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Original research

Comparison between Betamethasone, Fluorometholone and Loteprednol Etabonate on intraocular pressure in patients after keratorefractive surgery

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Abstract

Purpose: The aim of this study was to compare the ocular hypertensive effect of the commercially available Betamethasone, Fluorometholone in Iran and Loteprednol Etabonate in patients undergoing keratorefractive surgery.

Methods: In this prospective randomized clinical trial, 300 eyes of 150 patients were included, and patients were randomly assigned to 3 groups and used one of the 3 steroid drops (Betamethasone 0.1%, Fluorometholone 0.1%, and Loteprednol Etabonate 0.5%) after myopic photorefractive keratectomy (PRK). Intraocular pressure (IOP) was measured 2, 4, and 6 weeks post-surgery. Twenty-two mmHg was set as the threshold IOP for starting anti-glaucoma medication and tapering steroid drops.

Results: Of 300 eyes from 150 patients over the first 6 postoperative weeks, 2 eyes in Fluorometholone group (2%), 12 eyes in Betamethasone group (12%), and 16 eyes in Loteprednol group (16%) had IOP equal or more than 22 mmHg. Analysis of variance (ANOVA) test showed that the rise in IOP was significantly different between groups in the 2nd and 4th ($P \leq 0.001$) postoperative weeks but not at 6th week ($P = 0.230$). An IOP rise equal or more than 10 mmHg was detected in 13 and 15 eyes in Betamethasone and Loteprednol groups, respectively. None of the eyes in Fluorometholone group had such an IOP rise.

Conclusions: Loteprednol and Fluorometholone were associated with the most and least increase in IOP, respectively. The highest pressures were detected 4 weeks after surgery in the Betamethasone and Loteprednol groups and 6 weeks after surgery in the Fluorometholone group. Fluorometholone was the safest among the three examined steroid drops in terms of IOP rise.

Keywords: Steroid induced glaucoma; Loteprednol etabonate; Keratorefractive surgery; Photorefractive keratectomy

Introduction

Steroids are one of the most commonly used drugs in ophthalmology with a long list of possible indications; however their usage is limited because of their known side-effects, including ocular hypertension. This association has been confirmed in literature and different preparations are classified according to this association.

Patients whose intraocular pressure (IOP) rises significantly after using steroids are known as steroid responders which generally constitute 18–36% of the general population and in most cases IOP returns to baseline within 1–3 weeks of discontinuing treatment.[1]

Mechanism underline this hypertensive effect is related to increased extracellular matrix material that leads to trabecular meshwork (TM) spaces narrowing with increased outflow resistance.[2–4] Moreover, structural changes in TM cells have also been proposed as a possible mechanism,[5,6] and all of these have been attributed to a variety of gene expressions induced by steroids.[7]

Risk factors of steroid-induced ocular hypertension include primary open-angle glaucoma (POAG), first degree relative of

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POAG, glaucoma suspect, angle recession, high myopia, connective tissue diseases (especially rheumatoid arthritis in men), old age or less than 6 years, and type 1 diabetes mellitus (DM).[8]

There is evidence that the more potent the steroid preparation, the greater the ocular hypertensive effect[9] and earlier the onset.[2] It has been postulated that the duration and severity of response is inversely related to drug solubility.[10] Several studies showed that Fluorometholone and Medrysone, which are less potent corticosteroids, are associated with much less risk of IOP rise, and also new preparations such as Loteprednol and Rimexolone are comparable to Fluorometholone.[1,11,12]

Loteprednol is a c-20 ester corticosteroid that seems to achieve the balance between solubility/lipophilicity, tissue distribution, glucocorticoid receptor (GR) binding, and metabolic deactivation, and its absence of adverse effects such as cataract formation and ocular hypertension has been confirmed in some studies.[13,14] It has been proposed that Loteprednol undergoes hydrolysis in the cornea and aqueous humor to form inactive derivative and does not have a marked effect on the IOP.[15]

Topical steroids have been used frequently after keratorefractive procedures to decrease inflammation, pain and haze formation for many years.[16–18] With increased popularity of refractive surgeries, more cases of severe IOP rise after these surgeries have been reported.[19,20] In this study, we investigated the effect of three most frequently used steroid drops after keratorefractive surgery on IOP.

