Original Article

Efficacy and Safety of Latanoprost for Glaucoma Treatment: A Three-Month Multicentric Study in India

***Ravi Thomas**, MD; **Rajul Parikh**, MS; **Devendra Sood**, MS; **L Vijaya**, MD; **G Chandra Sekhar**, MD; **Narendra N Sood**, FRCS; **M Baskaran**, DNB; **K Kalyani Prasad**, MS;*
(For the Latanoprost India Study Group)

Purpose: To evaluate the short-term efficacy and safety of 0.005% topical latanoprost in Indian eyes.
Design: Prospective non-randomised open-label multicentric trial.
Methods: One hundred and fifty patients with ocular hypertension (OHT), primary open-angle, pseudoexfoliation or pigmentary glaucoma were enrolled at four centers. Each center contributed at least 20 patients. Following baseline measurements, 0.005% latanoprost was applied topically once daily in the evening for three months. Patients were examined at 2, 6 and 12 weeks. The primary outcome measure was mean intraocular pressure (IOP) reduction. The mean diurnal variation of IOP (difference between highest and lowest IOP) at baseline and at 12-weeks was compared.
Results: One hundred and thirty of 150 enrolled patients completed the study. One randomly selected eye of each patient was included for analysis. At three months, latanoprost reduced the mean IOP from 24.9 (± 3.16) mmHg at baseline to 16.10 (± 2.7) mmHg, a reduction of 35.25%. 83% had a reduction in IOP of > 25%. The IOP reduction was maintained throughout the study period, and was not affected by gender or age of the patient. One eye did not show any response to the drug. Daytime diurnal variation of IOP was reduced from 4.5 to 2.9 mmHg. 20 patients had conjunctival hyperemia. Six patients had side effects requiring withdrawal from the study.
Conclusions: In this short-term multicentric study, latanoprost effectively reduced IOP and stabilised the diurnal curve in Indian eyes. There were no clinically significant ocular or systemic adverse effects.

Key Words: Latanoprost, safety, efficacy, glaucoma, Indian eyes

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Glaucoma is an optic neuropathy and intraocular pressure (IOP) is a causal risk factor.[1] Several recent studies have reported the value of reducing IOP as treatment for primary open angle glaucoma (POAG).[2, 3] The initial treatment for POAG is usually medical with filtration surgery traditionally reserved for those in whom maximally tolerated medical therapy fails to control the disease.

LV Prasad Eye Institute (RT, GCS, KKP), Hyderabad, Schell Eye Hospital, Christian Medical College (RP), Vellore, Shroff Eye Hospital (DS, NNS), New Delhi, and Sankara Nethralaya (LV, MB), Chennai, India

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Correspondence to Dr. Ravi Thomas, LV Prasad Eye Institute, L V Prasad Marg, Banjara Hills, Hyderabad – 500 034, India. E-mail: <ravithomas@lvpei.org>

The safety and efficacy of latanoprost has been reported in several studies.[4-13] It is well known that there may be racial differences in the effect of drugs.[14, 15] India has an estimated 12.8 million patients suffering from glaucoma.[16] Recently Hedman et al[13] reported that latanoprost or timolol statistically significantly reduced the mean diurnal IOP in a heterogeneous global population. The greatest difference in the mean diurnal IOP-lowering effect of latanoprost or timolol was observed in Mexican and Asian clinical trials. Patients with higher baseline IOP had better IOP reduction; patients with glaucoma responded better to latanoprost than those with OHT. Latanoprost was equally effective in newly diagnosed and previously treated patients.[13] There is one report of the efficacy of latanoprost in a north Indian population[17].

The purpose of this 12-week open-label multicentric study was to investigate the IOP lowering effect and safety of 0.005% topical latanoprost in Indian eyes for a 12-week duration.

Materials and Methods

Sample size calculation

The sample size was calculated in order to detect a mean IOP reduction of 1.5 mmHg with the drug, with an error of 0.05 (two-sided), power of 0.80 and a within-patient standard deviation of 3.0 mmHg. The formula used was:

$$n = 2 \times std^2 \times (za_{/2} + zb)^2 / d^2$$

$$= 2 \times 3.0^2 \times (1.95 + 0.84)^2 / 1.5^2 = 64$$

The calculated sample size was 64.

