ww.nature.com/eye

SS Ermis, F Ozturk and UU Inan

CLINICAL STUDY

Comparing the effects of travoprost and brinzolamide on intraocular pressure after phacoemulsification

Abstract

Purpose To evaluate the intraocular pressure (IOP) lowering effect of travoprost and brinzolamide within the first 24 h after phacoemulsification cataract surgery. Methods This prospective, randomized, double-masked, controlled study comprised 90 eyes of 90 consecutive patients with senile cataract who had uneventful phacoemulsification surgery. Eyes in the first group received travoprost 0.0015%, second group received brinzolamide 1%. Eyes in the third group received balanced salt solution and were used as control. One drop was instilled immediately after surgery. IOP was measured 24 h preoperatively, 6 and 24 h postoperatively. Analysis of variance, Student's-t and γ^2 -tests were used for statistical analyses.

Results Preoperatively IOP was not significantly different among the three groups (P = 0.653). At 6 and 24 h postoperatively IOP was lower in both travoprost and brinzolamide group when compared to control group (P = 0.018 and 0.015 at 6 h, P = 0.010 and 0.012 at 24 h, respectively). The difference between travoprost and brinzolamide group was not significant (P = 0.859 at 6 h and P = 0.581 at 24 h). Both travoprost and brinzolamide significantly reduced IOP increases when compared to control eyes at 6 and 24 h (P = 0.036 and 0.029 at 6 h, P = 0.010 and 0.007 at 24 h, respectively). The difference in IOP increase at 6 and 24 h between travoprost and brinzolamide group was not significant (P = 0.744 at 6 h and P = 0.672 at 24 h).

Conclusion Both travoprost and brinzolamide significantly lowered IOP after small incision phacoemulsification cataract

surgery within the first 24 h without any side effect.

Eye (2005) **19**, 303–307. doi:10.1038/sj.eye.6701470 Published online 16 July 2004

Keywords: travoprost; brinzolamide; phacoemulsification cataract surgery; intraocular pressure

Introduction

A transient elevation in intraocular pressure (IOP) after cataract surgery is a well-known problem which may be caused by release of low and high molecular weight proteins liberated by manipulation of intraocular structures during surgery and by obstruction of trabecular outflow by inflammatory and viscoelastic material.^{1–3} If left untreated, uncontrolled postoperative IOP rise can result in pain, corneal oedema, glaucomatous nerve damage or anterior ischaemic optic neuropathy.^{4–7}

Travoprost is a $PGF_{2\alpha}$ analogue that reduces IOP by increasing the outflow of aqueous humour through the uveoscleral pathway.⁸

Brinzolamide is a topically active carbonic anhydrase inhibitor. It has high affinity and inhibitory potency against human carbonic anhydrase inhibitor-II, an isozyme found in the ciliary epithelia, which are involved with aqueous humour secretion.⁹

Several antiglaucomatous agents have been used to control IOP after cataract surgery.^{4,7,10–16} In this prospective, randomized, doublemasked, controlled study, we evaluated the IOP-lowering effect of travoprost and brinzolamide within the first 24 h after phacoemulsification cataract surgery. To our knowledge, this is the first study to evaluate the Department of Ophthalmology School of Medicine University of Afyon Kocatepe Afyon, Turkey

Correspondence: SS Ermis Dervispasa mah. Pirireis sk. Ceylan apt. A blok No:3/8 Afyon 03200, Turkey Tel: +90 533 7737358 Fax: +90 272 2172029 E-mail: sametermis@ hotmail.com

Received: 27 June 2003 Accepted: 29 December 2003 Published online: 16 July 2004

None of the authors has any financial or proprietary interest in any product or method mentioned.

effect of travoprost and brinzolamide to IOP after small incision phacoemulsification surgery.

Materials and methods

This study included 90 eyes of 90 consecutive patients with senile cataract who had uneventful phacoemulsification surgery and foldable intraocular lens implantation. Patients were excluded if they had a history of glaucoma, ocular hypertension, pseudoexfoliation, pigment dispersion syndrome, previous ocular surgery, laser treatment, or uveitis. Written informed consent was obtained from each patient. All subjects were treated in accordance with the requirements of the Declaration of Helsinki.

Patients were randomized to receive travoprost 0.0015% (Travatan, Alcon), brinzolamide 1% (Azopt, Alcon) or balanced salt solution (BSS). An ophthalmic resident made the randomization by rotationally allocating the eligible subjects to each group before the surgery. One drop was instilled to inferior fornix immediately after surgery. IOP was measured 24 h preoperatively, 6 and 24 h postoperatively using a Goldmann applanation tonometer attached to a slit lamp by a constant ophthalmologist who is blinded to the medication the patient had received.

