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Ketorolac plus Tobramycin/Dexamethasone versus Tobramycin/Dexamethasone after Uneventful Phacoemulsification Surgery: A Randomized Controlled Trial

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Key Words
Cataract · Lens · Phacoemulsification

Abstract
Background/Aims: To evaluate the benefit of adding a nonsteroid agent to an antibiotic/steroid combination after uneventful phacoemulsification, adopting a weekly follow-up, to gain insight into the optimal duration of postoperative treatment and to examine whether risk factors for inflammation exist. ***Methods:*** Patients were randomized to (i) tobramycin 0.3%-dexamethasone 0.1%, 1 drop q.i.d. (n = 72), and (ii) a combination of tobramycin 0.3%-dexamethasone 0.1%, 1 drop q.i.d., plus ketorolac tromethamine 0.5%, 1 drop t.i.d. (n = 73). On days 7, 14, 21 and 28, the frequency of inflammation-related signs (corneal edema, conjunctival hyperemia, anterior chamber or Tyndall reaction) as well as best-corrected visual acuity (BCVA) were measured. On day 21, logistic regression was performed to evaluate risk factors for inflammation. ***Results:*** The frequency of inflammation-related signs did not differ between the 2 groups at any time point, neither did BCVA. On day 21, pseudoexfoliation was associated with the presence of any inflammation-related sign (OR = 4.5; 95% CI: 1.2–16.0; p = 0.022). No evidence of clinically significant cystoid macular edema became evident in either group. ***Conclusion:*** The addition of ketorolac did not seem to offer any additional benefit in terms of inflammation-related signs. Four weeks appeared as an adequate treatment interval. Special attention should be paid to patients with pseudoexfoliation.

Introduction

Several combinations of postoperative treatment regimens/arms have been assessed after cataract surgery, such as a topical steroid plus antibiotic [1–3], a nonsteroid plus antibiotic [2], a steroid agent alone [4, 5], a nonsteroid agent alone [6, 7] or a combination of a nonsteroid with a steroid agent [5]. The different treatment regimens have aimed at reducing postoperative inflammatory response and infection rates after cataract surgery.

Interestingly, the duration of postoperative treatment remains an open field, as studies report various treatment intervals such as 2 weeks [4], 3 weeks [1, 3], 4 weeks [2, 8] or an unspecified range between 4 and 6 weeks [5, 6]. To our knowledge, no study has focused on the 'optimal' duration of postoperative treatment.

In the light of the above, this randomized trial has a triple aim: (i) to evaluate the effectiveness of the addition of a nonsteroid agent to a well-established antibiotic/ste-

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roid combination, i.e. tobramycin/dexamethasone plus ketorolac versus tobramycin/dexamethasone; (ii) adopting a close weekly follow-up to specify the optimal duration of postoperative treatment, measuring the frequency of inflammation-related signs (corneal edema, conjunctival hyperemia, anterior chamber or Tyndall reaction) as well as best-corrected visual acuity (BCVA) during a 28-day interval, and (iii) choosing postoperative day 21 as a representative point between weeks 2 and 4 to examine possible risk factors for the presence of inflammation-related signs.

Patients and Methods

Recruitment of Patients, Exclusion Criteria and Preoperative Assessment

The patients were recruited from the Department of Ophthalmology, Veroia General Hospital, Veroia, Greece, during the time period of October 1, 2009, to January 10, 2010. Preoperatively, all patients underwent a routine ophthalmological examination, i.e. slit-lamp examination, measurement of BCVA, tonometry and fundoscopy in addition to a complete medical history. Patient information included age, sex, educational and marital status, current smoking, and relevant clinical data such as presence of hypertension, diabetes mellitus (with or without diabetic retinopathy), pseudoexfoliation, glaucoma and age-related macular degeneration. Cataract was classified as immature (partially opaque lens, disk view hazy), mature (completely opaque lens, no disk view), hypermature (liquefied cortical matter) and morgagnian.

Exclusion criteria were the following: (i) history of intraocular surgery on the eye to be operated; (ii) any previous episode of uveitis in the eye to be operated; (iii) severe systemic disease (heart failure of the New York Heart Association stage III of IV, end-stage renal failure, pulmonary failure, receiving chemotherapy), and (iv) regular, systemic use of steroid or nonsteroid antiinflammatory drugs (NSAID) during the last 3 months.

