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Ophthalmology

A STUDY OF THE VARIOUS FACTORS AFFECTING THE FINAL OUTCOME OF THERAPEUTIC KERATOPLASTY

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ABSTRACT

Background: A prospective study of the various factors affecting the final outcome of therapeutic keratoplasty was carried out.

Methods: This was a prospective interventional study which included 35 patients having infective corneal ulcers and underwent therapeutic keratoplasty. It was done to study the indications, therapeutic outcome, complications and to document the factors affecting the final outcome of therapeutic keratoplasty. Paired t test to see change between different time period and unpaired t test to see the difference between two groups and pearson chi square for nominal data were used.

Results: The mean age was 44.63 ± 13.216 years. Cultures for fungus were present in 15 patients and for bacteria in 11 patients. Graft survival was found to be better in small ulcers with size <7mm, in small grafts <8.5mm, in patients where early keratoplasty (within 15 days of symptoms) was done and in cases affected with bacterial keratitis. Graft survival was found to be poor in ulcers involving limbus, fungal keratitis, where surgery was delayed and large ulcers which required larger grafts. Complications were found to be more in patients with larger grafts and ulcers with limbus involvement.

Conclusion: In therapeutic keratoplasty favourable outcomes in terms of better graft survival and less complications are seen in cases where small donor grafts < 8.5mm are used, in small ulcers with size <7mm, when early keratoplasty (within 15 days of symptoms) is done and in patients of bacterial keratitis.

KEYWORDS : therapeutic keratoplasty; microbial keratitis; graft failure

Introduction

Infective keratitis caused by bacteria, fungi, viruses or parasites is the major cause of monocular blindness in developing countries.[1,2,3] The avascular corneal stroma is particularly susceptible to infection and many patients have poor clinical outcome, if aggressive and appropriate therapy is not promptly initiated. Corneal infection results mostly from failure of one of the protective mechanisms of the ocular surface integrity. Most ocular pathogens cannot penetrate an intact corneal epithelium which is protected by eyelids and tear film that flushes away pathogens and contains antibacterial molecules, lysozymes, lactoferrin, secretory IgA and ceruloplasmin. Passive and active host defence mechanisms protect corneal tissue from bacterial invasion. Trauma is a major etiological factor for infective keratitis[1,3]. Based on laboratory studies and knowledge of the pathogen, a therapeutic plan is initiated. Over the past few decades, early diagnosis, a better understanding of the pathogenesis, and the availability of potent antimicrobial drugs have improved the chances for medical control of infectious keratitis. However, virulent and resistant forms of infectious bacteria, fungi and acanthamoeba species can still cause severe progressive keratitis, even with maximum medical therapy. Previous treatment can also mask the diagnosis or contribute to poor response[1,4,5]. This medically uncontrolled microbial keratitis may eventually lead to corneal perforation, infectious scleritis and secondary endophthalmitis. When corneal infection does not respond to appropriate and adequate medical treatment, other therapeutic options include conjunctival flap, tissue adhesive, patch graft and lamellar keratoplasty. However the most beneficial procedures for extensive infection or impending perforation remains surgical excision of the infected tissue and replacement with a corneal graft[1,5,6].

The incidence of microbial keratitis varies from 11 per 100,000 persons/year in the United States to 799 per 100,000 persons/year in Nepal. The epidemiological pattern and causative agents for suppurative corneal ulcer varies significantly from country to country, and even from region to region within the same country. It is important to determine the etiological pattern within a given region for comprehensive strategy for the diagnosis and treatment of corneal ulcer. The specific etiological organisms for infectious corneal ulcers have been found to vary somewhat over time and with geographic location[1,3]. The most common cause of infectious corneal ulceration in developed countries is Herpes simplex virus followed by bacteria, fungi and parasites[1]. On the contrary tropical country like India has more of fungal corneal ulcers. Even in India there is disparity wherein North India having Aspergillus more where as Fusarium has more preponderance in South India.

Penetrating keratoplasty (PKP) is one of the most common and successful tissue transplants worldwide with the major indications including: (1) optical purpose for improving vision (2) therapeutic purpose for controlling medical refractory disease and (3) tectonic purpose for re-establishing the structural integrity of the eye. Among the three indications, therapeutic PKP amounts to 2.6% to 17.9% of all cases receiving PKP from different studies. Of all the indications for therapeutic keratoplasty , uncontrolled infectious keratitis is the most common[5,7,8,9].

