Research Article

What is the Effect of Topical Diclofenac Sodium when Used in Conjunction with Travoprost in Chronic Open Angle Glaucoma?

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Abstract
Aim: To investigate the effects of concomitant topical application of diclofenac sodium as a NSAID on the IOP lowering effects of Travoprost as a prostaglandin analogue. **Methods:** 15 patients 15 eyes were included in the study. Topical Travoprost 0.004% was given before bed time for six weeks for baseline IOP determination. Topical Diclofenac sodium was added to one eye twice daily that is randomly selected forming the (NSAID group). The other eye was treated instead of NSAID with topical Hydroxy propyl methyl cellulose twice daily forming the (Control group). This regimen continued for 8 weeks. Double masking was done. **Results: T**he mean IOP in the NSAID group kept increasing, although such increase was not statistically significant at week 8 (p-value 0.102) but it became highly statistically significant in the following weeks (10,12,14) with p-value less than 0,001. **Conclusion:** The concomitant topical application of Diclofenac sodium with topical Travoprost hinders the IOP lowering effects of Travoprost.
Keywords: Travoprost, NSAID, Elzembely, Diclofenac, Glaucoma, IOP

Introduction
Prostagladin analogues has been used as a medical treatment for cases of chronic open angle glaucoma. Travoprost is a prostaglandin analogue that has been delivered to the market by Alcon, Fort Worth, TX, USA. Travoprost was commercialized as Travatan™ after gaining US FDA approval in March 2001.

The basic mechanism by which Travopost as a prostaglandin analogue reduces Intraocular Pressure (IOP) is by increasing uveoscleral outflow of the aqueous humor. The fine details of such mechanism are not fully understood.[1]

Unfortunately, we cannot rely on animal studies when the issue is the effects of prostaglandin analogues because it show species differences.[2]

This has led to the shift of the focus of evidence-based research in such area towards human trials whether on healthy volunteer subjects or on consenting patients. Kashiwagi et al.,[3] proved in 2003 that concomitant administration of topical Non-steroidal anti-inflammatory drug (NSAIDS) with Latanoprost hinders its IOP lowering effects.

Chiba et al., [4]in 2006 proved in a prospective double masked study that concomitant administration of topical Non-steroidal anti-inflammatory drug (NSAIDS) with Latanoprost hinders its IOP lowering effects in patients with primary open angle glaucoma and in patients with ocular hypertension.

This study explores the effects of topical application of diclofenac sodium as NSAID on the IOP lowering effects of topical Travoprost in patients with primary open angle glaucoma.

Aim of the study
To investigate the effects of concomitant topical application of diclofenac sodium as a NSAID on the IOP lowering effects of Travoprost as a prostaglandin analogue in patients with primary open angle glaucoma.

Patients and methods

A Prospective randomized study was performed in accordance with Helsinky declaration for human experiments. 15 patients 15 eyes were included in the study. Topical Travoprost 0.004% (Travatan Eye Drops) (Alcon, Fort Worth, Texas, USA) was given before bed time for six weeks for baseline IOP determination.

Topical Diclofenac sodium (Epifenac eye drops – EIPICO - 10th of Ramadan City – Egypt) was added to one eye twice daily that is randomly selected forming the (NSAID group). The other eye was treated instead of NSAID with topical Hydroxy propyl methyl cellulose (Normo-tears eye drops - EIPICO - 10th of Ramadan City – Egypt) twice daily forming the (Control group). This regimen continued for 8 weeks. Double masking was done.

Inclusion criteria: patients with primary open angle glaucoma

Exclusion criteria: prior ocular surgery or laser for glaucoma, any other ocular surgery and those with history of chronic intraocular inflammation.

All patients were subjected to written informed consent full ophthalmic examination at the time of enrollment to the study. Then visual acuity, IOP with Tonopen XL (Medtronic Solan, Jacksonville, FL, USA), slit lamp examination and fundus examination at 2 weekly intervals.

The software used was SPSS software, IBM, NY, USA. Paired t test was done to compare the amount of change in IOP in each group. Independent t test to compare between the two groups the NSAID group and the control group. The level of significance is $p<0.05$.

