IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN:2279-0853,p-ISSN:2279-0861.Volume 15,Issue 3Ver.VII(Mar.2016),PP51-58
www.iosrjournals.org

Efficacy and Safety Of Difluprednate Ophthalmic Emulsion And Prednisolone Acetate Ophthalmic Suspension In Post-Cataract Surgery Inflammation– A Comparative Study

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Abstract:
Purpose: *To evaluate and compare the efficacy and safety of Difluprednate ophthalmic emulsion 0.05% with Prednisolone acetate ophthalmic suspension 1%, administered for managing inflammation following cataract surgery.*
Study design: *Single blinded comparative study*
Study Period: *1 year*
Setting: *Assam Medical College & Hospital*
Methods*: 400 patients having senile cataract were enrolled. They were divided into 2 groups randomly. The 1st group received difluprednate eye drop and 2nd group received prednisolone eye drop post-operatively. We examined the patients in slit lamp for anterior chamber cells and flare , corneal edema on 1st day, 1st wk, 2nd week and 4th week post-operatively.BCVA and IOP were also measured at the end of the study.*
Results: *Mean age in Difluprednate group was 59.51±8.47 years (Mean±SD) and in Prednisolone group was 59.41±9.18 years (Mean±SD).On 1st week, 66% patients in Difluprednate group and 51% patients in Prednisolone group had Grade 0 corneal edema. (p<0.05) By 1st week, 42.5% patients in Difluprednate group and 22% patients in Prednisolone group had Grade 0 cells in the anterior chamber. (p<0.05). At the end of 4th week there was mean IOP elevation of 0.78 mm of Hg in Difluprednate group and that of 0.57 mm of Hg in Prednisolone group. By 7th day 45% patients in Difluprednate group had achieved 6/9-6/6 vision in comparison with Prednisolone group where 29.5% had achieved 6/9-6/6 vision.(p<0.05). At the end of 4 weeks, 96.8% patients of Difluprednate group and 94.2% of Prednisolone group had achieved a best corrected visual acuity of 6/9– 6/6(p>0.05).*
Conclusions: *Difluprednate Ophthalmic Emulsion 0.05% was as safe and effective as Prednisolone Acetate 1% Ophthalmic Suspension in treating post-operative inflammation following catatract surgery. None of the patients showed significant rise in IOP in both groups. Thus, Difluprednate Emulsion 0.05% appears to be a promising addition to the surgical armamentarium for treating post-operative inflammatory conditions.*
Keywords*: Difluprednate, Prednisolone, Best corrected visual acuity(BCVA), small incision cataract surgery(SICS), posterior chamber IOL(PCIOL)*

I. Introduction

Cataract is the most common cause of blindness in the world. For the treatment of cataract, lens extraction is the treatment of choice. This is the commonest ophthalmic surgery performed. A mild postoperative inflammation may be considered a normal accompaniment of cataract surgery rather than its complication.[1]Surgical trauma to the eye initiates an inflammatory reaction. This reaction includes the release of prostaglandins and the recruitment of neutrophils and macrophages to the site of trauma. Post-operative ocular inflammation after cataract surgery can be associated with complications, including corneal edema, uveitis, spikes in intraocular pressure (IOP), cystoid macular edema (CME), and posterior capsular opacification.[2]

This inflammation is self-limiting in many cases and invariably subsides within two or three days. Persistent and more severe uveitis can have a detrimental effect on the patient's final vision after surgery, and the control of inflammation is a chance to make a difference in the final visual outcome.[3]

In ophthalmic practice, corticosteroids are most frequently used to control post-surgical inflammation.[4] By inhibiting the release of arachidonic acid from the cell membrane phospholipids, corticosteroids prevent the formation of both leukotriens and prostaglandins, disrupting the inflammatory cascade.[5] Topical corticosteroids are a very effective treatment for postoperative ocular inflammation since they efficiently block the initial release of inflammatory mediators and offer local treatment without the risk of systemic adverse effects.[6] However, adverse effects of steroids are well known and include intraocular hypertension in susceptible patients (steroid responders), impairment of cicatrisation (inhibition of wound healing) and increased risk of infections particularly viral ones.[7] Prednisolone acetate 1% ophthalmic suspension, USP is a topical anti-inflammatory agent for common ophthalmic use. It is a potent steroid used in post cataract surgery to reduce ocular inflammation and pain, but it has some disadvantages like it comes in suspension form for which it has to be shaken well before use to mix drug properly. Caking in conjunctiva reduces its bioavailability and even the dosage of 6-8 times per day can have poor patient compliance.[8]

