Graefes Arch Clin Exp Ophthalmol
DOI 10.1007/s00417-008-0934-0

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Management of severe ocular burns with symblepharon

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Received: 6 March 2008 / Revised: 31 July 2008 / Accepted: 4 August 2008

Abstract
Background To evaluate the effect of lamellar keratoplasty combined with limbal stem cells, using amniotic membrane, autologous conjunctiva, and pseudopterygium to reconstruct external eyes for severe ocular burns with symblepharon.
Methods Thirty eyes of 29 patients had severe symblephara resulting from eye burns. According to the range of the symblepharon and the loss of limbal stem cells, partial lamellar keratoplasty combined with partial limbal stem cell treatment was performed in 19 eyes, and total lamellar keratoplasty with total limbus was performed in 11 eyes. All patients had amniotic membrane and autologous conjunctival transplantation, and the pseudopterygium was preserved to reconstruct the fornix.
Results Symblephara were completely relieved in 19 eyes. They remained partially in ten eyes in strip-like form, but seven of these were completely relieved after further autologous conjunctival transplantation. One eye was treated with tarsorrhaphy for eyelid malformation. The remaining pseudopterygium became thinner after the operation and showed no symblepharon. Immune rejection occurred in eight corneal grafts; clarity was restored in four of these, while there was graft neovascularization in the remaining four.
Conclusions Depending on the area of symblepharon and the loss of limbal stem cells, partial or total lamellar keratoplasty combined with limbal stem cells, using amniotic membrane, autologous conjunctiva and pseudopterygium to reconstruct external eyes appears to be effective in treating severe ocular burns with symblepharon. Pseudopterygium can partly substitute autologous conjunctiva in ocular surface reconstruction.

Keywords Eye burn · Symblepharon · Pseudopterygium

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A large number of patients suffer from ocular burns in China every year. Thermal and chemical burns have become major ocular injuries. Although the ocular surface can recover and gradually become stable after early management, the influence of the sequelae is permanent. Severe symblepharon at the late stage of ocular burns is one of the most challenging problems.

Symblepharon can be treated by various approaches. Obviously, the autologous conjunctival graft from the fellow eye can be used to restore destroyed conjunctiva [1]. For severe ocular burns, however, with involvement of the entire conjunctiva and cornea, reconstruction of the ocular surface often demands more mucosa than can be safely excised from the fellow eye. If an allogeneic conjunctiva is used, the graft would inevitably be confronted with immune rejection [2]. A gelatin sponge could not achieve favorable results for severe cases in preventing the formation of symblepharon [3]. Moreover, nasal mucosa is now used as an ideal substitute for the conjunctiva to relieve symblepharon, but its use cannot provide the eye with limbal stem cells, and the recurrence of symblepharon is high [4].

The extensive use of amniotic membrane has greatly improved the prognosis of acute ocular burns. However, the symblephara in severe burns cannot be treated with it [5, 6]. While it can lead to some success in treating mild symblepharon [7], amniotic membrane used as a patch is not effective in cases with severe stromal thinning and impending perforation [8]. Severe symblephara are often complicated, with large conjunctival deficiency, eyelid malformation, stem cell destruction, corneal opacification and corneal thinning. All these injuries are pathologically correlated with each other, but a single approach cannot resolve all the problems [9]. A combined surgery, including reconstruction of conjunctival sac, corneal transplantation and stem cell transplantation, might be more effective.

At our institution, from February 1998 to February 2003, we performed a combined operation in 30 eyes with severe symblephara resulting from eye burns. The surgical intervention depended on the extent of the symblepharon and the loss of limbal stem cells, and it included total or partial lamellar keratoplasty (LK) with limbal stem cells, amniotic membrane transplantation, and autologous conjunctival transplantation. Pseudopterygium was reserved as a substitute to reconstruct the fornix. The results were encouraging.

