A Single Intraoperative Sub-Tenon’s Capsule Injection of Triamcinolone and Ciprofloxacin in a Controlled-Release System for Cataract Surgery

Fernando Paganeli,1,2,3 José A. Cardillo,1,2,3 Luiz A. S. Melo, Jr,2 David R. Lucena,1 Arnobio A. Silva, Jr,4 Anselmo G. Oliveira,4 Ana L. Höfﬂing-Lima,2 Quan Dong Nguyen,5 Baruch D. Kuppermann,6 Rubens Belfort, Jr,2 and the Brazilian Ocular Pharmacology and Pharmaceutical Technology Research Group (BOPP)7

PURPOSE. To compare intraoperative injection of triamcinolone and ciprofloxacin in a controlled-release system (DuoCat) with prednisolone and ciprofloxacin eye drops after cataract surgery.

METHODS. In this randomized, double-masked, controlled trial, a total of 135 patients undergoing cataract surgery were randomly allocated to two groups: 67 patients treated after surgery with prednisolone 1% and ciprofloxacin 3% eye drops four times daily (week 1), three times daily (week 2), twice daily (week 3), and once daily (week 4) and 0.3% ciprofloxacin drops four times daily (weeks 1 and 2), and 68 patients treated at the end of surgery with a sub-Tenon’s injection of 25 mg triamcinolone and 2 mg ciprofloxacin in biodegradable microspheres. The patients were examined on postoperative days 1, 3, 7, 14, and 28. The main outcome measures were postoperative anterior chamber cell and flare, intraocular pressure (IOP), lack of anti-inﬂammatory response, and presence of infection.

RESULTS. No signiﬁcant differences were observed between the groups in anterior chamber cell (P > 0.14) and flare (P > 0.02) at any postoperative visits. The mean (99% conﬁdence interval) differences in IOP between the prednisolone and triamcinolone groups on days 1, 3, 7, 14, and 28 were −0.4 mm Hg (−2.1 to 1.3), 0.0 mm Hg (−1.4 to 1.3), 0.0 mm Hg (−1.1 to 1.1), −0.2 mm Hg (−1.1 to 0.8), and −0.1 mm Hg (−1.1 to 0.9), respectively. No patient had a postoperative infection.

CONCLUSIONS. One injection of DuoCat had a therapeutic response and ocular tolerance that were equivalent to conventional eye drops in controlling inﬂammation after cataract surgery. (Clinical Trials.gov number, NCT00431028.) (Invest Ophtalmol Vis Sci. 2009;50:3041–3047) DOI:10.1167/iovs.08-2920

Topical steroids effectively control ocular inﬂammation,1,2 but are associated with the well-known challenge of patient compliance.3 An intraocular steroid delivery system has been suggested; however, there is no evidence to support its routine clinical acceptance.1–7 Injection of depot corticosteroids into the sub-Tenon’s capsule is an established approach of treating various ocular inﬂammatory diseases.8–10 Its prolonged therapeutic effect has provided the ophthalmologist with an alternative tool for the treatment of different diseases11–16 that may be extended to the surgical arena to modulate postoperative inﬂammation.17–18

The use of topical antibiotic agents poses unique and challenging hurdles for drug delivery, especially because recent reports have suggested that the incidence of endophthalmitis may be increasing.19,20 The European clinical trial21 has showed that high intracocular antibiotic levels are key to patient protection. Exploiting the permeability of the sclera, subconjunctival routes may offer a more promising alternative for enhanced drug delivery and tissue targeting compared with topical routes.22–27 Clinical reports also have associated subconjunctival antibiotics administered during routine intraocular surgery with better outcomes.28–30 In theory, the combination of an antibiotic with a steroid in a controlled-release system delivered transcellerally is feasible after cataract surgery, to achieve several clinical objectives: eliminate topical medications, enhance patient compliance, and improve drug bioavailability.

Therefore, because of the lack of conﬁrmatory studies and our encouraging preliminary clinical results, we explored this hypothesis in a controlled trial of one intraoperative sub-Tenon’s capsule injection of triamcinolone and ciprofloxacin in a biodegradable controlled-release system compared with conventional postoperative prednisolone and ciprofloxacin eye drops, to treat ocular inﬂammation and for infection prophylaxis after cataract surgery.

