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Original Research Article

A COMPARATIVE STUDY OF EFFICACY OF TOPICAL DIFLUPREDNATE OPHTHALMIC EMULSION 0.05% EYEDROPS WITH BETAMETHASONE SUSPENSION 0.1% IN POSTOPERATIVE SMALL INCISION CATARACT SURGERY

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ABSTRACT

Postoperative operative inflammation following cataract surgery is common occurrence may be due to several surgery-dependent factors such as surgical trauma, intraocular lens type, and due to various physical, chemical and biological agents introduced during surgery and also on patient-dependent factors such as history of inflammatory disease and degree of iris pigmentation. Anti-inflammatory agents are routinely prescribed following cataract extraction surgery to resolve signs and symptoms of inflammation more rapidly and to improve patient comfort. For the treatment of postoperative ocular inflammation and pain the most widely prescribed topical corticosteroid is betamethasone 0.1%, and Difluprednate ophthalmic emulsion 0.05% a strong topical steroid. Hence, this study was to compare the efficacy and safety of topical corticosteroids-Difluprednate 0.05% and betamethasone 0.1%, in managing inflammation and pain following post cataract extraction surgery. In a total 100 patients were randomized into two groups Group –A (50 patients) prescribing topical Difluprednate emulsion 0.05% and Group-B (50 patients) prescribing betamethasone phosphate 0.1%. in our observation after 15 days no pain in group-A, after 30 days no one are having corneal oedema in group-A. Difluprednate emulsion 0.05% drug was efficient in the reduction of anterior chamber cells and flare with betamethasone phosphate 0.1% being more rapid. Based on our findings and previous study results, Difluprednate emulsion 0.05% can be used in post-operative management post cataract surgery, however, further clinical trials with long follow- up periods are required.

KEY WORDS: Betamethasone Phosphate, Cataract Surgery, Difluprednate Emulsion, Inflammation and Pain.

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INTRODUCTION

Postoperative operative inflammation following cataract surgery is common occurrence may be due to several surgery-dependent factors such as surgical trauma, intraocular lens type, and due to various physical, chemical and biological agents introduced during surgery and also on patient-dependent factors such as history of inflammatory disease and degree of iris pigmentation [1]. Over the past decade, major advancements have occurred in cataract surgery techniques, equipments and pharmacological strategies to decrease the degree of postoperative inflammation following cataract surgery and thereby to reduce patient's risk for inflammation related complications. Disruption of blood–aqueous barrier during cataract extraction surgery leads to postoperative ocular inflammation, increasing the risk of secondary ocular complications, consisting of mild iritis with increased cells and protein in the anterior chamber (AC).

Although often self-limited, untreated inflammation can interfere with the patient's visual rehabilitation and in rare cases can result in complications such as cystoid macular oedema, posterior capsule fibrosis, keratopathy, fibrin reaction, chronic uveitis, pain/discomfort, photophobia, corneal oedema, synechiae or glaucoma [2].

Anti-inflammatory agents are routinely prescribed following cataract extraction surgery to resolve signs and symptoms of inflammation more rapidly and to improve patient comfort. Topical corticosteroids are a very effective treatment for postoperative ocular inflammation since they efficiently supress the initial release of inflammatory mediators and offer local treatment without the risk of systemic adverse effects [2,3]. Currently, the most widely prescribed topical corticosteroid is dexamethasone 0.1%, betamethasone 0.1%, Prednisolone acetate 1%. Though these drug controls inflammation effectively, it has not been shown to consistently reduce postoperative pain and discomfort in a large clinical trial [3]. Difluprednate ophthalmic emulsion 0.05%, a strong topical steroid, was approved by US Food and Drug Administration (FDA) in June 2008, for the treatment of postoperative ocular inflammation and pain [2,3]. It is a synthetic difluorinated Prednisolone derivative, having greater potency, and proved to be safety and efficiently reduces postoperative pain and inflammation. It is also found to be effective in the treatment of Anterior Uveitis [3]. Since very few studies have been conducted on this drug in India, the objective of this study is to compare the efficacy and safety of topical corticosteroids-Difluprednate 0.05% and betamethasone 0.1%, in managing inflammation and pain following cataract extraction surgery.

