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ORIGINAL ARTICLE

Simple limbal epithelial transplantation method in the treatment of unilateral limbal stem cell deficiency due to chemical burn

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Abstract

Purpose: The objectives of the study were to evaluate the success of the simple limbal epithelial transplantation (SLET) method in the treatment of unilateral limbal stem cell deficiency (LSCD) due to chemical burn.

Methods: Seventeen patients with unilateral LSCD due to chemical burn were included in this retrospective study. Mean age of patients was 50.3±20.8 (28–75) years. Mean duration of follow was 18.9±6.9 (12–24) months. In the recipient eye following peritomy, pannus tissue was cleared and covered with amniotic membrane with fibrin glue. Limbal stem cell received from the fellow eye was implanted cornea surface 2–3 mm inside limbus with fibrin glue on the amniotic membrane and placed contact lens. In control examination of all patients who completed minimum 12 months postoperatively, regression in corneal vascularization, duration of epithelial healing, visual acuity, need for keratoplasty, and complications (dropping of contact lenses, separation of amniotic membrane, and graft failure) were evaluated.

Results: Corneal epithelization was completed between 4 and 6 weeks in all patients. Total and partial separations in the amniotic membrane occurred in two patients. Marked regression in corneal vascularization and increase in visual acuity was observed in all patients. Five patients (29.4%) underwent keratoplasty in the follow-up period. Limbal failure did not occur in healthy eyes. In two patients (11.7%), corneal vascularization recurred after 6 months.

Conclusion: SLET technique is an efficient method in unilateral LSCD in that it requires a lesser amount of donor tissue than keratolimbal autograft transplantation. Moreover, regress vascularization before keratoplasty in LSCD eyes may decrease graft rejection rates.

Keywords: Chemical burn; fibrin glue; limbal stem cell deficiency; Limbal stem cell transplantation.

Corneal blindness continues to be the second most common cause of blindness in the developing world.[1] Out of all the causes for corneal blindness, ocular burns carry a poor prognosis as they may result in damage to the limbal stem cells and cause limbal stem cell deficiency (LSCD).[2] Chemical eye injuries can affect patient's visual acuity and quality of life. There are various treatment approaches in acute and chronic period. Accomplished management of each stage of the disease results in the improved visual outcome and reduced complication rates.[3,4] LSCD is char-

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acterized by chronic epithelial defects, neovascularization, conjunctivalization, and stromal inflammation, leading to corneal opacification and loss of vision.[5,6] Since penetrating keratoplasty (PK) carries a poor prognosis in these patients, various other treatment modalities have been described over the past few decades.[7]

Stem cells located in limbal region are required for regular regeneration of epithelial layer and protection of avascular structure of cornea. Thus, transparency of cornea is maintained. Damage in limbal stem cells with various causes results in corneal vascularization and impairment of corneal epithelization.[1] Ocular surface burn is a common reason for LSCD.[8] In LSCD, treatment is adjusted according to the severity of disease. Lubrication of ocular surface, suppression of ocular surface inflammation, surface reconstruction with amniotic membrane, scleral lens employment, and transplantation of limbal tissue are among treatment options. In patients with unilateral LSCD, keratolimbal autograft (KLAL), cultured limbal epithelial transplantation (CLET), and simple limbal epithelial transplantation (SLET) are recommended, while in bilateral LSCD KLAL, allogenic CLET is preferred.[9–11]

SLET method was developed by Sangwan et al.[12] in 2012. In patients with unilateral LSCD, minimal donor tissue was transplanted from health eye. Transplanted tissue covered with amniotic membrane was placed over cornea, making in vivo spread of limbal stem cells possible. SLET technique eliminated the need for the excessive amount of limbal tissue which may lead to iatrogenic LSCD in the healthy eye and also in case of failure, tissue cannot be obtained again. Opposite to allograft transplantations which have a high risk of tissue rejection and require immunosuppressive treatment, SLET seems to be an advantageous method.

The aim of the current study was to evaluate the success of SLET method in unilateral LSCD eyes.

Materials and Methods

The patients who had SLET surgery due to LSCD secondary to chemical burns were involved in this study. The records of the patients were documented retrospectively. The study was performed in adherence to the tenets of the declaration of Helsinki and approved by Ankara City Hospital local ethics committee. The patients who had at least 12 months regular follow-up period were included in the study. Exclusion criteria were history of any other ocular disease, atopy, systemic disease (diabetes, hypertension, renal, or hepatic dysfunction), other LSCD causes and incomplete ophthalmology visits.

