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Limbal stem cell transplantation for primary pterygium

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角膜缘干细胞移植术治疗原发性翼状胬肉

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摘要

目的:评价自体角膜缘干细胞移植治疗原发性翼状胬肉的安全性和有效性。

方法:前瞻性观察性研究。采用自体角膜缘干细胞移植术治疗鼻侧原发性翼状胬肉 264 例(男性 142 例,女性 122 例)。患者平均年龄 54.22±15.24 岁。翼状胬肉术后 1、3、7d 及 1、3、6、9、12、36mo 进行定期随访。评估手术时间,角膜上皮愈合时间,术后复发率和手术并发症。

结果:平均手术时间为 25.7±2.6min。经过至少 3a 的术后随访,术后角膜上皮愈合时间为 3.85±0.72d。14 例患者出现眼科并发症。本研究未发现虹膜睫状体炎、睑球粘连、角膜溃疡等威胁视力的严重并发症。结膜移植片水肿 5 例,肉芽肿形成 3 例,结膜下血肿 6 例。随访 3a,11 例患者复发,复发率为 4.17%,首次出现复发时间为 3mo,平均 8mo。

结论:经长期随访,自体角膜缘干细胞移植术无严重并发症,复发率低,是治疗原发性翼状胬肉安全有效的方法。我们还建议对于原发性翼状胬肉手术,12mo 的术后随访为最佳时间。

关键词:复发率;并发症;翼状胬肉

Abstract

• AIM: To evaluate the safety and efficacy of limbal conjunctival autograft transplantation for treating primary pterygium over a period of 3y.

• METHODS: Prospective observational consecutive case series. In this study, 264 eyes of 264 patients (142 males and 122 females) with nasal primary pterygium were treated using the technique of limbal conjunctival autograft. The mean ages of the patients were 54.22±15.24a. After excision of the pterygium patients were followed up on 1, 3, 7d and at 1, 3, 6, 9, 12 and 36mo. Recurrence of pterygium, complications, operation time and corneal epithelialization time were evaluated.

• RESULTS: The average surgery time was 25.7±2.6min. With a minimum 3-year of follow-up, postoperative corneal epithelialization was completed in 3.85±0.72d. Complications were observed in 14 cases. Vision-threating complications such as iritis, scleral thinning symblepharon or ulceration were not detected in the study. 5 eyes with graft edema, 3 eyes with granuloma formation and 6 cases with a subconjunctival hematoma in the nasal conjunctiva. By the end of 3-year follow-up, recurrence was detected in 11 cases. The recurrence rate was 4.17%, and the onset of recurrence was 3mo, the average recurrence time was 8mo.

• CONCLUSION: There were no severe complications and few recurrences when limbal conjunctival autograft transplantation was performed after long-term follow-up, we suggest that limbal conjunctival autograft transplantation is a safe and effective technique in primary pterygium. We also recommend that 12-month follow-up is optimal on primary pterygium surgery.

• KEYWORDS: recurrence rate; complications; pterygium
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INTRODUCTION

Pterygium is a common external ocular surface disease which is characterized by a wing-shaped fibrovascular conjunctival growth of conjunctival encroachment onto the cornea[1-2]. It usually develops in people exposed to ultraviolet radiation[3], dust, heat, dryness, viruses[4] or chronic inflammation[5-6]. Symptoms of pterygium irritating the patients include foreign body sensations, persistent redness or even decreasing vision. Although many surgical techniques are recommended as good methods for the treatment of pterygium, recurrence remains the most concerned problem. Bare scleral excision is one of the oldest methods for pterygium surgery which is a quick procedure. In rural areas, bare scleral excision technique is prevalent and the reported rate of recurrence ranges from 24% - 89%[7]. Hence various techniques have been developed: adjuvant mitomycin C during or after scleral excision, conjunctival flaps, sub-tenon ranibizumab, cyclosporine, bevacizumab, conjunctival autograft, amniotic membrane graft and so on[8-13]. To prevent recurrence, an optimal pterygium surgery should be safe, with good cosmetic results and has a low rate of complication and recurrence. Intra - operative mitomycin C and limbal conjunctival autograft are commonly adopted nowadays for the reason that intra-operative mitomycin C needs less surgery time and limbal conjunctival autograft has a lower rate of recurrence[14-15]. The limbal conjunctival autograft is related to the conjunctival autograft and the graft contains averagely 0.5 mm of limbal and peripheral corneal tissue. It has been suggested that the healthy limbal epithelium is an important barrier to conjunctival migration onto the cornea[16]. Accordingly, some surgeons prefer this technique to other kinds to reduce the risk of recurrence. In the long run, some studies have showed the limbal conjunctival autograft has a statistically significant advantage over some other techniques[7,17]. The purpose of this prospective study is to evaluate the operating time, postoperative symptoms, 3-year follow-up complications and recurrence rate.