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. In June, 2008 difluprednate ophthalmic emulsion 0.05% was approved by the US Food and Drug Administration (FDA) for the treatment of inflammation and pain associated with ocular surgery.[9]Difluprednate is a new synthetic drug available in the market. It is a difluorinated prednisolone derivative. Difluprednate is more potent than prednisolone acetate. It reduces inflammation and pain more effectively and corneal penetration is also superior to prednisolone acetate. Corneal edema in postoperative cataract surgery is less with Difluprednate group (38%) as compared with Prednisolone acetate group (62%). Statistically visual acuity returns faster with Difluprednate eye drops 4 times per day than with the use of prednisolone acetate 8 times per day. The best corrected visual acuity is better on the first day itself.[10]

II. Aims & Objectives

To evaluate and compare the efficacy and safety of Difluprednate ophthalmic emulsion 0.05% with Prednisolone acetate ophthalmic suspension 1%, administered for managing inflammation following cataract surgery.

III. Method & Material:

Ethical clearance was obtained from the institutional ethics committee of Assam Medical College and Hospital, prior to the commencement of the present study.

Selection Of Patients:

Inclusion Criteria:	Exclusion Criteria:
1. Age more than 40 years. 2. Patients diagnosed to have senile cataract. 3. Scheduled to undergo Cataract Surgery with posterior chamber IOL implantation.	1.Known sensitivity to any of the ingredients in this study medication. 2.Signs of uveitis, iritis, intraocular inflammation due to previous intraocular surgery in either eye. 3.One eyed patients.

After obtaining the informed consent from the patients, they were scrutinized based on inclusion and exclusion criteria. Thereby total 400 patients were enrolled in the study. Among the selected patients odd number patints were included in group-A (Difluprednate) and the even number patients were included in group-B (Prednisolone). So each group contained 200 patients.The patients were assessed preoperatively, a complete history had been taken and assessment of visual acuity was checked by Snellen's visual acuity chart. They were undergone a detailed slit lamp examination, and fundoscopy examination with 20 D and 90 D lens.

Before operation following investigations were done-
(1) Measurement of intra-ocular pressure by applanation method
(2) Tests for lacrimal patency

(3) Random blood sugar
(4) Blood pressure
(5) Keratometry and A scan ultrasonography for calculation of IOL power

The pupil were dilated with a combination of 0.8 % tropicamide and 5 % phenylephrine hydrochloride eye drops. Surgeries were done under peribulbar anaesthesia and for this purpose mixture of 2% lignocaine with adrenaline, 0.5% bupivacaine and hyaluronidase was used as anaesthetic agent. Irrigating fluid used was ringer lactate in which injection adrenaline was mixed. Viscoelastic used was Hydroxypropylmethylcellulose. Polymethyl-methacrylate (PMMA) IOL was implanted in the capsular bag in every case.All the surgeries were manual small incision cataract surgery with PCIOL implantation and performed by a single experienced surgeon.
Each group had received the medication after 24 hours of surgery as allotted.

Group-A : Difluprednate 0.05% ophthalmic emulsion
1 drop 4 times daily for 2 weeks
1 drop 2 times daily for 1 week
1 drop once daily for 1 week

Group-B : Prednisolone acetate 1% ophthalmic suspension
1 drop 8 times daily for 1 week
1 drop 6 times daily for 1 week
1 drop 4 times daily for 1 week
1 drop 2 times daily for 1 week

Other medications common to both groups were-
1) Moxifloxacin 0.3% E/D
1 drop 3 times daily for 1 week.
2) Tropicamide 0.8% +Phenylephrine 5% E/D
1 drop once daily at bed time for 1 week.
3) Analgesic tablet SOS

Data Collection: The patients were examined postoperatively on day 1, 1st week, 2nd week and 4th week. At each visit, symptoms like pain, watering and any other experienced by the patient were noted. Visual Acuity had been assessed by Snellen's chart and a slit lamp examination had been done for evaluation of inflammation. The following were the parameters that were recorded at each visit. Each parameter were be Graded as 0, 1, 2, and 3.
1) Conjunctival congestion
2) Ciliary congestion
3) Corneal edema
4) Anterior chamber cells
5) Anterior chamber flare.

