ORIGINAL RESEARCH

Intraocular pressure changes after cataract surgery with topical difluprednate 0.05%

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Abstract

Background: Topical corticosteroids are commonly used after cataract surgery to decrease ocular inflammation. One of the common side effects of topical steroids include increased intraocular pressure (IOP). This study was undertaken to determine the incidence of increased intraocular pressure with the use of topical difluprednate 0.05%ophthalmic emulsion.

Methods: This hospital based, prospective, observational cohort study was done over a period of three months. The study involved a total of 75 non-glaucomatous eyes of consenting, inclusion-eligible adults of uncomplicated cataract. The cases were operated by same surgeon by manual small incision cataract surgery. All patients were given difluprednate 0.05% eye dropat a starting dose of four times per day which was tapered over a period of four weeks. Evaluation of patients at follow up visits included Goldmannapplanation tonometryat various time points till fourth postoperative week. Appropriate statistical tests like descriptive statistics, paired t-test and chi square test were used.

Results: Amongst the analyzed 65 patients with average age of 66.4 years, 62% were males and 38% females. Average baseline IOP was 14.4 mmHg. Rise in IOP above 20mmHg was found in three subjects (4.6%). Of these, one patient had an increase in IOP that was 5mmHg above baseline (>20% over baseline). IOP was managed by discontinuation of difluprednatedrop. All patients responded to treatment returning to baseline.

Conclusion: Patients receiving topical ocular steroids, especially difluprednate have to be followed regularly with IOP monitoring. Caution need be exercised for steroid-responders and the drug discontinued on elevation of IOP.

Keywords: Difluprednate, Intraocular pressure, Cataract surgery, Corticosteroids, Glaucoma.

Introduction

Topical corticosteroids have been routinely used in the treatment of post-operative inflammation following cataract surgery as well as after most other ocular surgical procedures.[1-6] Side effects of topical steroids include increased intraocular pressure(IOP), cataract formation and increased chances of infection.[7-9] Elevated IOP, if left untreated, may progressto corticosteroid-inducedglaucoma.[10,11]As per past literature, about 5% of the population may be classified as 'steroid responder'. These eyes have more chance of raised IOP. Some elements that have been implicated to increase the risk of corticosteroid-induced increase in IOP, include a history of glaucoma, advanced age, diabetes and high myopia.[12-15]In many developing countries, follow-up rates after ophthalmic surgeries are as low as 20-30%.[16]The compliance to postoperative regimen and proficiency of eye drop instillation is also poor in developing countries.In a study done in India on the knowledge, attitude and self- care practices pertaining to eye drop compliance, it was revealed that almost 30% of patients believe that there is no problem with 'back to back' eye drop instillation, 42% patients reported not washing their hands before instillation and about 45% missed their prescribed dosage.[17]It has been reported that compliance to medication improves dramatically as prescribed dose frequency decreases. One of the prime way to improve compliance is to select medications with the lowest daily dose frequency.[18]Owing to such reasons, it is logical that ophthalmologists would like to prescribe an eye drop with maximal efficacy and minimal frequency.Difluprednate ophthalmic emulsion 0.05% (DFBA) is an ophthalmic steroid with high glucocorticoid receptor-binding affinity and superior tissue penetration. It was approved in 2008 by the U.S. Food and Drug Administration(FDA) and is used for the treatment of inflammation and pain in postoperative eyes.[19]DFBA is superior to other topical steroids in controlling ocular inflammation and also has a lower frequency of two to four times daily depending on the severity of inflammation.[20]How-ever, reports have shown an increase in IOP when

used after ophthalmic surgery.[21-26]This study was undertakento determine the incidence of increased IOP with the use of topical difluprednate 0.05%eye drop.

