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Outcomes of Limbal Stem Cell Transplant
A Meta-analysis

Qihua Le, MD, PhD; Tulika Chauhan, MD; Madeline Yung, MD; Chi-Hong Tseng, PhD; Sophie X. Deng, MD, PhD

IMPORTANCE Limbal stem cell transplant (LSCT) can be categorized as direct autologous limbal transplant (AULT), direct allogenic limbal transplant (ALLT), cultivated autologous limbal stem cells transplant (cAULT), and cultivated allogenic limbal stem cells transplant (cALLT). To our knowledge, there is no study directly comparing the outcomes and complications of these procedures.

OBJECTIVE To evaluate the outcomes of different LSCT procedures.

DATA SOURCE We searched PubMed, EMBASE, Web of Science, and Cochrane without language filter for peer-reviewed articles about LSCT. The latest search was performed on June 30, 2019.

STUDY SELECTION Clinical studies with the outcome of at least 20 eyes after LSCT were included. Animal studies and studies of other surgical interventions were excluded.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently abstracted the data from each study. Heterogeneity was evaluated with the I^2 statistic, and a meta-analysis was performed using the random-effects model.

MAIN OUTCOMES AND MEASURES Outcome measures included the improvement of ocular surface, visual acuity (VA), and adverse events of recipient eyes and donor eyes.

RESULTS Forty studies (2202 eyes) with a mean (SD) follow-up of 31.3 (20.9) months met the inclusion criteria. The mean (SD) age of study participants was 38.4 (13.1) years, and men accounted for 74%. The number of eyes that underwent AULT, ALLT, cAULT, and cALLT were 505, 742, 771, and 184, respectively. Improvement of the ocular surface was achieved in 74.5% of all eyes, 85.7% of eyes after AULT (95% CI, 79.5%-90.3%), 84.7% after cAULT (95% CI, 77.2%-90.0%), 57.8% after ALLT (95% CI, 49.0%-66.1%), and 63.2% after cALLT (95% CI, 49.3%-75.2%). Autologous limbal transplantation resulted in a greater VA improvement rate (76%) than did the other 3 procedures (cAULT: 56.4%; ALLT: 52.3%; cALLT: 43.3%; all $P < .001$). The most common adverse events in all recipient eyes were recurrent/persistent epithelial erosion (10.5%; 95% CI, 7.2%-23.3%) and elevated intraocular pressure (intraocular pressure, 1.7%; 95% CI, 0.5%-7.8%). Patients who underwent ALLT had the highest rate of recurrent epithelial erosion (27.8%; 95% CI, 17.1%-41.9%) and intraocular pressure elevation (6.3%; 95% CI, 1.8%-19.4%).

CONCLUSIONS AND RELEVANCE These findings suggest LSCT can improve or stabilize the corneal surface with a low rate of severe ocular complications and that autologous LSCT may have a higher success rate and fewer complications than allogenic LSCT.

Supplemental content

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Limbal stem cell deficiency (LSCD) is an ocular surface disease caused by a decrease in the population and/or function of limbal epithelial stem cells (LSCs), which leads to the inability to sustain the normal homeostasis of the corneal epithelium.[1] The treatment of LSCD is challenging. Keratoplasty will fail if the normal function of LSCs is not restored first. Medication is only effective in partial LSCD.[2] For eyes with severe or total LSCD, limbal stem cell transplantation (LSCT) is necessary to restore the population of LSCs. With a better understanding of the biology of LSCs and the advancement of microsurgery, substantial progress has been made in the surgical management of LSCD.

The surgeries involving LSCT can be divided into 2 groups: grafting (direct transplantation) of limbal tissues and transplantation of cultivated LSCs. The source of donor tissue can be autologous or allogeneic. The technique of direct transplantation can be further divided into conjunctival limbal autograft, conjunctival limbal allograft, keratolimbal allograft, and simple limbal epithelial transplantation (SLET). Transplantation of cultured LSCs mainly refers to cultivated limbal epithelial transplant. To our knowledge, no study has directly compared the outcomes and the complications of different types of LSCT. Although many studies indicate a higher success rate for autologous transplantation,[3,4] previous reviews and meta-analysis of LSCT reported conflicting results.[5-8] The purpose of this meta-analysis is to systematically evaluate the clinical outcomes and complications of autologous and allogeneic LSCT based on available literature.

Key Points

Question What are the outcomes of different limbal stem cell transplant (LSCT) procedures?

Findings In this meta-analysis that included 40 studies (2202 eyes), autologous LSCT had a significantly higher rate of restoration of the ocular surface and lower rate of complications than allogeneic LSCT. However, the criteria of LSCD grading and other efficacy outcome measures varied greatly among different studies.

Meaning These findings support autologous LSCT in favor of allogenic LSCT, but randomized clinical trials using standardized efficacy measures are necessary to determine whether one approach is more effective than the other.

Methods

Search Strategy

This study was approved by the institutional review board at the University of California, Los Angeles. We searched PubMed, EMBASE, Web of Science, and Cochrane to identify peer-reviewed, published articles that described relevant studies. The following search terms were used: "limbal stem cell deficiency" AND ("surgical treatment" OR "limbal transplantation" OR "cultivated limbal epithelial transplantation" OR "simple epithelial transplantation" OR "conjunctival limbal autograft" OR "conjunctival limbal allograft" OR "keratolimbal allograft"). We also reviewed the references from retrieved articles to identify additional related studies. Neither the language filter nor the publication time filter was used. The non-English articles were translated into English to obtain the needed information. The latest search was performed on June 30, 2019.

Eligibility Criteria

We sought prospective or retrospective interventional cohorts or case series, nonrandomized comparative or noncomparative studies, and randomized clinical trials. Studies that involved fewer than 20 eyes were excluded. Literature reviews, animal studies, laboratory studies without the assessment of clinical outcome, letters to the editor, correspondence, notes, editorials, and conference abstracts were also excluded. Studies of keratoprosthesis (Kpro), amniotic membrane transplant (AMT), optical keratoplasty (penetrating/deep anterior lamellar keratoplasty) after LSCT, and cultivated oral mucosal epithelial transplant were excluded. To compare the outcomes when different donor sources were used, studies were considered to be eligible only when the exact number of allografts and autografts, and their outcomes were provided separately in the publication. If multiple reports were published from the same authors at the same institutions, only the most recent studies with a larger number of patients and a longer follow-up were included to avoid redundant outcomes from an overlapping group of patients. (See details in eMethods in the Supplement).

