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A Comparative Study to Evaluate Efficacy and Safety of Eye Drop Travoprost 0.004% with Tafluprost 0.0015% in Patient with Primary Open Angle Glaucoma

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Abstract: ***Background: Glaucoma is a leading cause of blindness worldwide. Elevated intraocular pressure (IOP) is considered a key risk factor for the progression of glaucoma. Prostaglandin analogs are among the most potent IOP lowering therapies currently available. Aims and Objective: This is a comparative and prospective study to evaluate the IOP lowering efficacy and safety of travoprost (TRAV) 0.004% compared with tafluprost (TAF) 0.0015% in patients with primary open-angle glaucoma (POAG) over 8 weeks. Materials and Methods: This prospective, randomized, comparative was conducted on 50 patients of POAG, The patients were assigned to one of the two treatment groups, either TRAV or TAF monotherapy administered as 1 drop daily at 8 pm. Intraocular pressure (IOP) was measured at each visit (1 week, 4 weeks, 8 weeks), slit-lamp bio-microscopy was done and side effects noted at each visit. Results: The mean IOP reduction in TRAV group from 28.04±3.05 to 19.28±1.59 thus resulting in fall of 8.76 ± 2.22 mm Hg (30.89%) and in TAF group it decreased from 27.52±2.74 to 19.64±1.44 resulting in fall of 7.88 ± 2.52 mm Hg (28.18%). These data suggest that both groups provides modest IOP control but this was statistically not significant. (p=0.197). In both treatment groups, the most frequently reported adverse event at 8 weeks was conjunctival hyperaemia observed in 7 (28%) patients of group A(TRAV) and 8(32%) patients of group B(TAF), though the difference was not statistically significant. Conclusion: Both Travoprost 0.004% and Tafluprost 0.0015% in patients with primary open angle glaucoma demonstrated good IOP control. Travoprost has a few advantages over Tafluprost including its potency &efficacy but these are not statistically significant, both exhibit almost similar safety profile.***

Keywords: Conjunctival hyperaemia, Intraocular pressure, Primary open-angle glaucoma (POAG), Prostaglandin analogs, Tafluprost, Travoprost.

1. Background

Glaucoma is a leading cause of blindness worldwide. It is characterized by optic neuropathy and progressive concentric vision loss. Based on the status of the anterior chamber angle, glaucoma can be divided into open and closed angle glaucoma. Open angle glaucoma, especially primary open angle glaucoma, affects the majority of patients.

Elevated intraocular pressure (IOP) is considered a key risk factor for the progression of glaucoma. As such, IOP reduction is a primary objective of the pharmacologic treatment of glaucoma. Several studies have demonstrated that IOP reduction does, in fact, slow glaucoma progression.[1-4]

Prostaglandin analogs:
Prostaglandin analogs are among the most potent IOP lowering therapies currently available. The $PGF_{2\alpha}$ analogs approved for clinical application include latanoprost, bimatoprost, travoprost, as well as the recently developed tafluprost. Prostaglandin analogs have demonstrated greater IOP-lowering efficacy than beta-adrenergic blockers and, for that reason, are commonly used as first-line therapy against glaucoma. In addition, all prostaglandin analogs have convenient once-daily dosing, whereas some other IOP-lowering therapies require dosing 2-3 times daily.

In 1996, latanoprost 0.005% was the first prostaglandin analog to be approved by the US Food and Drug Administration for the treatment of ocular hypertension and open-angle glaucoma. Travoprost (TRAV) 0.004% another prostaglandin analog was approved in 2001 for a similar indication. Tafluprost (TAF) 0.0015% is the most recently released prostaglandin analog, being approved in Europe in 2008.Tafluprost is a prostaglandin analogue, a selective FP prostanoid receptor agonist.

