



## A CLINICAL COMPARATIVE STUDY OF MYCOPHENOLATE MOFETIL VERSUS PREDNISOLONE FOR HIGH RISK PENETRATING KERATOPLASTY

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### ABSTRACT

**Purpose :** To study the efficacy and safety of Mycophenolate Mofetil (MMF) in preventing graft rejection in high risk Penetrating keratoplasty(PK). **Methods :** Data records of last five years of high risk corneal transplants at two tertiary care hospitals were reviewed. Cases were divided into those who received mycophenolate mofetil for one year versus those who were given systemic steroids. The main outcome measures were immune reaction free & clear graft survival. **Results :** A total of 400 patients, 210 in steroid group and 190 in MMF group, underwent PK in the affected eye including combined Cataract extraction in 146 eyes with mean follow up of 2 years 3 months. Significantly less graft rejection was seen in MMF versus steroid group ( 73 versus 19). **Conclusions :** Systemic immunosuppression with MMF reduces rejection rate with better corneal graft survival as compared to systemic steroids in high risk PK.

**KEYWORDS :** Penetrating Keratoplasty, High Risk, Mycophenolate Mofetil, Prednisolone

### Introduction :

Corneal transplant is among the most successful of tissue transplants, primarily due to the avascular immune privileged status of the cornea (Niederkon,1990). However this immune privilege is breached, in heavily vascularised corneal scars and inflamed eyes resulting in higher failure due to immune rejection, making them high risk for keratoplasty (Hamrah P, Djalilian ARand Stulting RD,2005). While topical immunosuppression with steroid drops is sufficient to prevent rejection in routine keratoplasty, in these high risk cases supplementation with systemic immunosuppression is needed. (Hill JC,1995). Systemic immunosuppression has its attendant risks which have to be weighed against the benefits. Though factors responsible for rejection have been well described (Williams KA, Ruder D, Esterman A, Muehlberg SM & Coster DJ.1992) there is still no consensus on the most effective method of immunosuppression. We describe the results of systemic immunosuppression with Mycophenolate Mofetil (MMF) versus systemic steroids in Penetrating Keratoplasty(PK) in high risk keratoplasty

### Materials and Methods :

Case records of high risk Penetrating keratoplasties performed over 05 years in two tertiary care hospitals were reviewed. The high risk characteristics included: corneas with more than two quadrants of deep stromal vascularisation, post chemical injuries, previously failed grafts, anterior synechia/adherent leucoma, pre-existing ocular inflammation and age less than 18 years. The preoperative ophthalmic evaluation included best correct Snellens visual acuity, intraocular pressure, tear film assessment, USG AB scan for posterior segment assessment and VEP for visual pathway conduction defects. Systemic evaluation included haemogram, blood sugars, X ray chest and ECG in all cases. The patients given systemic prednisolone as a first choice of immunosuppressant were segregated in group 1, and those in which MMF was used as a steroid sparing immunosuppressant due to intolerance to systemic prednisolone in group 2. MMF was given in consultation with physician. All cases received topical steroids. In cases where combined cataract extraction procedure was done Intraocular lens power was based on the other normal eye measurement. Only grade A donor corneas were used and corneal transplants were performed by single surgeon using 16 interrupted sutures and graft size 0.5 mm more than host bed. In both groups topical as well as systemic immunosuppression either tablet prednisolone or MMF was continued for 1 year with monthly gradual tapering over the last 6 months. All patients were followed up weekly for one month, fortnightly for next 2 months and thereafter monthly. Rejection episodes were managed with single pulse Methylprednisolone 500 mg IV and repeated after 48 hours if required. The outcome measures were proportion of clear graft corneas in each group, visual recovery, mean number of rejection episodes in each group and complications both systemic and ocular in each group. SPSS version 19 was used for statistical analysis, Unpaired T test used to compare the two groups with

an alpha error Of 0.05 %. Snellens visual acuity was converted to log MAR for statistical analysis.

**RESULTS :** There were total 400 patients 210 in group 1 and 190 in group 2 with mean age of  $63.7 \pm 7.8$  and  $65.5 \pm 8.1$  and gender distribution of 61 % male and 63 % males in group 1 and 2 respectively. The mean follow up was 2 years and 2 months ( Range 2 years to 4. 3 years) The distribution of cases in terms of indication and type of surgery were similar in the two groups .Table 1 about here. The outcome in terms of , graft failure , rejection episodes and visual recovery are listed in Table 2 and 3 more grafts remained clear in group 2 (MMF group) as compared to group 1 and the difference was statistically significant ( $p < 0.05$ ). Table 2 & 3 about here. All graft failures were following rejection reaction. There was a significantly higher rejection rate of 40 % in group 1, steroid group than in MMF group 12 % ( $p < 0.005$ ) The mean pre op visual acuity in both groups was hand movements (Log MAR 2.0, range PL + to Counting fingers at 1 feet) which improved to 2/60 (Log MAR 1.59 +/- 0.5 in group 1 and Log MAR 1.42 +/- 0.56 in group 2), range PL+ to 6/9 at the end of 12 months (table 5). Both groups showed statistically significant improvement in vision over preoperative vision but between the two groups the gain in visual recovery following surgery was not significantly different ( $P = 0.1$ ). There was a higher incidence of post operative glaucoma in steroid group( 50 %) compared to Group II (15 %) whereas both groups did not show any serious systemic adverse effects apart from nausea and gastritis which was more common in the steroid group.