SUBJECTS AND METHODS

This study was approved by the Institutional Review Board of Minhang Hospital Affiliated to Fudan University and adhered to the tenets of the Declaration of Helsinki.

Between August 2012 and December 2015, following informed consent, 264 eyes of 264 consecutive patients meeting the criteria were involved in our study. This study was conducted in Minhang Hospital Affiliated to Fudan University. All operations were performed under the operating microscope by the same surgeon (Zhang Y), among them, 142 were males and the other 122 were females, (age range: 49-70 years, mean: 54.22±15.24 years). All parents were followed-up for at least 36mo. Complete ocular examination was carried out and a detailed ocular and medical history was obtained.

The inclusion criteria for participants were as follows: 1) parents who had not previous undergone pterygium surgery before and the pterygium extends at least 3 mm beyond the limbus; 2) parents who had not had a severe ocular surface disease like dry eyes or severe systemic disease; 3) parents who demonstrated cosmetic problems or visual disturbance.

The exclusion criteria were the following: 1) the pterygiums being suspicious of pseudo - pterygium, recrudescent pterygiums and conjunctival intraepithelial neoplasia; 2) Recurrent cases of pterygium; 3) patients who had a history of previous ocular surgery; 4) patients who has primary temporal pterygium, which is relatively rare.

All parents underwent complete ophthalmological examination andsince the shape of the encroaching pterygium is similar to a triangle, the size of the pterygium was measured. The size of pterygium varied from 2-5.5 (mean 3.25±0.65) mm.

Surgical Method The concerned eye under standard sterile preparation and were performed under topical anesthesia. After an eye speculum was placed into the eye to expose the surgical field, the head of the pterygium was dissected and scraped clean from the cornea surface. The body of the pterygium together with the tenon's tissue was excised with Westcott scissors. A compass was used to measure the dimensions of the bare sclera. During this process, cauterization was not used to avoid any damage to the limbus of the cornea. A piece of conjunctiva, which was as thin as an onion' skin, was harvested from the super temporal bulbar conjunctiva. Care was taken to 0.5 mm of peripheral cornea and the free graft of similar size was sutured with interrupted 10/0 nylon suture to the recipient bed. The area where the conjunctival autograft was taken from was left with tenon's issues exposed.

The involved eye was patched for 24h after operation to prevent the eyeball from movement or blinking. From the second on, gentamicin and dexamethasone drops were applied four times daily together with antibiotics three times daily. Both of these eye drops were tapered off over the next 4wk. Patients were followed up and evaluated on 1, 3, 7 and 30d postoperative, and every 3mo for the first year and then every 6mo for the following year by the same surgeon (Gu YF). In the follow-up sessions, complications and recurrence starting times were recorded. A recurrence was defined as any fibrovascular regrowth encroaching more than 1 mm onto the cornea at the site of the surgery.

RESULTS

All the patients completed the 3-year follow-up. Surgery time was recorded when the eye speculum was placed between the eyelids until it was removed. The average surgery time was 25.7±2.6min, re-operations were performed if the pterygium appeared to be aggressive or the pterygium encroached more than 2 mm of the cornea. During the follow - up period, patients were required to see the doctor when any fibrovascular tissue was found to have encroached onto the cornea again. The slit - lamp examination was performed at each visit to observe the position and integrity of the graft. More attention

Table 1 Preoperative characteristics for patients

Categories	Characteristics
Total number of patients	264
Gender	
M	142
F	122
Age, a	
Mean±SD	54.22±15.24
Range	45-70
History, y	10±6
Range	2-26
Size of pterygium (mm^2)	
Mean±SD	18.6±8.2
Range	6-28

Table 2 Number of recurrences in limbal conjunctival autograft in 3-year follow-up

Postoperative duration	Number
3mo	4
6mo	3
9mo	1
12mo	1
18mo	2
24mo	0
36mo	0
Total	11

