammation after cataract surgery. Moreover, we included two (1%) studies reporting a combined analysis of AC inflammation using LFCP with aqueous humour sampling and 5 (3%) papers reporting the use of both LFCP and SUN grading.

Sixteen (9%) studies searched for evidence of macular changes after surgery, 12 (6%) using OCT, 3 (2%) using fluorescein angiography, and 1 (1%) aqueous humour sampling. Among these, 7 papers identified a positive correlation between the degree of AC inflammation and the frequency of

postoperative macular edema. In contrast, 2 papers did not confirm this association, and 7 studies did not attempt this analysis.[31],[17,40,65,69–80] Study characteristics and results are summarized in figure 2.

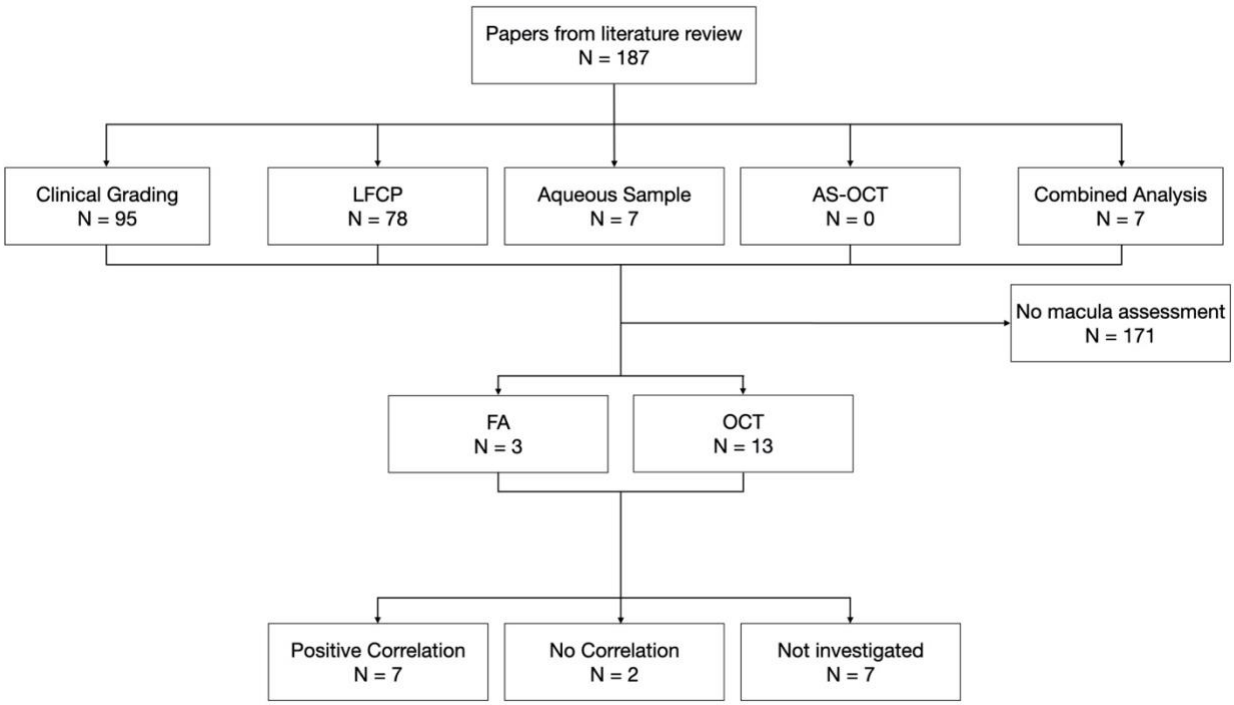

Figure 2. LITERATURE REVIEW PROCESS. LFCP = Laser Cell and Flare Photometry; AS-OCT = Anterior Segment Optical Coherence Tomography; FA = Fluorescein Angiography; OCT = Optical Coherence Tomography

DISCUSSION

Clinical grading

Slit-lamp examination is a commonly used technique to detect and grade AC inflammation in routine clinical practice. The herein review showed that the SUN scoring system is the most employed method of inflammation assessment in clinical trials conducted on cataract surgery. However, none of the studies in this group attempted to correlate AC inflammatory score to the macular changes that occurred postoperatively (Table 3).

The SUN clinical grading is a highly effective method to assess inflammation in routine clinical practice. In the field of uveitis, it allows clinicians to score visible inflammation rapidly and to titrate clinical decisions according to the variations of flare and cells present in the AC.[48] In contrast, we believe that the SUN may fail to provide a precise assessment of low grades of inflammation occurring after uncomplicated phacoemulsification. The inflammatory degree in uveitis is usually higher than after uncomplicated cataract extraction, and therefore the detection of minimum variations during follow-up may appear more complicated when a clinical grading system is adopted. Due to its qualitative nature, SUN grading has a moderate reproducibility for agreement between different observers; therefore, more objective techniques of AC inflammation assessment are desired, especially when different clinicians are involved.[81] Furthermore, different types of equipment are proved factors of variability. Various slit lamps and lighting sources influence the ability to recognize cells and flare.[82] Therefore, using SUN grading, standardization of the equipment, and observers training are crucial to collect consistent and comparable data on the inflammatory level when different centers are involved.

An additional limitation of SUN grading could be its low sensitivity. The close range of cells per high-power field between grade 1+ (6-15 cells/high power field) and grade 2+ (16-25 cells/high power field) may affect the ability in detecting minimum variations, within the lowest grades of inflammation.[83] This issue is relevant in the follow-up of patients after phacoemulsification, where lower amount of inflammation is expected compared to uveitis, and subtle improvements occurring over time may pass unrecognized using a clinical grading score.[84]

According to the SUN criteria, "improved activity" is, by definition, a 2-step improvement or recovering to grade 0[48]. As stated by these criteria, it is evident the lack of linear progression between different clinical scores. An improvement from 2+ cells (16-25 cells/high power field) to 0.5+ (1-5 cells/high power field) is rated the same as 3+ (26-50 cells/high power field) to 1+ cells (5-10 cells/high power field), even if the effective range of cells is different passing from grade 2+ to 0.5+ (decrease of 15-20 cells/high power field) and from grade 3+ to 1+ (decrease of 21-40 cells/high power field). In clinical trials, the lack of a linear progression may consistently affect the recording of clinical data and their analysis, neglecting possible improvements in some cases or worsening in

others. A treatment could be wrongly declared ineffective despite a consistent improvement in inflammation not accurately detected. Defining the efficacy of a novel therapy may benefit from a linear grading scale.

Laser Flare and Cell Photometer (LFCP)

LFCP, firstly described in 1988[49] and commercialized in 1989, adopts a laser beam to measures the back-scattered light from proteins and cells into the AC by a photomultiplier. In principle, the amount of backscattered light is proportional to the concentration of proteins, particles, or cells in the AC; therefore, the higher is the concentration, the higher is the output signal. The amount of inflammation is measured in photon count per milliseconds (ph/ms).[49,85]

Through the years, various models of LFCP have been commercialized. Differently from laser flare meters (KOWA FM-500, FM-600, FM-700), flare and cell meters (KOWA FC-1000, FC-2000) can also measure the number of cells adopting two optical scanners to analyze two-dimensionally a 0.5 mm^3 volume into the anterior chamber. The number of picks in the output signal corresponds to the number of cells into the scanned fixed volume.[85]

A faint flair (2.9-3.9 ph/ms between 20-40 years of age, increasing to 5.0-6.5 ph/ms between 70-80 years of age)[51,86,87] is present in physiological condition, but not detectable using a slit lamp. After cataract surgery, laser flare can reach values of a maximum of 30-40 ph/ms, considerably lower than those measured in uveitis.[88] Validation of measures obtained from LFCP results from laboratory studies demonstrated that ph/ms values correlate with the real protein concentration in the aqueous samples collected from patients with uveitis undergoing intraocular surgery.[51,54,86,89–91] Furthermore, Saari et al published a formula to calculate the real concentration of proteins using the photon counts of the LFCP.[89]

A correlation between laser flare values and the SUN grading system has been proved, specifically in the setting of uveitis, while no studies so far analyzed this correspondence after cataract surgery, probably because of the low inflammation amount after uneventful phacoemulsification. LFCP can detect a minimum variation of cells and flare within the same grade of the SUN system both at the lower or, the higher grades, confirming a high level of sensitivity, reproducibility, and repeatability of LFCP measurements.[85]

In the setting of cataract surgery, LFCP has been used to quantitatively investigate postsurgical inflammation allowing clinicians to compare between different surgical techniques[92–94], several postoperative anti-inflammatory treatments[31,74,95–97] and various eye conditions that may complicate with a higher level of inflammatory response after surgery.[31]

In the scenario of uncomplicated cataract surgery, we believe that an instrument able to detect the minimum amount of inflammation is mandatory to conduct rigorous research with no bias induced by interobserver variations or differences in the equipment employed among centres.

Each SUN clinical-grade presents a wide range of laser flare values, with an overlap of flare readings passing from the lowest to highest score.[85]

Tugalt-Tutkun I et al reported an increased coefficient of variation passing from grade 3+ to 0 (coefficient of variation is 81.4% for grade 0, 69.9% for grade 1, 42.2% for grade 2+, and 25.8% for grade 3+).[85] These results confirm that the human eye is not capable of distinguishing minimal, though clinically relevant inflammatory variations, especially at the lower grades as after cataract surgery. The overlap in the lower clinical grading reflects the difficulties in recognizing the real amount of inflammation when a subjective method of measurement is adopted. These values would correspond to 0 or 1 of the SUN grading, and it would be challenging to recognize minimum inflammatory variations using the slit lamp.

Several studies investigated the effect of different topical therapies on limiting the risk of CME after cataract surgery, but only a handful of them have analyzed the correlation between LFCP readings and the frequency of any macular changes or CME.

Ersoy L et al analyzed laser flare values in patients with clinically significant CME after uncomplicated cataract surgery.[70] Patients with CME had significantly higher flare values than pseudophakic patients without CME during and after the first month following phacoemulsification. As a marker for inflammation and breakdown of the blood-retinal barrier, LFCP values suggest that controlling postoperative inflammation might be the key to avoid or treat CME. Ursell PG et al used fluorescein angiography to detect CME after uncomplicated phacoemulsification.[17] They demonstrated that the laser flare readings were higher in patients with angiographic CME, but the difference was not statistically significant. Maca SM et al failed to prove any correlation between mean foveal thickness and AC laser flare photometry.[78] Conrad-Hengerer et al, investigating the inflammatory response after the femtosecond-assisted cataract surgery, demonstrated that laser flare values correlate with the postoperative OCT macular thickness and higher the ph/ms higher was the macular thickness.[71] Zaczek A et al found no correlation between laser flare value and total OCT macular volume after uncomplicated phacoemulsification.[72] Finally, Miyanaga M et al investigated the effect of Bromfenac ophthalmic solution on ocular inflammation following cataract surgery using the LFCP.[77] They reported a single case of CME in which the aqueous flare values were higher compared to the ones of patients without CME. Recently, Coassin et al reported on the effect of combined therapy using bromfenac and dexamethasone in patients with PEX who underwent cataract surgery. They observed that patients treated with combined therapy of steroid and NSAID presented

lower flare values and incidence of CME one month after surgery compared to patients treated with steroids alone.[31]

According to this review, 6 out of 11 studies employing LFCP documented some relationship between the degree of AC inflammation and the risk of CME after uncomplicated phacoemulsification.

Undoubtedly, LFCP presents some limitations. The instrument requires a longer processing time compared to the SUN clinical grading because several measurements (from 5 to 7)[85] are required to obtain an average value. Moreover, the examination needs to be conducted in a completely dark room and necessitates sufficient patient cooperation to obtain a reliable analysis. Corneal edema on the first operative day may impair the analysis, because of "background errors" that interfere with LFCP correct readings. Furthermore, this technology involves the costs of buying and maintenance.

Optical Coherence Tomography

The advent of OCT has optimized the diagnosis of pseudophakic CME by detecting very initial signs of macular swelling and cysts even before the reduction of visual acuity. Nowadays, last generation OCTs allows clinicians to analyze in detail all the retinal layers, the choroid, the vitreous cavity, and the AC. In the field of inflammation, the use of OCT for direct visualization of vitreous inflammatory cells in patients with uveitis has been recently described.[98] *Keane* et al obtained measurements of vitreous signal intensity from OCT in patients with uveitis with the aim of objectively and quantitatively evaluating the intraocular inflammatory activity. They demonstrated that Vitreous/Retinal Pigment Epithelium-relative intensity (VIT/RPE relative intensity) was significantly higher in eyes with active posterior uveitis compared to the vitreous signal of inactive uveitis or healthy controls. Moreover, the VIT/RPE-relative intensity showed a significant positive correlation with the clinical vitreous haze. These results provided evidence that OCT-derived measurements can provide a quantitative assessment of intraocular inflammation.[99]

In line with these findings, thanks to the technological refinements of anterior segment-OCT (AS-OCT), authors described the feasibility of AS-OCT to recognize inflammatory cells and flare and to obtain an objective quantification of the inflammation in the AC.[84]

Concerning cells, the majority of papers adopted a time-domain OCT with a spatial resolution larger than the white cells, arising uncertainty on the interpretation of the real nature of the "white spots" inside the AC. [55,100,101]

Spectral-domain OCT (SD-OCT) has a higher resolution than the previous models. Sharma S et al described the proficiency of SD-OCT in detecting inflammatory cells in the AC thanks to an automated algorithm that counts cells in a 3D volume scan. After comparing these data to the SUN grading, they demonstrated a high positive correlation between clinical grading and the number of cells identified by SD-OCT.[84] Recently, Inverinizzi A et al[56] proposed a new method to measure

both cells and flare using a swept-source AS-OCT. They adopted an optical density ratio calculated as the comparison between the signal inside the AC and the signal outside the eye (aqueous-to-air relative intensity [ARI] index). Active uveitis patients present a significantly higher ARI index compared with inactive uveitis and controls. Nonetheless, a positive correlation between the ARI index and the SUN clinical grading has been shown.

To date, no clinical trials have employed AS-OCT to measure AC inflammation after cataract surgery. The use of AS-OCT to analyze AC inflammation is still in its infancy, but it appears to be promising being a highly reproducible method for measuring flare and cells in the AC.

Aqueous Humor Sample Analysis

The pathogenesis of pseudophakic CME appears to be associated with postoperative inflammation primarily induced by prostaglandins and other proinflammatory mediators.[102],[30] Inflammatory mediators alter the blood-retinal and the blood-aqueous barriers, leading to increased vascular permeability.[103]. The majority of studies, so far, focused on a limited number of molecules present in humour aqueous.[104] Exploring a higher number of cytokines would provide broader insight into the inflammatory mechanisms involved.