### Discussion :

The high success rate of PK in avascular corneal beds cannot be replicated in corneal beds which are vascularised or in contact with vascular tissue(Maguire MG, Stark WJ, Gottschalk JD, Stulting RD, Sugar A and Fink NE,1994). Systemic immunosuppression in addition to topical steroids has been shown to decrease rejection and increase the success rate in such cases (Tham VM & Abbott RL ,2002). Various western studies have indicated that mycophenolate mofetil is safe and effective in such cases (Reinhard T, Reis A, Kutkuhn B, Voiculescu A & Sundmacher R ,1999 also Birnbaum F, Mayweg S, Reis A, Bohringer D, B Seitz, Engelmann K, Messmer EM Reinhard T,2009). Ours is the first comparative Indian study with a large sample size and long term follow up. Previously rejected vascularised grafts and vascularised scarred corneas were the commonest indication in this study. This case profile is similar to other studies on high risk keratoplasty( Birbaum et al, 2009). As far as possible the two groups were matched for the demographic profile indications, type of procedure and the results show that the two groups were quiet similar. The results show that MMF group had a statistically superior results for graft survival and lower rates of rejection as compared to the control group. The effectivity of mycophenolate in preventing rejection in high risk case has been shown in several studies (Reinhard T

, Reis A, Bohringer D , Malinowski M , Voiculescu A , Heering P , Godehardt E and Sundmacher R,2001 also Birnbaum Florian , Bohringer D , Sokolovska Y Sundmacher R , Reinhard,2005) . However in these studies MMF has been compared with another strong immunosuppressant cyclosporine and found to be equally effective. In our study the comparison was with systemic steroids and the results indicate that systemic steroids are inferior to MMF as far as prevention of failure of graft due to rejection.MMF was extremely well tolerated by all patients in this study . This corroborates well with other studies which have reported similar safety profile for MMF(Birbaum et al ,2009,Reinhard T 2001, Birbaum et al 2005). In this regard we feel that MMF may be a better choice as compared to cyclosporine which requires closer

monitoring of serum levels<sup>(16)</sup> . Although the MMF group had a better outcome for graft clarity and rejection episodes the overall visual recovery was similar in the two groups. This was because visual recovery is dependent on several other factors such as post operative astigmatism and health of optic nerve and macula which were not separately analysed in this study . The other limitations of this study is the retrospective design and possible bias in case selection.

**Conclusion** :The study indicates that systemic immunosuppression with MMF after high risk keratoplasty is safe and effective in preventing graft rejection and achieving higher rates of clear grafts . However further evidence is needed by randomised controlled trials.

**Table 1: Distribution of Type of Surgery and indications.**

SURGERY	Group I (Steroids Prednisolone)		Group II (Mycophenolate)	
	No	%	No	%
PK (Penetrating Keratoplasty)	140	65.0	114	60.0
PK + PCIOL	70	35.0	76	45.0
Total	210	100.0	190	100.0
Indication	Group I Steroid (n=210)		Group II Mycophenolate (n=190)	
1. Failed PK	105(50.0%)		114(60.0%)	
2. Adherent Leucoma	42(20.0%)		38(20.0%)	
3. PBK* with vascularisation	52(25.0%)		28(15.0%)	
4. PBK* with adherent leucoma	11(5.0%)		10 (5.0%)	

**Surgery type is statistically similar with p=0.716, Chi-square test, and student T test unpaired for indication P = 0.950.**

**Table 2 : Graft Clarity of patients in two groups studied**

Graft Clarity			
	6 months	1 year	Final Follow up
Group I			
Clear	20(100.0%)	179(85.0%)	137(65.0%)
Hazy	-	31(15.0%)	73(35.0%)
Group II			
Clear	20(100.0%)	180(95.0%)	171(90.0%)
Hazy	-	10 (5.0%)	19(10.0%)
P value I Vs II	1.000	0.09	0.041
Graft Rejection Episodes			
	6 months	1 year	Final Follow up
Group I	Nil	35 (17 %)	85(40 %)
Group II	Nil	10 (5%)	23 (12 %)
P Value I Vs II	Nil	0.041	0.02

**Table 3: Evaluation of two groups of patients based on BCVA**

	Group	6/6-6/9	6/12-6/18	6/24-6/36	6/60-5/60	4/60-1/60	Hand Movement	Counting Fingers	PL+
Pre-op BCVA	Group I	-	-	-	-	-	10(5.0%)	84(40.0%)	116(55.0%)
	Group II	-	-	-	-	-	19 (10.0%)	95 (50.0%)	76 (40.0%)
Post-op BCVA : Final	Group I	-	-	21(10.0%)	31(15.0%)	95(45.0%)	-	-	63 (30.0%)
	Group II	19 (10.0%)	-	10 (5.0%)	38(20.0%)	76(40.0%)	-	-	47(25.0%)
	P value	1.000		1.000	1.000	1.000	-	-	1.000

Log MAR	Group I (Mean)	Group II (Mean)	P value						
Pre-op	2.00±0.00 (HM CF/ PL+)	2.00±0.00 (HM CF/ PL+)	1.000						
Post-op Final	1.59±0.50 (2/60)	1.42±0.56 (2/60)	0.306						

BCVA : Best Corrected Visual acuity, PL : perception of light, Log MAR : Logarithm of Minimum Angle of Resolution, IOP : Intraocular pressure

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