Intraocular Pressure Changes in the Contralateral Eye After Topical Treatment: Does an "Ophthalmotonic Consensual Reaction" Exist?

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ABSTRACT: **Background:** The existence of "ophthalmotonic consensual reaction," a contralateral change in intraocular pressure in the fellow eye induced by treatment of the first eye only, was suggested in 1924. Since then, the validity of this mechanism has been controversial.

Objectives: To assess intraocular pressure changes in the contralateral fellow eyes of patients treated with IOP-lowering medication in one eye, and investigate the existence of an ophthalmotonic consensual reaction.

Methods: The study population included 38 patients with newly diagnosed bilateral ocular hypertension or early open angle glaucoma. One eye of each patient was randomly treated with one of five compounds: prostaglandin analogues, beta-blockers, alpha-2 agonists, carbonic anhidrase inhibitors and a combination therapy: dorzolamide hydrochloride–timolol maleate (Cosopt®, Merck Sharpe & Dohme). The eye with the higher baseline IOP was selected to be the treated eye. After 3 weeks a masked examiner measured the IOP in both the treated and untreated eye.

Results: Mean IOP of the treated eyes at baseline was 26.1 ± 4.2 mmHg and at follow-up 20.2 ±2.9 mmHg, a reduction of IOP from baseline of -6 ± 3.8 mmHg, a mean percent reduction of -22 ± 10.1%. In the contralateral eyes, the mean IOP at baseline was 24.2 ± 3 mmHg and 23.1 ± 3.1 mmHg at follow-up; IOP reduction from baseline was -1.2 ± 1.8 mmHg, or mean percent reduction -4.7 ± 7.1%. A major contralateral IOP decrease was seen only in the beta-blockers and the combination (Cosopt®) treatment groups (-6.1 ± 8.3% and -12.3 ± 8.3% mean percent reduction, respectively, $P < 0.05$). The contralateral eyes in the prostaglandin analogues, CAI or α2-agonist groups showed only a small change in IOP (-2.6 ± 4.6%, -3.2 ± 2.6%, +0.7 ± 3.3%, mean percent reduction, respectively, $P < 0.05$).

Conclusions: The existence of an ophthalmotonic consensual reaction was not supported.

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KEY WORDS: contralateral fellow eye, intraocular pressure, ophthalmotonic consensual reaction

In 1924 Weekers [1] was the first to describe an "ophthalmotonic consensual reaction," a change in intraocular pressure in the contralateral eye induced by treatment of one eye. A decrease in IOP in the fellow eye has since been reported after ocular compression, tonography, trauma, cauterization of the sclera, paracentesis, laser trabeculoplasty and trabeculectomy [2-7]. It is also known that beta-blockers, when instilled unilaterally, reduce the IOP in the contralateral eye. The most widely accepted theory for their contralateral effect is systemic absorption, primarily through the nasolacrimal mucosa [8].

To the best of our knowledge, there has not been a prospective randomized clinical trial to investigate the hypothesis of a centrally controlled mechanism of pharmacologically induced IOP reduction. The purpose of the present study was to assess IOP changes in the contralateral fellow eyes after 3 weeks of treatment with different classes of topically administered IOP-lowering medications. The hypothesis was that if an OCR indeed exists, a contralateral IOP decrease could be detected in all untreated fellow eyes, regardless of the type of IOP-lowering treatment instilled.

PATIENTS AND METHODS

We enrolled 38 consecutive patients with newly diagnosed bilateral ocular hypertension or early open angle glaucoma. The research was conducted at the Tel Aviv Sourasky Medical Center and approved by its Ethics Committee and in accordance with the Helsinki Declaration. Inclusion criteria were patients naive to any IOP-lowering treatment, age over 18 and IOP > 22 mmHg in both eyes. All persons gave their informed consent prior to their inclusion in the study.