The aqueous humour analysis is directed to the quantification and classification of the different cytokines and chemokines using the enzyme-linked immunosorbent assay (ELISA). A potential limitation of this technique is that it requires at least 50-100 µl of aqueous humour for every single molecule of interest. Considered that the aqueous sample amount collected is about 0.15-0.20 ml, it is challenging to test the complete pattern of inflammatory mediators, which amounts to over 650 different identified proteins.[61] This limitation is especially important in the setting of cataract surgery in which the eye is generally not inflamed at the time of surgery. The aqueous sample needs to be performed at the beginning of the procedure before any other fluid is introduced in the AC. In these circumstances, the amount of inflammatory mediators in the early phase of the procedure is too low to understand the multiple networks of cytokines and chemokines that may be involved. These technical problems have led to confusion in this field with no consistent results on the relevance of individual mediators in this specific condition.[62]

Nowadays, many alternative technologies allow a more comprehensive analysis of pro- and anti-inflammatory mediators using a smaller amount of aqueous humour. The most recent innovation in the analysis of the aqueous sample comes from the refining of proteomics technique.[61] Multiplexed beads immunoassay can perform simultaneous analysis of different mediators thanks to their individual fluorescent properties. The main advantage of this technique is the ability to measure numbers of molecules in a single aqueous sample of 25-100 µl.[62–64] These modern techniques allow clinicians to characterize the complex network of cytokines and chemokines both at rest or in

inflammatory conditions.[62]Chu et al[65], using multiplex assays, simultaneously measured the concentrations of 27 cytokines in aqueous humour samples as predictors of CME in non-diabetic patients following uncomplicated phacoemulsification surgery. The concentrations of IL-1β, IL-6, MCP-1, and VEGF were significantly higher in patients with CME. Also, the aqueous humour levels of IL-1β, IL-6, MCP-1, and VEGF correlated positively with postoperative central foveal thickness.

The introduction of femtosecond laser-assisted cataract surgery made it possible to evaluate the release of inflammatory mediators into the AC immediately after the application of the laser and before phacoemulsification. In a comparative study, Liu YC et al[105] reported that femtosecond laser treatment induced significantly higher humour aqueous levels of pro-inflammatory cytokines and PGE2 compared to standard phacoemulsification. Furthermore, the postoperative flare was higher, although not significantly, in the femtosecond-assisted group than in the standard phacoemulsification group; however, in this study, no analysis of the macula thickness was conducted.

Harvesting aqueous humour remains a controversial procedure in prospective clinical trials on cataract surgery, as it would be unethical to obtain consecutive samples in the same patients during follow-up due to the invasiveness of the procedure.

Currently, it is difficult to understand the real pattern of molecules involved in the inflammatory process after cataract surgery because sampling may be performed only at the beginning of the procedure, with a limited amount of inflammatory mediators that can be collected and investigated.

CONCLUSION

Proving a possible correlation between AC inflammation and the risk of postoperative CME is challenging as it inevitably requires quantitative methods of measurement. Clinical grading, according to the SUN method, has proved to be useful to score inflammation at slit lamp in routine clinical practice. However, the low sensitivity, reproducibility, repeatability, and the absence of a linear scale both for cells and flare are significant limitations, especially when numerical data are required to state the efficacy of novel treatments and to make a comparison with other clinical trials. No study has so far attempted or found a correlation between the clinical grade of postoperative AC inflammation and the risk of CME development.

The AS-OCT analysis is a non-invasive, objective, and quantitative method to measure intraocular inflammation. Though, it appears potentially useful in the setting of clinical trials on cataract surgery in order to provide comparable numerical data of AC inflammation. This technology needs to be improved by developing dedicated software of analysis that may allow introducing this technique to the routine clinical practice.

The most recent techniques of proteomics with the immunoassay have dramatically increased the overall knowledge of the complex network of cytokines and chemokines involved in AC inflammation. Future research should aim to extend the panel of the molecules investigated and to provide better diagnostic and prognostic information, identifying new therapeutic targets. The main limitation is that it is unethical to perform multiple aqueous sampling after surgery in order to prospectively address the real pattern of inflammatory mediators after phacoemulsification and their specific role in the pathogenesis of pseudophakic CME.

Probably, the LFCP may represent the right compromise in the setting of clinical trials based on cataract surgery. It allows precise measurements of both cells and flares inside the AC, and it correlates positively with clinical grading. However, flare and cell meters do not distinguish inflammatory cells from pigment and debris (lens particles) that may be mistakenly counted as cells. Since the inflammation after uncomplicated cataract surgery is extremely low, a laser flare meter is adequate to obtain a reliable measure of the blood-aqueous barrier breakdown. LFCP is characterized by a low learning curve, differently from the expertise required to provide a correct SUN score. Additionally, it is not excessively time-consuming, compared to AS-OCT, and may not affect too much the flow of routine clinical activity.

Despite no studies in the literature were specifically designed to correlate AC inflammation, measured by LFCP, and macular changes occurring after cataract surgery, some studies have documented a link between the degree of inflammation occurring after surgery and the frequency of CME.[17,31,70,71,74,77]

To measure inflammation and provide comparable numbers is the focal point in the setting of a clinical trial investigating treatment and prevention of inflammation and cystoid macular edema after cataract surgery. In order to acquire reproducible and comparable data, it is mandatory to adopt methods of measurements that precisely and quantitatively assess AC inflammation, aiming to correlate the inflammatory process to risk of development of cystoid macular edema after uncomplicated cataract surgery.

Table 3. Literature review on clinical trials and correlation with the risk of CME.

Author	Year of publication	Title	Research Field	Study Type	Surgical Technique	Sample Size	Follow-up	Index Test to asses inflammation	Macula Assessment	Incidence of CME clinical significant CME]	Correlation flare - CME
Rossetti L[40]	1996	Effectiveness of diclofenac eyedrops in reducing inflammation a nd the incidence of cystoid macular edema after cataract surgery.	Drug efficacy	Prospectiv e	ECCE, phacoemulsification	88	6 months	Clinical grading	Fluorescein angiography	9% [1%]	Not investigated
Gallenga P[75]	1997	Efficacy of diclofenac eye drops in preventing postoperative inflammation and long-term cystoid macular edema. Italian Diclofenac Study Group.	Drug efficacy	Prospectiv e	ECCE	281	5 months	Clinical grading	Fluorescein angiography	5%	Not investigated
Ursell PG[17]	1999	Cystoid macular edema after phacoemulsification: relationship to blood-aqueous barrier damage and visual acuity.	Surgical technique	Prospectiv e	Phacoemulsification	34	2 months	Laser Flare Cells Meter KOWA FC 1000	Fluorescein angiography	56%	Flare and cells were higher in CME patients at day 60, but the difference was not statistically significant.
Donnenfeld E[76]	2006	Preoperative ketorolac tromethamine 0.4% in phacoemulsification outcomes: pharmacokinetic-response curve.	Drug efficacy	Prospectiv e	Phacoemulsification	100	3 months	SUN grading	OCT	[4%]	Not investigated
Miyanaga M[77]	2009	Effect of bromfenac ophthalmic solution on ocular inflammation following cataract surgery	Drug efficacy	Prospectiv e	Phacoemulsification	72	2 months	Laser Flare Cells Meter KOWA FC 1000	OCT	1 case	Aqueous flare values in the subject with CME were higher than those for all other cases
Maca SM[78]	2010	Efficacy and tolerability of preservative-free and preserved diclofenac and preserved ketorolac eye drops after cataract surgery.	Drug efficacy	Prospectiv e	Phacoemulsification	102	1 month	Laser Flare Cells Meter KOWA FC 1000	OCT	0%	No correlation was found

Dieleman M[79]	2011	Single perioperative subconjunctival steroid depot versus postoperative steroid eye drops to prevent intraocular inflammation and macular edema after cataract surgery.	Drug efficacy	Prospective	Phacoemulsification	400	1 month	Laser Flare and Cell Meter KOWA FC 1000	OCT	6.5% [2.8%]	Not investigated
Chu L[65]	2013	Aqueous cytokines as predictors of macular edema in non-diabetic patients following uncomplicated phacoemulsification cataract surgery	Surgical technique	Prospective	Phacoemulsification	288	4 weeks	Aqueous Humor Sample	OCT	8.13%	Preoperative levels of IL-1β, IL-6, MCP-1, VEGF, and IL-10 may predispose to CME development.
Wang QW[80]	2013	Bromfenac sodium 0.1%, fluorometholone 0.1% and dexamethasone 0.1% for control of ocular inflammation and prevention of cystoid macular edema after phacoemulsification.	Drug efficacy	Prospective	Phacoemulsification	167	2 months	Laser Flare and Cell Meter KOWA FC-2000	OCT	4%	Not investigated
Ersoy L[70]	2013	Aqueous flare is increased in patient with clinical significant cystoid macular edema after cataract surgery	Surgical technique	Prospective	Phacoemulsification	121	-	Laser Flare Meter KOWA FM-500	OCT	-	Patients with CME had significantly higher flare values compared with pseudophakic patients
Conrad-Hengerer I[71]	2014	Femtosecond laser-induced macular changes and anterior segment inflammation in cataract surgery.	Surgical technique	Prospective	Femtosecond assisted cataract surgery Vs. Phacoemulsification	208	6 months	Laser Flare Meter KOWA FM-600	OCT	0%	Laser flare values correlate with the postoperative macular thickness.

Zaczek A[72]	2014	Nepafenac 0.1% plus dexamethasone 0.1% versus dexamethasone alone: effect on macular swelling after cataract surgery.	Drug efficacy	Prospective	Phacoemulsification	152	1.5 month	Laser Flare Meter KOWA FM-500	OCT	1.3% [0.6%]	No correlation was found
Coassin M[31]	2016	Bromfenac ophthalmic solution 0.09% as an adjunctive therapy to topical steroids after cataract surgery in pseudoexfoliation syndrome.	Drug efficacy	Prospective	Phacoemulsification	62	1 month	Laser Flare Meter KOWA FM-700	OCT	13.8%	Patients treated with a steroids single therapy presented a higher flare higher incidence of CME at 1 month after surgery
Giannaccare G[73]	2018	The Comparative Efficacy and Tolerability of Diclofenac 0.1% and Bromfenac 0.09% Ophthalmic Solutions after Cataract Surgery.	Drug efficacy	Prospective	Phacoemulsification	130	1 month	Laser Flare Meter KOWA FM-500	OCT	2%	Not investigated
Wielders LHP[44]	2018	European multicenter trial of the prevention of cystoid macular edema after cataract surgery in nondiabetics: ESCRS PREMED study report 1.	Drug efficacy	Prospective	Phacoemulsification	914	3 months	SUN grading	OCT	5% [3.4%]	Not investigated
Coassin M[74]	2019	Anterior Chamber Inflammation After Cataract Surgery: A Randomized Clinical Trial Comparing Bromfenac 0.09% to Dexamethasone 0.1%.	Drug efficacy	Prospective	Phacoemulsification	76	1 month	Laser Flare Meter KOWA FM-700	OCT	2.7%	Bromfenac single therapy or dexamethasone are equally effective in reducing AC inflammation, but patients treated with steroids showed a higher incidence of CME.

CME = Cystoid Macular Edema; OCT =Optical Coherence Tomography; SUN = Standardize Uveitis Nomenclatur

Chapter 6

Research Article - Adv Ther. 2019 Oct;36(10):2712-2722.

Anterior chamber inflammation after cataract surgery: a randomized clinical trial comparing bromfenac 0.09% to dexamethasone 0.1%

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ABSTRACT

Purpose: to compare the efficacy of bromfenac 0.09% and dexamethasone 0.1% on the treatment of anterior chamber inflammation after uncomplicated cataract surgery.

Methods: 76 patients with senile cataract and no other ocular comorbidities who underwent uneventful phacoemulsification were randomized 1:1 to receive dexamethasone ophthalmic suspension 0.1% or bromfenac ophthalmic solution 0.09% for two weeks. All patients were examined on the day before surgery and postoperatively at day 1, 3, 7, 9, 11, 14 and 30. Laser flare photometry was used to quantify anterior chamber inflammation and optical coherence tomography to measure macular thickness.

Results: bromfenac was as effective as dexamethasone in reducing inflammation in the anterior chamber of the eye. Laser flare increased the day after surgery and progressively decreased after starting the treatment with no statistically significant difference between dexamethasone and bromfenac at all time points. Visual acuity improved steadily after surgery in both groups. Mean macular thickness was similar in both dexamethasone and bromfenac arms at one month.

Conclusions: short-term therapy with topical bromfenac alone is as effective as dexamethasone in low-risk cataract surgery patients.

Key words: cataract surgery; laser flare photometry; nonsteroidal anti-inflammatory drugs

Trial Registration Number: NCT03317847

INTRODUCTION

Phacoemulsification is the most common surgical procedure performed in the Western countries.[106] After surgery, the operated eye routinely receives antibiotic and steroidal eye drops for four weeks.[107] This is aimed to prevent infections and to reduce ocular inflammation and discomfort. Recently, ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs) have received attention as possible adjuvants or substitutes of topical steroids after phacoemulsification.[108]

Several advantages of NSAIDs over steroids have been claimed: they do not induce changes in intraocular pressure (IOP); they may have a favorable pharmacological profile (fewer administrations); they may be more effective than steroids at reestablishing the blood-ocular barrier (BOB) after surgery; they can prevent pseudophakic cystoid macular edema.[34,109–114]

On the other hand, ocular steroids are generally considered stronger than NSAIDs in reducing anterior segment inflammation after cataract surgery. This is commonly postulated because steroids inhibit phospholipase, an enzyme higher in the inflammatory cascade than cyclo-oxygenase (the target of NSAIDs).[115] True is that evidence is lacking. Difficulties in measuring ocular inflammation limited

the ability to evaluate NSAID efficacy after cataract surgery.[33] The current grading system for ocular inflammation was developed to assess uveitis and is based on subjective examination of the anterior chamber by slit lamp.[48,81] This could be suboptimal to follow the mild inflammatory response caused by modern techniques of phacoemulsification and to demonstrate differences between therapies in clinical trials. Laser Flare Photometers allow precise measurement of inflammatory protein concentrations in the aqueous humor *in vivo.*[49,85]

Ideally, postoperative treatments should be limited to the necessary, in order to reduce costs and increase patients' compliance. This study compared for two weeks the anti-inflammatory effects of bromfenac 0.09%, the most recently introduced ocular NSAID, to dexamethasone 0.1% as monotherapy. Postoperative inflammation was precisely evaluated by Laser Flare Photometer with very close follow up visits. Special attention was used to include a homogenous population of patients affected by senile cataract but with no other ocular comorbidities.

METHODS

Study Design

This single center, assessor-blinded, randomized trial was conducted at the Ophthalmology Unit of the IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy between October 2017 and June 2018. The study protocol was approved by the local ethics committee and the trial was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients. This study was registered at ClinicalTrials.gov (NCT03317847) and the European Clinical Trials Database (EudraCT Number: 2016-004358-14).

Patients

Subjects aged ≥60 years were eligible for inclusion if they had reduced visual acuity due to development of cataract, defined as nuclear sclerosis of the crystalline lens graded ≥1 according to the Lens Opacities Classification System III (LOCS III classification).[116] Other inclusion criteria were: no topical, systemic, or inhaled NSAIDs within 1 week of surgery; no topical, inhaled, or systemic corticosteroids within 15 days of surgery; no oral tamsulosin; no glaucoma medications.

