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# A comparative study of the effect of topical 0.03% tacrolimus plus 1% topical prednisolone with 1% topical prednisolone alone in preventing rejection after penetrating keratoplasty

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ABSTRACT

**Background:** Immunologic corneal allograft rejection represents one of the main cause for graft failure. This study was conducted to observe and comparing the beneficial effect of topical 0.03% tacrolimus on corneal graft survival.

**Aim:** To compare the effect of topical 0.03% tacrolimus plus 1% topical prednisolone with 1% topical prednisolone alone in preventing rejection after PK.

**Materials and Methods:** 40 patients were randomly allocated into two groups:

Group A: patients received 0.03% topical tacrolimus ointment twice daily for a month plus 1% prednisolone acetate eye drops 2 hourly and tapered monthly. Group B: patients received 1% prednisolone acetate eye drop only 2 hourly and tapered monthly.

The clinical outcomes were assessed in terms of post-op complications, graft rejection, and visual acuity after 6 months of follow-up.

**Statistical Analysis used:** SPSS software, 20.0 version, IBM, Chicago were used for statistical analysis.

**Results:** Out of 40 patients, 29 (72.5%) were male and 11(27.5%) were female. Type of surgery and continuous suture closure was found to be statistically significant (p-value < 0.05) with post-op visual acuity in both groups. Types of graft rejection were found to be statistically significant (p-value < 0.05) with enucleation transplantation time(hours) in both groups and with secondary glaucoma (p = <0.001) in group A.

**Conclusion:** We conclude that 0.03% topical tacrolimus ointment along with 1% topical prednisolone shows promising results and can be considered as an effective modality for preventing complications like secondary glaucoma, graft rejection, and getting the better visual outcome, where p-value (<0.05) was statistically significant.

**Key message:** All patients should be instructed with regards to the reasonable use of topical tacrolimus to avoid any side effects.



## 1. Introduction

Corneal blindness has considerable health and economic burden on the community. Globally, at least 2.2 billion people have vision impairment of which 4.2 million are blind due to corneal diseases. [1,2]

As the majority of corneal blindness is avoidable, but once a corneal scar develops, surgical management such as Corneal transplantation is the definitive treatment. [3]

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Eduard Konrad Zirm (1877–1944) defined the principles of modern corneal transplantation. Using the cornea from the enucleated eye of an 11-year-old boy, Zirm performed bilateral penetrating grafts on a 45-year-old farmworker who had sustained bilateral alkali burns 16 months earlier.[4]

Risk factors for corneal graft rejection have been well recognized for decades and are used to place transplant recipients into a low or high-risk group. In "high-risk" graft rejection episodes occur in 30%–60% and up to 70% fail within 10 years despite immunosuppressive therapy.

Treatment of graft rejection depends on the type of rejection, however, topical corticosteroids are the mainstay of treatment, but in some cases, topical corticosteroids do not prevent rejection or cause cataract formation, and unacceptable elevation of IOP in steroid-responder patients.[5]

In 1989, Kobayashi et al first reported that tacrolimus suppressed corneal graft rejection in rabbits.[6] Since then, the use of tacrolimus has been of special interest in ophthalmology.

FK506 was first approved by the US FDA for use in liver transplantation.

Dhaliwal et al. used off-label topical 0.03% tacrolimus ointment in 4 patients with high-risk corneal graft and did not have any rejection episode.[7]

Tacrolimus is a novel macrolide immunosuppressant discovered in 1984 and derived from a fungus streptomyces tsukubaensis, It is a calcineurin inhibitor. FK506 inhibits the initial phase of T-cell activation and IL-2 transcription.[8]

It also affects the release of TNF-$\alpha$, IFN-$\gamma$, and other interleukins.

Therefore, in this study, we have added 0.03% topical tacrolimus to the gold standard topical corticosteroid treatment for observing and simultaneously comparing the beneficial effect of 0.03% topical tacrolimus on graft survival and hence visual outcome.