Table 3 Surgery complications

Complications	Number
Graft edema	5
Granuloma formation	3
Subconjunctival hematoma	6

was paid to look for any evidence of recurrence or complications. Corneal epithelialization times was also recorded. Eyes of 142 male and 122 female patients with primary pterygium were included in this study with a mean age of 54.22±15.24 years. Postoperative corneal epithelization was completed in 3.85±0.72d. Recurrence occurred in 11 eyes of 11 patients, the period from surgery to recurrence was 3-18mo in the study. Most recurrences occurred within the first year and 2 occurred after 15mo. Recurrences remained stationary and needed no operation with encroachment of the cornea of less than 1 mm. Complications were observed in 14 cases. There were no cases showing vision-threatening complications such as scleral thinning, iritis, symblepharon or ulceration and so on. 5 eyes with graft edema, 3 eyes with granuloma formation and 6 cases with a subconjunctival hematoma in the nasal conjunctiva.

DISCUSSION

Surgical excision is the main treatment for pterygium, however, there is no definite point of view as to which surgical operation is the most efficaciousone[12,18-19]. The presence of a pterygium is disturbing to both the surgeon and the patient because of its tendency to recur and its unsightly appearance. Various combinations of adjuvants and surgical options have been used to remove the pterygium and to prevent its recurrence. Although there are several approaches in the treatment of pterygium, surgeons' experience is the main factor that may determine which operation a surgeon will choose for a particular patient. Surgery time varies widely with the complexity of the operation chosen, the skill of the surgeon and cooperation of the patient. Therefore, these factors should be considered in the treatment of the patient. A variety of techniques have been reported to prevent the recurrence of pterygium[2,12,19], with lower recurrence rate and complications, the limbal conjunctival autograft technique has been suggested to lower the recurrence rate, the theory of which is that we can restore the anatomic integrity of the corneal limbus and supplement limbal stem cell[7,20].

During this process, some 0.5 mm of limbus corneal tissue of the graft is contained and attached to the limbal region of the bare area of the sclera. However, the mechanism of this skill has still been uncertain. Limbal conjunctival has only a theoretical advantage over the conjunctival autograft technique in terms of transplanting limbal stem cells and reconstructing the structure. The barrier function of the corneal limbus will be guaranteed once again and the pterygium recurrence will be much lower. The recurrence rates in the use of limbal conjunctival autograft technique were between 0% and 15%[7,21-22]. Both these techniques are considered demanding and time-consuming. In our study the average surgery time was 25.7±2.6min.

During the operation, we need to pay attention to three details: 1) remove the pterygium as thoroughly as possible; 2) match the size of the graft with the size of the exposed sclera, with 0.5 mm limbal stem cell tissue; 3) the graft should be flat and the conjunctival epithelium should face up. The greatest advantage of our research is its long follow-up period of 3y. We found that limbal conjunctival autograft technique is a safe and efficacious method to achieve a lower recurrence rate and complications of primary pterygium. This method not only has no vision-threatening complications but provides optimal cosmetic results. One limitation of our study is the lack of randomized clinical trials on limbal conjunctival autograft technique. Because there were no control group, the effect of this technique on the management of primary pterygium could not be compared with other operations. Secondly, there was a limited number of patients in our study. Therefore, further prospective randomized studies are required to support the findings of our research with a larger series. Thirdly, the factor that all these surgeries were performed by only one surgeon makes it difficult to draw a conclusion that all primary pterygiums performed will have the similar recurrence rate and complications.

In conclusion, there is evidence to suggest that the limbal

conjunctival autograft operation appeared to be a good, reliable technique in terms of recurrence rate and complications after pterygium excision. An optimal pterygium surgical technique should be safe, with low recurrence rate and complications as well as with good cosmetic results. Although the limbal conjunctival autograft in pterygium surgery is not the only technique to the problem, it may be the preferred treatment in spite of its extended operating time and discomfort from multiple sutures. Therefore, we recommend the limbal conjunctival autograft technique as the preferred technique in the treatment of primary pterygium because of its favorable outcomes in its long-term follow-up study. What is more, since there is no recurrence of pterygium after one year, we recommend that 12-month follow-up is optimal on primary pterygium surgery.