Subjects were excluded if they had: known hypersensitivity to any component of the investigational products, procedural medications, salicylates, or other NSAIDs; any active or chronic/recurrent systemic or ocular disease that was uncontrolled and was likely to affect postoperative inflammation or wound healing (including diabetes); history of ocular inflammation or trauma; previous surgery in the study eye; any form of corneal haze; pseudoexfoliatio lentis; any preoperative sign of intraocular inflammation in either eye; retinal vascular disease; any alteration of the foveal contour, such as macular edema or epiretinal membrane; moderate-to-severe age-related macular degeneration. Use

of corticosteroids, NSAIDs, opioids, narcotics and tamsulosin during the study was not permitted. Patients who experienced intraoperative complications such as posterior capsule rupture were excluded.

Treatments

Bromfenac ophthalmic solution 0.09% (Yellox ®; Bausch & Lomb, Italy), dexamethasone 0.1% ophthalmic suspension (Visumetazone ®; Visufarma SpA, Italy) and tobramycin 0.3% eye drops (Tobral ®; Alcon, Italy) were supplied by the hospital dispensary.

Study Protocol

Eligible patients who signed the consent form were randomized (1:1 ratio) to dexamethasone 0.1% (Group 1) or bromfenac 0.09% (Group 2) eye drops using computer-generated randomization codes. All patients underwent standard phacoemulsification and intraocular lens (IOL) implantation in the capsular bag. Cataract operations were performed by two experienced surgeons (LF, AS), masked to randomization, using the Whitestar Signature Phacoemulsification System (Johnson & Johnson Surgical Vision, USA) through a 2.2 mm temporal clear cornea incision. The same ocular viscoelastic device (Healon GV, Johnson & Johnson Surgical Vision, USA) and acrylic IOL (Tecnis ZCB00, Johnson & Johnson Surgical Vision, USA) were used in all patients. Duration of surgery was recorded.

The day after surgery, all patients started treatment with tobramycin 0.3% eye drops, two times daily for the first week. Patients randomized to Group 1 received dexamethasone ophthalmic suspension 0.1%, four times daily for the first week and two times the following week. Patients randomized to Group 2 received bromfenac ophthalmic solution 0.09% twice daily for two weeks. Bromfenac is registered in the E.U. as a 0.09% formulation and its use is approved for 14 days postoperatively.

Outcomes

The primary efficacy endpoint was the duration of postoperative inflammation. Anterior chamber inflammation was evaluated by Laser Flare Meter (FM-700, Kowa Co. Ltd, Tokyo, Japan) that employs a diode laser beam to quantify protein concentration in the aqueous humor.[85] The primary endpoint (duration of inflammation) was split in order to measure the differences between the two study groups in terms of:

- Time needed to recover from the postoperative inflammation. Measured as days with postoperative laser flare value higher than preoperative value.
- Proportion of patients with flare value at postoperative day 14 equal or inferior to the preoperative value.

Secondary endpoints were:

1) proportion of subjects with 20/20 Best Corrected Visual Acuity (BCVA) at day 14;

2) proportion of patients with central macular thickness (central subfield) greater than 300 microns at day 30; the number of patients developing cystoid macular edema will also be evaluated in both groups and classified as subclinical (BCVA ≥ 8/10) or clinically significant (BCVA < 8/10);

3) proportion of patients with no ocular discomfort at day 3; it was assessed by the ocular comfort grading assessment (OCGA) scale;

4) incidence of ocular or systemic adverse events.

Assessments

All patients were examined before surgery (baseline) and at postoperative days 1, 3, 7, 9, 11, 14 (±1 day) and 30 (±3 days). Clinical examination by slit-lamp biomicroscopy and dilated fundus examination, IOP by pneumotonometer, BCVA and laser flare photometry measurements were performed at each visit. BCVA was assessed using an electronic Snellen Chart and readings were converted to Logarithm of the Minimum Angle of Resolution (LogMAR) values. Optical coherence tomography (OCT) (Spectralis, Heidelberg Engineering, Germany) was used to quantify macular thickness at baseline and day 30. Measurements of BCVA, IOP, Laser flare photometry and OCT were performed by a certified technician unaware of treatment allocation. Ocular discomfort was determined using the subject-reported OCGA.[117] Patients graded each symptom as none (0), mild (1), moderate (2), or severe (3) at each visit. Ocular and systemic adverse events were recorded based on questioning patients or observation by investigators.

Statistical Analysis

Sample size calculations for the primary outcome measures assumed the following: expected proportion of patients reverting the flare to the preoperative or lower level in the dexamethasone arm: 17.2%;[31]expected proportion of patients reverting the flare to the preoperative or lower level in the bromfenac arm: 48.3%;[31] t-test for independent group comparison for homoscedastic data; α=5%; statistical power, 80%. Based on these assumptions, a sample size of 70 subjects (35/group) was calculated (nQuery Advisor, release 7.0, sheet MTT0). Based on a 10% drop-out rate, a final sample size of 76 patients (38/arm) was planned.

A general linear model with repeated measure test for independent group comparison was used to evaluate primary and secondary outcomes. Homoscedasticity was assessed by Levene test and, in case of statistical significance, Satterthwaite adjustments were adopted. For OCGA questionnaire data, each symptom was assessed separately. Results were expressed as mean values ± SD.

RESULTS

Subjects Characteristics

Four hundred and twenty-one patients were screened for eligibility during routine preoperative evaluation in the cataract clinic. All individuals meeting the inclusion criteria were invited to participate. Eleven patients declined to be included in the clinical trial. Seventy-six subjects were randomized and, after cataract surgery, received dexamethasone (37 patients) or bromfenac (39 patients). One patient in the bromfenac group left the trial at postoperative day 7.

Patients had moderate to advanced cataracts, mostly nuclear sclerosis type N2 (n = 39; 51%) or N3 (n = 24; 32%). Baseline characteristics did not differ significantly between treatment groups (Table 4). Phacoemulsification with IOL implantation was uncomplicated in all patients, with a similar mean duration of surgery in both groups (13.89 ± 2.98 vs 14.03 ± 2.95 minutes).

Table 4. Patients characteristics at baseline.

		Group 1 (n = 37) Dexamethasone 0.1%	**Group 2 (n = 39)** Bromfenac 0.09%
Age			
	Mean (years)	75 ± 7	77 ± 6
	Range (years)	60 – 85	61 – 86
Sex			
	Males (n)	14	14
	Females (n)	23	25
Mean BCVA (logMAR)		0.48 ± 0.20	0.48 ± 0.20
Mean laser flare (ph/ms)		7.88 ± 2.60	8.14 ± 2.18
Central macular thickness (micron)		272.27 ± 32.99	267.56 ± 26.88

BCVA = best corrected visual acuity

Efficacy

Ocular inflammation

Anterior chamber inflammation in the two treatment groups is shown in Figure 3 as time-to-event curves. The event was defined as postoperative flare equal or inferior to the preoperative flare value (primary endpoint, part one). The difference between the two treatments was not statistically significant for all time points (Log Rank Mantel-Cox p = 0.924). The number of patients returning to preoperative flare value by postoperative day is detailed in Table 5: most patients recovered at day 9. The number of patients with flare value at postoperative day 14 equal or inferior to the preoperative level (primary endpoint, part two) was similar for the two treatment groups (20 vs. 24, Chi-square =

0.04; p = 0.836). Seventeen patients in the dexamethasone group and 14 patients in the bromfenac group did not return to preoperative values at last follow up visit (day 30).

Mean laser flare values for the two groups at all time points are presented in Figure 2. As expected, in both treatment groups laser flare significantly increased the day after surgery and decreased after starting the treatment. There was no statistically significant difference between dexamethasone and bromfenac in terms of mean laser flare at all time points (F score = 0.011, p = 0.918). Treatment was discontinued at day 14 in both groups as per protocol.

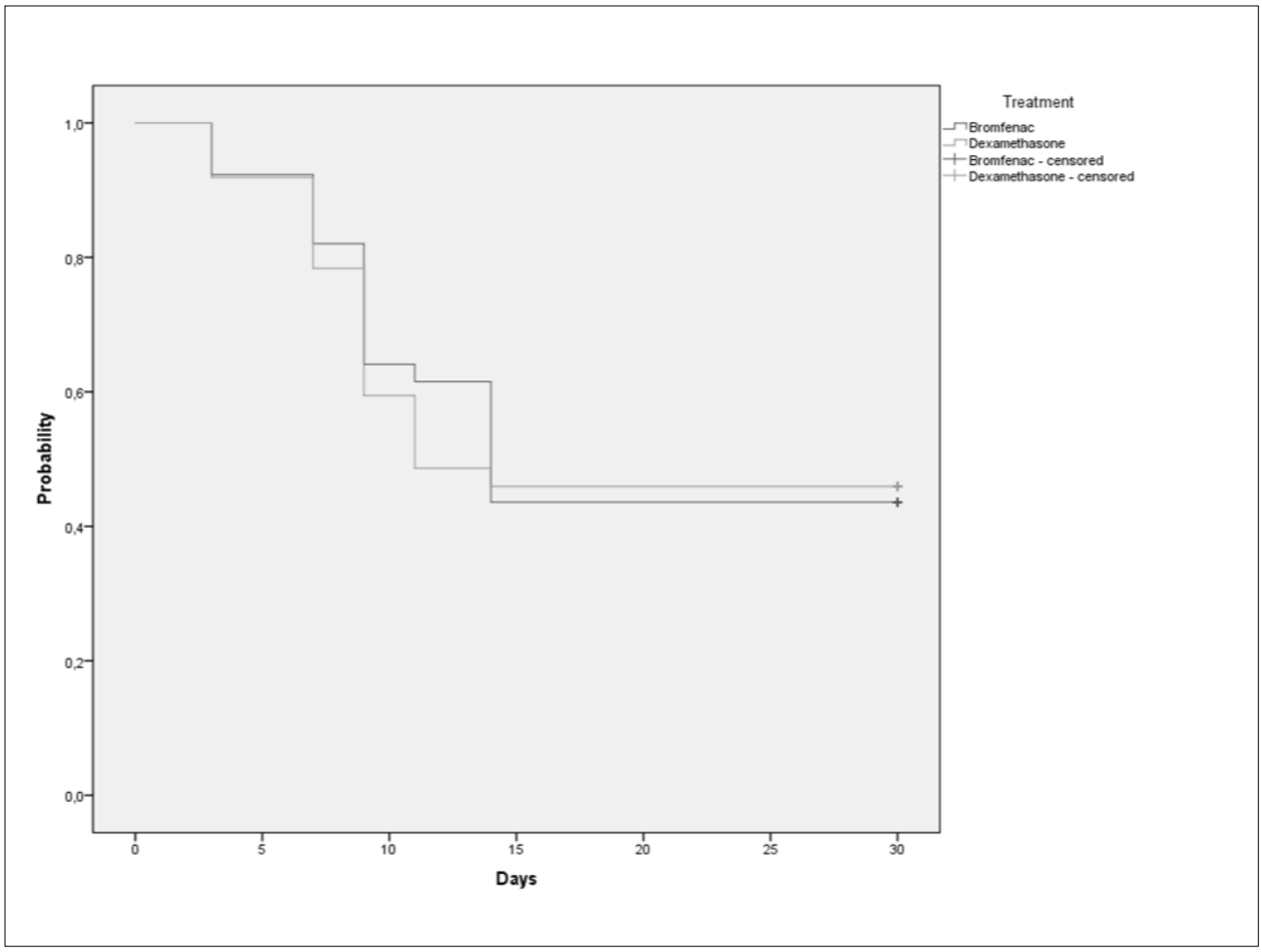

Figure 3. Inflammation in the anterior chamber in the two treatment groups described as time-to-event curves. The event was defined as postoperative flare equal or inferior to the preoperative flare value (primary endpoint, part one). The survival curve did not show any statistically significant difference between the two treatments groups at all time points (Log Rank Mantel-Cox p=0.924).

Table 5. Number of patients with laser flare value equal or inferior to preoperative value at different follow-up visits after cataract surgery.

Postoperative Visit	**N. of patients returned to preoperative values of laser flare**	
	Group 1 (Dexamethasone)	Group 2 (Bromfenac)
Day 1	0	0
Day 3	3	3
Day 7	5	5
Day 9	7	8
Day 11	4	0
Day 14	1	7
Day 30	0	1
Patients not returned to preoperative flare value by the end of the study	17	14
Lost to follow-up	0	1
Total	37	39

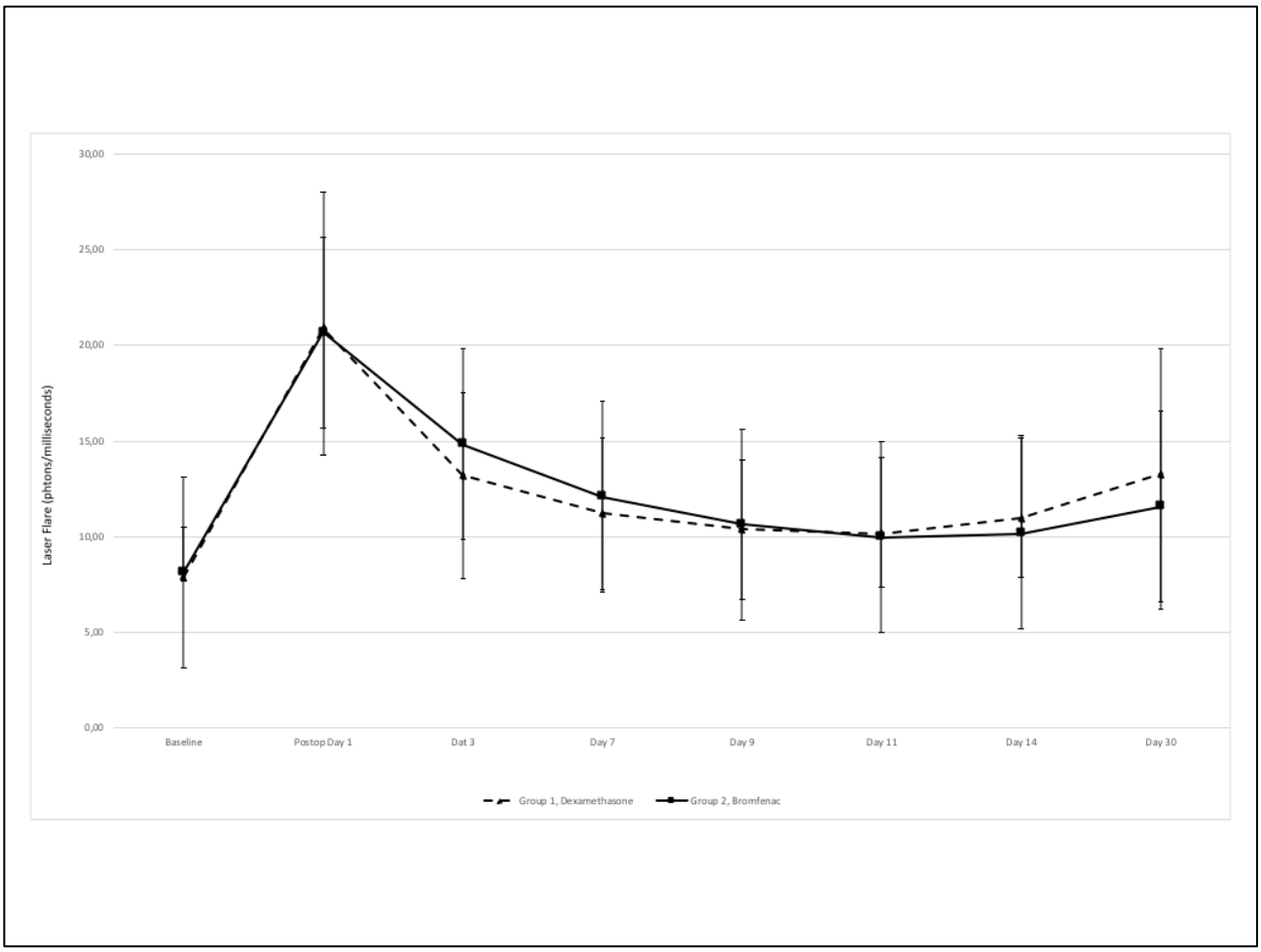

Figure 4 Laser flare photometry at each time point in both treatment groups. Mean laser flare values significantly increased the day after surgery and decreased after starting the therapies in a similar manner in the two groups. There was no statistically significant difference at all time postoperative points between dexamethasone and bromfenac groups. Bars represent standard error.

