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Factors influencing the long-term results of autologous microvascular submandibular gland transplantation for severe dry eye disease

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Abstract. We assessed long-term outcomes of autologous microvascular submandibular gland (SMG) transplantation for severe dry eye disease and investigated factors influencing long-term results. From August 1999 to January 2015, 185 patients (200 eyes) with severe dry eye received SMG transplantation. Subjective assessments and ophthalmologic evaluations were performed before and after transplantation. Follow-up results showed successful transplantation in 180 of 200 eyes (success rate: 90%), resulting in marked symptomatic relief of xerophthalmia. Surgery failed due to vascular thrombosis (15 glands) and duct obstruction (5 glands). Follow-up data were available for 163 eyes. Epiphora occurred in 98 (60.1%) eyes and was effectively managed by surgical reduction of graft, topical atropine gel and botulinum toxin injection. Wharton's duct obstruction occurred in 16 (10.6%) eyes and was treated by duct reconstruction. Subjective satisfaction was achieved in 143 (87.7%) eyes. Mean score of fluorescent staining reduced from 11.25 ± 1.42 to 7.25 ± 3.37. Postoperative best-corrected visual acuity improved in 85 (56.3%) eyes. Our clinical experience proved that SMG transplantation is effective and grants long-term improvement in severe dry eye. Secretory function of transplanted SMGs remains active and stable. Blood vessel thrombosis, Wharton's duct obstruction, and epiphora are primary factors influencing results.

Key words: keratoconjunctivitis sicca; submandibular gland transplantation; dry eye; long-term follow-up; influencing factors.

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According to the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007), dry eye disease, or keratoconjunctivitis sicca, is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface[1]. Symptoms vary from dryness and photophobia to keratoleukoma and visual acuity loss[1]. Dry eye can cause blindness because the precorneal tear film is essential for corneal transparency and marked dry eye conditions can lead to keratitis with subsequent ulceration and corneal opacification[1].

Present therapeutic options, such as artificial tear substitutes and occlusion of tear drainage, mostly focus on symptomatic treatment alone[1]. Although effective in mild cases, such treatment modalities are not adequate to manage severe conditions[1,7]. Therefore, management for severe dry eye has often been challenging for patients and ophthalmologists. Microvascular autologous submandibular gland (SMG) transplantation with implantation of Wharton's duct into the upper conjunctival fornix, which was first described by Murube-Del-Castillo in 1986[2], and followed by MacLeod[3], Kumar[4], Geerling[5], Sieg[6], Jia[7], and Paniello[8], offers a surgical alternative for permanent autologous substitution of tears using basal secretions of transplanted and revascularized SMGs. Results revealed that this technique was effective for symptomatic relief of dry eye[5–11]. However, long-term assessment with a large sample of patients with severe dry eye is necessary.

Based on an experimental study and use of this technique since 1999, our research group has treated numerous patients suffering from severe dry eye[12–16]. Results of our preliminary and short-term follow-up study were reported in 2004[12]. Here we assessed long-term outcomes of 185 patients (200 eyes) followed up for >1 year after microvascular autologous SMG transplantation and analysed factors influencing long-term results.

Materials and Methods

Indications and contraindications

Indications for surgery included persistently pronounced symptoms of dry eye and failure of other previous ophthalmologic treatments, along with a Schirmer's test value of <2 mm, a break-up time (BUT) value of <5 s, and positive fluorescence staining (when punctate staining was recorded for any area on the cornea surface) of the cornea during ophthalmologic evaluation. Contraindications were Sjögren's syndrome, obvious symptoms of xerostomia or whole salivary flow rate <0.3 g/min, and severe dysfunction of multiple major salivary glands on scintigraphy[12,14].

Patient collection

This study was conducted in accordance with the Declaration of Helsinki guidelines for human research. Following approval of the ethics committee of Peking University Health Science Center, 185 (83 male, 102 female) patients with a mean age of 30 (range: 7–71) years and suffering from severe dry eye were included in this study. All patients provided informed consent for surgical procedures and related examinations.

