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Research Article

Safety and Efficacy of Travoprost (0.004%) Versus Timolol (0.5%) In Patients with Open Angle Glaucoma or Ocular Hypertension: A Randomized Prospective Double-Blind Study

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ABSTRACT
Background: The ultimate goal of pharmacotherapy in glaucoma is to reduce the IOP. The current study is designed to audit the efficacy and safety of 0.004% travoprost over 0.5% timolol eye drops for the treatment of primary open angle glaucoma or ocular hypertension and to suggest appropriate intervention for the treatment of the disease.
Methods: A prospective, randomised, double blind, parallel group clinical study was conducted among adult patients aged 18 years and above of either gender, any ethnicity clinically diagnosed with primary open angle glaucoma or ocular hypertension without any recognizable secondary causes. 60 patients were randomly assigned in double blind fashion to the treatment groups (30 were in group A intervention other 30 were in Group B intervention). Efficacy and safety were assessed on periodic follow-up visits.
Results: There was no significant difference observed between the two groups in the first two weeks of follow up i.e. 2nd and 6th week. But by 9th week onwards statistically significant difference was observed. On 12th week difference was extremely statistically significant. Timolol group showed more of eye irritation (23.33%) followed by red eye in only 2 patients (6.67%). The Group B (Travoprost) patients showed eye irritation (40.7%), red eye (29.6%), Iris pigmentation (3.7%), eyelash growth (14.8%), periorbital pigmentation (3.7%).
Conclusion: Travoprost 0.004% eye drops once daily lowers the intra-ocular pressure significantly more than Timolol 0.5% eye drops twice daily. Though timolol has shown better tolerability, both travoprost and timolol were well tolerated and safe for use in patients with open angle glaucoma.
Keywords: Travoprost, Timolol, Open angle glaucoma, Ocular hypertension, RCT, IOP

INTRODUCTION

Glaucoma is a group of diverse ocular diseases characterized by progressive optic nerve degeneration and peripheral visual field loss, which may or may not be associated with rise of intraocular pressure (IOP), and if not treated promptly, leads to total blindness.(1)

The rapid assessment of avoidable blindness (RAAB) India study revealed that cataract, glaucoma, refractive errors as top three causes for low vision and blindness.(2) India is the second most populous country in the world, it is home to 23.5% of world's blind population. Glaucoma is the second most common cause of blindness in the world as well as in India following cataract. It accounts for 14% of the blindness worldwide.(3) While we were concentrating on eliminating cataract through surgeries achieving exceptional cataract surgery rates, glaucoma snuck up into the picture.(4) Recent surveys have demonstrated that the problem of blindness in India needs to be approached with a broader perspective than just cataract blindness.(3-5)

According to this study by H.A.Quingley et.al., from 2010 to 2020, the most detectable change in glaucoma worldwide will be its increase in India. Also India will replace Europe from second place in the world ranking for glaucoma.(5)

The ultimate goal of pharmacotherapy in glaucoma is to reduce the IOP. Pharmacotherapy is used commonly in POAG whereas sometimes for temporary or instant relief they are also used in PACG, Acute congestive glaucoma.[6]

Despite adequate IOP control with treatment, the patients might have continued visual field loss. Hence IOP control alone should not be the goal in modern glaucoma therapy. But an ocular hypotensive agent which provides improved ocular perfusion is considered optimal therapy. Thus drugs which increase the pulsatile ocular blood flow comes into play.[7] Another goal to be met is neuroprotection of the retinal ganglion cells i.e. decrease in the oxidative stress.

A study conducted in five European countries concluded that travoprost is a cost effective alternative to timolol and latanoprost.[8] The reason for choosing travoprost 0.004% concentration for this study is, as various studies have proved superior efficacy of 0.004% travoprost over 0.0015%.[9-11]
The additional advantage of travoprost eye drops is they need to be instilled only once daily to achieve same or higher reduction in IOP when compared with timolol 0.5% which has to be dosed twice daily which may bring down the compliance among patients.[11, 12] Another reason being, there are no recent studies comparing timolol and travoprost among Indian population.

The current study is designed to audit the efficacy and safety of 0.004% travoprost over 0.5% timolol eye drops for the treatment of primary open angle glaucoma or ocular hypertension and to suggest appropriate intervention for the treatment of the disease.