Material &Methods

This hospital based, prospective, observational cohort study was done over a period of three months from June 2019 to August 2019 at a medical college hospital in Central India. The study involved a total of 75 consecutive eyes of consenting, inclusion-eligible adults. Written informed consent was obtained from willing patients and participation was voluntary. No incentive was provided to the participants. All participants were informed about the scope and purpose of the study.The following formula was used to work out the sample size: n= (Z) 2 p (1 – p)/ e2 Where; n= desired sample size, Z= standard error of the mean which corresponds to 95% confidence level (1.96), p= prevalence of condition being studied, e= allowable error (0.05). Prevalence was taken 4.4% as reported in a recent study comprising a large sample size of 1337 cataract operated eyes on DFBA.[27] As per the calculations, 65 or more sample eyes were needed to have a confidence level of 95% so that the real value is within ±5% of the measured value. We included 75 patients in our study.Exclusion criteria for cases were: patients who have had past intraocular surgeries in the concerned eye; patients who had used steroids in any form in recent past; patients with past or present glaucoma/ ocular hypertension/ primary angle closure disease; patients with certain eye diseases as history of uveitis, diabetic retinopathy or maculopathy, pseudoexfoliation syndrome, retinitis pigmentosa, optic atrophy, anterior ischemic optic neuropathy, one-eyed patients etc., patients with significant postural and cognitive impairments and patients with a history of significant hypertension, diabetes mellitus, mental disease, immunosuppression and pregnant or nursing patients.The cases were operated by same surgeon by manual small incision cataract surgery with intraocular lens implantation. For each patient, one eye was included in the study. None of the eyes underwent a secondary intraocular surgery. The postoperative eye drop regimen was standardized across all cases and consisted of a DFBA (Diflucoreye drop, Ajanta PharmaLimited, Mumbai, India) and a fourth-generation fluoroquinolone. After screening, each subject received DFBA with instructions for self-administration, at a starting dose of four times per day. The eye drop was tapered over a period of four weeks.Patients underwent routine ophthalmological examination, including visual acuity assessment and slit lamp examination at all follow-up visits with IOP measurements taken by slit-lamp mounted Goldmannapplanation tonometerwith standardized calibration.The same instrument was used during all measurements. An average of three IOP readings was recorded at all times.IOP measurements in both eyes were collected at various time points, including one day before surgery(baseline- BP), two days postoperatively and at first(TP1), second(TP2) and third(TP3) follow-ups till fourth postoperative week, allowing for examination of time-dependent changes in IOP after cataract surgery.First review visit was taken as 5-10 days postoperatively, second review visit considered 11-18 days postoperatively and third follow up was 19- 30 days after surgery. IOP measurements were obtained in the morning clinic time of 10 am to 1pm. High IOP was defined in our study as measuredIOP ≥ 21 mmHgor an increase of IOP of ≥ 10 mmHg from baseline at any time period in the study eye. These values were chosen to concur with the definition of steroid response as well as being clinically significant.27 If any of the eyes reported high IOP, DFBA was replaced with nepafenac 0.1% eye drop. The study adhered to the tenets of the Declaration of Helsinki. Permission and ethical clearance was obtained from the Institutional Ethical Committee of the medical college where the study was conducted.

Statistical Methods

All data was coded, entered and analyzed using Microsoft excel 2010 and Epi info 7 (7.2.2.6, Center for Disease Control and Prevention). Demographic and clinical characteristics of the patients were reported using descriptive statistics. The paired t-test was used to assess the differences in the mean change of IOP from baseline. The relationship between intraocular pressure changes and demographic factors was analyzed using chi-square test of association. Probability value (P) ≤ 0.05 was considered statistically significant.

Results

In this series of 75patients, 10 patients got excluded due to non-compliance to DFBA and insufficient IOP record. There were no major intraoperative complications. Theanalyzed 65 patients had an average age of 66.4± 6.81years.The age of the patients ranged from 26 years to 80 years (Figure 1). 61.54% were males and 38.46% females with a male: female ratio of 1.6:1.Average baseline IOP was 14.4 ± 3.6mmHg (Range 8-18mmHg).Average IOP at first (TP1), second (TP2) and third (TP3) review visits were 14.54mmHg, 14.57mmHg and 14.86mmHg respectively (Figure 2). In majority of cases, there was no statistically significant difference in IOP in review period(Figure 3). High IOP was found in three subjects (4.62%) in the operated eye. Of these, one patient had an increase in IOP that was 5mmHg above baseline (29.41% over baseline). The other two patients had IOP rise of 16.67% and 22.22% from baseline. In all the three patients, IOP was managed by discontinuation of difluprednateeye drop and switching to nepafenac 0.1% eye drop. All patients returned to baseline IOP less than a week after cessation of DFBA.The mean baseline IOP of 14.4

mmHg increased to 14.86 mmHg (SD =2.67) at the third to fourth post-operative week. There was no statistically significant difference in IOP till second week. Statistically significant difference was noted around third to fourth week of follow-up (Table 1).When comparing association of age, gender, laterality of eye, diabetes with increase in IOP; no difference was found at any time point (Table 2).