$PGF_{2\alpha}$ analogs lower intraocular pressure by facilitating drainage of aqueous humor, predominantly through the uveoscleral outflow pathway, as well as to a lesser degree through the trabecular outflow pathway.[5] It has been suggested that $PGF_{2\alpha}$ analogs bind to prostaglandin F receptors, activate signal transduction (probably via protein kinase C), and upregulate the expression of matrix metalloproteinases. All these biological changes lead to remodeling of the extracellular matrix, elevation in uveoscleral outflow facility and controversial improvement in trabecular outflow facility.5

It is well-established that IOP is subject to the circadian variation in both healthy individuals and those with glaucoma, although IOP fluctuation is magnified in glaucomatous eyes. Thus, effective once-daily IOP-lowering medications must have consistent efficacy throughout the day to reduce the risk of IOP spikes, which have been associated with the progression of glaucoma.

Topical prostaglandin analogs, which have become first-line therapy in the medical management of glaucoma, have an excellent safety profile with regard to systemic side effects, but are associated with several ocular side effects. Some of these are common, with noserious consequences, whereas others are much less common but potentially sight-threatening side effects.

Oular Side effects: Increased iris pigmentation, eyelash, periocular pigmentation, Hypertrichosis, Keratitis, Cataract, Macular edema and Uveitis.

Systemic side effects: Angina, chest pain, Arthralgia, myalgia**,** Flu-like symptomsand Headache.

2. Materials and Methods

Ethics:
This study was approved by ethical committee of institution and Informed consent from participants was taken.

Study Design:
This was a prospective, randomized, comparative study.

Study population
Study was conducted on 50 patients of POAG who fall in the bracket of inclusion criteria and who presented to Ophthalmology Outdoor at Department of Ophthalmology, RNT Medical College, Udaipur from July 2015 to April 2016.

Sample size:
These eligible patients with POAG were randomly assigned to one of the two treatment groups, each having a sample size of 25 patients by computer generated randomization technique.

Group A: TRAV 0.004% with benzalkonium (BAK) chloride as a preservative, one drop administered at 8 pm every night.
Group B: TAF 0.0015% administered with BAK chloride as preservative, one drop administered at 8 pm every night.

In both the groups, the affected eye was considered as the study eye. If both the eyes were involved then the eye with more damage at presentation was treated as study eye or if the eyes had similar damage then by convention right eye was studied. The other eye was observed and managed as appropriate but was not figured in any of the published results.

Inclusion criteria:
- Male and female aged 18 years or more.
- A diagnosis of open-angle glaucoma.
- An untreated or after washout IOP of 22–34 mmHg in at least one eye at baseline.
- A best-corrected ETDRS visual acuity score of +0.6 logMAR (Snellen equivalent of 20⁄80) or better in each eye.
- Were willing to follow instructions.
- Have provided a written informed consent.
- Patients on prior glaucoma medication must have a minimum wash-out as shown below:
  ≥ 4 weeks for b-adrenergic antagonists
  ≥ 4 weeks for PG analogues
  ≥3 weeks for a-adrenergic agonists
  ≥7 days for carbonic anhydrase inhibitors
  ≥5 days for miotics.

Exclusion criteria
- Females who were pregnant, nursing or planning a pregnancy.
- Previous participation in any clinical trial in which tafluprost was an investigational drug.
- Any uncontrolled systemic disease (e.g. hypertension, diabetes).
- Prior filtration surgery or any other ocular (including ocular laser procedures) surgery within 6 months prior to screening in the treated eye(s).
- IOP >34 mmHg at any time-point in either eye at baseline.
- Known allergy or hypersensitivity to the study medications or their components, including benzalkonium chloride.
- Use of contact lenses at screening or during the study.
- Any active external ocular disease, inflammation, or infection of the eye and⁄or eyelids within 3 months from the study.
- Any ocular disease⁄condition that in the opinion of the investigator may place the patient at significant risk or may confound the study results or interfere significantly with the patient's participation in the study.
- Any corneal abnormality or other condition preventing reliable applanation tonometry.
- Anterior chamber angle less than grade 2 according to Shaffer's classification as measured by gonioscopy.
- Advanced visual field defect.
- Patients who cannot safely discontinue use of ocular hypotensive medications during the washout period.
- Use of any other antiglaucoma medications than the study medications during the study.
- Current alcohol or drug abuse.

