A Single Intraoperative Sub–Tenon's Capsule Triamcinolone Acetonide Injection for the Treatment of Post–Cataract Surgery Inflammation

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Purpose: To compare a single intraoperative sub–Tenon's capsule triamcinolone acetonide injection with steroid drops in the treatment of ocular inflammation after cataract surgery.

Design: Randomized, double-masked controlled trial.

Participants: A total of 100 patients were randomized prospectively into 2 groups: 50 patients treated with 1% prednisolone eyedrops (control group A) and 50 patients treated with sub–Tenon's capsule triamcinolone (treatment group B).

Methods: All patients underwent phacoemulsification and intraocular posterior lens implantation. After surgery, patients were randomized to receive either (group B) an intraoperative 40 mg triamcinolone acetonide sub–Tenon's capsule injection or (group A) 1% prednisolone acetate eyedrops, according to the following schedule: 1 drop 4 times daily (week 1), 3 times daily (week 2), 2 times daily (week 3), once daily (week 4). To mask the study, group B received vehicle drops administered on a similar schedule, and group A received an intraoperative sub–Tenon's capsule injection of a 1 ml balanced salt solution.

Main Outcome Measures: The main outcome measures included inflammation (cell, flare, ciliary flush), intraocular pressure, and lack of response.

Results: Triamcinolone was shown to have anti-inflammatory efficacy clinically equivalent to conventional 1% prednisolone eyedrops in reducing intraocular inflammation, as measured by clinical methods. Triamcinolone was found to be as safe as the prednisolone in terms of adverse effects, changes in visual acuity, intraocular pressure, and biomicroscopic and ophthalmoscopic variables. On the third, seventh, fourteenth, and twenty-eighth postoperative days, a significantly lower intraocular pressure ($P<0.01$) was noted in the triamcinolone group than in the prednisolone group.

Conclusions: A single intraoperative 40-mg triamcinolone acetonide sub–Tenon's capsule injection demonstrated a clinically equivalent therapeutic response and ocular tolerance compared with 1% prednisolone drops in controlling postoperative inflammation after uncomplicated cataract surgery and merits further investigation. *Ophthalmology 2004;111:2102–2108 © 2004 by the American Academy of Ophthalmology.*

Recent advances in cataract surgery, such as phacoemulsification techniques, small-incision surgery, and foldable intraocular lenses, have resulted in a decrease in the physical trauma associated with the surgery. Nonetheless, most patients still exhibit postoperative ocular inflammation after cataract surgery.[1] Topical steroids are effective in controlling ocular inflammation and usually are continued for several weeks after surgery.[2,3] In general, topical therapy is associated with the well-recognized problems of patient compliance and a variable amount of physician or staff time needed for patient instruction.[4] An intraocular steroid delivery system has been suggested; however, in addition to increased cost, there is no sufficient evidence to date to support its routine clinical acceptance.[5–7]

Sub–Tenon's capsule injection of depot corticosteroids is a currently established method for the treatment of various inflammatory eye diseases, with a good therapeutic response and ocular tolerance.[8–10] Its prolonged therapeutic

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*See "Appendix" for Group membership.

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effect has provided the ophthalmologist with an alternative tool for the treatment of different diseases[11–15] that may be expanded to the surgical arena to modulate postoperative inflammation.

The objective of the present study was to evaluate the therapeutic response and ocular tolerance of a single intraoperative sub–Tenon's capsule triamcinolone acetonide injection for the treatment of ocular inflammation after cataract surgery in comparison with steroid drops.

