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RESEARCH ARTICLE

TO COMPARE DOSAGE OF DIFLUPREDNATE OPHTHALMIC EMULSION 0.05% WITH PREDNISOLONE ACETATE OPHTHALMIC SUSPENSION 1 % IN POST OPERATIVE INFLAMMATION FOLLOWING CATARACT SURGERY

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ABSTRACT

Purpose: To compare dosage of difluprednate ophthalmic emulsion 0.05% with prednisolone acetate ophthalmic suspension 1 % in post operative inflammation following cataract surgery.

Methods: This was a prospective, randomized, interventional study on 204 patients who underwent small incision cataract surgery with posterior intraocular lens implantation. 102 eyes received the 0.05% difluprednate emulsion, and 102 eyes received the 1% prednisolone acetate suspension. Detailed preoperative assessments were done. The patients were followed up postoperatively on days 1st, 8th, 15th, and 30th.

Results: Parameters like BCVA was noted and there was no significant difference between the BCVA of both groups on 30th day.

Corneal oedema on day 1 was present in 18.61% and 26.47% of subjects in difluprednate group and in prednisolone group respectively. On 8th day corneal oedema resolved in 100% whereas in prednisolone group 5.88% of subjects had corneal oedema. Thus there was early resolution of corneal oedema earlier in difluprednate group.

On post-op day 8, AC inflammation cleared in 96.07% in difluprednate group while in prednisolone group 82.35 % had no AC inflammation. Grade I cells were still present in 3.92% in difluprednate group and 17.64% in prednisolone group, which suggested that clearing of AC inflammation was earlier in difluprednate group.
There was no significant IOP rise in both groups.

Conclusion

The response to 0.05 % difluprednate emulsion was equally effective to 1% prednisolone acetate suspension in controlling inflammation after Small incision cataract surgery, with added advantage of reduced dosage.

INTRODUCTION

Major advances in surgical technique and instrumentation have taken place in the past few decades however patient expectations of the surgical outcomes also have increased proportionately. Visual rehabilitation after cataract surgery is often delayed due to the inflammatory responses induced by the procedure. During ocular surgery there is disruption of blood aqueous barrier which leads to post operative ocular inflammation like conjunctival congestion, corneal oedema and iritis. The handling of anterior segment structures during surgery, releases arachidonic acid from cell membranes, which leads to the production of prostaglandins and leukotrienes[1]. These inflammatory mediators lead to cellular reaction and protein leakage which gives the clinical findings of cells, flare and cystoid macular oedema[2]. Chronic inflammations may lead to complications like secondary glaucoma, anterior uveitis or keratopathy[1]. Thus reducing the inflammation and its potential damage is very essential for better visual rehabilitation.

Post operative topical corticosteroids are used to reduce inflammation and improve the visual outcome in cataract surgery since they efficiently block the release of inflammatory mediators. Difluprednate is a first strong ophthalmic steroid developed in last 30 years and is effective in treating both operative inflammation and uveitis[1]. In June 2008 the US Food and Drug Administration approved difluprednate ophthalmic emulsion 0.05%, a potent topical

steroid, for the treatment of postoperative ocular inflammation.[3]

With the technological advances in ophthalmic preparations, the topical corticosteroids are now available in various forms. The dose uniformity of a ophthalmic preparation depends on the homogeneity of the of the formulation , which is present in a emulsion with increased bioavailability but still a concern for a suspension.[4] Emulsions are oil in water preparations with the drug molecule dissolved in the oil phase and aqueous-compatible surfactant provides emulsion stability . The active ingredient in each drop of emulsion delivers a consistent concentration of the drug without the need of thorough shaking. Prednisolone acetate ophthalmic suspension always requires vigorous shaking for a consistent concentration of the drug, which is often neglected. [7]

Difluprednate is a difluorinated prednisolone derivative with potent anti inflammatory activity. It is formulated as an ophthalmic emulsion that penetrates the corneal epithelium rapidly and acts on the glucocorticoid receptors. Difluprednate has a high affinity for the glucocorticoid receptor due to fluorination of C-6 and C-9 positions. The addition of an acetate ester at position C-21 increases the corneal penetration.[5]

Difluprednate has a convenient dosage 4 times a day for as compared to prednisolone acetate which is used in the dosage of 8 times a day to reduce the post operative inflammation.[6,7] The less frequency of instillation for difluprednate gives a better patient comfort and compliance . The frequency of prednisolone is slightly on the higher side for which patient has to take an extra efforts to remember the dosage and the compliance may reduce[7].

