·Clinical Research·

Effect of latanoprost/timolol and dorzolamide/ tiomolol on intraocular pressure after phacoemulsification surgery

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Abstract

• AIM: To evalaute the effect of fixed-combination latanoprost 0.005%/timolol maleate 0.5% and dorzolamide hydrochloride 2% /timolol maleate 0.5% on postoperative intraocular pressure after phacoemulsification cataract surgery.

• METHODS: This study is a prospective, randomized, double-masked and placebo-controlled. The study included 90 eyes of 90 patients which were scheduled to have phacoemulsification surgery. Patients were randomly assigned preoperatively to 1 of 3 groups (30 eyes of 30 patients). Two hour before surgery, the patients received one drop latanoprost/timolol (group 1), dorzolamide/timolol (group 2) and placebo (group 3, control group). The IOPs were measured at preoperative and postoperative 4, 8, and 24 hours.

• RESULTS: The preoperative mean intraocular pressure was not statistically significant between both drug groups and control group. In group 1 and 2, the postoperative mean IOP [group1: (14.03± 3.15)mmHg and group 2: (14.16± 4.43) mmHg] at 24 hours were significantly lower than the control group [(16.93± 3.70)mmHg, (P<0.05)]. In addition, the postoperative mean IOP of group 1 [(14.90± 3.69)mmHg] at 8 hours was significantly lower than the control group [(17.70± 3.89)mmHg, (P<0.05)], but there was no significant difference between group 2 [(16.16 ± 5.23)mmHg] and control group at 8 hours (P>0.05).

• CONCLUSION: When compared with placebo, the use of preoperative fixed combination of latanoprost/timolol and dorzolamide/timolol is an effective method for preventing intraocular pressure elevation in 24 hours after phacoemulsification surgery, but did not completely prevent IOP spikes.

• KEYWORDS: dorzolamide/timolol; latanoprost/timolol; intraocular pressure; phacoemulsification; cataract surgery

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INTRODUCTION

Intraocular pressure (IOP) may increase significantly in the first 24 hours after uneventful phacoemulsification surgery for cataract [1-5]. The elevated IOP can cause ocular pain, corneal edema and can damage optic nevre. The mechanism of the increased IOP is not completely understood. Various antiglaucomatous agents are used to prevent IOP spike after intraocular surgery[1,2,5-13].

Several fixed-combinations FC of commonly used IOP-lowering medications have been developed and most fixed-combinations contain timolol. The nonselective beta-blocker timolol and the carbonic anhydrase inhibitor dorzolamide both lower IOP. Timolol and dorzolamide have different mechanisms of action and their effects are additive when administered together. Fixed-combination (FC) Latanoprost/timolol is indicated for reduction of IOP in patients with open angle glaucoma (OAG) and ocular hypertension (OHT) who are inadequately controlled to monotherapy with topical beta-blockers or prostaglandin analogs. The concomitant administration of latanoprost and timolol produces an additive IOP reducing effect. This FC has been shown to be effective and well tolerated. The two drugs are frequently used to treat patients with glaucoma[14-20]. To our knowledge, it has not been evaluated with regard to the efficacy of fix combination of latanoprost/timolol and timolol/dorzolamide to IOP after phacoemulsification surgery. Thus, in this study, we conducted a prospective, randomized, placebo-controlled study of the efficacy of FC latanoprost/timolol and timolol/dorzolamide drops given

postoperatively in preventing IOP rise following cataract phacoemulsification surgery.

MATERIALS AND METHODS

This study is a prospective, randomized, double-masked and placebo-controlled and included 90 eyes of 90 patients which were scheduled to have phacoemulsification surgery and posterior chamber intraocular lens implantation at the Cumhuriyet University Medical Faculty, Department of Ophthalmology between July 2009 and August 2010. The study was performed according to tenets of the Declaration of Helsinki and approved by the Human Ethics Committee of Cumhuriyet University School of Medicine. All patients were informed about this study and they signed an informed consent form before the study.

Patients Exclusion criteria were a history of glaucoma, diabetes mellitus, previous ocular surgery or laser treatment, ocular hypertension, uveitis, pigment dispersion syndrome, exfoliation syndrome, use of systemic drugs affecting the IOP or topical medication, and any complication during surgery. All patients were given a complete ophthalmic examination that included Snellen visual acuity, applanation tonometry, and anterior and posterior segment evaluation before surgery. Patients with lower than 20mmHg IOP were included in study.

