Outcomes of Ipsilateral Simple Limbal Epithelial Transplantation, Tenonectomy, Mitomycin and Amniotic Membrane Transplantation for Treatment of Recurrent Pterygium

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Purpose: To report on the outcomes of recurrent pterygium treated by ipsilateral simple limbal epithelial transplantation (SLET), mitomycin, tenonectomy, and amniotic membrane transplantation.

Methods: A retrospective, interventional study was conducted including all patients with recurrent pterygium who underwent SLET surgery under a single surgeon using ipsilateral donor tissue with a minimum 6-month follow-up at Toronto Western Hospital, Canada. Outcome measures included the following: recurrence rates, best spectacle–corrected visual acuity, and postoperative complications.

Results: Ten eyes of 10 patients, aged 60.7 ± 18.5 years (range 23–79) with a mean follow-up time of 15.2 ± 10.0 months of which 50% (n = 5) were men, were included. Eight eyes (80%) had a history of 2 or less pterygium operations. Two patients had 3 and 5 previous pterygium operations, respectively. Concurrent limbal stem cell disease was noted in 6 eyes (60%). Average number of pterygium recurrences per eye was 1.9 ± 1.3 (range 1–5). Mean pre-op best-corrected visual acuity was 0.5 LogMAR (Snellen equivalent 20/60, range 20/20 to counting fingers). Best-corrected visual acuity remained the same or improved in 6 eyes (60%). Recurrence was noted in 1 eye (10%) with a history of 5 previous pterygium excisions and remained stable at the last follow-up. No patients required a second operation.

Conclusions: Ipsilateral SLET with mitomycin, tenonectomy, and amniotic membrane transplantation is a novel technique to address recurrent pterygium. Concurrent limbal stem cell diseases are often present. Initial results demonstrate low recurrence. Visual improvement is modest. Stabilization of the ocular surface to improve vision is possible.

Key Words: pterygium, SLET, limbal stem cell failure, LSCD

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Recurrent and primary pterygia reduce the quality of vision due to astigmatism and scarring, give rise to significant symptoms of tearing and discomfort, and are often cosmetically unacceptable to patients.[1] It is surmised that the underlying factors behind pterygium recurrence are multifactorial, such as genetic, environmental, and surgical technique-specific.[2,3] Many surgical procedures have been described to treat recurrent pterygia, including repeat conjunctival autograft, conjunctival-limbal autografting, amniotic membrane transplantation, and adjunctive use of subconjunctival 5-fluorouracil, mitomycin C, or bevacizumab application.[4] The use of a conjunctival or amniotic membrane graft reduces the recurrence rate of pterygium from as high as 89% to 5% to 10%.[4,5] Careful dissection and removal of underlying tenon tissue is also believed to aid in reduction of recurrence. However, no surgical procedure has been shown to be impervious to recurrence.

Simple limbal epithelial transplantation (SLET) was pioneered by Sangwan et al[6] for the management of unilateral stem cell deficiency in 2012. The original technique involved the contralateral harvest of healthy limbal stem cells and autologous transplantation to the affected eye. Since then, multiple studies have evaluated the efficacy of the technique for the management of unilateral chemical burns, ocular surface squamous neoplasia, and primary pterygium excision.[7–9]

This case series aims to evaluate the outcomes of ipsilateral SLET for the management of ocular surface reconstruction in the context of recurrent pterygium.

MATERIALS AND METHODS

A retrospective medical chart review was performed at a single corneal clinic at Toronto Western Hospital, Toronto, Ontario, Canada. Included were patients who underwent ipsilateral SLET for the indication of recurrent pterygium between January 2015 and July 2019, with a minimum of 6-

month postoperative follow-up. This retrospective observational case series received the Research Ethics Board approval by the University Health Network (Toronto Western Hospital, Toronto, Ontario, Canada) and was conducted in compliance with the tenets of the Declaration of Helsinki.

The data collected in this study included demographic characteristics, best-corrected visual acuity (BCVA), recurrent pterygium physical characteristics, family history of pterygium, number of pterygium surgeries pre-SLET, concurrent ocular conditions, intraoperative and postoperative complications, and donor tissue laterality and location as well as recurrence post-SLET.