Quality Assessment of Studies

A modified version of the Newcastle-Ottawa Scale was used to assess the quality of each cohort study.[9] The methodologic quality were evaluated independently by two authors (Q.L. and T.C.). In cases of disagreement, a third author (S.X.D.) was included to reach a consensus (eMethods in the Supplement).

Data Extraction

Two authors (Q.L. and T.C.) independently extracted the following demographic and clinical data from each study: study design, sample size, demographic characteristics, surgery type, postoperative treatment, and follow-up. The outcomes extracted from studies contained 3 aspects: restoration of an intact corneal epithelium, vision improvement, and complications (eMethods in the Supplement).

Statistical Analysis

Mixed-effects logistic models were used to analyze dichotomized outcomes, such as clinical success, with studies as random effects. Robust meta-analysis techniques[10,11] were used to estimate the change in LogMar VA before and after surgery. Study heterogeneity was quantified with I^2 statistic and evaluated with likelihood ratio test. Contour-enhanced funnel plots were generated to inspect publication bias.[12,13] A modified Macsskill test[14,15] was performed to examine publication bias. All tests were 2-sided and P less than .05 was considered statistically significant. All statistical analyses were carried out with R software (the R Foundation; eMethods in the Supplement).

Table 1. Demographic Characteristics of AULT, ALLT, cAULT, and cALLT

Characteristic	AULT	ALLT	cAULT	cALLT	*P* value
Studies, No. (%)	16 (28)	23 (40)	12 (20)	7 (12)	NA
Total sample size, No. (% of eyes)	505 (23)	742 (34)	771 (35)	184 (8)	NA
Mean sample size (range)	31 (10-125)	28 (6-165)	45 (7-200)	26 (8-80)	.19
Sex, No. (%)					
Male	297 (72)	332 (67)	577 (79)	108 (80)	<.001
Female	118 (28)	160 (33)	156 (21)	27 (20)	
Age, mean (IQR), y	30.8 (15.2-62.5)	41.8 (17-62.5)	46.5 (14.7-54.8)	36.8 (15.9-49)	.68
Etiology of LSCD, No. (%)					
Chemical burn/thermal injury	426 (84)	407 (55)	681 (88)	134 (73)	<.001
Chronic cicatricial ocular surface inflammation	15 (3)	152 (20)	13 (2)	28 (15)	
Others	64 (13)	183 (25)	77 (10)	22 (12)	
Range of LSCD, No. (%)					
Studies mentioned	11 (78)	10 (43)	6 (50)	5 (71)	.35
Percentage of total LSCD eyes	(74.5)	(98.7)	(79.2)	(86.3)	.66
Percentage of partial LSCD eyes	(25.5)	(1.3)	(21.8)	(13.7)	.14
Prior surgery, No. (%)					
Studies mentioned	9 (56)	4 (17)	8 (67)	2 (29)	.02
Percentage of eyes having prior surgery	(63.3)	(92.8)	(62)	(69.6)	.31
Percentage of eyes having prior LSCT	(34.2)	(25.8)	(4.9)	(13.2)	.23
Duration between Injury/onset of disease and surgery, mo (IQR)	37.3 (34.6-40)	42.3 (30.2-54.5)	30.5 (28.5-32.5)	36.3 (30.9-41.7)	.91
Follow-up, mean (IQR), mo	20 (6-47)	31.2 (12-109.2)	28.8 (9.7-96)	28.5 (12-57.6)	.12
Criteria used to define success, No. (%)					
Only "an intact epithelium and a stable ocular surface"	0	3 (13)	1 (8)	0	.23
"An intact epithelium and a stable ocular surface" plus 1 additional criterion	7 (44)	7 (30)	5 (42)	6 (86)	
"An intact epithelium and a stable ocular surface" plus 2 additional criteria	5 (31)	11 (48)	5 (42)	0	
"An intact epithelium and a stable ocular surface" plus 3 additional criteria	4 (25)	2 (9)	1 (8)	1 (14)	

Abbreviations: ALLT, allogenic direct limbal transplant; AULT, autologous direct limbal transplant; cALLT, allogenic cultured limbal stem cell transplant; cAULT, autologous cultured limbal stem cell transplant; IQR, interquartile range; LSCD, limbal stem cell deficiency; LSCT, limbal stem cell transplant; NA, not applicable.

Results

Literature Search

The original electronic database search identified 1159 nonduplicate articles, of which 1085 articles did not meet the inclusion criteria. The full text of the remaining 74 articles were reviewed. Forty studies[3,4,16-53] were eligible and included in this meta-analysis (eFigure 1 in the Supplement).

Characteristics of Included Studies

Details of all included studies are provided in eTable 1 in the Supplement. None of the included studies was a randomized clinical trial. Twenty-seven studies were retrospective or prospective cases series, 3 were retrospective cohort studies, and 10 did not have a clearly stated study design. Seventeen studies were comparative, and 23 were noncomparative. Three studies were conducted at multiple centers.

A total of 2202 eyes of 1999 patients were included for analysis (**Table 1**). Chemical burn and thermal injury were the leading indication for LSCT (1648 eyes [74.8%]) followed by chronic cicatricial ocular surface inflammation (Stevens-Johnson syndrome and mucous membrane pemphigoid; 208 eyes [9.4%]); and other etiologies in 346 eyes (15.7%). The extent of pretreatment LSCD involvement was reported for 1443 eyes (65.5%) in 23 studies. Total LSCD was diagnosed in 1232 eyes (85.4%), and partial LSCD in 211 eyes (14.6%). Only 18 studies (822 eyes [37.3%]) mentioned prior surgery before LSCT, and 78 eyes had prior failed LSCT.