Methods

In this prospective, randomized clinical trial, a total of 300 eyes of 150 patients were included. The sample size was calculated based on a type I error of 0.01 and with an assumed power of 95%. Candidates for photorefractive keratectomy (PRK) were randomized into 3 groups using computer-generated random numbers (each consisted of 100 eyes of 50 patients) and matched according to age and sex. All surgeries were performed by one surgeon, and to prevent bias, drops were given by somebody else. The study adhered to the tenets of the Declaration of Helsinki, and its protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences.

Inclusion criteria were candidates of PRK with spherical equivalent between −1 and −4 diopters (D) and central corneal thickness (CCT) of 520–560 μm based on Orbscan (OrbscanIIz, Bausch and Lomb) who signed the written consent to enter the study.

Exclusion criteria were any history of steroid induced ocular hypertension, POAG, first degree relatives of POAG, DM, glaucoma suspect, connective tissue disease, history of corticosteroid usage in the past 2 months, high baseline IOP (≥22 mmHg), any ocular condition contraindicating corticosteroid usage, and any systemic disease or medication capable of affecting IOP (i.e. hypothyroidism).

PRK procedure

Anesthetic drop was applied. Preparation with Povidone-Iodine 10% was done, and eyes were draped. After inserting a lid speculum, absolute alcohol was used for 20 s to loosen the epithelium. Epithelium was gently removed with sponge followed by excimer laser ablation of the stroma (Technolas, Bausch and Lomb). Mitomycin C 0.02% was applied to the surgical bed according to the depth of ablation, and the eye was thoroughly rinsed. Bandage contact lens was placed at the conclusion of surgery.

Topical levofloxacin (OFTAQUIX 5 mg, unit dose, Santen Pharmaceutical, Osaka, Japan) was started every 6 h for 1 week, topical steroid every 6 h for 10 weeks, and artificial tear (Artelac Advanced, Bausch Lomb, New York, United States) every 3 h for 2 months and every 6 h for 4 months. Bandage contact lens was removed after 1 week with confirmation of complete epithelial healing.

Betamethasone (Betasonate 0.1%, Sina Darou, Tehran, Iran), Fluorometholone (Fluocort 0.1%, Sina Darou, Tehran, Iran), and Loteprednol Etabonate (Lotemax 0.5%, Bausch Lomb, New York, United States) were given to each group every 6 h for 6 weeks. Loteprednol was recommended to be shaken completely before usage according to the manufacturer instruction. After 6 weeks all 150 patients used Fluorometholone up to 10 weeks based on the surgeon's previous protocol.

Baseline IOP was measured with Goldmann applanation tonometer (AT 900, Haag-Streit) and rechecked 2, 4, and 6 weeks postoperation and compared with baseline. The main goal was to compare the number and percentage of patients with IOP rise up to 22 mmHg or higher who needed anti-glaucoma medication in 3 groups, and secondary outcome measure was to compare the number of patients with IOP rise equal or more than 10 mmHg in 3 groups.

In each session if the IOP was 22 mmHg or higher, anti-glaucoma medications were started and steroid drop was tapered. We started with Timolol (Optimol 0.5%, Sina Darou, Tehran, Iran) for IOP less than 30 mmHg and added Dorzolamide (Dorzamid 2%, Sina Darou, Tehran, Iran) if the IOP was higher. For patients referred with IOP more than 40 mmHg, headache, and blurring of vision, oral Acetazolamide (Mehr Darou, Tehran, Iran) was prescribed. Patients visited one week later, and according to their response, anti-glaucoma medications titrated and appropriate follow-up visits were set. Last IOP measurement for this study was done 12 weeks after the procedure.