Ten eyes of 10 patients were collected during this study period. Diagnosis was based on the slit-lamp findings and a history of previous pterygium excision. Inclusion criteria were age older than 18 years and a healthy 2 clock hours of limbal stem cells. Excluded were patients with bilateral disease, severe dry eye, and autoimmune disease. In all cases, the diagnosis was confirmed on formal histopathology of the pterygium specimen removed during the SLET procedure.

Data were recorded in Microsoft Excel (2016) and analyzed using SPSS version 23 (SPSS Inc, Chicago, IL). Snellen visual acuity measurements were converted to LogMAR for analysis.

All cases underwent a similar SLET technique for recurrent pterygium as previously published by our group[10] and depicted in Figure 1. The donor tissue is harvested by using a crescent blade from a healthy area of limbus and divided into 10 to 12 pieces which are set aside in a balanced salt solution. The recurrent pterygium is excised in the usual fashion, followed by an extensive peritomy and tenonectomy depending on the extent of the disease. A superficial keratectomy is then performed to thoroughly remove all corneal pannus and fibrotic tissue. After mitomycin 0.02% application is performed for 2 to 3 minutes and rinsed away, the harvested donor pieces are distributed evenly over the deficient areas (either locally or circumferentially) aided by fibrin glue and a double layer of amniotic membrane (below and above the harvested donor pieces). Topical moxifloxacin is applied, and a bandage contact lens is placed with a patch overnight. Topical moxifloxacin is administered. In our series, all amniotic membranes were sourced from the Eye Bank of Canada, Ontario Division. Patients were counseled on their ocular findings, and all elected to have ipsilateral harvesting. All patients received autologous donor limbal tissue from a healthy portion of the ipsilateral eye by preoperative slit-lamp identification. From the following day, all patients received 0.1% dexamethasone sodium phosphate and 0.3% tobramycin antibiotic (Tobradex; Alcon, Mississauga, ON, Canada) eye drops 4 times daily for 1 month. Then, 0.1% dexamethasone sodium phosphate (Maxidex; Alcon) eye drops were tapered down according to inflammation and resolution of the amniotic membrane over the next few months.

RESULTS

Ten eyes of 10 patients, aged 60.7 ± 18.5 years (range 23–79) of which 50% (n = 5) were men, were included. No eyes were excluded because of insufficient follow-up time. Eight eyes (80%) had a history of 2 or fewer previous pterygium operations, and 2 patients had 3 and 5 previous pterygium operations each, respectively. Patients were white in 70% (n = 7) of the cases and of Asian descent in the rest (n = 3). The average follow-up was 15.2 ± 10.0 months (range 6–38 months). Patient demographics are demonstrated in Table 1.

Table 2 outlines the pterygium characteristics. The average height of pterygium recurrence was 6.4 ± 1.3 mm (n = 5, range 5–8 mm) and average width was 4.6 ± 1.3 mm (n = 5, range 3.2–6.5 mm). Four eyes had more than 75% involvement of the cornea involved (thus, height and width measurements were unable to be obtained). The average preoperative astigmatism was 3 ± 2.57 diopters (n = 8); the remaining 2 eyes had such severe disease that astigmatism was unable to be measured. Three cases had a double-headed pterygium in their previous history. Elevation and inflammation were graded as moderate to severe in all cases. Concurrent limbal stem cell diseases were noted in 6 eyes (60%) and were diagnosed by clinical examination (late fluorescein staining (vortex or punctate staining), epithelial irregularity, superficial neovascularization, or corneal stroma opacity and scarring.[11–13] Narrow angles were noted in 3 eyes (30%). Only 1 case had a family history of pterygium. The average number of pterygium recurrences per eye before SLET was 1.9 ± 1.3 (range 1–5). The average number of years after previous pterygium surgery was 10.1 ± 8.4 years (range 6 months to 27.5 years). Of the 5 eyes in which a detailed surgical history was able to be obtained, 3 eyes (30%) had no autoconjunctival graft applied for at least one of their previous pterygium operations.

The mean pre-op BCVA was 0.5 logarithm of the minimum angle of resolution (LogMAR) (Snellen equivalent 20/60, range 20/20 to counting fingers), and BCVA remained the same or improved in 6 eyes (60%).

