· Original article ·

The effect on intraocular pressure of Latanoprost with once every other day dosing in glaucoma patients

Rana Sorkhabi, Mohamadhosein Ahoor, Yashar Amizadeh

Foundation item: Supported by a grant from the Vice-Chancellor for Research at Tabriz University of Medical Sciences

Nikookari Eye Hospital, Tabriz 5138951389, Iran
Correspondence to: Rana Sorkhabi. Nikookari Eye Hospital, Tabriz 5138951389, Iran. sorkhabi_r@yahoo.com

Received: 2012-07-19 Accepted: 2013-04-10

拉坦前列素隔日给药对青光眼患者眼压的影响

Rana Sorkhabi, Mohamadhosein Ahoor, Yashar Amizadeh

基金项目:伊朗大不里士医科大学校科研基金

(作者单位:伊朗大不里士,Nikookari 眼科医院)
通讯作者:Rana Sorkhabi. sorkhabi_r@yahoo.com

摘要

目的:探讨隔日应用0.005%拉坦前列素对青光眼患者眼压(intraocular pressure, IOP)的效果。

方法:该研究中的开角型青光眼患者控制较好,在研究的第一阶段睡前给予拉坦前列素,每日一次,至少2mo。3次连续IOP正常后,改为隔日一次睡前用药,并且在研究第二阶段的1,2,4,6,8和12wk密切监测患者,进行IOP测量。遇到一次IOP异常升高,则患者被排除研究并且前期方案将重建。

结果:这项研究包括53例53眼开角型青光眼(男29例,女24例,年龄52~82岁)。27例患有原发性开角型青光眼,26例患有假性剥脱性青光眼。研究的第二阶段开始后,IOP有温和增长趋势,并分别在女性和男性患者中检测到。第1,2,4,6,8和12wk的P值分别为0.003,0.001,0.000,0.000,0.000和0.000。在第二阶段开始后的前2wk,66%的病例没有IOP改变,但此后,69.8%患者眼压增加。

结论:该研究显示常规用量0.005%拉坦前列素与隔日一次剂量相比,具有优越性,但至少在最初的几个星期,IOPs比较接近对方。进一步的多患者研究将扩大目前的研究结果。

关键词:拉坦前列素;隔日剂量;每日一次

引用:Sorkhabi R, Ahoor M, Amizadeh Y. 拉坦前列素隔日给药对青光眼患者眼压的影响. 国际眼科杂志 2013;13(5):841-844

Abstract

• AIM: To evaluate the effect on intraocular pressure (IOP) of Latanoprost 0.005% (Lataprost, Sina Darou, Iran) applied every other day.

• METHODS: Patients with well controlled open angle glaucoma were enrolled in the study. All patients had been given Latanoprost for at least 2 months with once daily dose at bed time at the first phase of the study. After recovery of 3 normal consecutive IOPs, the dosage was altered to once every other day at bed-time and they were closely monitored at week 1, 2, 4, 6, 8 and 12 within second phase of the study and IOPs were measured. As soon as an abnormally elevated IOP was encountered, patient was excluded from the study and the prior regimen was reestablished.

• RESULTS: This study included 53 eyes of 53 patients (29 male, 24 female; age range 52-82 years) with open angle glaucoma. Twenty-seven patients suffered from primary open angle glaucoma and 26 patients had pseudoexfoliative glaucoma. After beginning the second phase of the study, a mild trend of increasing IOP was recordable. A corresponding trend was even detected in female and male patients separately. The P values at week 1, 2, 4, 6, 8 and 12 were 0.003, 0.001, 0.000, 0.000, 0.000 and 0.000 respectively. In the first 2 weeks after initiation of the 2nd phase, 66% of cases have no change in IOPs, but thereafter, 69.8%, experienced increasing IOPs.

• CONCLUSION: The present study shows the superiority of the conventional dosage of Latanoprost 0.005% in comparison with once every other day dose but at least in first few weeks, the IOPs are reasonably close to each other. Further studies with higher number of cases would widen the present findings.

• KEYWORDS: Latanoprost; once every other day dose; once daily

DOI:10.3980/j.issn.1672-5123.2013.05.01

Citation: Sorkhabi R, Ahoor M, Amizadeh Y. The effect on intraocular pressure of Latanoprost with once every other day dosing in glaucoma patients. *Guoji Yanke Zazhi* (*Int Eye Sci*) 2013;13(5):841-844

INTRODUCTION

Prostaglandin analogues belong to the ocular hypotensive medication category used in the treatment of open angle glaucoma and ocular hypertension[1]. Latanoprost, a $PGF_2\alpha$-related compound, is a prodrug that must be metabolized to show meaningful pharmacological activity. After topical application, Latanoprost is rapidly hydrolyzed to latanoprost acid, a potent prostaglandin FP receptor agonist responsible for the subsequent reduction in the intraocular pressure (IOP)[2].

