

Unilateral Partial Limbal Stem Cell Deficiency: Contralateral Versus Ipsilateral Autologous Cultivated Limbal Epithelial Transplantation

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- PURPOSE: To report the outcomes of autologous cultivated limbal epithelial transplantation using the healthy part of the affected eye or the fellow eye as a source of limbal stem cells in patients with unilateral, partial limbal stem cell deficiency (LSCD).
- DESIGN: Retrospective, nonrandomized, interventional case series.
- METHODS: **SETTING:** L. V. Prasad Eye Institute, Hyderabad, India. **STUDY POPULATION:** Patients with unilateral, partial LSCD who underwent autologous cultivated limbal epithelial transplantation between 2001 and 2011. **INTERVENTION:** The limbal biopsy was taken either from the healthy part of the limbus of the same eye (ipsilateral group) or from the healthy fellow eye (contralateral group). Cells were cultivated using a xeno-free explant culture technique, and cultivated cells were transplanted onto the affected surface. **PRIMARY OUTCOME MEASURE:** Success of cultivated limbal epithelial transplantation, defined as a completely epithelialized, avascular, and clinically stable corneal surface.
- RESULTS: Seventy eyes of 70 patients were studied. The mean follow up was 17.5 ± 7 months. In 34 eyes the limbal biopsy was taken from the ipsilateral eye and in the remaining 36 eyes from the contralateral eye. Clinical success was achieved in 70.59% of eyes in the ipsilateral group and 75% of eyes in the contralateral group ($P = .79$). Limbal transplant survival rates at the final follow-up visit were $65.1\% \pm 0.09\%$ in the ipsilateral group and $53.6\% \pm 0.12\%$ in the contralateral group ($P = .74$).
- CONCLUSIONS: Ocular surface restoration in partial LSCD is possible with cell-based therapy. Outcomes are

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similar irrespective of whether the limbal biopsy is taken from the healthy part of the ipsilateral eye or the contralateral eye. (Am J Ophthalmol 2014;157:584–590. © 2014 by Elsevier Inc. All rights reserved.)

THE EPITHELIUM OF THE CORNEA IS THE FIRST SURFACE of the eyeball exposed to the external environment, and it constantly undergoes a process of renewal. A healthy, functional corneoscleral limbus is considered to be essential to normal corneal epithelial homeostasis. The limbus is believed to be a repository of stem cells, which constantly replenish the cells lost during epithelial turnover.¹ Limbal stem cell deficiency (LSCD) clinically manifests with recurrent or persistent epithelial defects, vascularization, pannus formation, conjunctivalization of the corneal surface, and loss of normal corneal clarity.²

Cell-based therapy using limbal stem cell transplantation (LSCT) for restoration of the ocular surface in limbal stem cell deficiency has been used with good results at various centers across the world.^{3,4} Our group has reported a success rate of 71% at a mean follow-up of 3 years in a series of 200 eyes with unilateral total LSCD treated with autologous cultivated limbal epithelial transplantation.⁵ Similarly, in 50 eyes with unilateral LSCD following a failed primary procedure, we have reported a success rate of 66% at a mean follow-up of 2.3 years using repeat autologous cultivated limbal epithelial transplantation.⁶ However, limited literature exists on management of partial LSCD.⁷⁻¹³

The conventional paradigm of cultivated limbal epithelial transplantation in unilateral LSCD rests on harvesting a limbal biopsy from the contralateral eye, cultivating it in a laboratory, and transplanting the resultant epithelial sheet onto the affected eye.^{5,14} In cases with partial LSCD, there are clinically normal-appearing areas of the limbus in the affected eye. We hypothesized that it may be possible to harvest limbal stem cells from the healthy part of the limbus in eyes with partial LSCD and cultivate them *ex vivo* for transplantation onto the same eye. We have been using the healthy part of the limbus in eyes with partial LSCD as a source of stem cells for cultivated limbal epithelial transplantation for many years. To the best of our knowledge, no study thus far has reported such a procedure, or compared the outcomes with conventional cultivated limbal epithelial transplantation using the

contralateral healthy eye as the source of limbal biopsy. This led us to the study question: Does the source of limbal biopsy (ipsilateral or contralateral eye) affect the outcome of autologous cultivated limbal epithelial transplantation for unilateral, partial LSCD? Our hypothesis was that it does not.

The purpose of this study was to compare outcomes of autologous cultivated limbal epithelial transplantation for unilateral, partial LSCD, using the healthy part of the affected eye or the fellow eye as a source of limbal stem cells in patients with partial LSCD.