Description of Procedure – Randomization of Patients

Three days before surgery, ketorolac tromethamine 0.5% (Acular®; Allergan; 1 drop × 3) and tobramycin 0.3% (TobraDex®; Alcon) were administered (1 drop × 5). All patients received half a tablet of acetazolamide 250 mg the night prior to surgery and on the morning before surgery.

On the day of surgery, the pupil was dilated with tropicamide 0.5% (Tropixal; Demo) and phenylephrine hydrochloride 5% (phenylephrine; Cooper) drops every 10 min for 30 min before surgery. The lid and the periorbital skin were cleaned and the conjunctival cul-de-sac was irrigated with povidone iodine. 1 amp of topical anesthetic lidocaine 2%-sodium hyaluronate 0.3% (Visthesia™; Zeiss) was administered 10 min prior to the beginning of surgery. The lid and periorbital skin were then draped and an open wide speculum was placed. The eye was irrigated with balanced salt solution (BSS®; Alcon).

A 2.8- to 3.0-mm clear corneal incision and side-port paracentesis were made. Viscoelastic sodium hyaluronate 1.4% (Healon GV® OVD; AMO) was injected into the anterior segment. Continuous curvilinear capsulorrhexis and hydrodissection with BSS were then performed. This was followed by phacoemulsification, irrigation and aspiration of cortical remnants via the phaco-chop method by using Alcon Series 20000® Legacy®. Healon GV infusion and implantation of the foldable posterior chamber intraocular lens was performed using the injector system recommended for each lens. Healon GV was subsequently removed and the surgical wounds were hydrated with BSS. No sutures were needed. All wounds were checked for leakage and found to be watertight. The duration of the application of ultrasound during phacoemulsification was recorded. All procedures were performed by the same surgeon (L.P.).

The patients were randomized to 1 of the 2 postoperative treatment arms: (i) tobramycin 0.3%-dexamethasone 0.1% (TobraDex), 1 drop 4 times per day (TD group; n = 72), and (ii) combination of tobramycin 0.3%-dexamethasone 0.1% (TobraDex), 1 drop 4 times per day, plus ketorolac tromethamine 0.5% (Acular), 1 drop 3 times per day (TD-K group; n = 73). The topical treatment was administered for 28 days after phacoemulsification. The study was masked to the patients, i.e. they received unmarked bottles so as to be unaware of which treatment they received. Patients who underwent vitrectomy due to posterior capsule rupture were excluded.

Follow-Up of Patients

Each patient was independently assessed by 2 ophthalmologists at each visit (I.P.C. and L.P.). The follow-up visits were on postoperative days 7, 14, 21 and 28. On all these visits, the patients were evaluated for (i) corneal edema, (ii) conjunctival hyperemia, (iii) anterior chamber (Tyndall) reaction, and (iv) BCVA. In case 1 inflammation-related sign (corneal edema, conjunctival hyperemia or Tyndall reaction) was present on day 28, the treatment was continued. On day 35, patients who needed continuation of the treatment were once again evaluated as above.

Irrespective of continuation, on day 42 all patients underwent fundoscopy and an Amsler grid test, so as to trace any suspicious signs for the development of clinically significant cystoid macular edema (CME). In addition, pain and ocular discomfort (itching or foreign-body sensation) were evaluated via a 0–10 visual analog scale on each follow-up visit.

Statistical Methods

Based on the presence of corneal edema (E), Tyndall reaction (T) and conjunctival hyperemia (H), a binary variable expressing the presence of any of them (designated as presence of any E/T/H, for reasons of brevity) was generated, i.e. 0 = no E/T/H, 1 = presence of E or H or T. The differences in frequency of E, H and T, as well as in the presence of any E/T/H, between the 2 groups were compared by the χ^2 or Fisher's exact test, as appropriate. Concerning BCVA, the descriptive statistics of the log of the minimum angle of resolution (logMAR) were computed as appropriate [9]. Differences in BCVA between the 2 groups were evaluated by the Mann-Whitney-Wilcoxon test for independent samples (MWW). Given that 4 comparisons (days 7, 14, 21, 28) took place, the Bonferroni correction for multiple comparisons was adopted; as a result, the threshold of statistical significance for p was set to 0.05/4 = 0.0125.