The mechanism by which Latanoprost reduces IOP is considered to involve an increase in uveoscleral outflow by remodeling the extraocular matrix and relaxation of the ciliary muscle[3-6]. It has been shown that twice and four times daily dosing of Latanoprost has less ocular hypotensive effect than once daily[7-9]. The mechanism behind this loss of effect is not clear, we decided to determine if an even lesser frequency of administration of Latanoprost would result in the same effect as once daily dosing on IOP. Thus the aim of this study was to evaluate the effect on IOP of Latanoprost 0.005% (Lataprost, Sina Darou, Iran) applied every other day.

MATERIALS ANDMETHODS

Subjects This was a prospective, self-control comparative study. The study protocol followed the tenets of the Declaration of Helsinki and was reviewed and approved by the medical ethics committee of Tabriz University of Medical Sciences. Informed consent was obtained from each individual. All participants had the following criteria: age older than 50 years and bilateral or unilateral open angle glaucoma (primary or pseudoexfoliative), mild or moderate visual field defect ($1.5<MD<12$) and achieving target IOP with current medications. Eyes with history of any pathologic ocular condition except glaucoma, intraocular surgery, severe glaucomatous damage ($MD>12$) and any kind of glaucoma except for primary open angle glaucoma (POAG) and pseudoexfoliative glaucoma (PEXG) and uncontrolled IOP were excluded the study.

Methods At a screening visit, a complete medical and ocular history was obtained, and patients underwent a complete ophthalmic examination including slit lamp biomicroscopy, dilated fundus examination, gonioscopy and automated perimetry (if not performed in the previous 6 months). All participants had the following Enrollment into the study was based on pre-study IOP-lowering medications. All patients must be treated with Latanoprost with once daily dose at least one month prior to eligibility visit. We measured IOP with a calibrated Goldmann applanation tonometry (Haag-Streit, Koniz, Switzerland) which was calibrated weekly. The pre-study IOP measurement was performed 3 times on different days and if the patient was eligible for the study the mean value from repeated IOP measurement was considered as the baseline IOP. After the calculation of baseline IOP, patients were given Latanoprost with every other day dosage. Thereafter, the IOP was checked repeatedly at first, second, fourth, sixth, eighth, and twelfth weeks after the alteration of the dosage. During these follow-ups whenever we observed any abnormally high IOP out of the acceptable ranges, corresponding patients were excluded from the study and the prior protocol was reestablished. Each time, the IOP was measured by the same ophthalmologist (R.S) at the same time (10a.m.). All IOP measurements were performed twice for each eye in sitting position. If the measurements differed by greater than 2 mmHg, a third measurement was performed. The mean of 2 or the median of 3 readings was used for analysis.

Table 1 Sex ratio, mean age and intraocular pressure in periods of times

Parameters	Total ($n=53$)	POAG ($n=27$)	PEXG ($n=26$)	P
Sex(Male/Female)	1.12	1.25	1.17	0.90[a]
Age (yr)	65.85	65.89	65.81	0.97[b]
Baseline IOP	16.07	16.52	15.61	0.19[b]
Second phase				
IOP 1st week	16.39	16.78	15.98	0.22[b]
IOP 2nd week	16.51	17.04	15.96	0.13[b]
IOP 4th week	16.95	17.48	16.4	0.18[b]
IOP 6th week	17.35	17.75	16.94	0.33[b]
IOP 8th week	17.23	17.48	17	0.50[b]
IOP 12th week	17.29	17.73	16.85	0.22[b]

[a]Chi square; [b]Independent t-test; POAG: Primary open angle glaucoma; SOAG: Secondary open angle glaucoma.

Statistical Analysis All the statistical analyses were performed by using SPSS 17 (SPSS Inc., Chicago, IL). $P<0.05$ was considered statistically significant. We had two categories of quantitative data. The first group harbors a normal distribution which consists of age, base and interval IOPs. We used independent t-test to compare these parameters. The second group had a skewed distribution according to Kolmogorov-Smirnov test and includes the IOP differences between each interval and base IOP. We applied Wilcoxon signed rank test. The qualitative data such as the male/female ratio was analyzed by Chi-square test.

