Comparison of anti-inflammatory effects of eye drops formulations after uncomplicated cataract surgery

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Abstract
Aim: The aim of this study is to compare the efficacy of different dexamethasone eye drops formulations in controlling postoperative inflammation.

Methods: Cataract surgery was carried out in 72 patients (35 males) divided into two groups: group A (36 patients, mean age = 78.0 ± 5.6) received four times daily for 2 weeks a suspension containing tobramycin 0.3% mg/ml + dexamethasone 0.1% mg/ml, and group B (36 patients, mean age = 76.2 ± 6.8) a solution containing tobramycin 0.3% mg/ml + dexamethasone 0.1% mg/ml. Both groups received ofloxacin 0.5% four times daily for 7 days, and nepafenac 0.1% three times daily for 3 weeks. Best-corrected visual acuity, intraocular pressure, corneal thickness, endothelial cells count, aqueous flare and macular thickness were evaluated preoperatively and at 1 day, 15 days, 1 and 2 months.

Results: In group A, intraocular pressure, corneal thickness and aqueous humour flare values preoperatively and at the end of follow-up were 14.3 ± 1.8 and 13.2 ± 1.8 mmHg, 546.4 ± 34.6 and 539.6 ± 36.1 µm, 11.84 ± 4.44 and 13.52 ± 5.54 ph/ms, respectively, with no statistically significant difference. In group B, intraocular pressure, corneal thickness and aqueous humour flare values preoperatively and at the end of follow-up were 14.3 ± 1.5 and 13.1 ± 1.7 mmHg, 552.9 ± 37.4 and 548.1 ± 39.3 µm, 11.45 ± 4.06 and 13.73 ± 4.99 ph/ms, respectively, with no statistically significant difference. No difference was detected in the macular thickness values in the parafoveal area preoperatively and at 2 months follow-up in group A (332.18 ± 16.19 and 337.71 ± 16.33 µm) and group B (329.11 ± 18.28 and 334.37 ± 20.86 µm), respectively.

Conclusion: The two different formulations of dexamethasone eye drops reached the same anti-inflammatory effects.

Keywords: anti-inflammatory effects, cataract, dexamethasone, flare

Introduction
Cataract surgery is one of the most successfully performed surgical procedures in developed countries, and the progress of surgical techniques has greatly improved postoperative functional results. However, there are still different causes of impaired postoperative vision among which one of the most important is macular oedema whose onset is linked to the release of factors of inflammation in the anterior chamber that reaches the retina causing an increase in the permeability of the perifoveal capillaries after cataract surgery. Steroids, nonsteroidal anti-inflammatory drugs (NSAIDs) or both are employed to avoid postoperative complications related to inflammatory response. Corticosteroids are currently available in the market in different forms: solution, suspension, ointment and gel. It is well known that the
concentration of steroid in every single drop and in the anterior chamber after topical administration is highly variable.5,6 The concentration of the active agent contained in a suspension, whatever shaking time is used, varies between 23% and 99%, while in gel, the concentration is high and constant.5 The drug concentration in a solution eye drop is constant; thus, ideally this is the best eye drops formulation.5 Moreover, depending on the formulation used, steroids penetrate the anterior chamber differently: suspension of dexamethasone penetrates in the anterior chamber three times more than a solution.6–11 Despite this, often in clinical practice, different steroid formulations are used indifferently even though the anti-inflammatory activity of the various formulations is not known with the possibility of under- or overdosage of the therapy performed.

To our knowledge, there are no studies that have investigated the anti-inflammatory efficacy of different steroid preparations: our work aims to evaluate with the flare meter the anti-inflammatory activity in the anterior chamber of two different formulations of dexamethasone eye drops, one in solution and the other in suspension, in patients who underwent uneventful cataract surgery. Inclusion and exclusion criteria

Adult (aged > 18) consecutive patients of both genders with age-related cataract who had undergone phacoemulsification with intraocular lens implantation were included in the study. Exclusion criteria were any previous ocular surgery and a history of uveitis or trauma, and eye diseases such as corneal pathologies, hypertension or glaucoma, pseudoexfoliation syndrome, any retinal or macular disease, such as cystoid macular oedema or epiretinal membrane, or any degree of age-related macular degeneration. The use of systemic corticosteroids or NSAIDs during the study was considered as an exclusion criterion. Patients who had any intraoperative or postoperative complications such as posterior capsule rupture, vitreous loss or postoperative anterior acute uveitis were also excluded from the study.

