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SAFETY AND EFFICACY OF LOTEPREDNOL ETABONATE 0.5% VERSUS PREDNISOLONE ACETATE 1% FOR THE TREATMENT OF PAIN AND INFLAMMATION AFTER CATARACT SURGERY- A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Cataract is one of the major health care problem faced by old aged people. It is responsible for 50% of blindness in the world, the overall prevalence rate varies from 1% to 4% of the population and 300,000 cataract surgeries are performed every year. Cataract surgery is usually a very effective and safe procedure, but a severe post-operative inflammation can be vision threatening. Corticosteroids are the first line drugs for the treatment of pain and inflammation after cataract surgery. This can lead to fluctuation in Intraocular pressure. Few randomized, controlled studies are available on the comparative safety and efficacy of common topical corticosteroids in the treatment of post-operative ocular inflammation. Newer corticosteroids that the retro-metabolically designed corticosteroid, Loteprednol Etabonate, offer similar anti-inflammatory efficacy to older corticosteroids like prednisolone acetate with less effect on Intraocular pressure. Loteprednol Etabonate, a novel C-20 ester-based corticosteroid, was retrometabolically designed to offer potent anti-inflammatory efficacy but with decreased impact on Intraocular pressure. The proportion of patients exhibiting an increase of C10 mmHg Intraocular pressure in clinical studies has emerged as the most clinically relevant parameter for ophthalmologists to consider when deciding on which topical corticosteroid to use.

KEYWORDS: Cataract surgery, Intraocular pressure, Topical corticosteroids, Loteprednol Etabonate, Prednisolone Acetate, Post-operative pain and inflammation.

INTRODUCTION

Cataract is the clouding of the natural intraocular crystalline lens that focuses the light entering the eye onto the retina. The crystalline lens is a transparent structure. Its transparency may be disturbed due to degenerative process leading to opacification of lens fibers. Cataracts are cloudy or misty patches that occur in the lens of the eye and causes blurred vision.

The most common causes of cataract are age, trauma, radiation, genetics, skin diseases, drug use and medications. Age is the most common cause of cataract. Lens proteins denature and degrade over time and this process is accelerated by diseases such as Diabetes Mellitus and Hypertension. Environmental factors, including toxins, radiation and ultraviolet light, have cumulative effects, which are worsened by the loss of protective and restorative mechanisms due to alterations in gene expression and chemical processes within the eye. Trauma is Blunt trauma causes swelling, thickening and whitening of the lens fibers. While the swelling normally resolves within time, the white color may remain. In severe blunt trauma or injuries which penetrate the eye, the capsule in which the lens sits can be damaged. Radiation is Ultraviolet light, specifically UVB, has been shown to cause cataracts, and some evidence indicates sunglasses worn at an early age can slow its development in later life. Microwave radiation has also been found to cause cataract. The genetic component is strong in the development of cataracts most commonly through mechanisms that protect and maintain the lens. The presence of cataracts in childhood or early life can occasionally be due to a particular syndrome. People with Schizophrenia often have risk factors for lens opacities (such as diabetes, hypertension and poor nutrition) but antipsychotic medications are unlikely to contribute to cataract formation. Miotics and triparanol may increase the risk. Cataract surgery is usually very effective and safe procedure but a severe post-operative inflammation can be vision threatening. It is the removal of natural lens of the eye that has developed and opacification which is referred to as cataract.

During cataract surgery, patients cloudy natural lens is removed. The symptoms may vary according to the location of the cataract in the eye. Depending on the type and extend of cataract patients may experience the following symptoms are Blurred vision at distance or near, Cloudy, fuzzy, foggy, or filmy vision, Glare (halos or streaks around lights, difficulty

seeing in the presence of bright lights), Difficulty seeing in low light situations (including poor night vision), Double vision, Loss of color intensity, Loss of contrast sensitivity, Increasing near-sightedness or change in refractive status. Most people with cataract have similar changes in both eyes, though one eye may be worse than the other often there are only mild vision changes.[4] placed with synthetic lens (IOL) to restore the lens transparency.

The major complications of cataract surgery are the following are Infection in the eye (endophthalmitis), Swelling and fluid in the center of the nerve layer (cystoid macular edema), Swelling of the clear covering of the eyes (corneal edema), Bleeding in the front of the eyes (hyphema), Problems with glare, Dislocated intraocular lens, Posterior capsular rupture, Retinal detachment, Glaucoma, Astigmatism or strabismus, Eye inflammation, Vitreous loss, Ocular hypertension.