RESULTS

Fifty-six patients were enrolled in this trial, 3 of whom were excluded on week 4 because of marked IOP elevation in the eye treated with once every other day Latanoprost. Finally, 53 eyes of 53 patients were included in this study. The mean age of patients was(65.9±8.8) years and the sex ratio(male/female) was 1.2. The mean IOP, at baseline, in the eyes receiving Latanoprost once daily was (16.1±2.5) mmHg. From a total of 53 patients, 27 had primary open angle glaucoma (POAG) and 26 patients suffered from pseudoexfoliative glaucoma (PEXG). Demographic characteristics and baseline IOP and IOPs in the second phase of study were illustrated in Table 1. The difference between the IOP of each week and base was calculated and analyzed by Wilcoxon Signed Ranks Test because of the skewed distribution of this parameter. The P values at week 1, 2, 4, 6, 8 and 12 were 0.003, 0.001, 0.000, 0.000, 0.000 and 0.000 respectively.

The mean serial IOPs in different consecutive time points were shown in Figure 1A. According to the charts, a mild trend of increasing IOP was recordable in all patients. The IOP changes from baseline as reference at all time points during the second phase of the study is shown in Figure 1B. Mean IOPs of POAG and PEXG patients in different consecutive time points were provided separately in a single chart (Figure 1C). The corresponding P values were incorporated in Table 1. A dramatic increase in the IOP of cases was demonstrated between 2nd and 4th weeks of second phase from 30.2% to 49.1%.

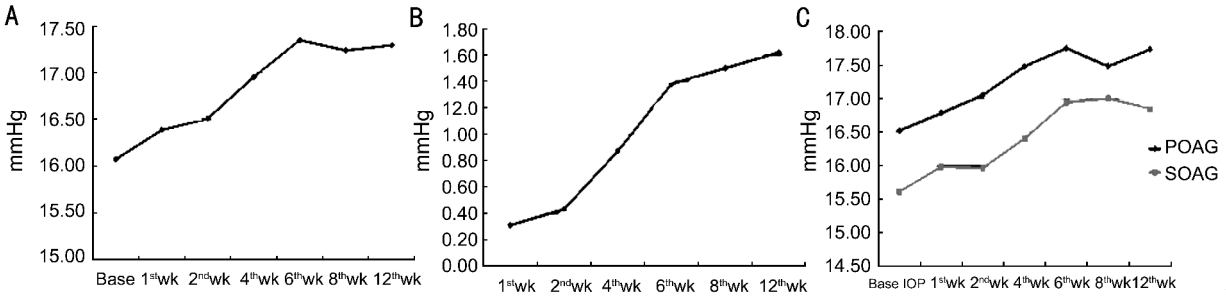

Figure 1 Mean IOP changes in different consecutive time points A: Glaucoma cases; B: Changes from baseline; C: POAG and PEXG patients; POAG: Primary open angle glaucoma; SOAG: Secondary open angle glaucoma.

Table 2 Percentages of the increasing, constant and decreasing IOP in different consecutive time points in comparison with base IOP

Time points	Decreasing	No change	Increasing	Excluded
IOP 1st week	1.90%	73.60%	24.50%	0%
IOP 2nd week	3.80%	66%	30.20%	0%
IOP 4th week	7.50%	43.40%	49.10%	0%
IOP 6th week	7.50%	28.30%	62.30%	1.9%
IOP 8th week	3.80%	18.90%	69.80%	7.5%

It is crystal clear that in the first 2 weeks after initiation of the 2nd phase in our study, the majority of cases (66%) did not have any change in IOP, but thereafter, the higher percentages (69.8%) were appeared in "increasing IOP" category (Table 2).

DISCUSSION

Prostaglandin analogues are effective ocular hypotensive agents and are being used increasingly in the treatment of elevated IOP. Dose-response based studies demonstrated 24 hours duration of action and long-term studies confirmed an effective control of IOP with such a dosing schedule. Therefore, these agents are typically dosed once daily[1-3].

Konstas *et al*[10] treated glaucoma patients with timolol 0.5% twice a day plus latanoprost 0.005% once a day; a group of patients at mornings and the other at bedtime. Finally, they extrapolated that in spite of acceptable IOP reduction in both groups, it is better to use it at night time in order to have a plausible IOP within waking hours. Therefore, in the 1st phase of our study, all patients were treated with Latanoprost 0.005% at bedtime.