Study protocol

All the patients had a complete ophthalmological assessment before the surgery and at 1 day, 15 days, 1 month and 2 months postoperative follow-up. The ophthalmological evaluation included uncorrected distance visual acuity (UCDVA) and corrected distance visual acuity (CDVA) measurement that was expressed in logMar, refraction, slit-lamp examination and intraocular pressure (IOP). The anterior chamber flare was evaluated measurement with the Kowa Laser Flare FM-700 (Kowa Co, Tokyo, Japan) without previous pupil dilatation, in scotopic condition. Ten consecutive flare readings with a background scatter of less than 15% were taken. The highest and lowest values were discarded, and the remaining values were automatically averaged to obtain the flare measurement. Laser flare values were expressed in photon counts/millisecond. Regular calibration of the laser flare meter (LFM) was performed according to the manual. Macular optical coherence tomography (OCT; Heidelberg Engineering, Heidelberg, Germany) was also performed; dense volume scan (20°×20°, roughly 6×6 mm²), 49 B-scans each spaced 120 µm apart, were obtained with the automatic real-time function operative. The main examination was focused on the central subfield macular thickness (µm), and the mean of the retinal thickness values of the four parafoveal areas between 1 and 3 mm around the fovea (mm³) was collected from each patient. The software automatically counts the posterior border of Bruch’s membrane as the boundary for retinal thickness measurements. The ophthalmological...
evaluation, the acquisition of flare and retinal thickness values were performed by examiners who were blinded to the treatment group assignment. The day of the surgery, patients were randomly assigned to one of two groups using a computer-generated randomization list (Group A dexamethasone 0.1% suspension and group B dexamethasone 0.1% mg/ml solution). All the procedures were performed by the same experienced surgeon (C.C.) who was blinded to the treatment group assignments. Mydriasis was obtained through the use of a phenylephrine and tropicamide insert (Mydriasert, Théa Farma SpA, Milan, Italy) into the eyelid fornix about 45 min before surgery. Every procedure was performed with topical anaesthesia (lidocaine 4%) using the Whitestar Signature phacoemulsification system (Abbott Medical Optics, Inc., Santa Ana, California, USA) and the stop-and-chop technique through a 2.2-mm temporal limbal incision. The same ophthalmic viscosurgical device (sodium hyaluronate 1.4%, Healon GV) and acrylic intraocular lens (AR40e, Abbott Medical Optics, Inc.) were used in all patients and the duration of surgery was recorded. At the end of the surgery, an intracameral injection of 0.1 mg cefuroxime solution was performed and patients were medicated with tobramycin 0.3% and dexamethasone 0.1% eye drops (Tobradex, Alcon Italia S.p.A., Milan, Italy). None of the surgeries had intraoperative complications.

Once discharged, all patients started treatment with ofloxacin 0.5% eye drops (Oftaquix, Santen Italia s.r.l., Milan, Italy) four times daily for the first week, and nepafenac 0.1% ophthalmic solution (Nevanac 0.1%, Novartis, Basel, Switzerland) three times daily for 3 weeks. Patients randomized to group A received tobramycin 0.3% and dexamethasone 0.1% suspension eye drops (Tobradex, Alcon Italia S.p.A., Milan, Italy) four times daily. No tapering down schedule was used.

**Statistics**
Quantitative variables were described by their mean and standard deviation (SD). The Shapiro-Wilk test was used to check whether the sample came from a normally distributed population. Depending on the statistical distribution, comparisons of means of two group independent variables were performed using the Student’s t test or the Mann-Whitney test. The longitudinal data were analysed with analysis of variance (ANOVA) for repeated measures for normally distributed continuous variables and with non-parametric Friedman tests assuming non-Gaussian distribution. A p value of <.05 was considered as statistically significant. Statistical analysis was completed using IBM SPSS Statistics 24 (SPSS, Inc., Somers, NY, USA).

