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Evaluation of Topical Monotherapy for Early Primary Open Angle Glaucoma Patient

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ABSTRACT

Background: primary open-angle glaucoma is asymptomatic optic neuropathic ocular disease characterized by enlarging optic disc cupping and visual field loss. World Health Organization estimated in a systemic review that glaucoma is the second commonest cause of blindness worldwide and topical ocular hypotensive medication was effective in delaying the onset of open angle glaucoma in individuals with elevated ocular pressure. **Aim of the work**: the study aimed to evaluate the safety and pressure-lowering efficacy of travoprost (0.004%) compared to timolol 0.5% and compared to brimonidine tartrate 0.2% as monotherapy in patients with primary open-angle glaucoma

Patients and methods: patients were randomized to 3 groups, the first group was received travoprost 0.004%, the second group was received timolol 0.5% and the last group was received brimonidine tartrate 0.2%. This study was carried out in Menoufia University during the period from January 2016 to January 2017.

Result: this study included 45 patients who were randomized to 3 groups, the first group received prostaglandins analogue, the second group received beta blockers and the last group received alpha agonists. Collected data indicated that the intraocular pressure–lowering efficacy of travoprost was significantly better compared to timolol and brimonidine at months 3, 6, 9, 12 (P <.001).

Conclusion: using primary monotherapy, the intraocular pressure–lowering efficacy of travoprost 0.004% was superior to timolol 5% and superior to brimonidine tartrate 0.2% in patients with primary open-angle glaucoma. Travoprost, timolol and brimonidine reduced intraocular pressure effectively in primary open angle glaucoma.

Keywords: glaucoma, intraocular pressure, prostaglandin analogues, beta blockers, alpha agonists.

INTRODUCTION

Primary open-angle glaucoma (POAG) is asymptomatic, progressive optic neuropathic ocular disease characterized by enlarging optic disc cupping and visual field loss. World Health Organization (WHO) estimated in a systemic review that glaucoma is the second commonest cause of blindness worldwide.

Elevated intraocular pressure (IOP) caused characteristic acquired optic atrophy of the optic nerve and loss of retinal ganglion cell and their axon. Visual acuity is the key player when assessing blindness in developed countries [(1)].

Topical ocular hypotensive medication was effective in delaying or preventing the onset of POAG in individuals with elevated IOP. Although this does not imply that all patients with borderline or elevated IOP should receive medication, clinicians should consider initiating treatment for individuals with ocular hypertension who was at moderate or high risk for developing POAG. Topical medication was changed and/or added until both of these goals were met or the participant received maximum-tolerated topical medical therapy. Medications were added and changed in one-eyed therapeutic trials [(1)].

There are five main groups of glaucoma drugs, each acting in a different way to reduce IOP and each group may be used as mono therapy or in combinations as the following. Prostaglandin analogues (bimatoprost, latanoprost and travoprost) increased uveoscleral outflow [(2)].

Beta-blockers consist of two main groups: selective (betaxolol) and non-selective (timolol, levobunolol), both of which decreased aqueous production [(2).]

Alpha-2 adrenergic agonists (apraclonidine, brimonidine and may open the drainage angle in angle-closure glaucoma by stimulating the iris sphincter muscle.), decreased aqueous production and increased uveoscleral outflow [(2)]. Inhibitors of carbonic anhydrase enzyme decreased aqueous formation and can be applied topically (brinzolamide, dorzolamide) or systemically (acetazolamide, methazolamide) [(2)].

Parasympathomimetics (pilocarpine, carbachol) increased aqueous outflow through the trabecular meshwork by means of ciliary muscle contraction[(2)].