One drop of Latanoprost contains approximately 1.5 μg of the drug. After topical administration to both eyes, the maximum plasma concentration of the free acid is 10^{-10} mol/L. The plasma half-life is 17 minutes. The free acid is metabolized by the liver to inactive metabolites. These metabolites are typically excreted primarily in the urine and don't accumulate with chronic dosing[11]. The peak aqueous humor concentration of the free acids of Latanoprost occurs between 2 and 3 hours after dosing[12].

Sjoquist and Stjernschantz evaluated aqueous samples from patients with cataract who were treated with Latanoprost at 0.5-24 hours before surgery. Latanoprost acid was detected by radioimmunoassay in all aqueous samples and reached a maximum of about 100nmol/L, approximately 2.5-fold the maximum mean level measured after a single dose of Latanoprost in this study(41.3nmol/L)[11].

In a study conducted by Dubiner *et al*[12] to compare diurnal IOP control with Latanoprost over a 44 hours period; they found that Latanoprost provides excellent diurnal IOP control through a 24 hours period.

In another study, the efficacy of once versus twice dailyLatanoprost was examined and elucidated that one drop a day is significantly better in regard to IOP reduction[10]. A similar result was recovered by Linden *et al*[14]. In addition, a group of investigators compared the effect of Latanoprost one or four times daily on each eye of healthy individuals. They detected a better IOP reduction in 4-dosage daily group just in first 2 days and thereafter, no significant difference was found[7]. Reduction of IOP by Travoprost and Latanoprost was significant up to 48 hours in a study[14], 84 hours in another one[12] and even 3 weeks in a study done in Sweden[7]. Obviously we could not argue about the cause of this finding but some other studies accused the prostaglandin receptor subsensitivity[12]. According to the above mentioned data we compared the efficacy of once daily with once every other day dosing of Latanoprost in a 12-week follow-up and we found that although the IOPs were lower than baseline in both groups (once at night *vs* once every other night), IOPs were significantly lower in once at night group.

According to the study of Nilforushan *et al*[15], Xalatan with dosage of once every other day was either effective in patients with primary open angle glaucoma or ocular hypertension (OHT). Our study was similar but did not include ocular hypertention cases. Also, we handled with Latanoprost (Lataprost, Sina Darou, Iran). In contrast to former study, we found a statistically significant lower IOPs in once at bedtime dosage in spite of plausible IOPs in both groups. Nilforushan et al[15] found the every other day dosage to be as effective as conventional one but our results were not as definite. A possible reason could be the incorporation of OHT cases which we excluded them. Demographic differences would be another culprit.

Up to 2 weeks after the initiation of 2nd phase of the study, 66% of patients did not encounter any change in their IOPs but after 2 up to 12 weeks (within 2nd phase) the number of patients who experienced elevated IOPs were gradually

increased and reached to 69.8 % in week 12 while only 18% still maintained the IOPs of 1st phase. This finding shows that the change in protocol, would not dramatically alter the IOP but as the time passes, the new protocol discloses its lower efficacy versus conventional dosage. We can attribute it to gradual washout of the high doses of the drug. The longer half-life of Latanoprost in aqueous humor and ciliary muscle would properly cover the first 2 weeks of 2nd phase but gradually this phenomenon fades. In the study of Linden *et al*[7,16,17], the efficacy of the 4 times a day Latanoprost was significantly better in first 2 days but not thereafter. They ascribed this entity to the subsensitivity of the receptors. Structural changes in the ciliary muscle have been reported with $PGF_2\alpha$, and additional studies suggest that Latanoprost is involved in the remodeling of the extracellular matrix in the ciliary muscle. This might explain why IOP was not increased to baseline after decreasing the dosage[18].

In different studies which were accomplished on prostaglandins, there were cases that faced side effects of medications such as ocular surface irritation, iritis, blurred vision and*etc*. So, some of them did not complete the study[7,16,17]. We excluded 8 cases within study due to approach of IOPs to unacceptable levels (3 of them in the 1st phase and 5 of them in the 2nd phase). If we concentrate on details, it is clear that 5 of them had 1st phase IOPs of 20 mmHg or higher. Therefore, we can cautiously conclud that patients with higher initial IOPs are prone to face higher IOPs by this novel protocol and following of the conventional instructions is equitable.

All studies have limitations that might affect the interpretation of the results. In this study, although the patients were changed to the once every other day protocol, however this was a short-term study on limited time points and due to ethical points we could not consider a washout drug free period for participants . Additional studies are needed to provide 24-hour IOP control after short term and long term decrease ofLatanoprost dosage and considering enough time as a washout period for drug.