Evaluation methods

Detailed medical history questionnaires regarding aetiology, course and past treatment were administered to subjectively assess dry eye symptoms. Detailed objective assessments, including ophthalmologic evaluation, oral and maxillofacial evaluation and scintigraphy with ^{99m}Tc-pertechnetate were performed in all patients before surgery and during follow-up (0–7 days; and >3 months postoperatively). Ophthalmologic evaluation included best-corrected visual acuity, Schirmer's test, BUT, and fluorescence staining of cornea and conjunctiva, as previously described[17–19]. In order to avoid the influence of local hyperthermia and physical activity on secretion of transplanted SMGs, room temperature was set at 23 °C, and patients rested for 30 min without any physical activity or glandular stimulation before each test[20]. Saliva was collected between 09:00 and 11:00 h. All patients were asked to refrain from eating, drinking, brushing their teeth, and using tobacco for at least 1 h before collection. Patients was positioned in a relaxed position leaning slightly forward and swallowed to clean the residual saliva in the oral cavity. Unstimulated whole saliva was drooled directly into a sterilized plastic tube for 5 min. The salivary flow rate was calculated by the following formula: salivary flow rate = (weight of the tube with collected saliva - weight of the empty tube)/5 min. Each patient underwent scintigraphy before surgery for glandular function evaluation and selection of suitable patients and donor SMGs. The method was previously reported in detail[21].

Operative procedures

The operative procedure was standardized[12]. Under general anesthesia, a caudally based temporal flap was elevated, preserving superficial temporal vessels. The SMG was exposed via a conventional cervical approach, preserving its structures and related blood vessels. The chorda tympani supplying the SMG was severed, whereas the lingual nerve was carefully protected. Wharton's duct was dissected, retaining a cuff of mucosa around the orifice. Subsequently, the freed SMG was transferred to the temporal region and revascularized to the superficial temporal vessels using standard microvascular techniques[13]. The distal end of Wharton's duct was sutured to form an opening in the upper lateral conjunctival fold. A nylon tube was inserted into the duct and maintained for 10 days for postoperative irrigation (Fig. 1). During the perioperative period, graft viability was checked by palpation. In our experience, Schirmer's test proved to be the best monitor of microvascular circulation in the transplanted gland. If needed, graft vitality was assessed by scintigraphy using ^{99m}Tc-pertechnetate[21].

Postoperative follow-up

All patients were checked by scintigraphy with ^{99m}Tc-pertechnetate 1 week after surgery to confirm vitality of the transplanted gland[21]. They were followed up and re-evaluated at 3 months and 1 year after surgery. All patients were asked to grade their treatment satisfaction on a scale. If results of examinations remained stable, patients would be recalled annually for evaluation (See Questionnaire in Supplementary material).

Lamellar keratoplasty

Trephination was performed using a manual trephine with a stromal thickness of approximately 60–80%, and partial-thickness anterior keratectomy was performed through dissection with a Bard–Parker blade or a disposable knife. The anterior stromal graft was sutured to the previously prepared recipient corneal bed using 10/0 nylon sutures.

Saliva and saliva–tear collection

During the period between May 2009 and January 2011, SMG saliva and saliva–tear samples were collected from consecutive patients with successful transplantation for comparison of the secretion compositions before and after operation. Before surgery, under the same condition with whole saliva