Patients and methods

Patients

Thirty eyes of 29 nonconsecutive patients with severe symblephara resulting from eye burns were recruited at our institution between February 1998 and February 2003. The mean age of the patients was 27.6 years (range, 16 to 53 years). The visual acuity was from hand movement to 0.8. The mean duration between injury and surgery was 36.9± 9.7 months (range, 8 to 60 months). The injuries included thermal burns by hot metal in 20 eyes (19 patients), alkaline burns in four eyes and acidic burns in six eyes.

The eligible eyes from patients in the study met the following inclusion criteria: (1) intact exact light location and intact color sensing of red and green; (2) tear film test showed either a mean Schirmer I test score≥10 mm (23 eyes), or a Schirmer I score <10 mm but Schirmer II score≥10 mm (seven eyes); (3) normal preoperative intraocular pressure (22 eyes), or pressure >21 mmHg that could be adjusted to normal range (four eyes); (4) no obvious changes of vitreous body and retina, as detected by B-scan ultrasound.

Clinical manifestation and surgical methods

All eyes had an extensive symblepharon in the inferior or superior fornix, and the cornea was partially or completely adhered to the symblepharon. The vision was obviously restricted in 19 eyes (Figs. 1a, 2a). The corneal limbus was destroyed with whole corneal neovascularization in eleven eyes (Fig. 3a).

All surgeries were performed with peribulbar anesthesia using 2% lidocaine and 0.75% bupivacaine. First, the pseudopterygium was removed from the cornea and sclera. The symblepharon was separated as completely as possible, until the eye globe could move freely, and the eyelid could shut completely. Then, the fibrous tissues under the pseudopterygium were separated by blunt dissection and excised to expose the exposed sclera. All the pseudopterygium was reserved during the whole process.

Second, total or partial LK was performed. When the eye was treated with partial LK, a mark between healthy and unhealthy areas of recipient bed was made using a trephine with a diameter of 11 to 12 mm. The cornea was cut by a depth of one half to three fourths of the corneal stroma along the mark. We ensured that the relatively healthy limbus was not cut, and then the neovascularized tissues were dissected and peeled away layer by layer using a sharp blade. Usually, two to three dissections were needed until the recipient bed became transparent. Only the Descemet's membrane remained in five patients. In this way, the relatively healthy cornea and limbus were preserved as much as possible. Thereafter, a fresh donor globe obtained within 24 h after

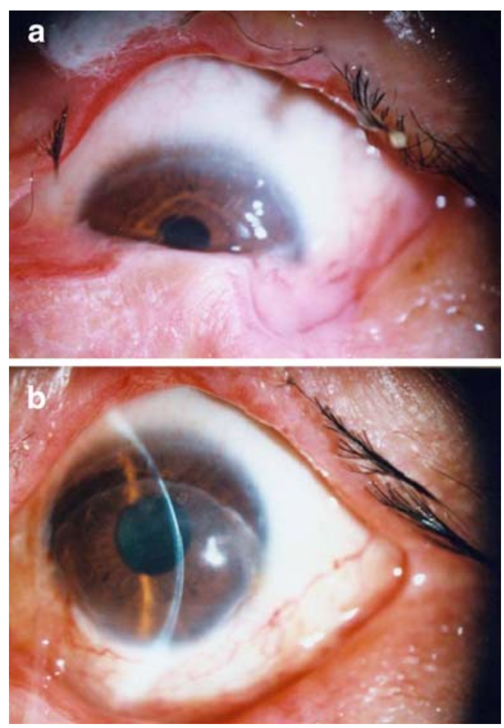

Fig. 1 **a** Extensive symblepharon occurred in the inferior fornix, the whole inferior fornix disappeared, and half of the cornea was adhered to it. **b** Symblepharon was completely released at 6 months after the partial LK

