·Clinical Research·

Comparison of brimonidine-timolol and dorzolamide-timolol in the management of intraocular pressure increase after phacoemulsification

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Abstract

• AIM: To compare the effectiveness of brimonidine/timolol fixed combination (BTFC) and dorzolamide/timolol fixed combination (DTFC) in the management of short-term intraocular pressure (IOP) increase after phacoemulsification surgery.

• METHODS: Eighty eyes of 80 patients undergoing phacoemulsification and intraocular lens (IOL) implantation were randomly assigned into three groups. Group 1 consisted of 28 eyes and represented the control group. Group 2 consisted of 25 eyes undergoing phacoemulsification surgery and BTFC was instilled at the end of surgery. Group 3 consisted of 27 eyes undergoing phacoemulsification surgery and DTFC was instilled at the end of surgery. IOP was measured preoperatively and 6, 24h and 1wk postoperatively.

• RESULTS: There was no statistically significant difference in preoperative baseline IOP among the three groups (P=0.84). However, IOP was significantly lower in groups 2 and 3 compared to the control group (P<0.05 for all comparisons) at all postoperative visits. There was no significant difference between groups 2 and 3 at any visit. Eight eyes (28.6%) in the control group, two (8%) in Group 2 and one (3.7%) in Group 3 had IOP >25 mm Hg at 6h after surgery (P=0.008). However, IOP decreased and was >25 mm Hg in only one eye in each group at 24h after surgery.

• CONCLUSION: BTFC and DTFC have similar effects in reducing increases in IOP after phacoemulsification surgery and can both be recommended for preventing IOP spikes after such surgery.

• **KEYWORDS:** cataract; brimonidine; dorzolamide; timolol; intraocular pressure; phacoemulsification; postoperative complication
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INTRODUCTION

Phacoemulsification surgery may lead to a decrease in intraocular pressure (IOP) at long-term follow-up. However, IOP rises in the early postoperative period in healthy eyes after uncomplicated phacoemulsification surgery have also previously been reported [1-9]. Although most IOP spikes will return to normal by 24h postoperatively, there is a possibility of overlooked extended IOP spikes in some patients[10,11]. A rise in IOP may also lead to vision-threatening complications [12]. As the exact mechanism underlying these IOP spikes is unclear, several agents have been used to prevent this phenomenon[9,13]. There is no commonly accepted treatment protocol to guide clinical management of this transient, short-term IOP elevation after phacoemulsification surgery.

Increasing numbers of ocular hypotensive drugs have entered the market, and fixed combinations of these agents are being formulated. Combinations of these drugs may offer the advantages of better patient adherence and reduced costs. Both the brimonidine/timolol fixed combination (BTFC) and the dorzolamide/timolol fixed combination (DTFC) have been shown to be potent and highly efficacious ocular hypotensive agents in several clinical trials[14,15].

There are no published comparative data regarding the effects of BTFC and DTFC in the treatment of early post-phacoemulsification IOP spikes. This study was designed to evaluate the IOP-lowering efficacy of BTFC compared to that of DTFC in the management of short-term IOP spikes after phacoemulsification surgery.

SUBJECTS AND METHODS

Our study adhered to the principles of the Helsinki Declaration. It was approved by the local Ethical Committee, and informed consent was obtained from each patient. This prospective double-masked randomized comparative study involved 80 eyes of 80 patients scheduled for phacoemulsification and intraocular lens (IOL) implantation.

Before surgery, all patients underwent complete ophthalmic examination, including slit-lamp biomicroscopy, applanation tonometry and gonioscopy. Patients were excluded if they had known sensitivity to any component of the study medications, ocular hypertension (IOP ≥22 mm Hg), glaucoma, narrow angle, previous ocular surgery, pseudoexfoliation, trauma, uveitis, corneal or retinal disease, diabetes mellitus or other serious systemic disease. Patients developing intraocular complications during phacoemulsification surgery were also excluded.