MATERIALS AND METHODS

In this Simple Randomization method included both the sex were diagnosed to have senile mature/immature cataract above 45 years of age of 100 patients diagnosed to have senile mature/immature cataract and scheduled for unilateral Small Incision Cataract Surgery (SICS) with Intra Ocular Lens (PCIOL) implantation under peribulbar anaesthesia were recruited for the study at Department of Ophthalmology, RAICHUR INSTITUTE OF MEDICAL SCIENCES HOSPITAL, RAICHUR. Informed, written consent was obtained from all subjects. A detailed history, visual acuity, slit lamp ocular examination, keratometry, A-scan, fundoscopy, physical examination and pre-operative routine investigations were done for all patients. The subjects were screened and those who meet all eligibility criteria were randomized into two groups Group –A (50 patients) prescribing topical Difluprednate emulsion 0.05% and Group-B (50 patients) prescribing betamethasone phosphate 0.1%. The dosing was initiated 24 hours after small incision cataract surgery. Known sensitivity to any of the ingredients in the study medications or similar medications, lack of intact corneal epithelium, corneal oedema in either eye, any active viral, bacterial, or fungal keratoconjunctival disease, any macular pathology of the retina, need for regional or general anesthesia during surgery, history of uveitis, iritis, intraocular inflammation or previous intraocular surgery in either eye, history of ocular trauma, glaucoma or history of steroid-related intraocular pressure (IOP) rise in the study eye, and uncontrolled systemic disease were excluded from the study.

Procedure: After randomization, each subject will receive the allotted drug with instructions for self-administration as per scheduled dosage, which will begin 24 hours after surgery. Difluprednate will be administered 1 drop in the operated eye 4 times daily for 1st week, followed by tapering week, and then tapering it. Betamethasone will be administered 1 drop in the affected eye 8 times per day, followed by tapering dose till 6th week. If the treatment response is found to be inadequate at any time point, subjects will be withdrawn from the study and will be switched to another suitable medication. Safety and efficacy parameters will be assessed on days 1, 7, 15, 30 days postoperatively and will be managed accordingly. Efficacy assessments include Anterior Chamber (AC) cell grade, AC flare, chemosis, bulbar conjunctival injection, ciliary injection, corneal oedema and ocular pain/discomfort. Ocular pain/discomfort will be assessed using a visual analogue scale (VAS scale 0–4) [4].

Efficacy noted: following parameters will be measured on each visit, and degree of parameter are graded as 0,1,2,3,4 etc**.**

Efficacy endpoint grading criteria [2]:

AC cell count:

Grade 0	absent
Grade 0.5+	1–5 cells
Grade 1+	6–15 cells
Grade 2+	16–25 cells
Grade 3+	26-50 cells
Grade 4+	>50

AC flare:

Grade 0	Complete absence
Grade 1	Very slight
Grade 2	Moderate
Grade 3	Marked
Grade 4	Intense

Corneal oedema:

Grade 0	Absence
Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe

Ocular pain/discomfort: Visual analogue scale (VAS) 0– cms (0 = absent, 4= extreme).

Safety assessments include Intra ocular pressure (IOP) after 1month of postoperative, Best-Corrected Visual Acuity (BCVA), Slit lamp examination to exclude persisting inflammation, Ophthalmoscopy to exclude Cystoid macular oedema or other fundus changes, comfort and tolerability assessment.

RESULTS

Table 1: Showing the Baseline intraocular pressure, and intraocular pressure at the end of 30 days.

Intraocular pressure	Baseline			
	Group-A		Group-B	
	No. of patients	percentage	No. of patients	percentage
12.2-13.4	10	20	13	26
14.6-15.9	25	50	15	30
17.3-18.9	15	30	22	44
Mean ± SD	15.55 ± 1.92		15.98 ± 2.28	
Intraocular pressure	**30 Days**			
	Group-A		Group-B	
	No. of patients	percentage	No. of patients	percentage
14	4	8	2	4
16	20	40	22	44
18	20	40	19	38
20	6	12	7	14
Mean ± SD	17.12 ± 1.62		17.24 ± 1.56	

Table 2: Showing the Pain in both Groups.