MATERIAL AND METHODS

The present study was a prospective, randomised, double blind, parallel group clinical study conducted from Aug 2016 to Aug 2017, in the Ophthalmology outpatient department of government general hospital (G.G.H), Kakinada, Andhra Pradesh. The study was conducted in accordance with Declaration of Helsinki and was approved by Institutional Ethics committee (IEC), Rangaraya Medical College (RMC) [Protocol No IEC/RMC/2015/069]. All the patients were explained thoroughly of the study details. Before enrolment, informed consent was taken from all patients, who were willing to participate in the study.

Adult patients aged 18 years and above of either gender, any ethnicity clinically diagnosed with primary open angle glaucoma or ocular hypertension without any recognizable secondary causes (pseudo exfoliation or pigment deposits) were included. In case any of the patients were using some kind of ocular hypotensive medications, completed a washout period of 3 weeks for prostaglandin analogues and beta blockers, 2 weeks for alpha blockers and CA inhibitors, 5 days for miotics. Following washout period, IOP measurements were done again; IOP inclusion criteria included IOP > 21 mmHg, < 37 mmHg in at least one eye. Wearing of contact lens during the study period was not allowed.

Exclusion criteria were chosen for patient safety concern and to further characterize the study population. Women of child bearing potential, IOP > 37mmHg, severe central visual field defects, gonioscopy angle less than 2, cup to disk ratio >0.80, severe progressive retinal diseases, any ocular inflammation or infection in the past 3 months, intraocular surgery or ocular trauma in the past year, advanced cataract or any corneal opacity. Patients with unstable, uncontrolled systemic (CVS, hepatic and renal) diseases or asthma were excluded.

Medication: Medications were masked using identical droptainer bottles with labels on it. Bottles containing Travoprost 0.004% was labelled "single drop morning (8AM) and bottles containing Timolol 0.5% was labelled "single drop morning (8AM), evening(8PM)."

Randomization: After enrolment of the patients and completion of washout period IOPs were measured again to check if they meet inclusion IOP criteria. Patients were randomized to receive either timolol 0.5% or travoprost 0.004%. Patients were assigned numbers in random manner using online software (openepi)

Procedure: Baseline evaluations were performed at the screening visit. General demographic information, medical and ocular history was collected. A complete basic ophthalmic examination which includes visual acuity, slit lamp biomicroscopy, perimetry,

fundus examination and IOP measurement was completed. A general physical exam and systemic exam was done. After this patient was given the respective trial medication and scheduled them for safety and efficacy evaluation on 2nd, 6th, 9th and 12th week. (11)

On each follow up visit interim history was taken and questions were asked regarding compliance, any discomfort. IOP measurement was taken on 2nd, 6th, 9th, 12th week at 9 am in the morning. IOP measurement was done using calibrated Schiotz tonometry. A total of three readings were taken, two readings with minimal difference was averaged and the mean IOP was calculated. During the follow ups general examination was done on only three occasions 2nd, 6th, 12th weeks.

Adverse Events: Safety parameters assessed by asking questions regarding ocular discomfort (any subjective symptoms), slit lamp examination to look for ocular hyperaemia, eyelash enlargement, iris pigmentation, upper eye sulcus deepening.

