Submandibular Gland Transplantation vs Minor Salivary Glands Transplantation for Treatment of Dry Eye: A Retrospective Cohort Study

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• PURPOSE: To compare submandibular gland (SMG) transplantation with minor salivary gland (MSG) transplantation for the treatment of different dry eye diseases (DED).
• DESIGN: Retrospective clinical cohort study.
• METHODS: A total of 73 refractory DED eyes were divided into 3 groups. Group A comprised 35 end-stage DED eyes that underwent SMG transplantation. Group B comprised 20 end-stage DED eyes with MSG transplantation. Group C comprised 18 non−end-stage DED eyes with MSG transplantation. Schirmer test (ST), tear break-up time (TBUT), corneal fluorescein staining (FL), and best-corrected visual acuity (BCVA) were measured before and after surgery.
• RESULTS: Hospital length of stay, length of operation, and hospital fee were significantly higher in group A than in group B or C. Eyes in group A showed the most severe DED disease, with preoperative ST, TBUT, FL, and BCVA of 0.36 mm per 5 minutes, 0.03 seconds, 10.97, and 0.11, respectively, which improved significantly to 20.23 mm per 5minutes, 1.74 seconds, 7.58, and 0.2 at >2-year follow-up. Group B had similar baseline data, and significant but limited improvement only in the ST (0.55 mm per 5 minutes to 3.79 mm per 5 minutes) and FL (11.10 to 9.58) after the operation. Group C had better baseline ST, TBUT, FL, and BCVA of 0.89 mm per 5min, 3.49 seconds, 1.83, and 0.81, respectively, which improved significantly (except for BCVA) to 9.35 mm per 5min, 9.08 s, 0.53, and 0.89 after MSG transplantation.
• CONCLUSION: SMG transplantation could be recommended to treat end-stage refractory DED. MSG transplantation may provide satisfying results for refractory DED with relatively less severe impairment of the eye. (Am J Ophthalmol 2022;241: 238–247.

Because of its multifactorial etiology, the management of dry eye disease (DED) is complicated. Recently, the Tear Film and Ocular Surface Society's Dry Eye Workshop II (TFOS DEWS II) proposed an evidence-based, multi-staged management algorithm to determine the most appropriate DED treatment for each patient. The treatment is recommended based on subjective and objective severity measurements. Health education, environmental modifications, ocular lubricants, tear conservation, and physical therapies are recommended first. When the above options are insufficient, prescription drugs, autologous/allogeneic serum eye drops, and therapeutic contact lenses are recommended. Surgeries are usually given for refractory DED.[1] Two surgical modalities of salivary gland transplantation, microvascular submandibular gland (SMG) transplantation and minor salivary gland (MSG) transplantation, are listed as the last recommendations when other treatments are inadequate.[1] However, further instruction on choosing between these 2 surgical approaches is still vague.[1-20]

Both SMG transplantation[2-13] and MSG transplantation[14-20] provide spontaneous, continuous, and endogenous lubrication with saliva as a tear substitute. Both treatments can improve severe symptoms and/or signs of dry eye, including Schirmer test score (ST), tear break-up time (TBUT), and some other ocular surface features. However, despite the above-listed similarities, these methods differ in surgical complexity or technical requirement, surgical trauma, secretory patterns, amounts of lubrication,

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and surgical complications. Besides, there is individual heterogeneity among these refractory DED patients, and the etiology and severity of the disease in these patients may vary. Taking into consideration significant differences between the 2 surgeries and the heterogeneity among the refractory DED patients, when salivary gland transplantation is indicated according to the current algorithm, an evidence-based choice between SMG transplantation and MSG transplantation is needed.

In this study, we compared the treatment effect of SMG transplantation and MSG transplantation in different refractory DED patients. We also analyzed surgical complications and treatment costs. The current study provides evidence-based indications for SMG transplantation and MSG transplantation for the treatment of severe refractory DED.

METHODS

• **PATIENTS:** Consecutive patients diagnosed with DED who underwent salivary gland transplantation at Peking University School of Stomatology between June 2010 and October 2018 were included in this retrospective clinical cohort study. The study was approved by the Ethics Committee of the Peking University School of Stomatology (PKUSSIRB - 202163043) and designed and carried out in full accordance with the World Medical Association Declaration of Helsinki. All patients provided informed consent to join the study.

• **INDICATIONS AND CONTRAINDICATIONS:** Indications for surgeries included persistently pronounced symptoms of dry eye and failure of other previous ophthalmologic treatments, along with an ST value of <2 mm, a TBUT value of <5 seconds, and positive fluorescence staining of the cornea during ophthalmologic evaluation. Contraindications were Sjogren syndrome or obvious symptoms of xerostomia.[8,13]

• **GROUPING:** Patients comprised 3 groups (groups A, B, and C) based on their surgical modalities, the severity of DED, and the etiologies of the DED (Table 1). Group A comprised DED patients secondary to cicatrizing conjunctivitis and meeting the level 4 grade of dry eye severity grading scheme in the 2007 International Dry Eye WorkShop (DEWS) criteria[21] who underwent SMG transplantation. Group B comprised level 4 DED patients secondary to cicatrizing conjunctivitis who underwent MSG transplantation. Group C comprised the DED patients with secondary to non-cicatrizing conjunctivitis who did not meet the level-4 grade in the DEWS criteria. The surgical modality was selected mainly according to the patient's intention after surgical techniques had been explained in detail.