Fifty percent (2 eyes) of the cases that did not experience visual improvement went on to undergo penetrating keratoplasty for corneal scarring once their ocular surface was stabilized. Five eyes (50%) experienced a transient elevation in intraocular pressure which was well controlled with topical medication only. One eye developed a pyogenic granuloma which resolved on topical steroids and another developed a symblepharon which was stable over the next 2-year course. No eyes developed optic nerve head changes, and all had stable visual fields.

Recurrence of pterygium was defined as present if any encroachment over the limbus and clinically significant if >1 mm. This was noted in only 1 eye which had a history of 5 previous pterygium excisions. This recurrence remained stable at the last follow-up visit. No patients required a second SLET operation (Table 3).

DISCUSSION

In the current study, 10 patients with recurrent large pterygium underwent ipsilateral SLET. Recurrence occurred in 10% of the cases. To the best of our knowledge, this is the first study to report the outcomes of ipsilateral SLET for recurring pterygia.

Rates of re-recurrence after treatment of recurrent pterygium range from 3.2% to 20%[2,14–19] and remain difficult to treat.

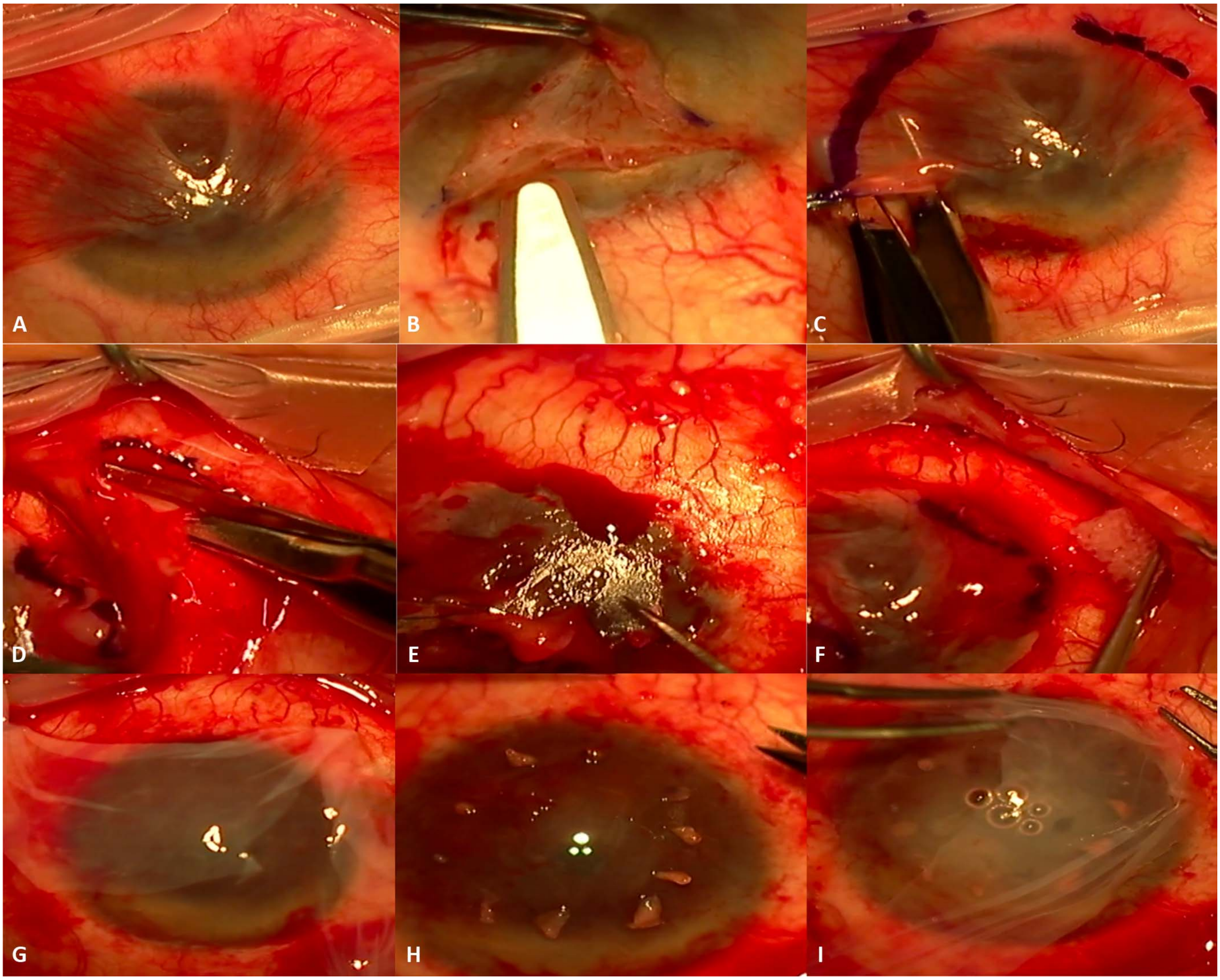

FIGURE 1. Simple limbal epithelial transplantation in a patient with a double-headed pterygium. A, Double-headed pterygium with an healthy area of limbal stem cells at an inferior aspect of photograph. B, Healthy 2 × 4 mm limbal area harvested and set aside in a balanced salt solution. C, Pterygium heads marked and excised. D, Extensive tenonectomy performed. E, Superficial keratectomy to remove the pannus and fibrosis. F, Mitomycin 0.02% application for 2 to 3 minutes under free conjunctival edge and rinsed thoroughly with balanced salt solution. G, First amnion layer attached with fibrin glue and sutures to the ocular surface. H, Harvested donor tissue cut into 10 to 12 pieces and distributed evenly and adhered with fibrin glue. I, Second layer of amniotic membrane fastened with glue and bandage contact lens placed over the top. (The full color version of this article is available on www.corneajrnl.com.)

Conjunctival autograft remains the most popular method[20,21] but is difficult to achieve for large recurrences[22] and can be associated with complications such as graft edema, donor site scarification, pyogenic granuloma, and conjunctival inclusion cysts. Sangwan et al[6] first described SLET in 2012 for the treatment of unilateral stem cell deficiency. Since then, its utility has been explored in the context of chemical burns, ocular surface squamous neoplasia, and primary pterygium.[7,8,23–25]