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list of abbreviations

Vocabulary	Meaning
C/D	Cup/Disc ratio
CAI	Carbonic anhydrase inhibitor
COX	Cyclooxygenase
CME	Cystoid macular edema
EMGT	Early Manifest Glaucoma Trial
FP	F prostaglandin receptor
GAT	Goldmann applanation
IOP	Intra-ocular pressure
LIID	Latanoprost induced iris darkening
NFL	Nerve fiber layer
OCT	Optical coherence tomography
PG	Prostaglandin
PAC	primary angle-closure
POAG	Primary Open Angle Glaucoma
ANOVA	one-way analysis of variance

PATIENTS AND METHODS

All subjects were given written informed consent before inclusion into the study. This was a prospective study that was carried out in Menoufia University Ophthalmic Hospital, Cairo Fatimic Hospital and Al. Rowad Eye Center during the period from January 2016 to January 2017. Patients were randomized to 3 groups, the first group received prostaglandins analogue as a monotherapy (travoprost 0.004%), the second group received beta blockers as a monotherapy (Timolol 0.5%) and the last group received alpha agonists as a monotherapy (brimonidine tartrate 0.2%).

Inclusion Criteria: this study included patients who fulfilled the following **Eligibility criteria**: patients aged over 40 years, intraocular pressure (IOP) between 20 mm Hg and 28 mm Hg., patients who had no systemic disease that impaired visual acuity (as diabetis mellitus), gonioscopically open angles, early visual field changes characteristic for glaucoma, early optic disc changes of glaucoma seen at clinical examination (vertical cup disc ratio not more than 0.6) and mild thinning of Nerve Fiber Layer (NFL) by optical coherence tomography (OCT).

Exclusion criteria: patients with the following criteria were excluded from this study: patients younger than 40 years old, visual acuity worse than 20/40, patients with history of previous intraocular surgery, patients with history of other diseases capable of causing visual field loss or optic disc deterioration (Diabetis mellitus or neurological diseases) and patient with diseases that contraindicate receiving topical therapy as bronchial asthma, cardiac asthma or light colored iridis.

Every patient included in this study was subjected to:

Detailed history taking, uncorrected visual acuity and best corrected visual acuity (UCVA and BCVA) measurements, slit lamp biomicroscopy examination, Goldmann applanation tonometry, gonioscopic examination, fundus examination, visual field test (perimetry) and OCT for retinal nerve fiber layer.

Patients who met the inclusion criteria at the screening visit and were taking glaucoma medications underwent a washout period (in which all glaucoma medications were discontinued) of 3 weeks for β-antagonists and prostaglandins, 2 weeks for α and α/β agonists, 5 days for miotics, 5 days for oral or topical carbonic anhydrase inhibitors, and 3 days if no ocular hypotensive medications were being used.

This study visits included diurnal time points to allow frequent safety and efficacy monitoring and included two eligibility visits for baseline data and on-therapy planned visits at 2 weeks and at months 1,3, 6, 9 and 12.

Examinations were performed at 8 AM, 10 AM, and 4 PM for the eligibility 1 and 2 visits and study visits at 2 weeks and at months 1,3, 6, 9 and 12. Examinations for the study visits were performed as follows: intraocular pressure, hyperemia and flare/ cells assessment, visual acuity, biomicroscopy and resting pulse and blood pressure. Two different, trained individuals (a reader and an operator) determined intraocular pressure measurements with a recently calibrated Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland). Hyperemia assessment was made in ambient light, before intraocular pressure measurements and instillation of fluorescein, by the same masked observer throughout the study using a standard set of photographs depicting ocular hyperemia.

The visual field evaluation was performed with Humphrey Field Analyzer (Humphrey Instruments, Inc, San Leandro, California) program 24-2.

Patients who were randomized to prostaglandin group received travatan eye drops (Travoprost 0.004%) once daily. Patients who were randomized to beta-blocker group received timolol eye drops (Timolol 0.5 %) twice daily;

whereas patients who were randomized to alpha-blocker group received Alphagan eye drops (Brimonidine tartrate 0.2%) twice daily. Patients were instructed to instill one drop in each eye at 8 PM or bed time for prostaglandin group. Patients were instructed to instill one drop in each eye at 8 AM and at 8 PM for beta-blocker group and alpha-blocker group.