The causes of cicatrizing conjunctivitis included Stevens–Johnson syndrome (SJS), mucous membrane pemphigoid (MMP), and graft-versus-host disease. Based on the DEWS dry eye severity grading scheme,[21] the inclusion criteria for level 4 DED were as follows: (1) severe constant discomfort of the eye and (2) constant visual diminution affecting the lifestyle; (3) corneal fluorescein staining (FL) score >6 in a standardized scoring scheme[22] with a maximum score of 12; (4) TBUT ≤1 second; and (5) ST ≤2 mm per 5 min.

• **TRANSPLANTATION PROCEDURES FOR MICROVASCULAR SUBMANDIBULAR AND MINOR SALIVARY GLANDS:** SMG transplantation was performed as previously described[13] (Figure 1). In brief, under general anesthesia, the SMG, including the branches of facial artery and vein and Wharton duct, was harvested from the submandibular triangle and transferred to the temporal region. The branches of the vessels from or going into the SMG had to be harvested together. Next, the facial artery and facial veins were subjected to anastomosis with the superficial temporal artery and vein, respectively. After subcutaneously passing through a tunnel prepared to the upper lateral conjunctival fornix, the distal end of the Wharton duct was sutured in the upper lateral conjunctival fold as an opening.

The MSG transplantation was performed as previously described (Figure 2).[23] Before surgery, the minor salivary gland flow rate (MSGFR) of 3 sites (upper labial, lower labial, and buccal mucosa) was measured and calculated as previously described.[23,24] The lower or upper labial glands with higher flow rates were used as the donor sites. In cases in which the flow rate of upper and lower labial glands was much lower than that of the buccal glands, the latter was used as a donor. Under general anesthesia, the graft was obtained from the donor bed and composed of salivary lobules and the covering mucosa. The recipient beds were prepared in the upper and lower bulbar conjunctiva and near the fornix. The graft's mucosa was covered by 8-0 Vicryl absorbable sutures and anchored to the underlying orbital septum with 1 interrupted suture passing through the donor tissue to achieve good contact between the graft and the graft underlying recipient bed. No other compression methods were used.

• **POSTOPERATIVE TREATMENTS:** Antibiotics were given for 4 to 5 days after the operation. Patients who underwent SMG transplantation paid special attention to protecting the anastomosis site from being pressed during the first 2 postoperative weeks. Also, capsaicin and carbachol were administered for 3 months after the operation to prevent Wharton duct obstruction.[25]

• **DATA COLLECTION AND FOLLOW-UP:** The medical records were reviewed for all patients, including demographic features, detailed disease history, hospital length of stay (LOS), length of operation (LOO), and hospital fee. The hospital fee was the total expense charged by the hospital during hospitalization, which included all of the medical

TABLE 1. Baseline Data of the 3 Study Groups

Characteristics		Group A	Group B	Group C	*P* Value	
					A vs B	B vs C
Grouping methods	DED etiology	Cicatrizing conjunctivitis	Cicatrizing conjunctivitis	Non-cicatrizing conjunctivitis		
	DED severity level	Level 4	Level 4	Level <4		
	Surgical modality	SMG transplantation	MSG transplantation	MSG transplantation		
Numbers	Patients	28	19	14		
	Eyes	35	20	18		
	Patients with bilateral surgeries	7 (25%)	1 (5.3%)	4 (28.6%)	.119	.138
Demographic features	Age (y)	29.6 ± 15.1	34.4 ± 10.5	28.2 ± 4.2	.211	.022
	Sex (female/male)	23/12	12/8	4/14	.672	.019
Disease history	Detailed etiology	SJS: 35	SJS: 17 GVHD: 3	AC: 13 Unknown: 5		
	Disease duration (y)	11.3 ± 11.6	10.5 ± 9.1	5.1 ± 3.2	.781	.020
Hospital parameters	LOS (day)	13.0 ± 1.1	7.8 ± 0.7	7.5 ± 0.7	<.001	.287
	LOO (h)	6.1 ± 0.6	1.9 ± 0.3	1.8 ± 0.3	<.001	.310
	Hospital fee (RMB)	28486.2 ± 2740.0	16006.7 ± 2217.6	16845.6 ± 3617.6	<.001	.389
Donor parameters (MSG)	Donor sites	——	Lower lip: 14 Upper lip: 5 Buccal: 1	Lower lip: 13 Upper lip: 5 Buccal: 0		.627
	Sizes (cm^2)	——	8.8 ± 2.5	6.6 ± 1.6		.003
	MSGFR (mg/min)	——	1.8 ± 0.6	3.2 ± 1.1		<.001
	Size × MSGFR	——	15.9 ± 6.5	21.1 ± 8.2		.045

AC = acute conjunctivitis; DED = dry eye disease; GVHD = graft versus host disease; LOO = length of operation; LOS = hospital length hospital stay; MSG = minor salivary glands; MSGFR = salivary flow rate of minor salivary glands; RMB = Renminbi; SJS = Stevens–Johnson syndrome; SMG = submandibular gland.

