

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

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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.^{1,2} Steroids, nonsteroidal anti-inflammatory drugs (NSAIDs) or both are employed to avoid postoperative complications related to inflammatory response.^{3,4}

Corticosteroids are currently available in the market in different forms: solution, suspension, ointment and gel. It is well known that the

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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.

Subjects and methods

This single-center, double-masked, randomized trial was performed at the Ophthalmology Section of the Department of Biomedical and Surgical Sciences, University of Perugia, Italy (Comitato Etico delle Aziende Sanitarie della Regione Umbria). The study protocol was approved by the local ethics committee (CEAS n. 3202/18), and the trial was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients. The study recruited patients with a diagnosis of cataract referred to the Department of Ophthalmology, University of Perugia and candidates for phacoemulsification and intraocular lens implantation. The primary outcome was 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. The secondary outcome of our work was to evaluate differences in postoperative comfort or in adherence to the prescribed therapy with the two different formulations of dexamethasone eye drops.

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 (Mydriaser, 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 (Oftequin, 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 for 2 weeks, while patients of group B received tobramycin 0.3% mg/ml and dexamethasone 0.1% mg/ml solution eye drops (Combitimor, SOOFT Italia SpA, Milan, Italy) four times daily for 2 weeks. 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,

Table 1. General data of patients of group A and group B.

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

Table 2. Best-corrected visual acuity of patients of group A and group B.

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

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 post-operative 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 post-operatively in both groups. No statistically significant differences were noted in visual outcomes (*p* > 0.05).

Table 3. Intraocular pressure (mmHg) of patients of group A and group B.

Time	Group A	Group B	<i>p</i>
Preoperative	14.3 ± 1.8	14.3 ± 1.5	>0.05
15 days	13.6 ± 1.9	14.0 ± 1.5	>0.05
30 days	13.6 ± 1.7	13.6 ± 1.4	>0.05
60 days	13.2 ± 1.8	13.1 ± 1.7	>0.05

Table 4. Corneal thickness (µm) of patients of group A and group B.

Time	Group A	Group B	<i>p</i>
Preoperative	546.4 ± 34.6	552.9 ± 37.4	>0.05
15 days	540.3 ± 36.6	553.6 ± 41.9	>0.05
30 days	537.5 ± 34.9	552.2 ± 41.8	>0.05
60 days	539.6 ± 36.1	548.1 ± 39.3	>0.05

Table 5. Endothelial cells count (cells/mm²) of patients of group A and group B.

Time	Group A	Group B	<i>p</i>
Preoperative	2379.3 ± 342.7	2313.7 ± 296.4	>0.05
15 days	2331.2 ± 344.2	2234.3 ± 309.4	>0.05
30 days	2239.3 ± 395.9	2204.5 ± 368.0	>0.05
60 days	2286.7 ± 357.4	2217.9 ± 340.7	>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

Table 6. Laser Flare Meter (ph/ms) of patients of group A and group B.

Time	Group A	Group B	<i>p</i>
Preoperative	11.84 ± 4.44	11.45 ± 4.06	>0.05
1 day	22.36 ± 7.47	20.58 ± 7.84	>0.05
15 days	13.59 ± 4.80	14.91 ± 5.25	>0.05
30 days	14.07 ± 5.01	15.16 ± 5.98	>0.05
60 days	13.52 ± 5.54	13.73 ± 4.99	>0.05

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.¹² 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.¹³ 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.¹⁴ Without a doubt, the use of topical NSAIDs remains very important,¹⁴ 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.^{1,15}

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 nondiabetic 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%).^{16,17}

However, there are limited studies on corticosteroid efficacy, whose effectiveness may further be

Table 7. Macular thickness (μm) of patients of group A and group B.

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

CSMT, central subfield macular thickness; PF, parafoveal thickness.

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.

