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Original Research Article

Efficacy of tacrolimus capsules in patients undergoing high-risk keratoplasty

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Abstract

Purpose: *To evaluate the efficacy of tacrolimus capsules in patients undergoing high-risk keratoplasty.*
Methods: *40 high-risk patients who underwent penetrating keratoplasty at The Third Hospital of Hebei Medical University, China between January 2016 and December 2021 were included in this study. These patients were divided into two groups based on the specific immunosuppressant administered post-surgery. Twenty patients were administered oral tacrolimus capsules in conjunction with 0.1 % tacrolimus eye drops, constituting the combination with systemic treatment group (group 1), while another twenty patients were solely administered 0.1 % tacrolimus eye drops, forming the topical treatment group (group 2). The occurrence of rejection, corneal neovascularization, corneal graft edema and visual acuity were documented in both groups.*
Results: *In comparison to patients in group 2, patients in group 1 exhibited a significant reduction in rejection rate ($p < 0.05$). Additionally, the average time of neovascularization in group 1 was delayed and the number of cases was lower ($p < 0.05$). Furthermore, a smaller proportion of patients in group 1 experienced corneal graft edema (25 vs 60 %, $p < 0.05$), while a higher percentage of patients in group 1 demonstrated improved visual acuity (90 vs 60 %, $p < 0.05$).*
Conclusion: *Concurrent administration of tacrolimus eye drops and capsules orally effectively mitigates anti-rejection reactions, regulation of neovascularization, management of graft edema and enhancement of visual acuity in high-risk keratoplasty patients when compared to the use of tacrolimus eye drops as a standalone treatment. These results have the potential to stimulate novel avenues of investigation in future clinical research.*

Keywords: *High-risk keratoplasty, Tacrolimus capsules, Tacrolimus eye drops, Rejection*

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INTRODUCTION

Corneal transplantation is presently considered a relatively efficacious therapeutic approach employed to reinstate visual acuity in individuals afflicted with corneal blindness. The incidence of immune rejection is significantly diminished in normal corneal tissues due to the absence of blood vessels and lymphatic structures in contrast to organ transplantation. However, for patients with high-risk corneal transplantation such as chemical burns, multiple or binocular

corneal transplantation and children, the incidence of rejection is often as high as over 60 % and the graft survival rate is greatly reduced [1]. Therefore, a new treatment method for anti-immune rejection is urgently required.

Glucocorticoids have been recognized as a crucial pharmaceutical agent in the context of anti-rejection therapy following corneal transplantation, serving to both prevent and address immune rejection occurrences. However, as a result of prolonged administration, glucocorticoid is commonly employed in conjunction with other pharmaceutical agents, owing to the occurrence of adverse effects such as hormonal glaucoma and cataract formation as well as the acceleration or exacerbation of infections [2,3]. The utilization of cyclosporine eye drops in conjunction with glucocorticoids has been effective but a majority of patients encounter pronounced symptoms of ocular irritation after administration, leading to suboptimal adherence. Studies have indicated that the temporary systemic administration of cyclosporine effectively diminishes the occurrence of postoperative rejection in individuals with corneal transplantation who are at a heightened risk. Nevertheless, subsequent hepatotoxicity, nephrotoxicity, hypertension and other adverse reactions are prevalent, limiting its suitability for long-term application [4].

Recently, tacrolimus, an immunosuppressive agent, has been shown to possess a strong immunosuppressive effect. Numerous studies have documented the beneficial impact of locally applied tacrolimus eye drops on high-risk corneal transplantation patients. Nevertheless, the rejection rate remains approximately 16 % [5]. Research has demonstrated that oral tacrolimus therapy is a secure and efficacious approach to diminish corneal graft rejection and prolong graft survival in high-risk corneal transplant recipients who have not responded to cyclosporine anti-rejection treatment [6]. Consequently, this study aimed to investigate the potential benefits of combining oral tacrolimus capsules with tacrolimus eye drops in high-risk patients following corneal transplantation.