Cataract surgery is a common procedure undergone by millions of patients worldwide. Surgical trauma to the eye, however, often results in an inflammatory response. This response is characterized by the release of phospholipids from cell membranes, culminating in the production of chemical inflammatory mediators such as prostaglandins and leukotrienes, and the recruitment of neutrophils and macrophages to the site of trauma. The most commonly administered class of anti-inflammatory agents is topical corticosteroids. They offer relief from a broad range of signs and symptoms of ocular inflammation and are used in a variety of ocular inflammatory conditions. However, they carry a risk of side effects, particularly an increase in intraocular pressure (IOP). If left untreated, this increase in IOP could lead to corticosteroid-induced ocular hypertension and eventually glaucoma. The exact mechanism of steroid-induced IOP elevation is not fully understood. Genetics clearly play a role in steroid-induced glaucoma. These changes include the formation of cross-linked actin fibers, increased deposition of extracellular matrix material, and inhibition of cell phagocytosis, which together result in an increased resistance to aqueous outflow and thus elevation of IOP.

Prednisolone, a corticosteroid, is generally indicated for the treatment of ocular inflammations, allergic reactions, and anterior uveitis. Topical drug delivery is the most preferred method of drug administration for the treatment of ocular diseases affecting anterior tissues of the eye. However, this method of drug administration faces numerous challenges including rapid tear turnover rate, drainage to systemic circulation, and non-specific absorption resulting in lower drug absorption in anterior ocular tissues. Moreover,

the apical surface of the corneal epithelium expresses drug efflux proteins such as P-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRPs). These efflux transporters actively pump drug molecules from the cornea back to the tear film. This process further limits drug accumulation in anterior ocular tissues. The cumulative effects of these obstacles result in less than 5% ocular drug bioavailability following topical administration. Importantly, to generate high transcorneal permeability following topical administration, drugs need to possess an optimum balance between hydrophilicity and lipophilicity properties. Prednisolone is a poorly water soluble drug and an excellent substrate of P-gp.

Loteprednol Etabonate is a novel corticosteroid produced by retrometabolic design. In retrometabolic drug design, an inactive and nontoxic metabolite of a reference compound is utilized as a starting point for conversion to a therapeutically active, metabolically labile compound. Preclinical studies demonstrated that Loteprednol Etabonate is highly lipophilic and has strong binding affinity to glucocorticoid receptors. Indeed, its lipophilicity was found to be 10 times greater while its binding affinity to the glucocorticoid receptor was found to be 4.3 times greater than that of prednisolone postoperative inflammation and pain, and to assess its efficacy and safety along with that of other corticosteroids.

MATERIALS AND METHODS

A Prospective observational study was conducted in the Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals, Salem. Patients of both the genders were included in the study. From the data of 100 Consecutive Cataract cases, 50 patients were administered with Loteprdnol Etabonate and other 50 patients were administered with Prednisolone Acetate and the data were collected during the time period of six months November 2016 – April 2017. The results are tabulated by simple statistical methods.

Patients were selected in between the age of at least 18 and atmost 80 are scheduled for routine cataract surgery. Patients were randomized to receive Loteprednol Etabonate or prednisolone acetate 4 times daily in addition to Bromfenac 0.09% and Moxifloxacin 0.6% after surgery. Visual acuity, IOP, and anterior chamber cell and flare intensity were assessed over 3 weeks after cataract surgery. The primary endpoint was the level of anterior chamber cell and flare intensity in patients treated with loteprednol etabonate or prednisolone acetate.

RESULTS

A total of 100 cataract patients from Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals, Salem were enrolled in the study conducted. Table no: 1 shows the different ranges of visual acuity in patients with Loteprednol Etabonate in post-operative cataract surgery. Out of 50 patients who have been administered with Loteprednol Etabonate, the patient with visual acuity range 6/6,6/9,6/12,6/18,6/36,6/60,5/60, CFCF and HM in visit 1 are 22%, 34%, 16%, 14%, 6%, 2%, 4%, 0% and 2% respectively followed by visit 2are 18%, 36%,30%,16%,0%,0%,0% and 0% respectively and visit 3 are 46%,28%,14%,12%, 0%,0%,0% and 0% respectively.

Table no: 1.