## 2. Materials and Methods

During the study period (December 2019- January 2021) 40 penetrating keratoplasty procedures were performed at our institute by our consultant, having experience of doing surgery for more than 12 years.

A total of 40 eyes of 40 patients were divided into two groups: group A included 20 eyes and group B included 20 eyes. The mean ages of groups A and B were 44.40 ± 14.96 (range, 18-72) and 57.05 ± 10.91 (range, 31-80) years. The mean Enucleation transplantation time (hours) were 51.20 ± 13.59(range, 30-72) in group A and 57.30± 14.06 (range, 36-72) in group B. (Table 1)

We included patients who were met high-risk criteria (prior failed corneal graft and other surgical procedure in the same eye, 2 or more quadrants of corneal vascularisation) and with no ocular or major systemic illness that may affect epithelial healing. Excluded cases that do not meet one of the criteria for high risk. The additional exclusion criteria were pregnant and lactating females, patients on the immunosuppressant or other ocular or major systemic illness that may affect epithelial healing, and children below the age of 2 years. This study was approved by the Institutional Review Board Ethics Committee. All participants have read and signed a written consent form that informed them about long-term treatment, adverse effects of drugs, need for regular follow-up.(Figure 1)

Each patient received a comprehensive ophthalmic examination including measurement of distant best-corrected visual acuity, anterior segment slit-lamp examination, IOP measurements, posterior segment evaluation, and routine blood investigations.

All donor corneas were kept in a special storage container and underwent gross examination to look for any epithelial defect, corneal edema, vascularization, and also for specular examinations to endothelial cell count.

### 2.1. Surgical procedure

PK was performed safely under local or general anesthesia using standard surgical procedure. The first step in PK was the preparation of the donor corneoscleral button by placing it on the Teflon block with the endothelial side up and was punched by a trephine of the required diameter. Similarly, the host cornea was removed by a trephine of the required diameter and the recipient bed was coated with the viscoelastic substance. The donor tissue was placed endothelial side down on the recipient's eye. The cornea was then sutured in place with either interrupted or continuous sutures using 10-0 nylon suture material. Viscoelastic material was removed and replaced with a BSS, then suture knots were buried on the donor cornea after that subconjunctival gentamicin and dexamethasone are injected.

Postoperatively, all patients received antibiotics and cycloplegic eye drops. Additional immunosuppressants were also given to patients according to group division.

All rejection episodes were treated in the same way in both groups, using 1% prednisolone eye drops 2 hourly and tapered monthly. In group A patients used 0.03% tacrolimus ointment twice daily for 1 month.

### 2.2. Outcome

All patients were followed up at 1st week, 2nd week and then 1st, 3rd, and 6th months. At each visit, tacrolimus adverse effects and baseline tests were monitored. Visual acuity, corneal clarity, IOP, state of sutures, and any clinical evidence of rejection were also documented. Graft rejection episodes were characterized by sudden diminution of vision, pain, photophobia cornea edema, epithelial line, Khodadoust line or keratic precipitates, etc

## 3. Result

A total of 40 eyes from 40 patients underwent penetrating keratoplasty. The most common indication for surgery in group A was perforated corneal ulcer(25%) and in the group B, was graft failure (30%). (Table 2) As already demonstrated Dandona et al(1997) study that the most common indications for PK were corneal infections either healed or active, followed by Graft failure.[9]

Mean enucleation transplantation time in group A is 51.20(13.59) and 57.30(14.06) in group B. There was no significant difference between the groups in terms of enucleation transplantation time (Hours) (W = 161.000, p = 0.275). (Table 3)

In this study, types of graft rejection were significantly associated (p<0.05) with the enucleation transplantation time(hours).[10]

In group B, mean the size of the graft is 7.00 (0.40), which was statistically significant (p<0.05) with synechiae formation (mean 7.38). (Table 4) As demonstrated in Gupta AR et al (2016) study that large graft could be attributed to the formation of peripheral anterior synechiae.[11]