Variable	Mean (mm Hg)	SD	P value of paired t-test
BP	14.4	2.36	Not applicable
TP1	14.54	2.65	0.44
TP2	14.57	2.67	0.34
TP3	14.86	2.67	0.01

Table 1: **Differences in intraocular pressure over the study period**

Abbreviations: BP- Baseline intraocular pressure, TP1- Intraocular pressure at postoperative 5 to10 days,TP2- Intraocular pressure at postoperative 11 to 18 days, TP3- Intraocular pressure at postoperative 19 to 30 days

Variable	P value of chi square test
Age	0.65
Gender	0.58
Laterality of eye	0.80
Diabetes	0.82

Table 2: **Association of variables with increase of intraocular pressure**

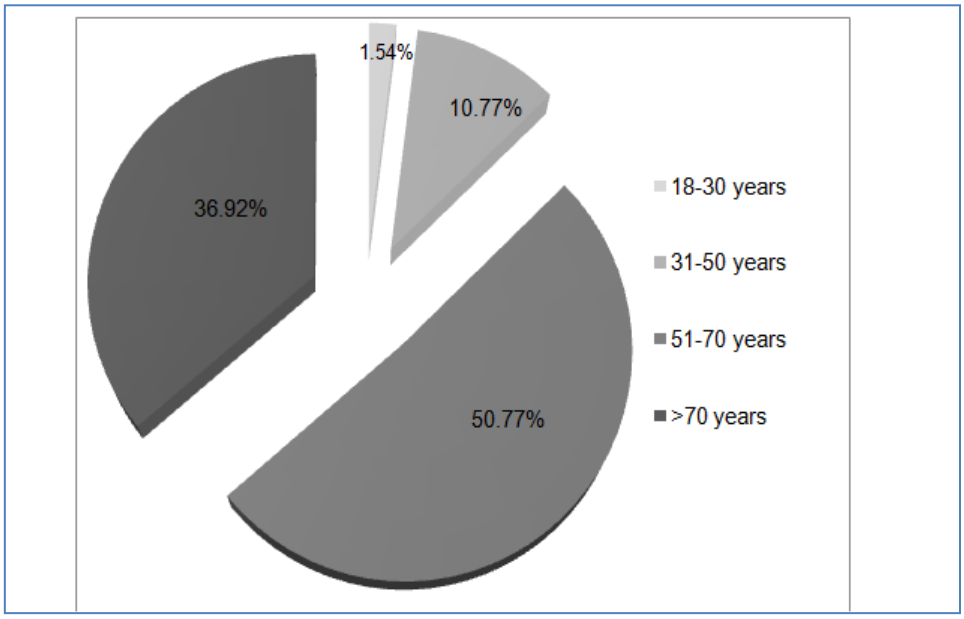

Figure 1: Age Distribution

Abbreviations: IOP- Intraocular pressure; TP1- Intraocular pressure at postoperative 5 to10 days; TP2- Intraocular pressure at postoperative 11 to 18 days; TP3- Intraocular pressure at postoperative 19 to 30 days