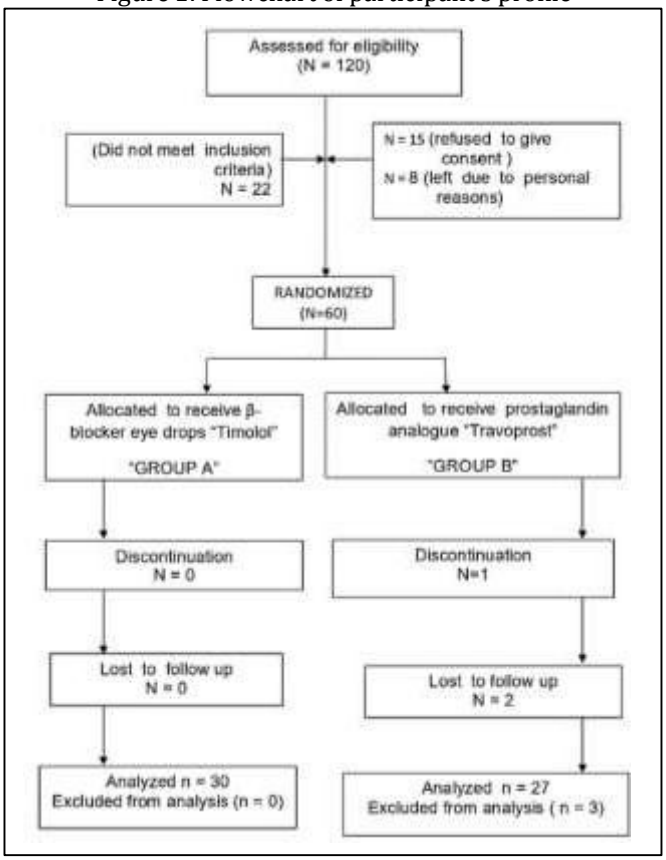
The primary outcome measures were mean IOP change from the baseline on weeks 2nd ,6th, 9th, 12th. Secondary outcome was based on the safety parameters.

The required data from the Case record forms (CRF) were entered in an excel sheet (Microsoft Inc. 2007). Graph Pad Prism and Quickcalcs software were used for the analysis of the final data collected. The data of the patients who completed 12 weeks of follow up was only considered. The data was divided into categorical and continuous data. The IOP's of the two groups were compared using unpaired't' test and the IOP's from the baseline to final week of each group was compared using paired 't' test. "p" value < 0.05 was considered statistically significant.

RESULTS

In this study a total of 120 patients were screened of which, 105 patients met the entry criteria. Of the 105 patients, 90 patients agreed to give explained, written informed consent and remaining 15 refused to give consent. 22 patients among them either did not meet the inclusion criteria or were excluded due to exclusion criteria. Rest of the 8 patients left due to personal reasons. Hence left with a total of 60 patients. (Figure 1)

Figure 1: Flowchart of participant's profile



These 60 patients were randomly assigned in double blind fashion to the treatment groups (30 were in group A intervention other 30 were in Group B intervention). At the time of analysis the blinding was revealed. And it was "Eyedrops Timolol 0.5%" intervention provided to group A patients and group B patients had received "Eyedrops Travoprost 0.004%"

During study period Group A patients completed their treatment for three months whereas, in Group B) one patient discontinued the treatment at 1st week for irritation and redness of eye and 2 patients were lost to follow-up at 4th week. A total of 57 (30 with group A intervention & 27 with group B intervention) patients had completed the 12 weeks follow-up assessment.

Both completers and dropouts are characteristically similar in baseline symptom severity measures. The data of the patients who had completed the full follow-up of 12 weeks were only analyzed.

Efficacy Parameters

The mean IOP in Timolol group at baseline (0), 2^{nd}, 6^{th}, 9^{th} and 12^{th} week were 27.4 ± 4.9, 24.3 ± 5, 20.2 ± 3.7, 17.5 ± 2.9, 16.1 ± 2.5 whereas the same in Travoprost were 27.0 ± 4.6, 23.4 ± 4.1, 18.7 ± 3. 15.8 ± 2.2, 14.1 ± 1.6. There was no significant difference observed statistically between the two groups in the first two weeks of follow up i.e. 2^{nd} and 6^{th} weeks by independent (unpaired) t – test. But by 9^{th} week onwards statistically significant difference was observed. On 12^{th} week difference was extremely statistically significant.

Baseline mean IOP's of Timolol and Travoprost were 27.4 ± 4.9 and 27 ± 4.6, whereas on 12^{th} week the IOP's were 16.1± 2.5 and 14.1 ± 1.6. The mean reduction of IOP from baseline till 12^{th} week 11.34 ± 0.58 and 12.87 ± 0.65.

The mean reduction of IOP's were extremely significant statistically for both timolol and travoprost with p-value <0.0001. These observations are tabulated in Table 1, 2.