Patients and Methods

A total of 100 eyes of 100 patients undergoing elective phacoemulsification and foldable lens (Alcon Acrysof MA60BM) implantation were enrolled in this investigation. The therapeutic response and ocular tolerance of a single sub–Tenon's capsule triamcinolone acetonide injection in the treatment of postoperative ocular inflammation was evaluated in an 8-week, randomized, double-masked, and parallel group study. The investigation was conducted from May 2003 through August 2003 at the Hospital de Olhos de Araraquara, São Paulo, Brazil. The protocol was reviewed and approved by the Ethics and Research Committees and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment in the study. Patients with uncomplicated, senile cataract were scheduled for phacoemulsification and foldable lens surgery using topical anesthesia. Patients also had to have a best-corrected visual acuity of 20/100 or better in the unoperated eye and had to be deemed likely to follow instructions and complete the entire course of the study. Patients were excluded if they took oral or topical anti-inflammatory agents, or if they had diabetes mellitus; a history of steroid-induced ocular hypertension, hypermature cataracts, or previous ocular surgery; preexisting uveitis; glaucoma; or corneal disease. All surgeries were performed by the same surgeon (FP), always using the same equipment, technique, and materials. Patients were instructed not to use any systemic anti-inflammatory drugs during the course of the study. Patients could choose to withdraw from the study at any time. Investigators could remove from the study any patient who had an unacceptable response to treatment or who 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: (1) an increase in cells or flare since the previous visit, (2) a combined cell and flare score that remained the same for 2 consecutive postoperative visits, and (3) any sign or symptom of inflammation that led the investigator to believe that it was not in the patient's best interest for him or her to continue the study.

Treatment Assignment and Study Masking

After uncomplicated phacoemulsification and intraocular lens surgery, qualified patients were assigned to 1 of 2 masked postoperative treatments using a table of computer-generated random numbers. Group A patients received conventional 1% prednisolone acetate eyedrops (Pred Fort, Allergan Inc., Olímpia, Brazil) self-instilled in the treated eye, according to the following schedule: 1 drop 4 times daily (week 1), 3 times daily (week 2), 2 times daily (week 3), once daily (week 4). Group B patients received a single intraoperative preservative-free 40-mg triamcinolone acetonide (Ophthalmos Laboratory, São Paulo, Brazil) sub–Tenon's capsule injection, and normal saline placebo eyedrops were prescribed following the same schedule. A sub–Tenon's capsule injection of an equal volume of balanced salt solution was used in group A. Ofloxacin, 0.3% topical drops (Oflox, Allergan Inc., Brazil), were instilled 4 times daily (week 1 and 2) for both groups. Clinical assessment of intraocular inflammation was performed by a masked investigator who was unaware of patient group status, and a masked statistician analyzed the data. Unfortunately, because of the milky appearance of the prednisolone, we faced some barriers to guarantee the masked fashion of this study. To overcome this potential problem, the observer was unaware of any detail of the patient treatment and the patients were asked not to provide any information regarding eyedrop instillation.

Surgical Procedure

All eyes were dilated with 2 drops of 10% phenylephrine eyedrop administered 5 minutes apart and 3 drops of 1% tropicamide eyedrops administered 3 minutes apart. Surgery was performed under topical anesthesia using 0.5% proxymetacaine hydrochloride eyedrops and 0.3 ml 1% intracameral lidocaine. The surgical approach consisted of phacoemulsification through a 2.75-mm clear corneal incision. The Alcon Legacy phacoemulsification unit and the stop-and-chop technique were used in all surgeries. For injection into the posterior sub–Tenon's capsule space, a previously described technique was used.[16] Briefly, the bulbar conjunctiva was grasped optimally approximately 10 mm away from the limbus using a forceps at the site of intended entry into the inferotemporal quadrant. At this point, entry was made into the episcleral space using the trocar of a 23-gauge intravenous cannula made of polytetrafluorethylene. The trocar and cannula were advanced together for approximately 3 mm within the episcleral space under direct visualization. Subsequently, the trocar was withdrawn entirely and the cannula alone was guided further posteriorly for approximately 10 mm. Balanced salt solution (group A) or triamcinolone (group B) then was injected using a syringe affixed to the intravenous cannula.