METHODS

Basic information about the patients

This study involved the selection of 40 high-risk patients who underwent penetrating keratoplasty at The Third Hospital of Hebei Medical University, China between January 2016 and December 2021. The patient cohort included individuals with chemical burns, multiple or binocular keratoplasty, children, large implants, herpes simplex virus keratitis, glaucoma and preoperative corneal neovascularization exceeding two quadrants, as indicated in Tables 1 and 2. Based on the type of immunosuppressant utilized post-surgery, the 20 cases were categorized into two groups: one receiving oral tacrolimus capsule combined with 0.1 % tacrolimus eye drops (referred to as the combined with systemic administration group), and the other receiving only 0.1 % tacrolimus eye drops (referred to as the local administration group).

Table 1: Clinical diagnosis of high-risk patients

Diagnosis	Number of patients	Percentage (%)
Chemical corneal injury	7	17.50
Herpes simplex virus keratitis	7	17.50
Corneal penetration injury	10	25.00
Fungal keratitis	5	12.50
Corneal dystrophy	6	15.00
Others	5	12.50

Table 2: Clinical data of all patients

Data	≤20	20-50	≥50
Age (years)	3	20	17
Gender			
Male	2	14	10
Female	1	6	7
Risk factors			
Herpes simplex virus keratitis	0	4	5
Chemical Burns	1	3	2
Previous failed grafts	1	5	5
Younger recipient age	1	0	0
≥2 quadrants of stromal vascularization	0	8	5

Table 3: Preoperative risk scoring for high-risk keratoplasty patients

High-risk factors	Score
Each quadrant of stromal vascularization	1
Each quadrant of peripheral anterior synechiae	1
History of glaucoma	1
History of glaucoma surgery	2
Each previous graft	1
Herpes simplex virus keratitis	2
Alkali burns	4
Limbal stem cell grafting had been performed	4

The preoperative risk scores were conducted in accordance with the high-risk corneal transplantation patient's preoperative risk scoring criteria outlined in Table 3 [6]. There was no significant difference in age and gender between both groups. The liver and kidney functions were normal before operation. Penetrating keratoplasty was conducted in both cohorts following established protocols. The surgeries were exclusively performed by a single surgeon, and no concurrent intraocular procedures were undertaken alongside keratoplasty.

Prior to participation, informed consent was obtained from each patient, encompassing a comprehensive explanation of the study's objectives and potential ramifications. Furthermore, all patients fulfilled the requirements for clinical trial registration, received approval from the Ethics Committee of the Third Hospital of Hebei Medical University (approval no. 2022-039-1) and adhered to the principles outlined in the Declaration of Helsinki [7].

Source of the corneal grafts

All corneal grafts utilized during the procedure were procured from the Hebei Red Cross Eye Bank within 8 hours of the cessation of brain function in local donors. Subsequently, they were preserved in Optisol-GS corneal storage medium (manufactured by Bausch & Lomb, Rochester, NY, US) at a temperature of 4 ^{o}C. Furthermore, all recipients underwent transplantation within a week following the acquisition of the grafts.

Drug use

Both groups of patients were administered tobramycin dexamethasone eye drops (Alcon, Novartis, USA) at a frequency of 6 times per day, with one additional dose per night (excluding cases of fungal infection), starting one week after the surgical procedure. Subsequently, the dosage was reduced to 3 times per day after surgery and the medication was completely discontinued after the third week post-surgery. Both groups received oral tacrolimus capsules and topical 0.1 % tacrolimus eye drops two weeks post-surgery. The combined treatment consisted of oral tacrolimus capsules (manufactured by Astellas Pharmaceuticals Ltd, Ireland) and 0.1 % tacrolimus eye drops (manufactured by Senju Pharmaceuticals Ltd, Japan). The initial dose of tacrolimus capsules was 1 mg twice daily and the eye drops were administered four times daily. The desired blood concentration range was set at 1 – 12 ng/mL and the dosage of tacrolimus capsules was adjusted accordingly to achieve the target blood concentration [1]. The mean blood concentration of 20 patients during treatment was determined to be 4.45 ± 1.99 ng/mL. In the topical group, twenty patients were administered an additional 0.1 % tacrolimus eye drops. With the exception of severe adverse reactions, the medication was administered for a minimum of 6 months post-surgery in both groups, gradually tapering until achieving stability and discontinuation of the drug. In the event of corneal graft rejection manifestations arising during treatment, the administration of tobramycin and dexamethasone eye drops (excluding cases of fungal infection) or tacrolimus eye drops and tacrolimus capsules was escalated. Upon successful management of the rejection, a gradual reduction in the dosage of these medications was implemented, ultimately restoring the dosage to its pre-rejection level.