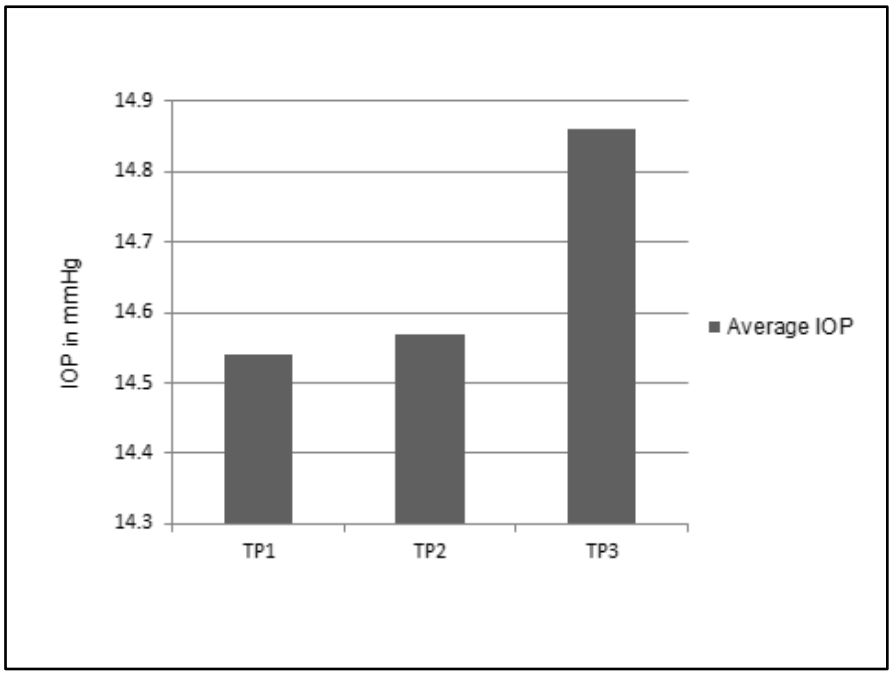

Figure 2: Average intraocular pressure across review visits

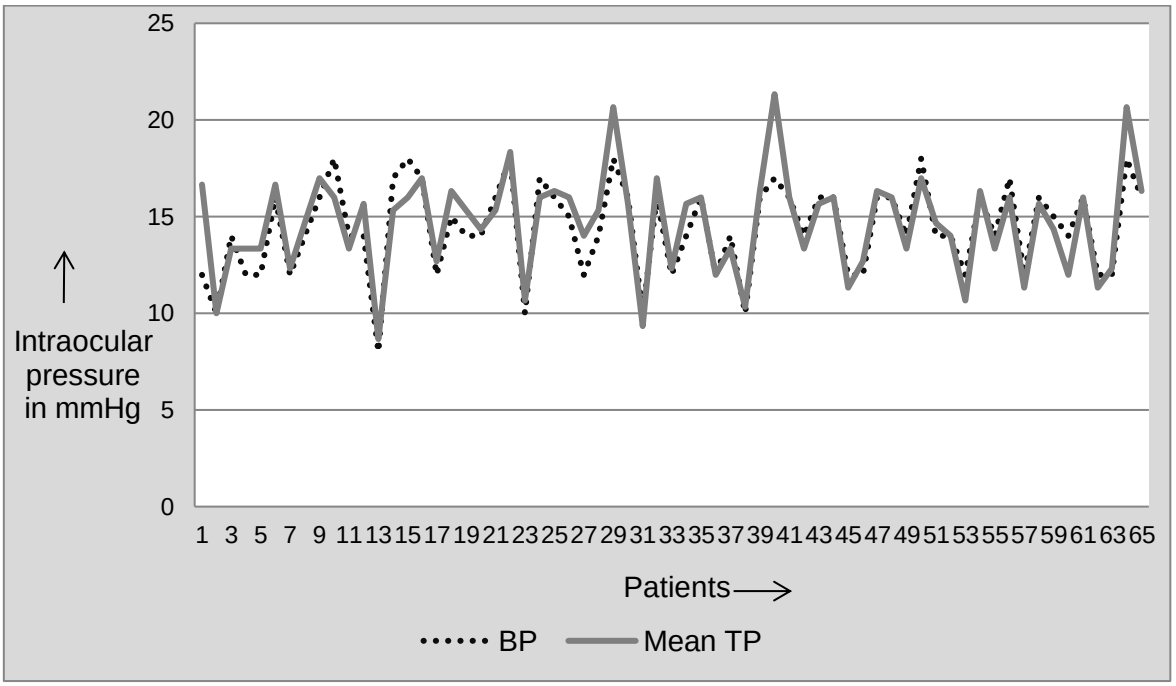

Figure 3: Comparison of baseline intraocular pressure with mean postoperative intraocular pressure in 65 eyesAbbreviations: BP- Baseline intraocular pressure; TP- Mean postoperative intraocular pressure