Methods:
Detailed ocular and medical history was noted along with the past treatment history and then required ophthalmological examination was done at baseline:
- Visual acuity by snellen's chart
- Slit lamp examination
- IOP measurement by Goldmann Applanation tonometer
- Angle of anterior chamber by Gonioscopy by shaffer's grading
- Perimetry by HFA
- Fundus examination by direct ophthalmoscopy and slit lamp biomicroscopy using +78D lens.

At follow up visits on 1week, 4week and last at 8weeks patient's history was taken regarding compliance of the drug and any side effects or problem noticed by the patient was recorded.Slit lamp examination was done for any side effects and IOP was measured by Goldmann Applanation tonometer.

Statistical Analysis
The study was analyzed by using SPSS (ver.16.0) software using chi-square test and independent t test. Variables were expressed as Mean ± standard deviation and percentages. ($p<0.05$ were considered statistically significant.)

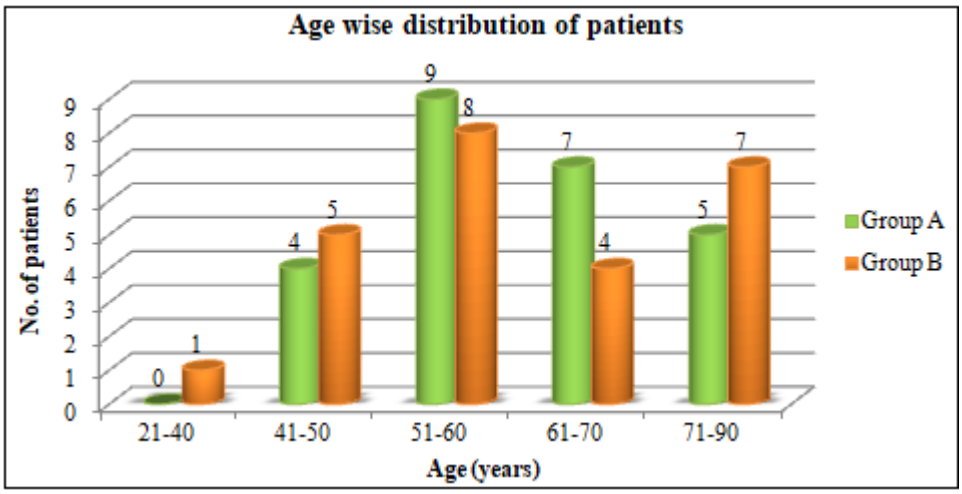
3. Results

The patients were randomly divided in two groups of 25 patients each. Among these 25 patients received one drop of Travoprost 0.004% (group A) and another 25 patients received one drop of Tafluprost 0.0015% (group B) at 8 p.m. and were followed up at week 1, 4 and 8 weeks.

Table 1: Age wise distribution

Age group	Group A		Group B		Total
	F	M	F	M	
21-40	0	0	0	1	1
41-50	3	1	3	2	9
51-60	5	4	3	5	17
61-70	2	5	3	1	11
71-90	0	5	2	5	12
Total	10	15	11	14	50

Above chart shows that most of the patients included in the study fell between age group of 51-60 yrs of age in both the groups.



Mean age in two groups

	Mean Age (yrs)	SD
Group A	60.28	10.32
Group B	59.48	13.26
P value	0.813(NS)	

(No significant difference between mean ages of two groups (P value = 0.81)

The mean age of the patients in the groups A & B were 60.28±10.32 years and 59.48±13.2 years, respectively. The groups were statistically similar at baseline with regards to age as p value b/w groups is 0.813 (p>0.05)

Table 2: Sex wise distribution

Gender	Group A	Group B
Male	15	14
Female	10	11

No significant group differences among both sex (P value = 0.89)

In both group M:F ratio is almost same i.e., 3:2.The distribution of male and female patients was similar in the groups with the difference being statistically insignificant (p>0.05)

Table 3: Baseline IOP or Pre-treatment IOP (in mmHg)