Statistical analysis was done using SPSS version 11.5 (SPSS Science Inc., Chicago, Illinois, USA). To compare IOP between groups in every follow-up, we used ANOVA test and Kruskal Wallis test. We also used the Post Hoc test and Mann Whitney test to compare each pair of groups.

Repeated measure test was used to study whether IOP was significantly elevated during follow-up time and if this was related to the type of used steroid drop.

Results

Three-hundred eyes from 150 patients were included. Table 1 provides preoperative characteristics of patients. There was no statistically significant difference between groups in age, sex, refraction, and CCT.

Table 1
Preoperative characteristics of patients.

	Fluocort	Betasonate	Lotemax	Total	*P*-value
Age (years)	n = 50	n = 50	n = 50	n = 150	
Mean ±SD	27.44 ± 0.551	29.06 ± 0.672	27.48 ± 0.664	27.99 ± 0.367	0.121
Median (range)	28 (19–38)	28 (19–44)	28 (19–41)	28 (19–44)	
Sex	n = 50	n = 50	n = 50	n = 150	
Male	Male = 24	Male = 24	Male = 25	Male = 74	0.974
Female	Female = 26	Female = 26	Female = 25	Female = 76	
Sphere (D)	n = 100	n = 100	n = 100	n = 300	
Mean ±SD	−3.045 ± 0.067	−2.956 ± 0.684	−3.098 ± 0.066	−3.034 ± 0.389	0.344
Median (range)	−3.00 (−4.00, −1.00)	−3.00 (−4.00, −1.25)	−3.00 (−4.00,−1.5)	−3.00 (−4.00, −1.25)	
Cylinder (D)	n = 100	n = 100	n = 100	n = 300	
Mean ±SD	−0.417 ± 0.042	−0.0307 ± 0.039	−0.39 ± 0.043	−0.371 ± 0.224	0.146
Median (range)	−0.5 (−1.00–0.00)	0.00 (−1.00–0.00)	−0.25 (−1.00–0.00)	−0.25 (−1.00, 0.00)	
CCT (μm)	n = 100	n = 100	n = 100	n = 300	
Mean ±SD	540.51 + 1.129	539.77 ± 1.131	539.67 ± 1.127	539.98 ± 650	0.848
Median (range)	541.5 (521–560)	542.01 (520–559)	541 (521–560)	541.5 (520–560)	

D: Diopter, SD: Standard deviation, CCT: Central corneal thickness.

Mean preoperative IOP was 13.07 (range, 10–17 mmHg), which was not significantly different between groups ($P = 0.06$). Two weeks postoperation and after starting steroid drops, the mean IOP was 13.29 (range, 11–18 mmHg), and it was not statistically significantly different between the 3 groups; however, in the Loteprednol group, IOP in 4 eyes were 19–20 mmHg. Anti-glaucoma drops were not indicated in any group.

Two weeks later, the situation was a bit different. The mean IOP increased to 13.97 (range, 11 to 42), and 16 eyes (5.3%) needed anti-glaucoma medications based on IOP equal or more than 22 mmHg; 8 eyes in the Betamethasone group (22–27 mmHg) and 8 eyes in the Loteprednol group (26–42 mmHg). For this subset of patients, more frequent visits were scheduled.

Six weeks postoperation, 2 eyes in the Fluorometholone group had IOP equal to 22 mmHg. Four eyes in the Betamethasone group (22–28 mmHg) and 8 eyes in the Loteprednol group (22–25 mmHg) had IOP equal to 22 mmHg or higher.

Overall, 2 eyes in Fluorometholone group (2%) 6 weeks postoperation, 12 eyes in Betamethasone group (12%), and 16 eyes in Loteprednol group (16%) 4–6 weeks postoperation had high IOP attributable to steroid use. Anti-glaucoma medication was started for them, steroid drops tapered, and patients were followed as previously stated. In the last visit after 12 weeks, all patients were free of steroid and anti-glaucoma medication with normal IOP.