Secondary outcomes

Visual acuity improved steadily after surgery in both groups at all time points (Figure 5); mean BCVA was >20/30 at postoperative day 1 and >20/25 by day 3. The number of subjects with 20/20 BCVA at postoperative day 14 was 23 (60%) and 28 (72%) in dexamethasone and bromfenac group, respectively (p = 0.371). There was no statistically significant difference between dexamethasone and bromfenac in terms of mean BCVA at all time points (F score = 0.369, p = 0.545).

The proportion of patients with central macular thickness >300 microns at day 30 did not differ significantly between treatment groups but was in favor of bromfenac (11 patients [30%] in dexamethasone group vs. 7 patients [20%] in bromfenac group).

On the regards of mean macular thickness, there was no statistically significant difference between dexamethasone and bromfenac groups one month after cataract surgery. (293.51 ± 61.55 vs 274.82 ± 28.17 microns, respectively; F score = 1.954; p = 0.166; Figure 6).

The presence of intraretinal cysts in all OCT images was investigated to detect the presence of subclinical cystoid macular edema. No bromfenac recipients showed intraretinal cysts in the OCT scans at any time; one patient in dexamethasone group showed intraretinal cysts one month after surgery.

None of the patients in either group had ocular discomfort at day 14. In general, very few patients reported postoperative ocular discomfort during the study. Comparison of the seven symptoms measured by the OCGA questionnaire (eye pain, tearing, itching, foreign body sensation, photophobia, eye discharge, and haziness) did not show significant between-group differences (data not shown). No significant difference existed among the two study arms in terms of intraocular pressure. No systemic adverse events were reported throughout the study period.

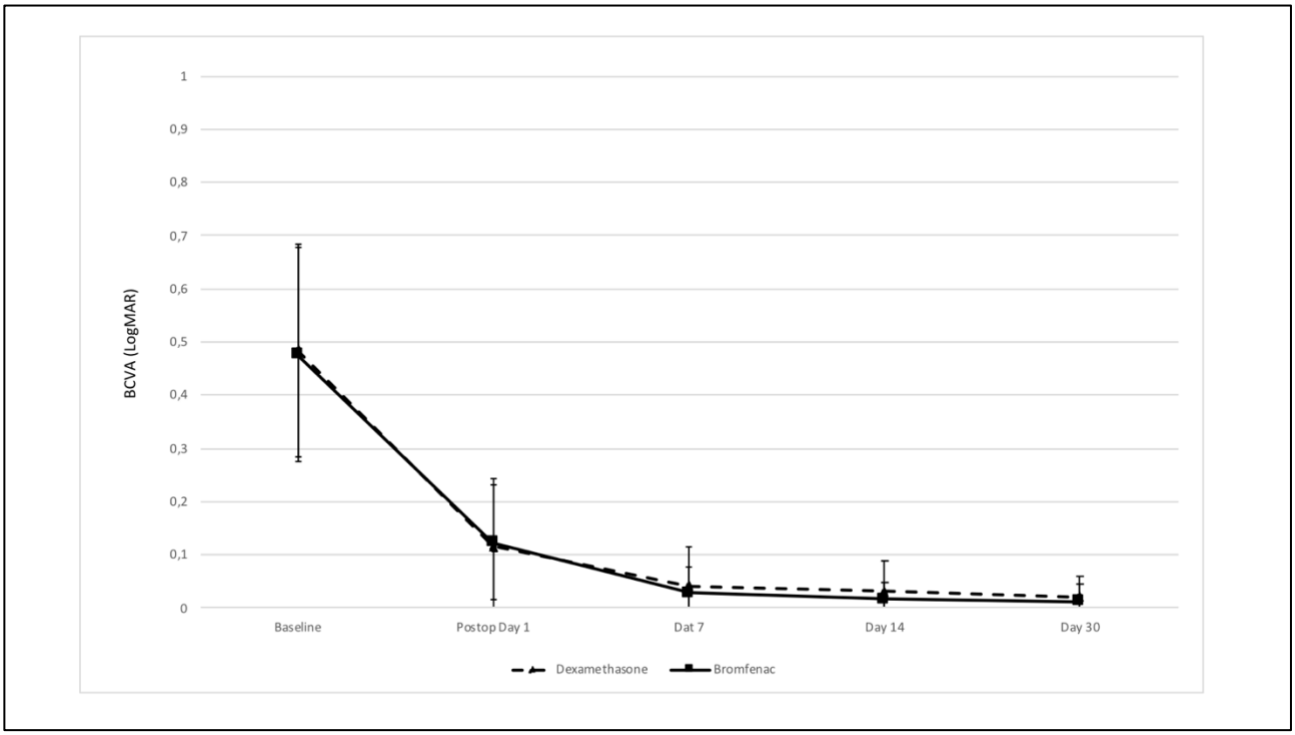

Figure 5. Best corrected visual acuity. Mean visual acuity improved steadily after phacoemulsification in both groups. BCVA was >20/30 at postoperative day 1 and >20/25 by day 3. Bars represent standard error. BCVA, best corrected visual acuity.

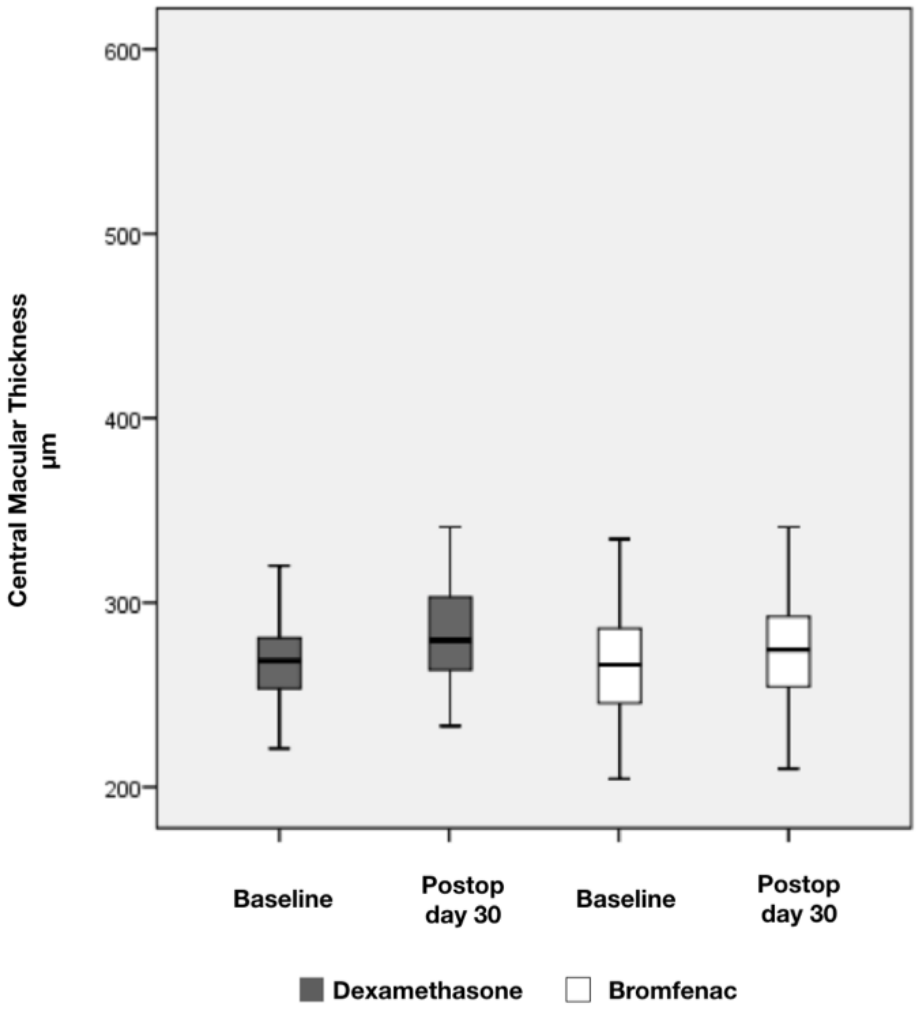

Figure 6. Macular thickness measured by OCT in both groups. Although mean macular thickness increased more in the dexamethasone group than in the bromfenac group at one month after cataract surgery, the difference between preoperative and postoperative values was not significative in both groups.

DISCUSSION

This clinical trial showed that bromfenac 0.09% was as effective as dexamethasone 0.1% in reducing anterior chamber inflammation after cataract surgery. Although the confrontation between ophthalmic NSAIDs and steroids will continue in the literature[36], our study tries to set new standards in the evaluation of postoperative inflammation by using laser flare photometry. The PREMED study recently demonstrated that topical NSAIDs are more effective than steroids in the prevention of macular edema after cataract surgery but failed to show differences between groups in terms of anterior segment inflammation.[44] Precise measurement of inflammation in the anterior chamber may demonstrate unseen, persistent, low-grade inflammation and explain why some eyes with no apparent signs of inflammation develop macular edema weeks after cataract surgery.

Laser flare photometry permits to accurately measure anterior chamber inflammation. This method is objective and highly reproducible.[85] Most published studies on topical NSAIDs after cataract surgery relied on subjective slit lamp evaluation of postoperative inflammation.[117] These grading systems were based on uveitis studies and might be inappropriate to evaluate clinical conditions where the amount of postoperative inflammation is minimal, such as after uncomplicated phacoemulsification.[81] The Standardization of Uveitis Nomenclature Working Group measured anterior chamber flare using a grading scale based on visibility of the iris details using slit lamp examination.[48] The updated Laser Flare Meter FM-700 can precisely differentiate anterior chamber flare on a scale from 2 to 1000 ph/msec.

This study presented new information on postoperative inflammation after uncomplicated phacoemulsification. Evaluation of operated eyes using the Laser Flare Photometer revealed subtle aspects of ocular inflammation that could not be detected by slit lamp. Inflammation measured as mean laser flare values increased after surgery and significantly decreased after starting topical treatment in both groups. Not all the patients returned to their preoperative laser flare values one month after cataract surgery, suggesting that a two weeks treatment may be inadequate for some patients. It would be very useful to individuate beforehand the eyes that will need a longer anti-inflammatory therapy after cataract surgery. This long-lasting inflammation might explain the occurrence of pseudophakic macular edema several weeks after uneventful cataract surgery in eyes that might have had prolonged subclinical inflammation but appeared unremarkable at slit lamp examination.[113]

Pseudophakic macular edema is caused by breakdown of the blood-retina barrier.[17] The incidence and the consequences on visual acuity of subclinical macular edema after phacoemulsification are certainly underestimated.[118,119] The rates of progression of subclinical macular edema to a symptomatic form are unknown.[23] Although the study was not designed to adequately estimate

macular edema and the differences between study groups were not statistically significative, it showed a trend toward increased macular thickness in the dexamethasone group one month after surgery. The proportion of patients with central macular thickness >300 microns at day 30 was greater in dexamethasone group. One patient in dexamethasone group showed OCT signs of subclinical cystoid macular edema. These differences could be clinically relevant because modest changes in macular thickness may induce remarkable reduction of contrast sensitivity.[120]

A debate on the role of topical NSAIDs after cataract surgery is currently ongoing. Although not accepted by all authors,[33] it has been recently demonstrated that NSAIDs, are more effective than topical steroids in preventing cystoid macular edema (CME).[45,69,108,112,121] Unfortunately, these papers focused on OCT findings and they were not able to accurately measure intraocular inflammation after surgery.[122] A recent Cochrane review was not able to make evidence-based recommendations for treatment of inflammation after uncomplicated phacoemulsification in non-diabetic patients.[36] Our clinical trial demonstrated that bromfenac and dexamethasone were equally effective in reducing anterior chamber inflammation after cataract surgery. Most of the published studies on postoperative outcomes after cataract surgery did not present precise methods to measure inflammation such as laser flare photometry. OCT is accurate but macular edema is a relative rare, tardive consequence of uncontrolled intraocular inflammation and breakdown of blood-retina barrier. One strength of the present study was the exact quantification of intraocular inflammation at several time points after cataract surgery. One limit of the study was the absence of a group of treatment based on the combination of bromfenac and dexamethasone. The use of a single anti-inflammatory agent may increase the compliance to postoperative therapy and reduce side effects. NSAIDs generally have a better pharmacological profile than steroids, requiring fewer administrations and carrying no risk to increase IOP.

This clinical trial shed more light into the controversy between ophthalmic NSAIDs and steroids, in the attempt to clarify their effect as monotherapy on the anterior chamber inflammation after routine cataract surgery. It implies that modern tools to objectively assess ocular inflammation should be included in future studies evaluating anti-inflammatory treatments for ocular diseases.

Chapter 7

Research Article - Adv Ther. 2020 Jul;37(7):3223-3233.

Persistence of inflammation after uncomplicated cataract surgery: a six-month laser flare photometry analysis

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ABSTRACT

Purpose: To evaluate, by laser photometry, the persistency of anterior chamber flare after uneventful phacoemulsification in asymptomatic patients with no signs of inflammation at the slit-lamp.

Method: 75 patients previously enrolled in a randomized clinical trial that evaluated inflammation after uneventful phacoemulsification in eyes treated with dexamethasone 0.1% ophthalmic suspension (Group 1) or bromfenac 0.09% ophthalmic solution (Group 2) for two weeks. Anterior chamber inflammation was investigated by laser flare photometry. After 30 days from surgery, laser flare showed persistently elevated values. For this reason, patients were further analyzed at 3 and 6 months. Additionally, optical coherence tomography was used to measure the central macular thickness (CMT) and to assess for postoperative pseudophakic macular edema.

Results: When compared to preoperative values, laser flare photometry demonstrated persistent ocular inflammation at postoperative day 90 and 180 in group 1, but not in group 2. Laser flare values showed a significant reduction in group 2 compared to group 1 throughout all the follow-up ($p<0.001$). The increase in mean CMT at day 90 and 180 respect to baseline was statistically significant in group 1 but not in group 2, where it decreased to levels similar to preoperative value. Group 1 showed a higher increase in mean CMT compared to group 2 throughout all the follow-up ($p<0.001$). The proportion of patients that developed pseudophakic CME was 14% (n=5) and 0% (n=0) in group 1 and group 2, respectively ($p=0.02$). The bivariate analysis demonstrated a positive correlation among laser flare and CMT values in group 1 but not in group 2.