Results

One of the 15 patients was missed immediately after baseline determination. 8 males and 7 females the missed case was a male making the percentage 50% for each gender. The age ranged from 50-66 years old with a mean of 57.2±4.49. The IOP before the beginning of the study ranged from 24-27 mmHg with a mean of 25.53±1.02. See table 1, 2

Table (1): The NSAID group

#	Gender (M) Male (F) Female	Age	Before Travoprost (Tr)	2 WKs	4WKs	6WKs	8WKs	10WKs	12WKs	14WKs
				Baseline determination			Travoprost and NSAID (NSAID Group)			
1	M	55	27	20	19	19	19	20	20	20
2	F	57	26	18	19	18	19	20	21	20
3	M	53	25	18	19	17	19	20	20	20
4	F	51	26	19	18	18	18	20	20	19
5	F	62	24	18	18	17	18	20	19	19
6	M	64	27	21	20	19	19	20	20	missed
7	M	66	25	19	18	19	19	20	missed	missed
8	M	55	26	20	19	19	19	20	21	20
9	F	60	24	18	18	19	19	20	20	20
10	M	54	26	19	19	18	19	19	20	19
11	F	58	25	18	17	17	18	19	19	20
12	F	57	27	20	21	20	21	21	21	21
13	F	50	24	18	17	17	18	19	19	19
14	M	60	26	19	19	18	missed	missed	missed	missed
15	M	56	25	18	17	18	18	18	19	19

Table (2): The control Group

#	Gender (M) Male (F) Female	Age	Before Travoprost (Tr)	2 WKs	4WKs	6WKs	8WKs	10WKs	12WKs	14WKs
				Baseline determination			Travoprost and Hydroxy propyl methyl cellulose (Control Group)			
1	M	55	27	20	19	19	19	18	19	18
2	F	57	26	18	19	18	18	18	19	18
3	M	53	25	18	19	17	18	17	17	17
4	F	51	26	19	18	18	18	18	17	17
5	F	62	24	18	18	17	17	18	18	17
6	M	64	27	21	20	19	19	20	19	missed
7	M	66	25	19	18	19	19	18	missed	missed
8	M	55	26	20	19	19	19	19	19	18
9	F	60	24	18	18	19	19	18	19	18
10	M	54	26	19	19	18	18	19	18	18
11	F	58	25	18	17	17	17	17	17	17
12	F	57	27	20	21	20	20	19	19	20
13	F	50	24	18	17	17	17	16	17	17
14	M	60	26	19	19	18	missed	missed	missed	missed
15	M	56	25	18	17	18	17	18	17	17

The mean IOP in the NSAID group kept increasing, although such increase was not statistically significant at week 8 (p-value 0.102) but it became highly statistically significant in the following weeks (10,12,14) with p-value less than 0,001. See table 3 and Figure 1

Table (3): Comparison between mean baseline and week8, week10, week 12 and week 14 among NSAID group

NSAID group	Mean± SD	p-value of difference from mean baseline
Mean baseline	18.52±0.94	
Eight wks	18.78±0.80	0.102
Ten wks	19.71±0.72	<0.001
Twelve wks	19.92±0.75	<0.001
Fourteen wks	19.66±0.65	<0.001

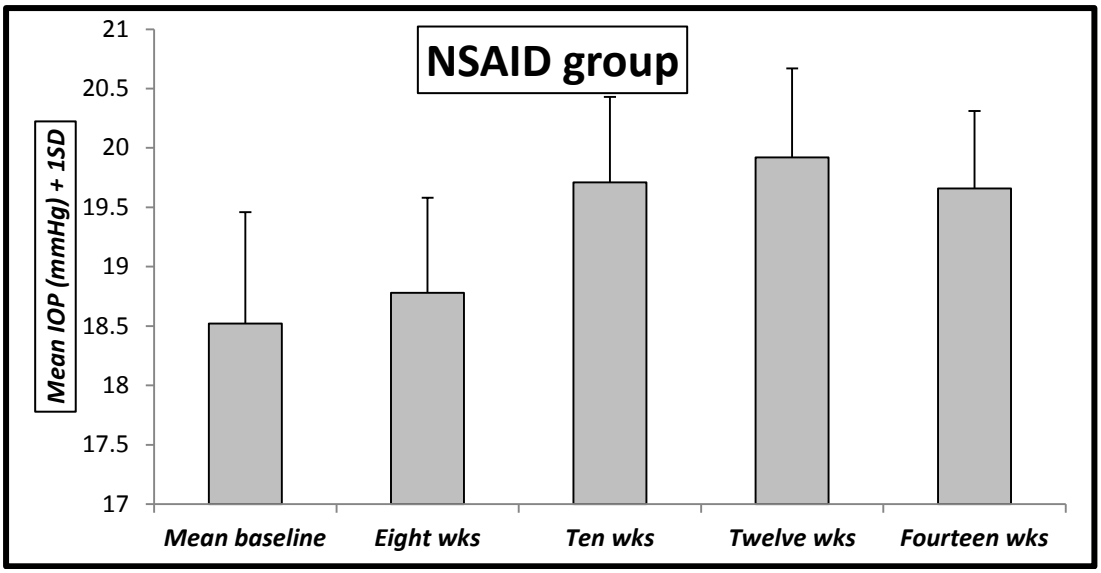

Figure 1: Show the increase in the mean IOP after baseline determination in the NSAID group.