P values for group A vs B and group B vs C were based on the χ^2 test for categorical variables (except for Fisher exact test for bilateral surgery) and the independent-samples *t* test for continuous variables.

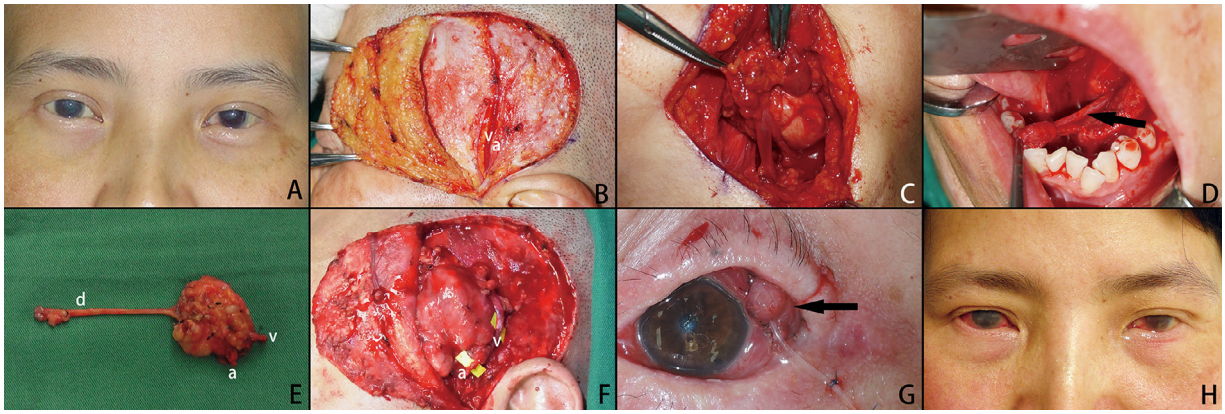

FIGURE 1. Procedures and treatment effect of submandibular gland transplantation. A: Bilateral dry eye disease secondary to Stevens–Johnson syndrome. B: Incision in the temporal region and dissection of the superficial temporal vessels (left side). C: Dissection of the submandibular gland. D: Dissection of the Wharton duct. E: Donor, including the submandibular gland, facial vessels, and Wharton duct. F: Anastomosis of the vessels (arrows). G: Reopening of the Wharton duct in the eye (arrow). A nylon tube was inserted and left in the duct for 7 days. H: Follow-up image 9 years after the operation. Compared with the untreated right eye, the left eye had plenty of lubrication and better ocular surface condition.

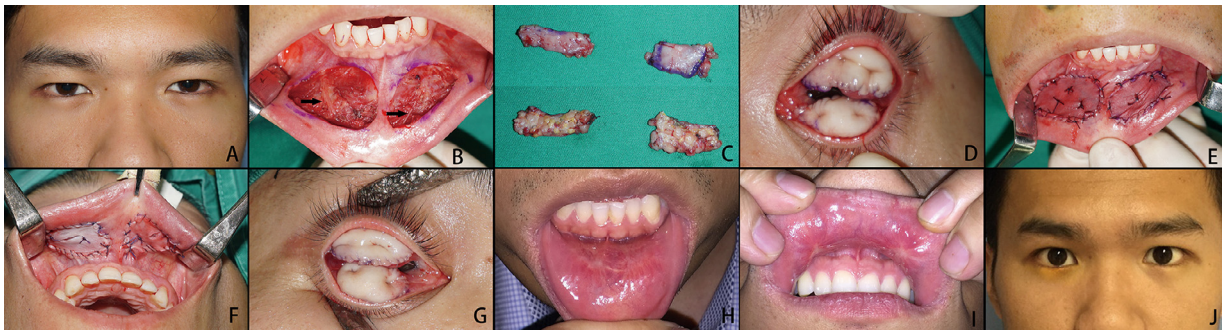

FIGURE 2. Procedures and treatment effect of minor salivary glands transplantation. A: Bilateral dry eye disease secondary to adenoviral conjunctivitis. B: Grafts were harvested from the lower lip above the muscles, and branches of the trigeminal nerve (arrows) were preserved. C: Two pieces of salivary lobules with the covering mucosa. D: Grafts were transplanted and fixed in the left eye. E: Wounds of the lip were repaired with an acellular dermal matrix. F, G: Right eye was treated 6 months later with the grafts from the upper lip. H-J: Follow-up images 4 years after the second operation. The incisions of the lips healed well, and the dry eye symptoms were relieved in both eyes.

items (eg, the fees for surgery, anesthesia, medicine, medical materials, etc). These data were acquired directly from the hospital information system.

Patients were followed up for 4.3, 5.8, and 3.7 years in groups A, B, and C, respectively. Patient questionnaires and the objective ocular surface disease parameters, including ST, FL, and TBUT, as well as best-corrected visual acuity (BCVA) at baseline, 3 months postoperatively, and the last time of follow-up, were collected.

