ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 6 | June - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

COMPARISON OF IOP LOWERING EFFECT OF LATANOPROST AND BIMATOPROST FOR THE TREATMENT OF POAG WHEN USED TOPICALLY

Ophthalmology

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ABSTRACT

Background: The present study was undertaken with the aim to compare the therapeutic efficacy of topical latanoprost (0.005%) and topical Bimatoprost (0.03%) in primary open angle glaucoma to assess the safety and efficacy of these drugs.
Material & Method: Both the groups produced significant pressure reduction in the second week of therapy. The IOP lowering efficacy of bimatoprost 0.03% was more than that of latanoprost 0.005% but this is not statistically significant.
Results: At the end of 3 months there was no significant change in the visual acuity, cup disc ratio and visual field changes in both the groups. The drugs were well tolerated though incidence of hyperemia were slight more with latanoprost but statistically not significant. No significant observable systemic side effects were seen in both the groups.
Conclusion: Bimatoprost has few advantages over latanoprost including its potency, efficacy, and tolerability but these are not statistically significant.

KEYWORDS

Bimatoprost, Latanoprost, IOP, Glaucoma, POAG

INTRODUCTION

Glaucoma is a chronic progressive optic neuropathy caused by a group of ocular conditions which leads to damage of the optic nerve with loss of visual function, for which intra-ocular pressure is most important risk factor. Recently, a large, randomized clinical trial demonstrated that the risk of progression of glaucomatous visual field loss is reduced at lower IOPs. In addition, results from the Ocular Hypertension Treatment study showed that a 20% IOP reduction from baseline decreased the risk of developing optic disk cupping and/or visual field loss in ocular hypertensive patients from 9.5% to 4.4%.

WHO statistics published in 1995, indicate that glaucoma accounts for blindness in 5.1 million person or 13.5% of global blindness, after cataract (41.8%) and trachoma (15.5%). Glaucoma occurs in all segments of our society with significant health and economic consequences[1] *(Leske,* 1983).

Glaucoma is classified by etiology into primary and secondary glaucoma. Primary glaucoma is further classified as: primary open angle, primary angle closure and developmental glaucoma. Primary open angle glaucoma alone accounts for about 75% of all primary glaucomas with an incidence of 1-2% in general population above 40 years of age. Primary open angle glaucoma in its typical form is defined by following three criteria: i) An intra ocular pressure above 21 mm of Hg in at least one eye. ii) An open normal appearing anterior chamber angle with no apparent ocular or systemic abnormality that may account for elevated IOP. iii) Typical glaucomatous field changes and / or optic nerve head changes.

Risk factors for POAG:

(A) General risk factors:

(i) Age: POAG is uncommon before age of 40 years. Therefore, prevalence tends to roughly double for each decade over 40 years.
(ii) Race: Prevalence of POAG is higher in black population. Intermediate in whites, Hispanics and South Asian population and lowest in North Asian population.
(iii) Family history: Having a first degree relative with glaucoma has been consistently associated with increased risk of POAG.

(B) Ocular risk factors:

(i) IOP: Most important risk factor.
(ii) Myopia: An association between myopia particularly high myopia has been recognized.

(C) Systemic risk factors:

Diabetes mellitus, hypertension, migraine, thyroid disorders, sleep apnoea and autoimmune risk factors

Pathogenesis:

Risk in IOP in POAG is related to an increased resistance to the outflow of aqueous at the trabecular meshwork caused by age related thickening and sclerosis of the trabecular and an absence of giant vacuoles in the cells lining the canal of schlemm.

The study of glaucoma deals primarily with the consequences of IOP, which is dependent on the rate at which aqueous humor enters the eye (inflow) and the rate at which it leaves the eye (outflow). When inflow equals outflow, a steady state exists and pressure remains constant.

Inflow is related to rate of aqueous humor production, while outflow depends on resistance to flow of aqueous from the eye and the pressure in episcleral veins. These can be expressed by Goldman equation[4].