Follow-up plan

The frequency of follow-up assessments was initially set at once a day during the first week, followed by once a week within the first month and subsequently reduced to once a month. The average duration of follow-up for the combined systemic treatment group was 13.25 ± 2.02 months, while it was 13.20 ± 2.07 months for the local treatment group.

Evaluation of parameters/indices

Rejection index (RI)

Rejection, corneal neovascularization, corneal graft edema and visual acuity were observed in the two groups. The establishment of rejection criteria involved utilizing the rejection scoring criteria outlined in Table 4. The Rejection index (RI) was determined by summing the scores of the three items and rejection was identified when RI ≥ 6.

Corneal neovascularization

The corneal neovascular growth was determined

using slit lamp *in vivo* microscopy (BQ900, Haag-Streit, Switzerland) and the scoring was conducted based on the rejection scoring criteria provided in Table 4.

Corneal graft edema

The iVue100 Optical Coherence Tomography device (Optovue Inc, China) was equipped with mapping tools to quantify the thickness of each layer of the cornea for the purpose of evaluating corneal graft edema. The edema was assessed based on rejection scoring criteria outlined in Table 4.

Visual acuity

The patient's naked eye visual acuity and corrected visual acuity were assessed using a 2.5-meter standard visual acuity chart. Intraocular pressure was measured using the Schiotz tonometer (YZ7A Suzhou Liuliu, China) with the average of three measurements recorded as the corresponding intraocular pressure value.

Blood concentrations of tacrolimus

The systemic medication group was subjected to monitoring of blood concentrations of tacrolimus (using a chemiluminescent particle immunoassay) at various time intervals (1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 9 months and 12 months) following surgery, with the aim of verifying the maintenance of target blood concentrations within the range of 1 – 12 ng/mL [1].

Liver function and renal function

Liver function and renal function indices of patients in the systemic medication group were assessed and analyzed every 3 months post-surgery.

Statistical analysis

Statistical analysis was performed using Statistic Package for Social Science (SPSS) 26.0 software. A t-test was done to assess the comparability of gender, age, preoperative risk score and follow-up time between the two groups. Additionally, an χ^2 test was utilized to compare the data on immunosuppressive activity evaluation between the two groups. A significance level of $p < 0.05$ was deemed statistically significant.

RESULTS

Preoperative risk scores

The preoperative risk scores were determined to be 4.65 ± 2.41 and 4.25 ± 2.40 for the two groups, respectively. Statistical analysis revealed no significant difference between the two groups ($p = 0.602$; Figure 1 a).

Incidence of rejection

In terms of the occurrence of anti-rejection reactions in the two groups, one patient in the combined systemic medication group experienced rejection reactions.

The incidence of rejection in this group was 5 % and the reaction manifested on the sixth month post-surgery. On the other hand, six patients in the local administration group experienced rejection, resulting in an incidence of 30 % (Table 5). Rejection episodes in this group occurred in the second, third, third, fifth, fifth and seventh months after surgery (Figure 2). The disparity between the two groups was found to be statistically significant ($\chi^2 = 4.329$, $p = 0.037$).

Table 4: Rejection index scoring criteria

Turbidity index	Edema index	Neovascular index	Score
The cornea is completely clear	Corneal epithelium and stroma layer without edema	No neovascularization	0
The cornea is slightly foggy	Mild edema of corneal stroma	Peripheral neovascularization	1
The cornea is cloudy and iris texture is visible	Diffuse stromal corneal edema	Neovascularization reaches the graft bed and creates the edge	2
Corneal opacity increased, visible pupil	Diffuse stromal corneal edema with subepithelial microcystic blisters	Neovascularization reaches the periphery of the graft	3
The cornea exhibits significant opacity, while the anterior chamber lacks visibility.	Bulla keratopathy	The graft is filled with new blood vessels	4