In our case series, the average patient tended to be older and white with no preponderance for gender or laterality. Most patients had at least 2 previous pterygium excisions each. There was a significant proportion presenting with concurrent limbal stem cell disease arising from previous treatments (60%) and being very large in size (6.4 × 4.7 mm). This is consistent with the findings by Aidenloo et al where vertical height of >6.7 mm or more was associated with a significantly higher recurrence rate. Jeon et al[26] reported 4-fold higher recurrence rates in the cases with higher vascularity indices, and this is supportive of our findings.

Our operative technique details an extensive superficial keratectomy and tenonectomy. The importance of the removal of conjunctival fibrovascular tissue and tenonectomy has been demonstrated in in vitro models pertaining to growth factor and angiogenesis modulation of pterygial fibroblasts by Kria et al.[27] Similar techniques involving large conjunctival autografting also use this technique in an attempt to reduce recurrent rates.

TABLE 1. Patient Characteristics

Patient Characteristics	n = 10	Range
Average age (yrs)	60.70 ± 18.4	23–79
Male	50%	
Left eye	60%	
Race		
White	70%	
Asian	30%	
Average months of follow-up	15.2 ± 10.01	6–38
% of patients with 2 or less recurrences	80%	
Mean pre-op BCVA* (Snellen)	20/60	20/20—HM†

*Best-corrected visual acuity.
†Hand Movements.

One case demonstrated a recurrence (defined as more than 1 mm extension from the limbus[28]) at 5 months but did not progress (the last follow-up at 8 months). Interestingly, this case had the highest number of recurrences (5 previous excisions) and had an extremely large-sized recurrence (8 × 6.5 mm). We postulate that the severity of concurrent limbal stem cell failure may have exceeded the ability of the ipsilateral SLET tissue amount (1 clock hour) to repopulate the limbal stem cell niche. We speculate that it may be prudent to harvest tissue from the other eye in such cases. Other studies have demonstrated that repeat SLET in unilateral chemical burns results in a 75% success rate of ocular surface reconstruction,[29] so repeat SLET may offer some utility should the recurrence progress. To date, however, the recurrence has remained stable.

