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To Study the Efficacy of Difluprednate Ophthalmic Emulsion and Prednisolone Acetate Ophthalmic Suspension on Post-operative Inflammation in Cataract Surgery

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Abstract: ***Introduction: Senile cataract is the most common cause of visual impairment. Removal of cataract and implantation of intraocular lens implantation (IOL) is the main surgical approach for cataract. The major block in quick visual rehabilitation of the patient is post-operative inflammation. To limit post-operative inflammation corticosteroids drugs are used in routine prophylactically. Topical prednisolone acetate 1% and betamethasone 0.1% remain gold standard to control post-operative inflammation but newer drugs like difluprednate, loteprednol are also effective in controlling inflammation. Aim: To study the efficacy of difluprednate ophthalmic emulsion and prednisolone acetate ophthalmic suspension on Post-operative inflammation in cataract surgery (clear corneal phacoemulsification with foldable IOL). Materials and Methods: This study was carried out on 100 patients having visually significant cataract requiring surgery, clear corneal phacoemulsification with foldable intraocular lens implantation was done in all patients. Patients were randomly divided into two groups. In group A topical 1% prednisolone acetate ophthalmic suspension was administered six times a day Post-operatively. In group B 0.05% difluprednate ophthalmic emulsion was administered six times a day post-operatively. Efficacy of drug was evaluated in terms of decrease in ocular pain, anterior chamber reaction in the form of aqueous cells and flare and final visual acuity at 4 weeks. Results: In this study, 92% of patients in group A and 90% of patients in group B had BCVA 6/6. None of the patients in group A had ocular pain. In group B, 96% patients had no ocular pain. Remaining 4% had mild discomfort but required no medication. 98% of patients in group A and 100% of patients in group B presented with clearance of aqueous cells at the end of study. Only 2% of patients in group A had showed cell score (±). Conclusion: Though prednisolone acetate has been the gold standard anti inflammatory agent, 0.05% Difluprednate ophthalmic emulsion is equally effective in treatment of post-operative inflammation. Difluprednate have added an advantage of uniform drug dosage and absence of harmful preservative.***

Keywords: Best corrected visual acuity, Corticosteroids, Intra ocular inflammation

1. Introduction

Cataract, the clouding or opacification of lens, is the foremost cause of blindness affecting tens of thousands of people's vision all over the world. There is no medical treatment for cataract. Surgical removal of cataract remains the only treatment option for patients with failing vision [1]. Cataract surgery is the most commonly performed surgical operation [2]. Micro incision cataract surgery using phacoemulsification has largely replaced extracapsular cataract extraction because of faster healing, smaller wound with improved visual outcomes [3]. However, post-operative ocular inflammation continues to cause visual impairment, pain and other sequel among patients. This condition is self-limiting but untreated inflammation can interfere with patient's visual rehabilitation and in rare cases can result in complications such as cystoid macular oedema, posterior capsule fibrosis, keratopathy or chronic uveitis [4-6]. Controlling and preventing inflammation is the most important concern in achieving optimal results following surgery. Corticosteroids and Non-steroidal Anti-Inflammatory Drugs (NSAIDs) are two main group of drugs used as post-operative anti inflammation following cataract surgery. Topical steroids like prednisolone acetate 1% and betamethasone 0.1% remain gold standard treatment for post-operative ocular inflammation [7]. Because of their anti inflammatory activity they inhibit oedema, capillary dilation, leucocyte migration, capillary proliferation and deposition of collagen. Prednisolone acetate is an adrenocortical steroid, which irreversibly binds with Glucocorticoid Receptors (GR) alpha and beta, inhibiting gene transcription for COX-2 and Cytokines which leads to suppression of post-operative inflammation in cataract surgery. Though it is most potent anti-agents, yet it is linked with side effects like Intra Ocular Pressure (IOP) elevation, potentiation of infections and posterior subcapsular cataract formation [7].

Newer drugs like rimexolone, difluprednate, and loteprednol etabonate are recent ophthalmic corticosteroids introduced. Difluprednate (difluoroprednisolone butyrate acetate) is the only diflourinated topical ophthalmic glucocorticoid available till date exhibiting enhanced penetration, better bioavailability and low incidence of adverse effects [8]. It is effective in treating post-operative inflammation and anterior uveitis. The present study was done to compare the efficacy of difluprednate ophthalmic emulsion and prednisolone acetate ophthalmic suspension on post-operative inflammation in cataract surgery.

2. Materials and Methods

This prospective study was intended to be carried out for a period of 6 months. Depending on previous experience it was proposed to include 100 patients above 18 years of age and with visually significant cataract requiring cataract surgery during study period after applying exclusion criteria.