METHODS

A total of 135 eyes of 135 patients undergoing elective phacoemulsification and intraocular lens implantation (Mediphacos Slim, Belo Horizonte, Brazil) were enrolled in this study. The therapeutic response...
and ocular tolerance of one sub-Tenon’s capsule injection of triamcinolone and ciprofloxacin to treat postoperative ocular inflammation and for prophylaxis against ocular infection were evaluated in a 4-week, randomized, double-masked, controlled trial. The investigation was conducted from September to November 2005 at the Centro Avançado de Retina e Catarata, Fortaleza, Brazil. The protocol was reviewed and approved by the Ethics and Research Committee and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients before enrollment in the study.

Consecutive patients with uncomplicated, age-related cataract were scheduled for cataract surgery. The cataract was graded based on the Lens Opacities Classification System III. To be included in this study, patients had to have best-corrected visual acuity (BCVA) of 20/100 or better in the fellow eye and be considered likely to follow instructions and complete the study. Patients were excluded if they were taking oral or topical anti-inflammatory agents or if they had a history of steroid-induced ocular hypertension, hypermature cataracts, a previous ocular surgery, preexisting uveitis, diabetic retinopathy, glaucoma, or corneal disease. If both eyes of a patient were eligible, the eye undergoing cataract extraction first was included.

Patients were instructed not to use any systemic anti-inflammatory drugs during the study. Investigators could exclude any patient who had an unacceptable response to treatment or could not complete the study for reasons unrelated to the study medication. The investigators used the following criteria as indications of an unacceptable response to treatment: increased cell or flare since the previous visit, and any signs or symptoms of inflammation that led the investigators to believe that continuing the study was not in the patient’s best interest. Patients with no response to either treatment received intensive topical corticosteroid (1% prednisolone acetate) treatment and were followed until the end of the study. Their data were analyzed with the treatment group to which they were originally assigned.

### Study Medications

Preservative-free 25-mg triamcinolone acetonide in 0.1 mL was prepared by the Ophthalmos Laboratory (São Paulo, Brazil). An optimized micronized solution was formulated especially for this study to avoid needle clogging, allowing the use of high drug concentrations and small-gauge needles. The triamcinolone injection dose of 25 mg was chosen based on a previous study (Tognin F, et al. IOVS 2005;46:ARVO E-Abstract 792).

Microspheres are colloidal drug carriers in the micro range. These systems were developed to control drug release and target the drug to specific tissues. The polyactic-co-glycolic acid (PLGA), used in the present study in a ratio of 50:50, is a copolymer widely accepted in ophthalmic controlled-release systems because of its biocompatibility and suitable biodegradation profile. For the present study, 2 mg ciprofloxacin hydrochloride–loaded PLGA microspheres (mean size, 1.07 ± 0.35 μm) with drug/polymer ratio of 1:2 and with encapsulation efficiency of 99% were prepared with a spray-drying technology. According to experimental studies in rabbit eyes with one sub-Tenon’s capsule injection, this system has a uniform and sustained-release profile, reaching therapeutic levels in the aqueous and vitreous for most endophthalmitis microorganisms up to 10 days (Silva AA, et al. IOVS. 2005;46:ARVO E-Abstract 5395). The drug is preservative-free and intended for use in one sub-Tenon’s injection administered with a 27-gauge needle. The combination of both drugs (25-mg triamcinolone acetonide and 2-mg ciprofloxacin in a biodegradable microsphere controlled-release system) is referred to in this study as the DuoCat system.