The present study is aimed at studying the indications, therapeutic outcome, complications and factors affecting the final outcome of therapeutic penetrating keratoplasty performed for severe refractory infectious keratitis.

Materials and Methods

This was prospective study conducted in the outpatient department of Ophthalmology at a tertiary eye care center where 35 patients underwent therapeutic keratoplasty from Oct 2012 to Oct 2013 were included in the study. Ethical clearance for the study was obtained from the Institutional ethical review board. Written informed consent from all subjects participating in the study was taken.

Inclusion criteria :

(a) Infective keratitis refractory to maximum medical treatment

wherein maximum medication includes fortified antibiotic eye drops (Vancomycin 10mg/ml, Ceftazidime 50mg/ml, fortified fungal eye drops and intrastromal Voriconazole in cases of fungal ulcers

(b) Infective keratitis with impending perforation

© Perforated infected corneal ulcers.

Exclusion Criteria:
(a) Infective keratitis with scleral involvement.
(b) Infective keratitis with endophthalmitis.
© Patient requiring tectonic graft.

Pre-operative work up:
(a) A detailed history was taken regarding the nature and duration of symptoms, nature of the injury if present. The history of previous treatment and its duration was recorded.

(b) Ocular examination
Visual acuity was recorded using Snellen's distance visual acuity chart. A thorough slit lamp examination was carried out, size of the epithelial defect after staining with fluorescein was measured with the variable slit and recorded in millimeters on a standardized proforma and size and depth of the stromal infiltrates were also recorded. The presence or absence of a hypopyon and its height was noted. The corneal ulceration was then graded (Table 1).

Table 1: Grading of Corneal Ulcer

Characteristics	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3)
Size of ulcer (mm)	<2	2-5	>5
Depth of ulcer (% age)	<33%	34-66%	>67%
Infiltrate stroma	superficial and limited to ulcer base	extending to mid deeper than mid stroma	

© Site of perforation, iris exposure and other clinical findings were recorded.

(d) Associated ocular signs like blepharitis, dacryocystitis, dry eyes and corneal sensations were noted.

Clinical diagnosis of microbial keratitis was made by history and ocular examination.

Microbiological Evaluation:
Ulcer scraping from base and margins was sent for Grams Stain, Giemsa, KOH wet mount and for culture and sensitivity on Blood agar, Chocolate agar and Sabouraud's agar. Special media were inoculated on requirement.

Surgical Procedure:
Therapeutic keratoplasty was done in patients fulfilling the inclusion criteria. Quality and size of graft was noted. Intraoperative complications were also noted. The recipient corneal button and donor corneoscleral rim was sent for culture and antibiotic sensitivity test.

Post Operative Follow Up:
All the Patients were followed up for 06 months. First follow up at 5-7 days, second at one month and third at 6 months. Postoperatively topical antibiotics and antifungals were continued depending upon the type of infection. At each follow up, detailed slit lamp examination was carried out and findings were documented.

Results
(a) Age of the 35 patients (21 male patients and 14 female patients) who underwent therapeutic Keratoplasty ranged from 11 to 75 years with mean age of 44.63 13.216 years. The graft survival in all three visits was found to be independent of patients age (p value > 0.05).

(b) History of injury was present in 18 patients only and the most common mode of injury was soil which was present in 09 patients. In all patients therapeutic keratoplasty was done for grade 3 ulcers wherein 57.1% of them were perforated ulcers. Fungal corneal ulcers were most commonly present in 15 patients followed by bacterial in 11 patients. Aspergillus was the most common fungus seen in 10 patients (table 02). No growth was seen in 05 patients.

Table 02: Culture Report

Organism	Species	Number	Percentage
Fungal	Fusarium	04	11.4%
	Asp flavus	10	28.57%
	Curvularia	01	2.8%
Bacterial	Pseudomonas	02	5.7%
	Streptococcus/staph	09	25.71%
Mixed		04	11.4%

© Graft survival was found to be better in following situations:

(I) When ulcers of various sizes were compared for the graft survival in all the three visits (Figure 01), it was found that during first visit (p value 0.251) and second visit (p value 0.692) the difference in graft survival was not statistically significant. However during the third visit difference was statistically significant (p value 0.049) and was better in cases where ulcer was less < 07mm. At the 2nd visit (01 month), it was found that in ulcers >07 mm , 63.1% grafts failed, whereas in ulcers with size 5-7mm (05 patients) i.e. 45.4% and in ulcers <05 mm (02 patients) i.e. 40% grafts failed. When grafts of different ulcer sizes were compared, it was seen that variation in survival rate between ulcer size > 05mm and 5-7mm was not statistically significant but difference of graft survival in ulcer size > 07mm was found to be poor as compared to 5-7mm ulcers and is statistically significant (p value 0.049). If we divide all the ulcers in two categories , i.e. size >07 mm and size <07mm, the survival of graft in ulcers <07mm was found to be more in second visit as compared with ulcers of >07mm but was not statistically significant (p value 0.404). On 3rd visit (06 months), survival in grafts <7mm was found to be better as compared to >7mm ulcers and was statistically significant (p value 0.025) (Table 3).

Table 3: On 3rd visit (06 months), survival in grafts <7mm was found to be better as compared to >7mm ulcers and was statistically significant (p value 0.025)

Ulcer size (mm)	Graft Clarity (3rd Visit) 06 Months					
	Failed		Clear		Total Count	
	Count	Percentage	Count	Percentage	Count	Percentage
>7	17	89.4%	02	10.5%	19	100%
<7	09	56.2%	07	43.7%	16	100%

(II) Where small grafts <8.5mm were used : The size of graft used for therapeutic keratoplasty varies from 6.5 mm to 11mm (figure 02). Graft size was >8.5mm in 17 patients and <8.5mm in 18 patients. The graft survival was compared between graft size >8.5mm and graft size <8.5 mm during all three visits and graft survival was better in small grafts as compared to large grafts but the difference was statistically significant during third visit only (p value <0.05) (table 4).

Table 4: Showing relation between size of graft and graft failure at 03 different visits

Size of Graft (mm)	Graft Failure		
	First Visit	Second visit	Third visit
>8.5(17 patients)	(03)17.64%	(12)70.58%	(16)94.11%
<8.5(18 patients)	(00)00%	(6)33.3	(10)55.55%
P value	0.062	0.028	0.009

(III) When early keratoplasty (within 15 days of symptoms) was done: During all three visits, the difference in graft survival is more in cases with early surgery but is not statistically significant because of small sample size.

(IV) In bacterial keratitis: It was found that during all visits the graft

failure was more in mixed and fungal ulcers. When results of fungal ulcers and bacterial ulcers were compared among the graft survival , results were found to be better in bacterial ulcers in all three visits. However the difference was not statistically significant because of small sample size.

(d) Graft survival was found to be poor in
(I) Ulcer involving limbus
(II) Fungal keratitis
(III) Ulcers where surgery was delayed
(IV) Large ulcers which required larger grafts

(e) No correlation was found between graft survival and
(I) Age of patient
(II) History of trauma

(f) During 06 months period of follow up, secondary glaucoma was the most important postoperative complication which was present in 34.28% of the patients. Other complications included peripheral anterior synechiae, recurrence of infection, persistent epithelial defect, and cataract. Complications were found to be more in patients with larger grafts and ulcers with limbus involvement.

Thus our study effectively establishes the efficacy of keratoplasty in infective corneal ulcers and elucidates various factors contributing to the final outcome in therapeutic keratoplasty.

Discussion

Infective keratitis is a sight-threatening problem. It usually calls for immediate, appropriate and intensive treatment. The recent availability of potent antimicrobial drugs that can be delivered topically to the cornea in high concentrations has improved the prognosis of these patients and reduced the need for surgery to treat the infection.[1,5] Although the need for surgical management to treat microbial keratitis has decreased dramatically, some surveys show there are 3% to 6% of bacterial, 18% to 29% of fungal keratitis and 71% to 86% of acanthamoebic keratitis still requiring therapeutic keratoplasty to eradicate the infection.[10] Factors that compromise the effectiveness of medical treatment on infection include the emergence of drug-resistant organisms, concurrent diseases impairing the host's defences, and the delayed diagnosis and treatment of the infection.[12]

The anatomic success rate for therapeutic keratoplasty published in the ophthalmic literature varies from 88-100%. The success rate in our series i.e. 95% of all globes salvaged is in line with these data and confirms that therapeutic keratoplasty is a valuable management modality.[14] Infective keratitis mainly affects young adults and older population since majority of them are outdoor workers, especially working in field. In our study, we had patients of age 11 to 75 years with mean age of 44.63 ± 13.216 years. Basak et al[10] reported the disease to be more common in young adults where 49.3% were of the age group of 21-40 years. Bimodality in the patient's age group can be attributed to the fact that young adults are physically more active and at a higher risk for corneal injury and older population might have predisposing ocular surface or eye lid diseases.