The diagnosis of LSCD was made with slit-lamp biomicroscopic examination based upon the absence of pigmented Vogt palisades, irregularity in cornea when stained with fluorescein, persistent epithelial defect, fibrovascular pannus, and conjunctivalization of corneal surface. LSCD in at least 2 quadrants underwent SLET. Total LSCD was seen in 3 eyes (17.6%) and 14 eyes (82.3%) had partial LSCD ranging from 6 to 9 clock hours of limbal involvement.

LSCD was described in 3 stages based on the amount of corneal and limbal involvement in biomicroscopic examination. Staging was defined depending central corneal involvement, such as normal corneal epithelium in central 5 mm (Stage I), affected central 5 mm of cornea (Stage II), and affected entire corneal surface (Stage III). In addition, limbal involvement was defined as substages (A, B, C) whether 0–100% of limbal cells are affected.[13] During visits, regression in corneal vascularization, duration of epithelial healing, visual acuity, need for keratoplasty, and complications (dropping of contact lenses, separation of amniotic membrane, and graft failure) were evaluated.

Visual acuity values were measured Snellen chart then convert to their logMAR results. Mean visual acuity was calculated by adding up all patients visual acuity according to logMAR then divided patients number.

Surgical Procedure

Two-hour quadrants of limbal tissue were removed from healthy eye using crescent knife and vannas scissors. In the recipient eye, after 360° peritomy was carried out, pannus tissue was cleared. Epithelium was completely removed. Amniotic membrane which was prepared previously and kept at −80° was placed to the extent of the peritomy with fibrin glue. Limbus tissue obtained from a healthy eye was divided into 8–10 pieces and distributed to all cornea surfaces 2–3 mm inside limbus on the amniotic membrane with fibrin glue and operation was completed by placing therapeutic contact lens. In post-operative treatment, topical moxifloxacin 0.1% drop (Vigamox®, Alcon) was used for 1 week and topical dexamethasone 0.1% drop (Maxidex®, Alcon) was performed 8 times a day for 1 week and dose was tapered during first 6 weeks.

Statistical Analysis

Data were analyzed using SPSS version 15.0. Descriptive statistics were expressed with mean±standard deviation and minimum-maximum. Changes in visual acuity were evaluated Wilcoxon signed-rank test and $p<0.05$ was considered statistically significant.

Results

A total of 17 eyes of 17 patients (1 female, 16 male) were enrolled. The mean age of the patients was 50.3±20.8 (28–75) years. The mean follow-up was 18.9±6.9 (12–24) months. Causes of chemical burn were alkali 11 eyes (64.7%), acid 5 eyes (29.4%), and unknown 1 eye (5.8%). The demographic characteristics of the patients and causes of LCHD were presented in Table 1. The median duration after injury to SLET procedure was 12 months (range: 6–45 months). The median duration of follow-up time was 15 months. Mean corneal epithelialization time was 5.14±1.02 (4–6 weeks) in patients. One patient (5.8%) had a total separation of the amniotic membrane and one patient (5.8%) had partial amniotic separation of the amniotic membrane. In these patients, the amniotic membrane was sutured to the surface and contact lenses were placed again. The other amniotic membranes were removed when contracted and separated from the corneal surface. Fibrovascular pannus and conjunctivalization of corneal surface regressed in all patients. LSCD was not observed in eyes with limbal stem cells. Table 2 shows the success and failure rates across different parameters. When a complete healing of epithelial defect and avascular corneal surface was evaluated as success criteria, our success rate was 88.23% (15 of 17 patients) (Stage I). Two male patients with alkali injury (11.7%) had revascularization after 6 months, but it did not reach to central 5 mm cornea (Stage II). These patients were treated with conjunctival recession and weekly subconjunctival bevacizumab for 3 months, but no regression was shown in two cases. Post-operative mean visual acuity (according to logMAR) was increased compared to pre-operative period after SLET (1.98±0.07, 0.66±0.05, respectively, p=0.001).

While pre-operative period visual acuity was <20/200 in 7 (41.1%) eyes, between 20/40 and 20/200 in 10 eyes (58.8%), after 6 month SLET period, visual acuity was <20/200 in 3 eyes (17.6%), between 20/40 and 20/200 in 13 eyes (76.4%) and >20/40 in 1 eye (5.8%). Five patients (29.4%) underwent keratoplasty at least 6 months after SLET. The images of eye who underwent SLET after chemical injury are shown in Figure 1a-c.