### Surgical Procedure

All surgeries were performed by the same surgeon (DRL). All eyes were dilated with 2 drops of 10% phenylephrine administered 5 minutes apart and 3 drops of 1% tropicamide administered 5 minutes apart. The cataract surgery was performed under topical anesthesia using 0.5% proparacaine hydrochloride eye drops and 0.3 mL of 1% intracameral lidocaine. A routine solution of 5% povidone-iodine was used 15 minutes before the surgery. Phacoemulsification was performed through a 2.75-mm clear corneal incision. A commercial phacoemulsification system (Infinity; Alcon, Fort Worth, TX) and the phaco chop technique were used during the surgeries. To boost targeting and penetration, depot formulation was placed forward under the sub-Tenon’s capsule. Briefly, the bulbar conjunctiva was grasped optimally with forceps approximately 5 mm from the limbus at the site of the intended entry into the inferotemporal quadrant. At this point, the episcleral space was entered with a 27-gauge needle under direct visualization and extended 3.0 mm to facilitate introduction of the medication. A 0.3-mL unloaded microsphere solution (prednisolone group) or 0.5 mL of a combined solution containing 25-mg triamcinolone acetonide and 2.0-mg ciprofloxacin in a biodegradable microsphere controlled-release system (triamcinolone group) was then injected. No drug reflux was observed.

### Treatment Assignment and Study Masking

After uncomplicated cataract extraction and intraocular lens implantation, patients were randomly assigned to either the prednisolone or triamcinolone group. The assignment was performed by block randomization based on a table of computer-generated random numbers. The allocation concealment was accomplished with sequentially numbered, opaque, sealed envelopes.

In the prednisolone group, the patients instilled 1% prednisolone (Pred Forte; Allergan Inc., São Paulo, Brazil) acetate and 0.3% ciprofloxacin hydrochloride eye drops (Ciloxan; Alcon Inc.) in the treated eye. The prednisolone eye drop was instilled after surgery according to the following schedule: 1 drop four times daily (week 1), three times daily (week 2), twice daily (week 3), and once daily (week 4). The ciprofloxacin eye drop was instilled four times daily during the first two postoperative weeks. In the triamcinolone group, patients received a sub-Tenon’s capsule injection of DuoCat at the end of surgery.

To mask the study, the patients in the prednisolone group underwent a similar sub-Tenon’s capsule injection of the polymer containing no drug, whereas the patients in the triamcinolone group received vehicle drops in bottles and schedules similar to those given to the prednisolone group. The bottles containing the eye drops were coded and not labeled with the name of the substance that they contained. Clinical assessment of postoperative outcomes was performed by a masked investigator (FP) who was unaware of the patient group status.

The primary efficacy variable was anterior chamber cell and flare. In addition, the number of patients who were unresponsive to treatment was considered a key indicator of treatment failure. Anterior chamber cells were graded based on a modification of the grading scale of Hogan et al. The number of cells was counted with a slit lamp biomicroscopy through an undilated pupil.

To ensure the masked nature of this study, the patients were asked not to provide any information regarding eye drop instillation to the masked investigator because of the milky appearance of the prednisolone.

### Outcome Measures

After cataract surgery, the patients returned for postoperative follow-up visits on days 1, 3, 7, 14, and 28. All efficacy variables were evaluated at baseline and during all follow-up visits by slit lamp biomicroscopy through an undilated pupil.

The primary efficacy variable was anterior chamber cell and flare. In addition, the number of patients who were unresponsive to treatment was considered a key indicator of treatment failure. Anterior chamber cells were graded based on a modification of the grading scale of Hogan et al. The number of cells was counted with a slit lamp (SL-3E, Topcon, Tokyo, Japan) in an oblique slit beam 3-mm long and 1-mm wide in front of the pupil. The anterior chamber cell was graded on a scale of 0 to 6+, where 0 is 0 to 4 cells, 1+ is 5 to 9 cells, 2+ is 10 to 19 cells, 3+ is 20 to 29 cells, 4+ is 30 to 39 cells, 5+ is 40 to 49 cells, and 6+ is 50 or more cells. Anterior chamber flare was graded on a scale of 0 to 4+, where 0 is complete absence, 1+ is faint flare (barely detectable), 2+ is moderate flare (iris and lens details clear), 3+ is marked flare (iris and lens details hazy), and 4+ is intense flare (fixed, coagulated aqueous humor with considerable fibrin). Additional efficacy variables were conjunctival erythema, graded on a scale of 0 to 4 based on standard photography, and ciliary flush,
also graded on a scale of 0 to 4. Patients were asked whether they had symptoms of ocular inflammation such as tearing, photophobia, and discomfort. These variables were evaluated on a scale of 0 to 4, in 1-grade increments, where 0 indicated none and 4 very severe.