Further after analysing the results of current study, power of study has come out to be 90% depending on difference between proportions of patients presenting with aqueous flare on day 1. Patients with history of diabetes, hypertension or any other systemic disease, use of ophthalmic analgesics, immunosuppressants, having any other ocular disease like uveitis, glaucoma and corneal disease, any known hypersensitivity to drugs used in study and any operative complications like PCR, nucleus drop, vitreous loss were excluded from study. They were randomlydivided into two groups Group A and Group B, each consisting of 50 patients all of which underwent phacoemulsification. Group A patients received 1% Prednisolone acetate ophthalmic suspension and Group B patients received 0.05% Difluprednate ophthalmic emulsion post-operatively. After routine preoperative investigations, Best Corrected Visual Acuity (BCVA), intra-ocular pressure, fundus examination, sac test, viral markers (HIV I and II, HBsAg and HCV), blood pressure and random blood sugar, Standard phaco-emulsification (clear corneal incision) with foldable posterior chamber IOL implantation was carried out in all the patients. Patients in group A were administered 1% Prednisolone acetate ophthalmic suspension drops six times a day and in Group B were administered 0.05% Difluprednate ophthalmic emulsion drops six times a day for 4 weeks.

Post-operative evaluation was done on day 1, 1st week, 2nd week, 4th week with following parameters: Snellen's visual acquity (uncorrected and BCVA) and IOP was measured using Goldmann Applanation tonometer. Visual Analog Scale (VAS) was used to record ocular pain and Slit lamp biomicroscopy was done to evaluate anterior chamber cells and flare [9]. Efficacy of drug was evaluated in terms of decrease in ocular pain, anterior chamber reaction in the form of aqueous cells and flare and final visual acuity.

Ocular Pain Score [9]
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 Cells [9]
Grade cells in field
0 <1
+ 1-5
+ 1 6-15
+ 2 16-25
+ 3 26-50
> 50

Grading of Aqueous Flare [9]
Description grade
Nil 0
Just detectable +1
Moderate (Iris and lens details clear) +2
Marked (iris and lens details hazy) +3
Intense (fibrinous exudates).

Statistical Analysis
Data entered was analysed using SPSS software (version20.0). Proportions have been expressed as percentages and finally chi-square test was applied to show difference between outcomes in two groups. Fisher-exact test and Yates modification was applied wherever required since many frequencies of subcategories were less than 5. The p-value <0.05 was taken as significant at 95% confidence interval.

3. Results

In our study, 45 patients were >60 years of age, 32 in the age group 51-60 years and 23 <50 years of age. In group A, out of 50 patients 26 (52%) were males and 24 (48%) were females. In group B there were 25 males (50%) and 25 females (50%).
On Day 1, 58% of patients in Group A had Grade 1 aqueous cell and 42% had Grade 2 while in Group B, 54% had Grade 2 cells and 40% had Grade 1 aqueous cells. At the end of the study, 98% of patients in Group A showed Grade 0 and all the patients in Group B showed Grade 0 cells as depicted in [Table/Fig-1].

On Day 1, 68% of patients in Group A had Grade 1 aqueous flare and 14% had Grade 2 while in Group B, 82% had Grade 1 flare and 12% had Grade 2 aqueous flare. At the end of the study, all the patients in both the groups showed Grade 0 as depicted in [Table/Fig-2].

On Day 1, 46% of patients in Group A had Grade 1 ocular pain and 50% had Grade 2 while in Group B, 44% had Grade 1 pain and 54% had Grade 2 pain. At the end of the study, none of the patients complained of any ocular pain in Group A and 4% patients had only mild discomfort as shown in [Table/Fig-3].

In Intra-group trend, the difference between aqueous cell score, aqueous flare and pain score on Day 1 and at the end of 4 weeks was statistically significant with p-value <0.05 in both the groups while on comparing two study groups, difference in Aqueous cell score [Table/Fig-1], aqueous flare [Table/Fig-2] and pain score [Table/Fig-3] was statistically non-significant on Day 1 and all subsequent follow up visits.

There was improvement in visual acuity in all the patients in both the groups at the end of the study with p-value<0.001. All the patients in both the groups had final best corrected visual acuity 6/9-6/6 with statistically non-significant difference between two study groups [Table/Fig-4].

