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Crossover randomized study comparing the efficacy and tolerability of preservative-free Tafluprost 0.0015% to Latanoprost 0.005% in patients with primary open-angle glaucoma

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Purpose: To compare the efficacy and the tolerability of preservative-free Tafluprost 0.0015% (TP) *vs* Latanoprost 0.005% (LP) in patients with primary open-angle glaucoma (POAG). **Methods:** Prospective, randomized, crossover study included patients with early POAG attending the outpatient clinic from July 2019 to February 2020. Patients were divided into 2 groups: group A included patients receiving TP and group B receiving LP. After 2 months, treatment was stopped for 1 month (washout period) then drops were switched between the groups for further 2 months. Intraocular pressure (IOP) was recorded at baseline and monthly until 5 months. Efficacy was measured by the IOP reduction at the end of each treatment period. Tolerability was assessed both subjectively (questionnaire on ocular comfort) and objectively (ocular findings) at the end of each period. **Results:** A total of 30 patients were allocated into two groups (15 patients each). There was no statistically significant difference between the 2 groups in baseline clinical examinations. All the eyes in both groups achieved IOP reduction >20% compared to baseline values, with no statistically significant difference in between. Corneal erosions and conjunctival hyperemia were significantly higher in LP-treated eyes throughout the study, regardless of the sequence. Tear break-up time scores significantly worsened after LP at the 2nd and 5th month ($P < 0.001$and $P = 0.026$ respectively) but not after TP treatment ($P = 0.719$ and $P = 0.164$). Significant exacerbation in all patients' symptoms was noticed on switching from TP to LP. **Conclusion**: Tafluprost was proved to exhibit a comparable effect on IOP control in POAG patients, as Latanoprost drops resulted in marked alleviation in both subjective and objective ocular discomfort manifestations.

Key words: Crossover, Latanoprost, ocular surface disease, preservative-free, primary open-angle glaucoma, Tafluprost

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Prostaglandin analogues (PGAs) have been widely used in the treatment of glaucoma; being one of the most effective drugs for lowering intraocular pressure (IOP).[1] During manufacturing, almost all drops have supplementary preservatives in their formulae in order to avoid denaturation of the product, thus conserving them for extended periods.[2] Benzalkonium chloride (BAK) is the most commonly used preservative with concentrations between 0.004% and 0.02%.[3] However, it was reported to induce ocular surface toxicities, corneal erosions, and conjunctival hyperemia. Furthermore, quite a lot of patients encounter ocular discomfort symptoms fluctuating among foreign body sensation, soreness, redness, and watering. These effects, in turn, influence the life-long compliance to the treatment.[4,5] Trials for reducing the use of BAK involved either substitutions[6-8] or preservative-free drops.[9]

Latanoprost 0.005% (LP) is one of the topical PGAs that contains high concentrations of BAK (0.02%). LP had been extensively used as the first line of treatment in many countries since it was introduced in the market back in 1995.[10] Though it proved to be effective on a wide range of glaucoma patients, some studies reported unsatisfactory IOP control in some patients. Moreover, poor compliance reported by a number of patients was mainly related to ocular surface complaints, mostly linked to its BAK constituent.[11]

Tafluprost 0.0015% (TP) was launched as the first preservative-free PGA in 2008.[12] Although both TP and LP are topical PGAs, they differ in their structure as well as their binding affinity for prostanoid FP receptor (a subtype of PG receptors), ensuing different IOP-lowering effects. Tafluprost exhibits superior binding affinity for the prostanoid FP receptor owing to the presence of two fluorine atoms in its structure.[12] TP was proved to alleviate the signs and symptoms of ocular discomfort in patients with ocular hypertension and normotensive glaucoma.[9]

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In the current study, we compared the efficacy and tolerability of TP versus LP in patients with primary open-angle glaucoma (POAG). The efficacy of each drug was determined by its IOP reducing ability at the end of the follow-up period compared to the baseline values. Tolerability was assessed both subjectively (questionnaire on ocular comfort) and objectively (ocular findings) at the end of each treatment period.