Inclusion and exclusion criteria

To be eligible for the study, at least one eye of each patient had to meet the following criteria: minimum age 18 years with unilateral or bilateral primary open angle (POAG), pseudoexfoliation, pigmentary glaucoma or ocular hypertension. All patients had mean IOP higher than 21 mmHg at the baseline visit (mean of the IOP readings on same day). Patients who were on medication for glaucoma were controlled on a single drug.

Exclusion criteria were baseline IOP lower than 21 mmHg (normal tension glaucoma), angle closure glaucoma or occludable angle on gonioscopy, IOP not controlled on more than one medication, history of ocular inflammation or infection within the last 3 months, history of intraocular surgery including laser procedures within 6 months prior to enrolment in the study, pregnant and lactating women, those already using latanoprost, ocular conditions precluding Goldmann applanation tonometry and known sensitivity to the vehicle component.

The diagnosis of glaucoma was based on baseline IOP higher than 21 mmHg with typical glaucomatous optic disc changes with corresponding visual field defects on automated perimetry.[1] Ocular hypertension was defined as IOP higher than 21 mmHg with open angles, normal disc and normal visual field.[1]

Study design and plan

The study was open-label and uncontrolled. The treatment period was three months. During the month preceding the start of the study, patients had a pre-study visit to assess for eligibility. Patients without previous glaucoma treatment could have their first visit at visit 1 (Baseline). The treatment period of three months comprised fourvisits, i.e. baseline (visit1), day14 (visit2), week6 (visit3), and week12 (visit4). A deviation of ±2days for visit2 and ±1week for subsequent visits was accepted (measur ed from visit1). Patients with persisting adverse events at study termination had a follow-up visit within 2-4weeks after end of treatment. Interim visits could be scheduled at the discretion of each investigator.

Patients who qualified for the study and were currently using ocular hypotensive medication underwent a minimal washout period as follows: topical β-adrenoreceptor antagonist 3 weeks, topical adrenergic agonist 2 weeks and cholinergic agonist and systemic carbonic anhydrase inhibitor for period of 5 days. The washout was followed by the pre-study visit.

Patients were enrolled in four centers from May 1999 to April 2000**.** Ethics committee approval was obtained from all centers before commencement of clinical trial. Informed consent was obtained from each patient.

All the patients underwent visual field examination at the first day and at the end of the study. Visual fields were performed on the Humphrey field analyzer using the SITA (Swedish Interactive Testing Algorithm) standard program.

Systemic medications including beta-blockers were continued during the study. New systemic medications were permitted provided they had no known effect on the IOP. If a drug with a known effect on the IOP was deemed necessary for the patient, the patient had to be withdrawn from the study.

At the baseline visit, medical history from each subject was obtained, including a list of all systemic medications. A complete ophthalmic examination was performed which included slitlamp examination, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, stereoscopic biomicroscopy of the optic disc with 60 or 90 diopter lens. IOP's were measured at 09:00 Hour (±1 hour), 13:00 Hour (±1 hour), and 17:00 Hour (±1 hour). Three IOP readings were recorded each time and mean of each was used for analysis. Slitlamp biomicroscopic examination was done before instillation of 2% fluorescein to look for aqueous flare and anterior chamber cellular response. Iris colour was noted at the baseline visit but no photographs were taken.

Each patient was given three vials of the study drug. Two vials were dispensed at the baseline and the third at the 6-week visit. The instructions were to change the vial at the end of 4 weeks and 8 weeks. Patents were asked to return the used vials. Patients were advised to install the eye drop at bedtime, preferably at the same time every day (8 PM). They were taught how to apply the medication with the help of a dummy vial.

Visual acuity was recorded at 2 weeks and 6 weeks. IOP was recorded at 09:00 Hour (±1 hour). Slitlamp examination was performed, especially to look for change in iris color and presence of uveitis.