Concerning the association between E/T/H on day 21 and possible risk factors, the following were evaluated using the appropri-

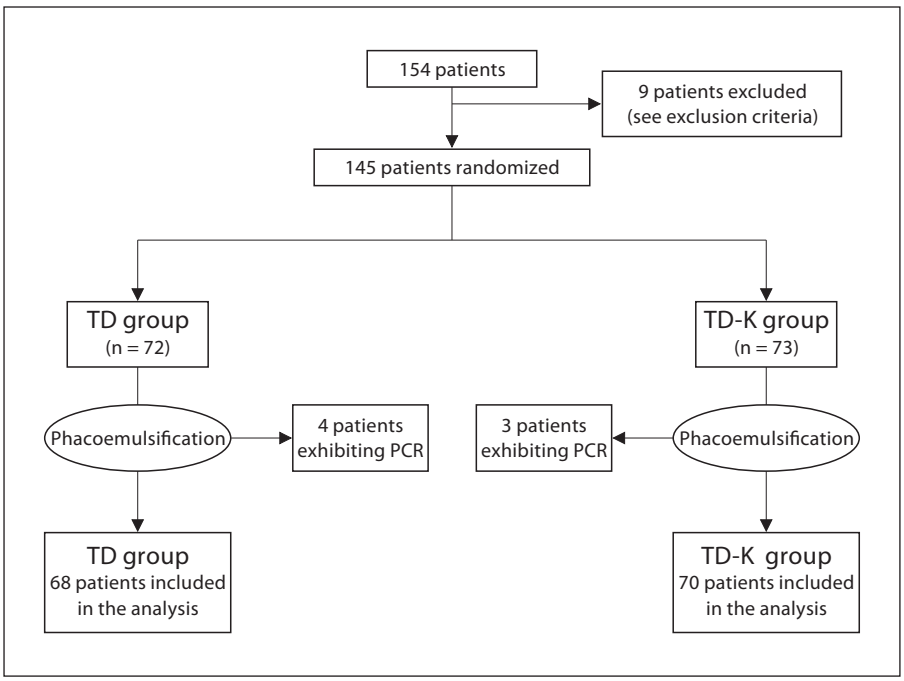

Fig. 1. Exclusion criteria and randomization of patients. PCR = Posterior capsule rupture.

ate univariate tests: sex, age, education, marital status, current smoking status, hypertension, diabetes mellitus, diabetic retinopathy, glaucoma, age-related macular degeneration, BCVA prior to phacoemulsification, pseudoexfoliation, cataract stage and duration of the application of ultrasound during phacoemulsification. In case of statistically significant associations, a logistic regression model was constructed, so as to estimate the OR along with its 95% CI.

Statistical analysis was performed with Stata 8.0 statistical software (StataCorp, College Station, Tex., USA). This study is in accordance with the Declaration of Helsinki and has been approved by the local institutional review board. Written informed consent was obtained from all patients.

Results

The study design as well as the randomization of patients to the 2 groups are depicted in the respective flow chart (fig. 1). Table 1 presents the demographic and clinical features as well as the lifestyle habits of the study groups.

The presence of corneal edema did not differ between the 2 groups at any time point (for TD and TD-K, respectively: 62/68 vs. 68/70 on day 7, $p = 0.162$, Fisher's exact test; 15/68 vs. 8/70 on day 14, $p = 0.094$, χ^2 test; 3/68 vs. 3/70 on day 21, $p > 0.99$, Fisher's exact test; 0/68 vs. 1/70 on day 28, $p > 0.99$, Fisher's exact test) (fig. 2a).

Table 1. Features of the 2 study groups

	TD group	TD-K group
Continuous variables		
Age, years	74.0 ± 7.6	74.3 ± 7.3
Duration of application of ultrasound during phacoemulsification, min	1.7 ± 0.8	1.6 ± 0.5
BCVA prior to phacoemulsification	2.6 ± 0.8	2.7 ± 0.7
Categorical and ordinal variables		
Male sex	40 (58.9)	43 (61.4)
Education		
Primary	56 (82.4)	60 (85.7)
Secondary	10 (14.7)	6 (8.6)
University	2 (2.9)	4 (5.7)
Marital status		
Married	66 (97.1)	68 (97.1)
Single/divorced/widowed	2 (2.9)	2 (2.9)
Current smoking status – yes	11 (16.2)	8 (11.4)
Hypertension – yes	62 (91.2)	61 (87.1)
Diabetes mellitus – yes	7 (10.3)	6 (8.6)
Diabetic retinopathy – yes	2 (2.9)	1 (1.4)
Cataract stage		
Immature	38 (55.9)	32 (45.7)
Mature	27 (39.7)	36 (51.4)
Hypermature	1 (1.5)	2 (2.9)
Morgagnian	2 (2.9)	0 (0.0)
Glaucoma – yes	5 (7.4)	7 (10.0)
Pseudoexfoliation – yes	13 (19.1)	12 (17.1)
Age-related macular degeneration – yes	5 (7.4)	4 (5.7)

Values denote means ± SD or numbers with percentages in parentheses.

