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ORIGINAL RESEARCH

Comparing Combination Drop Therapy to a Standard Drop Regimen After Routine Cataract Surgery

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Purpose: To evaluate the efficacy of a combined steroid/antibiotic/non-steroidal anti-inflammatory drop relative to a regimen of multiple drops after cataract surgery.
Setting: Single clinical practice in the USA.
Design: Prospective randomized contralateral eye study.
Methods: Subjects presenting for bilateral cataract surgery were enrolled with contralateral eyes randomly assigned to one of the two groups. Test eyes received a combination therapy (prednisolone acetate 1%, gatifloxacin 0.5%, and bromfenac sodium 0.075%) while control eyes received the same medications in separate drops (bromfenac sodium was 0.07%). Subjects were examined 1, 15 and 30 days after surgery. Visual acuities were measured, along with the refraction, intraocular pressure, patient pain and satisfaction, macular thickness and corneal pachymetry. The primary measure of interest was the change in macular thickness from baseline to the 15- and 30-day visits. The frequency and severity of reported ocular adverse events were tabulated for each group and compared.
Results: Thirty-three subjects completed the study. Changes in central macular thickness were similar between groups, with only one control eye exhibiting significant macular edema. No differences in visual acuity, corneal edema, cells or flare were observed between groups. There were eight mild adverse events reported for all eyes of all subjects; the difference in the number of eyes experiencing adverse events was not statistically significantly different between groups ($p \geq 0.05$ for all comparisons). While subjective symptoms were similar, all subjects indicated that they preferred the combination drop.
Conclusion: A combination drop showed similar efficacy to multiple drops and was overwhelmingly preferred by subjects.
Keywords: bromfenac sodium, gatifloxacin, prednisolone acetate, combination drop

Plain Language Summary

Cataract surgery involves making several incisions in the eye and removing the lens of the eye, replacing it with an artificial lens. During surgery, then, the eye is open to the environment. Surgeons and surgery centers are very careful to minimize the chance of infection inside the eye because it can be very serious. To further reduce the possibility of infection, and to help with inflammation, patients are usually provided several drops to take for several weeks after surgery. It can be confusing to patients as to which drops to take when. In this study, we compared different treatments in the two eyes of the same patient. One eye was treated using three different drops while the second eye was treated with a single drop that contained all the same ingredients. The single drop provided a much simpler regimen for patients after surgery. We found no difference in the amount of inflammation in the two eyes and no eye in the study had an infection.

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Symptoms after surgery, and during drop use, were reported to be similar. All of our subjects preferred the single drop, as it was much easier to manage.

Introduction

Cataract surgery is one of the most common surgical procedures in the world. The current standard of care usually involves prescribing several different prophylactic eye drops after surgery. These include antibiotic drops to reduce the risk of postoperative infection, and steroidal and nonsteroidal anti-inflammatory drops (NSAIDs) to reduce the risk and severity of intraocular inflammation.

Prophylactic antibiotics are routinely used to prevent serious postsurgical complications such as endophthalmitis. Endophthalmitis is arguably the most serious potential complication after cataract surgery because it can lead to significant vision loss and, in extreme cases, loss of the eye.[1] The delivery method of antibiotics differs by country and by surgeon but typically involves topical eye drops, intracameral injection, or subconjunctival injection.[2] Transzonular injections at the time of surgery may also be used, though this modality is less common.[3] A recent report by Jabbarvand et al[4] and a systematic review by Kessel et al[5] suggest that the use of intracameral injections may be more effective at reducing the incidence of endophthalmitis. Despite the routine use of prophylactic antibiotics, the incidence of endophthalmitis has been reported as high as 0.26%.[6–10]

In addition to the risk of postsurgical infection, cataract surgery may induce an inflammatory response in patients. This can lead to pseudophakic cystoid macular edema (CME), a postsurgical complication characterized by swelling of the fovea.[11] Patients with CME experience significantly worse visual outcomes. Prophylactic steroids and NSAIDs can both be effective in preventing, or reducing the severity of, CME after cataract surgery. Some studies have reported a reduced incidence of CME with NSAID use relative to the incidence when steroids are used.[12–14] However, even with routine preventative measures, the incidence of clinical CME has been reported as high as 2.35%.[15–17]

The inability to eliminate the incidence of endophthalmitis and CME may be partially explained by patient noncompliance to the prescribed medication regimens. Patient noncompliance with ocular medications can be as high as 80%.[18–21] After cataract surgery, patients are often instructed to instill multiple topical drops to prevent infection, inflammation, and pain, with each drop potentially on a different schedule. This can be confusing to patients and/or can be too burdensome for some, leading to non-compliance.