Conclusion: Anterior chamber inflammation persists for more than 30 days in a significant proportion of patients after uncomplicated cataract surgery and may be responsible for late onset of cystoid macular edema cases.

Keywords: cataract surgery; laser flare photometry; non-steroidal anti-inflammatory drugs

Trial Registration Number: NCT03317847

INTRODUCTION

Phacoemulsification with intraocular lens implantation is one of the most commonly performed surgical procedures in the world.[123] Constant improvements in equipment and techniques are at the base of the diffuse excellent results, and possibly of patient's increasingly high expectation. For successful outcomes, it is critical to control postoperative intraocular inflammation and prevent the delayed occurrence of pseudophakic cystoid macular edema (PCME) one to six months after surgery.[33,67]

Recent findings demonstrated that topical non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, alone or in combination, are effective to reduce the risk of PCME.[31,33,44,114,124] Unfortunately, there is limited data on the mechanisms intervening into the restore of the blood-aqueous barrier after the surgical trauma and the timing linking the supposedly persisting (but unseen)

postoperative anterior chamber inflammation and the rare (but sight-threatening) pseudophakic cystoid macular edema.[97,125]

Intraocular inflammation after modern uncomplicated cataract surgery is generally minimal and, therefore, difficult to measure. The Standardized Uveitis Nomenclature (SUN) grading system[48], often used in clinical trials, relies on slit-lamp examination and it is inadequate to describe low levels of anterior chamber flare or discriminate among the effects of different medications.[125,126] Laser flare photometers can measure anterior chamber inflammation very precisely, even when it is not clinically evident at the slit-lamp.[31,85,125] Laser flare photometry (LFP) has been very effective in clinical trials on therapeutic regimens after cataract surgery.[31,77,127]

In a recent randomized controlled trial, by LFP we measured anterior chamber flare after straightforward, uncomplicated cataract surgery.[124] Patients were divided into two treatment groups and received dexamethasone or NSAID eye drops for two weeks. Interestingly, apart from the demonstration that the two medications were equally effective, we noticed that the anterior chamber flare measured by LFP remained elevated and it did not return to baseline values after one month. Moreover, central macular thickness was statistically increased at postoperative day 30 when compared to day zero (before cataract surgery). After the conclusion of the previous trial, we decided to follow patients for five more months to extend the evaluation of postoperative intraocular inflammation by LFP.

METHODS

Study design

This single-center prospective observational comparative study was conducted at the Ophthalmology Unit of the Azienda USL – IRCCS di Reggio Emilia (Reggio Emilia, Italy). Patients enrolled in the Bromfenac Vs. Dexamethasone (BVD) Study[124] were recalled 90 and 180 days after cataract surgery to evaluate for long-term anterior chamber inflammation with a laser flare photometer. The local ethics committee approved the study protocol and the trial followed the principle of the Declaration of Helsinki. Written informed consent was obtained from all patients. No invasive procedures or experimental therapies were performed. The BVD Study was approved by the Italian Medicines Agency (AIFA) and registered on ClinicalTrials.gov (NCT003317847) and the European Clinical Trials Database (EudraCT Number: 2016-004358-14).

Clinical assessment and medications

All patients that completed the 30-day follow up of the Bromfenac Vs. Dexamethasone (BVD) Study were enrolled in the present clinical trial. Originally, subjects aged 60-year or older with decreased visual acuity due to cataract and no other ocular or systemic comorbidities were enrolled in the BVD

study. Patients were affected by a simple senile cataract and other ocular conditions, such as glaucoma, maculopathies or diabetic retinopathy were reasons for exclusion. For a complete list of inclusion/exclusion criteria and other technical details refer to the published article.[124]
Phacoemulsification and IOL implantation in the bag were routinely performed without special maneuvers or intraoperative complications (mean length of surgery was 14 minutes).[124]
The day after surgery, all patients started treatment with tobramycin 0.3% eye drops (Alcon, Italy), two times daily for the first week. Patients randomized to group 1 received dexamethasone ophthalmic suspension 0.1% (Visufarma, Italy), four times a day for the first week and two times the following week. Patients randomized to group 2 received bromfenac ophthalmic solution 0.09% (Bausch & Lomb, Italy) twice daily for 2 weeks. Bromfenac is approved in the European Union (EU) for the treatment of postoperative inflammation during the first 14 days following cataract surgery.
In the BVD study, patients were examined before surgery (baseline) and at postoperative days 1, 3, 7, 9, 11, 14 (± 1 day) and 30 (± 3 days). For the present study, patients were further examined at postoperative day 90 and 180. Best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, dilated fundus examination, intraocular pressure (IOP) by pneumotonometer, and flare by laser photometry were measured at each visit. Anterior chamber inflammation was evaluated by a laser flare meter (FM-700, Kowa Co. Ltd, Tokyo, Japan) that employs a diode laser beam to quantify the protein concentration in the aqueous humor.[85,128,129] Laser flare values were expressed in photon counts/millisecond (ph/ms). BCVA was assessed using an electronic Snellen chart, and readings were converted to the logarithm of the minimum angle of resolution (LogMAR) values. Optical coherence tomography (OCT) (Spectralis, Heidelberg Engineering, Germany) was used to quantify macular thickness and to search for intraretinal cystic changes. Measurements of BCVA, IOP, laser flare photometry and OCT were performed by a certified technician unaware of treatment allocation. Ocular discomfort (eye pain, tearing, itching, foreign-body sensation, photophobia, eye discharge and haziness) was determined using the Ocular Comfort Grading Assessment (OCGA).[117] Patients graded each symptom as none (0), mild (1), moderate (2) or severe (3) at each visit. Ocular and systemic adverse events were recorded based on questioning patients or observation by investigators.

Outcomes

The primary efficacy endpoint was the level of postoperative inflammation in the anterior chamber at postoperative day 180, evaluated by laser flare photometry. Secondary endpoints were: (1) laser flare values at postoperative day 90; (2) proportion of subjects with 20/20 best-corrected visual acuity (BCVA) at day 180; (3) central macular thickness (central subfield) at day 90 and 180; (4) proportion of patients with no ocular discomfort at day 90 and 180 assessed by OCGA scale; (5) incidence of ocular and systemic adverse events. The number of patients developing cystoid macular edema was

also evaluated by reviewing all the OCT scans acquired during the trial. PCME was defined as the presence of intraretinal cysts and classified as subclinical (BCVA ≥ 8/10 and CMT ≤ 300 microns) or clinically significant (BCVA < 8/10 and CMT > 300 microns).

Statistical Analysis

Statistical analysis was performed using SPSS software (v. 25, SPSS Inc.). Statistical analysis considered timepoints at postoperative day 0, 30, 90 and 180 (plus day 1 and 14 for LFP). A general linear model with repeated measures for independent group comparison was performed to evaluate normally distributed continuous variables and to test the overall statistical significance of the entire observation period. A paired sample t-test was used to determine statistical significance between two different time points within the same treatment group. Qualitative or categorical variables were reported as frequencies and proportions. Proportions were compared using the chi-square or Fisher exact test, whichever was applicable. All tests were two-sided. A P value of less than 0.05 was considered to indicate statistical significance. Pearson's correlation coefficient was used to assess the statistical relationship between LFP and CMT values.

RESULTS

Patients' characteristics

In the BVD Study, 76 subjects were randomized after cataract surgery into two groups. For the following two weeks, group 1 (37 eyes) received dexamethasone 0.1% ophthalmic suspension and group 2 (39 eyes) bromfenac 0.09% ophthalmic solution. One patient in group 2 was lost at postoperative day 7 and was not included in this study.[124] All seventy-five patients were successfully recalled for the present study. Baseline characteristics did not differ significantly between treatment groups (Table 6).

Inflammation measured by laser flare photometry

As previously reported, there were no statistically significant differences between groups at day 14 and 30, meaning that both treatments were equally effective in reducing intraocular inflammation when compared to postoperative day 1 (Fig. 7). However, when compared to preoperative day 0 (baseline), mean laser flare did not return to the presurgical levels either at the end of the treatment (day 14) or by the end of the BVD study (day 30) in the two groups (Tab. 7). Extending the observation period with the present study, we found that mean laser flare remained sustained and never returned to baseline value in group 1, where the differences between day 0 and day 90 and between day 0 and day 180 were statistically significant (Tab. 7). Differently, in group 2, mean laser flare diminished and returned to baseline value: the differences between day 0 and day 90 and

between day 0 and day 180 were not statistically significant (Tab. 7). The general linear model with repeated measures test applied from day 0 to day 180 showed a significant reduction of laser flare values in group 2 compared to group 1 ($p<0.001$).

Table 6. Patients' characteristics at baseline. BCVA = Best Corrected Visual Acuity

	Group 1 (Dexamethasone, n = 37)	**Group 2** (Bromfenac, n = 38)
Age		
Mean (y)	76 ± 6	77 ± 6
Range (y)	60 - 86	60 - 86
Sex		
Males (n)	14	14
Females (n)	23	24
Mean length of surgery (min)	13.89 ± 2.98	14.03 ± 2.95
Mean BCVA (logMAR)	0.48 ± 0.20	0.47 ± 0.20
Mean laser flare (ph/ms)	7.88 ± 2.60	8.16 ± 2.20
Central macular thickness (micron)	272.27 ± 32.99	268.03 ± 27.08

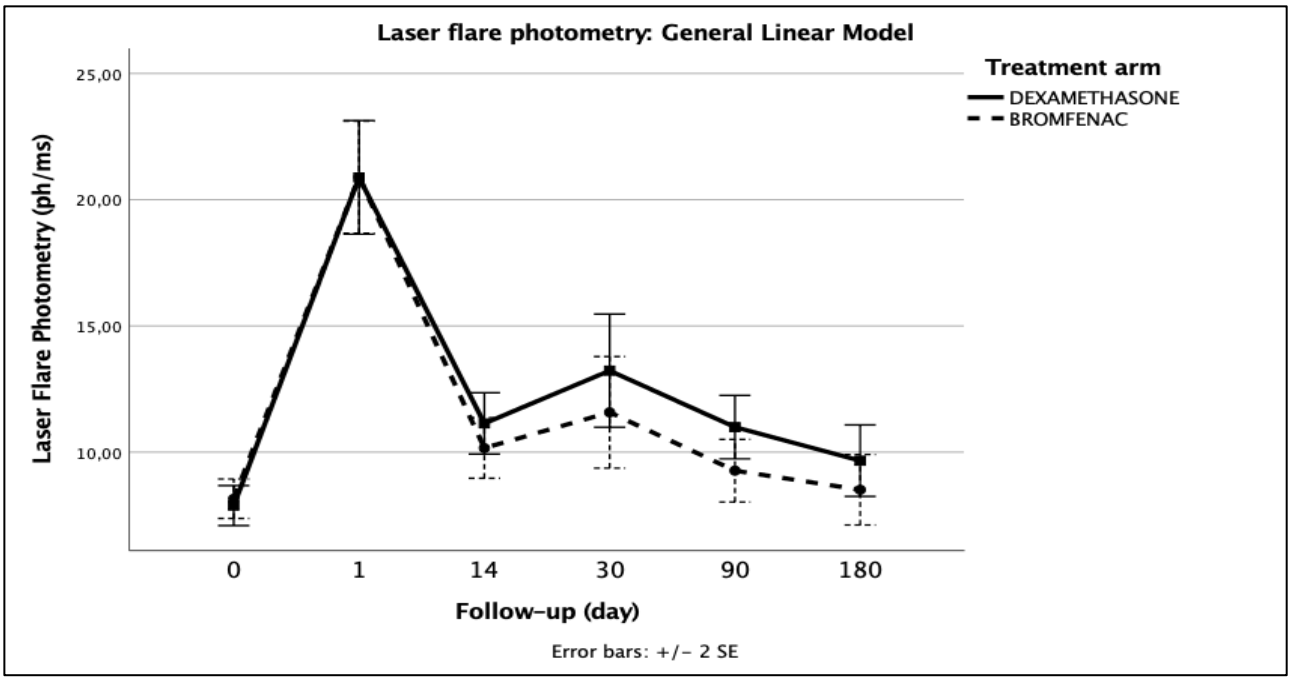


Figure 7. Laser flare photometry in dexamethasone (group 1) and bromfenac (group 2) treated patients. Therapies were equally effective in reducing intraocular inflammation when compared to postoperative day 1. However, when compared to preoperative day 0 (baseline), mean laser flare did not return to the presurgical levels either at the end of the treatment (day 14) or by the end of the BVD Study (day 30) in the two groups. Extending the observation period with the present study, we found that mean laser flare remained sustained and never returned to baseline value in group 1 at day 90 and 180. In group 2, mean laser flare significantly diminished and returned to baseline values at both day 90 and 180. The general linear model with repeated measures test applied from day 0 to day 180 showed a significant reduction of laser flare values in group 2 compared to group 1 ($p<0.001$).

Table 7. Differences between preoperative and postoperative values at different time points for laser flare photometry and central macular thickness in the two treatment groups. The *p* at each time point was calculated with a paired sample t-test.

Group 1 (Dexamethasone 0.1%)				
Laser Flare (ph/ms)				
	Day 0	Vs.	**Day 30**	
	7.88 ± 2.60		13.23 ± 6.58	*P < 0.001*
	Day 0	Vs.	**Day 90**	
	7.88 ± 2.60		10.99 ± 4.16	*P < 0.001*
	Day 0	Vs.	**Day 180**	
	7.88 ± 2.60		9.66 ± 4.60	*P = 0.014*
Central Macular Thickness (µm)				
	Day 0	Vs.	**Day 30**	
	269.22 ± 23.72		291.22 ± 62.41	*P = 0.009*
	Day 0	Vs.	**Day 90**	
	269.22 ± 23.72		282.51 ± 34.77	*P < 0.001*
	Day 0	Vs.	**Day 180**	
	269.22 ± 23.72		278.32 ± 27.75	*P < 0.001*
Group 2 (Bromfenac 0.09%)				
Laser Flare (ph/ms)				
	Day 0	Vs.	**Day 30**	
	8.16 ± 2.20		11.58 ± 7.03	P = 0.005
	Day 0	Vs.	**Day 90**	
	8.16 ± 2.20		9.27 ± 3.47	P = 0.057
	Day 0	Vs.	**Day 180**	
	8.16 ± 2.20		8.51 ± 4.00	P = 0.557
Central Macular Thickness (µm)				
	Day 0	Vs.	**Day 30**	
	268.03 ± 27.08		291.22 ± 62.41	*P = 0.023*
	Day 0	Vs.	**Day 90**	
	268.03 ± 27.08		282.51 ± 34.77	*P =0.075*
	Day 0	Vs.	**Day 180**	
	268.03 ± 27.08		278.32 ± 27.75	*P =0.082*

Best-corrected visual acuity

Mean BCVA improved after surgery in both arms, with no statistically significant differences between groups at day 180 (0.04 ± 0.06 vs. 0.02 ± 0.04; p = 0.202). The number of subjects with a BCVA of 20/20 at postoperative day 180 was 57% (n=21) and 69% (n=26) in dexamethasone and bromfenac group, respectively (chi square test, p=0.421). The general linear model with repeated measures method applied from day 0 to day 180 showed no differences among groups (p=0.656).