Safety variables included adverse events, IOP, BCVA, and biomicroscopic and ophthalmoscopic findings. Throughout the study, any signs or symptoms of adverse events were recorded, graded, and assessed for a relationship to the study medication. During each visit, the IOP was measured twice by Goldmann applanation tonometry; the mean of the two measurements was used in the analysis. Antiglaucoma medications were prescribed when IOP levels exceeded 25 mm Hg. BCVA was measured with the Snellen VA chart, and the measurements were converted to logarithm of the minimum angle of resolution (logMAR) for statistical analysis. The final VA measurement (day 28) was taken with the patient wearing the best spectacle correction.

**Statistical Analysis**

An intention-to-treat analysis was performed. The Mann-Whitney test was used to evaluate variables with ordered-response categories and logMAR VA. Multivariate analysis of variance was used to evaluate the IOP measurements. Fisher's exact test was used to compare the proportion of patients between the two groups who had unacceptable anti-inflammatory response. A generalization of the Mann-Whitney U statistic, derived by dividing U by the product of the two sample sizes (U/mn), was calculated as a measure of effect size for the difference between the groups in the anterior chamber cell and flare. A sample size of 65 patients in each study group provided a power greater than 80% to detect differences between groups of 0.4 unit or more on the anterior chamber cell grade scale and 2.3 mm Hg or more in IOP. The significance level was set at $P < 0.01$ (rather than 0.05), and 99% (rather than 95%) confidence intervals were used to adjust for multiple comparisons.

**RESULTS**

Of the 135 patients enrolled, 67 were assigned to the prednisolone group and 68 to the triamcinolone group. One patient in the prednisolone group and two in the triamcinolone group were lost to follow-up after the day-1 postoperative visit. Their clinical outcome measures at the day 1 visit did not differ from the other patients. No patients were discontinued because of improper entry or protocol violations. Figure 1 shows the flow chart of the patients throughout the study.

The demographic characteristics of the patient population are listed in Table 1. There were no significant differences...
between the treatment groups in age, sex, race, preoperative best-corrected VA, IOP, or lens opacity grading.

**Efficacy**

There were no significant differences between the groups in anterior chamber cell (P = 0.14) and flare (P = 0.02) on any postoperative day (Table 2).

One patient in each group had no response to the treatment (P = 1.00), which was observed on day 14. These patients received additional anti-inflammatory medication regimen (topical 1% prednisolone acetate) and had satisfactory clinical responses. No patient had a postoperative infection.

There were no significant differences between the groups in conjunctival erythema (P = 0.22), ciliary flush (P = 0.50), or any symptoms of ocular inflammation at any postoperative visit.

**Safety**

There were no significant overall differences between groups (P = 0.75) and no statistically significant interaction between group and follow-up visits (P = 0.91; Table 3, Fig 2). In both groups, the mean IOP changed over the course of the follow-up visits (P < 0.001). One patient in the triamcinolone group had an IOP exceeding 25 mm Hg (28 mm Hg at the day 1 visit). She received 0.5% timolol maleate, and her IOP decreased to 22 mm Hg on day 3 and to 15 mm Hg on day 7. The timolol was stopped, and the patient had an IOP of 12.5 mm Hg on the last postoperative visit (day 28). The median (range) logMAR VA levels in the prednisolone group and triamcinolone group were, respectively, 0.12 (0.0–0.3) and 0.15 (0.0–0.3) at the day 28 postoperative visit (P = 0.68).

**Biomicroscopy and Ophthalmoscopy**

There were no significant differences between groups in biomicroscopy or ophthalmoscopy safety variables. No patients in the prednisolone group or triamcinolone groups had clinically significant abnormal ophthalmoscopic findings. There was minimal to no conjunctival scarring. A cosmetically acceptable depot bleb at the injection site was observed in both groups until the day 28 postoperative visit.