At the end of six weeks, refraction was done to get the best corrected visual acuity and intraocular pressure had been measured using Goldmann applanation tonometer.

In follow up, 200 patients in each group attended 1st and 2nd visit, but 12 patients in Difluprednate group and 10 patients in Prednisolone group did not come for 3rd and 4th visit. Thats why we got 188 patients in Difluprednate group and 190 patients in Prednisolone group for 2nd week and 4th week follow up.

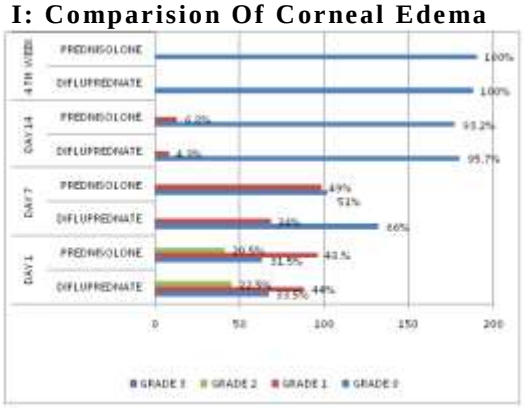
CONJUNCTIVAL CONGESTION ON DAY 1 CORNEAL EDEMA, DESCEMET'S FOLD ON DAY 1

Statistical Analysis: All the obtained data were calculated by calculating p-value using chi-square test with or without yate's correction. P value of (‹ 0.05) was considered statistically significant.

IV. Results

Mean age in Difluprednate group was 59.51±8.47 years (Mean±SD) and in Prednisolone group was 59.41±9.18 (years Mean±SD). Total 105 patients(52.5%) were males in Difluprednate group and 109 patients (54.5%)in prednisolone group were male.

Graph I: Comparision Of Corneal Edema

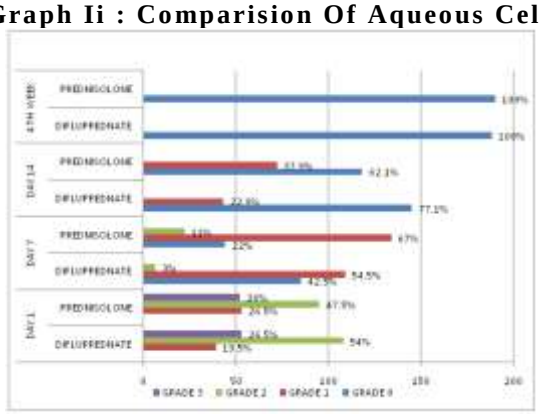


On Day 1, 67 patients (33.5%) in Difluprednate group and 63 patients (31.5%) in Prednisolone group had Grade 0 corneal edema. Grade 1 corneal edema was present in 88 patients (44%) in Difluprednate group and 96 patients (48%) in Prednisolone group .Grade 2 edema was present in 45 patients (22.5%) in Difluprednate group in comparison with 41 patients (20.5%) in Prednisolone group($p > 0.05$).

By 1st week, 132 patients (66%) in Difluprednate group and 102 patients (51%) in Prednisolone group had Grade 0 corneal edema. In Difluprednate group 68 patients (34%) had Grade 1 corneal edema in comparison with 98 patients (49%) in Prednisolone group($p < 0.05$).

By 2nd week, 180 patients (95.7%) in Difluprednate group and 177 patients (93.2%) in Prednisolone group were free of corneal edema. Only 8 patients (4.3%) in Difluprednate group and 13 patients (6.8%) in Prednisolone group had Grade 1 corneal edema($p > 0.05$).At the end of 4th week no patients in either group had corneal edema.