Out of 40 patients12 patients who underwent optical PK, post-op visual acuity in these patients improved in the range of 1/60- 6/18 on the Snellen chart, while in patients who underwent tectonic and therapeutic PK visual acuity improved up to 6/60 on the Snellen chart, although the difference between two groups was not statistically significant, but it statistically significant between the type of surgery and vision (6 Months Post-Operative) in both groups. (p<0.05) (Table 5)

Out of 40 patients, 11(27.5%) patients underwent no torque continuous closure and post-op visual acuity improved by 6/18 on the Snellen chart, while only 2(5%) patients underwent anti-torque continuous closure, and 27(67.5%) patients underwent interrupted suture technique. (Table 6)

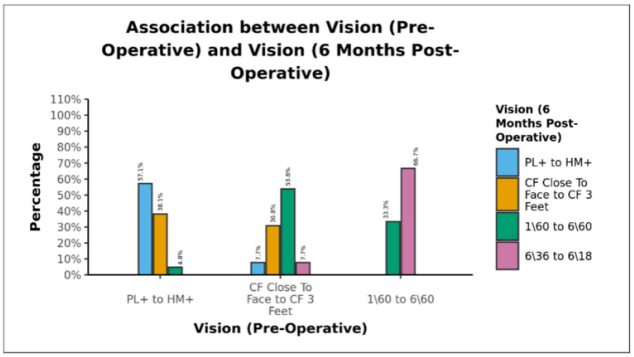
Continuous suture closure and post-op visual acuity were found to be statistically significant (p-value < 0.05) in both A and B groups.

20% of patients showed graft rejection in group A and 30% in group B. The post-operative complications such as synechiae 20% and secondary glaucoma 35% were more common in group B as compared to group A (15% synechiae, 25% secondary glaucoma). Statistically, a significant difference was observed between secondary glaucoma with graft rejection (P<0.001%) in group B. (Table 7)

In group A, maximum patients 7(35%) reported with visual acuity counting finger close to face to 3 feet and in group B, maximum patients 8(40%) reported with visual acuity PL+ or HM+, while 4 patients of group A and 6 patients of group B with graft rejection showed visual acuity PL+.

Therefore, in summation p-value was statistically significant between post-op visual outcome and graft rejection only in group A (p-value =0.001). (Table 8)

The post-operative visual acuity improved significantly (P < 0.001) in both groups, 21 (52.5%) of the participants had preoperative vision PL+ to HM+, while only 13 (32.5%) of the participants had postoperative vision PL+ to HM+.(Graph 1)




Graph 1: Associate between graft rejection and post op visual acuity in group A

However, the difference between the two groups was not significant (P> 0.05).(Table 9)

## 4. Discussion

Keratoplasty is the most successful transplantation in humans because of the inherent immune privilege of the cornea,[12] but in some cases depletion of corneal privilege by inflammation may be seen as cornea carrying few Bone marrow-derived cells capable of processing and presenting antigens and initiating the immune response.[13]

Endothelial cell count and preexisting glaucoma play an important role in graft rejection. Additional risk factors are donor age, storage media, graft size, preoperative vascularisation, dry eyes, history of previous graft failure, etc.

Synechiae formation and secondary glaucoma were seems to be the main factor associated with rejection, according to several studies.[14] We found no statistical difference in any of these variables between groups, but a significant difference was observed between postoperative complications such as synechiae formation and secondary glaucoma with graft rejection (P<0.001%) in group B.