Cyclopentolate 1% and phenylephrine 2.5% eye drops were used for mydriasis four times starting 1 h before the surgery. Topical anaesthesia was used in all cases; pieces of cell sponge that are impregnated with proparacaine 0.5% (Alcaine, Alcon) were placed deep into the superior and inferior fornix for 15 min prior to surgery. Endocapsular phacoemulsification was performed using Allergan Diplomax phacoemulsification unit by one of the three surgeons (SSE, FO, UUI), experienced in the technique, in identical manner. The surgeons and patients were unaware of the group assignments.

A three-step clear corneal tunnel incision was made with a 3.2 mm disposable metal blade and two side-port incisions were made with an MVR blade. After injection of sodium chondroitin sulphate 4.0%-sodium hyaluronate 3.0% (Viscoat, Alcon) into anterior chamber, a capsulorhexis of 5.0 mm diameter, hydrodissection and hydrodelineation were performed. A quadrant divideand-conquer technique was used for hard nuclei and chip-and-flip technique for soft nuclei. Residual cortex was removed using 21 G bimanual irrigation/aspiration handpieces (G-32000-G-32001, Geuder) through the two side-port incisions. Sodium hyaluronate 1% (Heal on, Pharmacia) was injected to extend the capsular bag and the incision was enlarged to 4.0 mm. A 6.0 mm optic, 13.0 mm haptic, three-piece foldable silicone or acrylic intraocular lens was implanted in the capsular bag. A meticulous standardized viscoelastic material removal was performed using the same bimanual tips for 45 seconds. The vacuum was set to 500 mmHg and flow rate to 30 cm³/min. No attempt was made to introduce the bimanual tips behind intraocular lens. Corneal incision was checked for water tightness and left unsutured. No miotic agent was used. Effective phacotime displayed by the phacoemulsification unit for each surgical procedure was recorded.

The study had at least an 80% power to exclude a 2.5 mmHg IOP difference between groups. An analysis of variance (ANOVA) was used to compare the age, effective phaco-time, IOP and IOP differences between the groups. In the case of significance, pairwise group differences were tested using a Student's *t*-test. The differences in the number of IOP spikes, distribution of patients among surgeons, and type of implanted intraocular lenses among groups were assessed using a χ^2 -test.

Results

Patient characteristics are shown in Table 1. No statistically significant differences were found among the three groups in age, sex, mean effective phaco-time, distribution of patients among surgeons and type of implanted intraocular lenses (acrylic/silicone) (P > 0.05). Preoperatively, IOP was not significantly different among the three groups (P = 0.653). At 6 and 24 h postoperatively, there were significant differences among the groups (P = 0.018 and 0.011). IOP was lower in both travoprost and brinzolamide group when compared to control group (P = 0.018 and 0.015 at 6 h, P = 0.010 and

Table 1 Patient demographics, mean effective phaco-time, types of intraocular lenses implanted and distribution of patients among surgeons

Group	Number of eyes	Mean $age \pm SD$ (years)	Mean effective phaco- time \pm SD (s)	Intraocular lens acrylic/silicone	Distribution of patients among surgeons
Travoprost	30	58.5 ± 10.7	23.9 ± 13.3	21/9	14/8/8
Brinzolamide	30	55.1 ± 9.7	27.2 ± 15.3	16/14	11/9/10
Control	30	58.0 ± 8.7	24.2 ± 11.6	19/11	9/12/9

Group	Preoperative	Postoperative 6 h	Postoperative 24 h
Travoprost	13.3 ± 3.7	16.1 ± 5.6	14.0 ± 4.1
Brinzolamide	13.9 ± 3.7	16.3 ± 4.5	14.5 ± 2.9
Control	14.0 ± 3.0	19.7 ± 5.8	$16.8\!\pm\!3.7$

Table 2 Mean IOP (mm-Hg) over time

Table 3 Mean IOP change (mmHg) from preoperatively to 6and 24 h postoperatively

Group	Postoperative 6 h–Preoperative	Postoperative 24 h—Preoperative
Travoprost	2.8 ± 4.5	0.8 ± 2.8
Brinzolamide	2.4 ± 5.7	0.4 ± 3.4
Control	5.6 ± 5.6	2.7 ± 2.7

0.012 at 24 h, respectively). The difference between travoprost and brinzolamide group was not significant (P = 0.859 at 6 h and P = 0.581 at 24 h) (Table 2). The mean IOP increases are shown in Table 3. The mean IOP increase from preoperatively to 6 and 24 h postoperatively were statistically significant among the groups (P = 0.040 and 0.010, respectively). Both travoprost and brinzolamide significantly reduced IOP increases when compared to control eyes at 6 and 24 h (P = 0.036 and 0.029 at 6 h, P = 0.010 and 0.007 at 24 h, respectively). The difference in IOP increase at 6 and 24 h between travoprost and brinzolamide group was not significant (P = 0.744 at 6 h and P = 0.672 at 24 h).

