ORIGINAL ARTICLE

Real-life experience study of the safety and efficacy of travoprost 0.004% / timoptol 0.50% fixed combination ophthalmic solution in intraocular pressure control

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Abstract

Purpose: To evaluate the safety and efficacy of timolol 0.5%/travoprost 0.004% combination (duotrav) as observed in primary open-angle glaucoma (POAG), ocular hypertension (OHT) and normal tension glaucoma (NTG) in real-life conditions.

Materials and Methods: Patients with uncontrolled intraocular pressure (IOP) on other medication and no contraindication to β-blockers were switched to duotrav in 56 eyes of 28 patients. The drop in IOP was the primary outcome measured.

Results: Switch to duotrav provided an additional IOP reduction after 3-month follow-up that was statistically significant for those on latanoprost (*P*=0.02857), bimatoprost (*P* =0.04978) and travoprost (*P* =0.0078). Patients on latanotrost had an additional 25.9% drop 3 months after switching to duotrav while those on bimatoprost and travatan had 18.04% and 17.59% drop, respectively, after the switch. It was effective in lowering the IOP to clinically significant levels of ≤18.5 mmHg in POAG, NTG and OHT (12.5-17.9% drop), but not in chronic angle closure glaucoma.

Conclusion: Duotrav was well-tolerated and produced significant additional IOP reduction when switched from other anti-glaucoma drugs in patients with uncontrolled glaucoma. It also achieved IOP of ≤ 18.5 mmHg in glaucoma patients.

Key words: Additional lowering, compliance, intraocular pressure, timolol, travoprost

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Introduction

Intraocular pressure (IOP) control remains the cornerstone in glaucoma management because, although the disease has multiple risk factors, modulating the IOP is the only proven strategy in reducing the risk of progressive retinal ganglion cell death. Ganglion cell death results in visual field loss and unacceptable quality of life.

Drugs play a frontline role in IOP reduction in glaucoma and for years, β-blockers were the leading medicines in use because of their capacity to slow the rate of aqueous humour production.[1-3]

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In the past decade and half, newer generation of anti-glaucoma drugs have emerged making this role even more significant. The prostaglandin (PG) analogs and prostamides are one such group.

Travoprost (Travatan ophthalmic solution, Alcon laboratories, Inc., Ft. Worth, TX) is a prostaglandin PGF2 -synthetic analog that is rapidly metabolized by corneal esterases to its active free acid. This has a high affinity

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for and full agonist efficacy at the FP receptor[4] and it is believed that interaction between the free acid and the FP receptor leads to structural changes within the ciliary body that facilitates aqueous outflow via the uveoscleral pathway.[5,6] Travoprost is safe and quite potent in lowering IOP and is now one of the first-line agents for IOP control in glaucoma.

However, monotherapy has been found inadequate in achieving targeted IOP control in 40% of patients[7] and therefore multidrug therapy is common in glaucoma management. This is usually prescribed as separate bottles or in fixed combination where possible. Separate bottles prescription has several drawbacks–low compliance rate, more preservatives and so likely more side effects and higher cost.

Travoprost and the β-blocker timoptol fixed combination (Duotrav) is one with complimentary mechanisms of action and with the advantage of reducing the concerns associated with using separate bottles. Earlier studies on this fixed combination have been carried out in clinical predesigned settings such as stopping earlier antiglaucoma medicines to allow for the washout periods and choosing the specific types of glaucoma for the study. While running clinics, however, we know that drug modifications in the event of lower than expected performance of earlier one (s) is effected without recourse to the above.

The purpose of this study was therefore to evaluate the safety and efficacy of this fixed combination (Duotrav) as observed in day-to-day glaucoma clinic conditions.

Materials and Methods

This was a nonrandomized prospective interventional study, carried out in the department of Ophthalmology, Pilgrim Hospital, Boston, England.

The already existing specialist glaucoma clinics run by two experienced ophthalmologists were used for the study.