Group	Mean Pre t/t IOP	SD
A	28.04	3.05
B	27.52	2.74

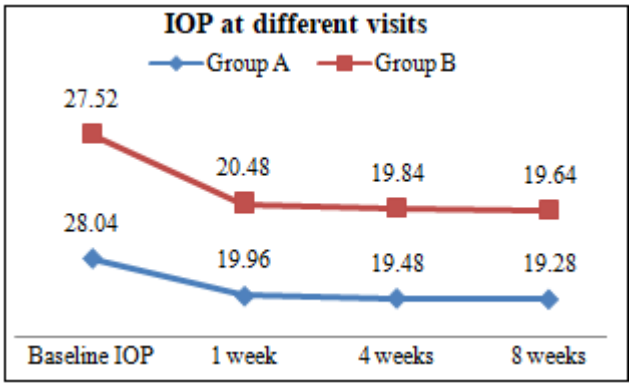
The mean baseline IOP was slightly higher in group A, as compare to group B but the difference was not significant (P=0.529).

Table 4: Mean IOP reduction at 8 weeks

Group	Mean Pre t/t IOP(mmHg)		Mean IOP at 8weeks (mmHg)		Mean reduction in IOP (mmHg)		P value
	Mean	SD	Mean	SD	Mean	SD	
A	28.04	3.05	19.28	1.59	8.76 (30.89%)	2.22	<0.001
B	27.52	2.74	19.64	1.44	7.88 (28.18%)	2.52	<0.001
P value (A/ B)	0.529 (NS)		0.406 (NS)		0.197 (NS)		

Mean IOP at 8 weeks was 19.28 ±1.59 in group A and in group B was 19.64 ±1.44 mmHg slightly higher in Group B but that was not significant (p=0.406).

Mean IOP reduction was 8.76 (30.8%) and 7.88 (28.2%) mmHg in both groups respectively which was also not significant (p=.197)



There was significant reduction in IOP in both groups after 4 weeks follow-up visits (p<0.001) also showing that IOP reduction was maintained throughout the study

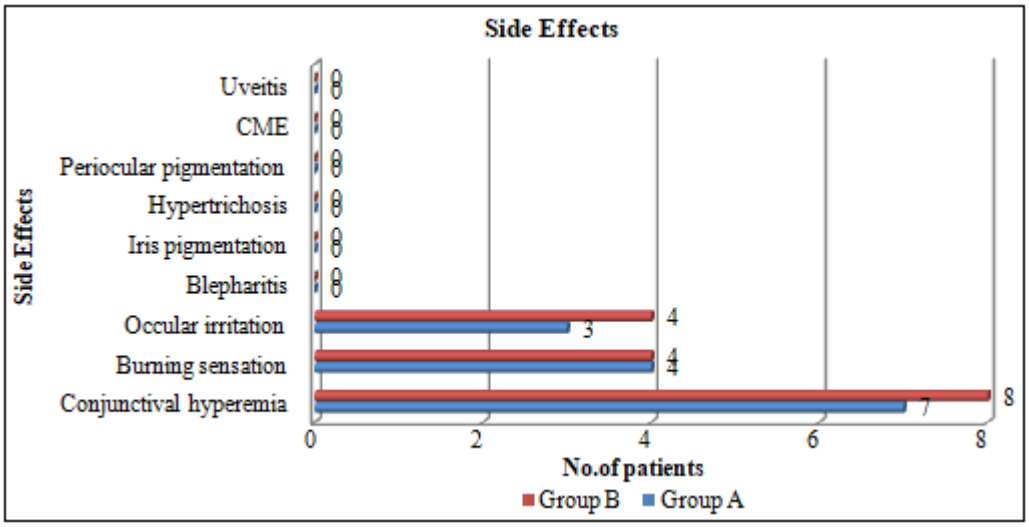
Table 5: Side effects

Side Effects	Group A	Group B
Conjunctival hyperaemia	7(28%)	8(32%)
Burning sensation	4(16%)	4(16%)
Ocular irritation	3(12%)	4(16%)
Blepharitis	0	0
Iris pigmentation	0	0
Hypertrichosis	0	0
Periocular pigmentation	0	0
CME	0	0
Uveitis	0	0

Patients were specifically asked for symptoms i.e. conjunctival hyperaemia and burning sensations and ocular discomfort for a short period of time after instillation of drugs.

