Calcineurin Inhibitor in Corneal Transplantation

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Objective: To evaluate the long-term efficacy and safety of topical calcineurin inhibitor, tacrolimus 0.003% suspension for the management of steroid-induced ocular hypertension post-penetrating keratoplasty (PK).

Design: A Retrospective Study.

Setting: Magrabi Aseer Eye Hospital, Khamis Mushait, Saudi Arabia.

Method: Twenty primary keratoplasties (primary PK) performed between 1 January 2012 and 31 December 2015 were included in the study. Prednisolone was replaced with tacrolimus 0.003% suspension after intraocular pressure (IOP) elevation. Primary outcome measure was immunologic graft rejection episodes and secondary outcome measures were pre and postoperative best-corrected visual acuity (BCVA).

Result: Twenty patients with keratoconus were included in the study; 12 (60%) were males and the mean age was 27 years. There were no reports of graft rejection or patients requiring glaucoma surgery. Tacrolimus was well tolerated; however, all patients reported a mild transient burning sensation in the eye during application. At the final follow-up, tacrolimus was tapered for all patients.

Conclusion: Topical tacrolimus 0.003% suspension is an effective second-line immunosuppressant for the management of primary, normal-risk corneal grafts in patients who are steroid responders.

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Keratoconus is a non-inflammatory ectatic disease. The prevalence of keratoconus varies with location, population, ethnicity, environmental factors and diagnostic criteria[1,2]. Penetrating keratoplasty (PK) is the most common type of corneal transplant[3]. Approximately 20% of normal-risk corneal transplants experience an episode of acute rejection[4]. Management of keratoconus varies with disease severity. Topical steroids are effective in the prophylaxis against immune reactions observed after PK[5].

Tacrolimus is an antibiotic isolated from the Actinobacteria Streptomyces tsukubaensis[6]. This calcineurin blocking agent impairs transcription of genes encoding IL-2 and other cytokines, which in turn suppresses T-cell proliferation and normalize immune function[7,8]. To the best of our knowledge, this is the first report describing tacrolimus suspension in steroid responders after PK in Saudi Arabia.

The aim of this study is to evaluate the efficacy and safety of off-label tacrolimus 0.003% suspension as an immunosuppressive agent in patients who had undergone primary PK for the treatment of keratoconus and developed elevated IOP postoperatively.

METHOD

All keratoplasties performed between 1 January 2012 and 31 December 2015 were included in the study. Patients were informed of the potential risks and complications associated with tacrolimus and written informed consent was obtained. The analysis was restricted to the records of normal-risk patients who had developed postoperative, steroid-induced ocular hypertension (HTN) and had subsequently been treated with tacrolimus 0.003% suspension as second-line immunosuppressive. Patients who had previous intraocular surgery, incomplete documentation, insufficient postoperative care or a follow-up of less than six months were excluded.

In addition to standard personal characteristics, the following data were collected: dosage and duration of a topical steroid, pressure-lowering medications used postoperatively, duration and timing of postoperative ocular hypertensive events. Pre and postoperative best-corrected visual acuity (BCVA) and uncorrected visual acuity (UCVA) were measured before surgery and at each postoperative visit. All patients were followed postoperatively. The first follow-up visit was at week one, after which, patients were seen once every two months.

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Corneal transplantation was performed by two experienced surgeons. Trephination was performed with 7.5 mm Barron Radial Vacuum Trephine. The donor grafts were 7.75 mm sutured to the recipient using 10-0 nylon with 16 interrupted sutures.

All patients were treated postoperatively with a standardized regimen of topical steroid drops (prednisolone acetate 1.0% ophthalmic suspension which was tapered to 12-hourly over six months). Patients were then maintained on one drop of steroid for another six months. Moxifloxacin HCl 0.5% ophthalmic solution (Vigamox® Solution, Alcon Laboratories, Fort Worth, TX, USA) was used every 6 hours for one month. When the first steroid-related IOP elevation (defined as IOP >21 mmHg) occurred, patients were instructed to replace prednisolone with tacrolimus 0.003% suspension. If IOP ≥30 mmHg, the anti-glaucoma drops dorzolamide-timolol solution (Cosopt®, Merck Sharp & Dohme Ltd, UK) and brimonidine 0.1% solution (Alphagan® P, Allergan, Irvine, CA, USA) were added every 12 hours for one week, then adjusted according to clinical response.