In conclusion, the present study shows the superiority of the conventional dosage ofLatanoprost 0.005% in comparison with one drop every other day but at least in first few weeks, the IOPs are reasonably close to each other. In higher initial IOPs, this protocol is not advisable because of the risk of an unacceptable IOP control. Further studies with more cases would elicit broader insight.

REFERENCES

1 Alexander CL, Miller SJ, Abel SR. Prostaglandin analog treatment of glaucoma and ocular hypertension. *Ann Pharmacother* 2002;36(3):504-511

2 Stjernschantz JW. From PGF(2alpha)-isopropyl ester to Latanoprost: a review of the development of Xalatan: the proctor lecture. *Invest Ophthalmol Vis Sci* 2001;42(6):1134-1145

3 Lee AJ, McCluskey P. Clinical utility and differential effects of prostaglandin analogs in the management of raised intraocular pressure and ocular hypertension. *Clin Ophthalmol* 2010;4:741-764

4 Mietz H, Esser JM, Welsandt G, Kociok N, Hueber A, Joussen A, Esser P, Krieglstein GK. Latanoprost stimulates secretion of matrix metalloproteinases in tenon fibroblasts both *in vitro* and *in vivo*. *Invest Ophthalmol Vis Sci* 2003;44(12):5182-5188

5 Lindsey JD, Kashiwagi K, Kashiwagi F, Weinreb RN. Prostaglandine action on ciliary smooth muscle extracellular matrix metabolism: implications for uveoscleral outflow. *Surv Ophthalmol* 1997;41(Suppl 2):S53-59

6 Sorkhabi R, Alipanahi R, Eftakhari-Milani A, Ghojazadeh L. The influence of topical Diclofenac sodium on the ocular hypotensive effect of Latanoprost in glaucoma patients. *J Glaucoma* 2011;20(4):240-243

7 Lindén C, Alm A. The effect on intraocular pressure of Latanoprost once or four times daily. *Br J Ophthalmol* 2001;85(10):1163-1166

8 Alm A, Widengård I, Kjellgren D, Söderström M, Friström B, Heijl A, Stjerschantz J. Latanoprost administered once daily caused a maintained reduction of intraocular pressure in glaucoma patients treated concomitantly with Timolol. *Br J Ophthalmol* 1995;79(1):12-16

9 Lindén C, Alm A. Effects on intraocular pressure and aqueous flow of various dose regimens of Latanoprost in human eyes. *Acta Ophthalmol Scand* 1997;75(4):412-415

10 Konstas AG, Nakos E, Tersis I, Lallos NA, Leech JN. A comparison of once-daily morning *vs* evening dosing of concomitant Latanoprost/Timolol. *Am J Ophthalmol* 2002;133(6):753-757

11 Sjöquist B, Stjernschantz J. Ocular and systemic pharmacokinetics of Latanoprost in humans. *Surv Ophthalmol* 2002;74(Suppl 1):S6-12

12 Bean GW, Camras CB. Commerically available prostaglandin analogues for the reduction of intraocular pressure : simillsrities and differences. *Surv Ophthalmol* 2008;53:S69-84

13 Dubiner HB, Sircy MD, Landry T, Bergamini MV, Silver LH, Darell Turner F, Robertson S, Andrew RM, Weiner A, Przydryga J. Comparison of the diurnal ocular hypotensive efficacy of Travoprost and Latanoprost over a 44-hour period in patients with elevated intraocular pressure. *Clin Ther* 2004;26(1):84-91

14 García-Feijoo J, Martínez-de-la-Casa JM, Castillo A, Méndez C, Fernández-Vidal A, García-Sánchez J. Circadian IOP-lowering efficacy of Travoprost 0.004% ophthalmic solution compared to Latanoprost 0.005%. *Curr Med Res Opin* 2006;22(9):1689-1697

15 Nilforushan N. A comparison of intraocular pressure-lowering effect of Latanoprost 0.005% with two different dosing regimen: once daily and once every other day. Abstract book of 19th Iranian congress of ophthalmology, 2009:94

16 Lindén C, Alm A. Latanoprost twice daily is less effective than once daily: indication of receptor subsensitivity? *Curr Eye Res* 1998;17(6):567-572

17 Gross RL, Peace JH, Smith SE, Walters TR, Dubiner HB, Weiss MJ, Ochsner KI. Duration of IOP reduction with Travoprost BAK-free solution. *J Glaucoma* 2008;17(3):217-222

18 Ocklind A. Effect of Latanoprost on the extracellular matrix of ciliary muscle. A study on cultured cells and tissue sections. *Exp Eye Res* 1998;67(2):179-191