An alternative to administering multiple drops on different schedules is to combine all medications into a single drop. In addition to improving compliance, a single drop may reduce ocular toxicity by reducing exposure to the preservatives typically found in eye drops.[22] One combination drop therapy (LessDrops™, Imprimis Pharmaceuticals Inc., San Diego, CA, USA) contains prednisolone acetate 1%, gatifloxacin 0.5%, and bromfenac sodium 0.075% (Pred-Gati-Brom). Prednisolone acetate provides the anti-inflammatory effect,[23] gatifloxacin hydrochloride is an effective antibiotic,[24] and bromfenac sodium is an NSAID used to manage pain and inflammation.[25] Other popular drop combination therapies include prednisolone acetate and nepafenac; prednisolone acetate and gatifloxacin hydrochloride; and prednisolone acetate, gatifloxacin hydrochloride, and nepafenac. Some studies have found topical and injectable combination therapies to be equally effective,[26–28] though Singhal et al[29] reported that the incidence of breakthrough inflammation was higher in eyes that received an injectable formulation of triamcinolone and moxifloxacin compared to separate topical drops. Cunha et al[22] reported similar efficacies of a combination drop containing prednisolone acetate and gatifloxacin hydrochloride and the use of the drops separately.

The purpose of this study was to evaluate the efficacy of the Pred-Gati-Brom formulation and compare it to a multiple drop regimen used for routine cataract surgery.

Methods

This was a prospective randomized contralateral eye study at a single site with a single surgeon (clinical trials.gov reference: NCT03578276). This study was reviewed and approved by an institutional review board (Salus IRB, Austin, TX) and was conducted following the principles of Good Clinical Practice and the tenets of the Declaration of Helsinki. Planned enrollment was thirty-five (35) subjects presenting for routine phacoemulsification and IOL implantation in both eyes, with one eye assigned to the test group and the contralateral eye serving as the control.

This was based on a calculated sample size of 30 subjects to allow for the detection of a 5-micron difference in the change in retinal thickness between eyes, given an alpha of 0.05, beta of 0.9, and a standard deviation of 6 microns for OCT macular thickness measurements; some dropout was expected. All subjects signed an informed consent to participate in the study. De-identified data will not be made available for sharing.

Eligible subjects had to have a potential best-corrected visual acuity of 20/30 or better. Subjects were excluded if they had severe preoperative ocular pathology, such as amblyopia, macular edema, advanced macular degeneration, or proliferative diabetic retinopathy; a history of chronic intraocular inflammation or retinal detachment; or any additional ocular surgical procedures at the time of cataract extraction (other than corneal incisions to correct astigmatism). Complications during surgery, such as uncontrollable intraocular pressure (IOP), significant vitreous loss, zonular or capsular rupture, or significant anterior chamber hyphema were also exclusion criteria.

Test eyes received the combination therapy, with the following dosing regimen: three times a day starting 1 day prior to surgery and continued for 2 weeks after surgery, then twice a day for a week and once a day for another week. The control eyes received gatifloxacin 0.5% (1 drop, four times a day for 3 days prior to surgery, continued for 2 weeks after surgery), bromfenac 0.07% (1 drop once daily starting 3 days before surgery and continued for 4 weeks after surgery) and prednisolone acetate 1% (four times a day after surgery for 2 weeks, tapered to twice daily for 2 weeks). The individual medications specified in the control group were prescribed by the surgeon so that patients could have the prescriptions filled at their local pharmacy.

Subjects who met the inclusion/exclusion criteria had their eyes randomly assigned to the Test or Control groups. Half of the subjects received the test regimen in the first eye surgery, and their second eye surgery was used as a control. The remaining subjects received the test regimen in the second eye surgery, while their first eye surgery was used as a control. Second eye surgeries were typically performed within 2 weeks of the first eye surgery.

Phacoemulsification and IOL implantation were performed using the surgeon's standard technique. Routine intraoperative medications, such as ophthalmic viscosurgical devices and intracameral antibiotics, were the same in both eyes. The use of antibiotics in the irrigation bottle was not permitted.