Drugs manufacturer details

Travatan (Alcon, Fort Worth, Texas, United States of America), Timolol (eipico,10th Ramadan,Cairo,Egypt), Alphagan (Pfizer and Allergan, New York, United States of America).

The study was approved by the Ethics Board of Menoufia University.

Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 19.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software BVBA, Ostend, Belgium).

Normality of numerical data distribution was examined using the Shapiro-Wilk test. Normally distributed numerical variables were presented as mean ± SD and intergroup differences were compared using the unpaired t test (for two-groups comparison) or one-way analysis of variance (ANOVA) (for multiple-groups comparison), The Tukey-Kramer post HOC test was applied when ANOVA revealed a statistically significant difference among the groups. Categorical variables were presented as ratio or number and percentage and intergroup differences were compared using Fisher's exact test. Time to event analysis was done using the Kaplan-Meier method.

RESULTS

This study included 45 patients and they were randomized to 3 groups, the first group received prostaglandins analogue as a monotherapy (travoprost 0.004%), the second group received beta blockers as a monotherapy (Timolol 0.5%) and the last group received alpha agonists as a monotherapy (brimonidine tartrate 0.2%), Collected data over treatment visits, indicated that the intraocular pressure–lowering efficacy of travoprost was significantly better compared to timolol and brimonidine at months 3, 6, 9, 12 (P <.001) **(Table1).**

The mean time to achieve target IOP in the three studied groups was 2.2 ± 0.4 weeks for prostaglandin group, 2.4 ± 0.6 weeks for Beta-blocker group and 2.9 ± 0.6 weeks for alpha-agonist group. There were clinically significant differences between the studied groups regarding time to achieve target IOP (P = 0.044) **(Table2)**.

As regard visual field improvement, there were no significant differences in the mean change from baseline in improvement of visual field between the studied groups except at 6th month evaluation (P = 0.020),the alpha agonist did not achieve any improvement of visual field**(Table3).** As regard RNFL, there were no differences in the mean change from baseline of the RNFL with average thickness 97.00um, (p =0.028) in improvement of between study group **(Table4).**

No serious related adverse events were reported in this study and adverse events that were reported were usually mild to moderate effect and resolved without treatment. There were no significant differences between the studied groups regarding drug-related adverse effects. The most frequent ocular adverse events included hyperemia, lashes changes, local irritation، discomfort, and itching. Ocular and non-ocular adverse events reported at an incidence of greater than 3% were identified in **table 5.**

LEGEND OF TABLES

Table (1): **Intraocular pressure in the three study groups**

		Prostaglandin (number=90)	**Beta-blocker (number=90)**	**Alpha-agonist (number=90)**	**p-value**
Intraocular pressure in millimeter mercury(mmHg)	Baseline	25.8 ± 1.1	26.1 ± 1.2	25.9 ± 1.1	0.650
	3 months	15.4 ± 1.5	17.6 ± 1.5	18.1 ± 1.6	<.001
	6 months	14.1 ± 2.1	16.0 ± 1.7	17.3 ± 1.8	<.001
	9 months	12.1 ± 1.3	13.5 ± 2.0	15.8 ± 2.1	<.001
	12 months	11.5 ± 0.8	12.4 ± 1.1	14.8 ± 1.6	<.001

* P<0.05 is significant

Table (2): Time to achieve target Intraocular pressure in the three study groups

	Prostaglandin group (number=15)	**Beta-blocker group (number=15)**	**Alpha-agonist group (number=15)**	**p-value**
Time to achieve target intraocular pressure (weeks)	2.2 ± 0.4	2.4 ± 0.6	2.9 ± 0.6	0.044

* P<0.05 is significant

Table (3): improvement of visual field in the three study groups

	Time	**Prostaglandin (number=90)**	**Beta-blocker (number=90)**	**Alpha-agonist (number=90)**	**p-value**
Improved visual field	3 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	Insig.
	6 months	6 (20.0%)	6 (20.0%)	0 (0.0%)	**0.020**
	9 months	7 (23.3%)	3 (10.0%)	2 (6.7%)	0.218
	12 months	2 (6.7%)	2 (6.7%)	0 (0.0%)	0.540