Outcome Measures

All efficacy variables were evaluated at baseline and during all follow-up visits by slit-lamp biomicroscopy without pupil dilation according to a previously published grade system.[17]

The primary efficacy variables were anterior chamber cells and flare. In addition, the percentage of patients dropped from the study for lack of efficacy was considered a key indicator of treatment failure. Anterior chamber cells were graded on a scale of 0 to 4 where 0 = none (no cells), 1 = mild (1–5 cells), 2 = moderate (6–15 cells), 3 = severe (16–30 cells), and 4 = very severe (>30 cells). Anterior chamber flare also was graded on a scale of 0 to 4, with 1-grade increments, where 0 = none (no Tyndall effect), 1 = mild (barely discernible Tyndall effect), 2 = moderate (moderately intense Tyndall beam in anterior chamber), 3 = severe (severely intense Tyndall beam), and 4 = very severe (very severely intense Tyndall beam with a white and milky appearance of the aqueous).

Additional efficacy variables were conjunctival erythema and ciliary flush. Patients were asked verbally whether they experienced symptoms of ocular inflammation such as foreign body sensation, tearing, photophobia, and pain. These variables were evaluated on a scale of 0 to 4, with 1-grade increments, where 0 = none and 4 = very severe.

Safety variables monitored included adverse events, intraocular pressure, visual acuity, and other biomicroscopic and ophthalmoscopic findings. Throughout the study, any signs or symptoms of adverse events were recorded, graded for severity, and assessed for their relationship to the study medication. At the end of each visit, intraocular pressure was measured by Goldmann applanation tonometry. Visual acuity in the study eye was measured using the Snellen visual acuity chart. In addition, complete biomicroscopic

Table 1. Characteristics of the Patient Population

Variables	Prednisolone (n = 50)	Triamcinolone (n = 50)	P Value
Age (yrs) ± standard deviation	65.3 ± 7.9	65.0 ± 7.9	0.885
Visual acuity (logMAR)*, mean (range)	0.73 (0.3–1.3)	0.73 (0.2–1.3)	0.859
Intraocular pressure (mmHg)*, mean (range)	14.1 (10–19)	14.2 (10–18)	0.979
Gender			0.423
Female	28 (56%)	24 (48%)	
Male	22 (44%)	26 (52%)	
Race			0.330
Black	27 (54%)	26 (52%)	
White	21 (42%)	24 (48%)	
Asian	2 (4%)	0 (0%)	

logMAR = logarithm of the minimum angle of resolution.
*Preoperative measures.

and ophthalmoscopic examinations were conducted at baseline and during all follow-up visits.

Data Analysis and Statistics

An intent-to-treat analysis was carried out. The Mann–Whitney *U* test was used to evaluate variables with ordered-response categories and continuous responses, and the chi-square test was used to evaluate categorical variables (race, gender, and exits resulting from lack of response). With 50 patients in each study group, a power of more than 80% was obtained for detecting differences of 0.3 U or more on the severity scale and 2.4 mmHg or more on the intraocular pressure scale. The significance level was set at 0.01 to adjust for multiple comparisons.

Results

Patient Disposition

Of the 100 patients enrolled, 50 were assigned to each of the 2 treatment groups. One hundred percent (100/100) of the patients in both groups completed the study. No patients were discontinued because of improper entry or protocol violations. Intrasurgical decisions not to include patients were mainly the result of posterior capsule rupture (2 patients) and a broken IOL (1 patient) during the insertion that needed to be replaced. No patients from either treatment group were dropped from the study for lack of response.

Patient Population Characteristics

The demographic characteristics of the patient population are listed in Table 1. Patient age ranged from 51 to 80 years, with a mean of 65.2±7.9 years. Fifty-two percent (52/100) of the patients were females and 48% (48/100) were males. There was no significant difference between the treatment groups in age, gender, race, preoperative best-corrected visual acuity, or intraocular pressure.

Efficacy

Anterior Chamber Cells and Flare. There was no statistically significant difference between the triamcinolone group and the 1% prednisolone acetate group in anterior chamber cell ($P \geq 0.491$; Fig 1) and flare ($P \geq 0.730$; Fig 2) at all postoperative days. The data are summarized in Table 2.