All studies were divided into 4 subgroups based on surgical technique and donor source: autologous direct limbal transplantation (AULT; 505 eyes), allogenic direct limbal transplantation (ALLT; 742 eyes), autologous cultured LSC transplantation (cAULT; 771 eyes), and allogenic cultured LSC transplantation (cALLT; 184 eyes). Simple limbal epithelial transplantation was categorized as direct limbal transplantation because cell culture was not involved. The mean sample size, mean age, and mean length of follow-up were similar among the 4 subgroups (Table 1).

Clinical Outcomes

Clinical Success and Improvement

The criteria to define success and partial success varied greatly among studies. The criterion "the reconstruction of an intact epithelium and a stable ocular surface" was adopted by all studies. Nevertheless, 1 or more additional criteria were used to define success and partial success in 37 studies, which included "the absence/recession of corneal neovascularization" (30 studies; 81%), "vision improvement" (13 studies; 35%), "improvement of the cellular phenotype" (11 studies; 30%), and "improvement of ocular symptoms and/or vision-related quality of life" (10 studies; 27%).

The overall success rate of all LSCT was 67.4% (95% CI, 62.1%-72.3%), and the overall improvement rate of the ocular surface was 74.5% (95% CI, 69.3%-79.2%), with a mean (SD) follow-up of 31.3 (20.9) months. The highest success rates were achieved after AULT (83.2%; 95% CI, 76.7%-88.1%) followed by cAULT (71.8%; 95% CI, 62.2%-79.9%, $P = .02$). The success rates after ALLT (53.9%; 95% CI, 45.6%-62.1%) and cALLT (52.1%; 95% CI, 39.1%-65.0%) were significantly lower than that after AULT (both $P < .001$) and cAULT (cAULT [83.2%] vs ALLT [53.9%]; $P = .005$; cAULT [83.2%] vs cALLT [52.1%]; $P = .004$, respectively; **Figure 1**). The surface improvement rates of AULT (85.7%; 95% CI, 79.5%-90.3%) and cAULT (84.7%; 95% CI, 77.2%-90.0%) were similar ($P = .79$; **Figure 2**). Although the overall failure rate after all LSCT was only 25.5% (95% CI, 20.8%-30.7%), this rate was significantly higher for allogeneic transplantation (ALLT: 42.2%; 95% CI, 33.9%-51.0%; cALLT: 36.8%; 95% CI, 24.8%-50.7%) than for autologous transplantation graft (AULT: 14.3%; 95% CI, 9.7%-20.5%; cAULT: 15.3%; 95% CI, 9. 9%-22.8%; all $P < .001$; **Figure 3**).

Visual Outcome

Thirty-one studies (1654 eyes) used 2-line improvement of Snellen VA, presurgery and postsurgery logMar VA, or both to describe visual improvement. Nine studies (548 eyes) did not report visual outcomes.[18,22,23,27,32,33,36,39,44] Five hundred and sixty-seven eyes underwent penetrating/lamellar keratoplasty or cataract surgery after LSCT.

Among 1576 eyes from 28 studies,[3,4,17,20,21,24,26,28-31,34,35,37,38,40-43,45-53] 922 eyes (58.5%) obtained 2-line improvement of Snellen VA after LSCT. Fifteen studies provided the details of preoperative and postoperative VA (eFigure 2 in the Supplement).[16,19,21,25,26,31,34,38,40,43,45-47,50,53] Mean (SD) LogMar VA improved from 2.1 (0.2) before LSCT to 0.7 (0.2) after the surgery ($P < .001$). Of the 955 eyes for which detailed VA results were available, 582 eyes (60.9%; 95% CI, 50.5%-73.8%) retained functional VA (Snellen VA ≥20/200 or LogMar VA ≤1.0) at the final visit. Vision declined in 63 eyes (6.6%).

Autologous limbal transplant resulted in the highest rate of 2-line visual improvement (76.6%; 95% CI, 66.3%-84.4%), and this rate was greater than those of cAULT (56.4%; 95% CI, 45.0%-67.1%; $P = .008$), ALLT (52.3%; 95% CI, 43.1%-61.3%; $P < .001$), and cALLT (43.3%; 95% CI, 31.4%-56.1%; $P < .001$). Functional VA at the final follow-up was worse after ALLT (51.3%; 95% CI, 46.0%-56.5%) than after AULT (68.8%; 95% CI, 59.5%-76.8%; $P = .001$), cAULT (64.7%; 95% CI, 60.0%-69.2%; $P = .002$), and cALLT (64.5%; 95% CI, 51.9%-75.4%; $P = .03$).

Complications

Recipient Eye

The most common complication after LSCT was recurrent/persistent epithelial erosion at 10.5% (95% CI, 7.2%-23.3%). The rate of recurrent or persistent epithelial erosion after LSCT was higher with allogeneic transplants (ALLT, 28.8%; cALLT, 18.5%) than after autologous transplants (AULT, 4.3%; cAULT, 3.4%; ALLT [28.8%] vs AULT [4.3%]; $P < .001$; ALLT [28.8%] vs cAULT [3.4%]; $P < .001$; cALLT [18.5%] vs AULT [4.3%]; $P = .006$; cALLT [18.5%] vs cAULT [3.4%]; $P = .02$). The overall rate of IOP elevation after LSCT was 1.7% (95% CI, 0.5%-7.8%). The rate of IOP elevation was also higher after ALLT (6.3%; 95% CI, 1.8%-19.4%) than after AULT (0.8%; 95% CI: 0.1%-4.2%; $P = .002$) and cAULT (0.3%; 95% CI, 0.04%-3.9%; $P = .02$). Direct allogenic limbal transplant had a higher rejection rate (27.6%; 95% CI, 20.3%-36.4%) than cALLT did (5.2%; 95% CI, 1.9%-13.9%; $P < .001$).

The rates of complications after AULT and cAULT were lower than or similar to those after ALLT and cALLT (**Table 2**). The only exception was hemorrhage underneath amniotic membrane after cAULT in which amniotic membrane served as the cell carrier (9.2%; 95% CI, 3.5%-22.1%). The rates of other complications were low and similar among the 4 types of LSCT.