Discussion

Corticosteroid induced IOP elevation is believed to be due to changes in trabecular meshwork(TM) cells and myocilin gene expression. Deposition of extracellular matrix material and cross linking of actin fibers of TM decrease the outflow of aqueous humor.[28] Structural changes in the TMcause corticosteroid-induced ocular hypertension, which might lead to secondary open-angle glaucoma.[29]Armaly classified IOP steroid response increase into 3 groups: low (≤ 5 mmHg), intermediate (6 to 15 mm Hg), and high (≥ 16 mmHg) with 6 mmHg as the lower limit of a clinically significant response.[30]Stewart et al proposed a significant response to be ≥10 mmHg over baseline.This value has since been adopted by the United States FDA and multiple studies have used this value as clinically significant.[31]In the present study, three eyes of the considered 65 eyes i.e. 4.62% developed high IOP.Korenfeld et al compared the efficacy and safety of DFBA with that of placebo in 438 patients with inflammation after ocular surgery in two studies.[2]In one study, DFBA and placebo were

instilled twice daily and these were used four times daily in the other. In both the DFBA groups, 3% of patients had a significant increase in IOP. IOP increase was noted in 1% of patients in the placebo group. In a similar study by Smith etal, three patients (3.7%) in the difluprednate group had a clinically significant increase in IOP (defined as observed value of ≥21 mmHg that was also a change from baseline of ≥10 mmHg) as compared with none of the patients in the placebo group.[22]Cable et al did a retrospective study wherein data from 100 consecutive, uncomplicated phacoemulsification patients treated with DFBA 0.05% twice dailypostoperatively were analyzed.[25]Increase in IOP was observed in 5% of patients. In Sowbhagya etal studyfrom India, out of 50 patients, four patients from the postoperative group treated with DFBA showed marked increase in IOP.[32]In a similar study to the present from Maharashtra, India, IOP> 21mmHg was reported in two of the 56 postoperative eyes i.e. in 3.57%.[34]In a retrospective study comparing post cataract surgery use of prednisolone acetate !% with difluprednate 0.05%, involving a large sample of 3488 eyes with 1337 eyes in DFBA group,4.4% were found to have significant IOP risein DFBA group.[27]In the retrospective study by Cable, 60% of IOP spikes were noted on first post-operative day and 40% by seventh post-operative day.[25] In Saman et al study, the increase in IOP in the first week in the DFBA group was12%.[35]In a prospective study of steroid usage following cataract surgery in pediatric patients, amongst the forty eyes on DFBA, it was found that the cases of IOP rise occurred between 8-29 days of difluprednate treatment that stabilized after one month.[36]In Sowbhagya et al study, amongst the five cases that showed IOP rise, the presentation was on second day, fifth day and remaining three cases presented with raised pressures on third, fourth and fifth week.[32]In the present study, though the IOP rise was noted through first and second week; but significant rise was noted at third to fourth week of follow up. As per Feroze&Khazaeni, increase in IOP is usually noted 3 to 6 weeks following topical steroid use.[37]Topical steroids have been shown to produce a steroid response over a period of weeks in both normal and glaucomatous eyes and Armaly showed this with provocation testing administering dexamethasone eye drops three times a day to the right eye for 4 weeks, using the left eye as a control.[15]This study has certain limitations. As per literature, post-surgical use of DFBA may reduce corneal thicknesswhich may affect IOP measurement viaGoldmannapplanationtonometry.[21,38]However,
central corneal thickness changes were shown to be most significant within 24 hours of corticosteroid use which return to baseline within 30 days.[21]In present study, IOP was not measured at the 24 hour time period. Hence, corneal thickness changes may not significantly reflect on the results. The effect of diurnal variation of IOP has been limited with IOP measurements at all instances being taken between 10am to 1pm.Difluprednate is the first ophthalmic steroid developed in the past 35 years and the first strong ophthalmic steroid approved by the FDA since 1973. It has high potency and a favorable safety profile.[20]This relatively new approved medication has been a welcome addition to the ophthalmologist's armamentarium and is being increasingly used.The results of this survey add to a growing body of literature that addresses IOP rise with usage of topicaldifluprednate ophthalmic emulsion.

Conclusion

In conclusion, patients receiving topical ocular steroids, especially difluprednate have to be followed regularly with IOP monitoring. All patients should be notified of the potential for increased IOP with the use of DFBA and the importance of follow-up requires to be emphasised. Caution need be exercised for steroid-responders and the drug discontinued on elevation of IOP.

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Source of Funding: None

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