$Po = F/C + Pv$
Where Po Is the IOP in mmHg
F is the rate of aqueous humor formation in uL/min
C is the facility of outflow in uL/min/mm Hg
Pv is the pressure in episcleral veins

The aqueous humor is produced by the ciliary processes at the rate of 2.4 ± 0.6 uL/min[2].

The aqueous humor outflow occurs through a system consisting of trabeculear meshwork, Schlemm's canal, intrascleral channels and scleral and conjunctival veins. This is the conventional system accounting for 83-96% of aqueous outflow. The rest 5-15% of aqueous leaves the eye via Uveoscleral or Uveovortex systems. The mean value of outflow facility is 0.28 ± 0.5 uL/min/mmHg.

The episcleral venous pressure is about 8-12 mm of Hg[3].

The mean intra ocular pressure is 15.5 mm of Hg with a standard deviation of 2.57. Two standard deviations on either of mean value is the normal range i.e. roughly from 10-20 mm of Hg. 21 mm Hg is usually taken as cut off point for glaucoma patients.

Raised intra ocular pressure is the only known factor that can be therapeutically manipulated. Reducing IOP in glaucoma patients limits disease progression and slows visual field loss. It is said that for every 1 mmHg drop in IOP, a 10% reduction in risk of glaucomatous progression is observed. Therefore, the primary goal in management of glaucoma is to lower the first and the most obvious target i.e. IOP to a predetermined level (target IOP) which is based on patient needs.

Tonometers devised for measuring intra ocular pressure have been devised which are of following types :-

1. Indentation tonometer of schiotz which measures the depth of indentation of anaesthetized cornea.
2. Applanation tonometer[4] *(Goldmanns, hand held Perkins* etc.). This is more accurate and is based on Imbert-Fick principle.

The normal mean IOP by *Goldmann*[4] tonometer is 15.5±2.57 mmHg. 2 S.D. from the mean comes within normal limit, so the normal range of IOP is from + 10.5 to + 20.5 mmHg = 21 mmHg.

3. Non contact tonometers also utilize the principle of applanation and is of importance in non cooperative patients and corneal surface disorders.

Management:

(I) Medical treatment
(ii) Surgical treatment

(A) Medical treatment:

(i) Prostaglandin analogue such as latanoprost and bimatoprost.
(ii) Parasympathomimetics like Pilocarpine
(iii) Adrenergic antagonists - beta-blockers (Timolol, Betaxolol etc)
(iv) Sympathomimetics - Brimonidine, apraclonidine
(v) Carbonic anhydrase inhibitors - Acetazolamide and Dorzolamide
(v) Hyperosmotic agents - mannitol, glycerol

(B) Surgical treatment:

(i) Laser trabeculoplasty
(ii)Trabeculectomy

Among these drugs prostaglandin analogue are one of the first line recommended drugs for POAG.

Latanoprost also known as PhXA41 (13, 14 di hydro-17-phenyl-18,19,20-trinor-PGF 2 alpha-1-isopropyl ester) is a new 17 phenyl substituted Prostaglandin analogue. It is a synthetic highly selective FP-receptor (PGF 2 alpha receptor) agonist that has been demonstrated to reduce IOP in patients with ocular hypertension, open angle glaucoma, normal tension glaucoma and also in normotensive subjects.

Latanoprost is effective using just one drop in the affected eye (s) once daily, which maintains uniform diurnal and circadian IOP reduction. It is used in 0.005% of concentration. Esterification of latanoprost was done for three fold rational. It reduces the superficial side effect, reduce the size of dose, and stabilizes the prostaglandin molecule chemically. In the clinical trials with latanoprost, the most commonly reported ocular reaction was mild conjunctival hyperemia, and episodes of mild punctuate corneal epithelial erosions[5,6].

The most significant side effect of latanoprost was increased pigmentation of the iris[5,6]. No significant systemic reactions were reported with latanoprost in any of the clinical trials.