Conjunctival hypaeremia was observed in 7(28%) patients of group A and 8(32%) patients of group B, burning sensations was observed by 4 patients of both groups. Occular irritation was observed in 3 patients of group A and 4 patients of group B.

In both groups, no systemic side effects were seen.



Most common side effect noted was conjunctival hyperemia 28% of cases in Group A and 32% of cases in Group B

4. Discussion

Although there are various risk factors associated with development and progression of glaucoma, but IOP is the most important and easily modifiable risk factor. IOP can be

managed both medically and surgically. Medical management is usually preferred as the initial treatment as it avoids surgical risks.

Various drugs and their combinations have been tried in treating primary open angle glaucoma. The newer of these drugs are Prostaglandin analogues Travoprost 0.004% and Tafluprost 0.0015%. These drugs are structural analog of prostaglandin which are used either singly or in combination with any drug to control the intra ocular pressure effectively.

Patients included in the study were both male and female of age 18 years and above with the diagnosis of POAG with untreated or after washout IOP of 22–34 mmHg in at least one eye.

IOP was recorded by Goldmann applanation tonometer. Patient's visits were scheduled at week 1, 4, and 8weeks. During this period out of 50 patients who completed study 25 patients were instructed to administer one drop of 0.004% Travoprost and 25 patients to administer one drop of 0.0015% Tafluprost at 8 p.m. daily.

Patients were instructed to return after 1 week of initiating therapy. If IOP control was satisfactory, the patient was instructed to return for the next scheduled visit.

Maximum number of patients in group A and B were in the age groups 51-60 years and i.e. 36% and 32% respectively (Table 1). These findings were also in consonance with the studies by *Bjornsson* (1967), *Wright* (1966) and *Martinez* (1982), who agreed that the prevalence of primary open angle glaucoma increases with the age of the population, when considered.

The demographic data in our study group shows that POAG is prevalent comparably in both men group A (60%) and group B (56%) while in women group A (40%) and group B (44%) with a slightly higher prevalence among men (Table 2). The findings were in consonance with the studies carried out by Segal *(1967), Kahn, Leibowitz et al (1977).*

The mean baseline IOP in group A and group B patients with applanation tonometry was 28.04±3.05 and 27.52± 2.74 mmHg (Table 3).

In our study both Travoprost and Tafluprost demonstrated good IOP control. The mean IOP readings after 8 weeks of treatment came out to be 19.28±1.59 mmHg and 19.64±1.44 mmHg for group A and B respectively.

So mean decrease in IOP at 8 weeks by Travoprost and Tafluprost was 8.76 ± 2.22 mm Hg (30.89%) and 7.88 ± 2.52 mm Hg (28.18%). These data suggest that both groups provides modest IOP control but this was statistically not significant. (p=0.197). (Table 4)

Similar result was mirrored by, a meta-analysis by *Van der valk et al* (2005) evaluating randomized clinical trials, estimated that travoprost is capable of an IOP reduction of between 31% (peak; 32%–29%) and 29% (trough; 32%–25%).[6]

Similarly *Uusitalo et al* (2010) found that after 24 months of treatment, the mean intraocular pressure reduction from baseline was 7.1 mmHg (29.1%) in the tafluprost-treated group.[7]

In a study by *Aihara et al* (2010) tafluprost reduced intraocular pressure by similar levels, ie, 6.6 ± 2.5 mmHg (27.6% ± 9.6%)[8]

In a crossover study by *Schnober et al (*2010) both travoprost and tafluprost demonstrated excellent IOP control, [9] showing a mean 7.6 mmHg IOP reduction for travoprost and a mean 7.1 mmHg IOP reduction from baseline for tafluprost but the difference was significant.($p<0.05$)

Ranno et al (2012) compared the ocular hypotensive effects of tafluprost (preservative-free formulation) with other prostaglandin analogs. The authors found that tafluprost had a comparable intraocular pressure lowering efficacy compared with travoprost or latanoprost at each time point following treatment.[10]

According to *Nisha Bachkheti* et al (2014) the mean IOP reduction in Travoprost group decreased by 8.55 (31.0%) and in Tafluprost group it decreased by 6.8 mm Hg (24.8%) and the difference was significant ($p<0.05$).[11]

Our study showed that in almost all visits Travoprost reduced IOP better than Tafluprost, and IOP reduction was maintained throughout the study but this was statistically not significant.