We selected one eye of each patient to be treated randomly with one of five agents, IOP-lowering eye drops (prostaglandin analogues, β-blockers, α2-agonists, carbonic anhidrase inhibitors, and the dorzolamide hydrochloride–timolol maleate combination (Cosopt®, Merck Sharpe & Dohme, USA). All medications were administered according to their respective labeling. The eye with the higher baseline

IOP = intraocular pressure
CAI = carbonic anhidrase inhibitors

OCR = ophthalmotonic consensual reaction

intraocular pressure was selected to be the treated eye. After 3 weeks of treatment, the same independent masked examiner measured the IOP in both the treated and untreated eye using Goldmann applanation tonometry. All efforts were made for the baseline and follow-up IOP measurement to be performed at about the same time of day.

Statistical analysis was performed using paired Student's *t*-test, with a *P* value ≤ 0.05 considered to be statistically significant.

RESULTS

Thirty-eight patients were included, 19 males and 19 females. The treated eye was randomized to one of five types of IOP-lowering medication. Nine patients were treated with prostaglandin analogs (latanoprost, bimatoprost or travaprost), 11 with β-blockers (timolol 0.5% or timolol 0.1% gel), and 6 each with topical CAI (dorzolamide), α2-agonists (brimonidine tartrate 0.2%, Alphagan®, Allergan, USA) and the β-blocker/CAI combination (Cosopt®).

The right eye was treated in 27 of the 38 patients and the left eye in 11. Mean IOP of all the treated eyes at baseline was 26.1 ± 4.2 mmHg and at follow-up 20.2 ± 2.9 mmHg; the reduction of IOP from baseline was -6 ± 3.8 mmHg, a mean percent reduction of -22 ± 10.1% from baseline.

In the contralateral untreated eye, the mean IOP was 24.2 ± 3 mmHg at baseline and 23.1 ± 3.1 mmHg at follow-up; IOP reduction from baseline was -1.2 ± 1.8 mmHg, or mean percent reduction -4.7 ± 7.1%.

Table 1 shows the mean reduction in IOP from baseline (mmHg, percent) in each group of topical treatment (in treated and untreated fellow eyes). In the prostaglandin group, treated eyes had a mean reduction from baseline of -7.3 ± 1.9 mmHg, or mean percent reduction -26.7 ± 8.2%. The untreated contralateral eye had a mean reduction from baseline of -0.7 ± 1.2 mmHg or -2.6 ± 4.6% mean percent reduction ($P < 0.05$).

In the β-blockers group, treated eyes had a mean reduction of -4.9 ± 2.3 mmHg or -18.9 ± 9.3%. The contralateral eye had a mean reduction of -1.5 ± 2.1 mmHg or -6.1 ± 8.3% ($P < 0.05$). A further intragroup analysis of the group treated with β-blockers showed that timolol maleate 0.1% gel had a mean percent IOP reduction of -19.7 ± 10.7% in the treated eyes vs. –5.8 ± 10.2% in the untreated eyes (not statistically significant, $P = 0.063$) while timolol maleate 0.5% had a mean percent IOP reduction of -18 ± 8.5% in the treated eyes, vs. -6.4 ± 6.6% in the contralateral eyes ($P < 0.05$).

In the combination group (timolol maleate–dorzolamide), mean reduction in treated eyes was -10.3 ± 6.6 mmHg or -32.6 ± 12.7%. The mean reduction in the fellow eye was -3.2 ± 2.1 mmHg or -12.3 ± 8.3% ($P < 0.05$).

In the CAI group, mean reduction in IOP among treated eyes was -2.7 ± 0.5 mmHg or -12.6 ± 2.1%. Untreated eyes had a mean IOP reduction of -0.7 ± 0.5 mmHg or -3.2 ± 2.6% ($P < 0.05$).

In the last group, the α2-agonists, treated eyes had a mean IOP reduction of -4.8 ± 0.7 mmHg or -19.5 ± 2.4%. Fellow eyes had mean IOP change of +0.2 ± 0.7 mmHg or + 0.7 ± 3.3% ($P < 0.05$).

Figure 1 shows the differences in mean IOP reduction (%) from each medication group baseline between treated and fellow eyes.