Patients enrolled in the study were randomly assigned into three groups: Group 1 consisted of 28 eyes as the control group. Group 2 consisted of 25 eyes undergoing phacoemulsification surgery and BTFC (Combigan®, Allergan Inc., Irvine, CA, USA) was instilled at the end of surgery. Group 3 consisted of 27 eyes undergoing phacoemulsification surgery and DTFC (Cosopt®, Merck and Co., Inc., Whitehouse Station, NJ, USA) was instilled at the end of surgery.

Baseline IOP was measured using Goldmann applanation tonometry (Haag-Streit AG, Bern, Switzerland) after instilled topical proparacaine (Alcaine, Alcon Laboratories, Fort Worth, TX, USA) 1h before surgery. All patients received cyclopentolate 1% 30min before surgery. All eyes performed standard phacoemulsification with IOL implantation by the same experienced surgeons (Ceylan OM and Gokce G) using an Infinity Phacoemulsification Unit (Alcon Laboratories, Fort Worth, TX, USA). Sub-Tenon's anesthesia was employed in all patients. Surgery was performed with the same size supero-temporal clear corneal incisions (3.2 mm), the same viscoelastic materials (Duovisc, Alcon Laboratories, Fort Worth, TX, USA) and the same foldable, three-piece hydrophobic acrylic IOLs (MA60AC-Alcon Laboratories, Fort Worth, TX, USA). No intraoperative complications developed in any patients, and no miotic agents were used in any cases. Phacoemulsification surgery was completed using similar methods in all patients. Side port corneal incision sites were closed with a balanced salt solution. Corneal incision site leakage control was performed with a spear sponge, and IOP values were regulated by touching a spear sponge to the ocular surface. Surgery was terminated once we were sure that all cases achieved similar normotensive IOP values. No patient had corneoscleral suture inserted at the end of surgery.

Since we thought that surgeon selection (Ceylan OM or Gokce G) might affect the postoperative results we took care to ensure that surgeon distribution was similar in all the study groups. Patients in groups 1, 2 and 3 were therefore operated with similar surgeon distributions. Surgeons were not informed which groups patients belonged to. Immediately after surgery, one drop of BTFC was instilled in the eyes in Group 2 and one drop of DTFC in Group 3. All patients received topical prednisolone acetate 1% (Pred Forte; Allergan, Westport Co., Mayo, Ireland) and topical moxifloxacin 0.5% (Vigamox®, Alcon Laboratories, Inc., Ft Worth, TX, USA) four times daily for 1mo. Routine follow-up was performed at 6, 24h and 1wk postoperatively. All postoperative measurements were made in the same time in order to reduce diurnal variations. All IOP measurements were taken by the same physician (Turk A), who was blinded to the patient groups.

Statistical Analysis The measurement results obtained from the study groups are expressed as mean±SD with minimum and maximum values. In statistical comparisons, as the sample size in each group was less than 30, non-parametric tests were used. The Wilcoxon test was used to compare dependent data in each group. Comparisons between the groups were completed using the Kruskal-Wallis test for continuous data. Binary Mann-Whitney U tests with Bonferroni correction were applied to data identified as significant differences by means of the Kruskal-Wallis test. The Chi-square test was used for discrete variables. SPSS 13.0.1 (SPSS, Chicago, Illinois, USA; license no: 9069728, KTU, Trabzon, Turkey) was used for statistical analysis, and $P<0.05$ was considered statistically significant differences.

RESULTS

Demographic and clinical findings from the cataract patients in the study are shown in Table 1. No significant difference was determined between the groups in terms of age or gender. One surgeon (Ceylan OM) operated on 13 (46.4%) of the 28 patients in the control group, on 13 (52%) of the 25 patients in the BTFC group (Group 2) and on 14 (51.9%) of the 27 patients in the DTFC group (Group 3). The rest of the operations were performed by the second surgeon (Gokce G). No significant difference in surgeon distribution was determined at statistical analysis ($P=0.896$).

