ejpmr, 2018,5(5), 575-580

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

A COMPARATIVE STUDY OF EFFICACY OF PREDNISOLONE ACETATE (1%) EYE DROPS ALONE AND WITH CYCLOSPORINE (0.05%) EYE DROPS IN OPTICAL PENETRATING KERATOPLASTY

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Article Received on 20/03/2018 **Article Revised on 10/04/2018** **Article Accepted on 30/04/2018**

ABSTRACT

Introduction - Keratoplasty or corneal transplantation is one of the most common and successful tissue transplantations worldwide. Corticosteroids, cyclosporine, and cytotoxic agents are all important therapeutic agents that can be used to treat inflammation and play role in prevention and treatment of graft rejection. **Objective** - To compare the efficacy of prednisolone acetate (1%) eye drops alone and with cyclosporine (0.05%) eye drops in optical penetrating keratoplasty. **Material and Methods**-30 patients undergoing optical penetrating keratoplasty in a tertiary health care hospital in north India were randomly divided into two groups. Patients in group 1 were put on prednisolone acetate 1% eye drops post – operatively for 24 weeks. Patients in group 2 were put on prednisolone acetate 1% and 0.05% cyclosporine eye drops for 24 weeks. Follow-up of the patients was done every 2 weeks for 16 weeks, and every month for next 2 months. At each visit, clinical evaluation of the transplanted graft was made and scoring was done for corneal transparency, corneal edema and neovascularisation of graft. **Results**- At the end of study, 4 patients (26.67%) in group 1 had diffuse marked stromal edema while only 1 patient (6.67%) in group 2 had diffuse marked stromal edema. Maximum number of patients (40%) in group 1 had new vessels invading the graft while in group 2, maximum number of the patients (53.33%) had new vessels invading less than 1/3 recipient bed. 8 patients (53.33%) in group 1 and 10 patients (66.67%) in group 2 had clear cornea. Five patients (33.33%) had white cornea in group 1 while 2 patients (13.33%) had white cornea in group 2. Graft rejection rate was calculated taking into account graft transparency. Graft transparency ≥3 was considered as rejection. At the end of 6 months, 6 patients (40%) in group 1 showed rejection as compared to three patients (20%) in group 2. Overall rejection rate after 6 months was 30%. However, difference in rejection rates between two groups is not statistically significant (p- valve > 0.05). **Conclusion**- Topical 2% cyclosporine A is an effective adjunct to topical steroids in preventing acute corneal graft rejection episodes or increasing rejection free time interval. But a large multi-centric trial should be carried out to support the evidence.

KEYWORDS: Keratoplasty, prednisolone, cyclosporine, graft rejection.

INTRODUCTION

Keratoplasty or corneal transplantation is one of the most common and successful tissue transplantations worldwide.[1] It is widely recognized that corneal allografts are endowed with unique properties that reduce their likelihood of arousing an immune response. The unusual properties of the cornea and the anterior chamber of the eyes led *Bellingham* and *Medawar* to coin the term "immune privilege" to convey the concept that the eye, especially the anterior segment was exempt from some forms of immune mediated inflammation.[2] Immune privilege of corneal allografts is abolished in virtually any condition in which inflammation, neovascularization or trauma is elicited in the cornea. Immune system rejection is the leading cause of graft failures accounting for up to 34% of failures.[3]

An immune reaction directed against epithelial cells is termed epithelial cell reaction and may manifest as epithelial rejection (Krachmer) line.[4] Stromal keratocyte rejection is uncommonly observed and may manifest as predominantly anterior stromal nummular inflammatory lesions (Krachmer Dots)[4] restricted to graft. Endothelial cells are of prime response in maintaining normal

corneal function. As such the loss of sufficient endothelial cells as a result of an allogeneic immune response can lead to irreversible graft edema.[4] An endothelial rejection is diagnosed if there are significant keratic precipitates on the donor tissue only, often in the form of an endothelial rejection line, an anterior chamber reaction and usually some oedema of the graft.[5] Corticosteroids, cyclosporine, and cytotoxic agents are all important therapeutic agents that can be used to treat inflammation and play role in prevention and treatment of graft rejection due to their ability to inhibit the synthesis and release of pro-inflammatory chemical mediators. However, corticosteroid use has many side effects. For prevention of corneal allograft rejection, cyclosporine is an effective alternative to the corticosteroids as it is free from side effects associated with corticosteroid use.