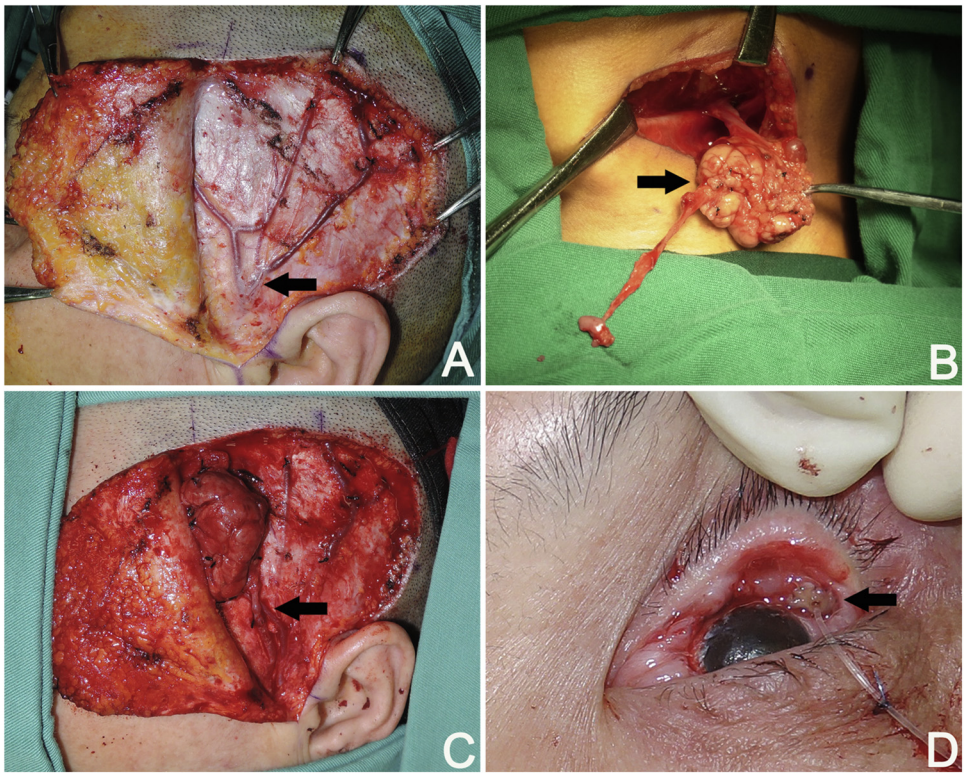

Fig. 1. Surgical procedures of submandibular gland (SMG) transplantation. (A) Temporal flap was elevated and superficial temporal vessels (arrow) were preserved. (B) SMG (arrow) was freed via a conventional cervical approach, preserving its structures, Wharton's duct and related blood vessels. (C) SMG was transferred to the temporal region and revascularized to the superficial temporal vessels (arrow). (D) The distal end of Wharton's duct was sutured to form an opening (arrow) in the upper lateral conjunctival fold, with a nylon tube inserted and left in the duct for 10 days.

collection, after putting a dry cotton roll at the parotid ductal papilla to absorb saliva from the parotid gland, SMG saliva was collected from the floor of the mouth by a micropipette connected to a suction device. From 1 day to 5 years (mean: 18 months) after transplantation, tear fluid samples were collected with microcapillaries dipped into the nasal angle of the eye, avoiding contact with conjunctiva and eye lid. This fluid was termed 'saliva–tears'. Natural tears were collected in healthy volunteers using the same method. All samples were collected between 08:00 and 11:00 h, at least 1 h after awakening. Both patients and healthy volunteers had abstained from exercise or food for at least 30 min. After collection, samples were immediately stored in 0.5-mL Eppendorf vials at −20 °C until analysis.

Laboratory analysis

Saliva and saliva–tears were examined in the Clinical Laboratory of the Peking University School of Stomatology. Specific parameters, including sodium, potassium, osmolality, amylase and total protein content were measured using routine laboratory methods as described below. Sodium and potassium levels were determined using a flame photometer. Amylase levels were assessed using enzymatic colour test (EPS-Amylase-Test, China National Biotec Group Co., Ltd. Beijing, China). Total protein content was measured using the pyrogallol red method. Osmolality was calculated according to the formula: Osmolality (mOsm) = 1.9 × (sodium + potassium) (mmol/L).

Statistical analysis

Clinical and laboratory data were compared from all patients at baseline, 3 months after surgery, and the last follow-up. Differences regarding subjective dry eye symptoms, ophthalmologic parameters, and saliva and saliva–tears composition were compared between baseline and follow-up using the Wilcoxon signed rank test. Overall, P values < 0.05 were considered statistically significant.

Results

Primary patient data

From August 1999 to January 2015, all patients received microvascular autologous SMG transplantation: 170 unilateral and 15 bilateral transplantations. In total, 200 eyes underwent surgery. Stevens–Johnson syndrome (118 eyes) was the primary aetiology of dry eye, followed by acute conjunctivitis (32 eyes) and other aetiologies (six eyes). Aetiology for 44 eyes was unclear.

Preoperative medical history ranged from 6 months to 51 years (mean: 10.7 years). In all patients, preoperative conservative measures including artificial tear substitutes and occlusion of tear drainage had been used but had proven unsuccessful in relieving discomfort and visual interference.

Primary survival rate of transplanted SMG

Successful microvascular SMG transplantation was achieved in 185/200 (92.5%) glands. Surgery failed in 15 glands: four due to anatomical abnormalities (no available donor vein), seven due to venous thrombosis, and four due to arterial thrombosis. In eight cases, non-revascularized glands were removed within 1 week after surgery. In the remaining seven cases, glands were left at the recipient site. No secondary infection occurred in these cases.