SL NO	VISUAL ACUITY	VISIT 1 (WEEK 1)		VISIT 2 (WEEK 2)		VISIT 3 (WEEK 4,6,8)	
		No. of pts.	%	No. of pts.	%	No. of pts.	%
1	6/6	11	22%	9	18%	23	46%
2	6/9	17	34%	18	36%	14	28%
3	6/12	8	16%	15	30%	7	14%
4	6/18	7	14%	8	16%	6	12%
5	6/36	3	6%	0	0%	0	0%
6	6/60	1	2%	0	0%	0	0%
7	5/60	2	4%	0	0%	0	0%
8	CFCF	0	0%	0	0%	0	0%
9	HM	1	2%	0	0%	0	0%
10	**Total**	**50**	**100%**	**50**	**100%**	**50**	**100%**

Figure no: 2 shows the different ranges of visual acuity in patients with Prednisolone Acetate in post-operative cataract surgery. Out of 50 patients who have administered with PA, the patient with visual acuity range 6/6, 6/9, 6/12, 6/18, 6/36, 6/60, 5/60, CFCF, HM and PL+ in visit 1 are 4%, 16%, 34%, 30%, 65, 20%, 2%, 0%, 4% and 0% respectively followed by visit 2 are 8%, 36%, 26%, 24%, 2%, 0%, 2%, 0%, 2% and 0% respectively and visit 3 are 16%, 48%, 14%, 20%, 2%, 0%, 0%, 0%, 0% and 0% respectively.

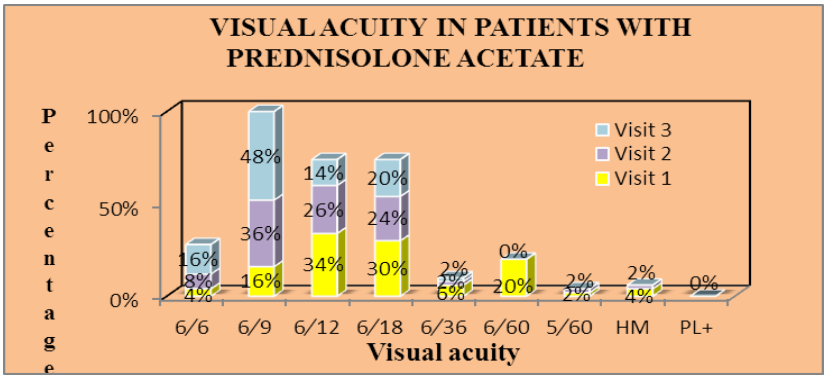

Figure no: 2.

Table no: 3 shows the different ranges of IOP values in patients with Loteprednol Etabonate in post-operative cataract surgery. Out of 50 patients who have been administered with LE, the patient with IOP range 10-13, 14-17, 18-21, 22-25, 25 above are60%, 28%, 12%, 0% and 0% respectively in visit 1 followed by visit 2 are 62%, 32%, 6%, 0% and 0% respectively followed by visit 3 are 72%, 28%, 0%, 0% and 0% respectively.

Table no: 3.

SL NO	INTRA OCULAR PRESSURE	VISIT 1 (WEEK 1)		VISIT 2 (WEEK 2)		VISIT 3 (WEEK 4, 6, 8)	
		No. of pts.	%	No. of pts.	%	No. of pts.	%
1	10-13	30	60%	31	62%	36	72%
2	14-17	14	28%	16	32%	14	28%
3	18-21	6	12%	3	6%	0	0%
4	22-25	0	0%	0	0%	0	0%
5	25 above	0	0%	0	0%	0	0%
6	**Total**	**50**	**100%**	**50**	**100%**	**50**	**100%**

Figure no: 5 shows the different ranges of IOP values in patients with Prednisolone Acetate in post-operative cataract surgery. Out of 50 patients who have administered with PA, the patient with IOP range 10-13, 14-17, 18-21, 22-25, 25 above are 24%, 46%, 30%, 0% and 0% respectively in visit 1 followed by visit 2 are 38%, 44%, 18%, 0% and 0% respectively followed by visit 3 are 60%, 26%, 14%, 0% and 0% respectively.