Predisposing risk factors for microbial keratitis vary tremendously with geographical location. Non-surgical trauma to the eye accounted for 48.6- 65.4% of all corneal ulcers in the developing countries like Nepal and India[10]. In our study history of injury to the cornea was present in 18 (51.4%) patients. The most common mode of injury (25.7% patients) was soil. Basak et al[11] found history of injury to cornea in 82.9% of patients out of which vegetative matter was the most common mode of injury and was present in 59.6% of patients.

In our study fungal keratitis was the leading indication for therapeutic keratoplasty. Fungus was identified in 15 (42.8%) patients and bacteria in 11 (31.4%) patients (Table 02). This is consistent with the study reported by Chen WI et al[12] where fungal keratitis was the leading indication for therapeutic keratoplasty and had a worse prognosis.

For cases with microbial keratitis refractory to medical management, the primary goal of emergent therapeutic keratoplasty is to eradicate the infection and restore ocular integrity with visual improvement being only a secondary consideration. In a study done by Chen WI et al[12] anatomical success rate was 90% but visual acuity was <20/60 in 63% of postoperative patients. In our study also more than 95% of globes were salvaged but vision improvement was only in 10% at the end of 06 months.

Our results are consistent with the literature in that both ulcer and graft size are important factors for the ultimate anatomical and functional outcome[14]. Du and associates[18] achieved clear grafts in 89% of their cases when the extent of the corneal infiltrate was 7.0 mm and no more than a small perforation was present. In our study also, graft failure was more in larger ulcers. We found 43.7% of clear grafts when the ulcer size was equal to or less than 7mm and 10.5% of success when the ulcers were more than 7mm in size.

Killingsworth and associates[15] also demonstrated the similar relationship reporting 83% of clear grafts when the grafts size was equal to or less that 9 mm and a 50% success rate when the grafts were equal to or more than 9.5 mm. In our study we also found that success rate was more in grafts <8.5 mm sized as compared to larger grafts of size >8.5mm. Larger grafts offer a worse prognosis because of the risk of developing peripheral anterior synechiae, higher chances of immunologic graft rejection, vascularisation and secondary glaucoma. Furthermore large grafts would have been used for more severe indications thus leading to increased chances of graft failure.

In our study graft survival was found to be better in patients where early keratoplasty was done. At one month follow up graft failure was 60% when the surgery was delayed for more than 15 days after the occurrence of symptoms and 20% when it was done with in 15 days. These findings may lead to the conclusion that early diagnosis and treatment of microbial keratitis can prevent the progression of ulcer and may lead to successful therapeutic keratoplasty.

Sony P et al[19] reviewed literature on various aspects of therapeutic keratoplasty and concluded that therapeutic keratoplasty has a definitive role in the management of progressive bacterial, fungal, acanthamoeba and viral keratitis refractory to medical treatment. Management of bacterial keratitis has better success rate compared with fungal, viral and acanthamoeba keratitis. In our study also we found that success rate was better in bacterial as compared to fungus[19]

We found limbus involvement as a major risk factor responsible for graft failure. At one month follow up graft failure was found to be 40% in ulcers involving limbus and 16% in ulcers without limbus involvement. At 06 months follow up we found graft failure was 76% in ulcers involving limbus and 49% in ulcers without limbus involvement and was statistically significant during the third visit (p value 0.028). The lower surgical curative rate in cases of limbus involvement is due to the fact that therapeutic keratoplasty cannot eradicate all infectious tissue in these cases[17,19].

In conclusion, in therapeutic keratoplasty favourable outcomes in terms of better graft survival and less complications are seen in cases where small donor grafts < 8.5mm are used, in small ulcers with size <7mm, when early keratoplasty (within 15 days of symptoms) is done and in bacterial keratitis. However graft survival is found to be poor in ulcers involving limbus, fungal keratitis, where surgery is delayed and large ulcers which require larger grafts. No correlation is seen between graft survival and age of the patient, operating surgeon being fellow or consultant and history of trauma. Common complications following therapeutic keratoplasty include secondary glaucoma, peripheral anterior synechiae, recurrence of infection, persistent epithelial defect and cataract. The incidence of these complications increases with a large donor graft and in ulcers with limbus involvement.

