Limbal Allografting From Living-Related Donors to Treat Partial Limbal Deficiency Secondary to Ocular Chemical Burns

Ting Huang, MD, PhD; Yujuan Wang, MD; Hong Zhang, MD; Na Gao, MD; Andina Hu, MD

Objective: To evaluate outcomes of limbal allograft transplantation from living-related donors to treat partial limbal deficiency secondary to ocular chemical burns.

Methods: Retrospective noncomparative case series comprising 17 patients (17 eyes) with partial limbal deficiency (≤50%) secondary to ocular alkali burns (11 eyes) or acid burns (6 eyes). Recipient eyes were treated by removing the conjunctivalized pannus. Superior limbal grafts (mean length, 3-5 clock hours) from HLA antigen–matched living-related donors were transplanted into deficient areas of recipient eyes. No recipients received systemic cyclosporin A therapy. Main outcome measures included corneal reepithelialization, reduction in vascularity, improved corneal clarity, and best-corrected visual acuity.

Results: All eyes achieved epithelialization a mean (SD) of 10.1 (1.9) days after surgery. Corneal reepithelialization, reduction in vascularity, and improved corneal opacity were seen in all eyes. No eyes demonstrated recurrent epithelial defects or fibrovascular tissue, but gradual recurrence of peripheral corneal vascularization was observed in 7 eyes during the follow-up period. Allograft rejection developed in 3 eyes (17.6%), all of which were successfully treated. Best-corrected visual acuity improved in all eyes, and 10 eyes (58.8%) had achieved best-corrected visual acuity of 0.5 or better (≥20/10 Snellen) at the last follow-up visit.

Conclusions: Transplantation of limbal tissue from live-related donors successfully reconstructed the ocular surface. Long-term graft survival in patients with partial limbal deficiency secondary to ocular chemical burns can be accomplished without the use of systemic immunosuppression.

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Limbal stem cells are located at the base of the limbal epithelium and are responsible for repopulation of cells in the corneal epithelium and for inhibition of conjunctival growth over the cornea. Limbal stem cell dysfunction or limbal deficiency can lead to ocular surface abnormalities, which are characterized by chronic epithelial defects, stromal inflammation, corneal vascularization, conjunctival epithelial ingrowth (conjunctivalization), and corneal opacification. Ocular chemical burns are the primary cause of limbal stem cell deficiency.

Stem cell transplantation is effective to treat limb stem cell deficiency. For patients with unilateral limbal deficiency, the contralateral eye can provide healthy limbal tissue for limbal autograft transplantation, whereas for patients with severe bilateral limbal deficiency, only homologous limbal tissue can be used for kerato-limbal allograft transplantation. Unfortunately, the graft rejection rate is high in allograft transplantation, and long-term systemic immunosuppressive treatment is required for these patients.

Theoretically, limbal allograft transplantation from an HLA antigen–matched living-related donor is a means to achieve long-term graft survival. However, to minimize damage to the cornea of the healthy donor, a limited amount of limbal tissue is obtained, and this is insufficient to reconstruct the ocular surface of patients with severe total limbal deficiency. Moreover, graft rejection can occur even in eyes with limbal allograft transplantation from HLA antigen–matched living-related donors. Among eyes with severe total limbal deficiency, previous studies have shown that long-term efficacy of limbal allograft transplantation from living-related donors is low. Herein, we propose an alternative procedure of limbal allografting from living-related donors to treat partial limbal deficiency secondary to chemical ocular burns.
METHODS

STUDY DESIGN

The study adhered to tenets of the Declaration of Helsinki. Approval of the study was obtained from the Institutional Review Board of Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China. Seventeen eyes of 17 patients undergoing living-related limbal allograft transplantation at Zhongshan Ophthalmic Center between February 4, 2005, and September 27, 2007, were retrospectively reviewed. All the involved eyes had partial limbal deficiency (≤50%) secondary to ocular alkali burns (11 eyes) or acid burns (6 eyes). Among the patients, 5 had unilateral injury, and 12 had bilateral injury; in all the patients, transplantation was performed in only 1 eye. Information obtained from patient medical records included age, sex, nature and duration of injury, best-corrected visual acuity, and prior medical management. Preoperative and postoperative states of the involved eyes were recorded using slitlamp photographs. Variables examined included degree of conjunctivalization or pannus, corneal vascularization, corneal opacification, epithelial defect status, and symblepharon formation. Degree of severity in all the patients was judged by one of us (T.H.). Preoperative patient data are given in Table 1 and Table 2.