Score	Day 1		Week 1		Week 2		Week 4	
	Group A	GroupB	GroupA	GroupB	GroupA	GroupB	GroupA	GroupB
0	0(0%)	0(0%)	22(44%)	25(50%)	39(78%)	41(82%)	49(98%)	50(100%)
±	0(0%)	2(4%)	21(42%)	18(36%)	11(22%)	9(18%)	1(2%)	0(0%)
+1	29(58%)	20(40%)	7(14%)	7(14%)	0(0%)	0(0%)	0(0%)	0(0%)
+2	21(42%)	27(54%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
+3	0(0%)	1(2%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
$\chi 2$, df, p-value	5.403^{NS} , 3, .144*		0.422^{NS} , 2, 0.809*		0.250^{NS} , 1, 0.617**		0.000^{NS} , 1, 1.000**	

[Table/Fig-1]:Post-operative aqueous cell score in both the groups.
*Fisher-exact test**Yates modification
Fig. in bracket indicate%

Score	Day 1		Week1		Week2		Week4	
	GroupA	GroupB	GroupA	GroupB	GroupA	GroupB	GroupA	GroupB
0	9(18%)	2(4%)	32(64%)	32(64%)	47(94%)	49(98%)	50(100%)	50(100%)
+1	34(68%)	41(82%)	17(34%)	17(34%)	3(6%)	1(2%)	0(0%)	0(0%)
+2	7(14%)	6(12%)	1(2%)	1(2%)	0(0%)	0(0%)	0(0%)	0(0%)
+3	0(0%)	1(2%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
+4	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
$\chi 2$,df, P-value	6.184^{NS} ,3, .103*		0.000^{NS} ,2, 1.000*		1.042^{NS} ,1, 0.307**			

[Table/Fig-2]:Post-operative aqueous flare score in both the groups.
*Fisher-exact test **Yates modification
Fig. in bracket indicate %

Grade	Day 1		Week 1		Week 2		Week 4	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
0	NIL	NIL	NIL	NIL	NIL	NIL	50(100%)	48(96%)
G1	23(46%)	22(44%)	41(82%)	43(86%)	49(98%)	45(90%)	0	48(96%)
G2	25(50%)	27(54%)	9(18%)	7(14%)	1(2.0%)	5(10%)	0	0
G3	2(4%)	1(2%)	0	0	0	0	0	0
G4	0	0	0	0	0	0	0	0
$\chi 2$,df, p-value	0.431^{NS} ,2,0.805*		0.073^{NS} ,1 ,0.785**		1.601^{NS} ,1 , .206**		0.51^{NS} ,1 ,0.475**	

[Table/Fig-3]:Post-operative ocular pain assessment in both the groups.
*Fisher-exact test **Yates modification
Fig. in bracket indicate %

Visual acquity	Day 1		Week 1		Week 2		Week 4	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	GroupB
6/36	3(6%)	3(6%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
6/24	9(18%)	7(14%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
6/18	12(24%)	16(32%)	3(6%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
6/12	14(28%)	11(22%)	7(14%)	3(6%)	0(0%)	0(0%)	0(0%)	0(0%)
6/9	10(20%)	10(20%)	19(38%)	17(34%)	7(14%)	8(16%)	4(8%)	5(10%)
6/6	2(4%)	3(6%)	21(42%)	30(60%)	43(86%)	42(84%)	46(92%)	45(90%)
$\chi 2$,df, P-value	0.761^{NS},5,0.979		6.299^{NS}, 3, 0.097*		0.078^{NS}, 1, 0.780**		0.000^{NS}, 1, 1.000**	

[Table/Fig-4]:Post-operative Visual Acquity(BCVA) assessment in both the groups.
*Fisher-exact test **Yates modification
Fig. in bracket indicates %

4. Discussion

Senile cataract is the most common cause of visual impairment. Removal of cataract and implantation of IOL is the main surgical approach for cataract. The major block in quick visual rehabilitation of the patient is post-operative inflammation. Post-operative inflammation is accepted as natural consequence of the procedure irrespective of type of surgery, surgical technique and instrumentation used. To limit post-operative inflammation corticosteroids drugs are used in routine prophylactically. Post-operative inflammation presents as protein flare and inflammatory cells in anterior chamber, hyperemia, oedema. Corticosteroids have remained the main stay of treatment for Post-operative inflammation after cataract surgery. Corticosteroids suppress the production of inflammatory mediators. It inhibits the release of arachidonic acid from cell membrane phospholipids and prevents the formation of both leukotrienes and prostaglandins. Prednisolone acetate ophthalmic suspension is a glucocorticoid and has 3-5 times anti inflammatory potency of hydrocortisone [7]. Difluprednate 0.05% ophthalmic emulsion (difluoroprednisolone butyrate acetate) is a new synthetic diflourinated prednisolone derivative. Unlike other corticosteroids, difluprednate is preservative free and a prolonged use does not cause irritation or dry eye and hence increases tolerance to drug [10]. It is also associated with

enhanced penetration, better bioavailability, and strong efficacy.

This study was done to compare the efficacy of difluprednate ophthalmic emulsion and prednisolone accetate ophthalmic suspension on post-operative inflammation in cataract surgery.