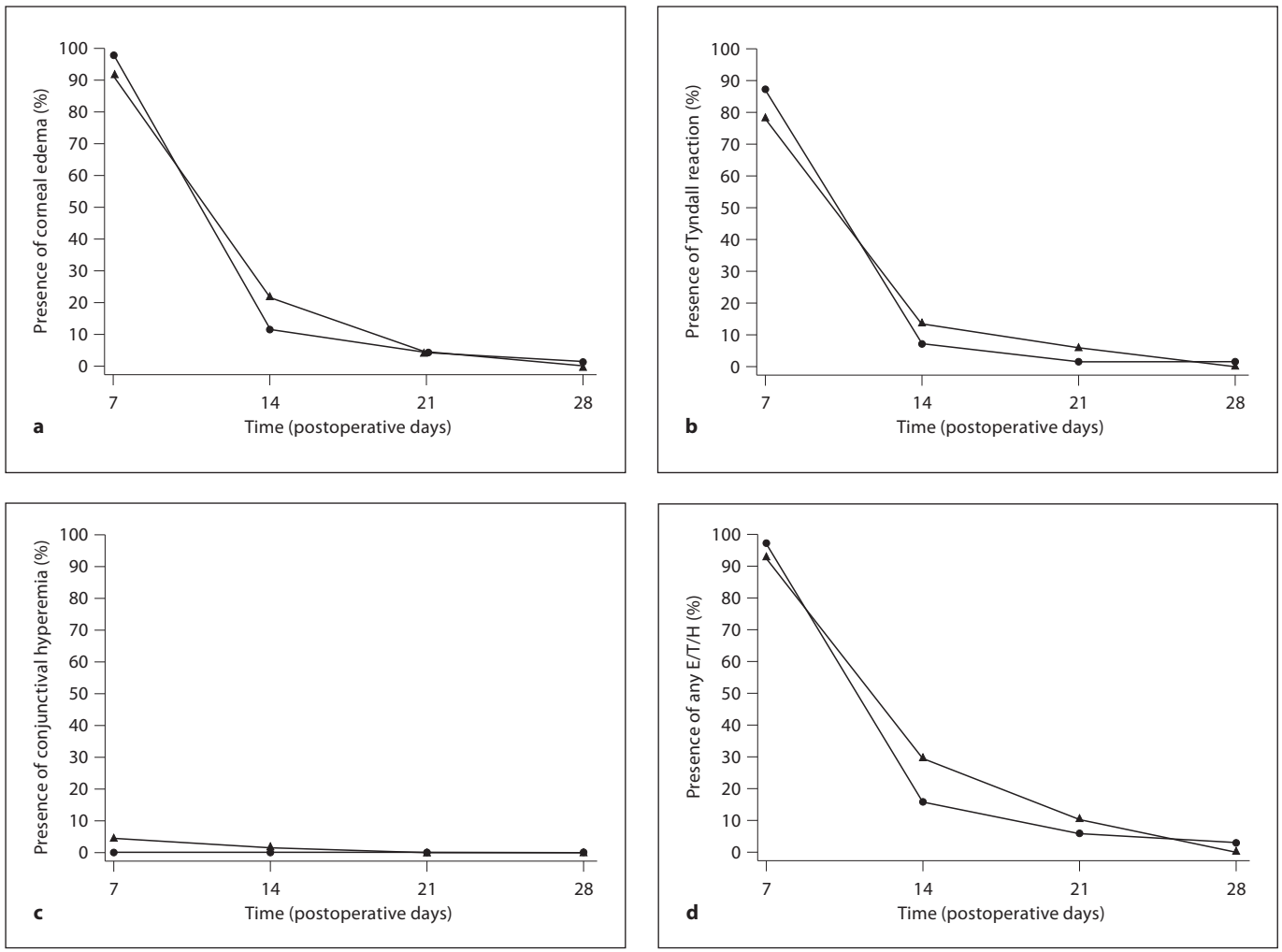

Fig. 2. Inflammation-related signs on postoperative days 7, 14, 21 and 28 in the TD group (▲) and the TD-K group (●). **a** Corneal edema. **b** Tyndall reaction. **c** Conjunctival hyperemia. **d** Presence of any E/T/H.