Follow-up

Among 185 eyes with viable transplanted SMG, five newly operated eyes were followed up for <1 year, duct obstruction of the transplanted SMG occurred in five eyes within 1 year, whereas we could not follow-up on 12 eyes because of changed contact information. The remaining 163 (88.1%) eyes were followed up for >1 year after surgery. No baseline differences were noted between patients with or without available follow-up information.

Glandular secretion regularity

In patients with successful transplantation, clinical observation revealed regular changes in the amount of secretion from transplanted glands after transplantation, which could be divided into four stages: transient hypofunction period (1–2 days after surgery), temporary epiphora period (3–6 days after surgery), latent period (1 week to 3 months after surgery), and functional recovery and stable period (>3 months after surgery).

During the initial 1–2 days after surgery, secretion was extremely limited. Subsequently, hypersecretion occurred during the temporary epiphora period (Schirmer's test median 35 mm; interquartile range (IQR) 23–47 mm), although secretion gradually declined over the next 3 months during the latent period (1.25mm; 0–3mm). Finally, the secretion rate increased again after 3 months (median 18mm; IQR 8.5–30mm). One year after transplantation, Schirmer's test results remained stable (median 19.5 mm; IQR 10–28mm). The lubricative effect of saliva–tears was deemed satisfactory as patients suffering from corneal irritation were either free of symptoms or experienced significant relief.

Complications

Obstruction of Wharton's duct of transplanted SMGs occurred in 16 cases. A solitary stone was found and removed in one patient. Duct blockages such as mucus plugs were cleared by irrigation in two grafts. In the remaining 13 patients, surgical opening was performed. Orifice reconstruction succeeded in six of the eight patients whose stenosis was near the orifice. Wharton's duct reconstruction with venous graft was successful in two of the five cases where stenosis was located in the middle segment of the duct.

Clinical symptoms of epiphora occurred in 98 (60.1%) eyes (93 patients)> 3 months after surgery (Schirmer's test >35 mm) and were induced by physical exercise and hot temperatures, which were successfully managed by reducing the graft size in 85 eyes: once in 57, twice in 25, three times in two, and four times in one eye. Moreover, nonsurgical methods including topical application of transcutaneous atropine gel[22] were used to control opportunistic epiphora in 30 eyes. Among these, a combination of reduction surgery with a nonsurgical method was applied in 17 eyes, and nonsurgical treatment alone was applied in 13 eyes. As a result, epiphora was significantly controlled in 83 eyes.

Patient questionnaire

Among 163 eyes followed up for >1 year, subjective relief of symptoms including dryness, burning, foreign body sensation, itching, and red eye was achieved in 151 (92.6%) eyes 3 months after transplantation. Use of artificial tear substitutes was discontinued in 146 (89.6%) eyes. No significant differences were noted in symptom relief between 3 months and >1 year after transplantation. Subjective satisfaction rate was 87.7% (143/163). Among 20 eyes of dissatisfied patients, 15 reported severe epiphora, while viscous secretions resulting from chronic obstructive sialadenitis of transplanted SMGs were reported in five eyes.

No xerostomia was reported after gland transplantation, even in the 15 cases with bilateral SMG transplantation.

Ophthalmologic evaluation

Schirmer's test values demonstrated that basal secretion with vital transplantation increased from a preoperative level of median 0mm ($n = 151$, IQR 0–1 mm) to median 18 mm ($n = 151$, IQR 8.5–30 mm) 3 months after surgery and remained virtually unchanged at a median of 19.5 mm ($n = 151$, IQR 10–28 mm) 1 year after surgery and 18.5 mm ($n = 51$, IQR 10–28.5 mm) 5 years after surgery. Significant differences were noted between preoperative and postoperative basal secretion at 3 months ($P < 0.001$). No significant differences were noted among 3-month, 1-year, and 5-year follow-up data ($P > 0.05$; Fig. 2).

As moisture and lubrication of the ocular surface increased, corneal morphological conditions improved (Fig. 3). Mean fluorescent staining scores reduced from 11.25 ± 1.42 before surgery to 7.25 ± 3.37 ($n = 151$) 1 year after surgery and 5.76 ± 3.67 ($n = 51$) 5 years after surgery. Significant differences ($P < 0.05$) were noted among preoperative values and 1- or 5-year postoperative values, while no significant difference was found between postoperative values ($P > 0.05$; Fig. 2).