Intra-group Intraocular Pressure Changes In the control group, a significant increase in postoperative IOP levels compared to baseline was observed in the first 24h. However, by 1wk, the rise in IOP was not statistically significant and had declined back to the pre-treatment level (Table 1). In the BTFC and DTFC groups, postoperative IOP levels were more stable compared to baseline in the first 24h. However, by 1wk, IOP levels were significantly lower compared to baseline.

Inter-group Comparisons of Intraocular Pressure There was no statistically significant difference in preoperative

Table 1 Intra-group and inter-group comparisons of IOP

Parameters	Group 1 (*n*=28)	Group 2 (*n*=25)	Group 3 (*n*=27)	*P*
Age (a)	68.6±6.5	64.3±9.4	69.7±9.6	0.057
Gender (F/M)	12/16	11/14	13/14	0.918
Preop IOP				
Baseline (mm Hg)	14.9±2.0	15.0±1.7	14.8±2.0	0.84
Postop IOP (mm Hg)				
6h	24.3±5.7	17.2±5.7	15.1±5.6	<0.001[a], <0.001[b], 0.10[c]
24h	18.6±4.0	15.6±4.2	14.2±5.2	0.003 [a], <0.001[b], 0.11[c]
1wk	14.7±1.3	12.9±2.7	12.5±2.3	0.009 [a], <0.001[b], 0.40 [c]
P^1	<0.001	0.07	0.72	
P^2	<0.001	0.82	0.23	
P^3	0.44	0.001	0.001	

[a]Group 1 *vs* Group 2; [b]Group 1 *vs* Group 3; [c]Group 2 *vs* Group 3. P^1: Baseline *vs* 6h of postop IOP; P^2: Baseline *vs* 24h of Postop IOP; P^3: Baseline *vs* 1wk of postop IOP.

Table 2 Postoperative IOP changes from baseline at each follow-up time

Time	Group 1 (*n*=28)	Group 2 (*n*=25)	Group 3 (*n*=27)	*P*
6h	9.4±5.9	2.1±5.5	0.3±5.2	<0.001[a], <0.001[b], 0.15[c]
24h	3.7±4.7	0.5±4.3	-0.5±4.9	0.001[a], <0.001[b], 0.10[c]
1wk	-0.1±1.2	-2.1±2.6	-2.2±2.7	0.001[a], 0.001[b], 0.91[c]

[a]Group 1 *vs* Group 2; [b]Group 1 *vs* Group 3; [c]Group 2 *vs* Group 3.

baseline IOP values among the three groups (P=0.84). However, at all postoperative visits, IOP was significantly lower in groups 2 and 3 compared to the control group (P< 0.05). There was no significant difference between groups 2 and 3 at any visit (Table 1). Eight eyes (28.6%) in the control group, two (8%) in group 2 and one (3.7%) in group 3 had IOP >25 mm Hg at 6h after surgery (P=0.008). However, IOP decreased and was >25 mm Hg in only one eye in each group at 24h after surgery.

Postoperative IOP changes are shown in Table 2. This shows that IOP change from baseline was significantly lower in BTFC and DTFC groups compared to the control group at 6 and 24h (P<0.05). In terms of IOP change there was no significant difference between the BTFC and DTFC groups at any visit time.

DISCUSSION

Our findings demonstrated that IOP increased significantly in the first 24h (peaking at 6h) after phacoemulsification surgery. This short-term increase resolved within 1wk of surgery in the control group. In the great majority of cataract patients, both BTFC and DTFC prevented IOP spikes and did not significantly alter the IOP levels from baseline at each follow-up for the first 24h postoperatively. However they significantly reduced IOP levels at 1wk following cataract surgery. When the two treatments were compared directly, they exhibited a statistically equal IOP level at each follow-up within 1wk postoperatively.