Central macular thickness

Mean central macular thickness was increased when compared to baseline values in both groups at day 30. At day 90 and 180, the difference in mean CMT respect to baseline remained statistically significant in group 1 but not in group 2, where it decreased to preoperative levels (Fig. 8 and Tab. 7). The general linear model with repeated measures test applied from day 0 to day 180 showed a significant increase in CMT in group 1 compared to group 2 ($p<0.001$; Fig. 8).

Bivariate analysis by Pearson's coefficient demonstrated a statistically significant positive linear correlation among laser flare and CMT values in group 1 at postoperative day 30 and 90, but not in group 2 at all the others time points. (Fig. 9 and Tables 8-13).

The proportion of patients that developed pseudophakic CME was 14% (n=5) and 0% (n=0) in group 1 and group 2, respectively (chi square test p=0.02). Cystoid macular edema did not occur in any of the patients who received bromfenac 0.09% solution after surgery. Five patients treated with dexamethasone 0.1% suspension developed signs of cystoid macular edema between day 30 and 180 after surgery. Among them, two were subclinical with BCVA of 20/20 and showed a single intraretinal parafoveal cyst at OCT during the planned visit at day 180. Three patients returned to the clinic with clinical significant PCME between day 30 and 180. One patient presented with a BCVA of 20/40, multiple intraretinal cysts and CMT of 511 microns after 6 weeks from surgery. Another eye showed BCVA of 20/50, multiple intraretinal cysts and CMT of 395 microns at day 90. Another patient complained of blurred vision (20/40) at day 120 and presented significant PCME with CMT of 315 microns.

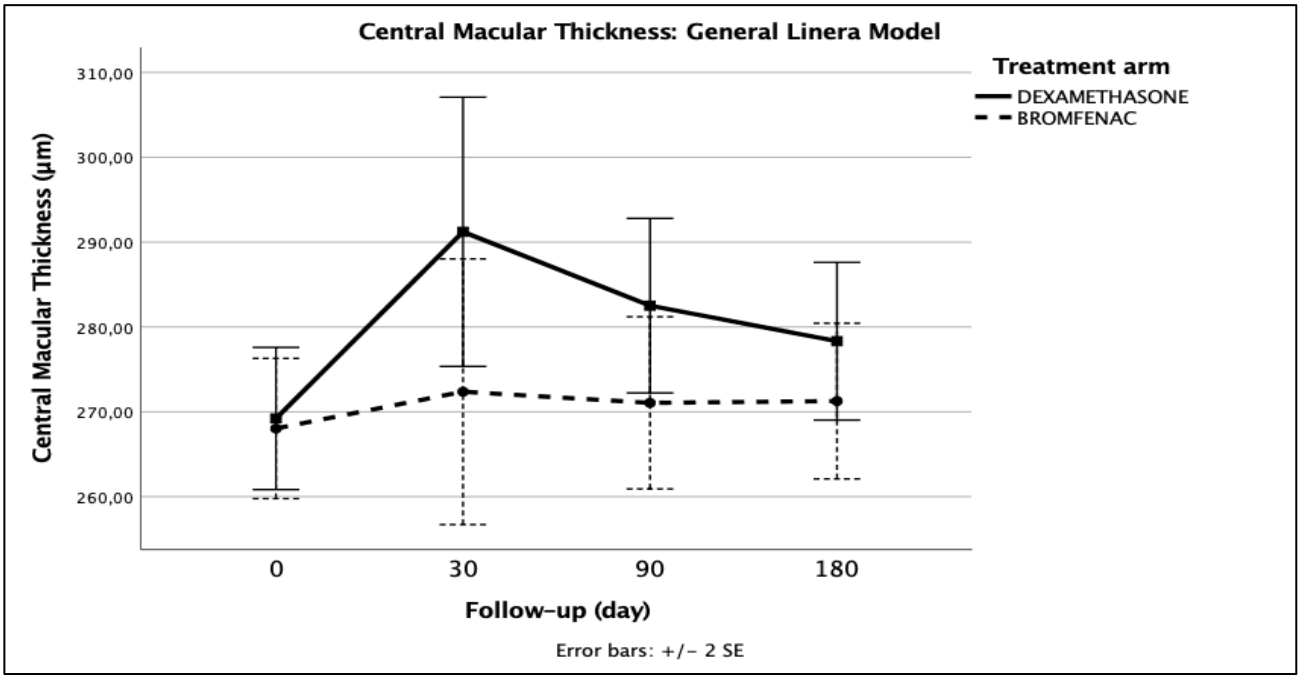
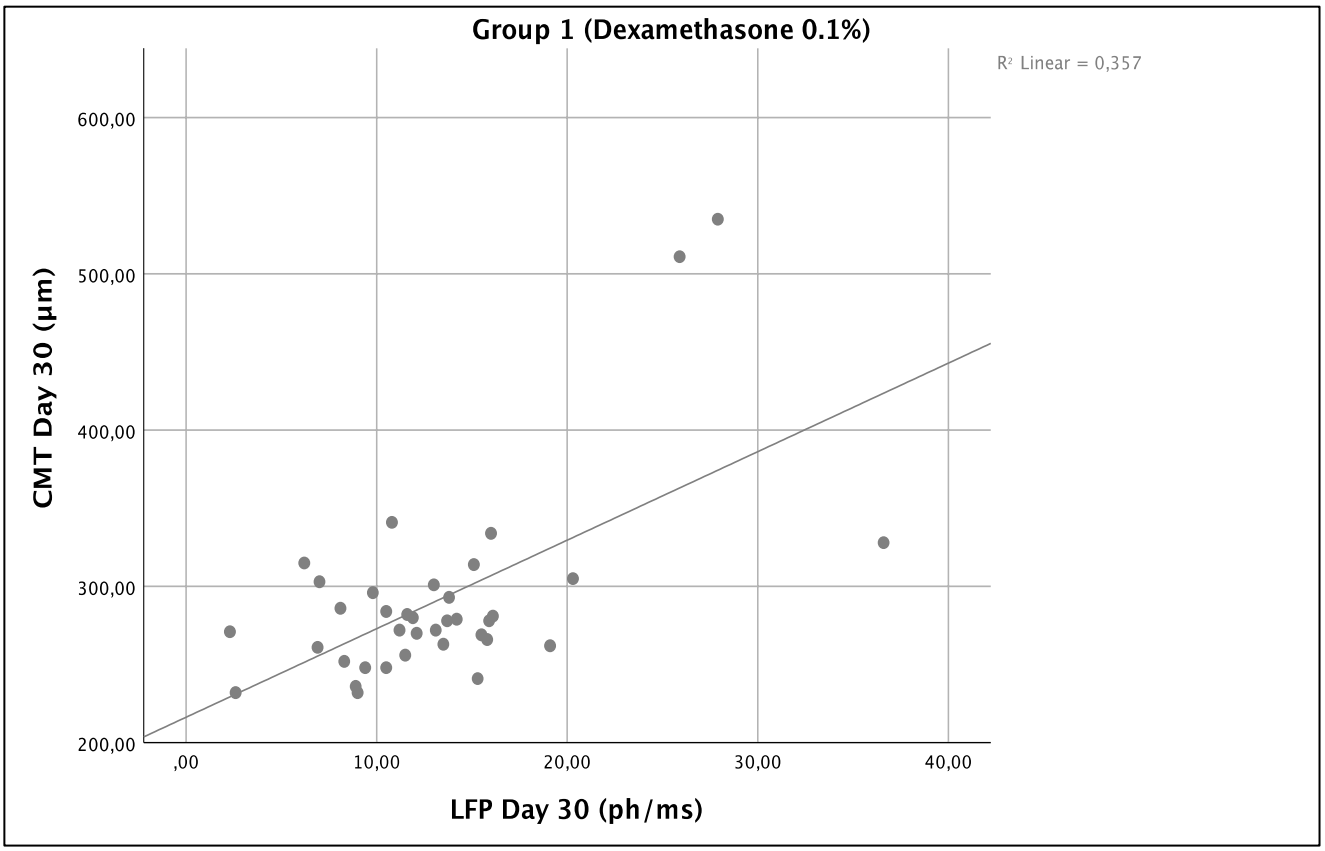


Figure 8. Central macular thickness (CMT) measured by OCT in dexamethasone (group 1) and bromfenac (group 2) treated patients. Mean central macular thickness was increased when compared to baseline values in both groups at day 30. At day 90 and 180, the difference in mean CMT respect to baseline remained statistically significant in group 1 but not in group 2, where it decreased to preoperative levels. The general linear model with repeated measures test applied from day 0 to day 180 showed a significant increase in CMT in group 1 compared to group 2 ($p<0.001$).

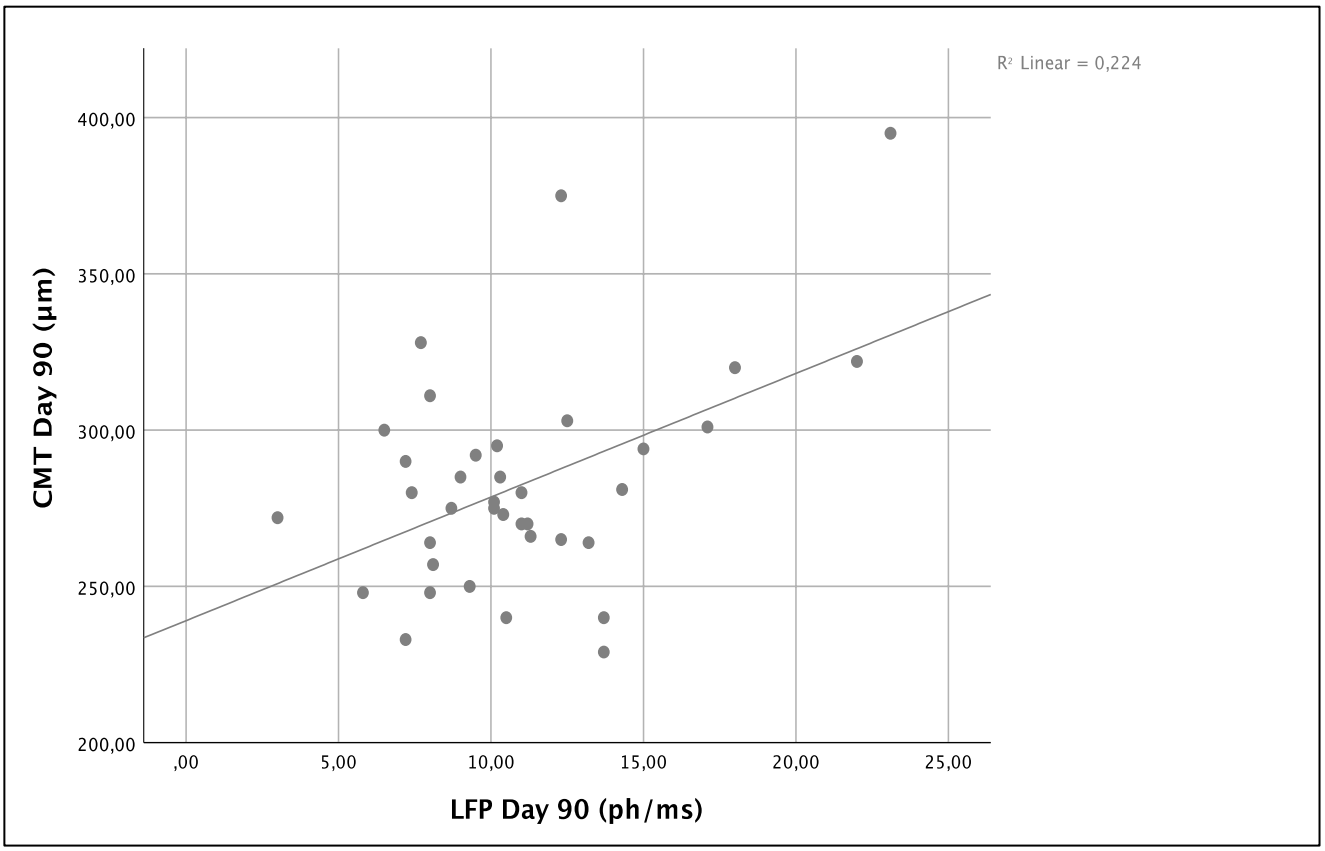


Correlations

		LFP Day 30	CMT Day 30
LFP Day 30	Pearson Correlation	1	0,597**
	Sig. (2-tailed)	-	0,0001
	N	37	37
CMT Day 30	Pearson Correlation	0,597**	1
	Sig. (2-tailed)	0,0001	-
	N	37	37

**. Correlation is significant at the 0.01 level (2-tailed).

Figure 9.A.1 and Table 8. Bivariate analysis of laser flare and macular thickness for Group 1 at day 30.
Scatter Dot and Pearson's correlation coefficient demonstrated a statistically significant positive linear relationship between laser flare photometry values and central macular thickness at postoperative day 30.