Methods Patients were randomly assigned preoperatively to 1 of 3 groups (30 eyes of 30 patients). Patients were randomized to receive either topical FC latanoprost 0.005% /timolol maleate 0.5% (group 1) (Xalacom, Pfizer manufacturing, Puurs, Belgium), or FC dorzolamide hydrochloride 2%/ timolol maleate 0.5% (group 2) (Cosopt, Merck Sharp&Dohme Lab, Clermont, France) or artificial tears (group 3). The randomization was performed as follows: externally identical bottles of drugs were labeled with numbers according to a computer-generated random number table. The patients and surgeons were unaware of an individual patient's treatment or number. The residents administering the study drops and measuring the IOP levels had no knowledge of the order of drops. All groups received one drop of medication at 2 hours before surgery and at 4, 8 and 24 hours postoperatively. Eyedrops was instilled by staff not involved in the investigation. All patients were operated on by two surgeons (H.E, M.K.A) in the same fashion. All surgical procedures were performed under topical anesthesia (5% proparacaine hydrodchloride). Surgery consisted of a 3.2mm temporal clear corneal tunnel incision, injection of viscoelastic material sodium hyaluronate 20g/L into the anterior chamber, creation of two sideports, continuous curvilinear capsulorrhexis, hydrodissection, phacoemulsification, bimanual aspiration of remaining cortical lens material, capsular bag and anterior chamber refilling with 1% sodium hyaluronate and insertion of a foldable hydrofobic acrylic intraocular lens (Zaraccom, Anadolu Tip Tek. A.S, Sivas, Turkey) in the capsular bag. The viscoelastic material was aspirated thoroughly sideports from the anterior chamber and capsular bag using a bimanual aspiration-irrigation cannula. The corneal incision was closed by hydration and 10g/L cefuroxime sodium was administered into the anterior chamber via sideport at the end of surgery. Intracameral acetylcholine was not used intraoperatively. All patients were hospitalized postoperatively for 24 hours. Dexamethasone and tobramycin eye drops were prescribed four times a day in the postoperative period. The IOP was measured using a Goldmann applanation tonometer the day before surgery and 4, 8 and 24 hours after surgery by the same clinician who was unaware of the patient's treatment group assignment. We also determined postoperative anterior chamber inflammatory reaction changes with slit-lamp biomicroscopy.

Table 1 Demographic data of the three groups

	Grup 1	Grup 2	Grup 3
Eyes (*n*)	30	30	30
Right\Left Eyes	12/18	18/12	14/16
Women\Men	15/15	16/14	18/12
Mean age±SD (year)	67.1±10.8	67.4±10.5	65.7±9.1

Statistical Analysis Results were presented as mean±SD. The chi-square test was used to evaluate intergroup differences in gender and number of left/right eyes. Statistical analysis of intragroup differences in age, as well as preoperative and postoperative IOP, was performed with an analysis of variance (one-way ANOVA) and Tukey HSD test. A P value less than 0.05 was considered satistically significant.

RESULTS

The demographic findings of patients are shown in Table 1. Between the groups there were no significant differences in terms of the demographic findings.

The preoperative and postoperative mean IOP of the three groups were shown in Table 2. There was no statistically significant difference in preoperative mean IOP among the three groups. The mean postoperative IOP of groups 1 and 2 were compared with group 3 (control group). In groups 1 and 2, the postoperative mean IOPs at 24 hours were lower than that of control group (P<0.05). However, there was no significant difference at 4 hours (P>0.5). In addition, in group 1 the mean postoperative IOP at 8 hours was lower than control group (P<0.05), but there was no significant difference between group 2 and control group (P>0.5).

The mean postoperative IOPs of all groups were compared

Table 2 Preoperative and postoperative the mean IOP of the three groups

Time	IOP, (mean±SD), (min and max)					
	Group 1 Latanoprost/timolol		Group 2 Dorzolamide/timolol		Group 3 Control	
Preop	14.13±1.85 (12-18)	NS	14.00±2.91 (8-21)	NS	14.13±2.58 (10-19)	NS
4h	15.80±3.26 (8-24) P=0.012	NS	16.30±6.23 (10-28) *P=0.039	NS	16.60±2.76 (13-25) P=0.001	0.001
8h	14.90±3.69 (8-24)	0.037	16.16±5.23 (9-30) *P=0.029	NS	17.70±3.89 (12-25) P=0.0001	0.037
24h	14.03±3.15 (8-22)	0.011	14.16±4.43 (10-23)	0.016	16.93±3.70 (12-28) *P=0.001	0.011