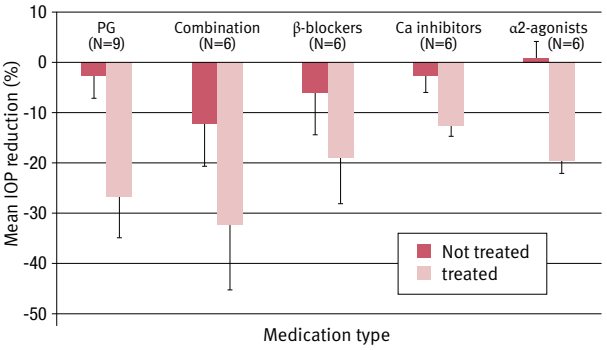
Table 1. IOP parameters in treated and fellow eyes, according to medication type

Medication type	N (%) *	Eye	Baseline mean IOP	Follow-up mean IOP	Mean IOP reduction (mmHg)	Mean IOP reduction (%)	*P* value **
Prostaglandin	9 (23.7)	Treated	27.9±2.8	20.6±3.8	-7.3 ± 1.9	-26.7 ±8.2	0.004
		Fellow	26.2±3.2	25.5±3.4	-0.7 ±1.2	-2.6 ±4.6	
β-blockers	11 (28.9)	Treated	26.1±1.4	21.2±2.9	-4.9 ±2.3	-18.9 ±9.3	0.001
		Fellow	24.7±1.9	23.2±2.3	-1.5 ±2.1	-6.1 ±8.3	
Combination	6 (15.8)	Treated	30±7	19.7±2.9	-10.3 ±6.6	-32.6 ±12.7	0.031
		Fellow	25.3±3.3	22.1±3.2	-3.2 ±2.1	-12.3 ±8.3	
CAI	6 (15.8)	Treated	21.2±2.8	18.5±2.5	-2.7 ±0.5	-12.6 ±2.1	0.031
		Fellow	20.5±2.5	19.8±2.4	-0.7 ±0.5	-3.2 ±2.6	
α2-agonist	6 (15.8)	Treated	24.7±1.4	19.9±1	-4.8 ±0.7	-19.5 ±2.4	0.031
		Fellow	23.1±1	23.3±1.4	+0.2 ±0.7	+0.7 ±3.3	

* Number of patients in each medication group, with percent of patients from the total number of patients (n=38).

** *P* value after comparing mean IOP reduction (%) in treated eyes vs. fellow eyes in each medication group.

Figure 1. Differences in mean IOP reduction (%) from baseline between treated and fellow eyes in each medication group. Treated eyes are shown in black, fellow eyes in light grey.



DISCUSSION

In 1924 Weekers described an "ophthalmotonic consensual reaction" – a change in intraocular pressure in the contralateral eye [1]. Following the original report, a reduction in IOP in the contralateral eye was reported after ocular compression,

tonography, trauma, cauterization of the sclera, paracentesis, laser trabeculoplasty and trabeculectomy [2-7].

The purpose of our study was to validate if indeed a central control mechanism or an "ophthalmotonic consensual reaction" of IOP really exists. The hypothesis was that if an OCR exists, a contralateral IOP decrease in all fellow untreated eyes occurs. Our results could not confirm the existence of a central or consensual control of the IOP. A major contralateral IOP decrease was seen only in the β-blockers and combination group (Cosopt®) (-6.1 ± 8.3% and -12.3 ± 8.3% respectively, mean percent reduction, $P < 0.05$). The other contralateral eyes in the prostaglandin analogues, CAI or α2-agonist groups showed only a small change in IOP (-2.6 ± 4.6%, -3.2 ± 2.6%, +0.7% ± 3.3%, mean percent reduction, respectively, $P < 0.05$).

The IOP changes in contralateral eyes have been noted in many studies. Cox et al. [9] described a contralateral IOP rise in animal eyes after unilateral optic nerve sections. They suggested a supraoptic nuclear control mechanism of IOP. Diestelhorst and Krieglstein [10] found an increase in postoperative aqueous humor flow in the unoperated eye 5 days after trabeculectomy in one eye. They suggested that filtration surgery in one eye triggers a central nervous system-mediated reflective increase in aqueous flow to maintain physiologic stability in the anterior chamber of the operated eye. This response reflected an ocular–CNS reflex. However, they found no statistically significant change in the IOP in the unoperated eye, meaning that increase outflow was sufficient to compensate for the increase in inflow. Vysniauskiene and co-authors [2] studied 24 patients who underwent trabeculectomy with mitomycin-C. They found an IOP reduction in the contralateral eye one month post-surgery, which suggests the existence of an OCR. Mean IOP in all contralateral eyes decreased from 15.5 ± 5.5 mmHg to 13 ± 4.7 mmHg. In contrast, Yarangumeli et al. [11] reported an increase in IOP in contralateral eyes in a third of the patients after trabeculectomy in one eye.