**Results**
In total, 72 patients were included in the study and no patients were lost at follow-up. The mean age was 78.0 ± 5.6 group A (36 patients of which 18 were females) and 76.2 ± 6.8 in group B (36 patients of which 19 were females) (Table 1). No patient was lost to follow-up and no patient reported postoperative disturbances or discomfort that lead to discontinuation of the prescribed therapy.

Table 2 shows preoperative and postoperative mean visual acuity in both groups. There was a statistically significant CDVA improvement postoperatively in both groups. No statistically significant differences were noted in visual outcomes (p > 0.05).

| Parameter | Group A (n = 36) | Group B (n = 36) | p |
|-----------|-----------------|-----------------|---|
| Age [years] | 78.0 ± 5.6 | 76.2 ± 6.8 | >0.05 |
| Range | 64.92 | 60.89 | >0.05 |
| Phaco time [s] | 45.5 ± 18.2 | 54 ± 20.6 | >0.05 |

| Time | Group A | Group B | p |
|------|--------|--------|---|
| Preoperative | 0.36 ± 0.11 | 0.40 ± 0.10 | >0.05 |
| 15 days | 0.98 ± 0.05 | 0.98 ± 0.05 | >0.05 |
| 30 days | 0.99 ± 0.02 | 0.98 ± 0.04 | >0.05 |
| 60 days | 0.99 ± 0.02 | 0.99 ± 0.02 | >0.05 |
In Tables 3–5, preoperative and postoperative IOP, corneal thickness and endothelial cell count values are reported with no significant differences ($p > 0.05$). The day after the surgery LFM values were significantly higher than before surgery in both groups; LFM values were gradually reduced throughout the entire follow-up reaching the preoperative levels after 60 days in both groups without statistically significant difference between the two groups ($p > 0.05$; Table 6). The macular thickness in subfoveal and parafoveal areas is shown in Table 7 and no significant differences between the groups ($p > 0.05$).

### Discussion

In our study, the comparison between two different formulations of dexamethasone administered to patients who underwent uneventful cataract surgery revealed that both showed the same efficacy in controlling the anterior chamber flare.

Steroids are widely used after cataract surgery because they control postoperative inflammation. In fact, it is known their effect on intercellular inflammatory mediators by inhibiting some enzymes as phospholipase-A2 that reaches high levels after surgery, thus reducing the levels of arachidonic acid. The aim of the control of inflammation after cataract surgery is to reduce the possibility of the onset of important complications, first of all cystoid macular oedema; it is, despite postoperative therapy, the most important cause of visual loss who can lead to irreversible damage of the visual function. There are few double-blind, randomized controlled trials performed to identify best prophylaxis of postoperative cystoid macular oedema, and its complex pathogenesis still needs to be better understood. Without a doubt, the use of topical NSAIDs remains very important, but topical corticosteroids are commonly used as monotherapy or in combination with NSAIDs and clinical studies have reported that concurrent corticosteroid and NSAID administration has an additive, rather than synergistic effect.

The PREMED study was conducted to clarify the optimum treatment for the prevention of postoperative cystoid macular edema after uneventful cataract surgery, and it showed that in non-diabetic patients, the lowest incidence of clinically significant macular oedema was observed in patients randomized to receive the combination of dexamethasone-bromfenac postoperative treatment (1.5%), compared with bromfenac (3.6%) or dexamethasone alone (5.1%).

However, there are limited studies on corticosteroid efficacy, whose effectiveness may further be
confounded by the frequent concomitant use of NSAIDs. In particular, there are no comparative studies that evaluate the anti-inflammatory efficacy of different steroid formulations with the use of the LFM.