The visual acuity, cup disc ratio and the visual fields did not show any change neither did they improve nor did they worsen in any patient taking topical therapy. There was no progression of visual fields defects, which were present initially, and none of the patients developed any new defect during the study period.

No unexpected safety concerns with either Travoprost or Tafluprost monotherapy were observed during the course of this clinical trial. Hyperemia is a class effect of prostaglandin analogs (*Holló et al 2007*).[12]

Regarding the local ocular side effects, c*onjunctival hyperemia* was present in 28% and burning sensation was present in 16% of the patients whereas ocular irritation was present in 12% of the patients in the group A patients. In group B, conjunctival hyperemia was present in 32%, burning sensation in 16% and ocular irritation was present in 16% of the patients. Similar results was seen in a study by *Netland et al (2001), Konstas et al (2006).*[13-14]

Both Travoprost and Tafluprost induced similarly modest levels of hyperemia. The most common side-effect noted was red eyes with 28% and 32% patient in Group A and Group B respectively i.e slightly higher in Group B.

Other side effects e.g. Cystoid macular edema, increased iris pigmentation, hypertrichosis, periocular pigmentation, uveitis etc. were not observed in our study.

In no case however, were ocular side effects sufficient to require discontinuation of topical drugs. The reported incidences of systemic side effects in our study were absent.

Limitations of this study

- This is a single-centre study with a limited number of patients.
- Our study was limited by its short time frame. 8weeks could be sufficient to evaluate changes in IOP levels and to assess the presence or absence of many potentially adverse events. However, longer follow-up periods are required to assess certain side-effects like eyelash lengthening, iris pigmentation and cystoid macular edema.
- Our study did not provide information about IOP during different time of day.

5. Conclusion

The present study was undertaken with the aim to compare the therapeutic efficacy of topical Travoprost (0.004%) and topical Tafluprost (0.0015%) in primary open angle glaucoma to assess the safety and efficacy of these drugs. Results in both groups were compared with each other, emphasis being on the hypotensive effect and the side effects.

Results were observed, analyzed and summarized as follows:

- Mean age of patients was 60.28 years in Group A and 59.48 years in Group B.
- Most of the patients included in the study fell within the age bracket of 51 to 60 years of age.
- 42 % of the study population were female, 68 % were male. The ratio of males to females was almost same i.e 3:2 in both the Groups.
- The mean baseline IOP in group A and group B patients was 28.04 ± 3.05 and 27.52 ± 2.74 mmHg respectively (p= 0.529), difference was statistically not significant.
- The mean IOP readings after 8 weeks of treatment came out to be 19.28±1.59 mmHg and 19.64±1.44 mmHg for group A and B respectively (p= 0.406), difference was statistically insignificant.
- So Mean decrease in IOP at 8 weeks by Travoprost and Tafluprost was 8.76 ± 2.22 mm Hg (30.89%) and 7.88 ± 2.52 mm Hg (28.18%).These data suggest that both groups provides modest IOP control but this was statistically not significant. (p=0.197)
- In both groups, a significant decrease in IOP was observed for all measurement points compared with baseline values (P < 0.0001).
- Conjunctival hyperaemia was observed in 7 (28%) patients of group A and 8(32%) patients of group B, burning sensations was observed by 4 (16%) patients of both groups. Ocular irritation was observed in 3 (12%) patients of group A and 4(16%) patients of group B.
- In both groups, no systemic side effects were seen.
- Both Travoprost 0.004% and Tafluprost 0.0015% in patients with primary open angle glaucoma demonstrated good IOP control.

Travoprost has a few advantages over Tafluprost including its potency, efficacy, and tolerability but these are not statistically significant.

However Tafluprost has the potential to become an important new medication in the therapeutic arsenal of glaucoma management. Since there was small number of patients, shorter duration of follow up, failure to study the diurnal curves we suggest studies in large number of patients treated for many years to ensure prolonged safety and efficacy.

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