We utilized a crossover study in which the same patient was switched from one treatment to another during the course of the study. This design is presumed to offer more precise evaluations of the treatment effects as they limit the confounding personal factors and permits the patients to go through their own comparison between the two studied drugs. This comparative process is made possible with half the number of the sample size usually needed for parallel studies.[13,14]

Methods

We conducted a prospective, randomized, crossover study adhering to the tenets of the Declaration of Helsinki and approved by the Institutional Review Board (IRB). All participants provided informed written consent. The study started in July 2019 and ended in February 2020, during which 30 patients were enrolled and completed their follow-up period. The study involved 2 treatment phases, each lasting for 2 months, separated by a 1 month washout period (2nd washout). Ethical approval by file no 1291 for year 2020.

The patients recruited were adults above the age of 40 years with a recent diagnosis of POAG or who were medically controlled with monotherapy (i.e., achieving their target IOP). IOP between 21 and 32 mmHg, with glaucomatous optic neuropathy (cup-disc ≥0.5, or the presence of notching) with a compatible visual field defect (glaucoma hemifield test "outside normal limits," and a cluster of three non-edge contiguous points on the pattern deviation plot with $P < 5\%$ not crossing the horizontal meridian) and normal open angles on Gonioscopy.

All the previously treated patients were informed to stop their anti-glaucoma medications for 4 weeks before being enrolled in the study (1st washout). All the recruited patients had either IOP >21 mmHg if they were first diagnosed or IOP >21 mmHg after the washout period of the anti-glaucoma medication used before.

Exclusion criteria included other types of glaucoma (primary angle closure or secondary glaucomas), advanced glaucoma (cup -disc ratio ≥0.9 and/or visual field loss within central 10° degrees) for fear of possible progression during the washout periods, previous ocular trauma, previous intraocular surgery, corneal surface disorders including contact lens wearer at the time of the study and patients receiving any PGA drops for >4 weeks. Pregnant or lactating females were also excluded.

Baseline examinations were conducted after the 1st washout period. For all patients, the following examinations and assessments were carried out at the baseline and monthly until the end of the follow-up period. IOP was measured using an applanation tonometer (Haag-Streit, Bern, Switzerland). Central corneal thickness (SP-2000; Topcon, Tokyo, Japan) was measured for adjusting IOP readings. Best-corrected visual acuity using Snellen's charts converted to LogMAR for statistical analysis was used. Visual field testing was done at the baseline and at the end of the follow-up period (Humphrey Instruments, San Leandro, CA, threshold examination of SITA 24-2 program).

Tolerability assessment was done objectively by the examination of the ocular surface, which included slit-lamp evaluation for the following parameters: 1) corneal erosion after staining with fluorescein was given scores according to the affected area (0 = no erosion, 1 = erosion affecting 1/3rd of the cornea, 2 = erosion in 2/3rd of the cornea, and 3 = erosions all over the cornea[7]); 2) tear break-up time (TBUT) was measured after installing one fluorescein drop, asking the patient to blink once then calculating the time elapsed until the first break in the tear film (0 >10 sec, 1 = 5–10 sec, 2 <5, 3 = immediate); 3) severity conjunctival hyperemia score (0 = no, 1 = mild, 2 = moderate, and 3 = severe).

Subjective tolerability was assessed by a modified simple questionnaire regarding ocular discomfort based on standard patient evaluation of eye dryness (SPEED).[15] Patients were asked whether they developed gritty sensation, watering (burning), redness, or eye fatigue (blurring) that are related to the use of the drops. The patients were asked to grade the frequency (0 = never, 1 = sometimes, 2 = often. and 3 = constant) and the severity (0 = none, 1 = tolerable, 2 = uncomfortable, 3 = bothersome, and 4 = intolerable). The total score was the sum of the frequency and severity.