In daily clinical practice, great care is always taken in choosing the steroid to be used, preferring high-powered steroids when an important inflammatory response is feared. However, the choice of the different steroid formulations, solution, suspension, gel or ointment is frequently based on the availability of the product or on the habits of the health care professional, and the anti-inflammatory activity obtainable with these preparations is not well known. This can lead to the use of steroid preparations whose intraocular concentration is high without an effective therapeutic advantage, or conversely at sub-doses when a high anti-inflammatory activity is required. There are many situations in which it is preferable to have a high penetration of the drug and a strong anti-inflammatory activity to control serious inflammatory processes, but in other cases it is necessary to prescribe prolonged topical therapies in which it is possible that the use of the steroids can lead to side effects such as glaucoma and cataract in susceptible individuals. It would be desirable to topically administer the steroid in a formulation that ensures an adequate penetration and a satisfactory anti-inflammatory effect with no or minimal risk of local and systemic side effects. Despite numerous studies on their pharmacokinetics, to the best of our knowledge, no data are yet available to determine the optimal corticosteroid concentrations required in various ocular inflammatory diseases and adverse effects continue to be reported after topical administration of steroids.9,11 Furthermore, although the blood absorption of topically applied dexamethasone is low, may considerably affect the haematic corticosteroids level.18

This study aims to assess the postoperative inflammatory efficacy of different formulations of dexamethasone eye drops in patients who underwent cataract surgery without complications. Using dexamethasone solution eye drops, high flare values were obtained only on the first day, while at 15 days, the values observed were similar to the preoperative ones; these values remained stable throughout the entire follow-up. Besides, levels of flare observed in group A were similar to those observed in group B. As observed in previous studies, this formulation reaches much higher concentrations in the anterior chamber.6 We did not observe differences in macular thickness between the two groups; however, still the group size is too low to evaluate the effectiveness of the assessed formulations for postoperative macular oedema prevention.

| Time     | Area   | Group A       | Group B       | \( p \)  |
|----------|--------|---------------|---------------|--------|
| Preoperative | CSMT   | 274.35 ± 24.26 | 276.26 ± 27.65 | >0.05 |
|          | PF     | 332.18 ± 16.19 | 329.11 ± 18.28 | >0.05 |
| 1 day    | CSMT   | 272.00 ± 24.47 | 277.11 ± 25.68 | >0.05 |
|          | PF     | 330.95 ± 17.38 | 327.98 ± 18.85 | >0.05 |
| 15 days  | CSMT   | 273.65 ± 24.60 | 278.00 ± 26.87 | >0.05 |
|          | PF     | 333.44 ± 17.34 | 330.83 ± 19.18 | >0.05 |
| 30 days  | CSMT   | 277.97 ± 25.47 | 280.26 ± 27.77 | >0.05 |
|          | PF     | 333.32 ± 20.75 | 332.26 ± 19.68 | >0.05 |
| 60 days  | CSMT   | 280.47 ± 24.84 | 282.29 ± 29.05 | >0.05 |
|          | PF     | 337.71 ± 16.33 | 334.37 ± 20.86 | >0.05 |

CSMT, central subfield macular thickness; PF, parafoveal thickness.
Our experience seems to indicate that lower concentrations of intraocular dexamethasone could have the same efficacy of the higher ones in patients undergoing uncomplicated cataract surgery.

To the best of our knowledge, there are no studies that investigated the concentration of steroids needed to prevent or reduce postoperative inflammation. We believe that knowing the intraocular penetration capabilities of topically used steroids and their relative anti-inflammatory action may help the surgeon to identify the correct therapeutic approach based on actual clinical needs.

Limitations of our work are related to the use of NSAIDs in all patients in the postoperative period: although the effect of NSAIDs might be minimal, this must be taken into consideration when evaluating the results. Another limitation is the relative smallness of the sample and it is possible that the short period of treatment with topical steroids did not allow us to observe increases in eye pressure.19,20 For these reasons, we consider these data as preliminary, and are working to increase the sample of patients to be analysed.

In conclusion, our study objectively compared the efficacy of two different dexamethasone eye drops formulation after uncomplicated cataract surgery, one in solution and one in suspension, showing that both drugs are effective in controlling the inflammation after surgery. This information can be useful for the physician called to manage patients who may need topical steroid therapies for a long time as in the case of chronic inflammatory diseases or after cornea or glaucoma surgery, to avoid the well-known side effects induced by steroid drugs.

Conflict of interest statement
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