The IOP rise was significantly different between groups in the 2nd and 4th postoperative weeks ($P \leq 0.001$ for both, ANOVA test); however, the difference was not statistically significant at 6 weeks ($P = 0.230$).

In comparing groups 2 by 2 with Post Hoc and Mann Whitney test, the IOP was not significantly different between the Fluorometholone and Betamethasone groups in any visit. When comparing the Fluorometholone and Loteprednol groups, the IOP was significantly higher in the Loteprednol group 2 and 4 weeks after surgery; however, the difference was not significant at the 6th week. Finally, comparing the Betamethasone and Loteprednol groups, IOP was significantly higher in the latter group 4 weeks after surgery.

Fig. 1 shows box plots of IOP 2, 4, and 6 weeks after surgery and starting steroid drops in the 3 groups.

We also classified eyes based on the magnitude of IOP rise in to 3 groups: Group A, less than 6 mmHg; Group B, equal or more than 6 but less than 10 mmHg; and Group C, equal or more than 10 mmHg. In the Fluorometholone group, 4 eyes were in Group B, and the others were in Group A. In the Betamethasone group, 6 eyes were in Group B, 13 eyes in Group C, and the others were in Group A. Finally in the Loteprednol group, 5 eyes were in Group B, 15 eyes were in Group C, and the remaining were in Group A (Table 2).

Fig. 2 shows comparison of mean IOP before and 2, 4, 6 weeks after surgery, and Tables 3 and 4 give numerical data with *P* value in each measurement time.

Discussion

Several studies indicated that the response to steroids depends on the baseline IOP of the patient.[1,8] In our study,

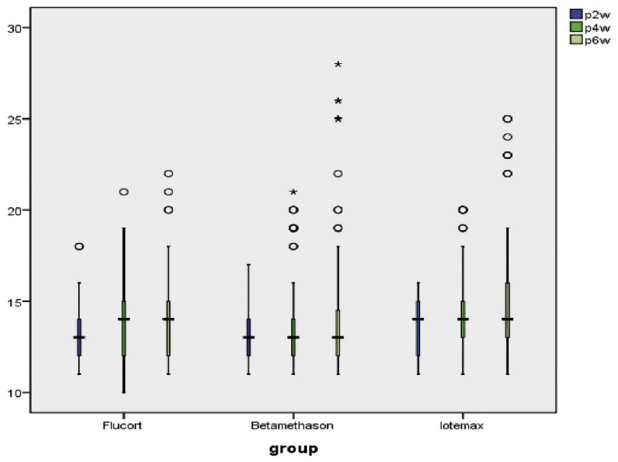

Fig. 1. Box plot of intraocular pressure (IOP) in Y axis and steroid drops in X axis. 2nd, 4th, and 6th week measurements exhibited in different colors.

Table 2
Magnitude of rise in intraocular pressure (IOP).

	Fluocort n = 100	Betasonate n = 100	Lotemax n = 100
Group A: Less than 6 mmHg	96	81	80
Group B: More than 6 and less than 10 mmHg	4	6	5
Group C: More than 10 mmHg	0	13	15

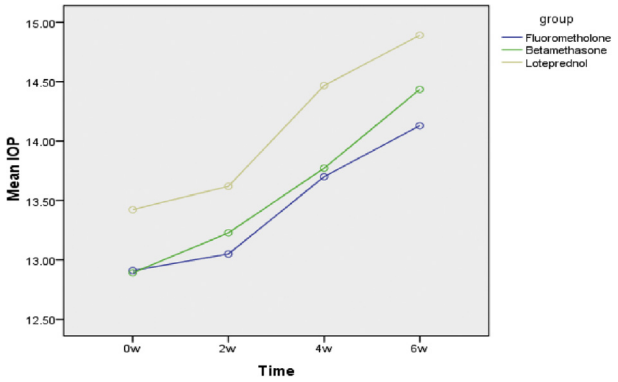

Fig. 2. Changing intraocular pressure (IOP) with time in 3 groups.