Pain	Day-1				Day-7				Day-15			
	Group-A		Group-B		Group-A		Group-B		Group-A		Group-B	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Grade 0 (None)	10	20	8	16	30	60	22	44	50	100	35	70
Grade 1 (Mild)	40	80	42	84	20	40	28	66	0	0	15	30
Grade 2 (Moderate)	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3 (Severe)	0	0	0	0	0	0	0	0	0	0	0	0
Total	50	100	50	100	50	100	50	100	50	100	50	100

DISCUSSION

A total 100 patients were diagnosed to have senile mature/immature cataract in this simple Randomization method included both the sex above 45 years of age and scheduled for unilateral Small Incision Cataract Surgery (SICS) with Intra Ocular Lens (PCIOL) implantation under peribulbar anaesthesia will be recruited for the study. The subjects were screened and those who meet all eligibility criteria were randomized into two groups Group –A (50 patients) prescribing topical Difluprednate emulsion 0.05% and Group-B (50 patients) prescribing betamethasone phosphate 0.1%. At base line Intraocular pressure the number of patients in the range of 12.2 to 13.4 mmHg was 10 (20%) in group-A and 13 (26%) group-B, 14.6 to 15.9 mmHg was 25 (50%) in group-A and 15 (30%) group-B and 17.3 to 18.9 mmHg was 15 (30%) in group-A and 22 (44%) group-B. after 30 days Intraocular pressure the number of patients in the range of 14 mmHg was 4 (8%) in group-A and 2 (4%) group-B, 16 mmHg was 20 (40%) in group-A and 22 (44%) group-B, 18 mmHg was 20 (40%) in group-A and 19 (38%) group-B and 20 mmHg was 6 (12%) in group-A and 7 (14%) group-B (Table-1).

40 in Group-A and 42 in group-B were faced pain after the 1st day of post operation, after 15 days 100% patients were in the Grade 0 in group-A but in the group-B only 70% patients were there (Table-2). Corneal oedema was found 15 in Group-A and 13 in group-B after the 1st day of post operation, after 30 days no one are having corneal oedema in group-A but in the group-B only 18% patients were having grade-1 corneal oedema (Table-3). Anterior chamber flare: on the 1st post-operative day, grade 1 anterior chamber flare was observed in 28 patients of group-B

Table 3: Showing the Corneal oedema in both Groups.

Corneal oedema	Day-1				Day-7				Day-15				Day-30			
	Group-A		Group-B		Group-A		Group-B		Group-A		Group-B		Group-A		Group-B	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Grade 0 (None)	15	30	13	26	38	76	28	56	46	92	35	70	50	100	41	82
Grade 1 (Mild)	26	52	28	56	12	24	20	40	4	8	15	30	0	0	9	18
Grade 2 (Moderate)	9	18	9	18	0	0	2	4	0	0	0	0	0	0	0	0
Grade 3 (Severe)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100

Table 4: Showing the Anterior chamber flare in both Groups.

Anterior chamber flare	Day-1				Day-7				Day-15				Day-30			
	Group-A		Group-B		Group-A		Group-B		Group-A		Group-B		Group-A		Group-B	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Grade 0 Absent	8	16	8	16	28	56	15	30	42	84	28	56	50	100	34	68
Grade 1 Mild (Barely detected)	32	64	28	56	15	30	26	52	8	16	22	44	0	0	16	32
Grade 2 Moderate (Iris & lens details seen	10	20	14	28	7	14	9	18	0	0	0	0	0	0	0	0
Grade 3 Severe (Iris & lens details not seen)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100

Table 5: Showing the Anterior chamber Cell in both Groups.

Anterior Chamber Cells	Day-1				Day-7				Day-15				Day-30			
	Group-A		Group-B		Group-A		Group-B		Group-A		Group-B		Group-A		Group-B	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Grade 0 (Absent)	4	8	3	6	28	56	18	36	44	88	28	56	50	100	38	76
Grade 1 (5-10 cells)	32	64	26	52	22	44	24	48	6	12	22	44	0	0	12	24
Grade 2 (11-20 cells)	14	18	21	42	0	0	8	16	0	0	0	0	0	0	0	0
Grade 3 (21-50 cells)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100

Table 6: Showing the Best corrected visual activity in both Groups.