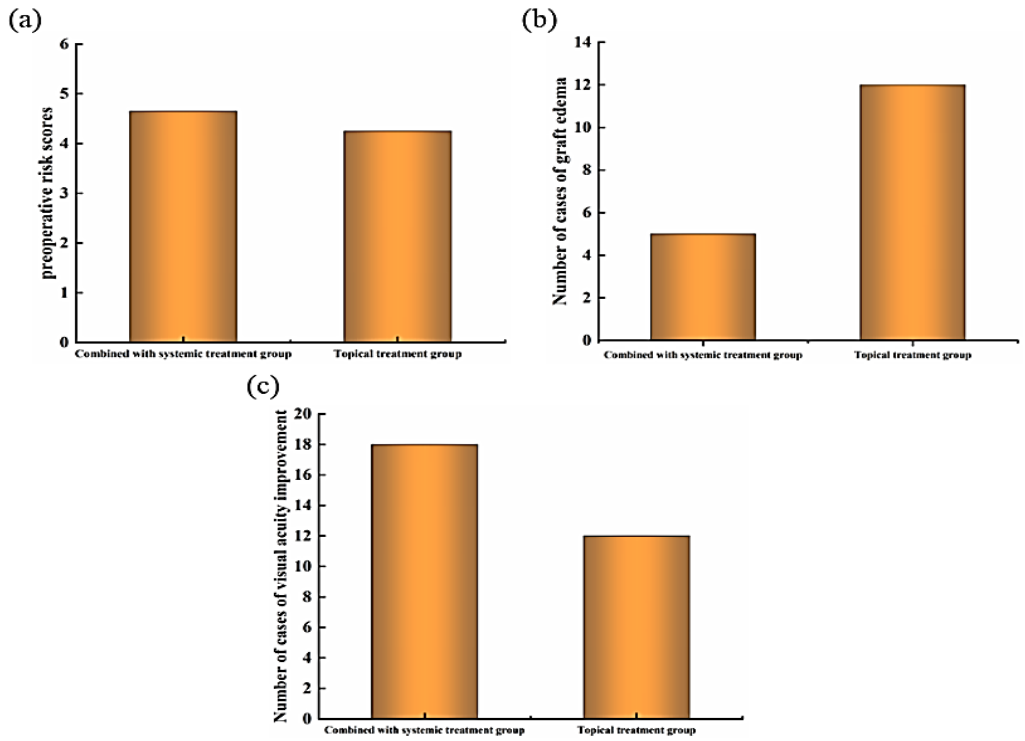

Figure 1: Comparison of several information in both groups: (a) preoperative risk scores (P = 0.602); (b) number of patients with implant edema (P = 0.025); (c) number of patients with visual acuity improvement (P = 0.025)

Table 5: Rejection incidences in the groups

Group	Number of rejection cases	Repulsion rate (%)
Combined with systemic treatment group	1	5
Topical treatment group	6	30

Curative effect indicators

In terms of the regulation of corneal neovascularization, 25 % of patients (n = 5) in the combined systemic medication group exhibited development of new blood vessels, with a mean score of 1.80 ± 0.84. The onset of neovascularization occurred between 5 – 12 months post-surgery, with an average duration of 6.80 ± 2.95 months. Conversely, in the local administration group, neovascularization was observed in 60 % of patients (n = 12), with a mean score of 2.08 ± 0.51. The initiation of neovascularization took place between 1 – 12 months after surgery, with an average duration of 5.58 ± 3.45 months (Table 6). The disparity between the two groups was significant (χ^2 = 5.013, p = 0.025).