**Discussion**

The present study substantiates a novel and more comprehensive therapeutic strategy for cataract surgery. Consistent with previous investigations, our results indicated that one 25-mg sub-Tenon’s capsule triamcinolone acetonide injection...
resulted in a therapeutic response and ocular tolerance comparable to 1% prednisolone acetate drops in controlling the signs and symptoms of ocular inflammation after cataract surgery. On the first postoperative day, all patients in both groups had anterior chamber cell and flare scores that gradually decreased over time. The parallel decreases in both groups suggested that triamcinolone is at least as effective as conventional prednisolone eye drops in reducing postoperative inflammation. As a result, a sub-Tenon’s capsule injection of depot corticosteroid, an already accepted method for the treatment of various inflammatory ocular diseases, could be useful in the surgical arena. It provides a new way of eliminating patient self-medicating, avoiding problems with compliance and instruction. Furthermore, when this demonstration of the anti-inflammatory effects is coupled with its ability to treat cystoid macular edema and diabetic macular edema aggravated by cataract,11–16,18,35 a clear role for triamcinolone as a simple and more rational management strategy for postcataract surgical inflammation begins to emerge.

One posterior sub-Tenon’s capsule triamcinolone injection also had ocular tolerance equivalent to prednisolone eye drops through 4 weeks of follow-up. There were no significant differences between the two treatment groups in the number of adverse events, changes in VA, or lack of response. The potential complications of sub-Tenon’s capsule injection of corticosteroids include inadvertent injection into the choroidal or retinal circulation,36–38 globe perforation,39–41 and occlusion of the central retinal artery.42 Blepharoptosis, proptosis, orbital fat atrophy, delayed hypersensitivity reactions, strabismus, conjunctival hemorrhage, chemosis, and infection also have been reported.42–45 Although the present study is not adequately powered to detect rare complications, these complications did not occur.

An increase in IOP after topical or systemic administration of corticosteroids is of particular concern.46 Patients who receive sub-Tenon’s capsule injections of corticosteroids may not respond to maximal anti-glaucomatous therapy and therefore may require surgical excision of the depot because of a persistently elevated IOP.47 Because increased IOP may be a function of the interaction between the disease itself and the use of topical or systemic corticosteroids, the role of posterior sub-Tenon’s capsule corticosteroids in ocular hypertension is not always clear; therefore, these concerns may not apply to patients who underwent surgery whose status in responding to corticosteroids is unknown. After a posterior 40-mg triamcinolone sub-Tenon’s capsule injection, a surprisingly lower-than-expected incidence of increased IOP was observed.17 In the present study, only one eye (triamcinolone group) had an IOP that exceeded 25 mm Hg, and the IOP returned to a normal level with topical antihypertensive drops. However, beyond our 28-day follow-up period, delayed onset of increased IOP must be considered. The depot formulation was placed forward under sub-Tenon’s capsule and, if an intractable IOP increase occurred, the remainder of the depot could have been easily removed.

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone, mean (SD)</td>
<td>13.8 (3.6)</td>
<td>13.2 (3.0)</td>
<td>12.4 (2.5)</td>
<td>11.9 (2.2)</td>
<td>12.2 (2.0)</td>
</tr>
<tr>
<td>Triamcinolone acetonide, mean (SD)</td>
<td>14.2 (4.1)</td>
<td>13.2 (3.1)</td>
<td>12.4 (2.4)</td>
<td>12.0 (2.0)</td>
<td>12.3 (2.2)</td>
</tr>
<tr>
<td>Difference</td>
<td>−0.4 (−2.1 to 1.3)</td>
<td>0.0 (−1.4 to 1.3)</td>
<td>0.0 (−1.1 to 1.1)</td>
<td>−0.2 (−1.1 to 0.8)</td>
<td>−0.1 (−1.1 to 0.9)</td>
</tr>
<tr>
<td>Mean (99% CI)</td>
<td>0.56</td>
<td>0.94</td>
<td>0.97</td>
<td>0.65</td>
<td>0.76</td>
</tr>
<tr>
<td>P</td>
<td>0.56</td>
<td>0.94</td>
<td>0.97</td>
<td>0.65</td>
<td>0.76</td>
</tr>
</tbody>
</table>