Graph Ii : Comparision Of Aqueous Cells

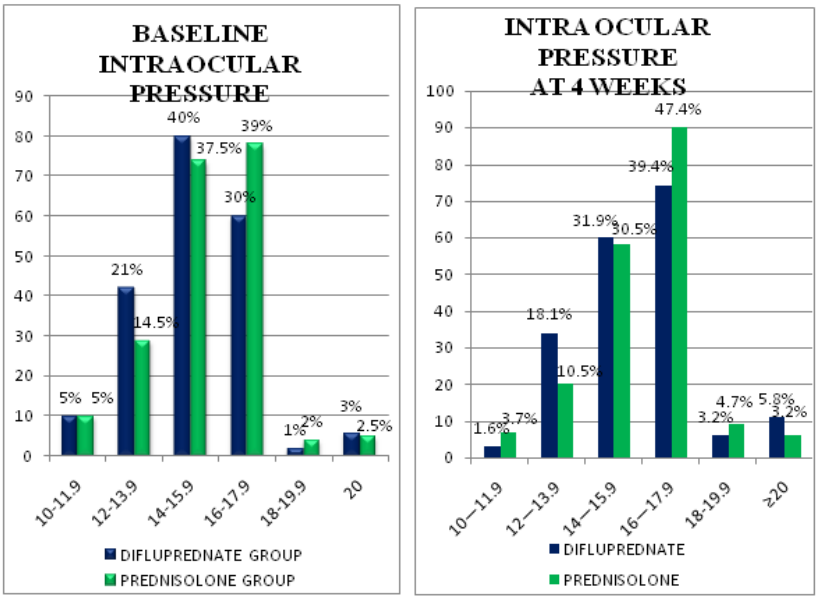


By 1st week, 85 patients (42.5%) in Difluprednate group and 44 patients (22%) in Prednisolone group had Grade 0 cells in the anterior chamber. Maximum number of patients- 109 (54.5%) in Difluprednate group and 134 (67%) in Prednisolone group had Grade 1 cells.Grade-2 cells in the anterior chamber was present in 6 patients (3%) in Difluprednate group in comparison with 22 patients (11%) in Prednisolone group($p<0.05$).

At the end of 2nd week, 145 patients (77.1%) in Difluprednate group and 118 patients(62.1%) in Prednisolone group had Grade 0 cells.Grade 1 cells was present in 43

patients (22.9%) in Difluprednate group in comparison with 72 patients (37.9%) in Prednisolone group($p< 0.05$). At the end of 4th week all patients in either group had grade 0 cells in the anterior chamber.

Graph Iii: Comparision Of Intra-Ocular Pressure



In Difluprednate group maximum number of patients 80(40%) had IOP in the range of 14-15.9, followed by 60 patients (30%) had IOP in the range of 16-17.9.Where as in Prednisolone group, maximum number of patients 78(39%) had IOP in the range of 16-17.9, followed by 74 patients (37%) had IOP in the range of 14-15.9. Mean baseline IOP in Difluprednate group was 14.93±2.23 mm of Hg(Mean±SD) and that of Prednisolone group was 15.38±2.23 mm of Hg(Mean±SD)($p> 0.05$).

In Difluprednate group maximum number of patients 74(39.4%) had IOP in the range of 16-17.9, followed by 60 patients (31.9%) had IOP in the range of 14-15.9.Where as in Prednisolone group, maximum number of patients 90(47.4%) had IOP in the range of 16-17.9, followed by 58 patients (30.5%) had IOP in the range of 14-15.9 Mean IOP in Difluprednate group was 15.71±2.25mm of Hg(Mean±SD) and that of Prednisolone group was 15.95±2.13 mm of Hg(Mean±SD) at the end of 6th week .No patient in either group had IOP more than 21 mm of Hg and IOP rise more than 10 mm of Hg from baseline IOP in any group at the end of 6th week($p> 0.05$).