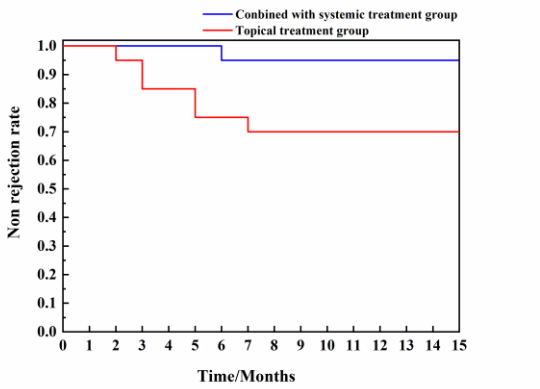

Figure 2: Kaplan-Meier curve of corneal graft rejection in 2 groups (P = 0.037)

Table 6: Curative effect indicators of patients in two groups

Indicator	Topical treatment group	Combined with systemic treatment group
Number of corneal neovascularization cases	12 (60%)	5 (25%)
Score of corneal neovascularization	2.08±0.51	1.80±0.84
Time of appearance of corneal neovascularization (month)	5.58±3.45	6.80±2.95
Number of cases of graft edema	12 (60%)	5 (25%)
Score of graft edema	3.42±1.98	2.08±0.84
Number of cases of visual acuity improvement	12 (60%)	18 (90%)

The occurrence of postoperative corneal graft edema was also observed in both groups. In the combined systemic administration group, 5 patients (25 %) exhibited corneal graft edema with a mean score of 2.08 ± 0.84 while the local administration group had 12 patients (60 %) with corneal graft edema, showing a mean score of 3.42 ± 1.98 (Table 6 and Figure 1b). The disparity between the two groups was found to be statistically significant ($\chi^2 = 5.013$, $p = 0.025$).

Following the surgical procedure, the combined systemic medication group exhibited a significant enhancement in the best corrected visual acuity in 18 instances, constituting 90 % of the cases. Conversely, the local medication group experienced an improvement in 12 cases, accounting for 60 % of the total. This difference was statistically significant, as indicated by Table 6 and Figure 1c ($\chi^2 = 4.800$, $p = 0.028$).

Among the cohort of 20 patients receiving systemic treatment, it was observed that 3 patients exhibited aberrant liver and kidney functions, characterized by elevated levels of homocysteine, total cholesterol, triglyceride, low-density lipoprotein cholesterol, very low-density lipoprotein, apolipoprotein A1, uric acid, and cystatin C, as well as reduced levels of gamma-glutamyl transpeptidase and glutamic-oxalacetic transaminase. However, upon reduction of tacrolimus capsule dosage, the liver and kidney function indices returned to their normal levels. Complications such as secondary glaucoma, neovascularization, graft opacity and edema in both groups were controlled by symptomatic treatment. All patients retained their eyeballs during follow-up. No patients dropped out of the study.

DISCUSSION

This study includes a subset of keratoplasty patients who are considered high-risk due to various factors, including chemical burns, multiple or binocular keratoplasty, children, large implants, herpes simplex virus keratitis, glaucoma and preoperative corneal neovascularization affecting more than two quadrants. These patients exhibit a disruption in their normal anterior segment structure. In individuals exhibiting corneal vascularization, there is an increased likelihood of immune cells and immune factors accessing the cornea. In patients experiencing inflammation in the anterior ganglia, immune function is actively engaged. In individuals with a history of corneal graft rejection, the immuno-mediators generated during that period may expedite the recognition of corneal antigen and hasten the onset of rejection. The presence of sympathetic response following corneal transplantation may result in the loss of immune privileges in patients undergoing a second transplantation, even if the contralateral cornea or an allograft with different MHC expression is used [9]. Additionally, immune function tends to be more active in children compared to adults.

The incidence of postoperative rejection in high-risk corneal transplantation patients is significantly elevated due to various factors mentioned above. In addition to conventional corticosteroid and cyclosporine therapies, novel immunosuppressants are progressively being employed. The purpose of this study was to observe and record the clinical course and therapeutic effect of patients with corticosteroids (except patients with fungal infection) combined with oral tacrolimus capsules as well as topical 0.1 % tacrolimus eye drops. In this study, both the combined systemic administration group and the local administration group showed certain effects in the anti-rejection of high-risk corneal transplantation, and the combined systemic administration group was superior to the local administration group in the ability to control rejection ($p < 0.05$). Previous reports have shown the effectiveness of tacrolimus eye drops in controlling the occurrence of rejection in high-risk patients after corneal transplantation.

