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Comparative analysis of the post-operative anti-inflammatory effect of topical 0.1% dexamethasone sodium eye drops, topical 1% prednisolone acetate eye drops and difluprednate 0.05% topical eye drops after small incision cataract surgery at a tertiary eye care institute in India

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ABSTRACT

Background & Objectives: Comparative analysis of the post-operative anti-inflammatory effect of topical 0.1% dexamethasone sodium eye drops, topical 1% prednisolone acetate eye drops and difluprednate 0.05% topical eye drops after small incision cataract surgery at a tertiary eye care institute in India.

Materials and Methods: The current study was a prospective randomised control study conducted from June 2019 to January 2021 at a tertiary eye care institute in India after taking due clearance from the institutional ethical committee. 300 eyes of 215 patients were enrolled into the study and divided into three groups consisting of 100 eyes in each group. Group A patients received topical Dexamethasone 0.1% eye drops, group B & C received Prednisolone acetate 1% and difluprednate 0.05% eye drops respectively. Level of significance was kept at $p < 0.05\%$.

Results: Baseline IOP values between the three groups did not show any statistical significance. Significant difference in the analgesia was observed in the difluprednate 0.05% group. AC cells & flare was decreased by around the 7th day of treatment in difluprednate and prednisolone acetate eye drops treated groups.

Conclusion: To conclude our study opines that, dexamethasone is non-inferior and equally efficacious to prednisolone and difluprednate in the management of post cataract surgery inflammation. Although difluprednate 0.05% provides superior analgesia and early clearance of AC cells & flare, which may further aid in early visual rehabilitation and recovery.

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1. Introduction

Ocular inflammation post cataract or any intraocular surgery is a common occurrence, although the severity varies among different patients depending on the type of intraocular surgery, co morbidities, intra ocular manipulations, viscoelastics, intraocular lens, irrigating solution etc.¹ The pathophysiology behind post operative inflammation post cataract surgery can be attributed to the break in the blood aqueous barrier leading to a barrage of exposure to various chemical mediators of inflammation. Primarily the most common ones are prostaglandins, leukotrienes and various

cytokines.^{2,3}

With the advent of development of corticosteroids in the 1970's suppression of post operative inflammation received a shot in the arm and has since remained as a mainstay for management of postsurgical intraocular inflammation.^{4,5} Corticosteroids act as anti-inflammatory and immunosuppressive agent by inhibition of phospholipase A2 which is a rate limiting step and thereby inhibiting the downstream events in the arachidonic pathway and hence inhibit prostaglandin & various cytokine synthesis. They also have an effect on the gene transcription and molecular cell signalling events.⁶

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Since the 1970's the most commonly used topical steroids for management of intraocular inflammation is either prednisolone acetate 1% & dexamethasone 0.1%. However the latest topical steroid to enter the market is difluprednate 0.05%, (difluoroprednisolone butyrate acetate, or DFBA) is a synthetic difluorinated prednisolone derivative indicated for the treatment of inflammation and pain associated with ocular surgery.^{7,8} Having said that, the safety and efficacy of corticosteroids has always been a controversial topic.⁹

In our current study we compared the efficacy and safety profile of the three commonly used topical corticosteroids in India, prednisolone acetate 1%, dexamethasone 0.1% and difluprednate 0.05%.

1.1. Pathophysiology of postcataract surgery intraocular inflammation

Post-cataract surgery inflammation despite all the recent advances is a common cause of patient discomfort, delayed recovery and reduced visual outcome affecting the patients quality of life.¹⁰ The degree of post operative inflammation varies among patients due to patient factors like type of cataract operated, prior treatment with prostaglandins for glaucoma, recurrent h/o of uveitis, h/o evaporative dry eyes or systemic comorbidities like hypertension or diabetes. Disruption of the blood aqueous barrier (BAB), due to the physical trauma of the surgery can induce an inflammatory response leading to release of prostaglandins, leukotrienes and various cytokines which along the way further activate many macrophages, T cells neutrophils which further release chemical mediators.^{10,11} These chemical mediators released from the arachidonic acid pathway trickle down onto the retina and further incite inflammation leading to more grave complications and vision deficits due to persistent cystoid macular edema. Other localized signs of inflammation following cataract surgery presents as aqueous flare due to protein exudation and inflammatory cells in the anterior chamber, associated with hyperaemia, miosis, corneal oedema, fibroblast proliferation and scar formation. Long standing untreated post-operative inflammation complications also include pain, photophobia, posterior synechiae, uveitis and elevated intraocular pressure (IOP) leading to secondary glaucoma.^{12,13}