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 we 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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References

1. Kim SJ, Schoenberger SD, Thorne JE, *et al.* Topical nonsteroidal anti-inflammatory drugs and cataract surgery: a report by the American Academy of Ophthalmology. *Ophthalmology* 2015; 122: 2159–2168.
2. McCafferty S, Harris A, Kew C, *et al.* Pseudophakic cystoid macular edema prevention and risk factors; prospective study with adjunctive once daily topical nepafenac 0.3% versus placebo. *BMC Ophthalmol* 2017; 17: 16.
3. Laurell C-G and Zetterstrom C. Effects of dexamethasone, diclofenac, or placebo on the inflammatory response after cataract surgery. *Br J Ophthalmol* 2002; 86: 1380–1384.
4. Grzybowski A and Kanclerz P. The role of steroids and NSAIDs in prevention and treatment of postsurgical cystoid macular edema. *Curr Pharm Des* 2018; 24: 4896–4902.
5. Nourry H, Viard C, Cambourieu C, *et al.* [A relevant choice for corticoid eye drops: solution or suspension?] *JFR Ophthalmol* 2011; 34: 691–696.
6. Cagini C, Cometa F, Torroni G, *et al.* Dexamethasone disodium phosphate penetration into the human aqueous humor after topical application. *Curr Eye Res* 2016; 41: 897–899.
7. McGhee CN, Watson DG, Midgley JM, *et al.* Penetration of synthetic corticosteroids into human aqueous humour. *Eye* 1990; 4: 526–530.
8. McGhee CN. Pharmacokinetics of ophthalmic corticosteroids. *Br J Ophthalmol* 1992; 76: 681–684.
9. Weijtens O, Schoemaker RC, Romijn FP, *et al.* Intraocular penetration and systemic absorption after topical application of dexamethasone disodium phosphate. *Ophthalmology* 2002; 109: 1887–1891.
10. Sigurdsson HH, Konráethsdóttir F, Loftsson T, *et al.* Topical and systemic absorption in delivery of dexamethasone to the anterior and posterior segments of the eye. *Acta Ophthalmol Scand* 2007; 85: 598–602.
11. Awan MA, Agarwal PK, Watson DG, *et al.* Penetration of topical and subconjunctival corticosteroids into human aqueous humour and its therapeutic significance. *Br J Ophthalmol* 2009; 93: 708–713.
12. Vane JR and Botting RM. Mechanism of action of anti-inflammatory drugs. *Scand J Rheumatol* 1996; 25(Suppl. 102): 9–21.
13. Tranos PG, Wickremasinghe SS, Stangos NT, *et al.* Macular edema. *Surv Ophthalmol* 2004; 49: 470–490.

14. Han JV, Patel DV, Squirrell D, *et al.* Cystoid macular oedema following cataract surgery: a review. *Clin Experiment Ophthalmol* 2019; 47: 346–356.
15. Kim SJ, Flach AJ and Jampol LM. Nonsteroidal anti-inflammatory drugs in ophthalmology. *Surv Ophthalmol* 2010; 55: 108–133.
16. Wielders LHP, Schouten JSAG, Winkens B, *et al.* European multicenter trial of the prevention of cystoid macular edema after cataract surgery in nondiabetics: ESCRS PREMED study report 1. *J Cataract Refract Surg* 2018; 44: 429–439.
17. Wielders LHP, Schouten JSAG, Winkens B, *et al.* Randomized controlled European multicenter trial on the prevention of cystoid macular edema after cataract surgery in diabetics: ESCRS PREMED study report 2. *J Cataract Refract Surg* 2018; 44: 836–847.
18. Krupin T, Mandell AI, Podos SM, *et al.* Topical corticosteroid therapy and pituitary-adrenal function. *Arch Ophthalmol* 1976; 94: 919–920.
19. Carnahan MC and Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. *Curr Opin Ophthalmol* 2000; 11: 478–483.
20. Razeghinejad MR and Katz LJ. Steroid-induced iatrogenic glaucoma. *Ophthalmic Res* 2012; 47: 66–80.

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