METHODOLOGY

This randomised interventional prospective controlled trial was carried out in the department of Ophthalmology at a tertiary care hospital of central India. A total of 204 patients were registered in our study which was carried out between June 2012 to December 2013. All subjects were explained regarding the study and informed consent taken. The study was approved by Institutional Ethics committee (IEC 68/2012) and followed the tenets of Helsinki. They were divided into a case group of difluprednate and control group of prednisolone acetate. Patients were selected randomly by a computer generated list into both the groups.

The inclusion criteria were both male & female patients above the age 40 yrs, all types of senile cataract and those willing to be part of the study. All cataract surgeries were performed by single surgeon using small incision cataract surgery (SICS) technique and the type of intraocular lenses were same in both the groups. The exclusion criteria were complicated cataracts, keratopathy, glaucoma or glaucoma suspect, macular or retinal pathologies in either eye. One eyed patients, patients with systemic illness like diabetes mellitus were excluded. Subjects in whom complications occured during the surgical procedure like posterior capsular rent, zonular dialysis or iridodialysis were also excluded. Those with any history of sensitivity to any drugs and patients not willing to participate were also not enrolled.

Informed consent were obtained and signed from all subjects, who met all the inclusion criteria. Patients were divided into two groups of equal number. All patients were examined thoroughly on slit lamp, BCVA, IOP and ocular findings noted. After baseline systemic investigations and physician fitness patients were posted for cataract surgery. Treatment was started after 4 hours of surgery in both the groups. In group one (difluprednate group) difluprednate ophthalmic emulsion 0.05% was instilled postoperatively in dosage of 4 times/day for 15 days followed by twice daily for next 15 days. The control group (prednisolone group) received prednisolone acetate 1% in the dose of 8 times a day with gradual tapering over the period of 6 weeks[6]. Along with this an additional topical broad spectrum antibiotic was given four times a day in both the groups for 2 weeks.

The follow-up was done on 1st, 8th, 15th & 30th day and BCVA, corneal oedema, conjunctival congestion and AC cells were noted .The criteria used for grading these parameters were as follows:

Corneal oedema[6] :

Grade 0	No oedema
Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe

Anterior chamber (AC) cell count [10] :

Grade 0	No cells
Grade 0.5+	1-10 cell
Grade 1+	10- 20 cells
Grade 2+	20-30 cells
Grade 3+	30-100 cells
Grade 4+	> 100 cells

IOP measurement was done with Goldman's Applanation tonometer on every follow up. The data was entered and statistical analysis was done using SPPS Version 21. The outcome measures were treated as paired data for each patient. Appropriate statistical tests were applied, between the treatment groups the means of pre and post operative difference in the means were conducted by Analysis of variance (ANOVA), paired and unpaired t-test. The confidence limit of the study was set to 95% and the power of the study was set at 80%. *p*-value was considered to be significant at <0.05 corresponding to the degrees of freedom.

RESULTS

Outcome of both the drugs were assessed on the basis of BCVA, grade of congestion, corneal oedema, AC cell grade and IOP changes in each group.

In group A (n = 102) the mean age was found to be 61± 9.89 SD years and the males were 42.15 % where as the females were 57.85 % . In group B the mean age was found to be 64 years± 8.57 SD and the males were 38.24 % where as the females were 61.76 % (Table 1)

Table 1 Subject demographics in two treatment group

Treatment group	Mean age	Standard Deviation	Sex				Total
			Male	%	Female	%	
Difluprednate	61	9.89	43	42.15%	59	57.85%	102
Prednisolone Acetate	64	8.57	39	38.24%	63	61.76%	102