Table 3
Mean, median and range of intraocular pressure (IOP) in each group with *P* values comparing 3 groups (ANOVA test).

Medication IOP	Fluocort	Betasonate	Lotemax	P-value
Preop				
Mean ± SD	12.91 ± 1.303	12.891 ± 1.379	13.424 ± 1.48	0.06
Median (range)	13 (10–16)	13 (10–16)	14 (11–17)	
2w postop				
Mean ± SD	13.05 ± 1.487	13.229 ± 1.491	13.62 ± 1.316	<0.001
Median (range)	13 (11–18)	13 (11–17)	14 (11–16)	
4w postop				
Mean ± SD	13.7 ± 1.97	13.77 ± 2.396	14.467 ± 2.146	
Median (range)	14 (10–21)	13 (11–21)	14 (11–20)	0.001
6w postop				
Mean ± SD	14.13 ± 2.135	14.435 ± 3.707	14.891 ± 3.243	
Median (range)	14 (11–22)	13 (11–28)	14 (11–25)	0.230

IOP: Intraocular pressure, Preop: Preoperative, Postop: Postoperative, SD: Standard deviation.

preoperative IOP of the participants was in the normal range and not significantly different between groups. Age and high myopia are among risk factors for steroid induced ocular hypertension. More studies need to be done in order to determine whether or not sex is a risk factor because the results are mixed.[8,21] Although high myopia is considered a risk factor for corticosteroid induced IOP rise, in Park et al.'s study, no correlation was demonstrated between high myopia and IOP elevation.[22,23] To minimize bias, we matched groups based on age and sex and omitted the effect of high myopia by selecting the participants with myopia between −1 and −4 D. Studies confirmed that IOP was underestimated in patients with lower CCT such as after keratorefractive procedures.[24] CCT was measured before surgery and was between 520 and 560 μm, which is the average thickness with good performance of Goldmann tonometer. In addition, as ablation in our study was for mild myopia, no adjustment seems to be needed for IOP measurements postoperation.

Different studies use different definitions of steroid induced ocular hypertension which makes comparison between them a bit difficult, but the most accepted criteria are a rise of ≥10 mmHg above baseline or IOP more than 21 mmHg, which were both used.

Becker first defined steroid responders in 1965 and reported that IOP rises in 30% of normal eyes to over 20 mmHg and in 4% to above 30 mmHg after using Betamethasone drop.[25] After that, Armaly studied topical administration of Dexamethasone for 4 weeks and reported IOP rise ≥15 mmHg in 4–6% of participants, approximately one-third of whom had an IOP rise of 6–15 mmHg, and the remaining two thirds had a pressure rise of less than 6 mmHg.[26] They also used topical corticosteroids for 4–6 months and reported IOP rise of 6–15 mmHg in 30% and 16 mmHg or more in 5% of patients.[27]

The incidence of steroid induced ocular hypertension after myopic PRK was studied in literature. Javadi et al. used Betamethasone 0.1% four times a day and reported that overall, ocular hypertension developed in 7.9% of eyes: in 40%, 2–3 weeks postoperatively, in 50%, after 4–6 weeks, and in 10%, 8–12 weeks after PRK.[28] In a study by Sang Myung Kim et al., IOP rise developed in 7.63% of subjects, and the average increase in IOP was 5.62 ± 3.73 mmHg.[29] Busool et al. defined ocular hypertension as an IOP elevation of 25% while on topical steroid treatment (minimum 28 mmHg) followed by an IOP drop of 25% when steroid treatment was discontinued and found that 2.97% of their participants were steroid responders.[21]

With an average IOP of 13 mmHg, we had 30 eyes of the total 300 with IOP exceeding 21 mmHg (10%) up to 6 weeks after starting steroid drops. Also, the frequency of IOP rise, equal, or more than 10 mmHg was 0%, 13%, and 15% in Fluocort, Betasonatem and Lotemax groups, respectively (average 9.3%).