Patients on regular follow up for primary open-angle glaucoma (POAG), normal tension glaucoma (NTG), ocular hypertension (OHT), chronic angle closure glaucoma (CACG), with inadequately controlled IOP/progressive disease on other medications and/or post-glaucoma surgery who fulfilled the following criteria were recruited.

1. All sex, race and age >18years.
2. No inflammatory or rubeotic glaucoma
3. No known contraindication to β-blocker or PG use.
4. No documented side effect from other antigalucoma medication

The patients were seen in the regular clinic setting during morning (09.00–13.00 hrs), afternoon (14.00 –17.00 hrs and evening (17.00–19.00 hrs) sessions and once a case was identified as suitable (vida supra), detailed ocular examination was repeated and these included best corrected vision, slit lamp examination of the anterior segment looking for anterior chamber inflammatory cells, IOP, gonioscopy, dilated fundoscopy and visual field. The IOP was measured with the Goldman applantion tonometer and optic disc assessed with the +78D or +90 D aspheric lens. Also documented was the type of glaucoma, the IOP at the time of initial diagnosis as well as that before commencement of the new treatment. For the purpose of this study, the IOP before the commencement of the duotrav eye drop was taken as the baseline.

All previous treatment for the disease was recorded and the patients told that the treatment required some modification aimed at better control of the IOP and thus the disease. Informed consent was sought, potential adverse effects explained and what to do if any occurred fully communicated to each one before whatever treatment the patient was on replaced with the fixed combination of timolol 0.5% and travoprost 0.004% fixed combination (duotrav) once daily. Each patient was reviewed at 3 months or earlier if indicated at the same period (morning or evening clinic) of the day when the duotrav was commenced.and the vision, slit lamp findings, fundoscopy, IOP, fields as well as any side effects (local and systemic) recorded.

Data analysis: Statistical analysis for efficacy and was based on protocol analysis of 50 eyes (25 subjects) while safety was based on 52 eyes (26 subjects). The primary efficacy outcome was mean IOP at the time of the 3-month follow-up compared with the baseline values of the intent- to- treat data set. Secondary efficacy variables included change in mean IOP from baseline in the different types of glaucoma and the total IOP drop from onset of diagnosis.

Potential relationship of any adverse events to the medication while on the treatment was evaluated by the investigators.

Analysis was performed by the SPSS.V16 for Windows. The tests for statistically significant differences between variables were performed using the Wilcoxon W test for nonparametric data. Two-tailed *P*-values <0.05 were taken to indicate significance.

Results

Fifty-six eyes of —28 patients were enrolled for the study of which 13 were females and 15 males. The mean age was 70 years (range 37-91). All were Caucasians.

Sixteen patients had POAG, six low tension glaucoma (LTG), four OHT and two CACG (post-YAG laser iridotomy).

Sixty percent of the patients were on monotherapy before the switch (β-blockers 4, latanoprost 4, bimatoprost 6 and travoprost 16). The others were combinations of β-blockers and PGs but not duotrav (8) and carbonic anhydrase inhibitors and β-blockers (12).

One patient with LTG relocated and another one with POAG failed to attend the 3-month follow-up clinic. One patient with POAG developed severe ocular redness with associated swelling within 4 weeks of treatment and the drug was discontinued.

Additional IOP lowering that was statisitcally significant ($P<0.05$) was seen in patients on latanoprost (5.25 mmHg; 25.9 % drop), bimatoprost (4.33 mmHg; 18.04% drop) and travoprost (3.38 mmHg; 17.59% drop) on switching to the Duotrav [Table 1 and Figure 1]. Although there was 3 mmHg (14.3%) drop for those switched from the β-blockers, this did not reach statistical significance ($P= 0.5714$). No significant IOP drop was achieved on switching from β-blockers plus other PGs or other combinations.

The fixed combination produced clinically relevant IOP reduction from baseline [Table 2 and Figure 2] for patients with OHT, POAG and LTG, but not those with CACG. For those with POAG and NTG, statistically significant ($P<0.05$) reduction was achieved.