Tear-film BUT increased in 86 eyes and remained unchanged in 65 eyes with a BUT of 0 both before and after surgery. Tear film formation and stability were noticeably improved, which changed from

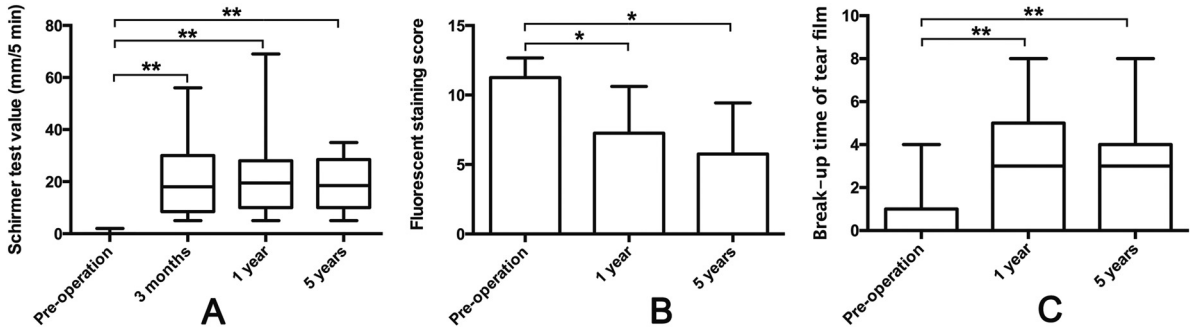

Fig. 2. Schirmer test value (A), fluorescent staining score (B) and break-up time of tear film (C) before and after surgery.

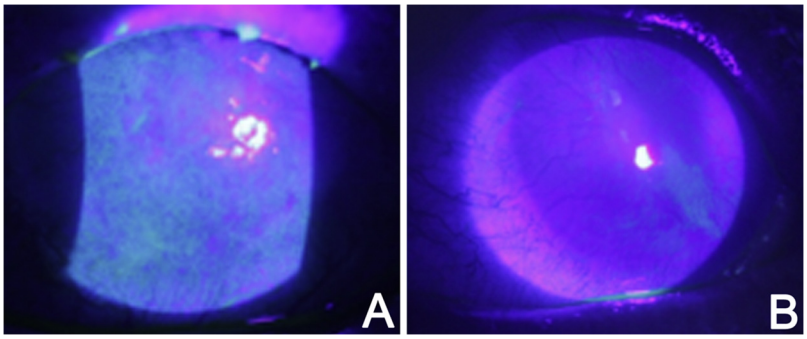

Fig. 3. Comparison of fluorescent staining on the cornea before surgery (A) and after surgery (B). Postoperative fluorescent staining diminished in intensity over time, and the number of staining spots was reduced.

unformed before surgery to gradually formed after surgery, but tear films in most patients were still irregular and nonuniform with poor quality. Mean BUT scores improved from 0 (IQR 0–1) before surgery to 3 at both 1 ($n = 151$, IQR 0–5) and 5 ($n = 51$, IQR 0–4) years after surgery. Significant differences were noted ($P < 0.001$) among preoperative values and 1- or 5-year postoperative values, while no significant difference was found between postoperative values ($P = 0.839$; Fig. 2).

Postoperative best-corrected visual acuity improved in 85 (56.3%) eyes. Blindness was eliminated in 31 patients. Low visual acuity became normal in 21 eyes. Visual acuity of 49 eyes remained unchanged but decreased in 17 eyes, which was related to epiphora ($\chi 2 = 15.866$; $P < 0.01$; Table 1).

Lamellar keratoplasty

Lamellar keratoplasty was performed in 15 cases. Among these, grafts remained transparent and patient's vision improved significantly in five cases after 3 years of follow-up (Fig. 4). Grafted cornea became opacified in the remaining 10 cases.

Biochemical investigation

Table 2 lists concentrations of electrolytes and proteins in normal SMG saliva and saliva–tears compared with same parameters in natural tears. Significant differences were noted for all analysed parameters in normal SMG saliva and saliva–tears ($P < 0.05$). Sodium, potassium, amylase, and total protein concentrations as well as osmolality increased over time and shifted to be more similar to those of natural tears (Table 2).