BCVA of the difluprednate group improved from 0.74 ± 0.19 SD of logMAR lines to 0.05 ±0.09 SD of logMAR lines and that of prednisolone group improved from 0.74 ± 0.19 SD

logMAR lines to 0.05 ± 0.10SD of logMAR lines on 30th day. There was no difference between the BCVA of difluprednate and prednisolone acetate on 30th day (*p* value > 0.05, table 2)

Congestion: On day 1 difluprednate group, 102 (100%) subjects and in prednisolone group 101 (99.01%) had mean grade 1 congestion. On 8th day improvement in the mean grade of congestion was 88 subjects (86.27%) in difluprednate group where as 75 subjects (73.52 %) in prednisolone group. On 30th day conjunctival and ciliary congestion was completely resolved in both the groups (table3). Improvement in the mean grade of congestion was better in the difluprednate group (86.27%) as compared to the prednisolone group (73.52%) table 2.

Table 2 Log MAR of BCVA

Treatment group	Log MAR	Mean	Std Deviation	P value of two groups	
				Pre op LogMAR	Post op LogMAR
Difluprednate group	Pre - op	0.744	0.199	0.002	0.001
	Post - op	0.055	0.098		
Prednisolone group	Pre - op	0.745	0.197		
	Post - op	0.055	0.101		

Corneal Oedema: Corneal oedema on day 1 was present in 19 subjects (18.61%) and in 27 subjects (26.47%) in difluprednate group and in prednisolone group respectively. On 8th day stromal oedema and striate keratopathy resolved in 102 subjects (100%) whereas in Prednisolone group 6 subjects (5.88%) of subjects had stromal oedema where as resolution of stromal oedema was similar in both the groups on 15th day. Thus there was early resolution of stromal oedema in the difluprednate group as compared to the prednisolone group (*p* = 0.019) that is statistically significant (table 3)

DISCUSSION

Smith S, Lorenz D *et al* [3] studied difluprednate ophthalmic emulsion 0.05% administered two times daily for managing ocular inflammation and pain following cataract surgery and concluded that twice daily dosage of difluprednate before and after surgery cleared ocular inflammation on day 14th. They also concluded that efficacy of 4 times daily difluprednate was better than twice daily difluprednate with reference to reducing ocular inflammation and pain. In their study percentage of patients with cleared ocular inflammation was 81.3% in the four times group where as it was 74.7% in the twice daily group. Whereas in our study on day 8th AC inflammation was cleared in 98 subjects (96.07%) in difluprednate group while in prednisolone group 84 subjects (82.35%) were having cleared AC inflammation. Thus, in conclusion four times daily difluprednate was well tolerated and quiet effective in the management of post operative ocular inflammation.

Donnenfeld E D, Edward J *et al*[6], in their multicenter randomized trial on post operative topical steroids found that the timing of the administration of the drug was very important . On 1st post op day they found that difluprednate in the pulse – dosing fashion provides better resolution of corneal oedema and vision as compared to prednisolone acetate. At day 30 the mean BCVA for the difluprednate group was better than the prednisolone group was 0.05 logMAR lines.

According to them a greater percentage of difluprednate treated eyes had BCVA of 20/30 or better and 20/40 or better than the prednisolone treated eyes.

Table 3 Post operative inflammatory signs in both treatment groups

		Day 1		Day 8		p-Value
		Diflupred	Prednisolone	Diflupred	Prednisolone	
Cornea	Clear	83	75	102	96	0.019
	Not Clear	19	27	0	6	
AC Cells	Clear	9	7	97	87	0.010
	Not Clear	93	95	5	15	
Congestion	Absent	0	1	88	75	0.011
	Present	102	101	14	27	

* The follow up findings of 1st and 8th day were only included, as the inflammatory signs were almost nil in both the groups after 8th day.

AC inflammation: On post-op day 1, AC inflammation in the difluprednate group was grade 0 in 9 subjects (8.83 %) where as grade 1cells were found in 84 subjects (82.35 %) and grade 2 cells were seen in 9 subjects (8.83%). In Prednisolone group grade 0 was noted in 7 subjects (6.8 %) whereas grade 1 were found in 76 subjects (74.50 %) while grade 2 cells in 19 subjects (18.62%). On day 8th AC inflammation cleared in 98 subjects (96.07%) in difluprednate group while in prednisolone group 84 subjects (82.35 %) had no AC inflammation. Grade I cells were still present in 4 subjects (3.92%) in difluprednate group and 18 subjects (17.64 %) in prednisolone group (Table 3).