In our study, the use of topical 0.03% tacrolimus decreased the incidence of graft rejection. There were fewer rejection episodes in group A (20%) as compared to group A (30%), although the difference was not statistically significant. Therefore, we conclude that the p-value was statistically significant between post-op visual outcome and graft rejection only in group A (p-value =0.001).(Graph 2)

**Table 1:** Association between group and parameters

| Parameters | Group | | p value |
|---|---|---|---|
| | A(n = 20) | B(n = 20) | |
| **Age (Years)*** ** | 44.40 ± 14.96 | 57.05 ± 10.91 | 0.004[1] |
| **Age** | | | 0.071[2] |
| 18-30 Years | 4 (20.0%) | 0 (0.0%) | |
| 31-40 Years | 5 (25.0%) | 1 (5.0%) | |
| 41-50 Years | 4 (20.0%) | 6 (30.0%) | |
| 51-60 Years | 5 (25.0%) | 6 (30.0%) | |
| 61-70 Years | 1 (5.0%) | 5 (25.0%) | |
| 71-80 Years | 1 (5.0%) | 2 (10.0%) | |
| **Gender** | | | 0.723[3] |
| Male | 15 (75.0%) | 14 (70.0%) | |
| Female | 5 (25.0%) | 6 (30.0%) | |
| **Pre-Operative Corneal Vascularisation** | | | <0.001[2] |
| Nil | 3 (15.0%) | 15 (75.0%) | |
| Grade 1 | 6 (30.0%) | 3 (15.0%) | |
| Grade 2 | 8 (40.0%) | 2 (10.0%) | |
| Grade 3 | 3 (15.0%) | 0 (0.0%) | |

***Significant at p<0.05, 1: t-test, 2: Fisher's Exact Test, 3: Chi-Squared Test, 4: Wilcoxon-Mann-Whitney U Test Table 2

**Table 2:** Association between group and indication for surgery(n = 40)

| Indication For Surgery | Group | | | Fisher's Exact Test | |
|---|---|---|---|---|---|
| | A | B | Total | $\chi$2 | P Value |
| Perforated Corneal Ulcer With Iris Prolapse | 3 (15.0%) | 6 (30.0%) | 9 (22.5%) | | |
| Graft Failure | 5 (25.0%) | 3 (15.0%) | 8 (20.0%) | | |
| Leucomatous Corneal Opacity | 4 (20.0%) | 4 (20.0%) | 8 (20.0%) | | |
| Non Healing Corneal Ulcer | 3 (15.0%) | 3 (15.0%) | 6 (15.0%) | 5.167 | 0.759 |
| Anterior Staphyloma | 1 (5.0%) | 2 (10.0%) | 3 (7.5%) | | |
| Bullous Keratopathy | 1 (5.0%) | 2 (10.0%) | 3 (7.5%) | | |
| Adherent Leucoma | 2 (10.0%) | 0 (0.0%) | 2 (5.0%) | | |
| Corneal Degeneration With Pseudophakia | 1 (5.0%) | 0 (0.0%) | 1 (2.5%) | | |
| Total | 20 (100.0%) | 20 (100.0%) | 40 (100.0%) | | |

Fisher's exact test

**Table 3:** Association between ETT (Hours) and types of graft rejection

| ETT (Hours) | Type of Graft Rejection | | | | Kruskal Wallis Test | |
|---|---|---|---|---|---|---|
| | Nil | Endothelial | Epithelial | Stromal | $\chi$2 | p value |
| Mean (SD) | 53.67 (13.85) | 63.60 (11.70) | 42.50 (8.39) | 72.00 (NA) | | |
| Median (IQR) | 48 (46.5-72) | 72 (54-72) | 46 (42-46.5) | 72 (72-72) | 8.090 | 0.044 |
| Range | 36 - 72 | 48 - 72 | 30 - 48 | 72 - 72 | | |

Kruskal Wallis Test

**Table 4:** Association between size of the graft (mm) and synechiae formation in Group B

| Size of the Graft (mm) | Synechiae Formation | | Wilcoxon-Mann-Whitney U Test | |
|---|---|---|---|---|
| | Yes | No | W | p value |
| Mean (SD) | 7.38 (0.25) | 6.91 (0.38) | | |
| Median (IQR) | 7.5 (7.38-7.5) | 7 (6.5-7) | 53.000 | 0.039 |
| Range | 7 - 7.5 | 6.5 - 7.5 | | |