Table 1. Severity and cause of LSCD

	Total (n=17) (%)
Limbal stem cell deficiency stages	
Stage I	(3 eyes, 17.6)
Stage II	(11 eyes, 64.8)
Stage III	(3 eyes, 17.6)
Cause of chemical burn	
Alkali	11 (64.7)
Acid	5 (29.4)
Unknown	1 (5.8)

LSCD: Limbal stem cell deficiency.

Table 2. Primary outcome in subgroups

Characteristics	Total numbers	Success (%)
Gender		
Male	16	14 (87.5)
Female	1	1 (100)
Age		
<40	11	11 (100)
>40	6	4 (66.6)
Agents		
Alkali	11	9 (81.8)
Acid	5	5 (100)
Unknown	1	1 (100)
Time interval to SLET		
<12 months	10	9 (90)
>12 months	7	6 (85.7)

SLET: Simple limbal epithelial transplantation.

Discussion

In the treatment of LSCD depending on chemical burns, new methods have recently been developed. As classical

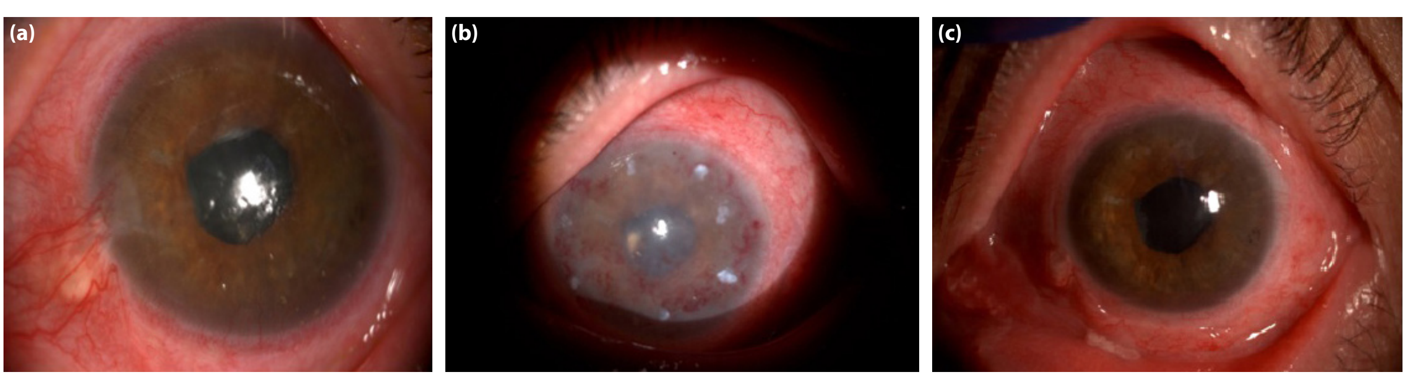

Fig. 1. **(a)** Partial limbal stem cell deficiency after chemical burn, **(b)** left eye ocular surface cover with amniotic membrane and after 1 week simple limbal epithelial transplantation (SLET), **(c)** left eye corneal vascularization regression after 2-month SLET

techniques used in the management of LSCD cause some complications and success rates are low, techniques using a lower amount of autograft have become more popular.[14,15] Among these techniques, SLET is one of the most popular. The aim of the present study is to evaluate the outcome of SLET procedure for the treatment of unilateral LSCD.

Chemical burn leads to high ocular inflammation, and the time between surgical intervention and chemical burn is very critical. Despite all of the interventions and anti-inflammatory treatment, further damage may continue and lead to severe vision loss.[16] Since ocular chemical burn is an emergency, treatment is prompt and should be begun with immediate continued irrigation. The purpose is supporting epithelialization, suppression of inflammation, and prevention of complications.[17] The milestones of treatment include lubrication, topical corticosteroid therapy, ascorbate, and biological medications. Amniotic membrane transplantation is a quick early-stage method for these patients. As it decreases inflammation and support epithelial healing. However, when corneal conjunctivalization is extensive, limbal stem cell transplantation is required, and final keratoplasty may be needed to improve visual acuity.[16] Inflammation should be controlled before limbal stem cell transplantation. In our study, we gave in an interval of at least 6 months for surgery after chemical burn.