The questionnaire included 2 items: "My dry eye symptoms were relieved after treatment" and "I am satisfied with the long-term treatment effect." Each item was analyzed using a 5-point Likert-type scale, ranging from "completely disagree" (1 point) to "completely agree" (5 points). A score of 4 or 5 was regarded as "subjective relief of DED symptoms" or "satisfaction with the surgery." Patients were asked to complete the questionnaire independently. For those with poor vision (ie, inability to read), the items were read aloud by a nonrelated person (ie, by someone other than the doctor or the patient's relatives).

The patients rested 30 minutes, during which they did not engage in any kind of physical activity or glandular stimulation before the ophthalmologic examination so as to avoid the influence of local hyperthermia and physical activity on the secretion of transplanted SMGs. The same ophthalmologist conducted the procedures following the guideline of the Chinese Medical Association expert consensus on clinical diagnosis and treatment of dry eye[22] in clinics with a temperature of 23°C and relative humidity of 40%.

BCVA was first tested, followed by FL, TBUT, and ST. A stopwatch was used for timing. BCVA measurement was applied with spectacle or contact lens correction. The standard logarithmic visual acuity chart (National Standard of the People's Republic of China GB11533-2011) was used. Test chart background luminance was ≥200 cd/m. In the FL test, the corneal surface was divided into 4 quadrants: upper nasal, lower nasal, upper temporal, and lower temporal, which were individually scored. The fluorescein score was analyzed as follows: 0 = no staining, 1 = minimal staining, 2 = mild/moderate staining, and 3 = severe staining. The sum of the above indicators was taken as the final FL score. In the TBUT test, patients were asked to blink 3 times after staining with the fluorescein strip. The time from the last eye-opening to the appearance of the first dry spot was measured 3 times. The mean value was the TBUT score. ST was performed for 5 minutes using Whatman No. 41 paper strips (35 × 5 mm; Tianjin Jingming New Technological Development Co, Ltd) without topical anesthesia. The length of the moistened paper strips was used as the score.

• **STATISTICAL ANALYSIS:** Considering the clinical interpretation, the baseline characteristics and longitudinal clinical outcomes of groups A and C were separately compared with that of group B. The comparisons between groups A and B indicated the differences in surgical modalities (SMG transplantation vs MSG transplantation), whereas the comparisons between groups C and B revealed the differences in DED severity levels (level 2/3 DED vs level 4 DED). For baseline characteristics, continuous variables were compared between groups using an independent-samples t test, whereas categorical variables were compared using the χ^2 test or Fisher exact test. For comparing hospital parameters and subjective long-term follow-up data (relief of symptoms and overall satisfaction), general linear regression and logistic regression (or exact logistic regression to deal with separation) were respectively used with adjustment for age and sex to account for possible confounding bias.

To evaluate the objective treatment effects within each group, the values of 4 objective ocular surface disease parameters at 3 months postoperation and the long-term follow-up (>2 years) were compared with the baseline (preoperative) values using a paired-samples t test. Differences

in treatment effects between groups (group A vs B, and group B vs C) were then tested using a linear mixed-effects model, with objective clinical parameters as dependent variables. Random intercept per eye was used to account for individual-level differences in clinical parameters. Fixed effects included time variables (3 time points) and patient group, with adjustment for age and sex. Interaction between time and the patient group was tested to determine the between-group differences in the improvements of these clinical parameters over time.

All analyses were conducted using SPSS 20.0 (SPSS Inc) and Stata 14.0 (StataCorp LLC). *P* values of <.05 (2-tailed) were considered statistically significant.

RESULTS

• **PATIENTS:** There were 28 patients in group A, 19 patients in group B, and 14 patients in group C. All patients were diagnosed with bilateral DED. In group A and group C, 25% and 28.6% of patients received bilateral surgeries, respectively, compared to 5.3% in group B. In total, 73 eyes were included in the analysis, and the data collections and analysis were based on "eye." In addition, there was no difference in age and sex between participants in group A and group B ($P > 0.05$), whereas participants in group C were slightly younger. Also, there were more male patients in group C compared to group B ($P < .05$) (Table 1).

• **BASELINE DATA OF DISEASE AND DONORS:** The DED in all 35 eyes in group A was caused by Stevens—Johnson syndrome (SJS), which was also the etiology of DED for most eyes (17 eyes, 85%) in group B. The remaining 3 eyes (15%) in group B were affected by graft-versus-host disease. For the majority of eyes (12 eyes, 66.7%) in group C, the disease was caused by adenoviral conjunctivitis, whereas for the remaining 6 eyes (33.3%) in group C, the etiology of DED was not clear. The mean disease duration in group A and B was more than 10 years, whereas in group C, it was 5.1 ± 3.2 years; the difference was statistically significant ($P < .05$) (Table 1). Eyes from both group A and group B sustained the most severe damage of the lacrimal gland and ocular surface, with the mean values of ST, TBUT, FL, and BCVA of 0.36 ± 0.65, 0.03 ± 0.17, 10.97 ± 1.94, 0.11 ± 0.14, and 0.55 ± 1.05, 0.05 ± 0.22, 11.10 ± 1.65, 0.15 ± 0.24, respectively (all *P* values for between-group difference >.05). The mean values of the ST, TBUT, FL, and BCVA in group C were 0.89 ± 1.02, 3.49 ± 1.36, 1.83 ± 1.76, and 0.81 ± 0.19, respectively, showing less severity compared to values in group B (*P* values <.05 except for ST) (Table 2).