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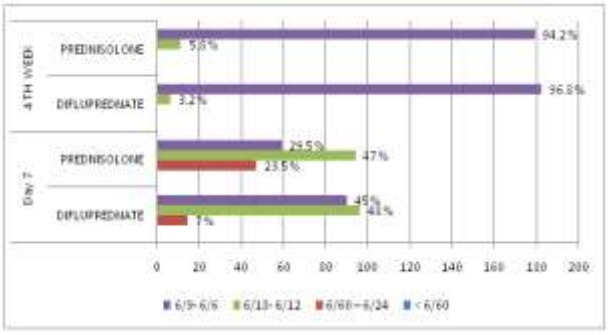
Graph Iv: Comparision Of Visual Acuity



By 1st week, 90 patients (45%) in Difluprednate group had achieved 6/9-6/6 vision in comparison with Prednisolone group where 59 patients (29.5%) had achieved 6/9-6/6 vision.In Prednisolone group, 47 patients (23.5%) had 6/60-6/24 vision whether in Difluprednate group it is only 14 patients (7%)($p< 0.05$).

At the end of 6 weeks, the number of patients with best corrected visual acuity of 6/18- 6/12 was 6 patients (3.2%) in Difluprednate group and 11 patients (5.8%) in

Prednisolone group. 182 patients (96.8%) in Difluprednate group and 179 patients (94.2%) in Prednisolone group achieved a vision of 6/9 – 6/6(p> 0.05).

V. Discussion:

In our study on first post-operative day, 33.5% patients in Difluprednate group and 31.5% patients in Prednisolone group had Grade 0 corneal edema. 44% patients in Difluprednate group and 96 patients (48%) in Prednisolone group had Grade 1 corneal edema.Grade 2 edema was present in 22.5% patients in Difluprednate group in comparison with 20.5% patients in Prednisolone group (p >0.05).

A similar study was done by Dr. Eric D. Donnenfold in America in 2011.He found that more eyes were without corneal edema in the Difluprednate group at Day 1(62%) v/s 38% in Prednisolone group (p=0.019).[11] He also found that corneal thickness at Day 1 was 33µm less (measured via pachymetry) in Difluprednate-treated eyes (p=0.026). This data doesn't match with our data because they had given study medicines 3 hour prior to the surgery and continued at every 15 minutes interval; here we had started study medicines 24 hours after surgery.

On 1st week, 66% patients in Difluprednate group and 51% patients in Prednisolone group had Grade 0 corneal edema. 34% patients in Difluprednate group had Grade 1 corneal edema in comparison with 49% patients in Prednisolone group (p<0.05).

One similar study was done by Bahubali Jain, M. Shrivastawa in 2014 in Karnataka, India to compare the safety and efficacy of difluprednate 0.05% emulsion and prednisolone acetate 1% in the post operative inflammation following cataract extraction with IOL implantation.They showed that on 5th day, Grade 0 corneal edema is present in 64% in difluprednate group in comparison with 40% in prednisolone group.This finding is almost comparable with our study finding though they assessed corneal edema on 5th post-operative day.[12]

By 1st week, 42.5% patients in Difluprednate group and 22% patients in Prednisolone group had Grade 0 cells in the anterior chamber.Maximum number of patients- 54.5% in Difluprednate group and 67% in Prednisolone group had Grade 1 cells.Grade-2 cells in the anterior chamber was present in 3% patients in Difluprednate group in comparison with 11% patients in Prednisolone group (p<0.05).

Stephen Smith et al conducted a study in 2010, USA.They compare difluprednate therapy with placebo therapy in controlling inflammation following cataract surgery.They showed that 48.1% patients in Difluprednate group had Grade 0 anerior chamber cells on 7th day in comparison with 22.5% of placebo group.[13]At the end of 2nd week, 77.1% patients in Difluprednate group and 62.1% patients in Prednisolone group had Grade 0 cells.Grade 1 cells was present in 22.9% patients in Difluprednate group in comparison with 37.9% patients in Prednisolone group.