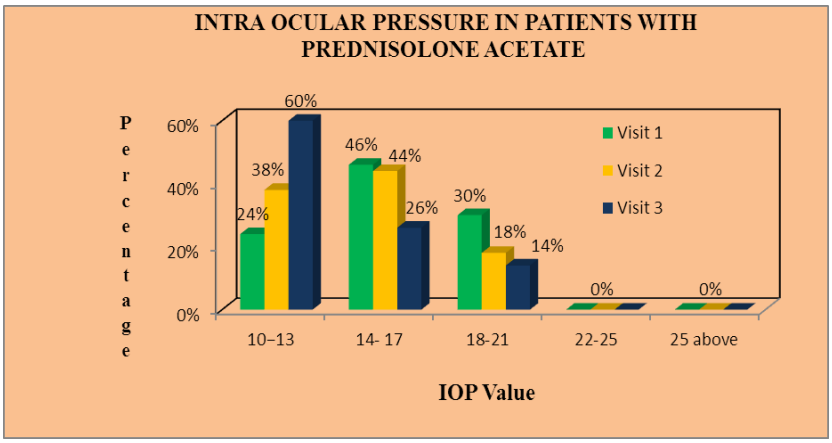

Figure no: 4.

Table no: 5 shows different ranges of pain scales in patients with Loteprednol Etabonate after cataract surgery. Out of 6 patients who have been administered with LE, the patients with SK+ showing pain scale 2 is 100%, SK++ showing pain scale 3 is 0% and Flare/cell is 0% in visit 1. In visit 2 and 3 the number of patients showing pain scale is 0%.

Table no: 5.

SL NO	PAIN SCALE	VISIT 1 (WEEK 1)		VISIT 2 (WEEK 2)		VISIT 3 (WEEK 4, 6, 8)	
		No. of pts.	%	No. of pts.	%	No. of pts.	%
1	SK+(2)	6	100%	0	0%	0	0%
2	SK++(3)	0	0%	0	0%	0	0%
3	Flare/cells	0	0%	4	0%	0	0%
4	**Total**	**6**	**100%**	**6**	**100%**	**6**	**100%**

Figure no: 6 shows different ranges of pain scales in patients with Prednisolone Acetate after cataract surgery. Out of 8 patients who have been administered with PA, the patients with SK+ showing pain scale 2 is 88%, SK++ showing pain scale 3 is 13% and Flare/cell is 0% in visit 1. In visit 2 and 3 the number of patients showing pain scale is 0%.

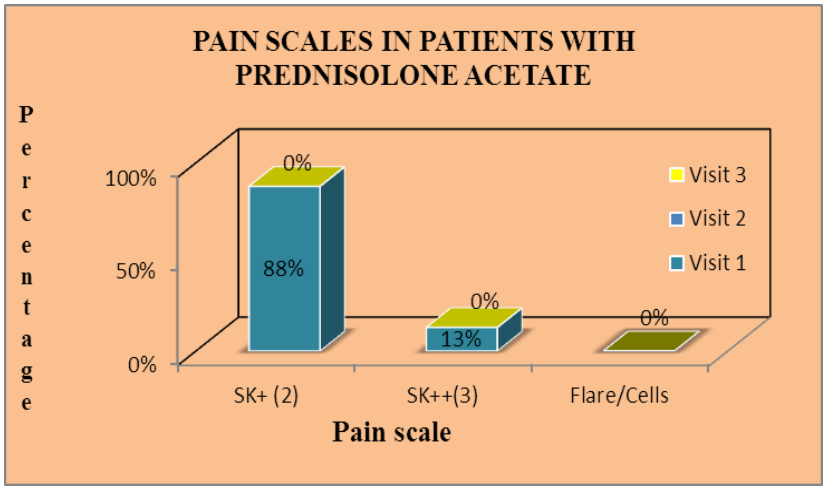

Figure no: 6.

DISCUSSION

Blindness has profound human and economic consequences in all societies due to loss of independence, self-esteem and economic productivity among those affected and their families. There are also additional costs involved in providing special needs education for children and rehabilitation services for those with irreversible loss of vision.

Here the data shows different ranges of distant visual acuity in pre-operative cataract patients. Visual acuity refers to the clariy of vision. It is the measure of ability of eye to distinguish the shape of objects. Visual acuity is assessed with the help of snellen distant visual acuity drum. 6/6- being normal and 6/60- worst in the snellen type. In this data, the higher population of pre-operative cataract patient have the visual acuity 5/60 which is about 21% followed by 6/60 in 15%, 4/60 in 14%, 6/36 in 12%, 6/24 in 11%, 2/60 & 1/60 in 8%,

HM in 7%, 3/60 in 4% and CFCF and PL+ are found to be 0%.From this data we can conclude that pre-operative cataract patients mostly have least visual acuity.

In this study different ranges of visual acuity in patients with Loteprednol Etabonate after cataract surgery were analyzed. The result of the study indicate LE was safe and effective for visual acuity after cataract surgery. It shows range of 22% in 6/6 during visit 1 which increases to 46% during visit 3 and 2% in 6/60 during visit 1 which decreases to 0% during visit 3.