METHODS

The study was a randomised controlled trial comprising of 30 patients in the age group of 20-60 years undergoing optical penetrating keratoplasty between January 2012 to October 2014 at Regional Institute of Ophthalmology, PGIMS, Rohtak, Haryana, India. The study followed the tenets of Declaration of Helsinki. Informed and written consent was obtained from all the patients enrolled in the study. The patients were randomly divided into two groups comprising of 15 patients each.

Group -1 included 15 post-operative cases of penetrating keratoplasty who were put on prednisolone acetate 1% eye drops post – operatively four times a day for 12 weeks. After 12 weeks, prednisolone acetate was tapered to three times daily which was used up to 24 weeks.

Group-2 included 15 post-operative cases of penetrating keratoplasty who were put on prednisolone acetate 1% eye drops postoperatively four times a day along with 0.05% cyclosporine eye drops four times a day for 12 weeks. 12 weeks after surgery prednisolone acetate was tapered to twice daily along with 0.05% cyclosporine eye drops twice daily which were used up to 24 weeks.

Detailed pre-operative work-up was done for every patient who underwent optical penetrating keratoplasty. Graft size ranged from 6.5mm to 8.0mm depending upon the size of corneal opacity. Interrupted type sutures were applied in all the cases. Patients with lagophthalmos, neuroparalytic keratitis, severe dry eye or ocular surface disorder, uncontrolled glaucoma, multiple graft failures and vascularized cornea were excluded from the study. Follow-up of the patients was done every 2 weeks for 16 weeks, and every month for next 2 months.

Graft rejection was diagnosed by presence of keratic precipitates, sub epithelial infiltrates, stromal oedema or an endothelial rejection line. In patients showing signs of graft rejection, the frequency of steroid instillation was increased to every one hour for seven days and then tapered to four times a day over the next three weeks.

Clinical evaluation of the transplanted graft was made as follows.[6] Net total score was calculated in each group at the end of study.

Corneal transparency: 0 (clear cornea)
1 (slight opacity)
2 (mild opacity with iris detail visible)
3 (moderate opacity with iris detail not visible)
4 (white cornea)

Corneal oedema: 0 (no oedema)
1 (slight oedema)
2 (diffuse and moderate stromal oedema)
3 (diffuse and marked stromal oedema)

Neovascularization: 0 (no observable growth of new vessels)
1 (new vessels invading < 1/3rd of recipient bed)
2 (new vessels invading <2/3rd of recipient bed)
3 (new vessels growing up to limiting ring of graft)
4 (new vessels invading the graft)

Graft opacity greater than or equal to three was considered as graft rejection.[6]

Statistical analysis was performed using chi square test. For the purpose of drawing statistical conclusion, p-value of 0.05 or less was considered significant.

RESULTS

The mean age of patients in group 1 was 50.46±2.58 years and in age group -2 was 48.66± 10.92. The difference in age was not statistically significant. Out of 30 patients, 21 patients (70%) were males and 9 (30%) were females. Majority of the patients in both the group underwent OPK for corneal opacity which was either post infective or post traumatic. (Figure -1). 30% of the total underwent triple surgery (3 patients in group 1 and 6 patients in group 2).