FIGURE 2. Intraocular pressure at each study visit. Differences between prednisolone and triamcinolone groups were not statistically significant at any visit. Symbols: mean; vertical bars: 99% confidence interval.
Although administration of topical antibiotics as a prophylaxis is acceptable among ophthalmologists, this common practice has no sound evidence base. Of interest, despite the advance of two fourth-generation fluoroquinolones, recent reports suggested that the incidence of endophthalmitis may be increasing.\(^\text{19–20}\) Beyond antibiotic potency, alternative means to enhance protection against infection during cataract surgery should certainly be explored. Exploiting the permeability of the sclera, subconjunctival routes may offer a promising alternative for enhanced drug delivery and tissue targeting compared with topical routes.\(^\text{22–27}\) The strategy studied in this investigation, though appealing and logical, still require validation in a large patient population.

The frequency of application is important for attaining adequate antibacterial concentrations, and poor compliance also prevents the drops from reaching efficacious levels. Compliance with topical therapy was studied by using an electronic device in ambulatory patients who underwent cataract surgery; all patients were noncompliant regarding total dose, time intervals, and premature discontinuation of therapy (Hermann MM, et al. IOVS. 2005;46 ARVO E-Abstract 3832). It is also important to ensure that the system chosen for cataract prophylaxis is safe and well tolerated, eliminating any potential toxic effects. The biodegradable polymer used in our system has a long history of safety and biocompatibility.\(^\text{48–50}\) In the present study, in addition to its minimally invasive and cosmetically acceptable nature, no drug or procedure-related adverse events occurred. However, this study was not powered to exclude any serious and rare adverse events including endophthalmitis; future trials with more patients would help to confirm our findings.

Finally, under the conditions of this study, DuoCat had an anti-inflammatory and anti-infective response profile consistent with conventional eye drops and possibly with other intraocular drug delivery systems.\(^\text{4–7}\) However, the inherent advantages of less invasive extraocular delivery and particularly regarding patient compliance and convenience may suggest that DuoCat is the preferred approach.

The present study has some limitations. No definitive conclusions concerning efficacy and long-term safety can be reached based on this small, limited phase II study. The follow-up was short, but most injection- and corticosteroid-related complications other than the development of late glaucoma should have occurred within the study interval. In addition, a more extensive protocol to assess the benefits of this new strategy in patients with complicated cataract is mandatory. Although we cannot draw definitive conclusions based on our initial findings, the results support further investigation. A large phase III multicenter trial is being considered to evaluate this potential treatment. Investigation of the latest-generation fluoroquinolone formulation combined with nonsteroidal anti-inflammatory drugs is currently underway in our laboratory and will be the next level of improvement for this suggested system.

In conclusion, the study findings neither advocate nor support the use of DuoCat for the treatment of ocular inflammation and as a prophylaxis to prevent infection after cataract surgery. However, our results suggest that topical drops and DuoCat injection may be equally tolerated and effective. DuoCat helped to eliminate noncompliance, and with experience, guided by future clinical trials, the role of this novel system will be more defined. A new anti-inflammatory and anti-infective paradigm that frees the patient from the nuisance and expense of topical therapeutics has been introduced into the modern cataract surgery arena and merits further consideration. Conventional postoperative eye drops remain the standard of care; the availability of a combined steroid and antibiotic controlled-release system raises the possibility of improving on the gold standard if the benefits of such treatment beyond eye drops could be validated experimentally and in sufficiently powered randomized clinical trials.

Acknowledgments

The authors thank Shintaro Kanayama for reviewing the manuscript.

APPENDIX

The Brazilian Ocular Pharmacology and Pharmaceutical Technology Research Group (BOPP)

Rogerio A. Costa, Hospital de Olhos de Araraquara; Daniel Lavinsky, Department of Ophthalmology, Federal University of São Paulo; Mirian Skaf, Hospital de Olhos de Araraquara and the Department of Ophthalmology, University of Araraquara; and Acácio A. Souza-Filho, Department of Ophthalmology, Federal University of São Paulo, São Paulo, Brazil.

References