In this study different ranges of visual acuity in patients with Prednisolone Acetate after cataract surgery were analyzed. It shows high range of 30% in 6/18, 18% in 6/12 during visit 1 that slightly reduced in visit 3 to 20% in 6/18, 14% in 6/12 and shows very less percentage in 6/6 from 4% to 16%.The result of the study indicate LE was safe and effective for visual acuity after cataract surgery than PA. Similarly, Edward J Holland *et al*[56] studied about LE 0.5% vs PA 1% for the treatment of inflammation after cataract surgery. The best visual acuity were found to be in patients with LE.

In this study the different ranges of intra ocular pressure fluctuation in pre-operative cataract surgery was analyzed. Intra ocular pressure is the fluid pressure inside the eye. Intra ocular pressure is measured with the help of non-contact tonometry (NCT). It is an important aspect in the evaluation of patients at the risk from glaucoma. The higher population of pre-operative cataract patient have the IOP of range 10-13 which is about 38% followed by range 14-17 in 34%, range 18-21 in 27%, range 22-25 in 0% and range above 25 in 1%.

Lane *et al* compared the efficacy and safety of Loteprednol Etabonate with that of Prednisolone Acetate in cataract patients. The IOP were higher in patients treated with PA than in LE. According to our study different ranges of intra ocular pressure values in patients with Loteprednol Etabonate after cataract surgery were analyzed. It is observed that patients who have been administered with LE the normal IOP range 10-13, 14-17 and 18-21 are 60%, 28% and 12% respectively in visit 1 which seem to be increased to 72%, 28% and 0% respectively and the higher IOP range 22-25 and 25 above are found to be 0% in both visit 1 and visit 3. Here, Loteprednol Etabonate is a potent and safe corticosteroid with low propensity to increase IOP.

According to our study different ranges of intra ocular pressure values in patients with Prednisolone Acetate after cataract surgery were analyzed. It is observed that patients who have been administered with PA, the normal IOP range 10-13, 14-17 and 18-21 are 24%, 46% and 30% respectively in visit 1 which seem to be increased to 60%, 26% and 14% respectively and the higher IOP range 22-25 and 25 above are found to be 0% in both visit 1 and visit 3. Here, Prednisolone Acetate is a less potent and safe corticosteroid with high propensity to increase IOP than LE.

According to this study different ranges of pain scale in patients with Loteprednol Etabonate after cataract surgery were analyzed. Pain scale measures a patients pain intensity or other features. It is based on self-report, observational datas. Out of 6 patients who have been administered with LA, the patients with SK+ showing pain scale 2 was found to be 100%, SK++ showing pain scale 3 was found to be 0% and Flare/cell was found to be 0% in visit 1. In visit 2 and 3 the number of patients showing pain scale is 0%.

According to this study different ranges of pain scale in patients with Prednisolone Acetate after cataract surgery were analyzed. Out of 8 patients who have been administered with PA, the patients with SK+ showing pain scale 2 was found to be 88%, SK++ showing pain scale 3 was found to be 13% and Flare/cell was found to be 0% in visit 1. In visit 2 and 3 the number of patients showing pain scale is 0%. Here, the two graphs indicate that the both drugs shows same effect on reducing the pain in patients after cataract surgery. Similarly, Michael Amon *et al* studied about the safety and efficacy of Loteprednol Etabonate ophthalmic suspension 0.5% for postoperative anti-inflammatory use. The impact of pain management were found to be same for both drugs.

CONCLUSION

As per the evidence collected from the comprehensive review of the above datas on the safety and efficacy of Loteprednol Etabonate verses Prednisolone Acetate, with long term use Loteprednol Etabonate is effective in resolving anterior chamber cells and flare, as well as in reducing post-operative pain and discomfort. As per the information obtained from the above statistical data, Loteprednol Etabonate is more potent and safe drug for increasing visual acuity in patients after cataract surgery. Based on the available data from the above studies of steroid responders, we can conclude that the impact of Loteprednol Etabonate on minimal IOP is greater than that of Prednisolone Acetate, there by Loteprednol Etabonate shows improved safety profile as compared to the other drug Prednisolone Acetate. While the

result provide significant insight into the effect of the newer corticosteroid Loteprednol Etabonate, high quality, active controlled randomized clinical trial between these compounds are needed to assess the comparable safety and efficacy.

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