Donors were evaluated before surgery to exclude the possibility of stem cell compromise. The nondominant eye of the donor was chosen for limbal tissue donation. Information obtained from donor records included reepithelialization time of the donor site, postoperative ocular discomfort, corneal vascularization, and visual acuity.

### Table 1. Preoperative Characteristics of Patients Undergoing Limbal Allografting From Living-Related Donors

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Nature of Burn Injury</th>
<th>Duration of Injury Before Surgery, mo</th>
<th>Follow-up Period, mo</th>
<th>Prior Surgery</th>
<th>Combined Surgery</th>
<th>Indication for Surgery</th>
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<td>26</td>
<td>SR, AMT, LAT</td>
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Abbreviations: AMT, amniotic membrane transplantation; CLE, correction of lower lid ectropion; CN, corneal neovascularization; LAT, limbal allograft transplantation from cadaveric donor; PED, persistent epithelial defect; PES, pseudopterygium; RP, removal of pannus; SR, symblepharon release; SYM, symblepharon.

### Table 2. Preoperative Stem Cell Deficiency in Patients Undergoing Limbal Allografting From Living-Related Donors

<table>
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<tr>
<th>Patient No.</th>
<th>Size of Superior Limbal Graft, Clock Hours</th>
<th>Degree of Conjunctivalization or Pannus</th>
<th>Corneal Vascularization</th>
<th>Corneal Opacification</th>
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</table>

Abbreviations: +, mild; ++, moderate; ++++, severe.
Indication for surgery was noted in all the patients. These included conjunctivalization of the corneal surface and corneal neovascularization (n=17), persistent epithelial defect (n=4), pseudopterygium combined with amniotic membrane transplantation (n=3), and symblepharon formation (n=3).

The nature of the surgical procedure was explained to all the patients and donors. Informed consent forms were signed by all the patients and donors before surgery. In 13 patients (76.5%), the donors were their mothers, and in 4 patients (23.5%), the donors were their fathers. HLA antigen typing was performed for all surgical procedures. Criteria for HLA antigen typing were similar to those adopted for high-risk penetrating keratoplasty, with some modifications, and patients and donors with a maximum of 2 mismatches on HLA-A, HLA-B, and HLA-DR loci were considered HLA antigen matched.

SURGICAL TECHNIQUE

All the procedures were performed by one of us (T.H.). Adult donors and recipients were operated on using retrobulbar anesthesia, and child recipients were operated on using general anesthesia. Surgery on the recipient was performed following surgery on the donor. Donor limbal tissue was harvested from the superior corneal limbus. The size of the donor area varied among eyes. The mean length was 3 to 5 clock hours and extended 2 mm on the conjunctival surface and 1 mm on the corneal epithelium. The donor site was left unsutured. A conjunctival peritomy adjacent to the deficient area in the recipient cornea was performed, and the limbal conjunctiva was undermined and allowed to retract posteriorly. The donor graft was secured in the recipient bed using a 10-0 nylon suture after the pannus was dissected and cauterized. The conjunctival portion of the graft was sutured to the underlying epithelial tissue, and the corneal edge of the graft was left unsutured. At the end of the procedure, the eye was patched to maintain pressure of the graft on the recipient bed.

Patients were given oral prednisone (30 mg/d) for 1 week before surgery and intravenous dexamethasone sodium phosphate (10 mg/d) combined with cefotaxime sodium (1.5 mg/d) for 3 days after surgery. When the cornea was reepithelialized, the recipient eye was treated with topical dexamethasone sodium phosphate (0.1%) every 2 hours, topical tobramycin sulfate (0.3%) 4 times daily, and topical tear substitutes 4 times daily. Topical corticosteroids were discontinued 3 to 4 months after surgery. No patients received systemic cyclosporin A or other systemic immunosuppressants.