Bimatoprost is a prostamide, a synthetic structural analog of prostaglandin, with potent lOP-lowering properties. Its chemical name is (Z)-7-[(1 R,2 R,3 R,5 S)-3,5-Dihydroxy-2-[1 E, 3 S)-3-hydroxy-5-phenyl-1 -pentenyl] cyclopentyl]-5-N ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is C 25 H 37 NO 4. Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water.

Clinical studies have demonstrated that bimatoprost is significantly more effective than timolol in reducing IOP in patients with glaucoma or ocular hypertension. Moreover, bimatoprost has been shown to help significantly more patients achieve low target lOPs than does either latanoprost or timolol. Bimatoprost is particularly effective in helping patients to achieve lOPs at or below 15 mmHg. Evidence suggests that these very low lOPs may be necessary to halt the progression of visual field loss in many glaucoma patients.

Preliminary reports also suggest that bimatoprost helps lower IOP as well as or better than common combination therapies. In a 3-month, investigator-masked trial *(Coleman* et al, American Academy of Ophthalmology AAO][8], 2001), bimatoprost provided better IOP-lowering efficacy than did a fixed combination product containing timolol and dorzolamide (Cosopt). In an open-label crossover comparison of bimatoprost with timolol/latanoprost combination therapy *(Dirks,* American Glaucoma Society[9] (AGS, 2001) the majority of bimatoprost-treated patients achieved IOP-lowering that was the same or better than that seen in timolol/ latanoprost-treated patients. These findings are important because it is clinically unwise to expose patients to the risk of the potentially additive adverse effects of dual therapy if a single agent is equally or more effective, unless the cost of the single agent out weighs its potential benefit.

Bimatoprost 0.03% ophthalmic solution has recently been approved by the US Food and Drug Administration for the reduction of intraocular pressure (IOP) in patients with glaucoma and ocular hypertension. Bimatoprost, the first synthetic prostamide analogue to be introduced to the clinic, selectively mimics prostamides to lower IOP. Six-month results of phase 3 comparison trials with timolol demonstrated that bimatoprost once daily reduced mean IOP throughout the day significantly more effectively and rendered patients significantly more likely to reach low target pressures.

Side effects

Bimatoprost ophthalmic solution has been reported to cause changes to pigmental tissues. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.

Bimatoprost may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes.

Precautions

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. They should be used with caution in patients with active intraocular inflammation (e.g. uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. It should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. It should not be administered while wearing contact lenses.

AIMS AND OBJECTIVES

To compare the intraocular pressure lowering effect of Latanoprost and Bimatoprost when used topically for the treatment of POAG.

MATERIALS AND METHODS

The study was conducted on 100 patients of POAG (50 patients were randomly selected for latanoprost and another 50 patients for bimatoprost) who presented to or were referred to Ophthalmology Outdoor at Department of Ophthalmology, RNT Medical College, Udaipur.

Ophthalmological examination was done of both eyes and best corrected visual acuity was recorded. IOP measurement by Goldmann Applanation Tonometer[4], angle of anterior chamber by Gonioscopy, field charting by Octopus Perimeter. Fundus examination was done by direct ophthalmoscopy and slit lamp biomicroscopy using +78D lens.

Inclusion Criteria:

- Unilateral or bilateral primary open angle glaucoma

Exclusion Criteria:

- Closed or barely open anterior chamber angle
- History of acute angle closure
- All secondary glaucoma
- History of ALT within 3 months.
- History of any ocular filtering surgery
- History of ocular inflammation or infection within 3 months
- Hypersensitivity reaction to Benzalkonium chloride or any other component in Latanoprost or Bimatoprost.