Additional benefits seem to be the restoration of the limbal stem cell niche such that the ocular surface is able to sustain a keratoplasty to improve vision limited from scarring,[30,31] successfully achieved in 2 cases in our series. This procedure also addresses the 2 problems of large donor contribution requirement and expense when taking a smaller amount of tissue and expanding the cells ex-vivo on amniotic membrane fixed to the recipient eye.[32] It potentially reduces the iatrogenic risk of worsening of limbal stem cell disease (LSCD) which may occur if a relatively large amount of healthy tissue is excised as is often performed in simple limbal autograft.[32]

TABLE 2. Pterygium Features

Pterygium features		
Average height (mm)	6.38 ± 1.3 (n = 5)	5–8
Average width (mm)	4.64 ± 1.3 (n = 5)	3.2–6.5
Average preoperative astigmatism (D)	3 ± 2.57 (n = 8)	0.5–8.5
Over 75% involvement of cornea	40%	
History of double-headed pterygium	30%	
Elevation	Mod-severe	
Severity	Mod-severe	
Average no. of yr after the last pterygium surgery	10.1 ± 8.37	0.5–27.5
Concurrent ocular conditions		
Concurrent LSCD*	60%	
Narrow angles	30%	
Other features		
Family Hx of pterygium	10%	
Previous grafting procedure	n = 5	
Average # of recurrence	1.9 ± 1.29	1–5

*Limbal stem cell disease.
Hx, history of.

TABLE 3. Postoperative Course

Postoperative complications	n = 10
IOP elevation	50%
Progression to glaucoma	0
Recurrence	1 (at 5 mo)
Symblepharon	1
Pyogenic granuloma	1
Further surgical procedures	
Penetrating keratoplasty	20%

IOP, intraocular pressure.

Furthermore, our series highlights the benefit of leaving the healthy eye untouched because many patients are highly reluctant to have their "good" eye operated on. Patients, however, should be reassured that no studies have reported serious adverse outcomes on the donor eye, in case their healthy eye is required to be a donor source in future. Main complications of the *donor* eye in *contralateral* SLET are pyogenic granuloma[23] and focal nonprogressive LSCD of the donor site not affecting visual acuity.[9,29]

The safety profile of the procedure also seems to be fairly good. The most common complication of SLET in the recipient eye is focal recurrence of LSCD (up to 31%).[9,23,24] A transient increase in intraocular pressure managed on topical medications alone was seen in 50% of cases, but no patients developed optic nerve head or visual field changes. One case with a history of 3 previous pterygia developed a symblepharon which was nonprogressive at the 2-year follow-up. One case developed a pyogenic granuloma at the donor site which resolved on topical steroids. There were no cases of infection.

One of the drawbacks of the SLET procedure is the lengthy amount of time taken for the amnion to completely dissolve (often months), and thus, patients should be counseled appropriately. Visual prognosis is also often guarded as the amnion slowly incorporates into the ocular surface, potentially adding to preexisting haze, scarring, and astigmatism despite stabilization of the aberrant growth. Intraoperative time also should be considered because the procedure usually takes approximately an hour to complete. The possibility of uncontrolled pressure development in this age group exists, especially in those with preexisting glaucoma. Future filtration or intubation procedures may be compromised by the conjunctival manipulation in this procedure.

This study has several limitations. Limitations include its retrospective nature, small number of patients, lack of a control group, and lack of a formal classification structure to stratify mild, moderate, and severe cases of recurrence. The diagnosis of healthy limbal areas was performed by clinical evaluation at the slit lamp and can be potentially fraught with error because the definitive method is to perform histopathological examination or impression cytology. We do not have access to impression cytology at our institution, and ipsilateral biopsy of the area of healthy tissue for histopathological diagnosis would cause a further depletion of the already limited healthy tissue in many of our cases. The short follow-up duration is also a limitation, although the literature shows that SLET failure is usually noted within the first 6 months postsurgery.[9,29] In addition, the role that concurrent mitomycin C and amnion usage contributes is unclear, and studies to compare SLET against these modalities warrant consideration. Nevertheless, the recurrence rate in this small series seems to be low and restricted to only the most severe cases (with the most recurrences).

In conclusion, ipsilateral SLET in the treatment of recurrent pterygium seems to have utility in addressing both pterygium recurrence and limbal stem cell deficiency component, allowing a cost-effective treatment to stabilize the ocular surface while simultaneously preserving the healthy eye. Patients should be counseled on the extended period of recovery and realistic expectations of guarded visual prognosis due to preexisting scarring and astigmatism.

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