* P<0.05 is significant

Table (4): **Optical coherence tomography of nerve fiber layer in the three study groups:**

	Time	**Prostaglandin (number=90)**	**Beta-blocker (number=90)**	**Alpha-agonist (number=90)**	**p-value**
Improvement of optical coherence tomography of nerve fiber layer	Average thickness	96.8um	97.2um	97.00um	0.028
	3 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	Insig.
	6 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	Insig.
	9 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	Insig.
	12 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	Insig.

* P<0.05 is significant

Table (5): **Drug-related adverse effects in the three study groups**

Drug-related adverse effects	**Prostaglandin group (number=15)**	**Beta-blocker group (number=15)**	**Alpha-agonist group (number=15)**	**p-value**
Conjunctival hyperemia	5 (33.3%)	2 (13.3%)	2 (13.3%)	.452
Local irritation	7 (46.7%)	6 (40.0%)	2 (13.3%)	.139
Lash changes	3 (20.0%)	0 (0.0%)	0 (0.0%)	.096
Periorbital pigmentation	1 (6.7%)	0 (0.0%)	0 (0.0%)	1.0
Burning / itching sensation	7 (46.7%)	5 (33.3%)	0 (0.0%)	.927

* P<0.05 is significant

DISCUSSION

Elevated intraocular pressure (IOP) is a risk factor contributing to optic nerve damage and subsequent visual field loss. Therefore, control of IOP in patients with glaucoma or ocular hypertension is the primary goal of successful glaucoma therapy [(3)].

All major clinical trials such as ocular hypertension treatment study (OHTS), early manifest glaucoma trial (EMGT) and advanced glaucoma intervention study (AGIS) showed that reduction of IOP slows down glaucoma damage. So IOP level is very important in determining visual field loss. Question is which level of IOP is safe? The European Glaucoma Society Guidelines suggested that treatment should aim at achieving at least a 20% reduction from the initial pressure at which damage occurred or in advanced glaucoma to lower IOP to a level below 18mmHg. A study showed that maintaining IOP

below this pressure reduced the risk of both the development and progression of glaucoma [4].

Topical nonselective β-blockers, such as timolol had been used as first-line therapy for elevated IOP because of their familiarity and IOP-lowering efficacy. The potential side effects of nonselective β-blockers on pulmonary, cardiovascular and central nervous system function are well known. A reduction in cardiovascular output caused by heart block and/or fall in blood pressure may occur secondary to systemic absorption of topical nonselective β-blockers. Patients with reactive airway disease and chronic obstructive pulmonary disease may be at significant risk for further airway compromise. Consequently, this class of drugs is usually contraindicated in these patients [5]. Prostaglandin (PG) analogues represented a class of potent ocular hypotensive agents were shown to effectively reduce IOP equivalent to nonselective β-adrenergic antagonists without the side effects associated with β-blockers. The most common side effects associated with PG analogues were ocular hyperemia, increased eyelash growth، eyelid skin darkening and change in iris pigmentation. Anterior uveitis and cystoid macular edema (CME) had been reported in some patients using PG analogues؛ thus their use may be contraindicated in those patients with a history of uveitis or recent ocular surgery[3]. Travoprost is a synthetic PG analogue. The reduction of IOP by PGF2α is largely caused by increased uveoscleral outflow of aqueous humor and because travoprost is a PGF2α analogue, it is thought that reduction of IOP by travoprost is primarily through the uveoscleral pathway [6].

Brimonidine is a highly selective α2-adrenergic agonist approved for the treatment of open-angle glaucoma. When applied to the eye, brimonidine activates α2-adrenergic receptors, resulting in decreased aqueous humor production and increased uveoscleral outflow. These effects on aqueous humor dynamics led to a reduction in intraocular pressure [7].