Wilcoxon-Mann-Whitney U Test

**Table 5:** Association between surgery done and vision (6 months post-operative) in both group

| Vision (6 Months Post-Operative) | Surgery Done | | | | Fisher's Exact Test | |
|---|---|---|---|---|---|---|
| | Optical PK | Tectonic PK | Therapeutic PK | Total | $\chi 2$ | P Value |
| PL+ to HM+ | 0 (0.0%) | 5 (35.7%) | 8 (57.1%) | 13 (32.5%) | | |
| CF Close To Face to CF 3 Feet | 0 (0.0%) | 7 (50.0%) | 5 (35.7%) | 12 (30.0%) | 31.608 | <0.001 |
| 1\60 to 6\60 | 7 (58.3%) | 2 (14.3%) | 1 (7.1%) | 10 (25.0%) | | |
| 6\36 to 6\18 | 5 (41.7%) | 0 (0.0%) | 0 (0.0%) | 5 (12.5%) | | |
| Total | 12 (100.0%) | 14 (100.0%) | 14 (100.0%) | 40 (100.0%) | | |

Fisher's exact test

**Table 6:** Association between suturing technique: Continuous and vision (6 months Post-Operative) in both group

| Vision (6 Months Post-Operative) | Suturing Technique: Continuous | | | | Fisher's Exact Test | |
|---|---|---|---|---|---|---|
| | Nil | No Torque | Anti Torque | Total | $\chi 2$ | P Value |
| PL+ to HM+ | 12 (44.4%) | 0 (0.0%) | 1 (50.0%) | 13 (32.5%) | | |
| CF Close To Face to CF 3 Feet | 10 (37.0%) | 1 (9.1%) | 1 (50.0%) | 12 (30.0%) | 23.241 | <0.001 |
| 1\60 to 6\60 | 5 (18.5%) | 5 (45.5%) | 0 (0.0%) | 10 (25.0%) | | |
| 6\36 to 6\18 | 0 (0.0%) | 5 (45.5%) | 0 (0.0%) | 5 (12.5%) | | |
| Total | 27 (100.0%) | 11 (100.0%) | 2 (100.0%) | 40 (100.0%) | | |

Fisher's exact test

**Table 7:** Association between complications: secondary glaucoma and type of graft rejection in (Group: B) (n = 20)

| Type of Graft Rejection | Complications: Secondary Glaucoma | | | Fisher's Exact Test | |
|---|---|---|---|---|---|
| | Yes | No | Total | $\chi 2$ | P Value |
| Nil | 1 (14.3%) | 13 (100.0%) | 14 (70.0%) | | |
| Endothelial | 3 (42.9%) | 0 (0.0%) | 3 (15.0%) | | |
| Epithelial | 2 (28.6%) | 0 (0.0%) | 2 (10.0%) | 15.918 | <0.001 |
| Stromal | 1 (14.3%) | 0 (0.0%) | 1 (5.0%) | | |
| Total | 7 (100.0%) | 13 (100.0%) | 20 (100.0%) | | |

Fisher's exact test

**Table 8:** Association between type of graft rejection and vision (6 months post-operative) in (Group: A) (n = 20)

| Vision (6 Months Post-Operative) | Type of Graft Rejection | | | | Fisher's Exact Test | |
|---|---|---|---|---|---|---|
| | Nil | Endothelial | Epithelial | Total | $\chi 2$ | P Value |
| PL+ to HM+ | 1 (6.2%) | 2 (100.0%) | 2 (100.0%) | 5 (25.0%) | | |
| CF Close To Face to CF 3 Feet | 7 (43.8%) | 0 (0.0%) | 0 (0.0%) | 7 (35.0%) | 15.000 | 0.001 |
| 1\60 to 6\60 | 4 (25.0%) | 0 (0.0%) | 0 (0.0%) | 4 (20.0%) | | |
| 6\36 to 6\18 | 4 (25.0%) | 0 (0.0%) | 0 (0.0%) | 4 (20.0%) | | |
| Total | 16 (100.0%) | 2 (100.0%) | 2 (100.0%) | 20 (100.0%) | | |