Two pivotal clinical trial are available in literature about Loteprednol, reporting IOP elevation ≥10 mmHg in 2.7% and 0.0% of participants; however, the duration of these studies

Table 4
P values comparing 3 groups 2 by 2 (Post Hoc test).

	P before			P 2w			P 4w			P 6w		
	Fluocort	Betasonate	Lotemax	Fluocort	Betasonate	Lotemax	Fluocort	Betasonate	Lotemax	Fluocort	Betasonate	Lotemax
Fluocort	–	0.918	0.081	–	0.117	<0.001	–	0.124	<0.001	–	0.493	0.088
Betasonate	0.918	–	0.244	0.117	–	0.14	0.124	–	0.020	0.493	–	0.315
Lotemax	0.081	0.244	–	<0.001	0.14	–	<0.001	0.020	–	0.088	0.315	-

was only 2 weeks.[30,31] Also according to previous studies, the cumulative proportion of patients exhibiting clinically significant IOP increases ≥10 mmHg) was 0.8% in short-term Loteprednol treatment (<28 days) and 1.5% in long-term (>28 days).[32] In our study, results were different. The highest rate of IOP rise (16%) was in the Loteprednol group, with several cases with IOP exceeding 40 mmHg. In the Betamethasone group, we observed IOP rise in 12% of subjects. In contrast, the lowest rate of IOP rise was in the Fluorometholone group with only 2% of subjects needing antiglaucoma medication.

In one recent study comparing the effect of Loteprednol and Fluorometholone on IOP rise after myopic PRK, the authors found no ocular hypertension (IOP rise >10 mmHg or IOP>21 mmHg) in 124 eyes of 62 patients; their results are in sharp contrast with previous studies and our study,[21,33] and this could be explained by differences in study population and ethnic backgrounds.

So this study indicates that the percentage of increase of IOP was most with Loteprednol and least with Fluorometholone. Moreover this steroid-induced ocular hypertension was evident 4 weeks after prescription in Betamethasone and Loteprednol groups and postponed to 6 weeks in Fluorometholone group.

We believe that there could be 3 reasons to describe this discrepancy with other published studies which claim that Loteprednol is one of the safest steroid drops in terms of IOP elevation. First, in almost all other studies, the investigators compare Lotemax with Fluorometholone and Betamethasone as a brand and not in their generic forms; however we compare Lotemax with Betasonate and Fluocort which are available in Iranian pharmacopeia, and this result can be attributed to the lower potency of these alternatives compared to the brands. Second, in contrast to the other 2 drops, Lotemax is a suspension and should be shaken vigorously before usage. It is possible that sticking to this instruction was difficult for the patients. Third, and the least probable explanation, is that the distribution of steroid responders was not uniform in the 3 groups.

Time of corticosteroid induced ocular hypertension depends on many factors such as type of drug, dosage, frequency, route of administration, and susceptibility of patient.[8] It was seen in our study that response to Betamethasone and Loteprednol was earlier and significantly more severe compared to Fluorometholone.

In summary, we had 30 eyes out of 300 with IOP more than 21 mmHg (10%) after initiation of steroid treatment, 43 eyes with IOP rise more than 6 mmHg (14.3%), and 28 eyes with more than 10 mmHg increase in baseline IOP (9.3%).

The shortcomings of current study were using commercial available brands of Fluorometholone and Betamethasone in Iran, which might be different from those available in other countries. Hence comparison with other studies is difficult, and the result cannot be generalized. Second, the duration of follow-up was short. Finally, as we compared 3 drugs we cannot use different drugs on 2 eyes of one person and omit the effect of being steroid responder or not.

In conclusion, among the available steroid drops in Iranian pharmacopeia which are routinely prescribed after keratorefractive surgery, Fluocort was the safest, and the others, Betasonate and Lotemax, were associated with IOP rises especially 4 weeks post-surgery. Ophthalmologists should be vigilant about this side effect and closely monitor IOP in post-refractive cases, especially when more potent steroids are used.

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