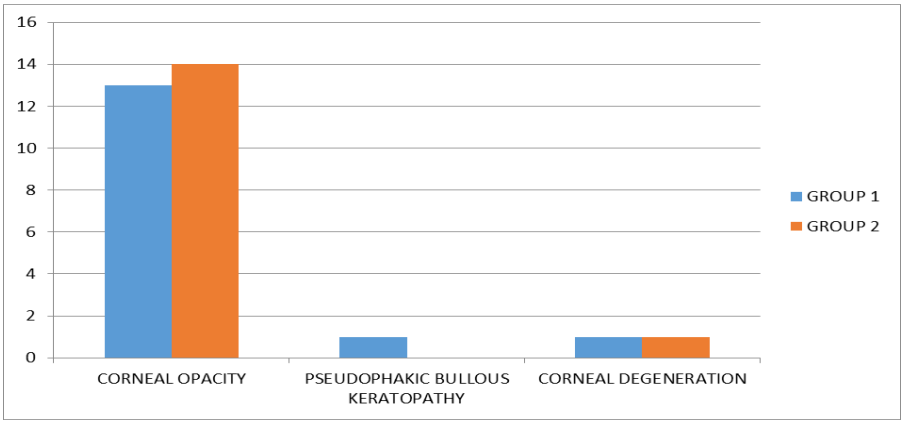

Figure 1: Bar diagram showing Pre-operative Diagnosis in both the groups.

On first post-operative day maximum number of (33.33%) patients in group 1 had best corrected visual acuity of 1/60 or hand movements close to face (HMCF) and in group 2 also 33.33% patients had visual acuity of 1/60 (Table-1).

Table 1: Visual Status on First Post-Operative Day.

Visual Status	Group 1	Group 2
HMCF	5 (33.33%)	1 (6.67%)
FCCF	1 (6.67%)	2 (13.33%)
1/60	5 (33.33%)	5 (33.33%)
2/60	3 (20%)	3 (20%)
3/60	0	3 (20%)
6/60	1 (6.67%)	1 (6.67%)

Thus, on first post op day most of the patients in both the groups had almost same visual acuity. After 12 weeks of follow-up, maximum number of patients (33.33%) had BCVA of 5/60 in group 1 and in group 2, maximum number of patients (33.33%) had BCVA of 6/60 (Table - 2). After 6 months, in group 1 maximum patients (26.67%) had BCVA of 6/36 (Table-3).

Table 2: Best Corrected Visual Status after 12 Weeks.

Best corrected visual acuity	Group-1	Group-2
6/36	1 (6.67%)	2 (13.33%)
6/60	2 (13.33%)	5 (33.33%)
5/60	5 (33.33%)	3 (20%)
4/60	2 (13.33%)	1 (6.67%)
3/60	1 (6.67%)	1 (6.67%)
2/60	2 (13.33%)	1 (6.67%)
1/60	1 (6.67%)	1 (6.67%)
HMCF	1 (6.67%)	1(6.67%)

Table 3: Best Corrected Visual Acuity after 6 Months.

Visual Status	Group 1	Group 2
6/18	1 (6.67%)	2 (13.33%)
6/24	1 (6.67%)	1 (6.67%)
6/36	0	4(26.67%)
6/60	1 (6.67%)	3 (20%)
5/60	0	1 (6.67%)
4/60	1 (6.67%)	0
3/60	3 (20%)	1 (6.67%)
2/60	1 (6.67%)	0
1/60	1 (6.67%)	0
FCCF	0	1 (6.67%)
HMCF	4(26.67%)	1 (6.67%)
Light perception only	1 (13.33%)	1(6.67%)

On first post-operative day, 13 patients (86.66%) in group 1 and 12 patients (80%) in group 2 had diffuse marked stromal oedema. In group 1 after 6 weeks of follow up, 10 patients (66.67%) had slight oedema and in group 2, 11 patients (73.33%) had slight oedema. At the end of study, 4 patients (26.67%) in group 1 had diffuse marked stromal oedema while only 1 patient (6.67%) in group 2 had diffuse marked stromal oedema. In group 1, 8 patients (53.33%) had no corneal oedema while in group 2, 12 patients (80%) had no corneal oedema (Table-4).

Table 4: Corneal Edema in Group 1 and Group 2.