In another same study done by Bahubali Jain, at the end of 2nd week 76% patients of Difluprednate group had Grade 0 anterior chamber cells where as it was present in 64% in Prednisolone group.This data correlates to the data made in our study.[12]Stephen Smith in his study showed that Grade 0 anerior chamber cells was present in 74.7% of Difluprednate group in comparison with 42.5% in placebo group at the end of 2nd week.[13]

However, Roopa Devi H.S., Nagabushan H, Manjula T R, performed a similar study in Karnataka, in 2014. In their study they showed that 84% in Difluprednate group and 32% in prednisolone group had Grade 0 anterior chamber cells.[13]In Difluprednate group maximum number of patients- 39.4% had IOP in the range of 16-17.9, followed by 31.9% had IOP in the range of 14-15.9.Where as in Prednisolone group, maximum number of patients- 47.4% had IOP in the range of 16-17.9, followed by 30.5% had IOP in the range of 14-15.9.(p>0.05)

Mean baseline IOP in Difluprednate group was 14.93±2.23 mm of Hg(Mean±SD) and that of Prednisolone group was 15.38±2.23 mm of Hg(Mean±SD).Mean IOP in Difluprednate group was 15.71±2.25 mm of Hg(Mean±SD) and that of Prednisolone group was 15.95±2.13 mm of Hg(Mean±SD) at the end of 6th week.So at the end of 6th week there was mean IOP elevation of 0.78 mm of Hg in Difluprednate group and that of 0.57 mm of Hg in Prednisolone group.This is in correspondence with the study done by Dr.Eric D. Donnenfold in 2011 who showed that IOP differences between the two groups were not statistically significant.In his study difluprednate patients had a mean pressure of 15.44 mm of Hg , and the prednisolone acetate patients had a 14.58 mm of Hg intraocular

pressure.[15]A clinically significant IOP rise is defined as an observed value ≥21 mmHg that is also a change from baseline IOP ≥ 10 mmHg at the same visit. In our study no patient in either group had IOP more than 21 mm of Hg and IOP rise more than 10 mm of Hg from baseline IOP at the end of 6th week.

However Smith et al in their study showed that 3.7% of Difluprednate patients had an elevated IOP of more than 21 mm Hg compared to no IOP elevation in placebo group.[14]Bahubali Jain et al. also showed in their study that there was mean IOP elevation of 3.5 mm of Hg in Difluprednate group and 1.2 mm of Hg in Prednisolone group.[109] But in our study there was mean IOP elevation of 0.78 mm of Hg in Difluprednate group Vs 0.52 mm of Hg in Prednisolone group. By 7th day 45% patients in Difluprednate group had achieved 6/9-6/6 vision in comparison with Prednisolone group where 29.5% had achieved 6/9-6/6 vision.In Prednisolone group, 23.5% patients had 6/60-6/24 vision whether in Difluprednate group it is only 7% ($p<0.05$).Roopa Devi et. al also showed that improvement of visual acuity was more in Difluprednate group($p=0.001$)[15].This difference was due to rapid clearing of corneal edema and anterior chamber cells and flare in Difluprednate group.At the end of 6 weeks, the number of patients with best corrected visual acuity of 6/18- 6/12 was 3.2% in Difluprednate group and 5.8% in Prednisolone group.96.8% of Difluprednate group and 94.2% of Prednisolone group achieved a vision of 6/9– 6/6($p>0.05$). There was no statistical significance was found to be present between two groups.

So, though there was rapid return of visual acuity in Difluprednate group at day 7, final visual outcome at 4 week was same in both groups.

VI.Conclusion

During last few decades, Prednisolone acetate has been considered as gold standard steroid for managing ocular inflammation including post-surgical inflammation.Difluprednate controlls post-operative inflammation rapidly with lesser time and lesser dose than Prednisolone. In our study, none of the patients showed significant rise in IOP in both groups from baseline till the end of 4 week.Best corrected visual acuity at the end of 4 week didn't show any statistical significant difference between two groups.In conclusion, Difluprednate Emulsion 0.05% appears to be a promising addition to the surgical armamentarium for treating postoperative inflammatory conditions. With proven efficacy of Difluprednate, we now have a new standard for potency in a topical corticosteroid, with excellent anti-inflammatory properties and an ideal formulation for our patients.

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