Regarding the contralateral effect of topical ocular antihypertensive drugs, a contralateral IOP decrease has been confirmed in topical β-adrenergic antagonists [8]. This effect is demonstrated also in our study. In fact a major contralateral IOP decrease was found only in the β-blockers and combination (Cosopt®) group, presumably attributed to the β-blocker in the combination.

A contralateral IOP reduction following topical β-blockers has been shown in numerous studies both in normal [13-15] and hypertensive eyes [12,14,16-18]. Overall, the contralateral effect is smaller in normotensive eyes than in hypertensive eyes [8]; however, there is great variability of results in both groups. The most widely accepted theory for their contralateral effect is systemic absorption, primarily through the nasolacrimal mucosa, resulting in transport of the β-blocker to the contralateral eye. Systemic absorption may also result in centrally mediated effects on IOP control in the contralateral eye. Other suggested mechanisms are contamination of the untreated eye and also OCR [8].

The Ocular Hypertension Treatment Study [8] is the largest study group available for evaluating the magnitude of the contralateral effect of topical β-blockers. In the OHTS, 817 patients received topical β-blockers in one eye. Mean reduction in IOP in the treated eyes was 5.9 ± 3.4 mmHg (22 ± 12%). Mean IOP reduction in the contralateral untreated eyes was 1.5 ± 3 mmHg (5.8 ± 12%) [8]. Our study demonstrates similar results: eyes treated with β-blockers had a mean percent reduction of -18.9 ± 9.3% in IOP, and the contralateral eyes -6.1 ± 8.3% ($P < 0.05$).

In the OHTS, factors associated with the magnitude of contralateral effect were the degree of IOP reduction in the treated eye and baseline IOP of the contralateral eye [8]. It is interesting to mention that our study found a similar contralateral decrease of IOP in both timolol 0.1% gel and 0.5% solution: -5.8 ± 10.2% ($P = 0.063$) and -6.4 ± 6.6% ($P < 0.05$), respectively. It is known that plasma levels of timolol 0.1% gel are significantly lower than those of timolol 0.5% drops [19], and thus the risk of systemic side effects is lower. We therefore could expect a lower contralateral IOP decrease in the 0.1% timolol gel compared to 0.5% drops, but this suggestion was not confirmed in our study. In the treated eyes, both drugs had a similar effect on IOP in our study (-19.7 ± 10.7%+ in timolol 0.1% gel, and -18 ± 8.5% in timolol 0.5% solution), which is similar to the data found in the literature [19].

In 21 patients, brimonidine was found to have a slight contralateral decrease in IOP (1.2 ± 0.6 mmHg) and in aqueous flow (12%) on day 8 of treatment [20]. In another study with 29 patients receiving brimonidine in one eye, there was a slight but significant reduction in IOP in the contralateral eye [21]. Our study found that in the α2-agonists group there was a small IOP increase in the contralateral eye (+0.7 ± 3.3%, $P < 0.05$).

Prostaglandin analogues are not known to have a crossover effect. Studies with latanoprost have not found a contralateral effect [22]. Our study noted a small reduction of IOP in the prostaglandin analogues and CAI group (-2.6 ± 4.6%, -3.2 ± 2.6%, $P < 0.05$).

We acknowledge that this study included only 38 patients, so the results should be interpreted with caution. A larger number of patients need to be evaluated in order to confirm our results. In summary, our study found a major contralateral IOP reduction only in the β-blockers and combination (Cosopt®) groups. This effect is probably primarily due to

CNS = central nervous system

OHTS = Ocular Hypertension Treatment Study

the known systemic absorption of β-antagonists and not due to an "ophthalmotonic consensual reaction," as this effect was not encountered in the contralateral eyes in the groups treated with prostaglandin, CAI or α2-agonists.