At the 12-week visit best-corrected visual acuity and objective refraction were recorded. IOP was measured at 09:00 hour (±1 hour), 13:00 hour (±1 hour), and 17:00 hour (±1 hour). A complete ophthalmic examination including dilated fundus examination was done. Visual field examination was repeated and compared to the baseline field.

Throughout the study duration, patients were monitored for ocular and systemic adverse effects. The

diagnosis of adverse effects including ocular hypersensitivity or allergy was left to the examiner. An adverse event was defined as any untoward medical occurrence in a patient during the course of the study period; the event did not necessarily need to have a causal relationship to the drug.

Adverse events (AE) were graded for severity as mild, moderate or severe. *Mild*: did not interfere with the subject's routine function. *Moderate*: interfered to some extent with subject's routine function. *Severe*: interfered significantly with subject's routine function. The occurrence of a severe AE led to withdrawal of patient from the study.

In case of an adverse event the investigator was required to assess the relationship to the study treatment (definite, possible, unlikely or none) and report the outcome. At every visit patients were queried specifically about ocular comfort.

For patients who had both eyes included in the study, only one randomly selected eye was included for analysis. Eyes were selected randomly using computer-generated blocks. In patients with only one eye eligible for the study, this eye was used for analysis.

Analysis

The primary outcome measure was mean IOP reduction. This was analysed by comparing mean IOP at 12 weeks to mean baseline IOP using Student's "t" test [18] The level of significance was set at $P < 0.05\%$. At baseline and at the end of study IOPs were measured at 09:00 hours (±1 hour), 13:00 hours (±1 hour), and 17:00 Hour (±1 hour). These IOPs were compared to determine the effect of latanoprost on daytime diurnal variation. Results were also analysed using percentage of IOP reduction. A reduction of 25% or more IOP from baseline IOP was considered success of treatment. 95 percent confidence intervals (C.I.) were used to compare IOP reduction in our study patients to other latanoprost multicentric studies.

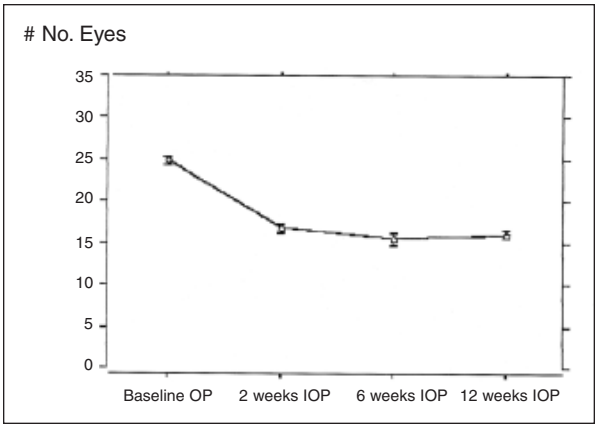

Figure 1. Mean IOP at baseline and various follow-up visits

Table 1. Number of patient withdrawals from study and reasons

	Patients
Inadequate wash-out of previous ocular hypotensive drugs	2
Study drug not taken	3
Eligibility criteria not met for study eyes	5
Serious side effects	6
Lost to follow up	4
Total	20

Results

130 of 150 enrolled patients followed the protocol and completed the study duration of 12-weeks and were available for analysis. Each centre contributed at least 20 patients. Table 1 shows details of the 20 patients who for various reasons were not included for statistical analysis. Table 2 shows demographic details of all patients. The iris colour was homogenously brown in 134 patients; 4 had a homogenously blue, grey or green; 1 each had blue-brown and yellow-brown colour. Mean best-corrected visual acuity (BCVA) was 0.91 (±0.04) logMar at first visit and 0.9(±0.06) logMar at last visit.

Intraocular pressure

Table 3 and Figure 1 show mean IOP at various follow-up visits. Mean IOP reduction at the last follow-up visit was 8.9 mmHg (± 1.7), a 35.25% IOP reduction from baseline. Compared to baseline measurements latanoprost caused a significant ($P < 0.001$) IOP reduction throughout the duration of therapy. It also shows mean IOP at baseline and three-month visit at 9 hours, 13 hours and 17 hours. IOP reduction was similar at all studied hours.