NS: no significance; *P* values: compared for control group; **P* values: compared for preoperative IOP

Table 3 Distribution of postoperative IOP elevation in 3 groups with respect to baseline

	Number of Eyes		
IOP (mmHg)	4 hours	8 hours	24 hours
Group 1			
0-5	15	13	9
6-10	5	2	4
11-20	0	0	0
Group 2			
0-5	11	8	10
6-10	3	7	3
11-20	4	2	0
Group 3			
0-5	17	15	14
6-10	5	7	6
11-20	0	2	1

with preoperative IOP values. In the control group the mean postoperative IOP was higher than the preoperative IOP. In group 1 and 2, the mean IOPs at 24 hours were not significantly different from the mean preoperative IOPs. The mean postoperative IOP of all groups at the 4th hour and the mean postoperative IOP of group 2 at 8 hours were significantly higher than the mean preoperative IOP.

Table 3 shows distribution of postoperative IOP elevation in three groups with respect to baseline. In group 1, there was mild to moderate IOP elevation between 6-10 mmHg (11 patients) seen at the postoperative period. However, in group 2 (6 patients) and group 3 (3 patients) had a significant IOP elevation between 11-20mmHg at the postoperative period.

None of the groups had significant anterior chamber inflammatory response, ocular and systemic adverse effect observed. Anterior chamber reaction averaged +1 to +2 in three groups.

DISCUSSION

Cataract extraction is one of the most commonly performed and successful surgical procedures. Phacoemulsification and intraocular lens implantation is one of the most cost-effective, elective surgical interventions. Raised intraocular pressure is one of the most common complications following cataract surgery, requiring specific treatment. In order to minimize postoperative IOP rise, prophylaxis may be adopted. Currently, there are no specific guidelines for IOP rise prophylaxis in uncomplicated cataract surgery. The exact mechanism of elevation IOP postoperatively is not known. It is attributed to many reasons, including occlusion of the trabecular meshwork by retention of viscoelastic and lenticular material, inflammatory cells [2,4,5,10]. The IOP elevations are statistically more common and generally high in glaucoma patients[21-24]. The timing of the first postoperative IOP check varied. 10.9% of surgeons reported the first IOP check was carried out on the same day, 29.7% on the first postoperative day, 20.8% by the first week, 26.9% at 2 weeks, and 9.5% beyond 2 weeks [8,25]. In the UK, 87% of surgeons who use IOP prophylaxis prefer oral Diamox over the topical agents[8].

The fixed-combination latanoprost/timolol and dorzolamide/ timolol is safe and well tolerated for long-term treatment in patients with open-angle glaucoma or ocular hypertension patients [15,19,26], but sometimes FC latanoprost/timolol was more effective than FC dorzolamide/timolol [17] or both similar ocular hypotensive effect [26]. Currently, there are no specific guidelines for IOP increase prophylaxis in uncomplicated cataract surgery. For this reason, we designed this study.

In our study, although the IOP values at 24 hours were significantly lower in both latanoprost/timolol and timolol/dorzolamide groups than control group; at 4 hours there were no significant difference among latanoprost/ timolol and timolol/dorzolamide and control groups. While IOP value of latanoprost/timolol group at 8 hours was lower than control group, there was no significant difference between timolol/dorzolamide and control group.

In our literature review, we did not find any study comparing the effect of the both FCs on postoperative IOP after phacoemulsification surgery. Although FC latanoprost/ timolol and dorzolamide/timolol were highly effective ocular hypotensive agents, this study have shown FC latanoprost/ timolol was more effective than placebo on IOP in the early

postoperative period. In addition, 30mmHg IOP spike in some patients had been seen in dorzolamide/timolol group, while high IOP spike was not detected in latanoprost/timolol group. Nevertheless, at the end of 24 hours, both FCs were effective on postoperative IOP when compared to the control group.