Conjunctival Erythema, Ciliary Flush, and Symptoms of Ocular Inflammation. There was no statistically significant difference between the triamcinolone group and the 1% prednisolone acetate group in conjunctival erythema, ciliary flush, or any of the symptoms of ocular inflammation at all postoperative days. The data are summarized in Table 2.

Patients Dropped for Lack of Response. No patients from either treatment group were dropped from the study because of lack of anti-inflammatory response.

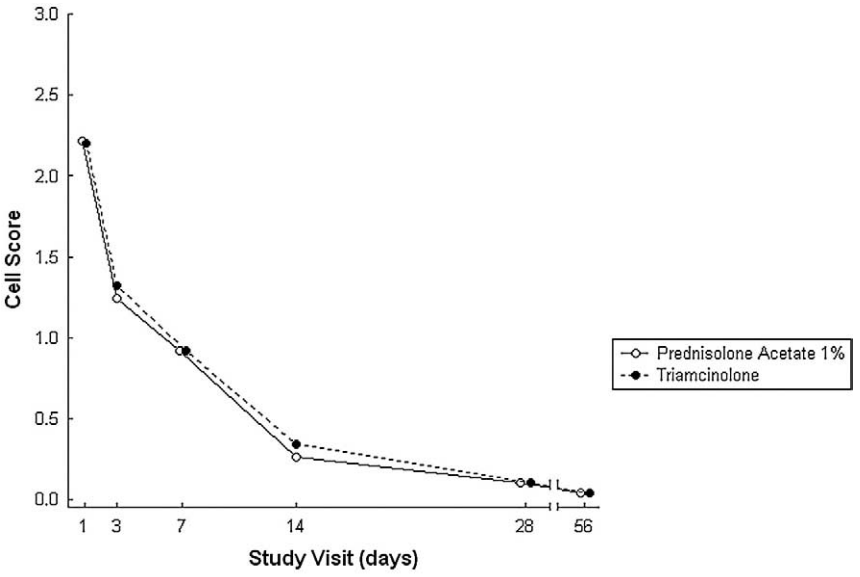

Figure 1. Anterior chamber cells at each study visit. The decrease from the first postoperative day was not statistically significant at any visit.

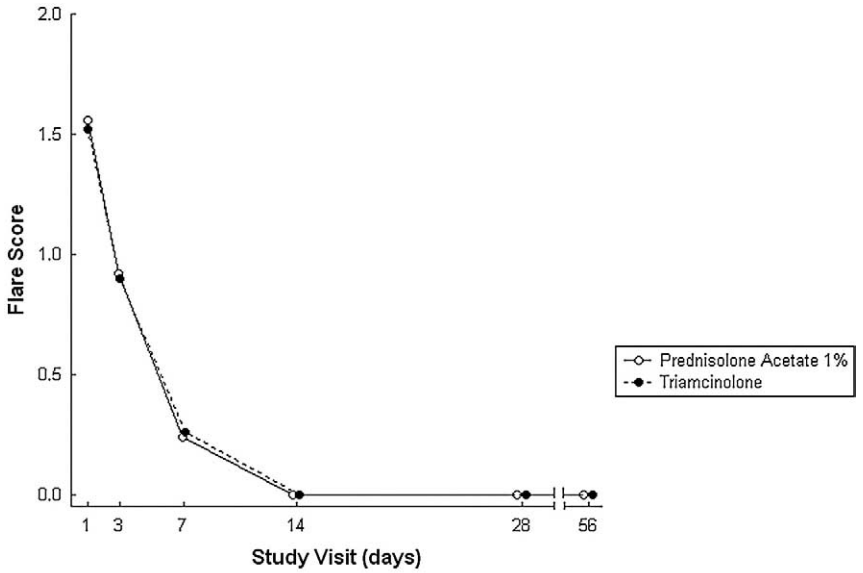

Figure 2. Anterior chamber flare at each study visit. The decrease from the first postoperative day was not statistically significant at any visit.