Ocular Pain Assessment: Ocular pain assessment was done using Visual Analogue Scale (VAS) and was compared in both the groups. At the end of study none of the patient in group A and 96% of patients in group B had no ocular pain (grade 1). Difference was statistically non significant in both the groups ($p>0.05$). Korenfeld MS et al., in his study showed decreased pain as well as inflammation with the use of Difluprednate ophthalmic emulsion 0.05% as compared to control group [10]. Foster CS et al., found in a study pain resolution with difluprednate was slightly faster as compared to prednisolone acetate ophthalmic suspension [11].

IOP Assessment: In the study, maximum number of patients had IOP in range of 14-15mmHg. Mean IOP was normal in both the groups and difference between two groups was found to be statistically insignificant. None of the patient showed clinically significant IOP rise >21 mmHg. This was in accordance with a study conducted by Jamal KN [12] which showed similar observations at the end of the study in IOP measurement while using difluprednate and prednisolone acetate eye drops. In another study with the use of these drugs Foster CS et al., found clinically significant increase in IOP in 11% of patients [11]. Korenfeld M S et al., however, found that with Difluprednate 0.05%, there was 3% increase in intraocular pressure as compared to 1% rise with control group [10]. Similarly, Meehan K observed increase in IOP with topical difluprednate use [13].

Aqueous Cell Assessment: At the end of study in 98% patients there was no cells in group A (AC cell score 0). A 2% patients showed cell score (±) whereas, 100% in group B showed AC cell clearance (AC cell score 0). Foster CS et al., found similar observations, at day 14, mean AC cell grade with difluprednate-treated patients was similar to prednisolone-treated patients (2.1 vs. 1.9 respectively) [11]. Smith S, showed AC cell grade of 0 (≤ 5 cells) and flare grade 0 (complete absence) was achieved in a significantly greater percentage of subjects treated with difluprednate, compared with placebo [14].

Aqueous Flare Score Assesment: No flare was detected in any study group at the end of the study. Foster CS et al., concluded that difluprednate was not inferior to prednisolone acetate in showing improvement in aqueous cells and flare clearing [11].

Visual Acquity: In the present study BCVA was recorded on day 1, week 1, week 2 and week 4. In group A, there were 92% patients who had BCVA 6/6 and 8 % who had best corrected visual acquity 6/9. In group B 90% patients had best corrected visual acquity 6/6 and 10% had BCVA 6/9. A study conducted by Stephen Smith administered difluprednate emulsion 0.05% post-operatively and found it to be highly effective for managing intra-ocular inflammation and pain with BCVA 6/6 in all patients [14]. Erric D Donnenfeld showed that with difluprednate uncorrected and BCVA was significantly better than prednisolone [15]. They concluded that difluprednate reduced inflammation, more rapid return of vision and superior at protecting cornea. Administration of difluprednate provides better vision and less corneal oedema as compared with prednisolone.

Wilson ME in his study in paediatric patients (age group 0-3year) found difluprednate to be equally safe and efficient in controlling post cataract surgery inflammation as prednisolone acetate eye drops [16].

Sheppard JD, in his study concluded that difluprednate 0.05% four times daily is equivalent to prednisolone acetate 1% eight times daily in management of intra ocular inflammation in endogenous anterior uveitis [17].

M Bartin in his study concluded that both difluprednate ophthalmic emulsion 0.05% as well as prednisolone Acetate 1% ophthalmic suspension are equally safe and effective in controlling postoperat ive inflammation after catatract surgery and both the groups achieved best corrected visual acuity of 6/9-6/6 at the end of 4 weeks [18].

In this study, difluprednate was found to have safety profile as prednisolone acetate in all follow-up visits and was well tolerated. Foster CS et al., found that drop concentration of difluprednate emulsion was uniform in patients usage conditions whereas the drop concentration of prednisolone acetate suspension was highly variable [12]. The difluprednate emulsion formulation does not require shaking and delivers constant concentration of active ingredient in each drop. Prednisolone acetate requires shaking before every instillation. Study conducted by Stringer W and Bryant R showed the amount of drug delivered by prednisolone acetate suspension is variable [19].

5. Limitation

In our study we evaluated parameters of anterior segment inflammation only. Other factors like Corneal oedema, Posterior segment manifestations of intraocular inflammation like vitritis, macular oedema depicted as increase in macular thickness were not evaluated.

6. Conclusion

There is no statistically difference in efficacy of difluprednate 0.05% ophthalmic emulsion and prednisolone acetate 1% ophthalmic suspension in treating post cataract surgery intra-ocular inflammation. Though prednisolone acetate has been the gold standard anti-inflammatory agent difluprenate ophthalmic emulsion is equally effective as 1% prednisolone acetate ophthalmic suspension in treatment of post-operative inflammation. Difluprednate have added an advantage of uniform drug dosage and absence of harmful preservative. From the observations seen in this study it is concluded that difluprednate is a new topical corticosteroid with efficient anti-inflammatory properties with ideal formulation for easy usage for patients.

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