Subjects maintained a logbook of drop use and were examined on postoperative days 1, 15, and 30. Subjects had a complete slit lamp exam and were evaluated for cells and flare. Uncorrected distance and best-corrected distance visual acuities were measured using standard Early Treatment Diabetic Retinopathy Study (ETDRS) charts at 4 m. Central macular thickness was determined by ocular coherence tomography (OCT) using the Cirrus HD OCT (Carl Zeiss Meditec, Jena, Germany), with software version 9.5. Refraction, IOP, patient pain and satisfaction, and corneal pachymetry were also evaluated.

The primary endpoint for the study was the change in central macular thickness (CMT) from the baseline preoperative examination to the 15- and 30-day visits; this is more sensitive than comparing actual CMT because CMT often varies by subject, introducing variability that is easily removed by considering only the change in CMT. Other measures of interest were changes in corneal thickness, the scores for subjective symptoms (eg, pain, foreign body sensation, burning/stinging) and subject satisfaction. The latter two were evaluated using unvalidated written questionnaires (see Appendix). Questions were read to subjects and responses were recorded. Where scale data were collected, the subject was instructed to draw a line on the relevant pain severity scale. In addition to the data above the type, severity, duration and frequency of reported ocular adverse events (whether treatment-related or not) were tabulated for each group. Comparison of treatment groups with respect to the proportion of study patients reporting adverse events was made using Fisher's Exact Test.

De-identified subject data were collected on appropriate case report forms and collated in an Excel file, with the resulting sheets imported into Access for preliminary tabulation and analysis (both Microsoft Corp, Redmond, WA). Statistical analyses were performed using the Statistica data analysis software system, version 12 (TIBCO Software Inc., Palo Alto, CA, USA). Parametric comparisons were made using analysis of variance (ANOVA) and non-parametric data were compared using the Chi-squared test or Fisher's Exact Test. All statistical tests were two-sided with $p = 0.05$ considered significant.

Results

Thirty-five subjects who met the inclusion/exclusion criteria were successfully recruited. One subject did not have their second eye surgery within the protocol window, and another advised that they had discontinued the drop regimen. No adverse events were associated with either of these subjects, but both were excluded from further analysis, leaving 33 subjects in the study. The demographic and preoperative characteristics of the subjects are summarized in Table 1. As can be seen, there were no statistically significant differences between the Test and Control eyes, or the primary surgical parameters used for each eye; comparisons were based on a between-eyes repeated-measures ANOVA.

Table 1 Demographics and Preop Measures (n = 33 Subjects, 66 Eyes)

Age (years) **Gender (F/M)**	**69.72± 6.6 (58 to 82)** **18/15 (55%/45%)**		
	Test	**Control**	**p**
Corneal Pachymetry (microns)	542.3 ± 50.4 (445.3 to 647.3)	545.6 ± 50.3 (441.3 to 645)	0.44
CMT (microns)	261.6 ± 24.0 (212 to 307)	262.6 ± 24.5 (212 to 307)	0.56
IOL Power (D)	20.0 ± 2.8 (14 to 26.5)	20.2 ± 3.0 (13.5 to 28)	0.32
Phaco time (seconds)	41.4 ± 13.0 (19.7 to 72.3)	43.1 ± 13.0 (20.4 to 79.0)	0.44
Cumulative dissipated energy (%-s)	5.32 ± 2.74 (0.76 to 11.62)	5.83 ± 2.52 (2.07 to 14.24)	0.18
Fluid use during surgery (mL)	46.8 ± 10.4 (30.0 to 68.0)	46.7 ± 11.9 (25 to 78)	0.96

Abbreviations: CMT, central macular thickness; IOL, intraocular lens; D, diopter; %-s, percent seconds; mL, milliliter.

Figure 1 shows the mean change in CMT over time and by group. There was no statistically significant difference in this change by group (p = 0.37), but there was a statistically significant difference with time – the change in CMT was significantly higher at 30 days postoperative (p = 0.048). There was no interaction effect between time and group (p = 0.36). The mean change in both groups at both time points was less than 7 microns. Table 2 shows a breakdown of the number of eyes with a change in CMT from baseline of more than 5 and more than 10 microns. The number of eyes with greater changes in CMT was higher for the Test group in all cases, but the differences were not statistically significant. Only one eye had a CMT increase of more than 40 microns, one Control eye at 30 days (change of 111 microns).