Safety

Intraocular Pressure and Visual Acuity. The between-group difference was statistically significant on days 3, 7, 14, and 28 ($P<0.01$; Fig 3). There were no significant differences between treatment groups in visual acuity at any follow-up visit. No increase in intraocular pressure higher than 25 mmHg or a 10-mmHg increase in IOP from baseline in any of the treated groups was observed.

Biomicroscopy and Ophthalmoscopy. There were no significant differences between treatment groups in any biomicroscopy or ophthalmoscopy safety variables.

None of the patients in the triamcinolone group or prednisolone acetate group showed clinically significant abnormal ophthalmoscopic findings.

Discussion

In the modern cataract surgery era, postsurgical inflammation is minimal, and a more comprehensive medical management strategy to treat such inflammation is still to be determined. Historically, corticosteroids have been the

Table 2. Efficacy and Safety Outcomes at Each Study Visit

Variable	Group	Study Visit					
		Day 1	*Day 3*	*Day 7*	*Day 14*	*Day 28*	*Day 56*
AC cell	Prednisolone	2.2 (1–3)	1.2 (1–2)	0.9 (0–2)	0.3 (0–1)	0.1 (0–1)	0.0 (0–1)
	Triamcinolone	2.2 (1–3)	1.3 (1–2)	0.9 (0–2)	0.3 (0–1)	0.1 (0–1)	0.0 (0–1)
	P value	0.842	0.491	0.989	0.491	1.000	1.000
AC flare	Prednisolone	1.6 (1–2)	0.9 (0–1)	0.2 (0–1)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)
	Triamcinolone	1.5 (1–2)	0.9 (0–2)	0.3 (0–1)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)
	P value	0.730	0.852	0.863	1.000	1.000	1.000
Conjunctival erythema	Prednisolone	1.4 (1–3)	0.6 (0–2)	0.2 (0–1)	0.1 (0–1)	0.0 (0–1)	0.0 (0–0)
	Triamcinolone	1.4 (1–2)	0.7 (0–2)	0.2 (0–1)	0.0 (0–1)	0.0 (0–0)	0.0 (0–0)
	P value	0.815	0.799	0.730	0.730	0.863	1.000
Ciliary flush	Prednisolone	0.1 (0–1)	0.0 (0–1)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)
	Triamcinolone	0.1 (0–1)	0.0 (0–1)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)
	P value	1.000	1.000	1.000	1.000	1.000	1.000
Photophobia	Prednisolone	0.7 (0–3)	0.5 (0–2)	0.2 (0–2)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)
	Triamcinolone	0.8 (0–3)	0.5 (0–2)	0.1 (0–1)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)
	P value	0.788	0.929	0.715	1.000	1.000	1.000
Pain	Prednisolone	0.6 (0–2)	0.4 (0–2)	0.2 (0–2)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)
	Triamcinolone	0.7 (0–3)	0.4 (0–2)	0.1 (0–1)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)
	P value	0.825	0.712	0.596	1.000	1.000	1.000
IOP (mmHg)	Prednisolone	17.5 (14–20)	17.0 (12–22)	16.1 (12–20)	15.0 (12–18)	14.3 (12–18)	14.0 (12–18)
	Triamcinolone	17.1 (12–24)	13.8 (10–20)	13.4 (10–18)	13.4 (10–16)	13.2 (10–18)	13.4 (10–20)
	P value	0.440	<0.001	<0.001	0.008	0.005	0.054

AC = anterior chamber; IOP = intraocular pressure.
Data are mean (range).