The mean IOP reduction was ≤18.5mmHg (12.5-17.9% drop) in those with POAG, NTG and OHT. As shown in Figure 2, the degree of IOP drop for each case from the time of diagnosis was quite significant for the three types of glaucoma. The mean IOP was, however, higher post-duotrav in the CACG group.

Two patients with POAG developed marked lid and conjunctival swelling and redness–one occurring a week to onset of treatment and the other 3 weeks into it. The drug was discontinued in both cases but a third that developed mild and transient conjunctival hyperemia remained on the course. None had any anterior chamber inflammation or systemic side effect. Thus withdrawal of treatment as a direct result of adverse effect from the drug occurred only in 3.84% of cases.

Discussion

IOP control remains the most significant strategy for glaucoma treatment and drugs are known to do this quite well. The clinical efficacy of multiple drug therapy is well

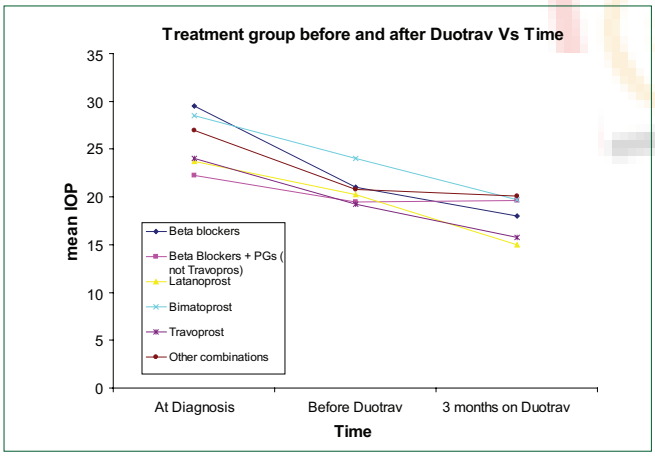

Figure 1: Additional IOP lowering effect after switch to duotrav

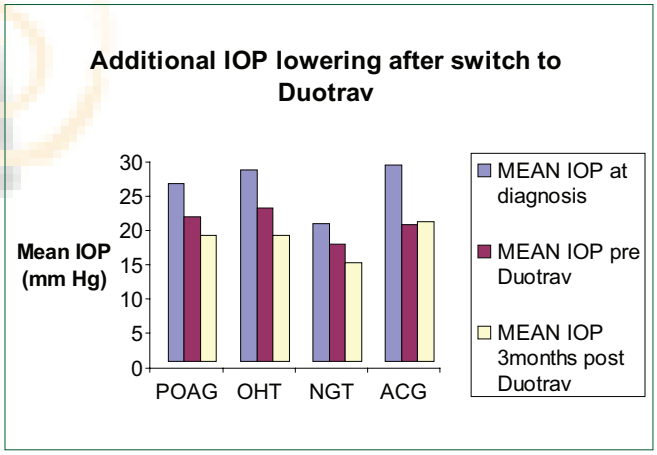

Figure 2: The mean intraocular pressures at diagnosis, on other treatments and 3 months after replacement with travatan/timolol fixed combination

Table 1: Differences in intraocular pressure at baseline and 3 months after the switch

Drug (s)/ Treatment	Mean Intraocular pressure (mmHg)					
	Diagnosis	Before duotrav	3 months on duotrav	Intraocular pressure drop (%)	SD	*P*-value
β-blockers	29.5	21	18	-3 (14.3)	2.944	0.5714
β-blockers + Prostaglandins (not travoprost)	22.25	19.5	19.6	+0.125 (0.64↑)	3.889	0.8545
Latanoprost	23.75	20.25	15.0	-5.25 (25.9)	1.414	0.02857
Bimatoprost	28.5	24	19.67	-4.33 (18.04)	3.669	0.04978
Travoprost	24	19.2	15.8	-3.38 (17.59)	3.600	0.0078
Other combinations	27	20.8	20.08	-0.75 (3.59)	3.629	0.6236

Table 2: Mean intraocular pressures before and 3 months post-tomolol/travatan fixed combination for the different types of glaucoma