Donor Eye

The most common adverse event of donor eyes was hemorrhage at the donor site (AULT: 0.31%; 95% CI, 0.04%-7.3%; cAULT: 0.1%; 95% CI, 0%-6.2%). The overall rate of iatrogenic LSCD was extremely low (0.004%; 95% CI, 0.01‰-0.55%). Of the 1276 autologous transplants, only 1 case of iatrogenic LSCD at the donor site was reported in the AULT group (Table 2).

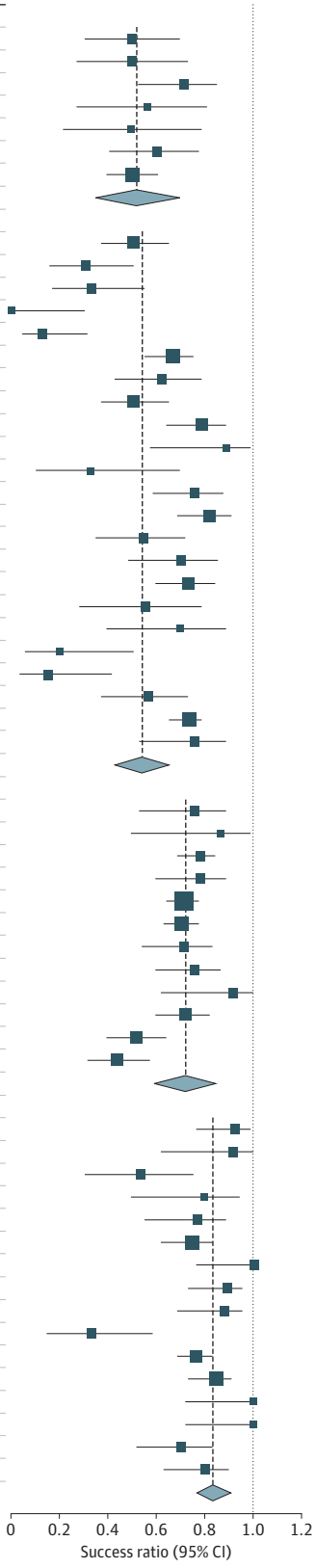
Other Factors Associated With Outcomes

Systemic immunosuppressive therapy often consists of 1 or more of the following medications: corticosteroids, tacrolimus, cyclosporine, mycophenoloate mofetil, and azathioprine.[23,24,28,31-34,36-38,49,50,53] Among 25 studies that used immunosuppression regimen, 5 studies in which a 3-medication regimen was used showed a higher success rate (81.2%; 95% CI, 65.0%-91.0%) than did those studies in which fewer immunosuppressants were used (odds ratio [OR], 3.844; 95% CI, 1.6-9.1; $P = .002$). However, the number and dose of medications were not associated with the improvement rate (OR, 2.575; 95% CI, 1.0-6.9; $P = .05$). Only long-term use of immunosuppressants yielded a higher success rate (74.9%; 95% CI, 57.3%-86.9%) and improvement rate (81.6%; 95% CI, 66.1%-91.0%; eTable 2 in the Supplement). Neither the dosage nor the duration of systemic corticosteroid therapy were associated with the clinical outcome.

In the 17 studies that evaluated cultivated LSCs, the cultivation methods without 3T3 feeder cells (327 eyes; 63%) resulted in a lower improvement rate than did the cultivation methods that used feeder cells (376 eyes [77%]; OR, 1.931; 95% CI, 1.3-2.9; $P = .001$). However, the use of 3T3 feeder cells

Figure 1. Forest Plots for Success Rate of Limbal Stem Cell Transplant

Author, y	No. eyes	Ratio (95% CI)
cALLT		
Shimazaki et al,[50] 2007	20	0.50 (0.30-0.70)
Pauklin et al,[46] 2010	14	0.50 (0.27-0.73)
Basu et al,[49] 2012	28	0.71 (0.53-0.85)
Ramirez et al,[41] 2015	9	0.56 (0.27-0.81)
Ganger et al,[42] 2015	8	0.50 (0.22-0.78)
Parihar et al,[29] 2016	25	0.60 (0.41-0.77)
Cheng et al,[48] 2017	80	0.50 (0.39-0.61)
Estimated rate		0.52 (0.39-0.65)
ALLT		
Tsubota et al,[38] 1999	43	0.51 (0.37-0.65)
Ilari et al,[37] 2002	23	0.30 (0.16-0.51)
Shimazaki et al,[24] 2004	21	0.33 (0.17-0.55)
Ozdemir et al,[25] 2004	9	0.00 (0.00-0.30)
Santos et al,[23] 2005	23	0.13 (0.05-0.32)
Maruyama-Hosoi et al,[36] 2006	85	0.66 (0.55-0.75)
Wylegala et al,[21] 2008	26	0.62 (0.43-0.78)
Wylegala et al,[21] 2008	43	0.51 (0.37-0.65)
Scocco et al,[35] 2008	39	0.79 (0.64-0.89)
Miri et al,[20] 2010	9	0.89 (0.57-0.99)
Miri et al,[20] 2010	6	0.33 (0.10-0.70)
Javadi et al,[33] 2011	32	0.75 (0.58-0.87)
Javadi et al,[33] 2011	40	0.82 (0.68-0.91)
Han et al,[34] 2011	24	0.54 (0.35-0.72)
Eberwein et al,[32] 2012	20	0.70 (0.48-0.85)
Baradaran-Rafii et al,[31] 2013	45	0.73 (0.59-0.84)
Barreiro et al,[27] 2014	11	0.55 (0.28-0.79)
Titiyal et al,[30] 2015	10	0.70 (0.40-0.89)
Titiyal et al,[30] 2015	10	0.20 (0.06-0.51)
Moreira et al,[18] 2015	13	0.15 (0.04-0.42)
Parihar et al,[29] 2016	25	0.56 (0.37-0.73)
Movahedan et al,[28] 2017	165	0.73 (0.65-0.79)
El-Hofi et al,[53] 2019	20	0.75 (0.53-0.89)
Estimated rate		0.54 (0.46-0.62)
cAULT		
Schwab et al,[47] 1999	20	0.75 (0.53-0.89)
Shimazaki et al,[50] 2007	7	0.86 (0.49-0.99)
Rama et al,[45] 2010	107	0.77 (0.68-0.84)
Pauklin et al,[46] 2010	30	0.77 (0.59-0.88)
Sangwan et al,[3] 2011	200	0.71 (0.64-0.77)
Pellegrini et al,[44] 2013	152	0.70 (0.63-0.77)
Vazirani et al,[17] 2014	34	0.71 (0.54-0.83)
Vazirani et al,[17] 2014	36	0.75 (0.59-0.86)
Ramirez et al,[41] 2015	11	0.91 (0.62-1.00)
Ganger et al,[42] 2015	54	0.72 (0.59-0.82)
Scholz et al,[40] 2016	61	0.52 (0.40-0.64)
Fasolo et al,[39] 2017	59	0.44 (0.32-0.57)
Estimated rate		0.72 (0.62-0.80)
AULT		
Kenyon et al,[26] 1989	26	0.92 (0.76-0.98)
Shimazaki et al,[24] 2004	11	0.91 (0.62-1.00)
Ozdemir et al,[25] 2004	15	0.53 (0.30-0.75)
Santos et al,[23] 2005	10	0.80 (0.49-0.94)
Wylegala et al,[21] 2008	21	0.76 (0.55-0.89)
Torres et al,[22] 2008	65	0.74 (0.62-0.83)
Miri et al,[20] 2010	12	1.00 (0.76-1.00)
Baradaran-Rafii et al,[31] 2012	34	0.88 (0.73-0.95)
Barreiro et al,[27] 2014	23	0.87 (0.68-0.95)
Moreira et al,[18] 2015	15	0.33 (0.15-0.58)
Basu et al,[49] 2016	125	0.76 (0.68-0.83)
Vazirani et al,[17] 2016	68	0.84 (0.73-0.91)
Arora et al,[16] 2017	10	1.00 (0.72-1.00)
Arora et al,[16] 2017	10	1.00 (0.72-1.00)
Gupta et al,[51] 2018	30	0.70 (0.52-0.83)
Basu et al,[4] 2018	30	0.80 (0.63-0.90)
Estimated rate		0.83 (0.77-0.88)