REFERENCES

1 Jaworski CJ, Aryankalayil-John M, Campos MM, Fariss RN, Rowsey J, Agarwalla N, Reid TW, Dushku N, Cox CA, Carper D, Wistow G. Expression analysis of human pterygium shows a predominance of conjunctival and limbal markers and genes associated with cell migration. *Mol Vis* 2009;15:2421-2434

2 Young AL, Cao D, Chu WK, Ng TK, Yip YWY, Jhanji V, Pang CP. The evolving story of pterygium. *Cornea* 2018;37(Suppl 1):S55-S57

3 Ozturk BT, Yildirim MS, Zamani A, Bozkurt B. K-ras oncogene mutation in pterygium. *Eye* 2017;31(3):491-498

4 di Girolamo N. Association of human papilloma virus with pterygia and ocular-surface squamous neoplasia. *Eye* 2012;26(2):202-211

5 Lan W, Petznick A, Heryati S, Rifada M, Tong L. Nuclear Factor-kappa B: central regulator in ocular surface inflammation and diseases. *Ocul Surf* 2012;10(3):137-148

6 Park CY, Choi JS, Lee SJ, Hwang SW, Kim EJ, Chuck RS. Cyclooxygenase-2-expressing macrophages in human pterygium co-express vascular endothelial growth factor. *Mol Vis* 2011;17:3468-3480

7 Kaufman SC, Jacobs DS, Lee WB, Deng SX, Rosenblatt MI, Shtein RM. Options and adjuvants in surgery for pterygium: a report by the American Academy of Ophthalmology. *Ophthalmology* 2013;120(1):201-208

8 Marsit N, Gafud N, Kafou I, Mabrouk A, Alatiweel A, Abdalla S, Sheghewi L. Safety and efficacy of human amniotic membrane in primary pterygium surgery. *Cell Tissue Bank* 2016;17(3):407-412

9 Rose L, Byrd JM, Qaseem Y. Subtenon injections of ranibizumab arrest growth in early recurrent pterygium. *Eye Contact Lens* 2017;43(6):399-405

10 Chen RX, Huang GF, Liu S, Ma WF, Yin XF, Zhou SY. Limbal conjunctival versus amniotic membrane in the intraoperative application of mitomycin C for recurrent pterygium: a randomized controlled trial. *Albrecht Von Graefes Arch Fur Klinische Und Exp Ophthalmol* 2017;255(2):375-385

11 Hwang S, Choi S. A comparative study of topical mitomycin C, cyclosporine, and bevacizumab after primary pterygium surgery. *Korean J Ophthalmol* 2015;29(6):375-381

12 Petrayevsky AV, Trishkin KS. Surgical treatment of pterygium. *Vestn Ophthalmol* 2018;134(1):85-88

13 Clearfield E, Muthappan V, Wang X, Kuo IC. Conjunctival autograft for pterygium. *Cochrane Database Syst Rev* 2016;2:CD011349

14 Koranyi G, Artzén D, Seregard S, Kopp ED. Intraoperative mitomycin C versus autologous conjunctival autograft in surgery of primary pterygium with four-year follow-up. *Acta Ophthalmol* 2012;90(3):266-270

15 Donepudi GD, Ramesh S, Govindarajulu M, Dhanasekaran M, Moore T, Ganekal S, Hiremath CS. Early postoperative outcomes of pterygium surgery: sutures versus autogenous serum *in-situ* fixation of limbal conjunctival autograft. *Life Sciences* 2019;221:93-98

16 Mednick Z, Boutin T, Einan-Lifshitz A, Sorkin N, Slomovic A. Simple limbal epithelial transplantation for recurrent pterygium: a case series. *Am J Ophthalmol Case Rep* 2018;12:5-8

17 Ozer A, Yildirim N, Erol N, Yurdakul S. Long-term results of bare sclera, limbal-conjunctival autograft and amniotic membrane graft techniques in primary pterygium excisions. *Ophthalmologica* 2009;223(4):269-273

18 Detorakis ET, Spandidos DA. Pathogenetic mechanisms and treatment options for ophthalmic pterygium: trends and perspectives (Review). *Int J Mol Med* 2009;23(4):439-447

19 Nuzzi R, Tridico F. How to minimize pterygium recurrence rates: clinical perspectives. *Clin Ophthalmol* 2018;12:2347-2362

20 Soliman Mahdy MA, Bhatia J. Treatment of primary pterygium: role of limbal stem cells and conjunctival autograft transplantation. *Oman J Ophthalmol* 2009;2(1):23-26

21 Malik KP, Goel R, Gutpa A, Gupta SK, Kamal S, Mallik VK, Singh S. Efficacy of sutureless and glue free limbal conjunctival autograft for primary pterygium surgery. *Nepal J Ophthalmol* 2012;4(2):230-235

22 Masters JS, Harris DJ Jr. Low recurrence rate of pterygium after excision with conjunctival limbal autograft: a retrospective study with long-term follow-up. *Cornea* 2015;34(12):1569-1572