The sample size of 30 patients (15 per group) offered 80% power based on previous similar studies. The study protocol involved 2 groups. Group A, started on TP for 2 months and then switched to LP for another 2 months. Group B, started on LP then switched to TP. Flipping coin sequence was set up before enrollment. In line with their visit order; 30 patients were assigned into the groups – 15 patients in each group – according to the pre-enrollment sequence: B-B-B-A-A-B-B-A-A-A-A-B-A -B-A-B-A-B-A-B-B-A-A-A-B-A-A-B-B-B. All the patients had a bilateral presentation. If there was a difference in the severity, the less severe eye was enrolled in the study. Whenever both eyes had the same severity of the disease; the right eye was taken in the results.

For each group, TP or LP drops were given once daily at bedtime. The IOP after the 2nd washout period was considered as the baseline IOP for the 2nd treatment period. Primary outcomes involved efficacy and tolerability assessment. Efficacy was measured by the IOP reduction at the end of each treatment period. In our study, all the patients were early POAG (mean deviation (MD) on visual field <-5dB), so the target was to achieve IOP reduction ≥20% compared to baseline values, with no progression on the visual field.[16] Tolerability was assessed both subjectively and objectively and compared within each group after the switching.

Statistical analysis

The collected data were analyzed using SPSS (Version 16.0, SPSS Inc., Chicago). Categorical data were noted with respect to the number and percentage, and compared via Fisher's-Exact test. Continuous variables were represented by means and standard deviations (SD). The statistical analysis of the continuous variables within the same group (intragroup/carry over) was done by a paired t-test between 2nd and 5th month, while intergroup comparisons were carried out using an independent t-test. Statistical significance was set at P values of ≤0.05.

Results

Demographic and baseline clinical data

The study included 30 patients (30 eyes) allocated into 2 groups (15 patients per group), 29 patients completed the follow-up period. The mean age of the participants was 59.1 ± 6.9 years, with 56.6% males. Almost half of the patients (43.3%) were newly discovered glaucoma patients with no history of anti-glaucoma treatment. Table 1 summarizes the demographic and baseline clinical data of the studied patients. There was no statistically significant difference between the 2 groups apart from prevalence of diabetes that was higher in group A ($P = 0.04$). None of the patients had a conjunctival injection or corneal erosions prior to the study.

Intraocular pressure evaluation

In group A (TP to LP), the mean ± SD of 1st baseline IOP was 25.5±1.6 mmHg, which decreased significantly to 17.4±4.08 mmHg at 2nd month ($P < 0.001$) with 31.5% IOP reduction. The mean ± SD of the 2nd baseline IOP was 23.5 ± 1.1 mmHg, which decreased to 15.1 ± 2.8 mmHg at 5th month after LP ($P < 0.001$) with 36% reduction. There was no statistically significant difference between the mean percentage of IOP reduction between the 2 treatment periods (paired *t*-test, $P = 0.106$).

For group B (LP to TP), the mean ± SD of 1st baseline IOP was 24.7 ± 1.7 mmHg. At the end of the first treatment period, it decreased to 15.8 ± 1.7 mmHg ($P < 0.001$) with 36.2% reduction. At 5th month, after use of TP, IOP was 15.5 ± 2.1 ($P < 0.001$) with 35% reduction compared to the 2nd baseline IOP (23.8 ± 1.8 mmHg). There was a significant reduction in IOP after both treatments without a significant difference between them (paired *t*-test, $P = 0.403$). There was a significant difference between the 1st and the 2nd baseline values in both groups ($P < 0.005$).

The efficacy in IOP reduction showed no statistical differences between the two groups, and this aspect remained constant throughout the 5-month study period. All the eyes in both groups achieved IOP reduction >20% compared to baseline values, with no statistically significant difference between them (intergroup comparison) [Table 2 and Fig. 1].

Visual function

Both mean deviation (MD) and BCVA remained unchanged in all patients in both groups.