The highest success rates were achieved after direct autologous limbal transplant (AULT) followed by cultivated autologous limbal stem cells transplant (cAULT). The success rates after direct allogenic limbal transplant (ALLT) and cultivated allogenic limbal stem cells transplant (cALLT) were lower than that after AULT.

Figure 2. Forest Plots for Improvement Rate of Limbal Stem Cell Transplantation

Author, y	No. eyes	Ratio (95% CI)
cALLT		
Shimazaki et al,[50] 2007	20	0.50 (0.30-0.70)
Pauklin et al,[46] 2010	14	0.71 (0.45-0.88)
Basu et al,[49] 2012	28	0.71 (0.53-0.85)
Ramirez et al,[41] 2015	9	0.67 (0.35-0.88)
Ganger et al,[42] 2015	8	0.62 (0.31-0.86)
Parihar et al,[29] 2016	25	0.60 (0.41-0.77)
Cheng et al,[48] 2017	80	0.81 (0.71-0.88)
Estimated rate		0.63 (0.49-0.75)
ALLT		
Tsubota et al,[38] 1999	43	0.51 (0.37-0.65)
Ilari et al,[37] 2002	23	0.30 (0.16-0.51)
Shimazaki et al,[24] 2004	21	0.33 (0.17-0.55)
Ozdemir et al,[25] 2004	9	0.44 (0.19-0.73)
Santos et al,[23] 2005	23	0.13 (0.05-0.32)
Maruyama-Hosoi et al,[36] 2006	85	0.79 (0.69-0.86)
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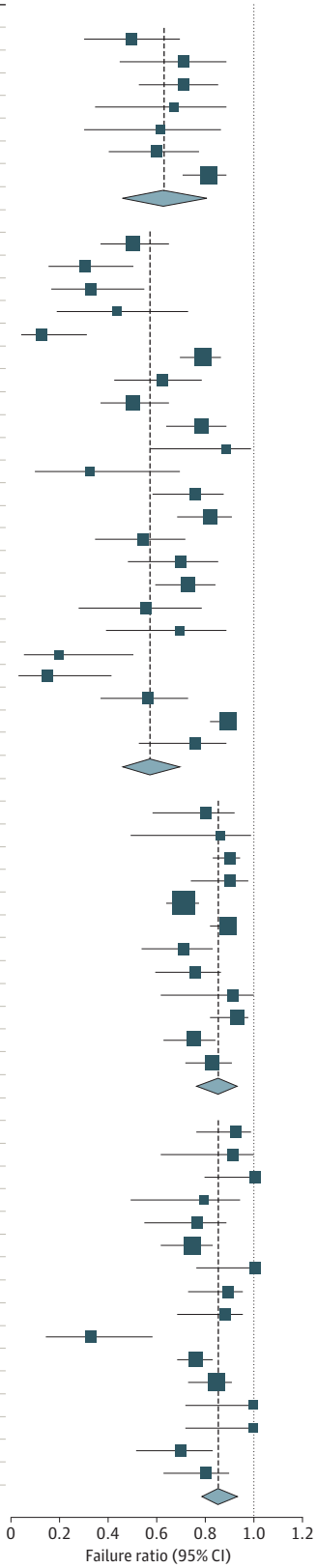
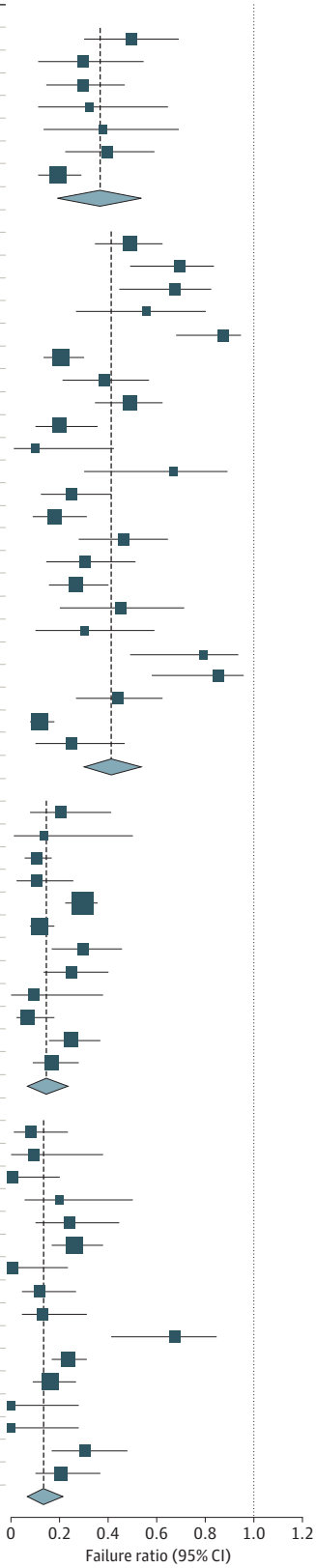
Moreira et al,[18] 2015	13	0.15 (0.04-0.42)
Parihar et al,[29] 2016	25	0.56 (0.37-0.73)
Movahedan et al,[28] 2017	165	0.88 (0.82-0.92)
El-Hofi et al,[53] 2019	20	0.75 (0.53-0.89)
Estimated rate		0.58 (0.49-0.66)
cAULT		
Schwab et al,[47] 1999	20	0.80 (0.58-0.92)
Shimazaki et al,[50] 2007	7	0.86 (0.49-0.99)
Rama et al,[45] 2010	107	0.90 (0.83-0.94)
Pauklin et al,[46] 2010	30	0.90 (0.74-0.97)
Sangwan et al,[3] 2011	200	0.71 (0.64-0.77)
Pellegrini et al,[44] 2013	152	0.88 (0.82-0.92)
Vazirani et al,[17] 2014	34	0.71 (0.54-0.83)
Vazirani et al,[17] 2014	36	0.75 (0.59-0.86)
Ramirez et al,[41] 2015	11	0.91 (0.62-1.00)
Ganger et al,[42] 2015	54	0.93 (0.82-0.97)
Scholz et al,[40] 2016	61	0.75 (0.63-0.84)
Fasolo et al,[39] 2017	59	0.83 (0.72-0.91)
Estimated rate		0.85 (0.77-0.90)
AULT		
Kenyon et al,[26] 1989	26	0.92 (0.76-0.98)
Shimazaki et al,[24] 2004	11	0.91 (0.62-1.00)
Ozdemir et al,[25] 2004	15	1.00 (0.80-1.00)
Santos et al,[23] 2005	10	0.80 (0.49-0.94)
Wylegala et al,[21] 2008	21	0.76 (0.55-0.89)
Torres et al,[22] 2008	65	0.74 (0.62-0.83)
Miri et al,[20] 2010	12	1.00 (0.76-1.00)
Baradaran-Rafii et al,[31] 2012	34	0.88 (0.73-0.95)
Barreiro et al,[27] 2014	23	0.87 (0.68-0.95)
Moreira et al,[18] 2015	15	0.33 (0.15-0.58)
Basu et al,[49] 2016	125	0.76 (0.68-0.83)
Vazirani et al,[17] 2016	68	0.84 (0.73-0.91)
Arora et al,[16] 2017	10	1.00 (0.72-1.00)
Arora et al,[16] 2017	10	1.00 (0.72-1.00)
Gupta et al,[51] 2018	30	0.70 (0.52-0.83)
Basu et al,[4] 2018	30	0.80 (0.63-0.90)
Estimated rate		0.86 (0.80-0.90)



The surface improvement rates of after direct autologous limbal transplant (AULT) and autologous limbal stem cells transplant (cAULT) were similar to the success rates shown in Figure 1.