One patient in both travoprost and brinzolamide group, three patients in control group had IOP more than 30 mmHg at 6-h examination and treated with oral acetazolamide. The IOP values of these patients were excluded from the study at 24-h examination. The difference in number of eyes having IOP spike of 30 mmHg or higher among the groups was not statistically significant (P = 0.429).

There was no reported adverse effect in any patient.

Discussion

Increasing number of cataract operations are being performed in outpatient setting and patients are discharged shortly after the surgery. The postoperative IOP elevation is the most common early complication necessitating intervention after cataract surgery. The IOP rise of 30 mmHg or higher may be associated with discomfort, pain, corneal epithelial oedema, anterior ischaemic optic neuropathy, increased risk of optic nerve damage, and central retinal artery or vein obstruction particularly in susceptible patients. Transient IOP elevation can cause optic nerve damage and visual field loss especially in pre-existing glaucomatous eyes.^{15,17} In

the ophthalmic literature, there are reports about the effects of antiglaucoma agents to IOP after cataract surgery. Several drugs have been found effective in lowering IOP, but IOP spikes remained existing despite to these agents even when they were used in combination.^{4,7,15,16,18} In our study IOP was statistically significantly lower in subjects who received travoprost and brinzolamide when compared to controls at 6 and 24 h after small incision phacoemulsification surgery. While there was one patient in both travoprost and brinzolamide group, three patients in control group had IOP spike of more than 30 mmHg; the number of subjects who had IOP spikes were not significantly different between groups. A larger study size may be required to investigate the effect of antiglaucoma agents to IOP spikes after cataract surgery. Although it seems impossible to prevent IOP spikes completely, studies reported that IOP spikes were blunted with the use of antiglaucomatous agents.13,18 It was shown that IOP spikes as high as 68 mmHg can develop after uneventful phacoemulsification cataract surgery in eyes without glaucoma or ocular hypetension.¹⁹ It may be important at least to blunt IOP spikes.

Travoprost is a topical ocular prodrug that is rapidly hydrolysed by esterases in the cornea to the biologically active, free acid, which is structurally similar to fluprostenol and other prostaglandin $F_{2\alpha}$ analogues. Travoprost acid has greater affinity for prostaglandin F receptor than either prostaglandin $F_{2\alpha}$ or latanoprost acid.^{8,20} The receptors are abundant in the longitudinal ciliary muscle of the human eye and iris sphincter.²⁰ The IOP-lowering efficacy of travoprost was found to be comparable to latanoprost and timoptic.⁸

Although orally administered carbonic anhydrase inhibitors suppress aqueous humour production by 20-35%, they are associated with significant side effects.^{14,21} Dorzolamide was the first topical carbonic anhydrase inhibitor used for lowering IOP. The relative efficacy of brinzolamide 1% has been compared to that of dorzolamide 2% for suppressing aqueous humour flow in normal volunteers. Reductions of daytime flow by brinzolamide and dorzolamide were 19 and 14%, respectively.²² Brinzolamide provides statistically significant IOP reductions from baseline that are clinically relevant in the majority of patients with elevated IOP.23 Brinzolamide is formulated at physiologic pH as an aqueous suspension and has been shown to produce less ocular discomfort (burning and stinging) on instillation than dorzolamide.23,24

There are conflicting results about the IOP-lowering efficacy of latanoprost after phacoemulsification.^{4,10,12} In the study of Rainer *et al*,⁴ the increase in IOP after phacoemulsification at 6 and 20-24 postoperative hours were 2.2 and 0.3 mmHg, the latter being not statistically

different from placebo. In our study after using travoprost, the IOP increase at 6 and 24 h were 2.8 and 0.8 mmHg, both being significantly different from placebo control. Viscoelastic material has been shown to remain trapped in the trabecular meshwork even after its aspiration from the anterior chamber following intraocular lens implantation.²⁵ Scherer *et al*¹⁰ found that latanoprost enhanced uveoscleral outflow to normal levels in eyes that had phacoemulsification cataract surgery and they reported that from a pharmacological standpoint, viscoelastic obstruction of the trabecular meshwork did not extend to uveoscleral pathway.