Type of glaucoma	Mean intraocular pressure (mmHg)					
	Diagnosis	Pre-duotrav	3 months on duotrav	Intraocular pressure drop (%)	SD	*P*-value
Ocular hypertension	28	22.4	18.4	-4.00 (17.9)	4.71	0.1064
Primary open-angle glaucoma	26	21.14	18.5	-2.64 (12.5)	3.58	0.0027
Normal tension glaucoma	20.2	17.1	14.4	-2.7 (15.8)	3.17	0.0284
Chronic angle closure glaucoma	28.8	20	20.5	+0.50 (↑2.5)	1.91	0.5714

proven but the drawback (low compliance, more side effects, less tolerance, higher cost, etc.) from the patients perspective has made fixed combination formulations attractive. In the study by Patel and Speath,[8] it was shown that percentage compliance rose from 51.1 % for patients on multiple topical medications to 67.7% for those on monotherapy. This difference becomes even more significant against the backdrop of the evidence that 70% of blindness in glaucoma patients on treatment is due to drug non-compliance.[9]

Concomitant use of PG and β-blocker led to further IOP reduction as against levels achieved by either drug possibly due to their synergistic mechanism of action. The β-blocker reduces aqueous secretion thereby reducing the preload, while the PGs increase the uveoslceral outflow and so reduce the aqueous volume leading to low IOP.

Orengo-Nania and associates[10] have demonstrated the efficacy of this combination in their study where timolol 0.5%/travoprost 0.004% combination (with the travoprost as an adjunct) was shown to lower the IOP by 23.1–27.7% from baseline.

Other studies[11,12] done which involved washout of the earlier anti-galucoma medications before commencing the dosing with the timolol 0.5% /travoprost 0.004% fixed combination showed similar clinically and statistically significant IOP reduction from baseline.

We, however, carried out our study as we would have the patients in real-life conditions. In the study, patients came in for the routine glaucoma follow-up evaluation and once the drug(s) he/she was on was found inadequate in lowering the IOP to the expected target level, this was switched to the timolol 0.5%/travoprost 0.004% fixed combination (Duotrav) once suitability has been ascertained. The 3-month follow-up results showed additional IOP reduction that was statistically significant for those on latanoprost (P=0.02857), bimatoprost (P =0.04978) and travoprost (P =0.0078). Patients on latanotrost had an additional 25.9% drop 3 months after switching to duotrav while those on bimatoprost and travatan had 18.04% and 17.59% drop, respectively, after the switch. These results did not differ from those of Raber[13] in his multicenter study under similar clinic conditions. Although, the drop for those who were initially on β-blockers alone did not reach statistical significance (P=0.5714), the 14.3 % drop was clinically significance considering that 1 mmHg IOP drop reduces the risk of visual field loss by 10%.[14] The study, however, showed that switching from other combinations or β-blockers/other PGs to duotrav did not lower the IOP to significant levels.

The study also demonstrated that this fixed combination reduced IOP equally well in OHT, POAG and NTG (between 12.5 and 17.9% additional IOP drop). The drop I patients with POAG (P=0.0027) and LTG (P =0.0284) reach statistical significance. However, it was unsuitable in cases of CACG. Although the data for this group was small, the non-response could not be explained by the mechanism of action of the drugs, since timolol reduces the preload and the PGs act via the uveoslceral outflow. The main drawback of the study was the small number of patients though the results still corroborated other similar ones. Also, there was no wash-off period to enable independent effect of the duotrav to be observed. However, the results should be considered clinically relevant because, in real life this is what patients and clinicians do.

Only in 7.6% of cases was the drug withdrawn because of side effect. The fixed combination has less preservative compared to the individual bottles, and this improves its tolerability.

Our study has demonstrated the effectiveness of duotrav in IOP reduction and its safety. These, coupled with the fewer dosing and possibly less cost compared with the individual drugs, should improve compliance. Better compliance would in turn lead to lower risk of disease progression and sustained good quality of life; the primary goal of glaucoma management.

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