Table 1: Mean IOP's of the patient on medication during week 2, 6, 9 & 12: Comparison of efficacy parameters between the groups

IOP	TIMOLOL (MEAN ± SD)	TRAVOPROST (MEAN ± SD)	P-VALUE
Baseline	27.4 ± 4.9	27 ± 4.6	-
Day 14	24.3 ± 5.0	23.4 ± 4.1	0.436
Day 42	20.2 ± 3.7	18.7 ± 3.2	0.095
Day 63	17.5 ± 2.9	15.8 ± 2.2	0.015
Day 84	16.1 ± 2.5	14.1 ± 1.6	0.0008

Table 2: IOP reduction within the group from baseline to weeks 2, 6, 9 and 12 of follow up for Timolol intervention group.

IOP reduction from baseline (DAY 0) to	Mean difference ± SD	SE of mean	P - value	95% confidence interval	
				Lower limit	Upper limit
Day 14	3.1± 0.12	0.02	<0.0001*	2.419	3.794
Day 42	7.2 ± 1.2	0.41	<0.0001*	6.37	8.05
Day 63	9.9 ± 2.9	0.52	<0.0001*	8.87	11.00
Day 84	11.34 ± 2.4	0.44	<0.0001*	10.152	12.528

*Extremely Significant

Table 3: IOP reduction within the group from baseline to weeks 2, 6, 9 and 12 of follow up for Travoprost intervention group.

IOP reduction from baseline (DAY 0) to	Mean difference ± SD	SE of mean	P - value	95% confidence interval	
				Lower limit	Upper limit

Day 14	3.59 ± 0.54	0.54	< 0.0001*	3.26	3.93
Day 42	8.31 ± 1.37	0.34	<0.0001*	7.62	9.00
Day 63	11.2 ± 2.36	0.55	<0.0001*	10.1	12.33
Day 84	12.87 ± 3.00	0.58	<0.0001*	11.52	14.21

*Extremely significant

There was a significant fall in the IOP with both Timolol and Travoprost. The percentage fall with Travoprost is 47.78% and with Timolol is 41.78%

Safety Parameters (Adverse reaction profile) The drugs given to respective intervention groups were well tolerated with following adverse effects: Timolol group showed more of eye irritation (23.33%) followed by red eye in only 2 patients (6.67%). The Group B (Travoprost) patients showed eye irritation (40.7%), red eye (29.6%), Iris pigmentation (3.7%), eyelash growth (14.8%), periorbital pigmentation (3.7%). The adverse effects red eye and eye irritation were commonly reported in week 2. Iris pigmentation and eyelash growth started showing up by 4^{th} , 6^{th} ,9^{th} week. The one case of "periorbital hyperpigmentation" was very mild and was reported/ observed on 12^{th} week follow up visit.

Although a patient might have two or more clinical adverse events, the patient is counted only once in a category by taking only main adverse event into account.

Table 4: Safety profile of the two intervention groups

Adverse events	**TIMOLOL (30)**		**TRAVOPROST (27)**	
	N	**%**	**N**	**%**
Eye irritation	7	23.33	11	40.7
Red eye	2	6.67	8	29.6
Iris pigmentation	0	0	1	3.7
Eyelash growth	0	0	4	14.8
Periorbital pigmentation	0	0	1	3.7

DISCUSSION

The current study was conducted to study the efficacy and safety of 0.004% travoprost over 0.5% timolol eye drops for the treatment of primary open angle glaucoma or ocular hypertension and to suggest appropriate intervention for the treatment of the disease.

The reduction and control of elevated IOP in OAG or ocular hypertension is classically managed by chronic, long term topical ocular therapy. The prostaglandin analogues are a novel class of intra-ocular tension lowering medication which can be used for the treatment of glaucoma. Travoprost diverges from the traditional IOP lowering agents because it can increase and maintain pulsatile ocular blood flow (pOBF) [(7)] as well as its safer drug with no systemic effect on pulse rate, blood pressure and bronchi.[(11)]

This study was based on the hypothesis that 0.5 % timolol twice daily and 0.004% travoprost once daily given as eye drops will have comparable efficacy in lowering IOP as well as safety parameters.

In accordance with the study conducted by Fellman R.L et. al. which states Travoprost 0.004% has greater efficacy than 0.0015% Travoprost daily [(10)] ,thus in the current study 0.5% Timolol was compared to 0.004% Travoprost.