Score	0 (no edema)		1 (slight edema)		2 (diffuse and moderate stromal edema)		3 (diffuse marked stromal edema)	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
First post-op day	0	0	0	0	2	3	13	12
2nd week	0	0	1	2	10	12	4	1
4th week	0	0	5	7	8	8	2	0
6th week	0	1	10	11	3	2	2	1
8th week	5	4	7	9	1	2	2	0
`10th week	8	7	3	8	1	0	3	0
12th week	7	9	3	5	2	1	3	0
14th week	8	10	3	3	1	1	3	1
16th week	9	11	2	2	0	1	4	1
20th week	9	12	2	1	0	1	4	1
24th week	8	12	3	1	0	1	4	1

On first post-operative day, none of the patients in group 1 or in group 2 had corneal neovascularization, after 6 months, maximum number of patients (40%) in group 1 had new vessels invading the graft while in group 2, maximum number of the patients (53.33%) had new vessels invading less than 1/3 recipient bed (Table-5).

Table 5: Neovascularisation of Graft in Group 1 and Group 2.

Score	0 (no observable growth of new vessels)		1 (new vessels invading <1/3rd of recipient bed)		2 (new vessels invading <2/3rd of recipient bed)		3 (new vessels growing upto limiting ring of graft)		4 (new vessels invading the graft)	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
First post-op day	15	15	0	0	0	0	0	0	0	0
2nd week	14	14	1	1	0	0	0	0	0	0
4th week	12	11	3	4	0	0	0	0	0	0
6th week	10	10	3	4	2	1	0	0	0	0
8th week	7	7	6	5	2	3	0	0	0	0
10th week	6	5	6	6	2	4	1	0	0	0
12th week	3	4	6	7	4	2	2	2	0	0
14th week	3	2	4	9	5	0	1	3	2	1
16th week	3	2	4	8	2	1	2	2	4	2
20th week	2	1	2	8	3	2	2	2	6	2
24th week	1	0	5	8	2	3	1	2	6	2

On first post-operative day, 10 patients (66.67%) in group 1 and 9 patients (60%) in group 2 had moderate opacity with iris detail not visible. At the end of 6 months, 8 patients (53.33%) in group 1 and 10 patients (66.67%) in group 2 had clear cornea. Five patients (33.33%) had white cornea in group 1 while 2 patients (13.33%) had white cornea in group 2 at the end of our study. Beside this one patient (6.67%) in each group had moderate opacity with iris detail visible (Table-6).

Table 6: Graft Transparency in Group 1and Group 2.

Score	0 (cornea clear)		1 (slight opacity)		2(mild opacity with iris details visible)		3(moderate opacity, iris details not visible)		4 (white cornea)	
	Group 1	Group 2	Group 1	Group 2	Group `1	Group 2	Group 1	Group 2	Group 1	Group 2
First post-op day	0	0	1	0	4	6	10	9	0	0
2nd week	0	0	4	1	5	12	6	2	0	0
4th week	1	0	3	7	9	8	2	0	0	0
6th week	1	2	6	8	7	4	0	1	1	0
8th week	3	3	5	8	3	3	3	1	1	0
10th week	4	6	5	6	1	1	4	2	1	0
12th week	6	7	4	5	0	0	4	2	1	1
14th week	6	11	4	1	0	0	4	1	1	2
16th week	7	11	3	1	0	0	2	1	3	2
20th week	7	11	2	1	1	0	0	1	5	2
24th week	8	10	1	2	0	0	1	1	5	2

Graft rejection rate was calculated taking into account graft transparency. Graft transparency ≥3 was considered as rejection. At the end of 6 months, 6 patients (40%) in group 1 showed rejection as compared to three patients (20%) in group 2. Overall rejection rate after 6 months was 30%. However, difference in rejection rates between two groups is not statistically significant (p- valve > 0.05).