Study data are given as means (SDs). The mean interval between ocular trauma and surgery was 15.5 (4.0) months (range, 9-22 months).

Before living-related limbal transplantation, patients in the study had undergone the following procedures: symblepharon release, amniotic membrane transplantation, and limbal transplantation from cadaver donor tissue (4 eyes [patients 1, 4, 7, and 11 in Table 1]); removal of the conjunctivalized pannus and limbal transplantation from cadaver donor tissue (6 eyes [patients 2, 5, 6, 9, 13, and 16 in Table 1]); removal of the conjunctivalized pannus, amniotic membrane transplantation, and limbal transplantation from cadaver donor tissue (2 eyes [patients 8 and 12 in Table 1]); and correction for lower eyelid ectropion (2 eyes [patients 10 and 14 in Table 1]). The mean follow-up period was 16.0 (4.2) months (range, 12-26 months).

After surgery, complete corneal reepithelialization was seen in all the patients, and no epithelial defects were observed during the follow-up period (Figure 1). The mean complete epithelialization was 10.1 (1.9) days (range, 7-14 days). Fibrovascular tissue did not recur in any eye. Preexisting peripheral neovascularization partially regressed at 1 to 3 months after surgery. However, gradual recurrence of corneal neovascularization occurred 7 to 10 months after surgery in 7 eyes, and mild symblepharon was seen in 3 eyes (Figure 2). Corneal opacification improved in all eyes (Figure 3).

After surgery, 3 eyes developed presumed allograft rejection at 3½ (patient 9), 5 (patient 4), and 6 months (patient 14), and these patients exhibited sectoral conjunctival injections, local epithelial defects, graft edema, and ocular pain. All 3 eyes were successfully treated with intensive topical corticosteroids and with high-dose intravenous dexamethasone sodium phosphate (10 mg/d for 3 days), followed by oral prednisone (1 mg/d/kg) for 2 to 3 months.

Best-corrected visual acuity improved in all the eyes during the follow-up period after surgery. Visual acuity in 5 eyes decreased gradually because of recurring peripheral neovascularization but was still better com-
pared with preoperative visual acuity. No eyes required secondary penetrating or lamellar keratoplasty for improvement of visual acuity.

Donor eyes were followed up for 3 months after surgery. All the eyes achieved reepithelialization within 5 days. No donors experienced vision loss, and postoperative courses were unremarkable.

Thirteen of 17 eyes had a maximum of 2 mismatches on HLA-A, HLA-B, or HLA-DR loci (ie, were HLA antigen matched). The other 4 eyes had more than 2 mismatches, and 3 of these eyes developed presumed graft rejection. Outcomes of living-related limbal allograft transplantation are summarized in Table 3.

Although limbal autografting provides excellent results in unilateral disease,15-18 ocular surface reconstruction is challenging in patients with bilateral limbal deficiency.15 Treatment of bilateral disease, which resulted from ocular chemical burns among patients in this study, requires allograft tissue transplantation. Heterologous limbal tissue can be obtained from cadaveric donors or from living-related donors.10,12,13,19

Although the cornea is considered an “immune privileged” site,24-26 transplantation of tissue into a vascularized limbus theoretically increases the risk of rejection.24,27 Previous studies12,20,22 have shown that HLA antigen matching is important in graft survival. However, the lengthy preservation time needed for HLA antigen matching results in limbal stem cell dropout.27 Furthermore, complete immunohistocompatibility between cadaveric donors and recipients is rarely obtained. As an alternative option, limbal allografting from living-related donors provides an approach for stem cell transplantation with some degree of histocompatibility.

COMMENT

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In previous studies, surgeons reported successful ocular surface reconstruction using limbal tissue from HLA antigen–matched living-related donors. However, there are obvious disadvantages in using living-related limbal allografts because limbal allografting is limited by the amount of tissue that can be transplanted. Clinically, a superior limbal graft length of 5 or 6 clock hours is the limit to protect a donor’s eyes and keep them healthy, whereas more limbal tissue and stem cells can be obtained from a cadaveric donor to restore the barrier to the entire limbus.