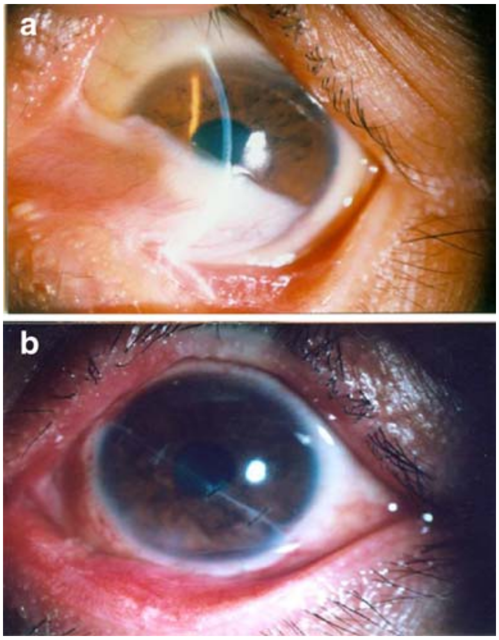

Fig. 2 **a** Symblepharon occurred in two quarters of the cornea, and the inferior fornix disappeared partially. **b** Symblepharon was completely released 6 months after partial LK

death and preserved in moisture chamber was slightly wrapped with disinfectant gauze. We used a trephine or a diamond knife to make a mark on the donor cornea. The diameter of donor tissues was 0.5 mm larger than the recipient

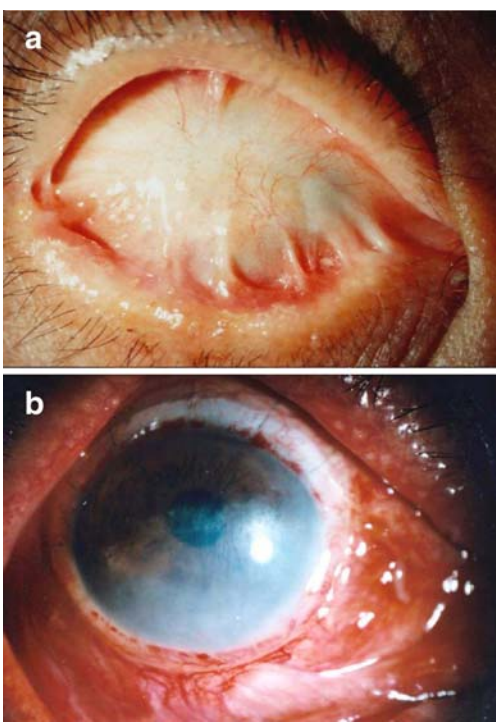

Fig. 3 **a** Extensive symblepharon completely covered the whole cornea, and all limbal stem cells were destroyed. **b** Symblepharon was completely released after total LK with limbal transplantation

bed, especially in the quarter with loss of stem cells (Fig. 4). Then, the full thickness corneal graft containing the limbus was placed into the recipient bed. The endothelium and Descemet's membrane of the graft were peeled away using a sharp blade before the donor button was sutured into the recipient bed with interrupted 10–0 nylon sutures. Patients with whole corneal neovascularization or complete symblepharon were treated with total LK with a total allogenic cornea and limbus. The surgical procedure was the same as that for the partial LK.

Third, the reconstruction of conjunctival fornices was performed. We receded the remaining pseudopterygium as the replacement of palpebral conjunctiva and fixed it inside the surface of eyelid with 10–0 nylon sutures, as well as on the exposed sclera and the fornix using amniotic membrane. A 4 ×6 mm of conjunctiva from the fellow eye was transplanted to the most seriously impaired area and sutured to the episclera. After the remnant conjunctival defect area was covered with routinely disposed amnion [5], which was fixed on the limbus with 10–0 nylon sutures, we had the entire ocular surface covered with a sheet of amnion.

Postoperative treatment

All patients were given intravenous cortisol (1–2 mg/kg) for 3 days immediately after the operation, after which prednisone (1 mg/kg was administrated for approximately during 1 month with a tapering of the dosage. The patients with total LK were also treated with oral cyclosporine A (4~6 mg/kg per day) for the first week, then 3~4 mg/kg per day for the following 6 months, and 2~3 mg/kg per day for at least 1 year. In conjunction with this treatment, 1% cyclosporine A eye drops, TobraDEX eye drops (Alcon, Fort Worth, TX), and artificial tears were used four times daily. When the conjunctival hyperaemia disappeared, TobraDEX eye drops were tapered. The 1% cyclosporine A eye drops were given for at least 1 year, and artificial tears were used for a longer time. The fellow eye that provided limbal and conjunctival grafts was given 3% ofloxacin eye drops four times daily (Tarivid, Santen, Osaka, Japan) for 2 weeks after the surgery.