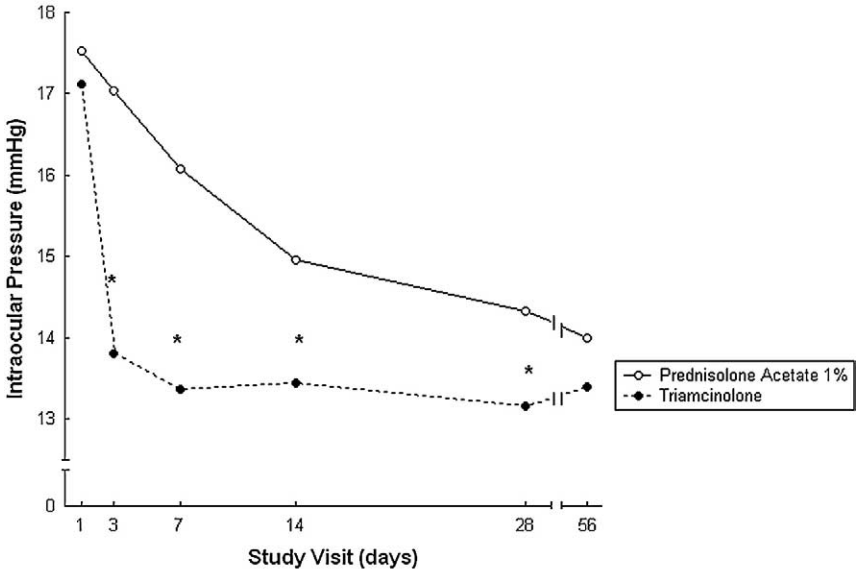

Figure 3. Intraocular pressure (mmHg) at each study visit. Differences between prednisolone and triamcinolone groups were statistically significant at *$P<0.01$.

drugs of choice for the prevention or treatment of postoperative ocular inflammation and are commonly used for several weeks. Recently, a perioperative drug delivery system has proven to be effective in eliminating the necessity for postoperative topical therapy.[5–7] The sustained anti-inflammatory effects associated with the use of triamcinolone in the ophthalmic setting have prompted the authors to consider its therapeutic use for controlling postcataract surgery inflammation. A sub–Tenon's capsule depot corticosteroid injection may satisfy all the requirements for an ideal anti-inflammatory strategy and may have distinct advantages for reducing complications related to patient noncompliance with eyedrop administration.

The present study is an extension of currently published reports in that it demonstrates that a single posterior 40-mg sub–Tenon's capsule triamcinolone acetonide injection has a therapeutic response and ocular tolerance comparable with 1% prednisolone acetate drops in controlling the signs and symptoms of ocular inflammation after cataract surgery. At baseline (first postoperative day), all patients in both treatment groups had cell and flare scores of at least moderate severity that gradually decreased in both groups during the course of the study. Equally in both groups, there were significantly greater decreases in anterior chamber cells from days 1 to 14 and in the anterior chamber flare from days 1 to 7. This effectiveness was maintained until the end of the study, and none of the eyes in both groups required any additional medication.

Clinical assessment of intraocular inflammation by the combined flare-and-cell slit-lamp grading technique did not show any significant difference in intraocular inflammation between group A and group B on any follow-up visit, suggesting that triamcinolone is at least as effective as conventional prednisolone eyedrops in reducing postoperative inflammation. In addition, no patient in either group had to be excluded for lack of response.

A single posterior sub–Tenon's capsule triamcinolone injection demonstrated an equivalent ocular tolerance to prednisolone eyedrops through the 8-week follow-up period. There were no significant differences between the 2 treatment groups in the number of adverse events, changes in visual acuity, or lack of response. Potential complications of posterior sub–Tenon's capsule injection of corticosteroids include inadvertent injection into the choroidal or retinal circulation,[18–20] perforation of the globe with or without intravitreal injection,[21–23] and occlusion of the central retinal artery.[24] Blepharoptosis, proptosis, orbital fat atrophy, delayed hypersensitivity reactions, strabismus, conjunctival hemorrhage, chemosis, and infection also have been reported in the literature.[25–27]