In severe total limbal stem cell deficiency secondary to severe chemical burns and Stevens-Johnson syndrome, the disadvantages of living-related limbal allograft transplantation, such as limited stem cell transplantation, may outweigh the benefits. Rao et al reported that 7 of 9 eyes achieved initial reepithelialization after living-related limbal allografting but that vascularization recurred in all the eyes after surgery. In another study, Shimazaki et al observed recurrence of conjunctivalization in eyes with limbal autografting or cadaveric limbal allografting. This indicates that transplanted limbal stem cells were unable to sustain sufficient long-term epithelial cell production for the entire limbus. Therefore, we performed living-related limbal allograft transplantation only in eyes with partial limbal deficiency (≤50%) secondary to chemical burns.

Controversy exists about surgical strategies in the case of partial stem cell deficiency. For partial stem cell deficiency with conjunctivalized epithelium on the cornea, sequential-sector conjunctival epitheliecctomy should be considered first. It preexists on the recipient cornea; this may aggravate inflammation of the host cornea after surgery. Limbal transplantation can remove neovascularization, recover the normal corneal architecture (rather than stem cells), and improve the microenvironment of the ocular surface, alleviating inflammation, reducing graft rejection, and improving graft survival after surgery.

All 17 eyes herein achieved successful ocular surface reconstruction, with complete corneal epithelialization, reduced neovascularization, and improved corneal opacification. In our series, the mean time to complete reepithelialization of 10.1 (1.9) days was shorter than the 13.4 (6.4) days reported by Rao et al. A possible explanation for this is that our patients had partial limbal deficiency instead of total limbal deficiency, as in the study by Rao et al, although the surgical procedures and amount of transplanted limbal tissue were similar between the 2 studies.

The rejection rate in our series was less than that in previous studies. In eyes with a presumed graft rejection, all grafts survived following the use of topical and systemic corticosteroids, and no systemic immunosuppressive agents, such as cyclosporin A, were administered. Variations in the use of immunosuppressive agents may explain the difference in rejection rates between our series and previous studies.

In patients with partial stem cell deficiency. However, in partial stem cell deficiency with a fibrovascular pannus covering the cornea, the pathologic entity tends to involve the stroma, except for the corneal epithelium. In contrast to conjunctivalized epithelium, fibrovascular pannus is difficult to scrape or brush off completely using topical anesthesia, and abnormal epithelium may remain on the denuded corneal surface. Abnormal epithelium influences contact inhibition of the corneal epithelium by the conjunctiva-derived epithelium. In partial stem cell deficiency with a fibrovascular pannus covering the cornea, limbal transplant may be required. Furthermore, sequential-sector conjunctival epitheliecctomy cannot remove superficial neovascularization that preexists on the recipient cornea; this may aggravate inflammation of the host cornea after surgery. Limbal transplantation can remove neovascularization, recover the normal corneal architecture (rather than stem cells), and improve the microenvironment of the ocular surface, alleviating inflammation, reducing graft rejection, and improving graft survival after surgery.

The rejection rate in our series was less than that in previous studies. In eyes with a presumed graft rejection, all grafts survived following the use of topical and systemic corticosteroids, and no systemic immunosuppressive agents, such as cyclosporin A, were administered. Variations in the use of immunosuppressive agents may explain the difference in rejection rates between our series and previous studies.

Table 3. Outcomes of Limbal Allografting From Living-Related Donors

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<td>15</td>
<td>13</td>
<td>Reduced</td>
<td>20/1000</td>
<td>20/33</td>
<td>Mother/matched</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>Reduced-recurred</td>
<td>20/3333</td>
<td>20/100</td>
<td>Mother/matched</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>17</td>
<td>12</td>
<td>Reduced-recurred</td>
<td>20/250</td>
<td>20/40</td>
<td>Mother/mismatched</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: +, mild.