Figure 3. Forest Plots for Failure Rate of Limbal Stem Cell Transplantation

Author, y	No. eyes	Ratio (95% CI)
cALLT		
Shimazaki et al,[50] 2007	20	0.50 (0.30-0.70)
Pauklin et al,[46] 2010	14	0.29 (0.12-0.55)
Basu et al,[49] 2012	28	0.29 (0.15-0.47)
Ramirez et al,[41] 2015	9	0.33 (0.12-0.65)
Ganger et al,[42] 2015	8	0.38 (0.14-0.69)
Parihar et al,[29] 2016	25	0.40 (0.23-0.59)
Cheng et al,[48] 2017	80	0.19 (0.12-0.29)
Estimated rate		0.37 (0.25-0.51)
ALLT		
Tsubota et al,[38] 1999	43	0.49 (0.35-0.63)
Ilari et al,[37] 2002	23	0.70 (0.49-0.84)
Shimazaki et al,[24] 2004	21	0.67 (0.45-0.83)
Ozdemir et al,[25] 2004	9	0.56 (0.27-0.81)
Santos et al,[23] 2005	23	0.87 (0.68-0.95)
Maruyama-Hosoi et al,[36] 2006	85	0.21 (0.14-0.31)
Wylegala et al,[21] 2008	26	0.38 (0.22-0.57)
Wylegala et al,[21] 2008	43	0.49 (0.35-0.63)
Scocco et al,[35] 2008	39	0.21 (0.11-0.36)
Miri et al,[20] 2010	9	0.11 (0.01-0.43)
Miri et al,[20] 2010	6	0.67 (0.30-0.90)
Javadi et al,[33] 2011	32	0.25 (0.13-0.42)
Javadi et al,[33] 2011	40	0.18 (0.09-0.32)
Han et al,[34] 2011	24	0.46 (0.28-0.65)
Eberwein et al,[32] 2012	20	0.30 (0.15-0.52)
Baradaran-Rafii et al,[31] 2013	45	0.27 (0.16-0.41)
Barreiro et al,[27] 2014	11	0.45 (0.21-0.72)
Titiyal et al,[30] 2015	10	0.30 (0.11-0.60)
Titiyal et al,[30] 2015	10	0.80 (0.49-0.94)
Moreira et al,[18] 2015	13	0.85 (0.58-0.96)
Parihar et al,[29] 2016	25	0.44 (0.27-0.63)
Movahedan et al,[28] 2017	165	0.12 (0.08-0.18)
El-Hofi et al,[53] 2019	20	0.25 (0.11-0.47)
Estimated rate		0.42 (0.34-0.51)
cAULT		
Schwab et al,[47] 1999	20	0.20 (0.08-0.42)
Shimazaki et al,[50] 2007	7	0.14 (0.01-0.51)
Rama et al,[45] 2010	107	0.10 (0.06-0.17)
Pauklin et al,[46] 2010	30	0.10 (0.03-0.26)
Sangwan et al,[3] 2011	200	0.29 (0.23-0.36)
Pellegrini et al,[44] 2013	152	0.12 (0.08-0.18)
Vazirani et al,[17] 2014	34	0.29 (0.17-0.46)
Vazirani et al,[17] 2014	36	0.25 (0.14-0.41)
Ramirez et al,[41] 2015	11	0.09 (0.00-0.38)
Ganger et al,[42] 2015	54	0.07 (0.03-0.18)
Scholz et al,[40] 2016	61	0.25 (0.16-0.37)
Fasolo et al,[39] 2017	59	0.17 (0.09-0.28)
Estimated rate		0.15 (0.10-0.23)
AULT		
Kenyon et al,[26] 1989	26	0.08 (0.02-0.24)
Shimazaki et al,[24] 2004	11	0.09 (0.00-0.38)
Ozdemir et al,[25] 2004	15	0.00 (0.00-0.20)
Santos et al,[23] 2005	10	0.20 (0.06-0.51)
Wylegala et al,[21] 2008	21	0.24 (0.11-0.45)
Torres et al,[22] 2008	65	0.26 (0.17-0.38)
Miri et al,[20] 2010	12	0.00 (0.00-0.24)
Baradaran-Rafii et al,[31] 2012	34	0.12 (0.05-0.27)
Barreiro et al,[27] 2014	23	0.13 (0.05-0.32)
Moreira et al,[18] 2015	15	0.67 (0.42-0.85)
Basu et al,[49] 2016	125	0.24 (0.17-0.32)
Vazirani et al,[17] 2016	68	0.16 (0.09-0.27)