Discussion

From our 15-year experience, autologous microvascular SMG transplantation offers favourable prognosis. Clinical and scintigraphic results proved that secretion of all viable glands maintained long-term function with stable basal secretion. Subjective questionnaires showed that in most successful cases, there was significant alleviation of typical symptoms of dry eye such as dryness, burning, foreign body sensation, itching and red eye. Objective examination showed improvement in repair of ocular surface damage within the observation period. Saliva–tears may provide an environment wherein the epithelium can improve its structure and function. Consistent with previous studies 9–11,18,19, our treatment proved beneficial to morphological conditions of the ocular surface, evidenced by ocular staining and tear film formation. Visual acuity improved in over half of the patients owing to amelioration on quantity and quality of tear film. Saliva–tears can replace natural tears to moisturize and lubricate the ocular surface, thereby reducing the patient's discomfort and improving quality of life[24,25]. All these results further demonstrate the effectiveness of SMG transplantation in severe dry eye.

Several factors may influence outcomes of SMG transplantation. First, to guarantee the success of the technique, transplanted SMGs should be viable to secrete saliva into the orbit to lubricate the ocular surface. However, as it entails transplantation of a small organ in the head and neck, this procedure is technique sensitive, and operative failure may occur due to vascular thrombosis. In the study by Borrelli et al., graft necrosis because of vascular complications or infection occurred in 6/44 transplanted glands with a primary survival rate of 86.4% (38/44)[9]. In our series, the primary survival rate of transplanted glands 1 week after surgery was 92.5% (185/200). Therefore, control of vascular complications is a key factor in achieving operative success.

Successful transplantation is just the beginning. Postoperative regulation of transplanted SMGs is the second step to ensure long-term outcomes. The regulation mechanism of secretion from denervated transplanted SMGs after surgery has undergone marked changes[10,14,21]. Secretion of the transplanted SMG is extremely low during the 'latent period', wherein duct obstruction may occur. Borrelli et al. reported that the secretory duct became obstructed leading to secondary graft atrophy in 2/44 transplanted SMGs[9]. In our series, duct obstruction occurred in 16 transplanted glands, and five glands finally failed to achieve duct patency after duct reconstruction with venous graft or recontouring of the duct orifice. Follow-up results of our study showed that viscous secretions resulted from chronic obstructive sialadenitis of transplanted SMGs, which was a primary cause of patient dissatisfaction[23]. Therefore, duct obstruction owing to low secretion of transplanted SMGs is another main factor influencing outcomes of this technique, and thus, promoting gland secretion during the 'latent period' to prevent duct obstruction is critical. Our group has performed systematic studies on the secretory mechanism in denervated transplanted SMGs[26–28]. Results showed that secretion-related receptors play an important role in regulating secretion of normal and denervated SMGs. Alteration of the transient receptor potential vanilloid subtype 1 (TRPV1) and muscarinic receptors is involved in functional and morphological changes early after transplantation. Administration of exogenous neurotransmitters, particularly carbachol and capsaicin, can improve early secretion after SMG transplantation[29–37]. Based on these findings, carbachol and capsaicin have been clinically used to regulate secretion of transplanted SMGs for prevention of duct obstruction due to minimal secretion during the ''latent period''[29,30,38,39].

Table 1. Best-corrected visual acuity comparison between preoperation and >1 year after operation (eyes).

	<0.05	0.05–0.1	0.12–0.3	0.4–0.6	0.8–1.0
Pre-operation	78	25	22	21	5
Post-operation	47	41	28	22	13

Wilcoxon signed rank test, $\chi^2 = 15.866$; $P < 0.01$.

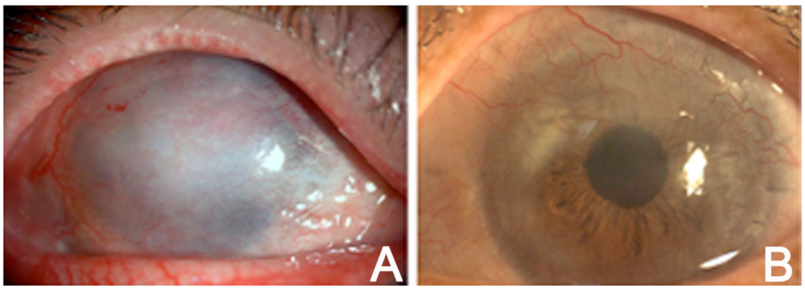

Fig. 4. Lamellar keratoplasty after transplantation of submandibular gland. (A) Cornea before lamellar keratoplasty; (B) grafts remained transparent and patient vision was improved significantly after 8 years of follow-up.

Table 2. Comparison of composition between normal submandibular gland saliva, saliva–tears and natural tears.