IOP: The mean IOP in both the groups remained within the normal limits without much post op variations. IOP raise of ≥ 10mm Hg from the base line was taken as significant rise[1]. In difluprednate group the mean pre op IOP was 12.66 mm Hg where as mean of post op IOP was 15.42 mm Hg. Similarly in prednisolone group the mean pre op IOP was 12.35mm Hg where as mean of post op IOP was 13.23 mmHg on 30th day of follow-up. Incidence of an IOP increase of ≥3 mm Hg was more for difluprednate versus 1.5mmHg in prednisolone acetate.

They also stated that on day1 percentage of eyes with no corneal oedema in difluprednate group was 70% where as it was 56% in the prednisolone group. In our study no corneal oedema was seen in 81.39% on 1st day in difluprednate group and in prednisolone group no corneal oedema was seen in 73.53 %.

Jamal K N *et al*[1], compared twice daily, 4 times daily of difluprednate with a placebo. They found 87% reduction of AC cells count in the 4 times daily difluprednate group as compared to 30 % reduction in the placebo on 3rd day. Similarly in our study, AC cell reduction was 82.35 % in difluprednate group and 74.50 % in prednisolone group on the 3rd day (Table 3). They also noted that the clinical response defined as cells less than 5 and no flare was noted significantly by 8th day. Similarly, in our study by 8th day there was a good clinical response in 96.7 % in difluprednate group where as it was 82.35 % in prednisolone group.

Stephen foster *et al*[7], did a comparison between the difluprednate and prednisolone acetate in the treatment of uveitis. They concluded that improvement of pain from the baseline, and clearing of AC cells and flare was faster with the difluprednate (four times daily) than with prednisolone acetate

(8 times daily). They also concluded that the incidence of an IOP increase ≥ 5 mmHg was in the difluprednate group where as in prednisolone group it was ≥3 mmHg. Similarly in our study, on day 8th, AC inflammation cleared in 98 subjects (96.07 %) in Difluprednate group while in prednisolone group 84 subjects (82.35 %). Whereas the IOP increase in our study was 2.76 mmHg in difluprednate group where as 0.88 mmHg in prednisolone group. The dosing frequency which is less is associated with better patient compliance which is reflected in clinical outcome.

Stringer W, Bryant R[4] studied dose uniformity of topical corticosteroid preparations difluprednate ophthalmic emulsion 0.05% versus branded and generic prednisolone acetate ophthalmic suspension and concluded that emulsions give a greater ocular bioavailability as compared to the suspensions.

Bahubali Jain *et al* [9], did a similar study with 50 patients divided into two groups. They noted a IOP increase of mean 3.5 mmHg in the difluprednate group and 1.5 mmHg inn prednisolone group, similarly in our study the mean increase of IOP was 2.76 mmHg in the difluprednate group where as it was 0.88 mmHg in the prednisolone group.

CONCLUSION

Difluprednate 0.05% emulsion given 4 times a day reduced postoperative inflammation effectively and faster as compared to prednisolone acetate 1% suspension. There was no significant IOP rise in both the groups.

Advances in cataract surgical techniques and equipments have allowed us to reach the patients expectations of good visual recovery. Similarly, pharmacological inventions have kept the complications after cataract surgery to a lower side, so that the above target is achieved. But frequency of instillation of the drug has always remain a concern. The reduced frequency of difluprednate instillation gives a better patient compliance and a good drug efficacy. In spite of prednisolone acetate being a time tested suspension and a gold standard used postoperatively, difluprednate emulsion is also an equally effective steroid with better bioavailability and an added advantage of reduced dosage.

Author disclosure statement

The authors have no financial involvement, financial interest or financial conflicts with any pharmaceutical company of difluprednate ophthalmic emulsion.

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