2. Materials and Methods

The current study was a prospective randomised control study conducted from June 2019 to January 2021 at a tertiary eye care institute in India after taking due clearance from the institutional ethical committee. 300 eyes of 215 patients were enrolled into the study and divided into three groups consisting of 100 eyes in each group. Group A patients received topical

Dexamethasone 0.1% eye drops, group B & C received Prednisolone acetate 1% and Difluprednate 0.05% eye drops respectively. After informed consent, all patients with senile cataract who underwent uncomplicated SICS with in the bag PCIOL implantation were enrolled in the study. Inclusion criteria parameters included uncomplicated senile cataract, no ocular co morbidities/disease, no previous ocular surgery, no h/o allergy to any drugs and all surgeries were conducted by a single surgeon, using the same techniques and instrumentation to eliminate the surgeon factor. The exclusion criteria parameters included patients with comorbidities like diabetes, hypertension, IHD, allergies, bronchial asthma, concurrent anticoagulant therapy, connective tissue disorders, vasculitis, immunological disorders, patients on systemic steroids and immunosuppressives.

Routinely all patients underwent preoperative screening and analysis, like visual acuity testing, Goldman's applanation tonometry, slit lamp biomicroscopy, keratometry, and fundus examination. Postoperatively the patients were followed up over the course of the next 6 weeks, on day 1, day 2, day 7, 4weeks later and 6 weeks post op. The postoperative medication was administered 6 times a day for 1 week and later tapered for rest of the period. Group A received Dexamethasone 0.1% eye drops 6 times a day, Group B received Prednisolone acetate 1% eye drops 6 times a day, whereas in group C difluprednate 0.05% eye drops was administered 4 times a day tapered off over 6 weeks. All patients were given gatifloxacin 0.3% eye drops 6 times a day for 6 weeks.

Grading of postoperative inflammation was done based on circumcorneal congestion, corneal oedema, anterior chamber cells and flare. Analgesia was subjectively estimated based on patient's complain of pain or discomfort.

Ocular Pain Score¹⁴ Grade 1: Trace—slight sensation of pain or discomfort, Grade 2: Mild—mild, tolerable aching of the eye, Grade 3: Moderate—moderate and prolonged aching sufficient to require the use of analgesics, Grade 4: Moderately severe—prolonged intense aching requiring the use of analgesics, Grade 5: Severe—prolonged sharp ocular or periocular pain

Grading of Anterior Chamber Cells¹⁴: Grade cells in field 0 <1, + 0.5 1-5, + 1 : 6-15, + 2 : 16-25, + 3 : 26-50, +4 : > 50

Grading of Aqueous Flare¹⁴: Nil 0, Just detectable +1, Moderate(Iris and lens details clear) +2, Marked (iris and lens details hazy) +3, Intense (fibrinous exudates) +4.

2.1. Statistical analysis

The results were analysed by using SPSS version 21. Level of significance was assessed at $p < 5\%$. ANOVA, Chi-square test with Yate's correction and Wilcoxon Signed Ranks test were used to find out the difference between the groups.

3. Observations & Results

The mean age in dexamethasone group was 61.17±6.32 years, prednisolone group was 62.45±4.48 years and in the difluprednate group was 61.77±7.32. The number of male and female patients were comparable in all the groups and exhibited no statistical significance at p<0.05 (p 0.465). The result is not significant at p < .05. All the 3 groups were comparable with regards to mean age and sex distribution in our study. Table 1

Table 1: Demographic data

Sex	Number	Group A- Dexamethasone	Group B- Prednisolone	Group C- Difluprednate
Mean age in years		61.17±6.32	62.45±4.48	61.77±7.32
Male	157	57	48	51
Female	143	43	52	49
Total	300	100	100	100

In our current study, the morphological type of cataract did not have any effect on the final outcome of the study as evidenced by p value >0.05, indicating that the three groups were comparable.

Table 2: Morphological type of cataract

	Immature cataract	Mature Cataract	Hyper mature Cataract
Group A-Dexa	71	23	6
Group B - Pred	66	30	4
Group C- Diflu	77	16	7

The baseline IOP readings taken before cataract surgery was compared with that of the IOP readings on day 1, 7, 15, 30 and 42 days did not yield any significant difference in the mean IOP values between the three groups, however a diurnal trend and detailed IOP analysis study would have provided a much more valuable understanding.