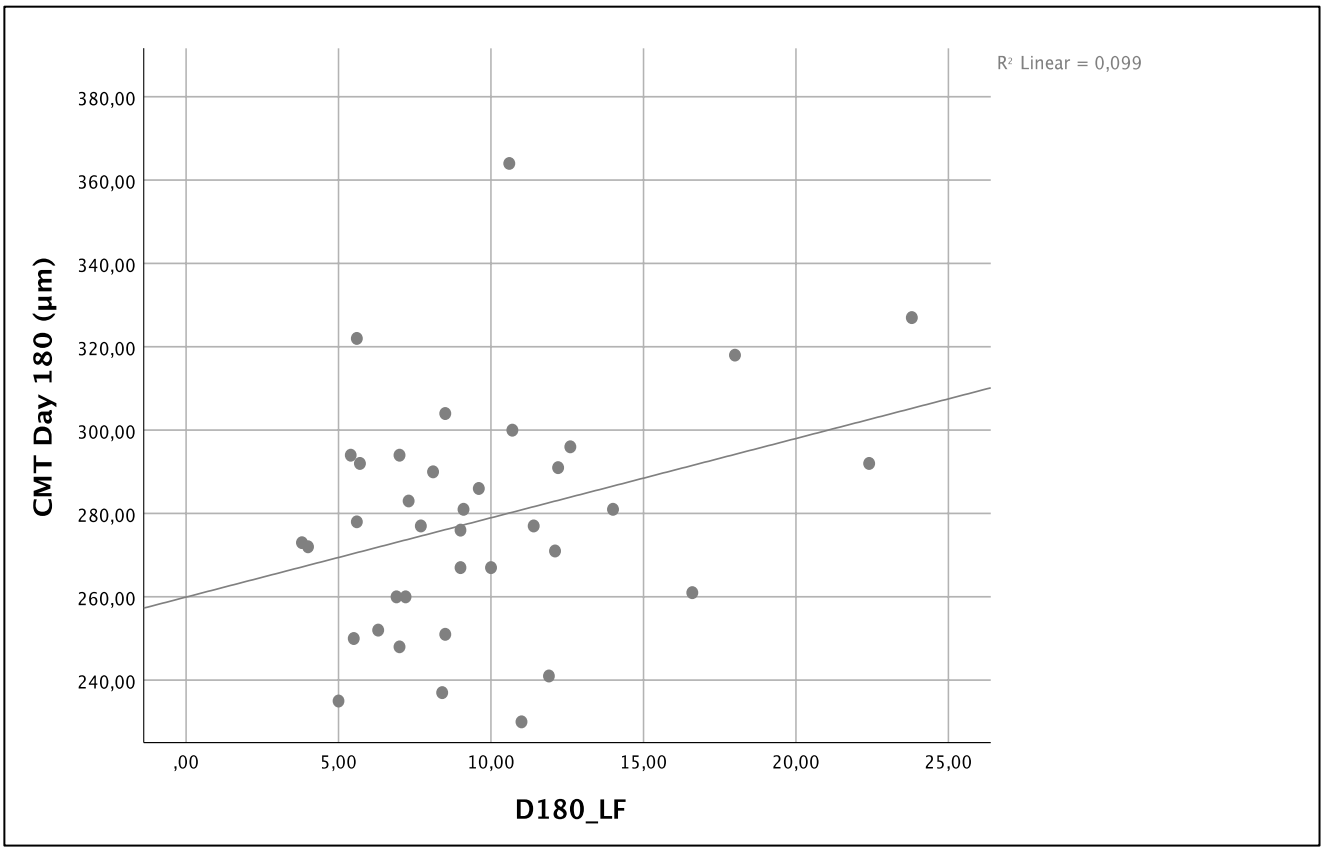


Correlations

		LFP Day 90	CMT Day 90
LFP Day 90	Pearson Correlation	1	0,473**
	Sig. (2-tailed)	-	0,003
	N	37	37
CMT Day 90	Pearson Correlation	0,473**	1
	Sig. (2-tailed)	0,003	-
	N	37	37

**. Correlation is significant at the 0.01 level (2-tailed).

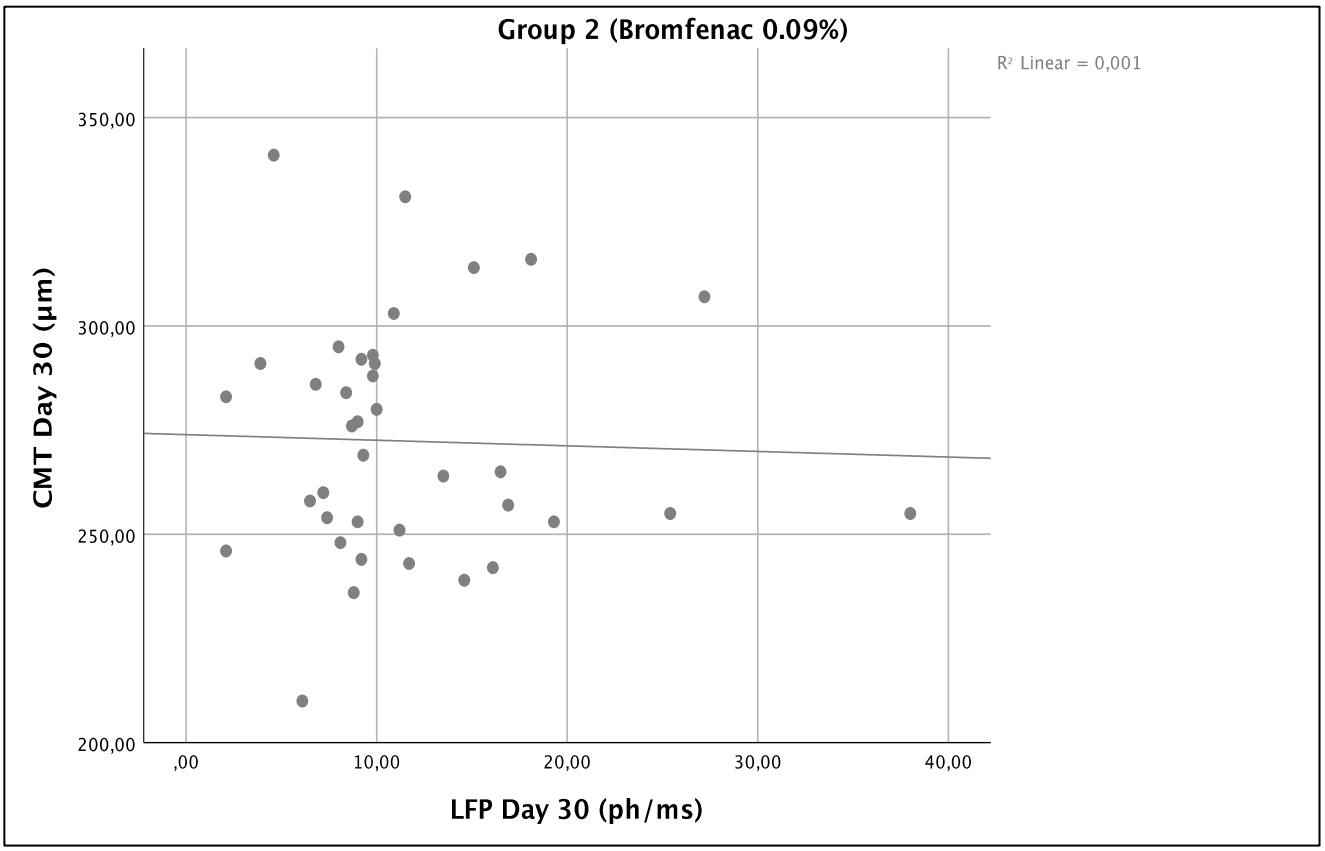
Figure 10.A.2 and Table 9. Bivariate analysis of laser flare and macular thickness for Group 1 at day 90.
Scatter Dot and Pearson's correlation coefficient demonstrated a statistically significant positive linear relationship between laser flare photometry values and central macular thickness at postoperative day 90.



Correlations

		LFP Day 180	CMT Day 180
LFP Day 180	Pearson Correlation	1	0,315
	Sig. (2-tailed)	-	0,057
	N	37	37
CMT Day 180	Pearson Correlation	0,315	1
	Sig. (2-tailed)	0,057	-
	N	37	37

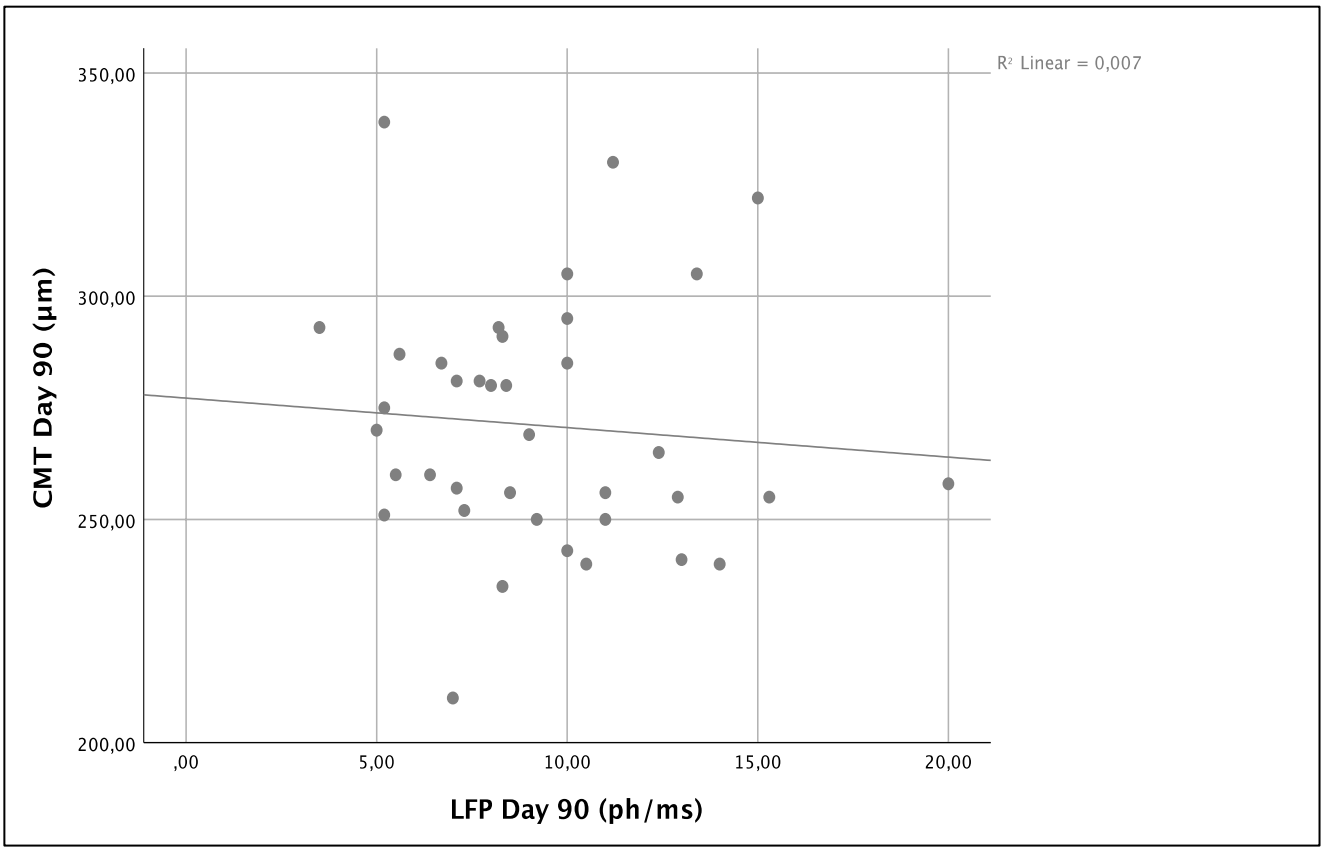
Figure 11.A.3 and Table 10. Bivariate analysis of laser flare and macular thickness for Group 1 at day 180.
Scatter Dot and Pearson's correlation coefficient demonstrated a positive linear relationship between laser flare photometry values and central macular thickness at postoperative day 180.



Correlations

		LFP Day 30	CMT Day 30
LFP Day 30	Pearson Correlation	1	-0,033
	Sig. (2-tailed)	-	0,843
	N	38	38
CMT Day 30	Pearson Correlation	-0,033	1
	Sig. (2-tailed)	0,843	-
	N	38	38

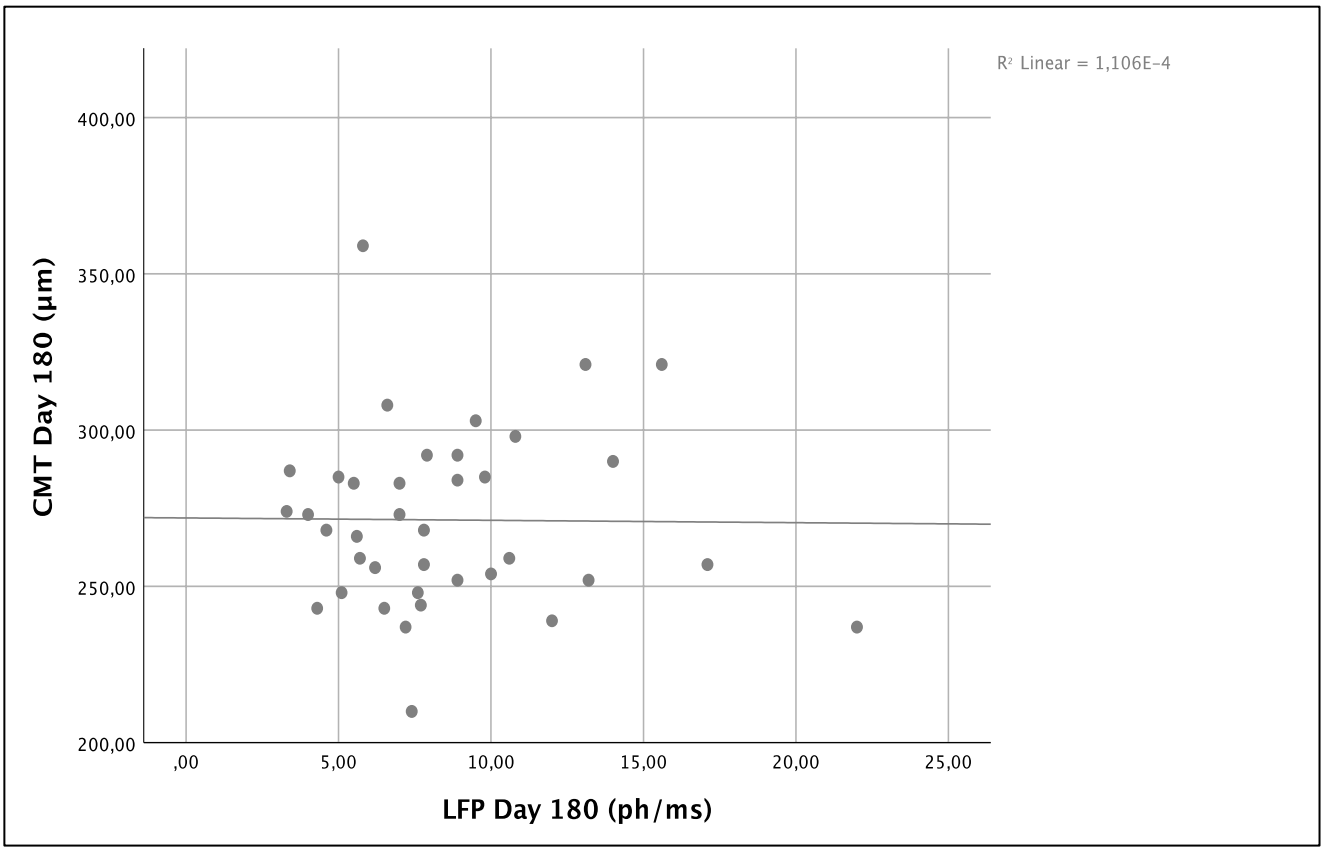
Figure 12.B.1 and Table 11. Bivariate analysis of laser flare and macular thickness for Group 2 at day 30.
Scatter Dot and Pearson's correlation coefficient demonstrated no correlation between laser flare photometry values and central macular thickness at postoperative day 30.



Correlations

		LFP Day 90	CMT Day 90
LFP Day 90	Pearson Correlation	1	-0,083
	Sig. (2-tailed)	-	0,618
	N	38	38
CMT Day 90	Pearson Correlation	-0,083	1
	Sig. (2-tailed)	0,618	-
	N	38	38

Figure 13.B.2 and Table 12. Bivariate analysis of laser flare and macular thickness for Group 2 at day 90.
Scatter Dot and Pearson's correlation coefficient demonstrated no correlation between laser flare photometry values and central macular thickness at postoperative day 90.