*Opacification improved in all patients after transplantation.*
tions in residual amounts of limbal stem cells among re-
cipient eyes may have contributed to different outcomes
herein vs previous studies. Eyes in this study had partial
stem cell deficiency, with 50% or more healthy stem cells.
Even if graft rejection after living-related limbal allograft
transplantation resulted in stem cell dropout, the amount
of residual stem cells was able to sustain sufficient epithe-
リアル cell production. Compared with rejection rates
reported by Kwitko et al20 (25%), Rao et al22 (33.3%), and
Daya and Ilari27 (25%), our rejection rate of 17.6% (3 of
17 eyes) was lower, despite not administering cyclospor-
in A, and overall graft survival seemed better.

Ocular status of the recipient may influence overall graft
survival. Rao et al22 demonstrated that unsatisfactory sur-
gical outcomes after living-related limbal allografting can
result from limbal ischemia due to advanced alkali burns.
In their study of living-related conjunctival limbal al-
lografting, Daya and Ilari27 reported that 2 of 10 eyes did
not achieve initial epithelialization because of severe in-
flammation. That study indicated that severe inflamma-
tion may be a major prognostic indicator of early graft fail-
ure. In our case series, all eyes of recipients were in a stable
late stage of chemical burns, and most patients under-
went prior surgical procedures to correct ocular structure
abnormalities. All patients received systemic corticosteroids
before and after limbal allografting to combat inflamma-
tion. These strategic procedures may partly account for
the differences in outcomes between this and previous
studies.

In our series, graft rejection occurred in 3 of 17 eyes,
and the use of topical and systemic corticosteroids alone
(without cyclosporin A) successfully inhibited rejection
and prolonged graft survival. Our experience suggests that
limbal allografting from living-related donors may not
require systemic immunosuppression. In contrast, Rao
et al22 and Shimazaki et al27 indicated that systemic im-
munosuppression is necessary even in HLA antigen–
matched limbal allografting. In their series, limbal allografting
in severely vascularized eyes was considered a high-risk transplantation. The Collaborative Con
eral Transplantation Studies research group reported that HLA
antigen compatibility is irrelevant to survival of high-
risk corneal grafts,24,31 and other researchers state that
patients require postoperative systemic immunosuppres-
sion even if their donors were HLA antigen matched.21,22
In comparison, the patients in our series were consid-
ered low risk because all the eyes were in the stable late
stage of chemical burns and had only partial limbal stem
cell deficiency. Previous studies24,31 have shown that cor-
neal allografting may result in approximately a 90% sur-
vival rate in uncomplicated and low-risk eyes without
the use of systemic immunosuppressive drugs. Some study,
6,12,20 findings have reported that a good HLA antigen match,
in which 2 or more class I antigens were matched, pro-
vided long-term graft survival in corneal allografting. In
developing nations, systemic immunosuppressive drugs,
such as cyclosporin A, are costly, and long-term use seems
impossible. Our study provides encouraging findings for
patients with partial stem cell deficiency.

In summary, limbal allograft transplantation from
living-related donors is effective for eyes with partial
(≤50%) limbal stem cell deficiencies resulting from
chemical burns. Partial stem cell deficiency may be the
best indication for living-related limbal allografting.
Moreover, the graft failure rate herein was low even
without application of systemic immunosuppressants.
Limbal allograft transplantation from living-related
donors is a good option for individuals with bilateral
partial stem cell deficiency.

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Author Contributions: Dr Huang had full access to all
the data in the study and takes responsibility for the in-
tegrity of the data and the accuracy of the data analysis.
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Ravin has pointed out that three ophthalmologists have been awarded Nobel Prizes, the most noted being Allvar Gullstrand (1862-1930), but also Fritz Pregl (1869-1930) and Walter Hess (1881-1973) for work in other fields. One other ophthalmologist, Johan Albin Dalén (1866-1940) accepted, but did not win, a Nobel. His brother Nils Gustaf Dalén (1869-1937) was awarded the 1912 Nobel Prize in Physics for his invention of a regulator for beacons on lighthouses and buoys. Earlier that year Gustaf was blinded in a laboratory explosion, and his brother accepted his prize for him. Albin worked at the Karolinska Institute and is best remembered for his description of the characteristic pathology of sympathetic ophthalmia, Dalén-Fuchs nodules.