Previous studies reported that dorzolamide effectively reduced IOP increase during the first 24 h after cataract surgery.^{4,15} Zohdy *et al*¹⁵ reported a mean IOP increase of 2.5 mmHg at 4 h postoperatively. In the study of Rainer *et al*⁴ the mean IOP increase was 1.9 and -0.9 mmHg at 6 and 20–24 postoperative hours. In our study, we detected a mean IOP increase of 2.4 and 0.4 mmHg at 6 and 24 postoperative hours using brinzolamide.

The contradictory results in studies dealing with postoperative IOP spike after phacoemulsification cataract surgery may be the result of many factors such as variations in the surgical technique and surgeon's experience,¹⁶ technique of wound closure, time of administration of the medication,²⁶ type of viscoelastic material used,¹⁶ technique and duration used in aspirating viscoelastic material at the end of surgery, intracamerally injected medications to, constrict the pupil,¹⁰ the routine postoperative medications, and type of intraocular lens used (three piece *vs* plate haptics).²⁷

Although the exact mechanism of postoperative IOP rise is not yet fully understood, a major reason seems to be the retention of viscoelastic material at the end of surgery, which obstructs the trabecular meshwork. It is nearly impossible to remove viscoelastic material completely from anterior chamber without injuring vulnerable structures of the eye.^{17,18} Viscoelastic agents exit the eye without being metabolized. The IOP rise usually starts 2-4 h after phacoemulsification surgery and lasts for 24 h.27 The IOP can peak between 6 and 8 h postoperatively.²⁶ In studies carried out with travoprost in the laser monkey model, reductions in IOP were observed beginning 2 h after administration and peaked by 12-20 h after dose.8 The onset of IOP lowering of brinzolamide in the laser-treated monkey model was seen by 1 h, peak IOP lowering occurred by 3 h after dosing.⁹ Although the time of onset of action and peak IOP-lowering effect of two drugs did not coincide with each other, we administered both drugs immediately after surgery in order to keep the variables to a minimum when comparing their effect on IOP.

In our study, although neither a single drop of travoprost nor brinzolamide prevented IOP spikes of

30 mmHg at 6 h postoperatively, IOP was significantly lowered after small incision phacoemulsification cataract surgery within the first 24 h without any side effect. The IOP rise in the immediate period after phacoemulsification surgery must be kept in mind.

Acknowledgements

None of the authors has any financial or proprietary interest in any product or method mentioned.

References

- Shingelton BJ, Wadhwani RA, O'Donoghue MW, Baylus S, Hoey H. Evaluation of intraocular pressure in the immediate period after phacoemulsification. J Cataract Refract Surg 2001; 27: 524–527.
- 2 Campbell DG, Grant WM. Trabecular deformation and reduction of outflow facility due to cataract and penetrating keratoplasty sutures. ARVO abstract. *Invest Ophthalmol Vis Sci* 1977; **16**(Suppl): 126.
- 3 Naeser K, Thim K, Hansen TE, Degn T, Madsen S, Skov J. Intraocular pressure in the fist days after implantation of posterior chamber lenses with the use of sodium hvaluronate (Healon). *Acta Ophthalmol* 1986; 64: 330–337.
- 4 Rainer G, Menapace R, Schmetterer K, Findl O, Georgopoulos M, Vass C. Effect of dorzolamide and latanoprost on intraocular pressure after small incision cataract surgery. J Cataract Refract Surg 1999; **25**: 1624–1629.
- Hayreh SS. Anterior ischemic optic neuropathy. IV
 Occurrence after cataract extraction. *Arch Ophthalmol* 1980;
 98: 1410–1416.
- 6 Savage JA, Thomas JV, Belcher III CD, Simmons RJ. Extracapsular cataract extraction and posterior chamber intraocular lens implantation in glaucomatous eyes. *Ophthalmology* 1985; **92**: 1506–1516.
- 7 Byrd S, Singh K. Medical control of intraocular pressure after cataract surgery. *J Cataract Refract Surg* 1998; **24**: 1493–1497.
- 8 Netland PA, Landry T, Sullivan EK, Andrew R, Silver L, Weiner A *et al.* Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2001; **132**: 472–484.
- 9 DeSantis L. Preclinical overview of brinzolamide. *Surv Ophthalmol* 2000; **44**(Suppl 2): S119–S129.
- 10 Scherer WJ, Mielke DL, Tidwell PE, Hauber FA. Effect of latanoprost on intraocular pressure following cataract extraction. J Cataract Refract Surg 1998; 24: 964–967.
- 11 Kanellopoulos AJ, Perry HD, Donnenfeld ED. Timolol gel versus acetazolamide in the prophylaxis of ocular hypertension after phacoemulsification. J Cataract Refract Surg 1997; 23: 1070–1074.
- 12 Lai JSM, Loo A, Tham CCY, Ho SY, Lam DS. Preoperative latanoprost to prevent ocular hypertension after phacoemulsification and intraocular lens implantation. *J Cataract Refract Surg* 2001; 27: 1792–1795.
- 13 Fry LL. Comparison of the postoperative intraocular pressure with Betagan, Betoptic. Timoptic, Iopidine, Diamox, Pilopine gel, and Miostat. J Cataract Refract Surg 1992; 18: 14–19.