In a study aimed at assessing the clinical effectiveness of 0.1 % tacrolimus eye drops and 1 % cyclosporine eye drops in patients undergoing high-risk penetrating keratoplasty, two groups of patients were administered either 0.1 % tacrolimus eye drops or 1 % cyclosporine eye drops, respectively [5]. The results showed that the rejection rate of the tacrolimus eye drops group was lower than that of the cyclosporine eye drops group. In their study, Magalhaes *et al*. investigated the efficacy of combining 0.03 % tacrolimus eye drops with 1 % prednisolone eye drops for high-risk corneal transplant patients [10]. The findings indicated that the combined application of 0.03 % tacrolimus eye drops was more effective in controlling the occurrence of irreversible rejection compared to the use of 1 % prednisolone eye drops alone. However, animal experimental studies have demonstrated that while tacrolimus eye drops effectively prevent acute corneal transplant rejection, the concentration of tacrolimus in the aqueous humor, specifically less than 0.13 ng/mL, does not adequately control the occurrence of endothelial rejection. Consequently, it is reasonable to hypothesize that solely relying on the administration of eye drops may not be sufficient to achieve the desired reduction in

rejection rates. A systemic application of tacrolimus to high-risk corneal transplant patients has been attempted to evaluate its effectiveness. A study of oral tacrolimus in addition to topical steroid hormone therapy in patients confirms its safety as well as its effectiveness in reducing the incidence of rejection and extending graft survival in high-risk corneal transplant patients [1]. In a separate investigation, a total of 11 patients (11 eyes) experienced irreversible rejection following corneal transplantation and subsequent treatment with systemic cyclosporine [12]. These patients were subsequently switched to oral tacrolimus therapy after graft replacement. Throughout the observation period, only 2 patients encountered rejection, which was effectively managed by augmenting the dosage of corticosteroid and tacrolimus. The findings further demonstrated the efficacy of systemic tacrolimus in preventing rejection, surpassing the effectiveness of systemic cyclosporine therapy. In the present study, the combined administration of tacrolimus capsule and tacrolimus eye drops resulted in a rejection rate of 5 % compared to the rejection rate of 30 % observed with the use of tacrolimus eye drops alone ($p < 0.05$).

In the present study, the combined systemic administration group exhibited superior efficacy in controlling the growth of corneal neovascularization compared to the local administration group. Notably, the average time of neovascularization in the combined systemic administration group was delayed and the incidence of cases was significantly lower ($p < 0.05$) compared to the local administration group. The development of blood vessels is intricately linked to the manifestation of rejection, with vascular congestion being regarded as an initial indication of rejection. Blood vessels serve as a conduit for the transfer of graft immune cells and immune factors, thereby augmenting the likelihood of immune rejection. Furthermore, research has demonstrated that the potential for reversing corneal graft rejection is contingent upon extent of corneal vascularization [13]. Consequently, proficiently managing the growth of corneal neovascularization plays a significant role in regulating the rejection of corneal transplantation. In a subset of high-risk patients undergoing corneal transplantation, the impairment of limbal stem cells can be attributed to primary factors like chemical burns, while the development of corneal neovascularization is strongly associated with the presence of limbal stem cells [14,15]. The absence of limbal stem cells in the corneal epithelium results in inadequate growth and healing, thereby increasing the likelihood of conjunctivization and vascular growth. In patients of this nature, prolonged ocular surface inflammation is present, leading to the migration of inflammatory cells and factors toward the graft through neovascularization, thereby increasing the likelihood of immune rejection.