Correlations

		LFP Day 180	CMT Day 180
LFP Day 180	Pearson Correlation	1	-0,011
	Sig. (2-tailed)	-	0,950
	N	38	38
CMT Day 180	Pearson Correlation	-0,011	1
	Sig. (2-tailed)	0,950	-
	N	38	38

Figure 14.B.3 and Table 13. Bivariate analysis of laser flare and macular thickness for Group 2 at day 180.
Scatter Dot and Pearson's correlation coefficient demonstrated no correlation between laser flare photometry values and central macular thickness at postoperative day 180.

Other results

None of the patients reported postoperative ocular discomfort during the study.[124] Comparison of symptoms measured by OCGA questionnaire did not show significant between-group differences at day 90 and 180 (data not shown). No significant difference existed among the two study arms in terms of intraocular pressure. No systemic adverse events were reported throughout the study period.

DISCUSSION

The surprising and novel aspect of our study is the demonstration that intraocular inflammation persists for 6 months after routine cataract surgery. These levels of inflammation were detectable only by laser flare photometry and not perceptible at the slit lamp, but very likely they were clinically significant. Remarkably, increased flare values were related to increased macula thickness in subjects that received a short course of postoperative steroidal eye drops. In the same group of patients, five demonstrated unequivocal signs of cystoid macula edema at OCT. Although needing confirmation, our findings shed more light into tardive CME after routine cataract surgery.

It should be said that this study was not initially conceived to last 6 months. Another limitation is that it was meant to compare two short therapies after cataract surgery and not to evaluate the "natural history" of anterior chamber inflammation after uneventful phacoemulsification. Our clinical trial was underpowered to compare the occurrence of pseudophakic macular edema in different treatment arms. Nor to prove the correlation between laser flare value and the risk of macular edema after phacoemulsification. Other limitations are small population size and absence of an arm treated with combined therapy (topical steroid plus NSAID). The duration of intervention was limited because bromfenac is approved in EU for only 14 days after surgery. Nonetheless, we strongly believe that our results provide valuable insights since no other studies investigated the course of inflammation with LFP for such an extended follow-up.

Figure 7 combines the results obtained from the BVD Study and the present one for both dexamethasone and bromfenac groups. Notably, inflammation in the anterior chamber remained sustained for the first postoperative month independently of the treatment when compared to baseline values.[124] This is in line with two previous publications where eyes were analyzed by laser flare photometry after cataract surgery: in both studies, laser flare values did not return to baseline after one month.[31,127] After three and six months, flare diminished to baseline levels in the group initially treated with bromfenac but not in the group that received dexamethasone. The two curves were statistically different between day 30 and day 180, with group 2 showing a significant reduction of laser flare values in the long term. Two-week therapy with topical NSAID can diminish anterior chamber inflammation to preoperative levels in most cases.

Figure 8 shows changes in mean central macular thickness at day 0, 30, 90 and 180 in both groups and confirms previous reports.[19–21] After one month from surgery, the macular thickness was increased when compared to baseline in both groups, but this remained true only for group 1 at postoperative day 90 and 180. Group 1 showed a higher elevation of mean CMT when compared to group 2 for all the postoperative time points. Topical NSAID seems to protect the retina in the long-term also in terms of cystoid macular changes seen at OCT. We reviewed all the postoperative OCT scans performed on enrolled patients and we found no intraretinal cysts in group 2. Five patients in group 1 showed variable degrees of pseudophakic cystoid macular edema at different timepoints. These results are in line with the PREMED study, where bromfenac had protective effects against PCME after three months from cataract surgery.[44]

Figure 9 shows a moderate positive correlation between laser flare and macular thickness in group 1 by bivariate analysis at day 30 and 90. There was no significant correlation at day 180 in group 1 and all time points for group 2. These results are in line with the time of presentation of clinically detectable cystoid macular changes, since 4 out of 5 patient developed CME before six months from the surgery. Although this correlation among laser flare and macular thickness cannot completely explain the pathogenesis of PCME, it confirms what is generally accepted: persistent anterior chamber inflammation after cataract surgery is a major cause of pseudophakic cystoid macular edema.

It is believed that surgical trauma and manipulation within the anterior chamber may disrupt the blood-aqueous barrier, leading to the release of arachidonic acid from the iris and production of leukotrienes and prostaglandins via the lipoxygenase and the cyclooxygenase pathway, respectively.[17] Inflammatory mediators may diffuse posteriorly into the vitreous and damage the blood–retinal barrier, causing increased permeability of the perifoveal capillaries and fluid accumulation in the macula.[23] Authors believe that NSAIDs may be more effective than steroids at modulating these inflammatory processes and preventing PCME.[34,109,111–114] Our findings may support this evidence, in particular, if we consider group 1 data. Postoperative treatment in that arm (dexamethasone 0.1% eye drops, four times a day in the first week and two times the second) was probably underdosed, revealing a correlation between anterior chamber inflammation and macular edema that otherwise remains unnoticed, especially if laser flare photometry is not available. Additionally, independently from the duration of therapy, our results are also supported by the well documented pharmacological properties of NSAID vs steroids. NSAIDs agent are believed to suppress the inflammatory cascade in the early postoperative period[38], reducing the accumulation of inflammatory mediators and, thus, lowering the chance of developing of PCME. Presumably, our 2 weeks single-therapy with bromfenac was protective against macular edema because inflammatory

molecules might not have reached critical values. Further studies with multiple aqueous samples are mandatory to confirm this hypothesis.

On the other hand, in terms of slit-lamp examination, routine cataracts that were included in our study had an unremarkable postoperative course. Very few patients reported ocular discomfort during the study. Visual acuity markedly improved with most of the eyes achieving a best-corrected visual acuity of 20/25 or better by postoperative day 3 in both groups.[124] With the exclusion of the five subjects that developed clinically significant macular edema, patients did not require additional topical or systemic therapies.

In conclusion, this study found unexpectedly prolonged levels of anterior chamber inflammation after uneventful cataract surgery. The amount of inflammation detected by laser photometry was minimal but had apparent clinical consequences in the arm where it persisted significantly longer. In fact, not only group 1 showed increased macular thickness both when compared to baseline and group 2, but also 14% of its eyes developed signs of pseudophakic macular edema. Remarkably, none of the eyes treated with a short course of topical NSAID demonstrated intraretinal cysts at OCT. Finally, the levels of anterior chamber inflammation seem to correlate to the increased macular thickness in the group of patients that received topical dexamethasone for two weeks after phacoemulsification.

CONCLUSION

Although questions on the optimal postoperative therapy remain (i.e., combined topical steroid plus NSAID), the present study demonstrated that postoperative intraocular inflammation might last longer than we believe if not adequately treated. The individual risk factors and the mechanisms behind the occurrence of unexpected PCME after uncomplicated cataract surgery in patients that routinely receive longer postoperative anti-inflammatory therapy should be investigated in larger controlled clinical trials.

Chapter 8

CONCLUSION

Modern phacoemulsification is safer than ever, but pseudophakic CME remains one of the most frequent postoperative complications leading to unfavorable visual outcomes.[102]

Although CME is a well-defined clinical entity, its exact pathogenesis has not been fully clarified. The inflammatory theory consequent to surgical trauma seems to be the most probable.

However, it is still hard to define the risk of CME based on the amount of inflammatory mediators in the AC, because inflammation after uncomplicated phacoemulsification is generally low and not easily clinically detectable.[130]

Postoperative inflammation after surgery is routinely assessed by grading cells and flare in the AC with the slit lamp and adopting the Standardization of Uveitis Nomenclature (SUN) system.[48] Although it is an extremely valid method in case of evident alteration of aqueous humor optical properties (such as in uveitis), it is subjective and not suitable for discriminating unremarkable levels of inflammation.[130]

Our literature review showed that trough years, more sensitive and sensible method of analysis had been proposed in order to assess inflammation quantitatively.

Undoubtedly, modern laboratory tests are the most efficient to this scope. However, they present several limitations: they are invasive, require a consistent amount of aqueous fluid to perform tests on different molecules, they cannot be performed multiple times throughout the follow-up to titrate inflammatory proteins because of risks for the patients and ethically reasons.

It appeared evident the necessity to obtain consistent and comparable data but in a non-invasive manner. Several authors described the feasibility of anterior segment OCT[55,56] to recognize inflammatory cells and flare and to obtain an objective quantification of the inflammation in the AC. However, this application is still in its infancy, and no clinical trials on phacoemulsification have been published. Future clinical trial will be specifically designed to develop this promising technology, also considering that OCT is a fundamental tool of routine clinical practice.

Our data demonstrated that the LFP is an excellent tool for this scope, because it discriminates minimum variations between shallow levels of inflammation in a non-invasive way[85], and can be used to follow patients over time.[124,131] The adoption of LFP permits the acquisition of objective data, eliminating the discrepancy in the grading of flare, between examiners with different level of experience.[132] These characteristics are crucial in the research field to produce consistent and comparable data eliminating bias of interobserver subjective inflammation analysis.

The literature review highlights the existence of signs of correlation between the breakdown of the blood-aqueous barrier due to post-surgical inflammation (even if low) and the risk of CME development. The analysis of the laser flare values in patients affected with clinically significant pseudophakic CME revealed higher ph/ms counts compared to patients without CME.[70,124,131]
We believe that LFP values could be considered as biomarkers of the blood-retinal barrier breakdown. It might help to identify patients who are at risk in advance and prescribe the best anti-inflammatory therapy to treat CME.
However, like any analysis tool, LFP has some limitations, such as acquisition time and several measurements (from 5 to 6) to process reliable results on inflammation. Compared to LFCP, the clinical grading requires only a few seconds of observation at the slit lamp and allow clinicians to assess inflammation at a glance. LFCP needs to be placed in a completely darkened room, and it requires reasonable cooperation from patients to perform a good acquisition. More often than not, the first day after surgery, patients might present with a corneal haze that can alter the quality of the measurements, even if we did not experience this problem in our clinical trials. Flare and cell meters do not distinguish inflammatory cells from pigment and debris (lens particles) that may be mistakenly counted as cells. Finally, the instrument requires the costs of purchase and maintenance, and not all structure can cope with this economic effort.
As regards the first objective of this thesis, our review confirms the existence of a correlation between the degree of anterior chamber inflammation measured with LFCP and the risk of CME after uncomplicated phacoemulsification. To reinforce these findings, it is mandatory to adopt quantitative methods of analysis, especially in the setting of clinical trials in which it is indispensable to produce accurate and comparable data. Despite the undoubted usefulness of clinical grading in routine clinical practice, especially to manage the high flux of patients, it is not suitable to produce objective statistical analysis with a potential clinical application.
The confirmation of a link between anterior chamber inflammation and CME through the follow-up might help ophthalmologist to identify patients at risk in advance, aiming to titrate therapy to prevent an unsatisfactory visual impairment.
Laser flare photometry is a non-invasive technique and, thanks to its high sensitivity, reproducibility and repeatability, might be a new standard to quantitatively explore inflammation after cataract surgery, which is characterized by a shallow inflammatory reaction.
Based on the evidence derived from the analysis of the literature, our data provide valuable findings on the current knowledge about PCME and the best anti-inflammatory postoperative therapy to cure or prevent it. In 2018, the PREMED study [45] attempted to provide clear evidence showing that the steroid - NSAID combination reduces the risk of PCME by five times compared to monotherapy.

Despite the beneficial and exciting results, it is evident that the PREMED study provided indirect data on the treatment of postoperative inflammation and therefore, on the risk of PCME. The inflammation analysis in the PREMED study, as in many others, was conducted according to subjective and not quantitative methods. The enrolled patients presented levels of inflammation equal to 0 or 1 of the SUN system, therefore clinically irrelevant. Moreover, it was impossible to produce comparative statistical analysis based on these only two inflammatory grade.

We believe that the adoption of LFP is necessary to test the anti-inflammatory effect of different drugs.[124,131] We decided to compare Bromfenac 0.09% with Dexamethasone 0.1% as a single therapy to control postoperative inflammation measured by LFP after uncomplicated cataract surgery. The BVD study[124] showed that bromfenac 0.09% was as effective as dexamethasone 0.1% in reducing anterior chamber inflammation after cataract surgery. Although the comparison between different therapy protocol will continue to be investigated, our study tries to promote a new standard of evaluation of postoperative inflammation after cataract surgery. According the current state of art, we strongly believe that it is more important to measure the real anti-inflammatory effect of steroids or NSAID on the anterior chamber and where the inflammation begins, rather than the indirect therapeutic effect on PCME.

LFP allowed us to obtain new information on the natural course of postoperative inflammation after uncomplicated cataract surgery and to highlight subtle aspects unseen in previously published papers on this topic. As reported by other authors, inflammatory flare significantly increase the day after surgery and gradually decrease after the starting of therapy. However, we found a prolonged inflammatory response up to 6 months measured with LFP that had not been documented by any other study in the literature.[131] These findings correlate with results published in the PREMED study because patients treated with Bromfenac 0.09% presented an overall lower level of laser flare count and a lower incidence of PCME compared to patients treated with dexamethasone 0.1%. On the other hand, patients treated with dexamethasone 0.1% presented an overall higher level of central macular thickness during the follow-up. Interestingly, the level of LFP correlated positively with the macular changes after surgery, because the higher the ph/ms count, the higher the CMT. Our long-term analysis demonstrated that the long-lasting inflammation is a potential risk factor for the late occurrence of PCME, also several weeks after uneventful surgery in eyes that might have had prolonged subclinical inflammation but appeared unremarkable at the slit-lamp examination.

Finally, our findings support the evidence that NSAIDs may be more effective than steroids at reestablishing the blood-retinal barrier and preventing CME. Patients treated with steroid only presented a greater incidence of PCME compared to patients treated with NSAID. Probably, our 2-weeks single-therapy with bromfenac 0.09% prevent the development of PCME because

inflammatory molecules did not reach critical values. We believe that this correlation is likely because of the well-established positive correlation between the readings of laser flare value with the real concentration of molecules into the aqueous humor measured with laboratory tests.

This data confirms that NSAIDs are effective in reducing the risk of CME and that LFP could be considered as a valuable biomarker to predict the risk of CME.

Our results support the use of the LFP as a tool to identify patients with a higher and abnormal inflammatory reaction after surgery and, if necessary, to intensify postoperative anti-inflammatory therapy.

The most important limitations of our studies are the limited number of patients in the sample and the absence of a combined steroid-NSAID therapy group. On the other hand, we confirmed that a single therapy with NSAID is effective in controlling inflammation, sparing the adoption of steroids for more complicated cases and avoiding their adverse reaction.

We are planning to perform a future study that will investigate not only the single therapy schedule but also the combination NSAID-Steroid. Moreover, it will study if the pretreatment of patients with NSAID can downregulate the inflammatory cascade corresponding to a lower level of LFP and, consequently, to a lower risk of PCME in the follow-up.

In conclusion, inflammation after cataract surgery and the prevention of PCME are still topics of debate. Laser flare photometry might be the new standard to measure inflammation after surgery, especially in the setting of clinical trials, thanks to its high reproducibility and sensitivity, with no additional risk for patients. Moreover, our results demonstrate the efficacy of NSAID to restore inflammation and prevent CME, with a better pharmacological profile compared to steroids.

Future studies on inflammation after any eye surgery require quantitative methods of analysis to produce objective and comparable data.

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