METHOD:

100 patients were randomly assigned. 50 patients received 0.005% latanoprost and another 50 patients received 0.03% bimatoprost single drop daily at night time. Patient were instructed to put drop regularly at instructed time in conjunctival sac and to close the eye gently for five minutes after putting drop. They were asked to review in eye OPD after 1 week and three weeks. At first follow up visits patient history was

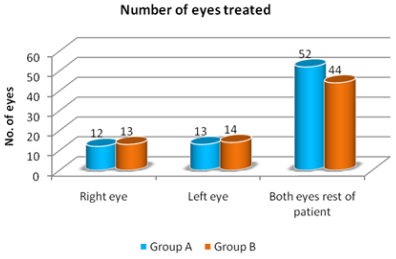
taken regarding compliance of the drug and any side effects or problem noticed by the patients were recorded. S/L examination was done to check for any side effects. IOP was taken by Goldmann Applanation Tonometer[4]. After 3 weeks patients were asked for second follow up visits and again patients' history and S/L examination regarding side effects was done. Then IOP was measured by Goldmann Applanation Tonometer

RESULTS

The patients were randomly divided in two groups of 50 and 50 patients. Among these 50 patients received one drop of latanoprost 0.005% (group A) and another 50 patients received one drop of bimatoprost 0.03% (group B) at the 8 p.m. and were followed up at the one week, three week and three months.

Mean age in group B was slightly higher than the mean age in group B but the difference was not large.

In group A male : female ratio is 3:2 and in group B male : female ratio was 7:3



In group A out of 50 patients 77 eyes and in group B out of 50 patients 71 eyes were qualified for statistical analysis on the basis of baseline IOP and pretreatment IOP

Table 1 Mean IOP at 3 months

	Mean IOP at 3 months	Mean IOP reduction between pretreatment IOP and 3 months
Group A	19.078±1.14	8.39
Group B	18.485±1.65	8.83

Mean IOP at three months was 19.078 ±1.14 in group A and in group B was 18.485 ±1.65 mmHg. Mean IOP reduction was 8.39 and 8.83 in both groups respectively

Table 2 Glaucomatous disc changes in group A and B

	Group A	Group B
Glaucomatous disc changes present	56(72.22%)	55(77.46%)
Apparently healthy/suspicious disc	21(27.27%)	16(22.53%)

In group A, 72.22% eyes were showing glaucomatous disc changes and in group B, 77.46% eyes were showing glaucomatous disc changes.

In our study most commonly encountered disc changes were deep and /or enlarged cup, nasal shifting of vessels, notching in neuroretinal rims, beyonatting of blood vessels.

In group A 27.27% and in group B 22.53% eyes shows apparently healthy or suspicious looking disc i.e. showing asymmetrical cupping in both eyes, enlarged but symmetrical cupping in both eyes etc .

Table 3 Side effects

Side Effects	Group A	Group B
Conjunctival hyperemia	5(6.49%)	4(5.63%)
Burning sensation	4(5.19%)	4(5.63%)
Itching	2(2.59%)	2(2.81%)
Allergic conjunctivitis	0	0
F.B. sensation	0	0
Blepharitis	0	0
Total no. of occurrence	11(14.28%)	10(14.08%)

Patients were specifically asked for symptoms i.e. conjunctival hyperemia and burning sensations for a short period of time after instillation of drugs. Conjunctival hyperemia was observed in 5 patients of group A and 4 patients of group B , burning sensations was observed by 4 patients of both groups. In both groups, no systemic side effects were seen.

Table 4 IOP (mmHg) in all patients

	Group A	Group B
Baseline IOP	19.87±0.80	19.94±0.80
Pre-treatment IOP	27.47±1.59	27.32±1.94
End of 3 months treatment	19.078±1.14	18.485±1.65
Mean decrease from baseline IOP	0.792	1.455
Mean decrease from pre-treatment	8.392	8.835
% reduction from baseline IOP	3.98%	7.32%
% reduction from pretreatment IOP	30.54%	32.33%

No Significant difference between mean pretreatment IOP and mean IOP at 3 months of treatment (P value=0.879) in between two groups.