Tolerability

Corneal erosions and conjunctival hyperemia were significantly higher in LP-treated eyes throughout the study, regardless of the sequence. The severity of the hyperemia decreased along the follow-up period in both treatments [Table 3]. Compared to the baseline values, TBUT scores significantly worsened after LP at the 2nd and 5th month (paired *t*-test, $P < 0.001$ and $P = 0.026$, respectively), while they remained insignificant

Table 1: Demographic and baseline clinical examination of the studied groups

Parameter	Group A (TP then LP) *n*=15	Group B (LP then TP) *n*=15	*P*
Age (years)			
Mean±SD	58.2±6.73	60.0±7.24	0.487
Minimum-Maximum	(44-69)	(49-71)	
Gender			
Male	10 (66.7)	7 (46.7)	0.462
Female	5 (33.3)	8 (53.3)	
Baseline IOP (mmHg)			
Mean±SD	25.5±1.6	24.7±1.7	0.279
Minimum-Maximum	(23-27)	(22-27)	
Baseline BCVA (log MAR)			
Mean±SD	0.25±0.14	0.27±0.09	0.539
Minimum-Maximum	(0.0-0.5)	(0.1-0.4)	
Previous medications (*n*. of patients/%)			
None (naïve patients)	6 (40)	7 (46.7)	0.478
ß-blockers	5 (33.3)	6 (40)	
α-adrenergic agonists	2 (13.3)	0 (0)	
Topical CAIs	1 (6.7)	0 (0)	
Latanoprost	1 (6.7)	2 (13.3)	
Mean deviation on VF (dB)			
Mean±SD	-3.81±1.2	-4.08±0.8	0.467
Vertical Cup-disc ratio			
Mean±SD	0.58±0.067	0.59±0.08	0.812
Min-Max	(0.5-0.7)	(0.5-0.7)	
TBUT (score)	0.6±0.73	0.8±0.67	0.445
Systemic disease (*n*. of patients/%)			
Diabetes Miletus	9 (60)	5 (33.3)	0.04*
Systemic hypertension	7 (46.7)	7 (46.7)	1.00
Smoking	4 (26.7)	5 (33.3)	0.690

SD=standard deviation; IOP=intraocular pressure, LP=Latanoprost, TP=Tafluprost, BCVA=best corrected visual acuity; Log MAR=logarithm minimal angle of resolution; VF=visual field; TBUT=tear break up time, CAIs=carbonic anhydrase inhibitors; *P* value=comparison between the 2 studied groups (independent *t*-test used & Fisher's-Exact test). Significance at $P \leq 0.05$*

Table 2: Comparison between the IOP values among the studied groups during the 2 treatment periods

Treatment period 1				Treatment period 2			
IOP (mmHg)	Group A TP *n*=15	Group B LP *n*=15	*P*	IOP (mmHg)	Group A LP *n*=14	Group B TP *n*=15	*P*
1st Baseline	25.4±1.6	24.7±1.7	0.279	2nd Baseline	23.5±1.1	23.8±1.8	0.598
1st month	15.9±2.9	14.3±2.4	0.109	4th month	14.2±2.6	15.0±1.7	0.344
2nd month	17.4±4.08	15.8±1.7	0.174	5th month	15.1±2.8	15.5±2.1	0.670
P2 (baseline vs 2nd month)	<0.001*	<0.001*		P2 (baseline vs 5th month)	<0.001*	<0.001*	

IOP=intraocular pressure, LP=Latanoprost, TP=Tafluprost, P1=comparison between the 2 studied groups (independent *t*-test used), P2 comparing the value of the IOP in last visit to the baseline values within each group (paired *t*-test used). Significance at $P \leq 0.05$

Table 3: Comparison of ocular surface evaluation between the two studied groups

	Group A			Group B		
Parameter (scores) Mean±SD	At 2nd m TP *n*=15	At 5th m LP *n*=14	*P*	At 2nd m LP *n*=15	At 5th m TP *n*=15	*P*
Corneal erosion	0.14±0.4	0.57±0.8	0.008	0.53±0.83	0.2±0.4	0.019
TBUT	0.67±0.7	1.5±0.65	0.013	1.7±0.59	0.93±0.8	0.001
Conj. hyperemia	0.85±0.8	1.35±0.6	0.013	1.06±1.1	0.46±0.5	0.033