The spherical equivalent refraction at 15 and 30 days was not statistically significantly different between the groups (p = 0.76), nor was there any statistically significant difference in the best-corrected distance visual acuity (p = 0.23). Uncorrected distance visual acuity (UDVA) was about one letter better at the 30-day visit relative to the 15-day visit (p = 0.03), but there was no difference in UDVA between the groups at either time point and no interaction effect between time and group.

There was no statistically significant difference in mean pachymetry at any visit and no difference in the change in

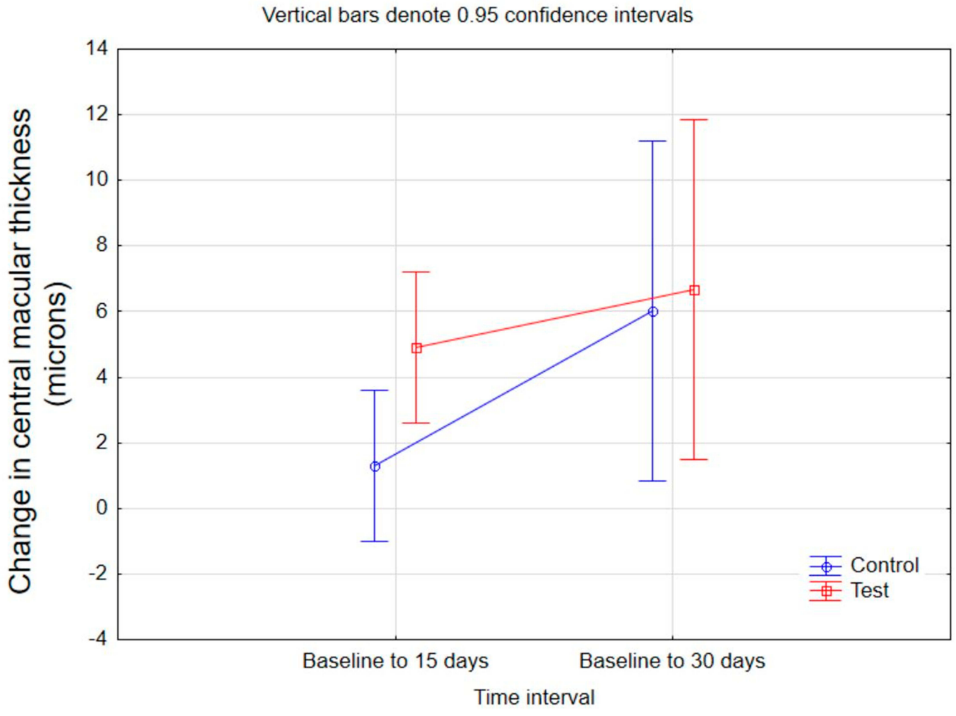

Figure 1 Mean change in central macular thickness over time.

Table 2 Categorized Changes in Central Macular Thickness

Time Interval (Baseline to)	Group	Change in CMT (Microns)			p (5)[a]	p (10)[b]
		≤ 5	> 5 and ≤ 10	> 10		
15 days	Control Test	28 23	4 6	1 4	0.12	0.18
30 days	Control Test	26 20	4 4	3 9	0.09	0.054

Notes: [a]Fisher's Exact Test, proportion of eyes with change > 5 microns. [b]Fisher's Exact Test, proportion of eyes with change > 10 microns.
Abbreviation: CMT, central macular thickness.

Table 3 Reported Symptoms by Group and Time (n = 33)

		Control	Test	p*
15 days	Burning Foreign body sensation Pain	11 3 1	5 2 0	0.07 0.50 0.50
30 days	Burning Foreign body sensation Pain	3 1 0	1 2 0	0.31 0.50 1.00

Note: *Fisher's Exact Test.

pachymetry from baseline between groups at either 15 or 30 days ($p > 0.34$). The IOP change from baseline was significantly lower at 30 days than at 15 days (-0.3 ± 3.3 mm Hg at 15 days vs -0.9 ± 3.9 mm Hg at 30 days, $p = 0.03$), but there was no statistically significantly difference between the groups ($p = 0.84$). No eye exhibited measurable flare at either the 15- or 30-day visit. Only one eye in each group exhibited more than trace cells at the 15-day visit and none had more than trace cells at 30 days.