Item	SMG saliva ($n = 30$)	Saliva–tears ($n = 30$)	Natural tears (n) = 30)
Na^+ (mmol/L)	$7.26 \pm 2.23^{***}$	$23.66 \pm 12.95^{***}$	$156.0 \pm 20.34^{***}$
K^+ (mmol/L)	12.8 ± 3.63	$22.28 \pm 6.11^{*}$	$18.4 \pm 8.93^{*}$
Osmotic pressure ($mOsm/kgOH_2O$)	$16.9 \sim 92.7^{***}$	$106.3 \sim 113.8^{***}$	$176.8 \sim 460.1^{***}$
Amylase (U/L)	$30900 \pm 20000^{**}$	$73772 \pm 92040^{**}$	1854 ± 1200
Total protein (g/L)	$0.447 \pm 0.277^{**}$	$0.858 \pm 0.517^{**}$	3.603 ± 1.071

Osmolality (mOsm) = 1.9 × (sodium + potassium) (mmol/L). SMG, submandibular gland. Wilcoxon signed rank test.
* Significant difference when compared with natural saliva samples.
** Significant difference when compared with natural tear samples.
*** Significant difference between the three groups.

Epiphora due to oversecretion of transplanted glands is another factor influencing outcomes. In our study, subjective satisfaction correlated negatively with obvious epiphora. Among the 20 eyes of dissatisfied patients, 15 were due to severe epiphora. Decreased visual acuity in 17 eyes was also related to severe epiphora. Therefore, effective control of epiphora is important. In recent years, we have applied transplantation of partial SMG in patients with ample and normal functioning SMGs, wherein dry eye symptoms were alleviated and incidence of severe postoperative epiphora was markedly reduced[16]. Moreover, topical application of atropine gel can effectively control mild epiphora[22]. Botulinum toxin A injection is also effective for epiphora treatment[15]. Conventional reduction surgery of transplanted SMGs is the treatment choice for most severe cases with epiphora.

When cornea of severe dry eye patients is completely opacified, corneal grafts are the primary method to recover visual acuity. However, corneal graft is not an option in cases of severe dry eye syndrome. SMG transplantation improves their comfort and ocular humidity, thereby offering an opportunity for corneal graft. In this cohort, lamellar keratoplasty was performed in 15 patients following SMG transplantation, and five grafts remained transparent after a mean follow-up of 3 years[18,19]. SMG transplantation made corneal transplantation a possible option in these severe dry eye patients. However, at present, the success rate of such corneal grafts is low. Further investigation is warranted on factors that influence graft healing to improve transplantation success rates, including influence of postoperative saliva–tears and immunological rejection.

Although SMG transplantation can provide substitute tears and alleviate patients' severe discomfort after surgery, natural SMG saliva not only differs from natural tears in its quantity of secretion but also in its composition[24,25]. Whether secretion of transplanted glands has any long-term harmful effects on the ocular surface is of interest to both physicians and patients. In this study, we collected the saliva tear from the patients with successful operation. And the laboratory analysis showed secretion of transplanted glands became similar to that of natural tears. Potassium and sodium concentrations were increased in saliva–tears, and consequently, osmolality increased as well, since total protein was lower than that in natural tears. The underlying mechanism of these composition changes of transplanted SMG secretion is still not clear. Geerling et al. found that the ocular surface was susceptible to minor changes of tear osmolality. Hypotonic tears may induce osmotic cell oedema, possibly accounting for focal epithelial oedema[18,19,24,25]. It is more obvious when patients have severe epiphora. In our study, both patients' subjective satisfaction and decreased visual acuity were related to severe epiphora. Therefore, effective control of epiphora is crucial, and future studies should focus on improving the composition of saliva–tears to mimic physiological tears.

In conclusion, our 15-year study on long-term outcomes of 163 glands demonstrated that autologous SMG transplantation is an effective treatment with stable results in severe or refractory dry eye. The secretory function of transplanted SMGs remained stable and active. Primary factors influencing results were blood vessel thrombosis, Wharton's duct obstruction and epiphora. Surgical technique is the key factor to ensure success of transplantation, and postoperative secretion regulation of transplanted SMGs is also crucial.

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Competing interests

The authors have no conflicts of interest to declare.

Ethical approval

This study was approved by the ethics committee of Peking University Health Science Center (NO. IRB000 01 052 -08048).

Patient consent

Written patient consent was obtained to publish clinical photographs.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijom.2018.07.006.

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