The donors of MSG were harvested from similar sites in groups B and C. The donor secretory functions of group C were better than in group B, as the MSGFR of group C was significantly higher ($P < .05$) (Table 1). Although the donor sizes of group C were smaller than those of group B, the total flow rate of the grafts (size × MSGFR) was still significantly higher in group C ($P < .05$) (Table 1).

• **TREATMENT COSTS AND COMPLICATIONS:** The surgical trauma and hospital costs were significantly higher in group A and were similar between groups B and C, as reflected by LOS, LOO, and hospital fees (Table 1). These results did not significantly change after adjusting for age and sex. In group A, surgery was not successful for 2 eyes (5.7%), and the grafts were lost because of vascular thrombosis after transplantation. Thirteen eyes (39.4%) in group A developed intermittent corneal epithelial microcystic edema, and patients complained of blurred vision. The hypotonic saliva elicited corneal edema when postoperative epiphora occurred, which is a relatively common complication of SMG transplantation.[12,13] Epiphora were managed by surgical reduction of graft, topical atropine gel, and botulinum toxin injection. Ranula and Wharton duct obstruction were reported in 1 eye (3%), respectively, and were surgically cured.

All transplantations were successful in groups B and C. In 1 eye (5%) in group B, only, partial graft developed necrosis early after the operation. The residual tissue showed good healing after local debridement. Partial grafts in the lower lid were visible and led to cosmetic problems after the operation in 2 eyes (10%) from group B and in 1 eye (5.6%) from group C. Local transient hypaesthesia of the lower lip was reported in 7 eyes (35%) from group B and in 5 eyes (27.8%) from group C, showing spontaneous remission within 6 months. The complication rates did not differ between the 2 groups ($P > .05$).

• **INTRA-GROUP COMPARISONS OF OBJECTIVE PARAMETERS BEFORE AND AFTER OPERATIONS:** Objective examination results were missing for 2 eyes from group A and 1 eye from group C at 3 months and at >2 years postsurgery, and in 1 eye from group B at >2 years postsurgery. The objective parameters were analyzed for 31 eyes in group A, 20 eyes in group B, and 17 eyes in group C at the 3-month follow-up, and for 31 eyes in group A, 19 eyes in group B, and 17 eyes in group C at the >2-year follow-up.

For group A and C, the results of the ST, TBUT, and FL were all significantly improved at the 3-month follow-up and the long-term follow-up compared with the preoperative values (all $P < .01$) (Table 2). In contrast, the results of the ST, FL but not TBUT, significantly improved at both follow-ups in group B (both $P < .05$). The BCVA was significantly improved in group A at the long-term follow-up ($P < .05$) (Table 2).

• **BETWEEN-GROUP COMPARISONS OF OBJECTIVE PARAMETERS BEFORE AND AFTER OPERATIONS:** To exclude the possible impact of objective baseline parameters on the follow-up results, changes in objective parameters before and after operations were used in between-group comparisons. A linear mixed-effects model was used. The results

TABLE 2. Mean Levels of Objective Clinical Parameters for the 3 Study Groups at Baseline and Follow-up

Objective Parameter	Time Points		
	Preoperative(71 Eyes)	3-mo Postoperative(68 Eyes)	Long-Term (>2- year) Follow-up(67 Eyes)
Schirmer test (mm per 5 min)			
Group A	0.36 ± 0.65	20.29 ± 9.41**	20.23 ± 7.31**
Group B	0.55 ± 1.05	3.30 ± 2.47**	3.79 ± 2.99**
Group C	0.89 ± 1.02	7.71 ± 4.09**	9.35 ± 7.78**
TBUT (s)			
Group A	0.03 ± 0.17	1.58 ± 2.03**	1.74 ± 2.21**
Group B	0.05 ± 0.22	0.10 ± 0.45	0.00 ± 0.00
Group C	3.49 ± 1.36	9.53 ± 5.68**	9.08 ± 6.26**
FL			
Group A	10.97 ± 1.94	7.55 ± 2.23**	7.58 ± 2.36**
Group B	11.10 ± 1.65	10.10 ± 1.77*	9.58 ± 2.17*
Group C	1.83 ± 1.76	0.71 ± 1.16**	0.53 ± 1.33**
BCVA			
Group A	0.11 ± 0.14	0.15 ± 0.15	0.20 ± 0.21**
Group B	0.15 ± 0.24	0.19 ± 0.25	0.20 ± 0.25
Group C	0.81 ± 0.19	0.88 ± 0.14	0.89 ± 0.14

BCVA = best-corrected visual acuity; FL = corneal fluorescein staining; TBUT = tear break-up time.