Baseline variables between both the groups were comparable. At the end of 3 months / 12 weeks there was a statistically significant differences between both the groups in terms of efficacy measured by IOP values, But Travoprost 0.004% once daily was more effective than 0.5% timolol twice daily. Both the drugs were tolerated well.

During the study period, there was clear cut fall in the IOP from baseline to week 12, which favoured more towards treatment with travoprost. A similar study was conducted in 16 different countries across Europe and Australia in 2001 by Goldberg et. al. [(12)] This was a 9 month study which involved 573 patients. The mean difference is slightly higher in the current study. This could be due to difference in sample population and the difference in tonometer as mentioned before.

But the difference between the groups is more or less the same approximately 2 mmHg. (1.6 mmHg in the current study and 1.7 mmHg in Goldberg study).

Orengo-Nania. et al, studies (2001), a prospective, multicentre double blind, randomized parallel group study to evaluate effect of travoprost as adjunctive therapy in patients with uncontrolled IOP while on timolol 0.5 % revealed that travoprost produced clinically relevant and statistically significant additional lowering of intra-ocular pressure reduction from baseline when used adjunctively with timolol. [13] This study also has used two different concentration of travoprost 0.0015% and 0.004%. Similar findings were obtained in another study that evaluated the role of travoprost as an adjuvant.[14]

In the current study travoprost was not evaluated as an add on therapy because: According to Goldmann, after one of the existing effective ocular hypotensive agents lower the IOP it becomes harder to further reduce IOP. Also absolute reduction in IOP more for a given molecule as the initial agent than as an additive agent.[15]

Earlier studies like that of Fellman et. al, showed IOP reductions with travoprost up to 2.0mmHg greater than Timolol [10] so as in the current study. There are no much head to head comparison data available for timolol and travoprost. Probably study conducted by Fellman et al[10] and Goldberg et al[12] were the only head to head comparison available now. The current study methodology was similar to the study conducted by Fellman et. al. Both these have shown that treatment with travoprost has better efficacy than timolol.

The therapeutic role of travoprost in the treatment of glaucoma when compared with latanoprost and bimatoprost differs in that when there is a decrease in IOP it subsequently increases the pulsatile ocular blood flow (pOBF) thus offering neuroprotection from further damage and Cardascsia et. al, 2003 [7] proved this in meticulous study as follows : pOBF is an indirect estimate of optic nerve blood flow. pOBF is estimated from ocular pulse which is directly proportional to perfusion pressure and inversely related to IOP and vascular resistance. Following their study, they demonstrated that treatment with travoprost and latanoprost has a beneficial effect on pOBF by increasing the average flow by day 15 after beginning the treatment which corresponds with peak reduction in the IOP observed on day 15. Thus the increase in pOBF can be interpreted as a direct consequence of IOP lowering. However it was found that only travoprost maintains the increase in pOBF for a longer period. This can be attributed to the greater specificity of travoprost to PG receptors."

Agarwal C.H et al trial, in 2003 studied the effects of changing from concomitant timolol/pilocarpine to bimatoprost monotherapy on OBF and IOP in primary angle closure glaucoma. Bimatoprost monotherapy was found to improve ocular blood flow and provided a better diurnal IOP control than concomitant timolol - pilocarpine and was well tolerated with minor local side effects.[16]

Barnbey et al studies [13] in 2005, conducted a study to compare the safety and IOP lowering efficiency of Fixed combination of travoprost 0.004% and timolol 0.5% dosed once daily in the morning is superior in reducing mean IOP compared with either single agent therapy. But the side effects are similar to travoprost when given alone as monotherpay. In the current study we did not use a fixed drug dose combination to avoid bias.

Fundoscopy was done at last 12th week visit but no significant change related to glaucoma was seen in any of the subjects.

In the current study, commonly observed complications were hyperaemia and eye irritation was statistically significant in both the groups. The rates of both of these complications were observed to be higher in travoprost group. Both of these were self-limiting condition which resolved spontaneously. In all the studies mentioned above the most common side effect with both the drugs was ocular hyperaemia or redness of the eye.[9-12, 17, 18]. Only one patient from travoprost group withdrew from the study due to irritation and redness of eye.