All the patients were followed-up every 2 weeks for the first 2 months, monthly in the next 3 months, and thereafter at different intervals. Improvement of the conjunctival sac, corneal graft rejection, development of conjunctival limbal autograft, and fates of the remaining pseudopterygium and transplanted amniotic membrane were recorded. Nonparametric statistics were used to compare the preoperative and postoperative visual acuity.

Postoperative complications, such as immune rejection, and interbedded blood or fluid, were addressed appropriately [10]. The eyes with a persistent epithelial defect that was not controlled by medications received tarsorrhaphy

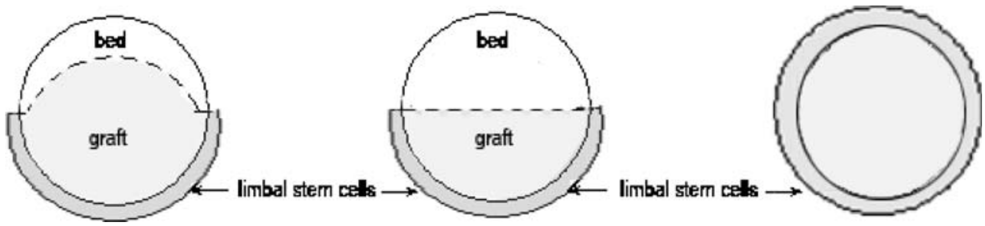

Fig. 4 *Dashed lines* separate the healthy and unhealthy cornea. We used a trephine or a diamond knife to make a mark on the donor cornea and the limbus and to cut the area with a blade. The diameter of the donor tissue was larger than the recipient bed, especially in the quarter with loss of stem cells

until the epithelium was completely healed. The patients with obvious recurrent symblepharon were recorded and treated with further symblepharon separation combined with conjunctival limbal autograft transplantation at 1 to 3 months after the first surgery. We obtained a conjunctival patch from the relatively healthy fornix or the follow eye to cover the lesions.

Statistical analysis

Data was analyzed using SPSS 10.0 software. The Chi-square test or Fisher's exact test were applied wherever applicable. A value of $p<0.05$ was considered statistically significant.

Results

The mean follow-up of the patients was 22 months (range, 12 to 48 months).

Reconstruction of conjunctival sac

Symblephara were completely released in 19 eyes (63.3%) at 3 months after surgery (Fig. 1b), and there was no recurrence among these. Ten eyes (33.3%) had recurrence of band-like symblepharon at the conjunctival lesion covered only with amniotic membrane; seven of these had further symblepharon separation combined with conjunctival limbal autograft transplantation. After 1 year, symblepharon was completely released in seven of the ten eyes (Fig. 2b), and mild symblepharon remained in three eyes (Fig. 3b). In the 30 operated eyes, the conjunctival autograft of one eye suffered edema and shrank because of irreformable lagophthalmos, and symblepharon recurred. The corneal epithelial defect in the eye was treated with tarsorrhaphy and eyelid dysraphism to retain the eye globe.

Development of transplanted amnion and pseudopterygium

All the transplanted amnia began autolyzing at 1 week after surgery. When the sutures were taken out at 2 weeks, the amnia covering the defect area fell off in 23 eyes. Recurred symblepharon was observed in the area covered with amnion. The remnant amniotic membrane could hardly be detected at 1 month and completely disappeared on the third postoperative month.

The reserved pseudopterygium was hyperaemic and thick shortly after the operation, but atrophied when the inflammatory response quieted down. There was no distinct difference in appearance compared with natural conjunctiva at 6 months after surgery (Figs. 1a, 2a, 3a).