Borazan *et al*[27] compared the effectiveness of brinzolamide 1%, brimonidine 0.2%, acetazolamide 250 mg, intracameral acetylcholine, and timolol 0.5% in preventing IOP peaks during the early period after phacoemulsification surgery. They found that brinzolamide, brimonidine, acetazolamide, intracameral acetylcholine, and timolol had similar effects in reducing IOP increase after phacoemulsification surgery. Iopidine and timolol are the most common topical agents used for postoperative IOP prophylaxis as shown in the survey. A number of clinical trials studying the effect of pre and post-operative use of apraclonidine and timolol in reducing postoperative rise have shown variable results[2,6,28,29]. Unal *et al*[1] found that prophylactic use of one drop of bimatoprost before phacoemulsification cataract surgery failed to produce significantly different effect on IOP levels from placebo at 3 hours postoperatively, but it caused a significant IOP reduction at 24 hours.Lai *et al*[2] showed that a single dose of latanoprost given after phacoemulsification and PC IOL implantation did not produce a significant IOP-lowering effect when compared with a control group in the first 24 hours postoperatively. A single dose of timolol gel produced a significant postoperative IOP decrease as soon as 2 hours and up to 24 hours after surgery. Timolol gel and latanoprost are safe, but timolol is more effective than latanoprost in preventing postoperative ocular hypertension. But we found that FC latanoprost/timolol and dorzolamide/timolol cause a significant reduction on mean postoperatively IOP at 24 hours when compared with placebo. We thought this difference may be due to FC of the drugs usage. O'Brien *et al*[21] concluded that higher mean baseline IOP was significantly associated with postoperative IOP spikes. They found that patient age, sex, operating surgeon, absolute phacoemulsification time, lens nuclear color, cortical opacity, and posterior opacity were not significantly different between groups with or without an IOP spike. In the current study, we did not include patients with higher than 20mmHg IOP. Ozkurt *et al*[9] compared the effects of dorzolamide-timolol combination and brimonidine on intraocular pressure after phacoemulsification surgery. At the end of study, prophylactic treatment with dorzolamide-timolol fixed combination was more effective than brimonidine in reducing IOP at 6 hours and 24 hours after phacoemulsification surgery. Our results were different from this study. In our study, dorzolamide-timolol fixed combination was not effective in reducing IOP at 8 hours after phacoemulsification surgery.

Although IOP levels after phacoemulsification surgery tend to normalize during 24 hours postoperatively, some reports show that high levels of IOP were still present with or without prophylactic treatment at 24 hours[6,7,30-32]. It has been shown in many studies that IOP rises after phacoemulsification surgery. IOP increasing trend started during the first few hours [21,22,31,33,34]. Although the maximum IOP reduction effect of some drugs appear 2 weeks later, Latanoprost pharmacologically enhanced uveoscleral outflow immediately after cataract extraction [35]. After administration of a single drop (30μL) of tritium-labeled latanoprost 50μg/mL, the maximum concentration of latanoprost averaged (32.6 ±20.6)ng/mL at 2.5 hours [36]. Therefore, in the current study we preferred to instill both drugs 2 hours before the study because their IOP lowering effect begins during the postoperative IOP elevation period. According to our study results, IOP lowering effect of latanoprost/timolol was achieved after 8 hours, but dorzolamide/timolol achieved after 24 hours. After phacoemulsification and intraocular lens implantation surgery, surgeons should be aware of and check for IOP variability (low and high) that can occur in normal, glaucoma and glaucoma-suspect eyes within one day[22].

Endogenous prostaglandin release induced by anterior segment inflammation can lead to blood aqueous breakdown, inflammatory mediators reaching the macula, and cystoid macular edema (CME). It is known that long time use of latanoprost causes CME after cataract surgery. CME is reported to be higher in patients with posterior capsular rupture with vitreous loss, aphakia, complicated cataract surgery, history of uveitis, diabetes, and retinal inflammatory or vascular disease. In our study we didn't determine CME because patients with risk factors were not included in this study [37-40]. In addition, any systemic and ocular adverse reactions due to both FC have not been determined. Postoperative anterior chamber reactions of the study groups were similar and between +1-+2.

In this study, we found that FC latanoprost/timolol and dorzolamide/timolol cause a significant reduction on mean postoperatively IOP at 24 hours when compared with placebo. In addition, FC latanoprost/timolol was also effective at 8 hours. This can be due to drainage increasing effect of latanoprost on aqueous humor by uveoscleral pathway together with secretion decreasing effect of timolol. Our results showed that the use of preoperative both FC was an effective method for preventing IOP elevation in the first day after phacoemulsification cataract surgery. However, it did not completely prevent IOP spikes.

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