Autologous limbal stem cell transplantation has been used successfully for about three decades and developed from conventional conjunctival limbal autografting to the more sophisticated methods such as SLET and CLET.[9,10] However, in CLET, 1×1 mm size tissue is obtained from limbal region and cultured in vitro to increase the number of cells and transplant again to the impaired eye. Success rate of this method has been established to vary between 73% and 100%.[18,19] There is no precise protocol for cell culture for CLET and it includes different substrates in culture media. Thus, success rates are variable.[20,21] Limbal cells are harvested from a healthy autologous or allogeneic donor limbus. Because of allogeneic cases, including the risk of immunoreactivity, autologous CLET grafts tend to show better outcomes compared with allogeneic in LSCD eyes.[22,23] Although it has advantages use of very little limbal tissue, possibility of repetition, and not needing for immunosuppressive treatment, cost is high because cell cultures are used.[24] Unlike CLET, SLET success is not affected by age and chemical cause. In our study, patients were predominantly male. Because male subjects work with chemicals much more than females, their ratio in these injuries is higher. Since we have only one female subject, we could not compare SLET success according to gender. When we looked at chemical cause 2 patients whose success was lower than others had alkali injury; however, the chemical cause did not affect the success rate.

Age-matched comparison studies show that SLET was more effective than repeat CLET in children. The author interpreted that though the size of the biopsy is the same as that in SLET, the biopsy is divided into two pieces, but only one is used for transplantation. Thus, the number of transplanted cells is higher in SLET than CLET.[24] The success of SLET in this study was 88.23% at a median follow-up of 15 months. This is more or less comparable to the recent data about SLET. Some major SLET studies done in recent years have described their success as 76% (Basu et al.),[26] 66% (Jain et al.),[25] and 83% (Vazirani et al.),[27] with a mean follow-up period of 35.5 months, 6.2 months, and 12 months, respectively. In addition, SLET may be a reasonable alternative in unsuccessful CLET cases.[28,29] For example, in the study of Basu et al.,[29] when CLET surgery failed in 30 cases of unilateral chemical burn, SLET was shown to be successful, with an increase of visual acuity, regression in conjunctivalization, and vascularization in 80% of patients. They stated that SLET is a good alternative method in LSCD after CLET failure. Moreover, they claimed that the number of effective cells may be higher in SLET as fresh limbal stem cell is transplanted without undergoing any laboratory procedure.

The advantages of SLET have been reported to be its low cost, no need for laboratory infrastructure and no requirement for immunosuppressive treatments. In the multicentric study, 68 autologous SLET operations have been carried out in eyes with LSCD. When a complete healing of epithelial defect and avascular corneal surface is considered as success criterion, 57 cases (83.8%) success was reported to be obtained. After 12 months of follow-up, the presence of symblepharon and keratoplasty procedures in the same session was found to be associated with clinical failures.[29] Many studies were shown that the simultaneous performance of PK with SLET correlates the graft rejection. In addition, SLET evolves the corneal environment, which may promote self-clearing of the stroma. Thus, PK is recommended for at least a year after SLET.[30–32] In our cases, the success rate was 88.23%. The high success rate can be explained by the fact that we performed keratoplasty after waiting for at least 6 months, although the recommendation time 1 year, not in the same session, and the low prevalence of symblepharon in patients.

Singh et al.[31] described performance of deep anterior lamellar keratoplasty in pediatric patients 9–15 months post-SLET giving visual improvement of 64%. Lower success rate in children can be explained by more inflammation and undergo surgery earlier (before inflammation is fully controlled) in children.[32,33] Because of not including the pediatric case in the current study, our outcomes may have been more successful.

Although SLET has been described as a method of unilateral LSCD, in some studies, SLET was taken from the cadaver in patients with bilateral LSCD despite the risk of immune rejection. Although these studies have shown that SLET surgery from relatives or cadavers is beneficial in bilateral LSCD cases, the risk of rejection should always be kept in mind.[34,35] Therefore, transplantation of limbal stem cells to be obtained by stimulating pluripotent stem cells with developing technology will be beneficial for patients with bilateral LSCD.[36]

Our findings have to be considered in the context of the limitations of this study, which include its retrospective nature, the small number of eyes studied. The limited patient numbers did not allow the formation of subgroups and because of this small sample size. Furthermore, the absence of a control group who received solely medical therapy or limbal cell transplantation without amniotic membrane was another limitation of the study. Since there were not groups without using amniotic membrane, we could not comment on whether amnion has additional benefits.

Conclusion

SLET is a promising surgical method, especially in unilateral LSCD. The main advantage is the low cost due to the lack of laboratory dependence and no need for immunosuppression. To see long-term results, studies in larger series are needed about SLET.

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