This study was designed to evaluate the safety and IOP-lowering efficacy of travoprost (0.004%) compared to timolol 0.5% and compared to brimonidine tartrate 0.2% as monotherapy in patients with primary open-angle glaucoma. When used as primary therapy, the results of this study showed that travoprost were superior to timolol and superior to brimonidine in lowering intraocular pressure at all treatment visits in patients with open-angle glaucoma.

A conservative approach was taken in the analysis of intraocular pressure response to treatment using criteria of 30% or greater intraocular pressure reduction from diurnal baseline or a final intraocular pressure of 17 mm Hg or less. The mean intraocular pressure reduction at the end of this study was 14.3 mmHg for travoprost compared to 13.7 mmHg for timolol and 11.1 mmHg for brimonidine [7].

Goldberg and his colleagues in their study have shown that mean intraocular pressure, which was combined across study visits, was lower with travoprost 0.004% than with timolol 0.5%. The mean intraocular pressure reductions ranged from 6mmHg to 8.1mmHg for travoprost compared to timolol, which ranged from 4.7 to 7.1mmHg [4].

Fellman *et al*. reported that mean IOP reductions ranged from 6.5 to 8.0 mmHg with travoprost 0.004% vs 5.2 to 7.0 mmHg with timolol 0.5% While, **Cantor *et al.*** reported mean IOP reductions for travoprost ranged from 4.6 to 7.2 mmHg (19%-29%) vs 7.4–8.8 mmHg (34%–36%) for bimatoprost [8].

Dubiner *et al.* found that the mean reduction of IOP from baseline at month 3 was 6.8mmHg with brimonidine and 6.5mmHg with lantanoprost . Another study reported a mean IOP reduction of 20 – 35% with latanoprost and 16-26% with brimonidine [9].

In a meta-analysis of studies of open angle glaucoma medications showed generally that in patients with POAG the prostaglandins were the class of medicine with the greatest 24-hour reduction from untreated baseline (24%–29%), of which bimatoprost and travoprost showed the greatest efficacy. Timolol, a β -adrenergic blocker, demonstrated a 24-hour reduction (19%) equal to that of dorzolamide, a carbonic anhydrase inhibitor. The α-adrenergic agonists (i.e., brimonidine, dosed twice daily) manifested a 24-hour pressure decrease (14%) [10].

Netland *et al*. reported that travoprost was equal or superior to latanoprost and superior to timolol with mean intraocular pressure over visits and time of day ranging from 17.9 to 19.1 mm Hg (travoprost 0.0015%), 17.7 to 19.1 mm Hg (travoprost 0.004%), 18.5 to 19.2 mm Hg (latanoprost)، and 19.4 to 20.3 mm Hg (timolol) [11]. All treatment-related ocular adverse events were more frequent after travoprost than after timolol or brimonidine. No serious, related adverse events were reported in this study and adverse events that were reported were usually mild to moderate and resolved without treatment. There were no significant differences between study groups regarding drug-related adverse effects.

Other ocular adverse events included discomfort and pruritus. Brimonidine tartrate 0.2% was well tolerated systemically, with no clinically significant changes from baseline in blood pressure or heart rate observed during the study period. These findings are consistent with those of a previous study that found no reduction in heart rate following treatment with brimonidine [(9)].

Katz reported that treatment with brimonidine or timolol was associated with a similar incidence of adverse events. More patients receiving timolol reported ocular burning and stinging, while ocular allergic reactions, conjunctival follicles, lid edema, and dry mouth were observed more frequently in patients received brimonidine [(9)].

CONCLUSION

The present results indicated that when used as primary monotherapy the intraocular pressure–lowering efficacy of travoprost (0.004%) was superior to timolol 5% and superior to brimonidine tartrate 0.2% in patients with primary open-angle glaucoma. Travoprost, timolol and brimonidine reduce IOP effectively in POAG. All the three drugs were well tolerated and safe for use in newly diagnosed patients of primary open angle glaucoma.

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