Table 2: Demographic data of study population

		N=130
Gender	Male	87 (67 %)
	Female	43 (33 %)
Diagnosis	POAG	92
	Pseudoexfoliation glaucoma	5
	Pigmentary glaucoma	2
	Ocular hypertesion	31
Study eye(s)	Right	71
	Left	59

PoAG – Primary open angle glaucoma

Table 3. Mean IOP reduction at study visits

Visit	Mean IOP mm Hg (± SD)	Mean IOP Reduction mm Hg (±SD)	p value	Mean IOP 9 hours	13 hours	17 hours
Baseline	24.90 21 (± 3.15)	——	——	25.3 (± 3.14)	25.1 (± 3.19)	24.7 (± 3.12)
2 weeks	16.75 (± 3.40)	8.10 (± 1.75)	P < 0.0001	16.75 (± 3.40)		
6 weeks	15.50 (± 4.00)	9.40 (± 1.85)	P < 0.0001	15.5 (± 4.00)		
12 weeks	16.10 (± 2.70)	8.90 (± 1.70)	P < 0.0001	16.2 (± 2.70)	16.2 (± 2.72)	16.1 (± 2.70)

Table 4 and Figures 2 and 3 shows percentage IOP reduction and eyes achieving specific IOP level at last visit. 108 eyes (83.1 %) had 25% or more IOP reduction. One eye did not show any response to the drug. 105 (80.8 %) eyes achieved IOP of 18 mm Hg or less and 65 (50 %) eyes achieved less than 16 mm Hg IOP at last visit.

Table 5 shows the mean daytime diurnal variation of IOP at baseline and at 12 weeks. The difference between the highest and lowest mean IOP recordings at baseline was 4.5 mmHg; this was 2.9 mmHg at the final follow up. This difference was statistically significant (P < 0.001).

IOP reduction in the glaucoma group was 36. 5% compared to 31.8 % IOP reduction in OHT group. In previously treated glaucoma patients latanoprost reduced IOP by 37.4 % compared to 28.9% in those newly diagnosed and previously untreated. This difference was significant (P =0.01).

Ocular adverse events

Conjunctival hyperemia was the most common side effect; this occurred in 20 patients (15.4 %). No one required discontinuation of medication. Other side effects are listed in Table 6. At the final visit, two patients were suspected to have worsening of the visual field. Both were advised repeat fields. The worsening could be confirmed in one patient; the other was lost to follow up.

No patients had alteration in any of the following baseline measurements: visual acuity, slitlamp biomicroscopic examination, anterior chamber flare or cellular response.

As photographs were not a part of the protocol, it is not possible to comment on the change in iris colour. No patients had a gross change in iris colour.

Two patients had to be withdrawn from the study due to ophthalmic side effects. One complained of

