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Effect of Dexamethasone, Loteprednol and Difluprednate Eye Drops on Intraocular Pressure and Blood Glucose Levels in Diabetic Patients After Cataract Surgery: A Prospective Observational Study

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Abstract: Cataract surgery commonly induces postoperative inflammation managed with topical corticosteroids, which while effective, can elevate intraocular pressure (IOP) and reduce infection resistance. Variations in corticosteroid potency and side effects, particularly IOP elevation require careful selection. This study aimed to compare the effects of three commonly used topical steroids, loteprednol, dexamethasone and difluprednate eye drops, on intraocular pressure (IOP) and blood glucose levels in patients with diabetes after cataract surgery. This prospective observational study included 90 patients with diabetes aged > 50 years who underwent cataract surgery. Patients received loteprednol (Group I: 0.1%), dexamethasone (Group II: 0.05%) or difluprednate (Group III: 0.5%) eye drops for six weeks. Baseline intraocular pressure (IOP) and fasting blood sugar (FBS) levels were recorded. IOP was measured at 2 and 6 weeks and FBS was measured at 3 weeks post-surgery. Among the 90 patients, most were aged 55-64 years (35.6%) and 64.6% were female. Significant baseline IOP differences existed among the groups, although the postoperative differences were not statistically significant. Clinically significant IOP elevations (≥ 10 mmHg) were observed in 3 patients in Group III. Group II exhibited a higher mean IOP increase at 3rd postoperative week, and Group III at 6th postoperative week. Dexamethasone showed a greater increase in blood glucose levels than loteprednol and difluprednate, which was statistically insignificant. This study demonstrated the varying effects of loteprednol, dexamethasone, and difluprednate on post-cataract surgery outcomes. Difluprednate caused significant IOP elevation, while dexamethasone increased blood glucose levels compared to difluprednate and loteprednol. It is crucial to monitor initial intraocular pressure and blood glucose levels, especially with difluprednate and dexamethasone, to manage potential complications in diabetes mellites patients undergoing cataract surgery.

Keywords: Cataract surgery; Topical corticosteroids; Intraocular pressure; Blood glucose levels; Diabetes

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Introduction

Cataract surgery is a common ocular procedure globally, with over 10,000 surgeries performed per million people in countries such as India. Postoperative inflammation is a concern, leading to complications, such as corneal oedema, elevated IOP, cystoid macular oedema, posterior synechiae formation, and posterior capsular opacification. Postoperative treatment regimens can vary significantly among physicians, particularly with regard to the administration of anti-inflammatory medications. Topical steroids are often preferred because of their potent anti-inflammatory effects, while NSAIDs are widely used for pain and inflammation management, with a lower risk of increasing intraocular pressure. The choice between these drugs depends on factors such as the patient's risk, the surgeon's experience, and the latest clinical evidence. While some studies suggest the superiority of a single drug group, topical steroids remain a prevalent choice in postoperative regimens following cataract surgery.

Corticosteroids exhibit a broad range of mechanisms of action. Corticosteroids inhibit both initial and subsequent stages of inflammation. In the early phase, it reduces capillary expansion, recruitment of leukocyte, and vascular permeability. During the later phase, they impede the proliferation of inflammatory cells and chemokines, and accumulation of fibrin.[1] However they are, they can cause side effects like elevated IOP, reduced infection resistance, cataract risk, and decreased wound healing.[2] Topical steroidal eye drops have varying potency and ability to penetrate the anterior chamber (AC), with higher potency providing quicker ocular inflammation control, but increasing the risk of side effects, especially elevated intraocular pressure. (IOP). Post-cataract patients experience elevated IOP owing to biochemical and structural alterations in the trabecular meshwork, resulting in greater resistance in the outflow of aqueous humour.[3] An increase in intraocular pressure induced by steroids occurs in 18-36% of individuals who respond to steroids. Risk factors for this condition include glaucoma history,[4] familial predisposition, or high myopia.[4,5]

Corticosteroids from earlier generations, including fluorometholone, prednisolone, and dexamethasone are used to manage inflammation after surgery. In contrast, more recently developed corticosteroids, such as loteprednol etabonate, difluprednate, and rimexolone, are employed to reduce intraocular pressure. Potent steroids like prednisolone, dexamethasone, and betamethasone are known for their anti-inflammatory properties.[6] Although serum drug levels are apparently low in patients receiving topical corticosteroids, there may be variations in the levels of plasma cortisol and adrenocorticotropic hormones. Fukushima et al. found an early effect on serum glucose levels in diabetic and nondiabetic rats after dexamethasone injection, and a transient increase in blood glucose levels on surgery day in diabetic patients, but no reports were found on the impact of topical steroid drops on human serum glucose levels.[7,8]