METHODS

- **STUDY DESIGN AND SUBJECTS:** This was a retrospective, nonrandomized, interventional case series. This study was approved by the Ethics Committee of L. V. Prasad Eye Institute, Hyderabad, India, and was conducted in strict adherence to the tenets of the Declaration of Helsinki. Prior written informed consent was obtained from all patients or guardians, as appropriate for the surgical procedure. Charts of all patients who underwent cultivated limbal epithelial transplantation for the treatment of limbal stem cell deficiency between January 1, 2001, and December 31, 2011 were reviewed. Patients who underwent autologous cultivated limbal epithelial transplantation for unilateral (defined as no clinical signs of ocular surface disease in the other eye) and partial LSCD (defined as superficial corneal vascularization, diffuse fluorescein staining of the corneal surface with or without persistent epithelial defects, conjunctivalization of the corneal surface involving the visual axis, and absence of the palisades of Vogt in less than 360 degrees of the limbus) were included in this study.

The following exclusion criteria were applied: (1) patients who had bilateral LSCD or had allogeneic limbal transplantation; (2) patients with dry eye disease (Schirmer test without anesthesia of <10 mm in 5 minutes); (3) patients with no visual potential, as determined by clinical examination and electrophysiological testing; (4) patients with untreated concurrent problems, such as entropion, trichiasis, glaucoma, and infection; (5) patients with age at injury of less than 8 years.

- **DATA COLLECTION:** The following parameters were collected: age and sex of the patient; date and etiology of LSCD; details of prior surgery (if any); best-corrected visual acuity (Snellen) at presentation and at each follow-up visit; extent of symblepharon (in clock hours); extent of limbal involvement (in clock hours); duration between injury and cultivated limbal epithelial transplantation; details of surgery performed, including source of limbal biopsy (ipsilateral or contralateral eye); duration of follow-up; and ocular surface status at each visit. Patients were divided into 2 groups, based on whether the limbal biopsy was

obtained from the healthy part of the ipsilateral eye or from the contralateral eye.

- **OUTCOME MEASURES:** The primary outcome measure in each group was success of cultivated limbal epithelial transplantation, defined as a completely epithelialized, avascular, and clinically stable corneal surface. Failure was defined as recurrence of superficial corneal vascularization, persistent epithelial defects, or conjunctivalization of the cornea. Survival time was calculated from the date of surgery to the date of failure or last follow-up, as per the outcome. Secondary outcome measures were change in best-corrected visual acuity (BCVA) and complications, if any, in each group.

- **TECHNIQUE OF LIMBAL BIOPSY:** A collage of clinical photographs showing the difference in limbal biopsy techniques in the 2 groups is shown in [Figure 1](#). The choice of the source of limbal biopsy—either from the healthy part of the limbus of the affected eye or from the healthy contralateral eye—was made at the discretion of the operating surgeon (V.S.S.), who has extensive experience in limbal stem cell transplantation techniques. For the limbal biopsy, a limbus-based conjunctival flap was raised, and dissection in the subconjunctival plane was carried out toward the limbus, extending 1 mm into clear cornea. Conjunctiva posterior to the pigmented palisades was incised, and less than 2 clock hours of pigmented limbus tissue was obtained ([Supplemental Video](#), available at [AJO.com](#)).

- **TECHNIQUE OF LIMBAL CULTURE:** Our technique of limbal culture has been described earlier.¹⁵ Briefly, the biopsied tissue was transported in human corneal epithelium medium to the stem cell laboratory, where it was shredded into small pieces and placed on the basement membrane side of de-epithelialized human amniotic membrane. A feeder cell-free submerged explant culture system was used to obtain a confluent monolayer of epithelial cells, usually at 10-14 days.

- **TECHNIQUE OF LIMBAL TRANSPLANTATION:** Symblepharon release was done, if it prevented insertion of an eye speculum. Peritomy was performed and fibrovascular pannus excision was carried out, starting from the peri-limbal sclera and proceeding inward onto the cornea. Apparently healthy areas of limbus were not disturbed. The human amniotic membrane with the monolayer of cultivated epithelial cells was transferred to the ocular surface with the epithelial side facing up, and was secured to the surface using either sutures or fibrin glue (TISSEEL Kit; Baxter AG, Vienna, Austria).

- **POSTOPERATIVE MANAGEMENT:** Topical medication included 1% prednisolone acetate eye drops, started 8 times per day and tapered to once daily by 4-6 weeks, as well as 0.3% ciprofloxacin hydrochloride eye drops used 4 times

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