The primary outcome measure was the number of immunologic graft rejection. The secondary outcomes for our study were pre and postoperative BCVA. Statistical analysis was performed using SPSS version 22. A P-value of <0.05 was considered statistically significant.

RESULT

Twenty patients with keratoconus were included in the study. The mean age of the patients was 27 years, the range was 14 to 34 y, see table 1 for patient characteristics and treatment history.

Table 1: Patient Personal Characteristics and Values

Patients/eyes (*n*)	20/20
Age, mean (range [r], year)	27 (range 14 to 34)
Gender, *n* (%)	
Women	8 (40)
Men	12 (60)
Ocular Pathology, *n* (%)	
Keratoconus	20 (100)
Corneal neovascularization	0
IOP, mean (r, mmHg)	
Pre-operative	16 (range 11 to19)
Post-operative	17 (range 14 to 18)
UCVA*	
Preoperative	0.05
Postoperative	0.5 (p<0.05)
BCVA*	
Preoperative	0.05
Postoperative	0.7 (p<0.05)

*** decimal**
BCVA=best corrected visual acuity
UCVA=uncorrected visual acuity

After surgery, all patients were treated prophylactically with topical prednisolone acetate 1% and moxifloxacin 0.5% ophthalmic solution. During the postoperative period, all patients experienced steroid-related elevations in IOP (≥22 mmHg). At that time, topical prednisolone was replaced with 6-hourly tacrolimus 0.003% suspension. Those who had an IOP elevation ≥30 mmHg were also treated with topical antiglaucoma drugs. All patients reported a transient burning sensation in the eye when applying tacrolimus. There were no significant postoperative complications after surgery. There were no episodes of graft rejection or herpes simplex virus infection reported and no patients required glaucoma surgery.

The mean postoperative follow-up time was 13.7 months (range 8 to 18 months); and the mean tacrolimus treatment duration was 8.6 months (range 4 to 10 months), see table 2. At the final follow-up, all patients had been successfully tapered off tacrolimus. The BCVA had improved from a mean preoperative 0.05 to 0.7 and the UCVA had improved from 0.05 to 0.5. The mean postoperative IOP had increased from a preoperative value of 16 mmHg (range 11-19 mmHg) to 17 mmHg (range 14-18 mmHg).

Table 2: Tacrolimus 0.003% and Prednisolone

Patient	Tacrolimus 0.003%		Prednisolone
	Start Treatment (month post-PK)	Treatment Length (months)	Month Discontinued
1	8	4	8
2	3	9	3
3	6	6	6
4	5	7	5
5	3	9	3
6	5	7	5
7	6	6	6
8	2	10	2
9	2	10	2
10	3	9	3
11	3	9	3
12	2	10	2
13	4	8	4
14	2	10	2
15	5	7	5
16	4	8	4
17	3	9	3
18	2	10	2
19	2	10	2
20	3	9	3
mean	3.7	8.6	3.7
range	2-8	4-10	2-8

DISCUSSION

Topical steroids, such as prednisolone acetate 1% are routinely used to manage postoperative inflammation after PK. However, there are side effects associated with steroid use, including increased risk of infection, decreased wound healing and cataract formation. Steroid-induced post-keratoplasty IOP elevation was reported in 35% of patients at some point during

the 12-month follow-up period and in 78% of eyes 3-6 months post-keratoplasty[10].

Topical tacrolimus has emerged as an effective second-line immunosuppressant for the management of high-risk grafts without the side effects of steroids[9]. In a randomized, clinical trial enrolling 40 patients who had undergone normal-risk PK, topical tacrolimus was more effective immunoprophylaxis than steroid[5]. Our study showed that topical tacrolimus 0.003% suspension was a successful long-term treatment option for normal-risk PK patients who were steroid responders.

CONCLUSION

Tacrolimus was safe and effective. The only adverse event reported was a mild transient burning sensation on application. Topical tacrolimus 0.003% suspension may be considered as an alternative treatment to reduce or replace topical steroids; however, further studies are needed to elucidate the potential role of topical tacrolimus after PK.

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