*$P < .05$, **$P < .01$, based on paired-samples t test comparing postsurgical time points with presurgical level within each group separately. The mean duration of the long-term follow-up was 3.2, 3.8, and 3.6 years for group A, B, and C, respectively ($P > .10$).

showed that group A had significantly larger improvement in the ST, TBUT, and FL at both the 3-month and long-term follow-up compared with group B (P for time × group interaction < .01) (Figure 3). The longitudinal changes in BCVA did not significantly differ between groups A and B ($P > .05$). Compared with group B, group C had a significantly larger magnitude of improvements in the ST and TBUT (P for time × group interaction < .01), but not in FL and BCVA at both follow-ups (Figure 4).

• **BETWEEN-GROUP COMPARISONS OF PATIENTS QUESTIONNAIRE RESULTS:** Patients' questionnaires were obtained for all of the eyes except for the 2 eyes with unsuccessful transplantation in group A. The questionnaire results were analyzed for 33 eyes in group A, 20 eyes in group B, and 18 eyes in group C at the >2-year follow-up. Groups A and C showed a higher rate of relief of DED symptoms (100% and 83.3%) than did group B (60.0%). Results of logistic regression indicated a significant difference in the subjective relief rate between groups A and B ($P < .001$) but not between groups B and C ($P = .589$) after adjusting for age and sex. Similarly, the overall subjective satisfaction was significantly higher in group A (93.9%) than in group B (70.0%, $P = .032$); no significant difference was detected between groups B and C (83.3%, $P = 0.892$). Two group B patients who did not experience noticeable relief from the DED symptoms expressed satisfaction, considering that they had gotten rid of the symblepharon after the operation.

DISCUSSION

This retrospective cohort study compared the efficacies of SMG transplantation and MSG transplantation treatment in 73 eyes with different refractory DED. In the end-stage DED cases with severe impairment of the eye secondary to cicatrizing conjunctivitis, SMG transplantation showed a very good treatment effect (group A). Abundant lubrication (a postoperative ST value of 20.23 mm per 5 minutes) provided by SMG significantly improved tear film stability and ocular surface, as shown in TBUT, FL, and BCVA examinations, and all patients in this group experienced relief of the DED symptoms. In contrast, in most severe DED cases, MSG transplantation led to lower lubrication (3.79 mm per 5 minutes) in group B. Both TBUT and BCVA showed no improvements, and the relief rate of DED symptoms was only 60%. Compared with group B, patients of group C had less severe DED, which was secondary to non-cicatrizing conjunctivitis, and obtained satisfying treatment effects from MSG transplantation. The ST increased from 0.89 mm per 5minutes to 9.35 mm per 5 minutes, the TBUT increased from 3.49 s to 9.08 s, the FL score was reduced from 1.83 to 0.53, and 83.3% of patients experienced relief of the symptoms. The between-group comparison further confirmed that SMG transplantation was significantly superior to MSG transplantation for treating end-stage DED secondary to cicatrizing conjunctivitis. In addition, for DED secondary to non-cicatrizing