SD=standard deviation; TBUT=tear break up time; conj. = conjunctival; TP=Tafluprost; LP=Latanoprost. *P* value=intragroup comparison using paired *t*-test. Significance at $P \leq 0.05$

Table 4: Comparison of patients' discomfort scores between the two studied groups

	Group A			Group B		
Parameter (scores) Mean±SD	At 2nd m TP *n*=15	At 5th m LP *n*=14	*P*	At 2nd m LP *n*=15	At 5th m TP *n*=15	*P*
Gritty sensation	0.27±0.7	2.14±2.7	0.048	1.7±2.5	0.3±0.9	0.021
Redness	1.02±1.0	3.4±2.3	0.001	2.46±2.8	0.93±0.8	<0.001
Watering	0.27±0.7	2.07±2.2	0.047	1.6±2.4	0.33±1.0	0.006
Blurring of Vision	0.13±0.5	0.0	-	0.13±0.5	0.0	-

SD=standard deviation; TP=Tafluprost; LP=Latanoprost. *P*=intragroup comparison using paired *t*-test. Significance at $P \leq 0.05$

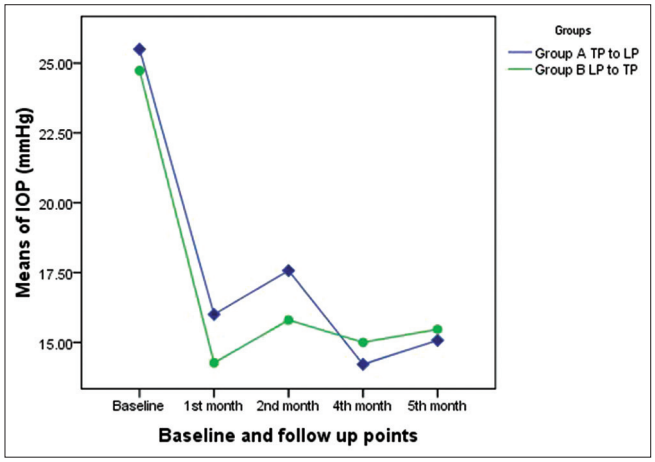

Figure 1: Baseline and post-treatment intraocular pressure (IOP) values among the 2 studied groups along the follow-up points (repeated measures Anova test used)

after TP treatment (paired *t*-test, $P = 0.719$ and $P = 0.164$) at corresponding points. Shifting treatment from TP to LP in group A resulted in significant shortening in TBUT i.e., higher scores ($P = 0.013$) with counter improvement on shifting from LP to TP ($P = 0.001$).

Patient discomfort

Ocular discomfort symptoms, especially redness, were present in nearly all the patients during the first 2 weeks of the treatment, which subsequently improved markedly. One patient in group A was withdrawn from the study after 4 days from the use of LP as he complained of severe redness and gritty sensation and preferred to continue on TP. Significant exacerbation in all patients' symptoms was noticed on switching from TP to LP with comparable improvement on the switch from LP to TP [Table 4].

Adverse events

None of the patients in either group noticed or developed any adverse effects at the end of the follow-up period (no trichiasis, no periocular/iris hyperpigmentation or anterior chamber reaction).

Discussion

Quite a lot of PGAs are now available in the market; thus, the selection usually is based on their IOP-lowering ability weighed against the tolerability and possible adverse effects.[17] We conducted a prospective, randomized, crossover study comparing the efficacy and the tolerability of two topical PGAs; the well-known Latanoprost and the first preservative-free Tafluprost in patients recently diagnosed with POAG. The

study protocol involved 2 treatment periods each lasting for 2 months with a 1 month washout period in between. Two groups A and B with 2 sequences of the treatment were set up (TP to LP and LP to TP). At the end of each treatment period, the IOP control with both subjective and objective scores of ocular surface affection were compared. Any observed side effects were recorded.