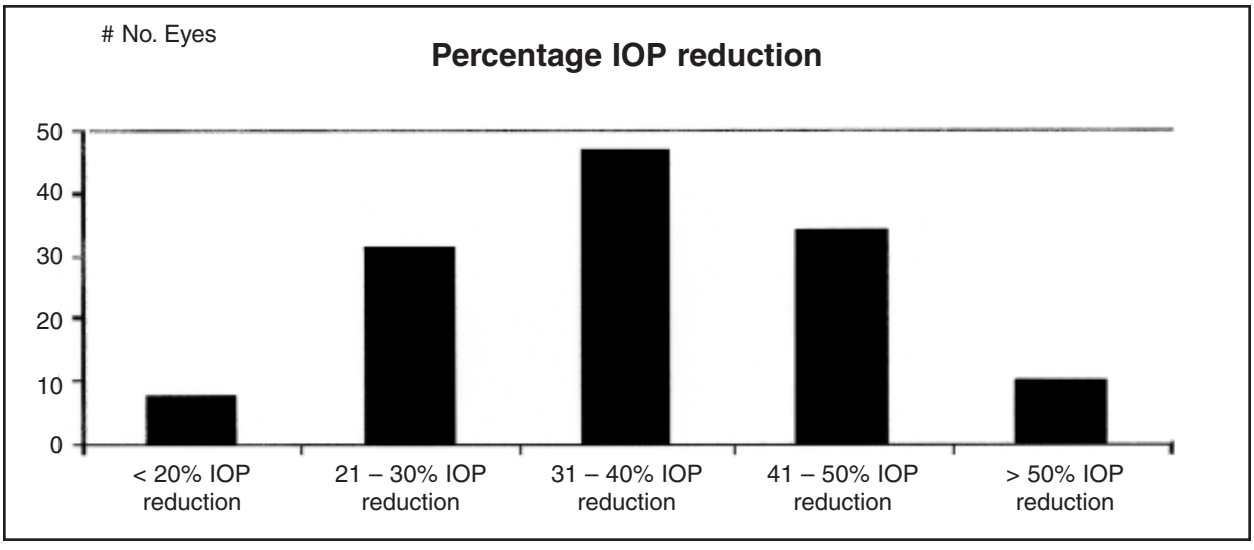

Figure 2. Number of eyes achieving percentage IOP reduction at last visit

Table 4. Percentage IOP reduction and patients achieving specific IOP level at last visit

IOP reduction (%)	Eyes (%)	IOP at last visit	Eyes (%)
≥ 25 %	108 (83.1 %)	≤21 mmHg	125 (96.15 %)
≥ 30 %	099 (76.15 %)	≤ 18 mmHg	105 (80.8 %)
≥ 40 %	052 (40 %)	≤ 16 mmHg	065 (50 %)

colored haloes; the symptoms disappeared on stopping the drug. Another patient developed acute angle closure glaucoma. This patient had advanced cataract. The investigator ascribed the angle closure to lens intumescence.

Systemic adverse effects

Serious adverse events occurred in 5 patients (4%). None could be directly attributed to the drug. 20 patients (15.4 %) reported the adverse events listed Table 6.

Five patients had systemic illnesses requiring hospital admission that were not drug related adverse events. Latanaprost was discontinued for the following reasons: two patients were hypertensives who required additional systemic medication for control; one was admitted to hospital with a lower respiratory tract infection and stopped latanoprost on his own; the fourth patient was a severe diabetic who had to be admitted and the drug stopped. One patient had a fracture and required admission to hospital. All these were considered severe adverse events, though none were related to the drug.

Table 5. Daytime diurnal variation at baseline and 12 weeks

IOP	Baseline visit		12 weeks visit	
	Highest (mm Hg)	Lowest (mm Hg)	Highest (mm Hg)	Lowest (mm Hg)
Latanoprost	27.1 (± 3.25)	22.7 (± 3.10)	17.6 (± 2.83)	14.7 (± 2.59)

Discussion

In the current era of globalisation we may be called upon to treat people from different countries. With the introduction of newer medications for the management of glaucoma, studies that consider IOP lowering efficacy and safety in different ethnic groups are important in clinical decision-making.[19]

We found a 35% reduction in IOP amongst patients who completed the study duration of 12 weeks. The effect of drug was evident at the first visit and was constant during the study period. It is known that Latanoprost's action starts within the first 2 weeks, maximizes within first 6 weeks and than onwards stabilises without short or longterm drift.[10] Our results are similar except that due to short-term nature of study we cannot comment on the drift.

The literature reports IOP reduction ranging from 25% to 32%.[11-14] Table 7 and Figure 4 compare our results with other multicentric studies. The lack of masking and regression to the mean might explain the greater pressure lowering effect seen in our study. Our results were similar to that reported by the U.K Latanoprost