Subjective scores of burning, foreign body sensation and pain on drop instillation were recorded. Summary data are shown in Table 3. There were no statistically significant differences between the Test and Control groups with regard to the incidence of these symptoms. Of 29 reported instances of subjective symptoms, 24 (83%) were graded as "Mild". One subject reported mild pain in their Control eye at the 30-day visit, but there were no other reports of pain.

There were eight mild adverse events reported for all eyes of all subjects. One subject had rebound inflammation in both eyes, while another had high IOP in both eyes. Unilateral adverse events included high IOP in one subject, punctate epithelial erosions in another, rebound inflammation in a third and macular edema in a fourth; all four unilateral cases involved the Control eye. The difference in the number of eyes experiencing mild adverse events was not statistically significantly different between the Test and Control groups ($p \geq 0.5$ for all comparisons, Fisher's Exact Test).

All subjects but one were satisfied or very satisfied with their surgery in both eyes; subjects were "Very Satisfied" with 85% (28/33) of Test eyes and 79% (26/33) of Control eyes. All subjects indicated that they preferred the Test eye to the Control eye in terms of their postoperative care (Chi-squared test, $p < 0.0001$).

Discussion

To the best of our knowledge, this is the first study to assess the efficacy of a formulation containing prednisolone acetate, gatifloxacin hydrochloride, and bromfenac sodium used as a combination drop therapy before and after routine cataract surgery compared to instilling each drop separately.

Both therapies generally performed well. We found no postoperative infections and only one case of CME with either the combination therapy or the separate drop therapy. We found no significant differences between the two therapies for postoperative changes in macular thickness, corneal thickness, pain, anterior chamber cells and flare, or IOP. These results suggest that the combination therapy and the separate drop therapy are similarly effective at preventing postoperative complications. Similar results were found in another study using a prednisolone acetate and gatifloxacin combination drop.[22]

Patient satisfaction was high with both therapies. The majority of subjects reported being satisfied or very satisfied with the results of their cataract surgery. There were no significant differences in patient-reported satisfaction between the combination drop and separate drop therapies. However, when asked to choose which therapy they would select if they had to "do it all over again", patients unanimously preferred the combination therapy. It is likely that patients prefer the relatively simpler regimen of instilling one combination drop versus several separate drops when they experience no other differences in their recovery. Results here are similar to those reported in a previous study comparing a combination drop therapy to an intravitreal injection which eliminated the need for drops altogether. Despite no differences in outcomes, patients preferred the less burdensome option of the injection for both postoperative outcomes and postoperative experience.[28] As a final comment in this regard, enrollment for this study was relatively slow, as it was difficult

to find eligible patients willing to use the three different drops instead of the combination drop; the latter is the standard of care in our clinic.

Prophylactic NSAIDs and steroids are routinely used in cataract surgery to prevent inflammation and patient discomfort. The anti-inflammatories used in this study (prednisolone acetate and bromfenac) have been shown to be safe and effective after cataract surgery.[23,25] We found that both the combination drop and separate drop therapies were similarly effective at reducing inflammation, generally without increasing IOP. We found only one case of CME with either therapy.

Serious postoperative infections, such as endophthalmitis, can be prevented through the use of prophylactic antibiotics. The antibiotic used in this study, gatifloxacin, is a fluoroquinolone agent and has been shown to be safe and effective for this purpose.[24,30] Reports have indicated that gatifloxacin can penetrate into the aqueous at high enough concentrations to be effective against infections.[1,24,31] However, Donnenfeld et al[32] observed that the concentration of gatifloxacin may not be high enough to be effective against some drug-resistant strains. Effective removal of ocular pathogens prior to cataract surgery is crucial, and arguably more important, for preventing intraocular infections. Torkildsen et al[33] reported high enough concentrations of gatifloxacin in the conjunctiva to be effective against drug-resistant strains of staphylococcus. We observed that both the combination drop and separate drop therapies were similarly effective at preventing infection.

The primary limitation to the current study was the sample size. While it was chosen to allow for the detection of changes in central macular thickness, more eyes might have aided in the detection of other differences between the two therapies. The study was significantly underpowered for the detection of endophthalmitis because of the very low incidence of this complication.

In summary, the use of a combination drop for postoperative cataract surgery care demonstrated similar performance to the use of the three components of the drop when instilled separately. With similar apparent effectiveness (though again, no statement regarding endophthalmitis is possible in this sample size), and a much less burdensome regimen, subjects overwhelmingly preferred the combination drop.

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