IOP increase is one of the most common complications following cataract surgery [16]. An IOP spike has often been observed in cataract patients, although without reaching extremely high levels [10,12,13,17]. The mechanisms involved in postoperative IOP increase are not well understood. Preoperative cataract density has been reported to be of no value in predicting IOP spikes[18]. However, IOP spikes in the early postoperative period may be encountered in cases with higher preoperative IOP values and cases with glaucoma[19]. There was no statistically significant difference in terms of preoperative IOP values among the patients constituting our three groups, and no diagnosis of glaucoma was present in any patient.

Other agents implicated in post-phacoemulsification IOP increases include hemorrhage, pigment dispersion, inflammation and retained viscoelastic material or lens debris [12,20]. Care was taken in our study that no viscoelastic material or lens debris should be retained with the similar surgical approach employed in all our cases. In addition, no finding of hemorrhage or severe ocular inflammation was encountered in any of our patients.

Many drugs are available to control IOP increase after phacoemulsification [21]. With the recent widespread use of fixed combinations of IOP-lowering agents to treat IOP spikes after phacoemulsification surgery, comparison of these agents has become important for clinicians. Few studies have evaluated and compared the effectiveness of fixed combinations in preventing postoperative IOP increases. The purpose of this study was to evaluate the efficacy of BTFC compared to DTFC in the management of short-term IOP increase after phacoemulsification surgery.

Our scan of the literature revealed no studies comparing the effect of both BTFC and DTFC on postoperative IOP spikes

after phacoemulsification surgery. However, there are some variable results from different sources regarding the effect of fixed combination drugs on IOP spikes after cataract surgery. Erdogan *et al* [16] compared the effectiveness of latanoprost-timolol fixed combination and DTFC. They suggested that the preoperative use of these drugs is effective in eliminating IOP spikes for 24h postoperatively, but that they do not completely prevent such spikes. Moreover, DTFC was not effective at 8h postoperatively. In contrast to our study, in which topical agents were applied immediately after surgery, they instilled the study drug before the procedure, and this may explain the ineffectiveness of DTFC in the early postoperative period. Georgakopoulos *et al* [22] showed that a single dose of BTFC prevented IOP spikes during the first 24h postoperatively. Rainer *et al* [23,24] reported that DTFC reduced postoperative IOP more effectively and prevented any increase in IOP greater than 30 mm Hg compared to latanoprost monotherapy. They also reported that DTFC reduced IOP by approximately 1 mm Hg after 6h and 3 mm Hg after 24h. Ozkurt *et al* [25] reported a mean IOP change of 1 mm Hg after 6h and -1.2 mm Hg after 24h in their DTFC group. In our study, the mean IOP change was 0.3 mm Hg after 6h and -0.5 mm Hg after 24h in the DTFC group. The mean IOP changes in the control groups were similar in these two studies [25]. Pharmakakis *et al* [26] reported that BTFC prevented IOP spikes during the first 24h following cataract surgery. However, in Kandarakis' study, although it significantly reduced IOP elevation following cataract surgery, brimonidine monotherapy did not completely prevent IOP spikes[27].

In contrast to previous studies [18,22,24], we defined a spike as IOP greater than 25 mm Hg. IOP peaks above 25 mm Hg were determined in eight eyes (28.6%) in the control group, two (8%) in the BTFC group and one (3.7%) in the DTFC group at 6h after surgery. However, IOP then decreased and was >25 mm Hg in only one eye in each group at 24h after surgery, and both BTFC and DTFC were effective in eliminating the spikes within 24h.

This study is strengthened by its prospective, double-masked and randomized design. The main limitations were that phacoemulsification surgery was performed by two different surgeons, a short follow-up period and the low number of time points employed.

In conclusion, BTFC and DTFC had similar effects in reducing IOP increases after phacoemulsification surgery. Not only did they significantly reduce IOP levels within 1wk following cataract surgery, they also successfully prevented IOP spikes in the first 24h postoperatively. Both drugs can be recommended for the management of IOP spikes after phacoemulsification surgery.

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