The results of the present study demonstrated that both drugs were equally effective at controlling IOP in patients with POAG for the 2 months period of the study. Also, the transition from TP to LP, and contrariwise, did not affect the IOP control. The patients in both groups experienced a significant decrease in IOP before and after switching drops without a difference that designate clinical importance. At this point, our results coincide with earlier studies that reported comparable ability in reducing IOP for LP and TP.[18,19]

Remarkably, the mean values of IOP at the start of the 2nd treatment period (2nd baseline) did not return back to their original values and were significantly lower than the baseline of the 1st treatment period (1st baseline) in both groups. Hence, we relied on the percentage of the IOP reduction compared to the baseline and not on final IOP numerical values. Although all participants continued the 4 weeks washout period, there might be a possibility of a residual effect of the drops used in the first treatment period. A number of studies reported 4 weeks period as the most common washout period for PGAs. It was also suggested that different products within PGA class may differ in their washout period. Moreover, some patients may also exhibit lingering effects to PGA drops.[20]

Evidence of the toxic effect of BAK preservative on the ocular surface integrity has been accumulated over the past few years.[6,7] In the current study, substantial alleviation of almost all the ocular discomfort signs and symptoms was observed on switching between LP eye drops with the high BAK concentration (0.02%) and TP the preservative-free drops. The incidences of the corneal erosions and the conjunctival hyperemia were nearly tripled under the use of LP. These findings correlate well with previously published studies focusing on the tolerability aspect of these drugs.[21] In one study comparing the tolerability of 4 PGAs agents; Bimatoprost, Latanoprost, Travoprost, and Tafluprost in glaucoma patients; LP seemed to be the least tolerated among the four studied drugs.[22]

SPEED questionnaire was adopted in many surveys as it was proved to be worthy in sorting out asymptomatic from symptomatic participants. Being faster than other questionnaires as Ocular surface disease index (OSDI),[22] it was recommended to be applied in epidemiological studies as a valid tool for assessment of dry eye symptoms. On running the questionnaire on our participants, it was fast, expedient, and easily answered without confusion. Scrutinizing SPEED results revealed that both the severity and the frequency of ocular discomfort symptoms were significantly lower with TP drops regardless the sequence of treatment applied. Accordingly, it seems that the non-preservative drug enhanced the subjective satisfaction, which in turn is of essence for maintaining patient compliance for the product during prolonged periods of use.

Overall the 2 drops proved to be well tolerated. Neither group encountered local side effects. There was no change in iris color or periocular area in either group. This might be expected owing to the short treatment period and the dark iris color of our study population.

The essence of crossover studies is to run a carryover comparison. Hence, during the interpretation of our results we focused more on the difference within each group after switching the drops than parallel comparison between the 2 groups. Crossover studies are sometimes contradictory. The study is performed on one subject utilizing two different drugs, thus controlling many variables. Yet, these studies can be deceptive. Adverse effects of the first drug may continue after switching, causing inevitable misinterpretation of the results. On the other hand, the patient's experience increased along the course of the treatment so patients might be more aware and compliant to the drops by time.[13] During the course of the current study, the patients became more aware of the symptoms and their severity by the time and could report the difference and stated their preference meticulously. Switching the drops from TP to LP caused one patient to withdraw himself from the study owing to the intolerable ocular discomfort compared to TP.

The current study was limited by being open-label that could not be avoided, as the preservative-free Tafluprost has a special dispenser, unlike all other drops. Besides, the 5-month duration of the study did not offer the evaluation of long-term effects. However, the study design with the focus on the tolerability and the integration with modification of the SPEED questionnaire in our population all added to the merits of the study.

Conclusion

Tafluprost was proved to result in a comparable effect on IOP control in POAG patients to Latanoprost drops with marked alleviation in both subjective and objective ocular discomfort manifestations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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