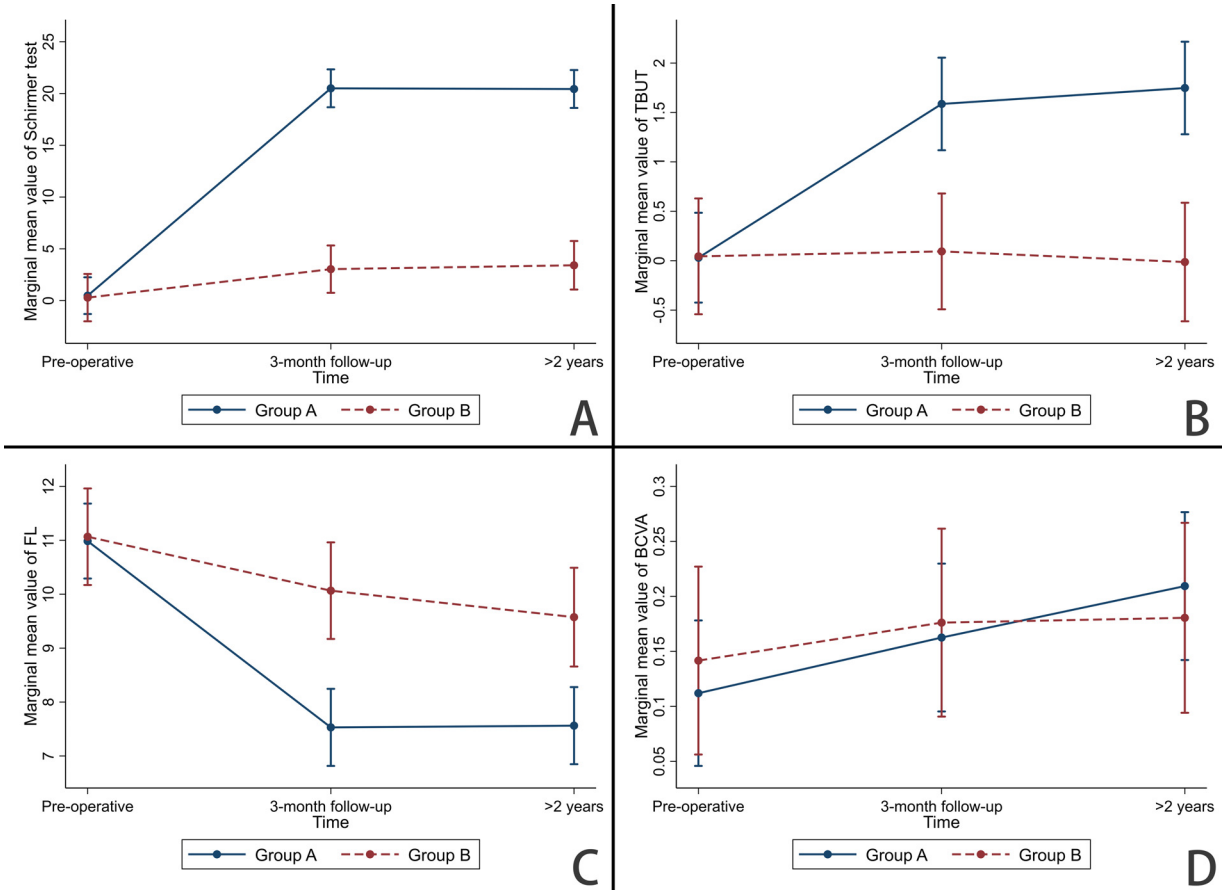

FIGURE 3. Longitudinal changes of objective clinical parameters in group A compared to group B. Group A had significantly larger improvements in the Schirmer test, tear break-up time, and corneal fluorescein staining at 3-month and >2-year follow-up compared with group B ($P < .01$). A: Schirmer test. B: Tear break-up time. C: Corneal fluorescein staining. D: Best-corrected visual acuity.

conjunctivitis with less severe eye impairment, MSG transplantation offered a significantly superior treatment effect compared to that achieved in patients with end-stage DED. These conclusions were also verified by comparing the rates of bilateral operations. Although all patients in the present study had bilateral DED, we insisted that the operation for the other eye be performed at least 6 months after the initial operation. Contralateral surgery provided definite evidence that patients were satisfied with the treatment effect of the initial operation. In the present study, 25% of patients from group A and 28.6% of patients from group C underwent another surgery for the other eye after the initial operation, whereas this was the case with only 1 patient from group B (5.3%).

The treatment costs and complications were also compared among groups. SMG transplantation, which is small organ transplantation that requires vascular anastomosis, showed significantly higher LOS, LOO, and hospital fees compared to MSG transplantation, which is a free tissue graft that does not require any vascular anastomosis. It must be pointed out that only the major economic spending of the patients (hospital fees) was included, whereas other expenses such as travel costs were not included. All MSG transplantations were successful, whereas the SMG transplantation was unsuccessful in 2 eyes. Besides, epiphora occurred in 39.4% of the eyes, thus requiring operation or other management after SMG transplantation, which was consistent with the literature reports.[7,26] In contrast, except for 1 eye, there were no complications requiring a secondary medical intervention after MSG transplantation. The surgical trauma, risk, and treatment burden should be taken into full consideration before SMG transplantation. Accordingly, we did not perform SMG transplantation for the relatively less severe DED. This is the reason why there were only 3 groups of patients in this study.

Considering both risks and benefits, for refractory DED patients who do not have other treatment options, surgical modalities should be chosen according to the severity of the disease. For the patients with DED secondary to noncicatrizing conjunctivitis and for those with less severe impairment of the tear film stability and ocular surface (eg, group C), MSG transplantation might be recommended as a first choice. Most patients could benefit from adequate lubrication and substantial improvements with minor treat-