Best corrected visual activity	Group-A		Group-B	
	No.	%	No.	%
6/12 (p) - 6/12	5	10	2	4
6/9 (p) – 6/9	35	70	32	64
6/6 (p) -6/6	10	20	16	32
Total	50	100	50	100

and 32 patients of group-A, grade 2 anterior chamber flare was noticed in 14 patients under group- B and 10 patients' group-A. On the 7th postoperative day, grade 1 flare was seen 26 patients of group-B and 26 patients of group-A, 7 & 9 patients in each group A and B had been noticed with grade 2 flare. On the 15th post-operative day, grade 1 flare was observed in 8 & 22 patients of each group respectively. On the 30th day of post-operative day still 16 patients were in the grade 1 (Table 4). Anterior chamber cells: on 1st post –operative day grade 1 cells in the anterior chamber was found in 32 patients of group-A and 26 patients of group-B, grade 2 cells were observed in 14 patients of group-A and 21 patients of group-B. On 7th post-operative day, 22 patients of group-A and 24 patients of group-B had grade 1 cells. On 15th postoperative day, grade 1 cells were noticed in 6 patients of group-A and 22 patients of group B. on the 30th day only in group-B grade-1 12 patients are present (Table 5).

Best corrected visual acuity after 1 month of postoperative period; There were 5 patients with best corrected visual acuity of 6/12(p)- 6/12 in the group-A and 2 patient in group-B, 35 patients in group-A and 32 patients in group-B was found with best visual acuity of 6/9(p)-6/9, best visual acuity of 6/6(p)-6/6 was found in 10 patients of group-A and 16 patients of group-B (Table 6).

Smith s. et al were shown the efficacy of Difluprednate ophthalmic emulsion 0.05% administered two times daily for managing ocular inflammation and pain following cataract surgery (3). Stringer W et al. conducted a study to compare the dosage of Difluprednate ophthalmic emulsion 0.05% with other drugs and has shown that patient compliance is better and efficient in reducing the postoperative inflammation (4). Korenfeld MS et al conducted a multicentric, randomized, placebo-controlled,

phase 3 trial on patients with significant post-operative ocular inflammation (>10 Anterior chamber cells) and demonstrated that both 4-times-daily and 2-times-daily Difluprednate, beginning 24 hours after unilateral ocular surgery, effectively reduced inflammation and pain, when compared with placebo [5]. Another multicentred, randomized, double-masked, placebo-controlled, phase 3B trial conducted by Smith S et al, on patients who underwent unilateral cataract extraction surgery, concluded that twice-daily Difluprednate, dosed alone, beginning 24 hours before surgery, was well tolerated and effective for the management of postoperative ocular inflammation and pain in subjects undergoing cataract extraction, when compared with placebo [3]. Foster CS et al [6] conducted a phase 3, multicentric, randomized trial on patients with endogenous anterior uveitis (>10 anterior chamber cells and an anterior chamber flare score of e"2 in at least 1 eye) and found that Difluprednate administered QID is effective in resolving the inflammation and pain associated with endogenous anterior uveitis.

Donnenfeld et al conducted a study on an update of Difluprednate for the prevention of ocular inflammation post-surgery and demonstrated the stronger glucocorticoid receptor binding activity of the active metabolite of Difluprednate which has good potency and found that Difluprednate can be dosed less frequently with having better patient compliance, safe and efficacious in the treatment of postoperative inflammation and pain following cataract surgeries [2]. Another multicentric, randomized, controlled trial of pulse-dosed Difluprednate 0.05% versus Prednisolone acetate 1% in cataract surgery conducted by Donnenfeld ED et al, showed that Difluprednate reduces inflammation more effectively than Prednisolone acetate, resulting in more rapid return of vision and also Difluprednate is superior in protecting the cornea and reducing macular thickening after cataract surgery [7]. Rajshree Reddy et al., observed both Difluprednate and dexamethasone drugs were efficient in the reduction of anterior chamber cells, Corneal edema, and flare with Difluprednate being more rapid and no clinically significant IOP elevation in both difluprednate and dexamethsone group. Difluprednate was found to be more effective in controlling pain compared to dexamethasone [8].

CONCLUSION

Based on our findings and previous study results, the manage inflammatory conditions and pain after cataract surgery is the Difluprednate ophthalmic emulsion 0.05% eyedrops appears to be a suitable medicine. Henceforth, Difluprednate emulsion 0.05% can be used in post-operative management post cataract surgery, however, further clinical trials with long follow- up periods are required.

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