Arora et al,[16] 2017	10	0.00 (0.00-0.28)
Arora et al,[16] 2017	10	0.00 (0.00-0.28)
Gupta et al,[51] 2018	30	0.30 (0.17-0.48)
Basu et al,[4] 2018	30	0.20 (0.10-0.37)
Estimated rate		0.14 (0.10-0.20)



The failure rate was significantly higher for direct allogenic limbal transplant (ALLT) and cultivated allogenic limbal stem cells transplant (cALLT) than for direct autologous limbal transplant (AULT)and cultivated autologous limbal transplant (cAULT).

Table 2. Rates of Adverse Events Among AULT, ALLT, cAULT, and cALLT

Event	Rate (95% CI)					*P* value
	Overall	AULT	ALLT	cAULT	cALLT	
Recipient eyes						
Recurrent/persistent epithelial erosion	10.5 (7.2-23.3)	4.3 (2.0-9.2)	28.8 (17.1-41.9)	3.4 (1.0-11.1)	18.5 (7.7-38.0)	ALLT vs AULT: *P* < .001; ALLT vs cAULT: *P* < .001; cALLT vs AULT: *P* = .006; cALLT vs cAULT: *P* = .02
Infectious keratitis	2.3 (1.8-4.4)	2.9 (1.1-7.2)	4.2 (2.2-7.8)	2.1 (0.8-5.3)	1.3 (0.2-10.1)	NA
Corneal melting/perforation	2.6 (1.5-4.6),	1.7 (0.6-5)	5.6 (3-10.1)	1.9 (0.7-5.1)	4.2 (1.1-14.5)	AULT vs ALLT: *P* = .02
Symblepharon	0.4 (0.01-4.2)	1.3 (0.1-10.3)	0.11 (0.01-1.8)	0.5 (0.05-4.9)	0.7 (0.04-13.0)	NA
Rejection	3.5 (1.2-9.3)	0 (0-0.6)	27.6 (20.3-36.4)	0 (0-1)	5.3 (1.9-13.9)	ALLT vs AULT: *P* < .001; ALLT vs cAULT: *P* < .001; cALLT vs AULT: *P* < .001; ALLT vs cALLT: *P* < .001; cALLT vs cAULT: *P* < .001
Hemorrhage under amniotic membrane	0.3 (0.04-3.6)	1.8 (0.5-5.7)	0.16 (0.02-1.4)	9.2 (3.5-22.1)	0 (0-7.1)	cAULT vs AULT: *P* = .03; cAULT vs ALLT: *P* < .001; cAULT vs cALLT: *P* = .04
Necrosis/loss of transplant	0.4 (0.1-2.1)	0.9 (0.1-7.6)	0.4 (0.04-3.2)	0.2 (0.04-5.1)	0 (0-7.1)	NA
Elevated IOP	1.7 (0.5-7.8)	0.8 (0.1-4.2)	6.3 (1.8-19.4)	0.3 (0.04-3.9)	2.1 (0.01-45.3)	ALLT vs AULT: *P* = .002; ALLT vs cAULT: *P* = .02
Others	1.3 (0.4-4.8)	0.5 (0.01-3.6)	5.4 (1.4-18.6)	1.4 (0.14-12.1)	6.5 (0.6-44.7)	AULT vs ALLT: *P* = .004
Donor eyes						
Hemorrhage	0.18 (0-12.3)	0.3 (0.04-7.3)	0 (0-16.8)	0.1 (0-6.2)	NA	NA
LSCD	0.04‰ (0.01‰-0.6)	0.2 (0.04-1.4)	0 (0-16.8)	0 (0-0.5)	NA	NA

Abbreviations: ALLT, allogenic direct limbal transplant; AULT, autologous direct limbal transplant; cALLT, allogenic cultured limbal stem cell transplant; cAULT, autologous cultured limbal stem cell transplant; IOP, intraocular pressure; LSCD, limbal stem cell deficiency; NA, not applicable.

did not affect the success rate. Human leukocyte antigen-matched allografts, the use of amniotic membrane in AULT and ALLT, the use of serum during LSC culture, and the substrate on which LSC sheets were cultivated did not show association with the success rate and improvement rate (eTable 2 in the Supplement).