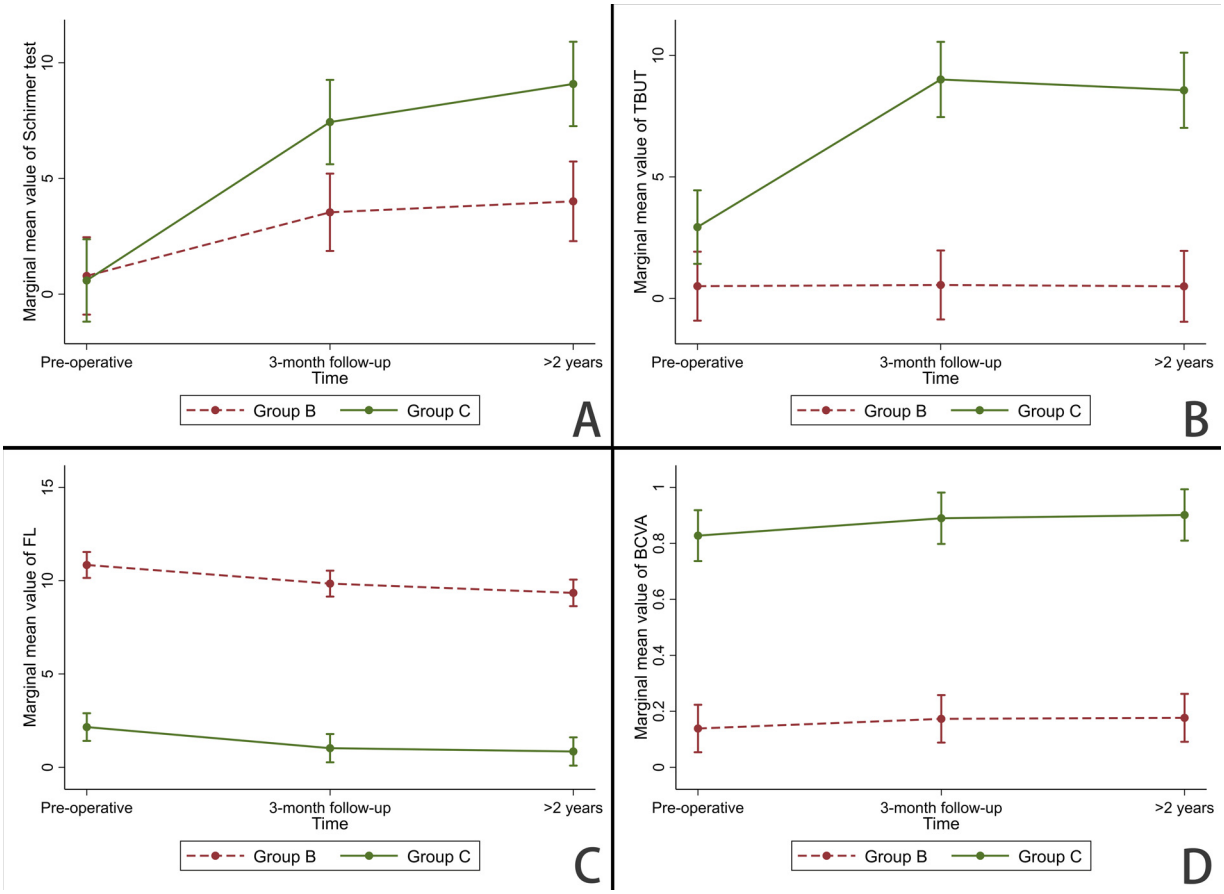

FIGURE 4. Longitudinal changes in objective clinical parameters in group B compared to group C. Group C had significantly larger improvements in the Schirmer test and tear break-up time at the 3-month and >2-year follow-up compared with group B ($P < .01$). A: Schirmer test. B: Tear break-up time. C: Corneal fluorescein staining. D: Best-corrected visual acuity.

ment risk and cost. However, for end-stage DED secondary to cicatrizing conjunctivitis (as in groups A and B of this study), the treatment effect of MSG transplantation may be limited (<4 mm per 5 minutes of lubrication and 60% of symptoms relief rate); thus, SMG transplantation might be recommended.

The differences observed in the treatment effect of MSG transplantation on different kinds of DED may be explained as follows. First, most cases of DED in group B were caused by SJS, which could impair not only the lacrimal gland but also the MSG.[27] In contrast, adenoviral conjunctivitis does not have an impact on MSG. Our data of donor secretory functions at baseline confirmed the significantly higher secretory flow rate of MSG in group C than in group B. A previous study suggested that the preoperative flow rate of MSG is positively correlated with postoperative lubrication and the treatment effect.[23] Consequently, group C had better treatment results than group B. Second, cicatrizing conjunctivitis such as SJS causes severe scar formation in the affected eye, which is the location of the recipient bed of the free grafted MSG tissues. The poor condition of the recipient bed is likely to be harmful to the survival of the grafted tissues. At the same time, this pitfall was not found in patients with adenoviral conjunctivitis.

The different treatment effects of SMG transplantation and MSG transplantation on the most severe DED may be explained as follows: as a major salivary gland, SMG has a much stronger secretory function compared with MSG. Besides, SMG transplantation could preserve the function to the greatest extent, considering that blood circulation is rebuilt during operation. Thus, the amount of lubrication after SMG transplantation is much greater than that after MSG transplantation.

Considering that most of the patients had bilateral DED, the proportion of patients undergoing bilateral SMG transplantations was relatively limited, which was consistent with reports from other groups.[4-7,9-11] We obtained a possible explanation for the cause of this issue, based on our communications with the patients. These patients with end-stage DED experienced a marked decrease in vision, and fears of blindness and disability were the most powerful motivation for accepting the surgery. After the 1-sided operation, the eye vision might be preserved, and the patients can already be protected from becoming blind and disabled.

They might then lose the motivation to accept 1 more instance of organ transplantation surgery. However, further evidence is needed for this explanation.

This study has a few limitations. First, as a retrospective cohort study, grouping of patients was not random; future randomized controlled trials of surgical modalities are warranted to validate our findings. Moreover, only 3 study groups were examined; we did not perform SMG transplantation for the relatively less severe DED. However, a negative correlation between subjective symptoms and objective examination is not rare in DED.[28] Patients could have severe pain with only relatively moderate impairment of the eye. It is still unclear whether these patients could benefit from SMG transplantation when other treatments failed, and MSG transplantation does not provide an effective cure.

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