Corneal graft

On the second postoperative day, interbedded blood or fluid occurred in six eyes; two of these eyes had blood between the corneal graft and recipient beds and received operations to clear out the blood for prevention of the corneal ensanguining. The blood between the donor and recipient bed faded away at 1 week, while the interbedded fluid in the other four eyes disappeared gradually within 1 week.

When the amnion above the graft sutures was removed on the 14th postoperative day, the corneal epithelia were intact in 21 eyes. Visual acuity is from finger counting to 0.6. Five eyes with epithelial defect were treated only with ointment to accelerate the epithelialization. Three of these re-epithelialized within 1 to 2 weeks, and the other two suffering persistent epithelial defects were treated with temporary tarsorrhaphy after 1 month. One was opened after 2 months, and the epithelium was completely healed. Another one was left closed because of irreformable lagophthalmos, as mentioned above.

Eight eyes, including five with thermal burns and three with alkaline burns, suffered corneal immune rejection at 3 to 6 months after surgery, showing corneal edema, opacity, and neovascularization. Four of them had restored clarity after local and systematic anti-rejection treatment, but the other four became neovascularized. The rejection did not recur, and the remnant new vessels gradually shrank until only vessel traces could be seen at 1 year after the surgery. The postoperative visual acuity was from 0.02 to 1.0, with a significant difference compared with that before the operation ($\chi^2=12.04$, $p<0.001$) in 29 eyes, except for one eye with tarsorrhaphy.

Discussion

Severe ocular burns, especially thermal burns, can destroy the eyelid, conjunctiva, limbal stem cells, and cornea. Because of extensive tissue necrosis, severe late-stage burns inevitably result in severe symblepharon, which significantly affects visual acuity. In this study, we performed the appropriate operation according to the area of symblepharon and the corneal condition to achieve better results in the management of severe ocular burns with symblepharon.

In our patients, both stem-cell transplantation and keratoplasty were needed. Partial LK could be performed in those with relatively healthy stem cells. For those patients with total stem cell destruction and whole corneal neovascularization, total LK was required. The efficacy of LK using fresh donor tissues containing limbus combined with conjunctival limbal autograft transplantation and amniotic membrane transplantation was evaluated so as to provide evidence for the best approach for a one-stage surgery such as external eye reconstruction and reconstruction of the conjunctival fornices. The aim of partial or total LK is to recover the corneal transparency and stimulate the growth of epithelium.

Severe burns may result in diverse symblephara due to the absence of conjunctiva and the loss of stem cells. Autologous conjunctival transplantation (first using the conjunctiva of the wounded eye and if not enough, using the conjunctiva of the fellow eye) or nasal mucosal transplantation was useful for mild symblephara [4, 9] but not effective for severe ones [11]. It is difficult to obtain extensive autologous conjunctiva from the healthy fellow eye, especially when the patient is injured bilaterally. Allogenic conjunctiva may be used as a substitute, but there was a high risk of transplant rejection, and, eventually, conjunctival graft rejection may have a negative influence on the outcome of penetrating keratoplasties in these high-risk patients [12]. Various other substitutes such as lip mucosa [13] and buccal mucosa [14] have been used to prevent the recurrence of symblepharon and reconstruct the ocular surfaces with unfavorable results. Autologous nasal mucosa transplantation was considered promising [4]; unfortunately, the long-term outcome was also here not ideal.

Previously, we used amniotic membrane as a substitute to treat symblepharon, but there were many recurrences (the results are not shown here). In this study, all the recurrent symblepharon occurred in the area covered only with amnion. All the transplanted amnia disappeared within 3 months. We hypothesized that amnion could alleviate inflammation and serve only as a temporary shelter. It could not substitute for conjunctiva completely.