The use of steroids may lead to elevated IOP, requiring careful observation of changes in both blood glucose levels and IOP to enable early detection and timely treatment. However, there is a scarcity of comparative data examining how various topical steroids influence intraocular pressure (IOP), clinically significant IOP, and elevations in blood glucose levels. A study revealed a considerable rise in blood sugar levels following dexamethasone eye drop administration, emphasising the necessity to consider the possibility of clinically considerable intraocular pressure elevation (IOP ≥ 10 mmHg) and blood glucose levels when selecting a steroid. This study aimed to assess and compare the influence of three widely utilised topical steroids, loteprednol, dexamethasone, and difluprednate eye drops, on IOP and blood glucose levels in patients with diabetes mellitus after cataract surgery, focusing on their glycaemic control.

Materials And Methods

This prospective, observational investigation was carried out in the Department of Pharmacology and Ophthalmology, S.S Institute of Medical Sciences and Research Centre, Davangere, Karnataka, over a two-month period after obtaining approval from the Institutional Ethics Committee (IERB No: 641-

2023). The study included 90 patients with diabetes aged > 50 years who underwent cataract surgery and had senile cataracts of either sex. Patients with diabetes aged < 50 years, known instances of glaucoma, ocular hypertension history, trauma/vitreous haemorrhage, ischaemic proliferative diabetic retinopathy receiving systemic corticosteroids or other drugs that could affect blood glucose at the time of the study, and systemic diseases known to influence blood glucose levels were excluded from the study. Signed informed consent forms were obtained from patients after explaining the study details. A total of 90 diabetic patients were grouped into 3 groups. Group I: patients who will be receiving loteprednol eye drops (0.1% for six weeks), Group II: patients who will be receiving dexamethasone eye drops (0.05% for six weeks and Group III: patients who will be receiving difluprednate eye drops (0.5% for 6 weeks)

Steroid eye drops were applied for six weeks, as advised by the ophthalmologists. On the first postoperative day, it was administered every hour for 24 h and then gradually tapered. The dosage was gradually decreased to 6 times/day over the next 6 weeks and then gradually tapered to 5 times/day in the second week, 4 times/day in the third week, 3 times/day in the fourth week, 2 times/day in the fifth week, once a day in the sixth week, and then stopped. Demographic details such as age and sex, baseline intraocular pressure (measured by ophthalmologists using Goldmann's applanation tonometer only), and FBS before cataract surgery were recorded. Following cataract surgery, intraocular pressure (IOP) was evaluated at two and six weeks, FBS was assessed in the 3rd week post-surgical procedure. Other adverse effects were also observed. Patients were followed up for a period of one and a half month. Data were analysed using descriptive statistics and inferential statistics using SPSS version 10.

Results

In this investigation, 90 patients participated, with the majority aged–55-64 years (n=32, 35.6%), followed by those aged 65-74 years (n=23, 25.6%), 45-54 years (n=18, 20%), 35-44 years (n=11, 12.2%), and over 74 years (n = 6, 6.7%). The majority were females (n=58, 64.6%), and 35.6% were males (n=32). Regarding the surgery type, 58.9% (53 patients) underwent surgery for a left-eye cataract (LEC), while 41.1% (n=37) underwent surgery for a right-eye cataract (REC). (Table 1)

There was a significant difference in the baseline intraocular pressure among the 3 groups, and no significant difference was found in the mean intraocular pressure among the groups postoperatively. However, a notable elevation in intraocular pressure was seen in a few subjects. In Group III, 3 patients showed a clinically considerable elevation in intraocular pressure (≥ 10 mmHg from baseline), with an overall intraocular pressure of ≥ 21 mmHg. Of the 90 patients, 4 patients showed a rise in intraocular pressure of ≥ 5 mmHg from baseline, and 2 patients showed an elevation of ≥ 10 mmHg from baseline at the third postoperative week. Approximately 8 out of 90 patients experienced a moderate rise in intraocular pressure of ≥ 5 mmHg, and 3 out of 90 patients showed an elevation of ≥ 10 mmHg. This suggests that, while the overall postoperative IOP may not vary considerably across groups, a few patients still experience clinically relevant IOP increases, which is important for postoperative monitoring and management. (Table 2)