These complications are relatively infrequent and were not found in the present study; however, this is not an adequately powered study to detect rare complications. A rise in intraocular pressure after topical or systemic administration of corticosteroids is of particular concern. Posterior sub–Tenon's capsule injections of corticosteroids seem to be less likely than anterior sub–Tenon's capsule injections to produce ocular hypertension or glaucoma.[28] It also has been reported that patients who receive sub–Tenon's capsule injections of corticosteroids may not respond to maximal antiglaucomatous therapy and, therefore, may require surgical excision of the depot because of a persistent increase in intraocular pressure.[29] However, in the study of Akduman et al,[29] it was specifically noted that the corticosteroid depot in 2 described cases was located anteriorly, and this might have been the reason for the increase in intraocular pressure in those patients. Mueller et al[30] reported that sub–Tenon's capsule injection of corticosteroids is a safe procedure and does not induce a clinically significant increase of intraocular pressure when the corticosteroid depot is injected posteriorly into the sub–Tenon's capsule space. In our study, special care was taken during every

injection to verify that the liquid was placed in the posterior sub–Tenon's capsule space. We did not note an increase in intraocular pressure above 24 mmHg in any of the treated groups. In our series, a lower-than-expected incidence of increased intraocular pressure was observed after injection. Surprisingly, on the third, seventh, 14th, and 28th postoperative days, a significantly lower intraocular pressure ($P<0.01$) was noted in the triamcinolone group than in the prednisolone group. Because increased intraocular pressure 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, and these concerns may not apply to operated patients whose status in responding to corticosteroid is not known. Although this finding cannot be explained fully in the present initial study, it forms the groundwork for further investigation. There may be a delayed onset of increased intraocular pressure for up to several months after corticosteroid injection.[31] In our series, no patient showed increased intraocular pressure for up to 2 months of follow-up visits.

The conventional technique of posterior sub–Tenon's capsule injection involves the use of a sharp tipped 26-gauge, 5/8-inch needle that must be inserted up to its hub to obtain adequate placement of the drug into the posterior sub–Tenon's capsule space. With this technique, the risk of perforation of the globe, although minimal, remains a potential complication. In the method used here, the risk of inadvertent globe perforation possibly can be eliminated because of the insertion technique and the nature of the polytetrafluoroethylene intravenous cannula. In addition, there is minimal to no subconjunctival scarring, and in most cases, it is difficult even to detect that an injection was made into the posterior sub–Tenon's capsule space.

Sub–Tenon's capsule injection of depot corticosteroids is an accepted method for the treatment of various inflammatory eye diseases.[8–10] In the present study, a posterior sub–Tenon's capsule triamcinolone injection demonstrated good ocular tolerance and therapeutic performance in the elimination of postoperative inflammation, supporting an expansion of this anti-inflammatory technique into the surgical arena. It provides the ophthalmologist with an alternative approach to costly controlled drug delivery and eliminates the need for patient self-medication, which avoids problems with compliance and instruction. Such an approach could be especially important in the third world, where topical medications may not be available after intraocular surgery. In addition, when this demonstration of the anti-inflammatory effects is combined with its other known therapeutic properties, a clear role for triamcinolone as a simple and more rational new therapeutic management strategy for postcataract surgical inflammation begins to emerge. The ability of triamcinolone to prevent postoperative inflammation, to treat diabetic macular edema aggravated by cataract, and potentially to treat cystoid macular edema (Klancnilk JM. Short-term optical coherence tomographic (OCT) follow-up of posterior sub–Tenon's capsule triamcinolone for refractory macular edema: visual and anatomic results. Paper presented at: 21nd Annual Meeting American Society of Retina Specialists, August 16 to 20, 2003; New York, New York) suggests that triamcinolone could be used effectively after cataract surgery to achieve several clinical objectives with a single medication.[11–15]

In summary, the present study shows that a single intraoperative sub–Tenon's capsule 40-mg triamcinolone acetonide injection has a clinically equivalent therapeutic response to conventional 1% prednisolone eyedrops in controlling postoperative ocular inflammation. Its technical simplicity, lack of complications, and low cost encourage additional research into triamcinolone acetonide sub–Tenon's capsule injection to clarify its potential safety and usefulness in treating inflammation occurring after cataract surgery. Investigation of an antibiotic–triamcinolone formulation for sub–Tenon's capsule application currently is underway in our laboratory and may anticipate the reality of no need for postoperative medication in the modern cataract surgery era.

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