Pseudopterygium growing onto the cornea could prevent infections of the damaged tissues. Conventionally, however, pseudopterygium was excised during the operation. In this study, we peeled off the pseudopterygium from the cornea and preserved it to reestablish conjunctiva palpebrae. We designed the operation this way for several reasons: (1) tissues that are conventionally discarded can be utilized effectively; (2) preservation of pseudopterygium can obviously diminish the conjunctival defect, requiring fewer conjunctival grafts to reestablish ocular surface; (3) pseudopterygium is an autologous tissue, and there is no immune rejection. We found that the hyperaemia of the eye began fading away at 1 to 3 months after the operation. Subsequently, the preserved pseudopterygium became gradually atrophied. There was no significant difference in appearance compared to natural conjunctiva at postoperative 6 months. This may be related to the reduction of related cytokines after the corneal epithelial reconstruction. Whether the reserved pseudopterygium resembles the natural conjunctiva in tissue construction and function remains unclear, and a further investigation is necessary.

The leading cause of pseudopterygium is the destruction of the corneal stem cells and persistent defects of the corneal epithelium. Autologous corneal stem cell transplantation has been proven to be effective [11, 15, 16], but the source is limited. Allogenic stem cell transplantation is another alternative. However, allogenic grafts usually suffer immune rejection, and the recurrence rate of pseudopterygium is fairly high [17, 18]. Even if few new vessels extend into the cornea, the function of superior limbal stem cells cannot be assessed as complete dysfunction as their function is only temporarily depressed. When the inflammatory response subsides, the "shocked" stem cells might revive, and the new vessels retreat. Therefore, in this study, if limbal stem cells were not completely destroyed, we tried to perform partial LK instead of total LK to save the autologous limbus of the cornea. And a large diameter trephine was indispensable, which made it feasible that more healthy stem cells could be obtained during the operation. Also, this could facilitate the inosculation of corneal grafts with recipients. To further confirm the outcome of stem cell transplantation, we used fresh donor tissues in a moisture chamber no more than 24 h after death and preserved the corresponding corneal limbus in corneal transplantation. By this means, the limbal autograft and allograft could reinforce each other in the severely destructed areas. The exposed sclera of the symblepharon in these patients was very large. The amnion covered the exposed sclera, and autologous conjunctiva was sutured on the most serious symblepharon area. Thus, we could save more autologous conjunctiva and avoid excessive damage to reconstruction. In this study, we observed that the recurrence was present on the amnion surface in a strip-like shape, which made the secondary surgeries easier. The patients were treated with topical and systemic immunosuppressives. The success rate was improved significantly.

Although a one-step operation is logical, an appropriate multi-step operation is sometimes more effective. If the symblepharon is too severe, a complete separation would result in extensive conjunctival defects, it is difficult to obtain a substitute, and the recurrence rate of symblepharon may be high. Therefore, we did not separate the symblepharon completely in one step as long as the eye globe could turn freely and the eyelid could shut completely. Except for the case where the remnant symblepharon still influenced vision, a further operation was not necessary. Even if the influence was small, the remnant symblepharon was greatly lessened. We could easily separate it and cover the wound area with a small healthy autologous conjunctiva. It should be emphasized that the autologous conjunctiva was best obtained from the superior fornix of the suffering eye, as excessive external aids might result in dysfunction of the stem cell and conjunctiva in the fellow eye. We observed that the conjunctival fornices could be used one to three times for transplantation without any influence on the functions, because the conjunctival fornices were loose and large enough.

In summary, a one-stage combined surgery was necessary for severe symblepharon resulting from late-stage eye burns. The principles we upheld were as follows: (1) try to save the autologous limbus of cornea as much as possible; (2) first use the conjunctiva of wounded eye for transplantation, and if that is not sufficient, use that of the fellow eye; (3) the pseudopterygium can partly substitute for autologous conjunctiva in ocular surface reconstruction; (4) the amniotic membrane transplantation is best only for the temporary construction of the conjunctival fornices, and the membrane on the exposed sclera has a partial effect in preventing symblepharon recurrence. More attention should be given to the major postoperative complications of immune rejection and corneal epithelial defects. It is important that the treatment for a symblepharon varies according to the severity of the eye burn.

Acknowledgement This study was supported in part by the Qingdao Municipal Science and Technology Bureau (02KGYSH-01). The authors thank Ms. Ping Lin for her editorial assistance.

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