Fisher's exact test

**Table 9:** Association between vision (pre-operative) and post-op visual acuity(n=40)

| Vision (6 Months Post-Operative) | Vision (Pre-Operative) | | | | Fisher's Exact Test | |
|---|---|---|---|---|---|---|
| | PL+ to HM+ | CF Close To Face to CF 3 Feet | 10 to 60 | Total | $\chi 2$ | P Value |
| PL+ to HM+ | 12 (57.1%) | 1 (7.7%) | 0 (0.0%) | 13 (32.5%) | | |
| CF Close To Face to CF 3 Feet | 8 (38.1%) | 4 (30.8%) | 0 (0.0%) | 12 (30.0%) | 35.480 | <0.001 |
| 1\60 to 6\60 | 1 (4.8%) | 7 (53.8%) | 2 (33.3%) | 10 (25.0%) | | |
| 6\36 to 6\18 | 0 (0.0%) | 1 (7.7%) | 4 (66.7%) | 5 (12.5%) | | |
| Total | 21 (100.0%) | 13 (100.0%) | 6 (100.0%) | 40 (100.0%) | | |

Fisher's exact test

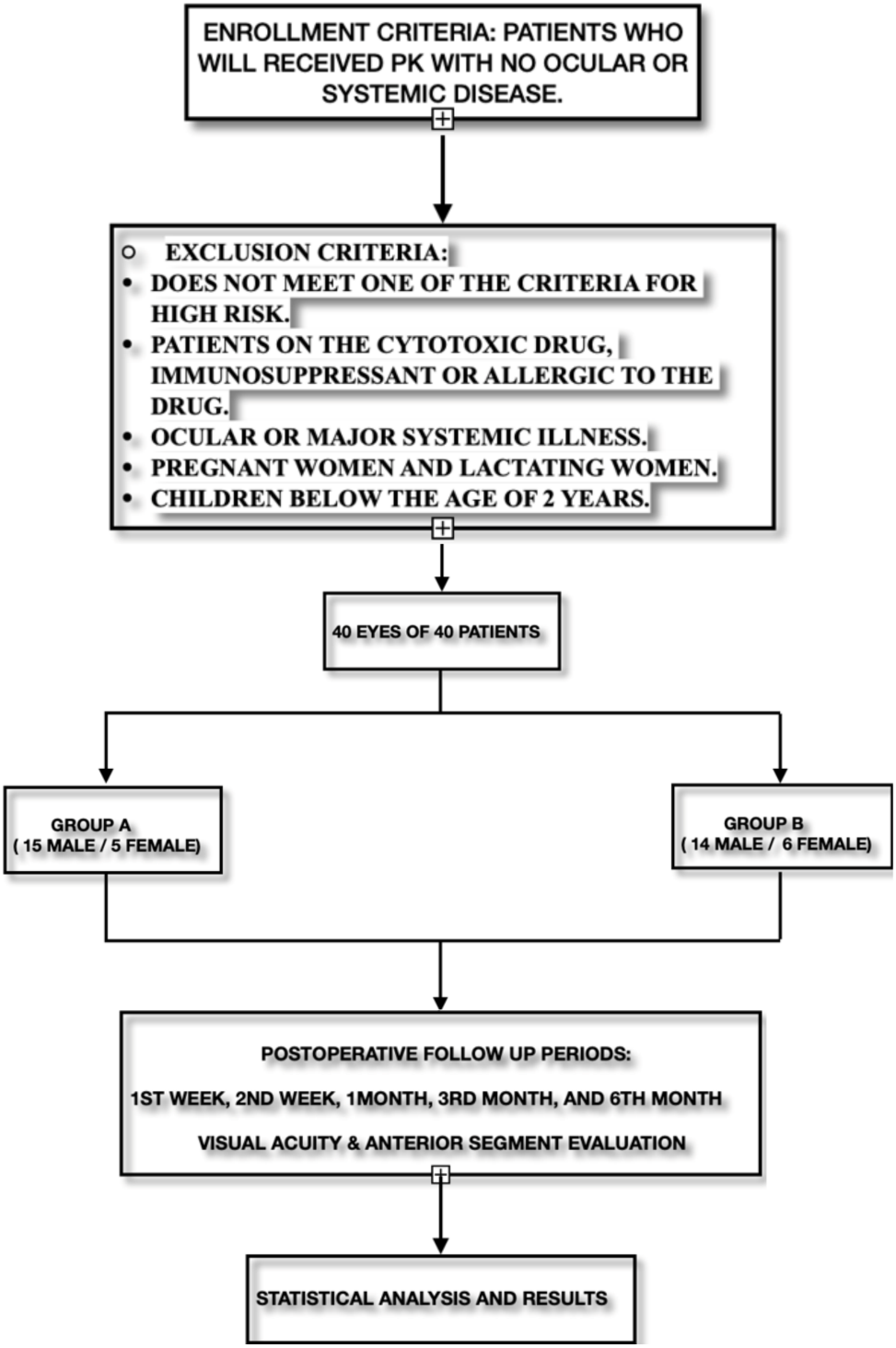
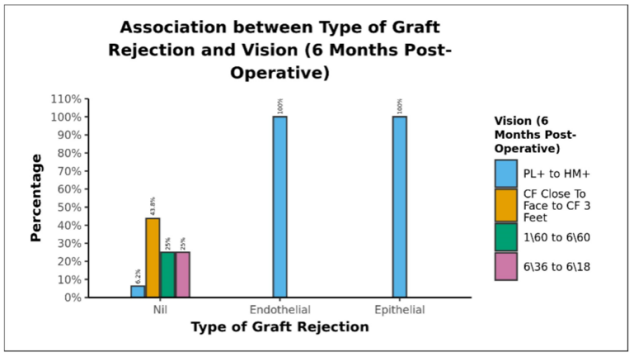