The postoperative effects of 3 different treatments (Dexamethasone, Loteprednol, and Difluprednate) on the blood glucose levels and IOP were compared. IOP Increase at 3rd Week Postoperative showed that Group II had the highest elevation in intraocular pressure with a mean of 4.22 ± 3.77, whereas Group III had a mean elevation of 3.71 ± 4.07 and Group I had the lowest mean elevation in intraocular pressure at 2.09 ± 1.45. IOP Increase at 6th Week Postoperatively observed Group III had the greatest mean elevation in intraocular pressure at 8.57 ± 12.01 whereas Group II had a mean elevation of 4.11 ± 2.93 and Group I had the lowest mean elevation in intraocular pressure at 2.67 ± 1.88. The differences in the IOP increase among the groups were not statistically considerable. Blood Glucose Levels Postoperatively observed that Dexamethasone caused a greater increase in blood glucose levels, with a mean of 255.2 ± 71.4 after 1 month, Loteprednol had a mean blood glucose level of 188.3 ± 35.0, and

Difluprednate had a mean blood glucose level of 192.3 ± 36.5. There was no significant difference in blood glucose levels between the groups. (Table 3)

Table 1 Distribution of patients based on gender, age and diagnosis of cataract

	Group I Loteprednol (n/%)	Group II Dexamethasone (n/%)	Group III Difluprednate (n/%)	Total
Age wise distribution of the patients in years				
35-44	7 (23.3%)	4 (13.3%)	0 (0%)	11 (12.2%)
45-54	2 (6.7%)	4 (13.3%)	12 (40%)	18 (20%)
55-64	8 (26.7%)	12 (40%)	12 (40%)	32 (35.6%)
65-74	10 (33.3%)	7 (23%)	6 (20%)	23 (25.6%)
Above 74	3 (10%)	3 (10%)	0 (0%)	6 (6.7%)
Total	30 (100%)	30 (100%)	30 (100%)	90 (100%)
Gender wise distribution of the patients				
Male	8 (26.7%)	12 (40%)	12 (40%)	32 (35.6%)
Female	22 (73.3%)	18 (60%)	18 (60%)	58 (64.4%)
Total	30 (100%)	30 (100%)	30 (100%)	90 (100%)
Diagnosis of cataract				
Left eye cataract	17 (56.7%)	29 (66.7%)	16 (53.3%)	53 (58.9%)
Right eye Cataract	13 (43.3%)	10 (33.3%)	14 (46.7%)	37 (41.1%)
Total	30 (100%)	30 (100%)	30 (100%)	90 (100%)

Table 2. Preoperative and postoperative intraocular pressure and increase of IOP among the groups

Pre-operative and postoperative intraocular pressure in all three groups in mmHg							
	Group I Loteprednol (Range / Mean ± SD)		**Group II Dexamethasone (Range / Mean ± SD)**		**Group III Difluprednate (Range / Mean ± SD)**		**p value**
Pre-operative							
Baseline	8-22	14.03 ± 4.24	10-20	13.83±2.52	9-22	16.27 ±3.79	0.017
Post-operative							
3rd week	7-23	12.60 ± 3.58	8-25	12.80±3.77	5-30	13.80 ± 5.05	0.495
6th week	9-21	14.03 ± 3.46	9-22	13.23±3.71	9-48	15.40 ± 7.60	0.280

Proportion of patients with increase in IOP of ≥ 10mmHg from baseline andoverall IOP ≥ 21mmHg			
	Group I Loteprednol (n)	**Group II Dexamethasone (n)**	**Group III Difluprednate (n)**
≥10 mmμg increase and Overall IOP >21mmμg	0	0	3

Increase in IOP from Baseline in all three groups

Duration	**Group I Loteprednol**		**Group II Dexamethasone**		**Group III Difluprednate**	
	3rd week	**6th week**	**3rd week**	**6th week**	**3rd week**	**6th week**
Increase in IOP of ≥ 5 mmHg from baseline	1	4	2	4	1	1
Increase in IOP of ≥ 10 mmHg from baseline	0	0	1	0	1	2

Table 3. Mean increase in intraocular, preoperative and postoperative blood glucose level among the groups

	Group I Loteprednol (Mean ± SD)	**Group II Dexamethasone (Mean ± SD)**	**Group III Difluprednate (Mean ± SD)**	**p value**
Mean increase in IOP from baseline				
3rd week	2.090909 ± 1.445998	4.222222 ± 3.767552	3.714286 ± 4.070802	0.299
6th week	2.666667 ± 1.877181	4.111111 ± 2.934469	8.571429 ± 12.0119	0.111
Pre-operative and postoperative blood glucose level in all three groups inmg/dL				
Preoperative Baseline	179.5 ± 32.9	176.5 ± 25.8	175.2 ± 31.8	0.190
Postoperative 3rd week	188.3 ± 35.0	255.2 ± 71.4	192.3 ± 36.5	0.316