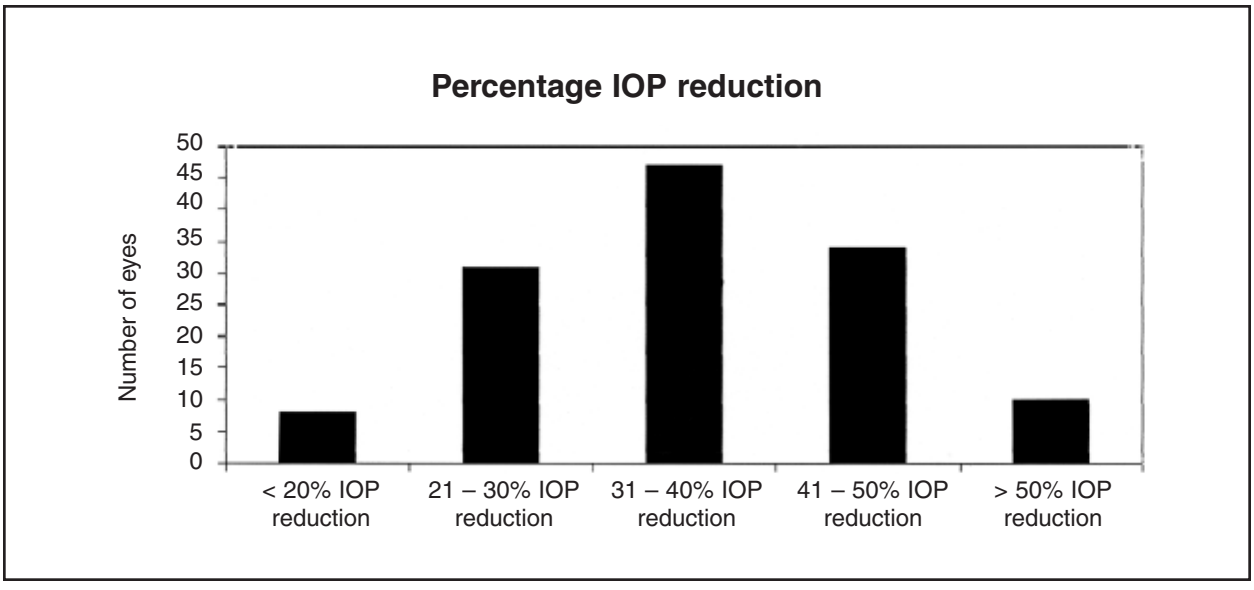

Figure 3. Patients achieving specific percentage of IOP reduction level at last visit

Table 6. Ocular and systemic adverse events

Ocular Adverse Events	N (%)
Drug related	
Conjunctival congestion	20 (15.4 %)
Punctate corneal disorder	1 (0.8 %)
Irritation	2 (1.6 %)
Unrelated to drug	6 (4.8 %)
Refractive errors	
Pain	4 (3.2 %)
Angle closure glaucoma	1 (0.8 %)
Visual field progression	2 (1.6 %)
Chalazion	2 (1.6 %)
Meibomitis	2 (1.6 %)
Coloured haloes	1 (0.8 %)
Progression of cataract	3 (2.4 %)
Systemic Adverse Events	
Drug related: none	
Unrelated to drug	
Upper respiratory tract infection	4 (3.2 %)
Pruritus	2 (1.6 %)
Skin disorder	1 (0.8 %)
Muscle contractions, involuntary	1 (0.8 %)
Headache	1 (0.8 %)
Hypertension	3 (2.4 %)
Diabetes mellitus	1 (0.8 %)
Hyperglycemia	1 (0.8 %)
Allergy	1 (0.8 %)
Back pain	1 (0.8 %)
Fracture	1(0.8 %)
Gastritis	1(0.8 %)
Urinary tract infection	1(0.8 %)
Inguinal hernia	1(0.8 %)

Study Group; IOP reduction was significantly more than in the US and Scandinavian multicentric studies. The Baltimore survey reported that the black population was less responsive to medical management.[20] While 21% of the U.S Latanoprost Study group was pigmented there was no difference in IOP reduction between pigmented and white races.[13]

At 12 weeks a 25% reduction from baseline was obtained in 108 eyes (83.1 %); a 30% reduction in 99 eyes (76.1 %). Two patients had IOP reduction less than 10% and one did not show any response to the drug. Latanoprost significantly reduced daytime diurnal variation in our patients; diurnal variations are known to be an independent risk factor for progression of glaucoma.[21]

Side effects other than conjunctival hyperaemia were minimal. The frequency of hyperaemia is similar to that reported.[22] The patient who developed acute angle closure was explained by rapid progression of the cataract. We could speculate that in a predisposed eye rapid egress of aqueous from the peripheral anterior chamber might actually precipitate acute closure. Even if this mechanism were possible, it would be unlikely in a wide-open angle, which was the inclusion criterion. As a glaucoma specialist examined the case, an error in gonioscopy was a remote possibility. Cells and flare were not detected on slitlamp examination. Other studies including those using laser flare meters report similar findings,[5-12, 23, 24] and Hotehama and Mishima. (IOVS, abstract 1992;33:s2142).