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References

1. Weekers L. Modification experimentales de l'ophtalmotonous. Reaction ophtalmotonique consenuelle. *Arch Ophthalmol (Paris)* 1924; 41: 641-58.
2. Vysniauskiene I, Shaarawy T, Flammer J, Haefliquer IO. Intraocular pressure changes in the contralateral eye after trabeculectomy with mitomycin C. *Br J Ophthalmol* 2005; 89: 809-11.
3. Brooks AMV, West RH, Gillies WE. Argon laser trabeculoplasty five years on. *Aust N Z J Ophthalmol* 1988; 16: 343-51.
4. Nagata N, Kurimoto S, Matsuka M. A study of consensual ophthalmotonic reaction. *Acta Soc Ophthalmol Japan* 1954; 58: 38-46.
5. Prijot EL, Stone HH. A study of consensual ophthalmotonic reaction. *Am J Ophthalmol* 1956; 42: 50-8.
6. Stocker FW. On changes in intraocular pressure after application of the tonometer. *Am J Ophthalmol* 1958; 45: 192-6.
7. Wilmer WE. Discussion on the results of operative treatment of glaucoma. *Trans Ophthalmol Soc UK* 1927: 47: 230-3.
8. Piltz J, Gross R, Shin DH, et al. Contralateral effect of topical b-adrenergic antagonists in initial one-eyed trials in the ocular hypertension treatment study. *Am J Ophthalmol* 2000; 130: 441-53.
9. Cox CE, Fitzgerald CR, King RL. A preliminary report on the supraoptic nucleus and control of intraocular pressure. *Invest Ophthalmol* 1975; 14: 26-8.
10. Diestelhorst M, Krieglstein G. The effect of trabeculectomy on the aqueous humor flow of the unoperated fellow eye. *Graefes Arch Clin Exp Ophthalmol* 1991; 229: 274-6.
11. Yarangumeli A, Koz OG, Kural G. The effect of trabeculectomy on the intraocular pressure of the unoperated fellow eye. *J Glaucoma* 2003; 12(2): 108-13.
12. Zimmerman TJ, Kaufman HE. Timolol: a β-adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol* 1977; 95: 601-4.
13. Martin XD, Rabineau PA. Intraocular pressure effects of timolol after unilateral instillation. *Ophthalmology* 1988; 95: 1620-3.
14. Gibbens MV. The consensual ophthalmotonic reaction. *Br J Ophthalmol* 1988; 72: 746-9.
15. Dunham CN, Spaide RF, Dunham G. The contralateral reduction of intraocular pressure by timolol. *Br J Ophthalmol* 1994; 78: 38-40.
16. Zimmerman TJ, Kaufman HE. Timolol dose response and duration of action. *Arch Ophthalmol* 1977; 95: 605-7.
17. Kwitko GM, Shin DH, Ahn BH, Hong YJ. Bilateral effects of long term monocular timolol therapy. *Am J Ophthalmol* 1987; 104: 591-4.
18. GLT Research Group. The glaucoma research trial 4: contralateral effects of timolol on the intraocular pressure of eyes treated with ALT. *Ophthalmic Surg* 1991; 22: 324-8.
19. Rouland JF, Morel-Mandrino P, Elena PP, Polzer H, Sunder Raj P. Timolol 0.1% gel (Nyogel 0.1%) once daily versus conventional timolol 0.5% solution twice daily: a comparison of efficacy and safety. *Ophthalmologica* 2002; 216: 449-54.
20. Toris CB, Gleason ML, Camras CB, Yablonski ME. Effects of brimonidine on aqueous humor dynamics in human eyes. *Arch Ophthalmol* 1995; 113(12): 1514-17.
21. Toris CB, Camras CB, Yablonsky ME. Acute versus chronic effects of brimonidine on aqueous humor dynamics in ocular hypertensive patients. *Am J Ophthalmol* 1999; 128: 8-14.
22. Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. *Ophthalmology* 1995; 102: 1743-52.