Conflicts of interest

All authors have none to declare.

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References

1. Ogawa GSH, Hyndiuk RA, Smolin G, Thoft RA.The Cornea: scientific foundations and clinical practice. New York: Little, Brown and Company, 1994; 11:115- 167.
2. Amstrong M. The laboratory investigation of infective keratitis. Br J Biomedical science 1994; 51 :65-72.
3. Srinivasan M, Gonzales CA, George C, Cevallos V, Mascarenhas JM, Asokan B et al. Epidemiology and aetiological diagnosis of corneal ulceration in Madurai, south India. Br J Ophthalmol 1997; 81 :965-971.
4. McLeod SD, LaBree LD, Tayyanipour R, Flowers CW, Lee PP, McDonnell PJ. The importance of initial management in the treatment of severe infectious corneal ulcers. Ophthalmology 1995; 102: 1943- 1948.
5. Singh G, Malik SR. Therapeutic keratoplasty in fungal corneal ulcer. Br J Ophthalmol 1972; 56:41-45.
6. Miedziak AI, Miller MR, Rapuano CJ, Laibson PR, Cohen EJ. Risk factors in microbial keratitis leading to penetrating keratoplasty. Ophthalmology 1999; 106:1166-71.
7. Claerhout I, Beele H, Van den Abeele K, Kestelyn P. Therapeutic penetrating keratoplasty: clinical outcome and evolution of endothelial cell density. Cornea 2002; 21: 637-42.
8. Bredehom T, Genest K, Langer C, Brandt S, Eichhorst A, Duncker GI et al. Follow-up and results of penetrating keratoplasty. Transplantation Proceedings. 2002; 105: 2348.
9. De Oliveira FC, Dantas PE, de Marco ES, de Oliveira AC, Nishiwaki-Dantas MC. Long-term follow-up of a case series of therapeutic corneal transplant. Arq Bras Oftalmol. 2007 Jul-Aug; 70(4):625-31.
10. Malik SR, Singh G. Therapeutic keratoplasty in pseudomonas pyocyaneus corneal ulcers. Br J Ophthalmol 1971; 55:326-30.
11. Basak SK, Basak S, Mohanta A, Bhowrnick A. Epidemiological and microbiological diagnosis of suppurative keratitis in Gangetic West Bengal, eastern India. Indian J ophthalmol 2005; 53: 17-22.
12. Chen WL, Hu FR, Wang IJ. Changing indications for penetrating keratoplasty in Taiwan from 1987 to 1999. Cornea 2001; 20: 141-44.
13. Anshu A, Parthasarathy A, Mehta JS, Htoon HM, Tan DT. Outcomes of therapeutic deep lamellar keratoplasty and penetrating keratoplasty for advanced infectious keratitis: a Comparative study. Ophthalmology. 2009;116: 615-23.
14. Sharma N, Sachdev R, Jhanji V, Titiyal JS, Vajpayee RB. Therapeutic keratoplasty for microbial keratitis. Current Opinion in Ophthalmology 2010; 21 :293-300.
15. Killingsworth DW, Stern GA, Driebe WT, Knapp A, Dragon DM. Results of therapeutic penetrating keratoplasty. Ophthalmology 1993;100:534-41.
16. Tan DTH, Janardhanan P Zhou H, Chan Y, Htoon HM, Ang LPK, Lim LS. Penetrating keratoplasty in Asian eyes. The Singapore corneal transplant study. Ophthalmology 2008; 115:975-982.
17. Wei-LI C, Chun-Ying WU, Fung-Rong HU, Wang I. Therapeutic penetrating keratoplasty for microbial keratitis in Taiwan from 1987 to 2001. Am J Ophthalmol 2004;137:736-743.
18. Du NZ, Chen JQ, Gong XM, et al. Therapeutic keratoplasty in the management of purulent corneal ulceration: report of 100 cases. Japanese Journal of Ophthalmology. 1979; 23 :412-20.
19. Sony P, Sharma N, Vajpayee RB, Ray M. Therapeutic keratoplasty for infectious keratitis: a review of the literature. CLAO J 2002; 28:111-118.
20. Wiggins R.E., Cobo M, Foulks G.N. Results of penetrating keratoplasty by residents, Arch Ophthalmol.1990;122: 851 -53.