Heterogeneity Analysis and Publication Bias

The heterogeneity analysis showed the I^2 value was 33% for the success rate, 36% for the improvement rate, and 36% for the failure rate; thus, the between-study heterogeneity was not significant. Analyses of publication bias regarding the success rate and the improvement rate were based on both the absolute rate and log-odds. Contour-enhanced funnel plots (eFigure 3 in the Supplement) showed a symmetrical plot distribution, indicating an absence of publication bias.

Discussion

Both our study and previous systemic review[54] confirmed that LSCT can restore a stable ocular surface in most eyes. The success rate and improvement rate were both significantly higher for autologous transplants than for allogeneic transplants, with an average follow-up of 31 months. Two 2019 studies[55,56] reported that ocular surface stability was achieved in 71% to 78% of eyes at up to 72 months after autologous LSCT, confirming its long-term efficacy. The success rate of AULT was slightly higher than that of cAULT, as previously reported.[57] The improvement rates of AULT and cAULT were similar, probably because some studies distinguished success from partial success while the others used success rate to account for both.

Even with the use of immunosuppressive therapy in most studies, a mean of 42.2% cases had total surface failure after allogeneic transplantation. A progressive decline of allograft survival and ambulatory vision with time was oberseved.[7,8,56] However, 3 meta-analyses[5,54,58] did not find a difference in success rates between autografts and allografts. These studies only focused on the outcome of cultivated limbal epithelial transplantation, with a mean length of follow-up less than 2 years. Moreover, these studies included many small cases series with sample sizes of less than 10 patients. Selection bias caused by a small sample size and a shorter length of follow-up might be the main reasons for their finding of similar outcomes between autologous and allogenic cultivated limbal epithelial transplantation.

Similar success rates and improvement rates were found between the HLA-matched and unmatched allografts. A 2018 systematic review[59] drew the conclusion that the current literature did not show which regimen or allograft type was most efficacious in treating the different etiologies of LSCD. Our study confirms that immunosuppression regimens varied significantly in the selection, combination, and dosage of different immunosuppressive agents. A higher rate of elevated intraocular pressure occurred after ALLT, which was likely caused by systemic and topical use of steroids. Randomized controlled studies are necessary to demonstrate the efficacy, safety, and the length of treatment of different immunosuppressive regimens.

The safety of limbal biopsy of the donor eye is a major concern associated with autologous LSCT, especially AULT with

an exception of SLET, because the biopsy carries the potential risk of iatrogenic LSCD in the donor eye. Previous studies reported that iatrogenic LSCD was found in the donor eyes with a history of contact lens wear.[60,61] To our knowledge, only 1 study[62] investigates the rate of iatrogenic LSCD in donor eye. The true rate of iatrogenic LSCD is unknown.

Our study found that 60.9% of eyes achieve a best-corrected VA of at least 20/200 after LSCT with a mean follow-up of 31.3 months. Boston type I Kpro (KproI) has been used to treat eyes with LSCD. A systematic review[63] of the outcome of KproI for the treatment of LSCD after chemical injury reported that 64.1% of eyes achieved a best-corrected VA of at least 20/200, with a mean follow-up period of 25 months after cases of Kpro extrusion (12%) were excluded. Glaucomatous optic neuropathy was the most common cause for best-corrected VA less than 20/200 in eyes (66.7%) that retained the Kpro.[63] In contrast, intraocular pressure elevation was only found in 1.7% eyes after LSCT. Other complications such as corneal necrosis/melt far rarely occurred after LSCT than after KproI. Posterior complications such as retinal detachment, endophthalmitis, sterile vitritis, and cystoid macular edema occurred in 21.6% of eyes after KproI while none was reported after LSCT. Limbal stem cell transplantation appears to have far fewer complications than KproI.

There was a lack of standardized criteria to stage the severity of LSCD and to define success, partial success, and failure; thus, comparison of the actual outcomes among different treatments was challenging. Only 26% of studies used diagnostic tests, such as impression cytology and/or in vivo confocal microscopy, to confirm the diagnosis of LSCD.[64] The limitation of using clinical signs in the diagnosis of LSCD needs to be recognized.[65,66] The International LSCD Working Group has established a consensus on the diagnosis, classification, and staging of LSCD, which will serve as a guideline for future clinical studies.[1] Although visual improvement has been used as an additional criterion to define success in many studies, a lack of vision improvement does not necessarily indicate LSCT failure because LSCT restores LSC function but does not treat the residual corneal stromal opacity.

Limitations

This study has limitations. First, to our knowledge, there is no randomized clinical trial comparing different LSCT. Therefore, the efficacy of each approach could not be evaluated. Second, among 25 studies using immunosuppression treatment, only 5 studies used 3 immunosuppressive medications. Considering that the subgroup analysis revealed a significantly higher success rate and improvement rate when pooling data from these 5 studies, the results of immunosuppression need to be interpreted with caution.

Conclusions

In summary, this meta-analysis supports that LSCT improves the corneal surface with a low rate of severe ocular complications and that autologous LSCT may have a higher success rate and fewer complications than allogenic LSCT. However, lack of standardization of efficacy measures precludes determining whether one approach is superior to the other. Randomized clinical trials are necessary to compare the efficacy of different LSCT.

ARTICLE INFORMATION

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Concept and design: Deng.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Le, Chauhan, Tseng.
Critical revision of the manuscript for important intellectual content: Le, Yung, Tseng, Deng.
Statistical analysis: Chauhan, Tseng.
Obtained funding: Deng.
Administrative, technical, or material support: Yung, Deng.
Supervision: Deng.

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