Table 3: Mean Intraocular pressure comparison at each followup visits

	Group A - Dexa	Group B- Pred	Group C- Diflu	
Baseline IOP	15.1±2.55	14.98±1.9	14.77±2.43	p=0.874
Day 1	17.1±1.98	16.92±1.99	17.87±1.86	
Day 7	16.62±1.78	17.94±1.45	17.93±2.98	
Day 15	16.4±1.42	17.85±1.63	17.79±1.65	
Day 30	16.01±1.49	17.64±1.22	17.98±1.77	
Day 42	17.08±1.23	17.9±1.51	17.54±1.87	

On analysis of the pain following cataract surgery in the three groups there was a statistically significant difference

(p<0.05) observed in the three groups with a higher degree of analgesia observed in patients who were on difluprednate 0.05% than the other two groups.

Table 4: Pain Scoring and assessment in the three groups under study

Pain	Group A Frequency (n)	Group B Frequency (n)	Group C Frequency (n)	P value
Day 1				
Grade 0 (None)	15	19	19	p=0.9
Grade 1 (Mild)	85	81	80	
Grade 2 (Moderate)	0	0	1	
Grade 3 (Severe)	0	0	0	
Day 7				
Grade 0 (None)	78	80	90	p=0.047
Grade 1 (Mild)	22	20	10	
Grade 2 (Moderate)	0	0	0	
Grade 3 (Severe)	0	0	0	
Day 15				
Grade 0 (None)	100	100	100	N/A
Day 30 (Grade 0)	100	100	100	N/A
Day 42 (Grade 0)	100	100	100	N/A

On analysis of the corneal edema over 42 days of followup, the study did not yield any significant difference in between the three groups and confirmed by a statistically insignificant value over all followup time frames.

On analysis of the AC flare, there was a statistically significant difference observed in patients between the three groups on the 7th day follow up with the difluprednate 0.05% treated patients showed a lesser degree of protein exudates in the AC than when compared with dexamethasone, whereas on intergroup comparison between difluprednate and prednisolone acetate did not show any statistical difference. However no significant difference was observed in the other follow up days of the study.

On analysis of the AC cells, there was a statistically significant difference observed in patients between the three groups on the 7th day follow up with the difluprednate 0.05% treated patients showed a lesser degree of cells in the AC than when compared with dexamethasone, whereas on intergroup comparison between difluprednate and prednisolone acetate did not show any statistical difference. However no significant difference was observed

Table 5: Corneal edema assessment in the three groups

Day 1	Group A	Group B	Group C	p value
Grade 0 (None)	23	26	27	0.0734
Grade 1 (Mild)	60	65	53	
Grade 2 (Moderate)	17	9	20	
Grade 3 (Severe)	0	0	0	0.41
Day 7				
Grade 0 (None)	85	90	92	
Grade 1 (Mild)	15	10	08	0.41
Grade 2 (Moderate)	0	0	0	
Grade 3 (Severe)	0	0	0	
Day 15				0.723
Grade 0 (None)	98	99	98	
Grade 1 (Mild)	2	1	2	
Grade 2 (Moderate)	0	0	0	n/a
Grade 3 (Severe)	0	0	0	
Day 30 (Grade 0)	100	100	100	
Day 42 (Grade 0)	100	100	100	n/a

Table 6: AC flare assessment in the three groups

Day 1	Group A	Group B	Group C	p value
Grade 0 Absent	15	15	13	0.06
Grade 1 Mild (Barely detected)	52	55	58	
Grade 2 Moderate (Iris & lens details seen)	33	30	29	
Grade 3 Severe (Iris & lens details not seen)	0	0	0	0.043*
Day 7				
Grade 0 Absent	46	60	63	
Grade 1 Mild (Barely detected)	42	29	30	0.043*
Grade 2 Moderate (Iris & lens details seen)	12	11	7	
Grade 3 Severe (Iris & lens details not seen)	0	0	0	
Day 15				0.9
Grade 0 Absent	87	95	94	
Grade 1 Mild (Barely detected)	13	05	6	
Grade 2 Moderate (Iris & lens details seen)	0	0	0	n/a
Grade 3 Severe (Iris & lens details not seen)	0	0	0	
Day 30 (Grade 0 Absent)	100	100	100	
Day 42(Grade 0 Absent)	100	100	100	n/a

in the other follow up days of the study.