**Fig. 1:** Penetrating keratoplasty study flow chart




Graph 2: Association between pre op and post op visual acuity after 6 months

Joseph et al. found that tacrolimus is relatively safe and effective in reducing rejection and prolonging graft survival in patients with high-risk keratoplasty.[15]

Otavio A Magalhaes et al. (2013) after follow-up they conclude that topical 0.03% tacrolimus was effective in preventing irreversible rejection in patients with high-risk corneal transplantation without increasing IOP.[16]

Vaishali et al(2019) conclude that PK is the most commonly performed allograft and can visually rehabilitate patients with corneal blindness. The prognosis depends on many variables, including the etiology of corneal blindness in recipients, the donor cornea, the surgical technique, and early identification and management of complications.[17]

Amir Faramarzi et al (2021) found that 0.03%topical tacrolimus was as effective as systemic MMF(mycophenolate mofetil) as adjuncts to topical and systemic corticosteroids in reducing endothelial graft rejection.[18]

As already demonstrated in other studies, that tacrolimus is effective in preventing graft rejection as adjuncts to topical corticosteroids.

## 5. Conclusion

Though the size of this study was not very large, yet we may conclude that 0.03% topical tacrolimus ointment along with 1% topical prednisolone shows promising results as compared to 1% topical prednisolone eye drop alone and can be considered as an effective modality for preventing complications like secondary glaucoma, anterior synechiae, graft rejection and getting the better visual outcome, where p-value (<0.05) was statistically significant.

Therefore, topical administration of tacrolimus along with topical corticosteroids is effective in decreasing the incidence of immune rejection in high-risk keratoplasty.

## 6. Source of Funding

None.

## 7. Conflict of Interest

The authors declare no conflict of interest.

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