The presence of Tyndall reaction did not differ between the 2 groups at any time point (for TD and TD-K, respectively: 53/68 vs. 61/70 on day 7, p = 0.154, χ^2 test; 9/68 vs. 5/70 on day 14, p = 0.236, χ^2 test; 4/68 vs. 1/70 on day 21, p = 0.205, Fisher's exact test; 0/68 vs. 1/70 on day 28, p > 0.99, Fisher's exact test) (fig. 2b).

The presence of conjunctival hyperemia did not differ between the 2 groups at any time point (for TD and TD-K, respectively: 3/68 vs. 0/70 on day 7, p = 0.117, Fisher's exact test; 1/68 vs. 0/70 on day 14, p = 0.493, Fisher's exact test; 0/68 vs. 0/70 on days 21 and 28, p not estimable due to the presence of 2 zero cells in the 2 × 2 contingency table) (fig. 2c).

As expected in the light of the above, the presence of E/T/H did not differ between the 2 groups (for TD and TD-K, respectively: 63/68 vs. 68/70 on day 7, p = 0.271, Fisher's exact test; 20/68 vs. 11/70 on day 14, p = 0.054, χ^2 test; 7/68 vs. 4/70 on day 21, p = 0.362, Fisher's exact test; 0/68 vs. 2/70 on day 28, p = 0.496, Fisher's exact test) (fig. 2d). As is evident from the aforementioned, the 2 patients presenting E/T/H in the TD-K group on day 28 needed further continuation of the treatment; on day 35, both patients were free of signs.

BCVA (logMAR) did not differ between the 2 groups at any time point (for TD and TD-K, respectively: 0.22 ± 0.11 vs. 0.22 ± 0.10 on day 7, p = 0.955; 0.08 ± 0.09 vs. 0.06 ± 0.07 on day 14, p = 0.425; 0.04 ± 0.07 vs. 0.04 ±

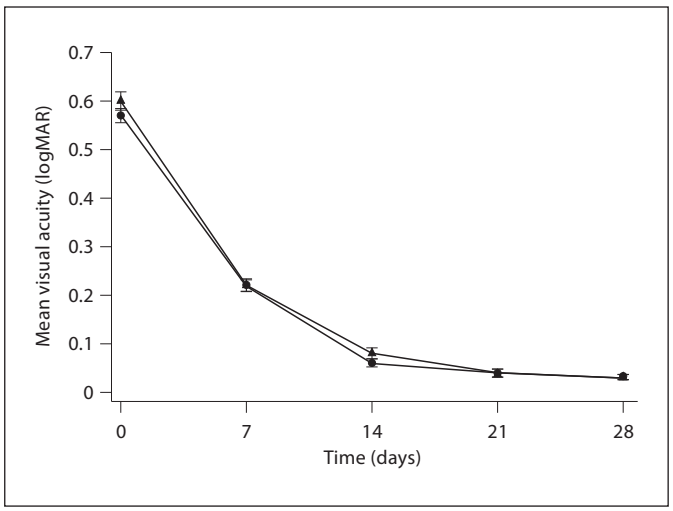

Fig. 3. BCVA (logMAR) on postoperative days 7, 14, 21 and 28 in the TD group (▲) and the TD-K group (●). Means ± SE.

0.06 on day 21, p = 0.887; 0.03 ± 0.06 vs. 0.03 ± 0.05 on day 28, p = 0.373; all MWW) (fig. 3). Worthy of note, all patients reported pain and ocular discomfort lower than 1/10 on the visual analog scale at all time points. It is also worth reporting that on day 42, no evidence of clinically significant CME was detected in any patient via fundoscopy and the Amsler grid test.