DISCUSSION

The basic approach in a case of glaucoma is to prevent loss of visual field and in turn loss of visual acuity and visual functions in general. Primary open angle glaucoma is usually asymptomatic and unfortunately because of lack of awareness and high illiteracy it is diagnosed usually when the disease has progressed to the extent that visual fields become severely affected or visual acuity is significantly decreased.

If the IOP begins to rise after long term treatment with a particular topical regimen, the explanation may be either a progression of the disease or a loss of responsiveness to the medication. Before increasing the drug concentration, it is best to add a new drug to the present regimen and to see its effect. Approximately 20% to 30% of patients will eventually require combination drug therapy for optimal reduction of IOP. When choosing drugs for combination therapy, it is important to consider both the addictively of the ocular hypotensive effect and the tolerability of these products.

Various drugs and their combinations have been tried in treating primary open angle glaucoma. The newer of these drugs are Bimatoprost 0.03%and latanoprost 0.005%. These drugs are structural analog of prostaglandin which are used most commonly either singly or in combination with any drug to control the intra ocular pressure effectively.

IOP was recorded by Goldman applanation tonometer. Patients visits were scheduled at week 1, 3, and 3rd month. During this period patients were instructed to administer one drop of 0.03% bimatoprost and one drop of latanoprost at 8 p.m. daily.

In group A 72.22% of eyes were showing glaucomatous disc changes and visual field losses. In group B 77.46% of eyes shows glaucomatous fundus changes or visual field losses. Most frequently encountered disc changes were deep and / or vertical elongation of cup and peripapillary atrophy. These findings were similar to Caprioli et al (1985) who demonstrated 46% incidence of nasal cupping and 44% incidence of peripapillary atrophy in cases of open angle glaucoma.

In our study the mean baseline IOP was 19.87±0.80 mmHg for group A and 19.94± 0.80 mmHg for group B patients.

The efficacy of topical bimatoprost (0.03%) and topical latanoprost (0.005%) therapy is demonstrated. The results of this study show that IOP was lowered by 30.54% and 32.33% from pre treatment IOP measured at 3 months after initial IOP measurements in group A and group B respectively but this is statistically not significant.

The mean IOP readings after 3 months of treatment with topical latanoprost and topical bimatoprost came out to be 19.078±1.14 mmHg and 18.485±1.65 mmHg for group A and B respectively. So there was a mean decrease of 0.792 mmHg and 1.455 mmHg IOP from the *baseline IOP* in group A and B respectively, showing an overall reduction of 3.98% and 7.32% IOP for the respective groups.

Our study showed that in almost all visits bimatoprost reduced IOP better than latanoprost, and IOP reduction was maintained throughout the study but this was statistically not significant. As regards the long-term effect of bimatoprost, there was no short-term escape or long term

drift as proposed by Boger WP III[10] (1979) seen in our study. The IOP lowering effect was maintained throughout the study period. Perhaps the follow up period was too small to notify any drift.

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.

Regarding the local ocular side effects, *Conjunctival hyperemia* were present in 6.49% and burning sensation were present in 5.19% of the patients whereas itching was present in 2.59% of the patients in the group A patients. In group B , conjunctival hyperemia were present in 5.63% , burning sensation in 5.63% and itching was present in 2.81% of the patients which are in consonance with the study done by Camras et al[7] (1995, 1996), Watson et al[6] (1996). Other side effects e.g. Cystoid macular edema (Heir et al, 1998), increased iris pigmentation (Johnston 1997), hypertrichosis (Johnston, 1997) Wand et al, 1997) were not observed in our study. Our study group may have been too small and observation period too short to show these changes.

CONCLUSION

In conclusion, bimatoprost has few advantages over latanoprost including its potency, efficacy, and tolerability but these are not statistically significant. The result of this study confirms better safety and efficacy of bimatoprost. However bimatoprost 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 and inability to strictly randomize the patients on racial basis we suggest studies in large number of patients treated for many years to ensure prolonged safety and efficacy.

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