A study conducted by Liang and his colleagues involved the treatment of 10 consecutive patients (12 eyes) with complete limbal stem cell deficiency following kerato-transplantation [16]. These patients were administered long-term systemic mycophenolate and tacrolimus, along with short-term prednisone and acyclovir. The average serum concentration of mycophenolate was maintained at 1.6 ug/mL, while tacrolimus was controlled at 4.5 ng/mL. The findings of this study indicated that the implementation of an immunosuppressant protocol has the potential to enhance the prognosis of keratoplasty in individuals with panlimbal stem cell deficiency. Specifically, the average blood concentration of tacrolimus in the combined systemic administration group, consisting of 20 patients, was determined to be 4.45 ± 1.99 ng/mL. This concentration was found to be more effective than local administration in regulating the growth of new blood vessels. Results from this study observed graft edema following corneal transplantation in two distinct patient groups. The combined systemic medication group exhibited 5 cases of graft edema, whereas the local medication group displayed 12 cases. The observed difference between the two groups was found to be statistically significant ($p < 0.05$). Furthermore, the best corrected visual acuity demonstrated improvement in 18 cases within the combined systemic medication group and 12 cases within the local medication group. This discrepancy was also determined to be statistically significant ($p < 0.05$). The findings of this study demonstrated that the concurrent oral administration of tacrolimus capsule exhibited greater efficacy in managing corneal graft edema and enhancing postoperative visual acuity compared to the use of tacrolimus eye drops alone.

Corneal graft rejection is characterized as a delayed hypersensitivity reaction, which can be classified into subepithelial, stromal and endothelial categories. Subepithelial rejection may manifest as subepithelial infiltrating foci, and in severe instances, the presence of a rejection line and epithelial defect can be observed. However, it is sometimes difficult to distinguish incomplete epithelialization from subepithelial rejection because the epithelium of donor graft may be incomplete in the early stage after keratoplasty, and the length of complete epithelial healing varies in different patients. In

cases of stromal rejection, the stroma typically experiences infiltration by focal aggregates, leading to graft opacity. The predominant and severe form of rejection encountered in clinical settings is the endothelial type, constituting approximately 65 % of all rejection occurrences [11]. This type of rejection typically manifests around three months following keratoplasty. In endothelial rejection, a linear white sediment of varying sizes is seen on the corneal endothelium, with anterior chamber cells and flashes in severe cases. Endothelial cells constitute the aqueous barrier of cornea and the function of active water pumping to maintain the cornea in a relatively dehydrated state, which is also one of the important reasons for the cornea to maintain transparency. Impairment of endothelial function results in edema of the posterior elastic layer, stroma, and epithelium, thereby increasing the overall thickness of the graft. This not only impacts patients' visual acuity to a certain degree but also significantly diminishes the graft's survival rate. The corneal aqueous humor barrier restricts the concentration of tacrolimus eye drops in the aqueous humor, rendering it lower than the concentration on the corneal surface. Consequently, the efficacy of late anti-endothelial rejection through tacrolimus administration is limited. Therefore, the long-term effect of tacrolimus alone on endothelial rejection after high-risk corneal transplantation is not very satisfactory [17]. Oral administration of tacrolimus is commonly employed in liver, heart, kidney, pancreas and other organ transplantations due to its potent anti-rejection properties, achieved by diminishing the systemic immune response. In high-risk corneal transplant recipients, the concurrent use of oral tacrolimus effectively lowers the immune response, thereby mitigating the risk of rejection. The present study demonstrates that the combined systemic medication group exhibited superior outcomes in terms of corneal graft edema reduction and visual improvement compared to the local medication group, with statistically significant differences observed between the groups ($p < 0.05$). This observation suggests that the utilization of oral tacrolimus capsules in conjunction with tacrolimus eye drops may yield superior outcomes in managing advanced anti-rejection reactions.

Limitations of this study

Given the limited number of participants in this study, additional clinical trials are imperative to ascertain the most effective management strategy for high-risk patients following corneal transplantation.

CONCLUSION

In high-risk patients undergoing corneal transplantation, the administration of tacrolimus capsules in conjunction with regular monitoring of liver and kidney function and blood concentration moderately decreases the occurrence of rejection following the procedure. Additionally, the combined administration of tacrolimus capsules orally and eye drops has shown some efficacy in managing corneal neovascularization and graft edema, leading to improved visual outcomes and enhanced overall effectiveness of corneal transplantation for patients. These results have the potential to stimulate novel avenues of investigation in future clinical research.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Xiaorong Zhang, Jia Yao designed the study and carried it out; Xiaorong Zhang, Jia Yao, Tengfei Ma, Haoyu Chen, Hengju Xu, Yinghui Ye, and Liying Zhai supervised the data collection, analyzed and interpreted the data, prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

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