Discussion

Topical ophthalmic steroids, which are frequently utilized for postoperative inflammation after the cataract surgical procedure, vary in their effects on intraocular pressure (IOP). This investigation evaluated the effect of loteprednol, dexamethasone, and difluprednate eye drops on intraocular pressure and blood glucose levels to detect and prevent steroid-induced glaucoma. Although all 3 steroids elevated the intraocular pressure, the differences were more with difluprednate. Our study included predominantly female patients aged 55–64 years. Among these patients, three in the difluprednate group showed a clinically considerable rise in intraocular pressure of ≥10 mmHg, consistent with the findings of Ostrov et al., who reported no considerable intraocular pressure variations among steroid groups,

except for difluprednate. According to Stewart et al., a clinically significant increase in intraocular pressure (IOP) ≥10 mmHg was proposed.[9]

In our study, 4.44% of patients showed such an increase, with one case in the dexamethasone group and three cases in the difluprednate group. Additionally, 14.44% showed a moderate rise in intraocular pressure of ≥5 mmHg, comparable to those reported by Dodiya et al., where approximately 21% of patients had an elevation in intraocular pressure of ≥6 mmHg. Previous studies have shown varying results concerning increase in intraocular pressure with different steroids.[10] Laurel and Zetterstrom observed higher mean intraocular pressure in the dexamethasone group in comparison to placebo, but no patients had an intraocular pressure elevation of ≥10 mmHg.[11] Our study, however, found one subject in the dexamethasone group with such an increase, indicating the possibility of dexamethasone causing significant IOP elevation. Smerdon et al. compared prednisolone with placebo in controlling postoperative inflammation, noting that 24% of prednisolone-treated patients had elevation of intraocular pressure to ≥22 mmHg, although no increases in IOP of ≥10 mmHg were reported.[12]

In our study, no patients in the loteprednol group had an elevation in intraocular pressure of ≥10 mmHg, and only five had a moderate increase to ≥5 mmHg, suggesting a lower risk of loteprednol. Korenfeld et al. reported that about 3percent of subjects using difluprednate had an elevation in intraocular pressure of ≥10 mmHg, consistent with our finding that 3 cases in the difluprednate group experienced such an increase.[13] Similarly, Smith et al. found 3.7% of difluprednate-treated patients had an elevation in intraocular pressure of ≥10 mmHg.[14] Another study analyzed 100 patients treated with difluprednate postoperatively, finding that five with a history of open-angle glaucoma reported ocular hypertension, with an average intraocular pressure rise of 17.8 mmHg.[15]

Our study found that 3.33% of the cases in the difluprednate group had an elevation in intraocular pressure of ≥10 mmHg, with IOP reaching ≥21 mmHg, indicating a higher potential for intraocular pressure rise with difluprednate. Among the 3 patients, one showed elevated IOP in the 3rd week and the other two in the 6th week, indicating that it can cause an early rise in intraocular presure. Similar results have been reported by Jeng et al.[16] and Meehen et al.[17] Regarding glucose levels in blood, our study found that dexamethasone increased glucose levels in blood compared to loteprednol and difluprednate. Feldman-Billard et al. showed that periocular injections of dexamethasone induced marked hyperglycemia in type 2 diabetes subjects.[18] Our findings align with those of Bahar et al., who noted significant blood glucose increases only in the diabetic dexamethasone group. Corticosteroids can cause hyperglycaemia by increasing glucose intolerance, glucagon secretion, hepatic glucose production, and reducing glucose transport in adipocytes. While healthy adults can counteract corticosteroid-induced hyperglycaemia, diabetes mellites patients may experience aggravated insulin resistance. Stress-related activation of the sympathetic nervous system also contributes to increased blood glucose levels and insulin resistance.

The research findings indicated notable differences in how the 3 corticosteroids influenced the IOP and blood glucose concentrations. Difluprednate showed a high potential significant and early increase in intraocular pressure compared with dexamethasone and loteprednol. Dexamethasone was linked with increased blood glucose levels compared with the other 2 steroids. These observations highlight the necessity of considering the specific effects of corticosteroids on blood glucose levels and IOP in clinical decision making. The judicious usage of these medications, along with constant monitoring, is emphasized to minimize adverse reactions and optimize patient outcomes after cataract surgical procedure. Advances in the development of safer topical steroids aim to reduce the risk of complications, including an increase in intraocular pressure, while effectively managing postoperative inflammation.

Conclusion

The findings of this investigation demonstrated that all 3 steroids have the potential to increase IOP; this increase was clinically significant in the difluprednate group. Additionally, dexamethasone was

linked to a higher increase in blood glucose levels compared to the other groups. Therefore, it is recommended that IOP and blood glucose levels in diabetic patients be monitored early during treatment with difluprednate and dexamethasone ophthalmic solutions.

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