Table 7: Assessment of AC cells

Day 1	Group A	Group B	Group C	P value
Grade 0 (Absent)	10	8	11	0.086
Grade 1 (5-10 cells)	69	71	66	
Grade 2 (11-20 cells)	14	13	18	
Grade 3 (21-50 cells)	7	08	5	0.02*
Day 7				
Grade 0 (Absent)	50	67	70	
Grade 1 (5-10 cells)	50	33	30	0.02*
Grade 2 (11-20 cells)	0	0	0	
Grade 3 (21-50 cells)	0	0	0	
Day 15				0.234
Grade 0 (Absent)	94	97	96	
Grade 1 (5-10 cells)	06	03	03	
Grade 2 (11-20 cells)	0	0	0	0.943
Grade 3 (21-50 cells)	0	0	0	
Day 30 (Grade 0)	100	100	100	
Day 42 (Grade 0)	100	100	100	0.9

Best corrected visual acuity on the 42nd day of follow-up did not reveal any statistically significant difference between the three groups. All groups had BCVA limits, which were comparable, indicating that in the long term all the topical steroids produce a consistent and reliable index of anti-inflammatory activity.

Table 8: BCVA assessment

BCVA	Group A	Group B	Group C	P value
6/12 (p) - 6/12	21	18	20	0.632
6/9 (p) - 6/9	50	54	50	
6/6 (p) -6/6	29	28	30	
Total	100	100	100	

All these observations and results show that topical 1% prednisolone acetate and difluprenate 0.05% has more anti-inflammatory activity, with a higher propensity to clear AC cells, AC flare as early as the 7th day, than when compared to dexamethasone 0.1% and is clinically and statistically more effective in early postoperative period to control the inflammation in uneventful cataract surgeries. Analgesia due to difluprednate 0.05% was much more effective than that of prednisolone 1% and dexamethasone 0.1%. Long term IOP variation due to three groups needs to be evaluated further although our study did not reveal any difference.

4. Discussion

Post-operative inflammation following cataract surgery irrespective of type of surgical technique and instrumentation used is a common feature. Inflammatory signs presenting as protein flare and inflammatory cells in anterior chamber, hyperemia, corneal oedema is usually managed by corticosteroids which till today have remained the mainstay of management of post op inflammation following cataract surgery.⁴ The current study was done to compare the efficacy of dexamethasone 0.1%, prednisolone acetate 1% and difluprednate 0.05% ophthalmic emulsion on post-operative inflammation in cataract surgery.⁶

The variation of the IOP from the baseline between the three groups were not clinically or statistically significant, although study designs for IOP measurement should include more stringent parameters like diurnal variation and age matched controls. However, Korenfeld M S et al., study observed a 3% rise in IOP in difluprednate 0.05% group, as compared to 1% rise with control group.¹

On estimation of pain/analgesia following surgery, difluprednate scored a higher value on the 7th day, when compared with dexamethasone and prednisolone. These findings were in line with Foster CS et al.,¹⁵ study who observed that pain resolution with difluprednate was slightly faster as compared to prednisolone acetate ophthalmic suspension.

Aqueous cell and flare assessment at the end of 7th day followup showed a steady and early clearance of AC cells and flare in both the difluprednate group and the prednisolone group, than when compared with that of the dexamethasone group. Foster CS et al.,¹⁵ found similar observations, mean AC cell grade and flare with difluprednate-treated patients was similar to prednisolone-treated patients and concluded that difluprednate was not inferior to prednisolone acetate in showing improvement in aqueous cells and flare clearing.

Best corrected visual assessment at the end of the study period of 42 days did not reveal any significant difference between the three groups indicating that in the long term all three drugs were equally good or non inferior in managing post operative inflammation following cataract surgery. Although a study by Donnenfeld et al observed a higher BCVA with difluprednate than with prednisolone group.¹⁶

5. Conclusion

To conclude our study opines that, dexamethasone is non inferior and equally efficacious to prednisolone and difluprednate in the management of post cataract surgery inflammation. Although difluprednate 0.05% provides superior analgesia and early clearance of AC cells & flare, which may further aid in early visual rehabilitation and recovery. Further from earlier studies difluprednate achieves uniform concentration levels and is free of the BKC preservative hence more safer. Long term benefits

need to be assessed with further studies.

6. Conflicts of Interest

All contributing authors declare no conflicts of interest.

7. Source of Funding

None.

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