- 14 Maus TL, Larsson L-I, McLaren JW, Brubaker RF. Comparison of dorzolamide and acetazolamide as suppressors of aqueous humor flow in humans. *Arch Ophthalmol* 1997; **115**: 45–49.
- 15 Zohdy GA, Rogers ZA, Lukaris A, Sells M, Roberts-Harry TJ. A comparison of the effectiveness of dorzolamide and acetazolamide in preventing post-operative intraocular pressure rise following phacoemulsification surgery. J Roy Coll Surg Edin 1998; 43: 344–346.
- 16 Kasetti SR, Desai SP, Sivakumar S, Sunderraj P. Preventing intraocular pressure increase after phacoemulsification and the role of perioperative apraclonidine. J Cataract Refract Surg 2002; 28: 2177–2180.
- 17 Rainer G, Menapace R, Findl O, Kiss B, Petternel V, Georgopoulos M *et al.* Intraocular pressure rise after small incision cataract surgery: a randomised intraindividual comparison of two dispersive viscoelastic agents. *Br J Ophthalmol* 2001; **85**: 139–142.
- 18 Rainer G, Menapace R, Findl O, Sacu S, Schmid K, Petternel V et al. Effect of a fixed dorzolamide–timolol combination on intraocular pressure after small-incision cataract surgery with Viscoat. J Cataract Refract Surg 2003; 29: 1748–1752.
- 19 Hildebrand GD, Wickremasinghe SS, Tranos PG, Harris ML, Little BC. Efficacy of anterior chamber decompression in controlling early intraocular pressure spikes after uneventful phacoemulsification. *J Cataract Refract Surg* 2003; 29: 1087–1092.
- 20 Davis TL, Sharif NA. Quantitative autoradiographic visualization and pharmacology of FP-prostaglandin

receptors in human eyes using the novel phosphor-imaging technology. *J Ocul Pharmacol Ther* 1999; **15**: 323–336.

- 21 Silver LH. Dose–response evaluation of the ocular hypotensive effect of brinzolamide ophthalmic suspension (Azopt). *Surv Ophthalmol* 2000; **44**(Suppl 2): S147–S153.
- 22 Ingram CJ, Brubaker RF. Effect of brinzolamide and dorzolamide on aqueous humor flow in human eyes. *Am J Ophthalmol* 1999; **128**: 292–296.
- 23 Silver LH. Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol* 1998; **126**: 400–408.
- 24 Stewart R. The ocular comfort of TID-dosed brinzolamide 1.0% compared to TID-dosed dorzolamide 2.0% in patients with primary open-angle glaucoma or ocular hypertension. ARVO abstracts. *Invest Ophthalmol Vis Sci* 1997; 38(4, Suppl): S559.
- 25 Jacobi PC, Engels B, Dietlein TS, Krieglstein GK. Effect of trabecular aspiration on early intraocular pressure rise after cataract surgery. J Cataract Refract Surg 1997; 23: 923–929.
- 26 Bomer TG, Lagreze WD, Frunk J. Intraocular pressure rise after phacoemulsification with posterior chamber lens implantation: effect of prophylactic medication, wound closure, and surgeons' experience. *Br J Ophthalmol* 1995; **79**: 809–813.
- 27 Mastropasqua L, Carpineto P, Ciancaglini M, Falconio G. Intraocular pressure changes after phacoemulsification and foldable silicone lens implantation using Healon GV. *Ophthalmologica* 1998; **212**: 318–321.