In the control group, the mean IOP did show any statistical difference between baseline values and weeks 8, 10, 12 with p-values (0.017, 0.015, 0.037) respectively. Comparing the two groups a statistically significant difference between the two groups started to appear at week 10 and continued till the end of the study. There was no statistically significant difference at week 8 (p-value 0.102). See table 4 and Figure 2

Table (4): comparison between mean baseline and week8, week10, week 12 and week 14 among studied groups

	NSAID group	**control group**	**p-value**
	Mean± SD	Mean± SD	
Mean baseline	18.53±0.90	18.53±0.90	-
Eight wks	18.78±0.80	18.21±0.97	0.102
Ten wks	19.71±0.72	18.07±0.99	<0.001
12 wks	19.92±0.75	18.07±0.95	<0.001
14 wks	19.66±0.65	17.66±0.88	<0.001

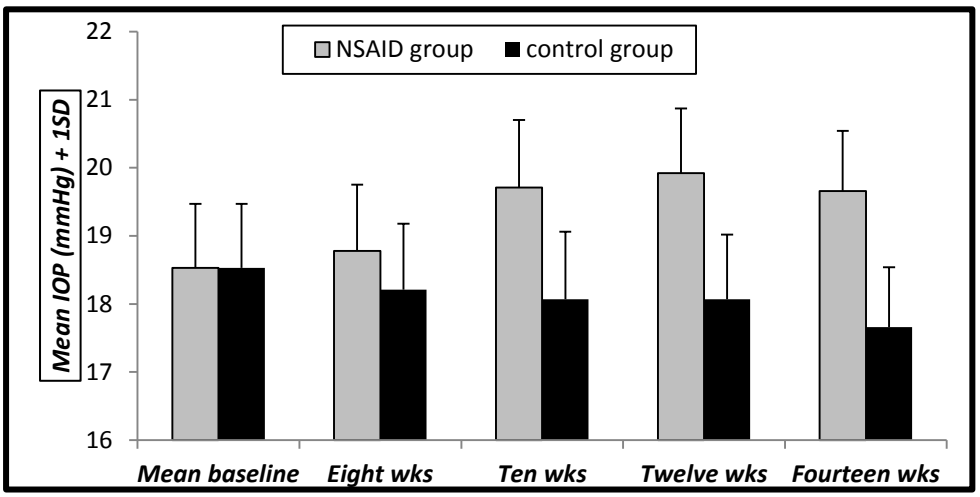

Figure 2: Shows the difference in the mean IOP between the two groups

Discussion

Statistics show that concomitant administration of topical NSAID with travoprost hinders IOP lowering effects of Travoprost. Statistically significant difference was present both on comparing baseline and consequent weeks in the NSAID group, and comparing both groups.

The results of this study agreed with a study that was conducted using animal experiments[5], with that conducted on healthy human volunteers[3], and with that conducted on patients primary open angle glaucoma or ocular hypertension[4] All the fore-mentioned studies used the combi-nation of latanoprost as a prostaglandin analogue and bromofenac sodium as a NSAID. This study add more evidence on that concomitant administration of of topical NSAID has an inhibitory effect on the IOP lowering effects of prostaglandin analogues not just latonoprost and bromofenac sodium.

The reason of choice of Hydroxy propyl methyl cellulose as a control is the preservative. Benzalkonium chloride in Epifenac (Diclofenac Sodium) is 0.05mg, while in Normo-Tears (Hydroxy propyl methyl cellulose) is 0.02mg. the production of endogenous PGs has been reported on using medications with benzalkonium chloride as a preservative.[6,7] In our study the preservative used in the control as well as the study group is comparable.

A study by Sponsel et al.,[8] showed no such inhibitory effect of NSAID on IOP lowering effect of latanoprost. Sponsel et al., used additional systemic administration of indomethacin.

A larger clinical multicenter randomized trial may be beneficial to study the different combinations of prostaglandin analogues with different NSAID, giving also more emphasis on the effects of concomitant administration of systemic NSAID.

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