Iris pigmentation is a recognised complication of latanaprost treatment reported by most long-term trials.[10] The short duration of treatment and purely clinical examination used to grade a change in pigment does not permit us to comment on this complication. It appears that a certain type of iris is at particular risk for this complication.[10] In our study we had 95% of patients with homogenous brown iris compared to only 51% in the US study group. Our darker irises may mask the effect of Latanoprost.

Our study had several limitations. The most important was the open label and non-randomised design. Lack of masking and regression to the mean might explain the better results obtained. In summary this multicentric Indian trial reports the efficacy of latanoprost in Indian eyes. It demonstrates an IOP

Table 7. Comparison with other multi-centric study results

	Baseline IOP (mmHg)	IOP reduction (mmHg)	Std. Dev.	Mean IOP reduction (mm Hg) (95 % CI)
USA	25.5	6.7	3.4	6.2 – 7.2
Scandinavian	25.1	7.7	2.9	7.3 – 8.1
UK	25.2	8.6	2.6	8.2 – 9.0
India	24.9	8.8	3.4	8.2 – 9.2

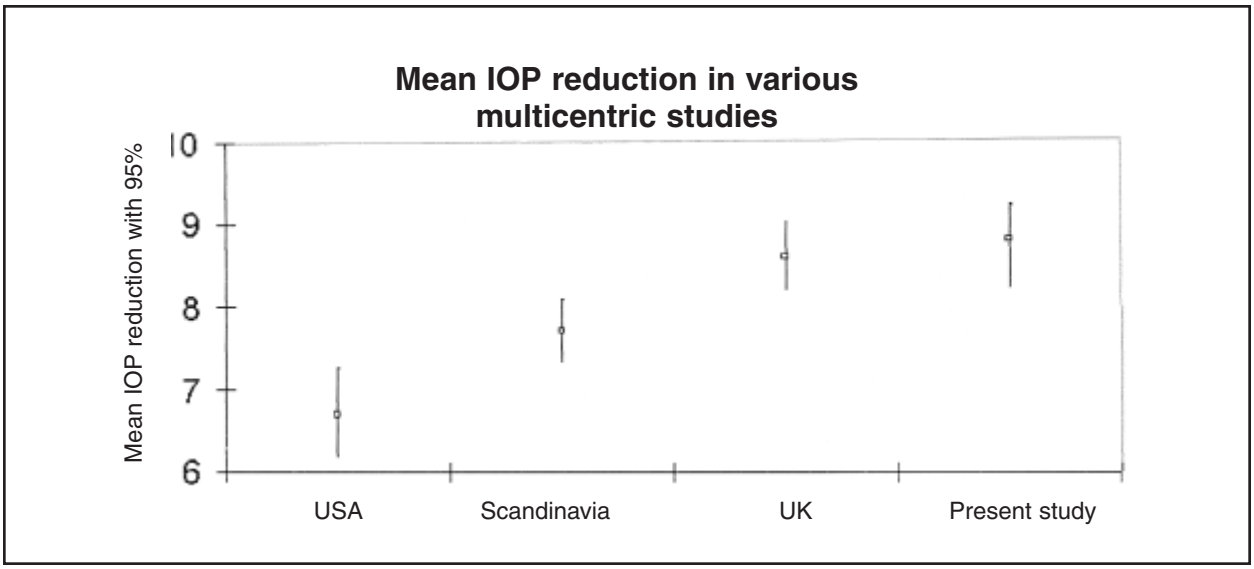

Figure 4. X-axis shows the various centers in the study. Y-axis shows mean IOP reduction with 95% confidence interval

lowering effect similar to the ones reported worldwide; lack of response was rare. Latanoprost also stabilised the daytime diurnal curve. There were only two drug-related side effects requiring withdrawal of drug.

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