Other complications observed in the travoprost group were eyelash growth, iris pigmentation and periorbital hyperpigmentation. The eye irritation in the current study includes all

subjective symptoms like pruritus, pain, dry eye, foreign body sensation and discomfort which have been estimated separately in Fellman et al study.[10] No patients discontinued from the study due to eyelash growth, iris pigmentation or periorbital hyperpigmentation.

The ocular side effects of bimatoprost, like redness and itching, was found to be more in incidence and severity when compared with travoprost. 6.3 % of the patients developed eyelash growth whereas none developed it in travoprost group in a study conducted by Chander et al.[17] Thus proving that it takes longer time with travoprost to develop side effects like eyelash growth and iris pigmentation, as proved in various other trials.[9, 10, 12, 13, 17-22]

Thus timolol has better local tolerance when compared with patients who received travoprost. Park Juan et et. al. conducted a clinical investigation on changes to upper eye lid orbital fat from use of topical bimatoprost, travoprost and latanoprost. The mean adipocyte density of bimatoprost was found to be maximum indicating maximal atrophy followed by travoprost. Latanoprost did not have a statistically significant increase in density. No deepening of orbital sulcus was seen in the current study. This is because fat atrophy changes take place more than a year.[23]

A systematic review by Slattery in 2016, pointed out that large cross - sectional studies as well as retrospective case reviews of monocular Prostaglandin analogues users have demonstrated its chronic use is associated with upper eye lid ptosis, meibomian gland dysfunction, periorbital fat atrophy leading to sunken eyes. These effects are more pronounced with bimatoprost than with travoprost. In the current study these side effects could not be evaluated since this takes years to develop.[24]

Strengths of the study were, this study included homogenous population: Since all the patients were enrolled from same city the population will have more or less the same baseline characteristics and lesser degree of inter - individual changes. Head-to-head studies: This might be one of the few head on head comparisons study. Probably first study among Indian population. After an extensive search with the limited resources, no studies were found to be conducted among Indian population that compares timolol with travoprost so far.

There were some limitations present in the study short study duration: Patients were treated only for 12 weeks for changes in visual field it takes more than a year. It is known that for prominent changes in iris color and eyelash changes it takes more than 2 – 3 months whereas for periorbital atrophy it takes more than 6 months to year. Inclusion of both POAG and OHT: Patients with OHT have been reported to have ocular haemodynamics that differ from those of patients with POAG. Single reading at various time points : An ideal agent for treatment of glaucoma should consistently lower intraocular pressure with minimal fluctuations and maintain its efficacy throughout 24 hours.[26] In the current study only one reading was taken whenever the patient presented to the OPD. Hence diurnal fluctuations could not be noted. Single centre study: This current study was a single centre study. Replication and extension of this work are needed to determine how generalizable the findings are. Since even within India there is a wide range of genetic polymorphisms. Very small sample size: This may have affected the statistical power of findings for secondary analyses. Other parameters: This study did not take into account the visual field changes, due to non-availability of perimeters in the centre where study was conducted. Intention to treat analysis: It was not done to deal with missing data in the current study Subjective adverse effects reporting: Adverse effects were obtained exclusively from patient reporting.

It is necessary to do studies in ocular hypertension and primary open angle glaucoma with prostaglandin analogues like travoprost especially with adequate sample size and longer duration for the following reasons: To evaluate the long-term side effects of travoprost. To evaluate if patients develop resistance to treatment like in case of timolol where an add on drug is required later. To determine duration of treatment until which travoprost has effect on maintaining pulsatile ocular blood flow and other ocular haemodynamics.

For now, with this study, we can safely say Travoprost can be considered as first line monotherapy in a government hospital if it's

made available at lower cost especially for POAG patients who have high IOP. This drug also ensures a better compliance due to single dosing. Timolol can be used as reserve drug for very high IOP in angle closure glaucoma and other types of glaucoma.

CONCLUSION

Travoprost 0.004% eye drops once daily lowers the intra-ocular pressure significantly more than Timolol 0.5% eye drops twice daily. Though timolol has shown better ocular tolerance than travoprost, both drugs were well tolerated and found to be safe for use in patients with open angle glaucoma.

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