Concerning the associations between the presence of E/T/H on day 21, it is worth mentioning that E/T/H was strongly associated with pseudoexfoliation; specifically, presence of E/T/H was noted in 20% (5/25) of the patients with pseudoexfoliation, whereas the respective percentage was only 5.3% (6/113) in the patients without pseudoexfoliation. The respective univariate logistic regression model yielded an OR of 4.5 (95% CI: 1.2–16.0; p = 0.022) for the effect of pseudoexfoliation on the risk for E/T/H. No other statistically significant associations were demonstrated, including a null association with diabetes mellitus (presence of E/T/H was noted in 1/13 patients with diabetes mellitus vs. 10/125 patients without diabetes mellitus; $p > 0.999$; Fisher's exact test).

Discussion

The principal message of this study is that the addition of an NSAID (ketorolac) after uneventful phacoemulsification surgery did not seem to offer any additional benefit with regard to corneal edema, Tyndall reaction, conjunctival hyperemia or recovery of BCVA when compared to the antibiotic/steroid group. Concerning the profile of inflammation-related signs in both groups, the close weekly follow-up revealed a marked analogy: corneal edema and Tyndall reaction seemed to be the most prevalent signs, whereas conjunctival hyperemia was a rather infrequent condition in both groups.

The rationale for the benefit of a regimen including both topical steroid antiinflammatory drugs and NSAID after uneventful phacoemulsification pertains to the prevention of CME [5]; noticeably, in our series, no case of clinically significant CME appeared, as evaluated by fundoscopy and the Amsler grid test. CME can be classified as 'clinically significant' and 'angiographic' [7]; a variety of trials have demonstrated beneficial effects of NSAID for the prevention of 'angiographic' CME [7, 10, 11]. However, evidence for the prevention of 'clinically significant' CME remains less convincing, similar to the long-term benefits of NSAID treatment, if any.

The incidence of acute CME after uneventful phacoemulsification reaches its peak at 4–6 postoperative weeks; importantly, the majority of cases resolve spontaneously [7]. As a result, the cost/benefit ratio of NSAID treatment remains obscure, given the low incidence (as in our study) and self-limited nature of clinically significant CME. In the light of all the above, the present study is in line with skepticism about the need for NSAID in the context of uneventful phacoemulsification. Nevertheless, the antibiotic component is given as a routine part of care to prevent the occurrence of a postoperative bacterial infection, even though the incidence of postoperative endophthalmitis is very low over the years [1, 12].

Regarding the duration of postoperative treatment, this study points to 4 weeks as an adequate and reasonable choice; this seems in accordance with the study by Laurell and Zetterström [8]. Contrary to studies reporting 2 [4] or 3 weeks [1, 3], such a duration seems inadequate as the incidence of any E/T/H was approximately equal to 10% on day 21. In any case, given that the degree of inflammation is a function of time, it seems that future trials on topical agents after phacoemulsification should examine the heterogeneity in treatment duration, if any, and provide analyses of the effect of treatment duration on their examined outcomes.

Pseudoexfoliation emerged as the only risk factor for inflammation-related signs on day 21. This may be attributed to the disruption of the blood-aqueous barrier, which has been well described in the context of pseudoexfoliation [13, 14]. Indeed, pseudoexfoliation should be taken into account before phacoemulsification as it is as-

sociated with intraoperative and postoperative complications [14, 15]. Preoperatively, patients may have poor dilation, and intraoperatively, they may have zonular weakness and thus complications such as posterior capsule rupture. Worthy of note, diabetes mellitus was not confirmed as a risk factor for inflammation-related signs although previous studies have demonstrated increased blood-aqueous barrier breakdown after eye surgery in diabetic patients [16].

Nevertheless, some limitations of the study need to be declared. Optical coherence tomography has not been included in the study design; consequently, macular thickening could not be optimally monitored. Noticeably, however, fundoscopy and the Amsler grid test did not reveal any suspicious signs for clinically significant CME in any patient, and no significant visual impairment was noted (as reflected in BCVA); this is in accordance with studies demonstrating the relative rarity of CME after uneventful phacoemulsification [2, 17]. In addition, the assessment of inflammation by laser flare measurement could have yielded more sensitive, objective results. Given that a lengthier operation time might potentially modify inflammation-related signs and be a direct consequence of pseudoexfoliation, future studies should encompass this parameter in their analyses; in the present study, operation time was not recorded. Moreover, the evaluation of additional treatment regimens would be desirable as the present results may not be safely extrapolated to other regimens.

In conclusion, the addition of an NSAID (ketorolac) did not seem to offer any additional benefit in terms of inflammation-related signs. Four weeks appeared as an adequate treatment interval. Special attention should be paid to patients with pseudoexfoliation.

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