DISCUSSION

In our study, as far as preoperative diagnosis is concerned, 90% of the patients had corneal opacity (post infectious or post traumatic) as indication for optical penetrating keratoplasty. These results are similar to studies done by *Dandona et al* where corneal scarring (71.5%) was the most frequent indication for penetrating keratoplasty.[7] However, studies by Sugar showed that post cataract surgery corneal edema was the most common indication for penetrating keratoplasty and the subgroup of pseudophakic corneal edema made a majority of the cases (21.1%), Fuch's dystrophy (13.4%) and keratoconus (13.4%) were the next largest groups requiring keratoplasty.[8] Corneal opacity as the leading cause for keratoplasty in our study can be attributed to agricultural background in our set up accounting for vegetative and other injuries.

In our study, we assessed corneal transparency, stromal edema and neovascularisation as indicators of graft rejection. Scores were given for each parameter. With each follow –up, group 2 patients were showing better results in terms of individual scores for each parameter as well as total mean scores. Even the rejection rates were 40% in group-1 and 20% in group -2. However, the differences were not statistically significant.

Studies done by *Nejabat et al* also showed similar results. In group 1, 30% patients receiving only topical and systemic steroids showed irreversible graft rejection. In group 2, 10% patients who received cyclosporine 2% eye drops showed irreversible graft rejection. However, there was no statistical difference in the results.[9]

Our results were contrary to the results shown by *Cosar et al*.[10] They used 2% cyclosporine eye drops and topical prednisolone in one group and only topical prednisolone in the other group. The rejection free graft survival rate was 88.9% in one group and 38.5% in the control group. This difference in rejection free graft survival rate between the groups was statistically significant. The difference from our study can be attributed to use of 2% topical cyclosporine in their study unlike 0.05% cyclosporine in present study which is less effective then 2% cyclosporine.

Price et al have studied the incidence of immunologic corneal graft rejection episodes in 52 corneal transplant recipients who were considered low risk for graft rejection. The patients in the study group were treated with topical cyclosporine 0.05%. They analyzed that topical cyclosporine 0.05% was not as effective as use of topical prednisolone acetate 1% for prevention of graft rejection episodes in low-risk corneal transplants. The authors hypothesized that cyclosporine 0.05% does not penetrate into the endothelium and anterior chamber adequately and a higher concentration may be more effective.[11]

In another study done by *Poon et al* where they used cyclosporine 0.05% in conjunction with topical prednisolone acetate for the treatment of acute graft rejection, they found that the use of commercially available 0.05% cyclosporine as an adjunct to topical steroids did not appear to improve the outcome of graft rejection.[12]

Inoue et al evaluated long term effects of topical cyclosporine A treatment after penetrating keratoplasty and concluded that it is effective in reducing risk of allograft rejection in high risk patients.[13] They reviewed the records of 83 patients who had undergone penetrating keratoplasty and received cyclosporine A treatment post operatively; also the records of 95 penetrating keratoplasty patients who received the same treatment except for the 2% cyclosporine A eye drops and served as controls. The patients were further subdivided into high risk and low risk groups. In the high risk patients, the rejection free graft survival rate was 69.7% in the cyclosporine A group and 45.4% in the control group,

but there was no significant difference in the graft survival rate between the two groups.

In a study by *Sinha et al* in India,[14] 78 eyes, which were at high risk of rejection after penetrating keratoplasty, were studied. The study group received topical cyclosporine A 2% drops and control group received polyvinyl alcohol 1.4% drops. In addition, both groups received corticosteroid eye drops after surgery. They concluded that there was no statistically significant difference in incidence of graft rejection between the study and the control group. However, the reversal of rejection episode was seen in significantly greater number of eyes in the study group. The rejection-free time period in the eyes that had rejection was more in the study group; however, the difference was not statistically significant.

Limitation

The main limitation of this study was its small sample size. A large multi-centric trial should be carried out to support the evidence.

CONCLUSION

Topical 2% cyclosporine A is found to be an effective adjunct to topical steroids in preventing acute corneal graft rejection episodes or increasing rejection free time interval.

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