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Insular infraorbital neurovascular pedicle labial salivary gland transplantation for the treatment of severe dry eye disease: an IDEAL stage 0, 1 and 2a study

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ABSTRACT

Objectives To address the lack of nerve and blood supply after labial salivary gland transplantation (LSGT) resulting in glandular atrophy. We designed a modified LSGT, called insular infraorbital neurovascular pedicle LSGT, and evaluated the postoperative efficacy.

Design This is a prospective, single-centre, self-contained study.

Setting The research was conducted at Beijing Tongren Hospital, Capital Medical University from July 2019 to March 2024.

Participants Eight patients (nine eyes) with severe dry eye disease (DED) were enrolled in this study.

Interventions All patients underwent insular infraorbital neurovascular pedicle LSGT and were followed up for at least 6 months postoperatively.

Main outcome measure Key evaluation indices were best-corrected visual acuity (BCVA), Ocular Surface Disease Index (OSDI) score, tear break-up time (TBUT), Corneal Fluorescence Staining (CFS) score, and Schirmer I test (SIT).

Results With a mean follow-up of 17.56±11.72 months, BCVA improved in four eyes and stabilized in five. OSDI score decreased from 59.33±14.37 to 26.27±10.14 ($p<0.001$). SIT improved from 0.00±0.00 mm to 5.44±2.01 mm ($p<0.0001$). TBUT increased from 0.23±0.48 s to 5.48±4.67 s ($p=0.008$). CFS scores decreased from 12.56±2.65 to 7.56±3.09 ($p<0.001$). All glands remained viable with good blood supply, and no serious complications were observed.

Conclusion Insular infraorbital neurovascular pedicle LSGT for severe DED is a feasible and effective treatment, maintaining good secretory capacity and blood supply long-term.

Trial registration number ChiCTR2200056015.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Salivary gland transplantation is an important treatment for severe dry eye disease (DED).
⇒ Submaxillary gland (SMG) transplantation is a complex procedure requiring intraoperative vascular anastomosis.
⇒ In addition, epiphora and duct obstruction often occur postoperatively. Labial salivary gland transplantation (LSGT) is a simpler and less invasive choice.
⇒ However, the transplanted glands during the procedure are completely disconnected from the nerves and blood vessels, often leading to gland atrophy and resulting in surgical failure.

WHAT THIS STUDY ADDS

⇒ Our study designed a novel technique named insular infraorbital neurovascular pedicle LSGT, which combined the advantages of LSGT and SMG transplantation.
⇒ In contrast to the SMG transplantation, the secretion of labial glands was stable. Compared with LSGT, this procedure preserved the neurovascular pedicle associated with the labial gland.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Long-term postoperative follow-up revealed significant improvement in the patient's symptoms and signs, with good secretory capacity and blood supply of the gland.
⇒ This procedure provides a new option for patients with severe DED.

INTRODUCTION

Dry eye disease (DED) is defined as a multifactorial disease of the ocular surface, with a prevalence rate of 5% to 50%, and is characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms such as foreign body sensation, photophobia, and pain, which severely affect the quality of life of patients.[1 2] DED is divided into four levels according to severity, staged treatment is very important.[3–6] For mild-to-moderate DED, the main treatment is warm compress meibomian gland treatment and topical medications (eg, artificial tears, mucin secretagogues, immunomodulatory agents, and nanomedicines).[7] In severe DED caused by Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis, and post lacrimal gland surgery, treatment with topical medications has poor efficacy and surgery like salivary gland transplantation is a good option for improving symptoms and ocular lubrication.[4 8]

In 1951, Filatov and Chevartsev[9] proposed parotid transplantation. However, this procedure often resulted in epiphora and the length of the parotid duct was frequently insufficient to reach the conjunctival sac.[10 11] In 1986, Murube-del-Castillo[12] proposed submandibular gland (SMG) transplantation. Long-term clinical studies have shown that SMG transplantation can relieve symptoms and improve Schirmer test results, with 72% of SMG grafts remaining viable at the last follow up.[13 14] However, one out of three patients often experienced epiphora after surgery, which severely affected their vision and required subsequent gland reduction surgery.[15]

In contrast to major salivary gland transplantation, labial salivary gland transplantation (LSGT) has the advantages of easier operation, less invasive, glandular sufficiency, and stable glandular secretion.[16–18] Nevertheless, the probability of glandular atrophy after LSGT is higher than SMG transplantation requiring vascular anastomosis, which may be due to the absence of nerve and blood supply to the graft. Research in animals reported severe scarring of the labial glands, reduced alveolar gland tissue, and structural abnormalities at 3 months postoperatively, with only one out of eight of the grafts maintaining their original size.[19] Pathological examination of patients who underwent LSGT also revealed minor acinus atrophy, duct with mucin content, and lymphocyte infiltration.[20 21] Currently, there are no studies proposing solutions for postoperative glandular atrophy.

With the dual aims of providing stable innervation and blood supply to the graft, we designed a modified LSGT technique. Here, we described the surgical approach named insular infraorbital neurovascular pedicle LSGT and the long-term results of using it for the treatment of severe DED.

METHODS

IDEAL stage 0: conceptualization of the technique and preclinical simulation

Three embalmed Chinese cadavers were autopsied with the approval of the Ethics Committee (ethics number: TRECKY2016-010). In all specimens, latex containing a red coloring agent was injected through the common carotid artery to reveal the courses of its branch arteries. The skin, subcutaneous tissues of the face, zygomaticus muscle, levator labii superioris muscle, and other facial expression muscles were removed. The infraorbital artery (IOA) and infraorbital nerve (ION), as well as their branches, were exposed (figure 1a). To confirm the feasibility of the procedure, the labial gland with the neurovascular pedicle was detached and turned upward to make the graft reach the orbit (figure 1b).

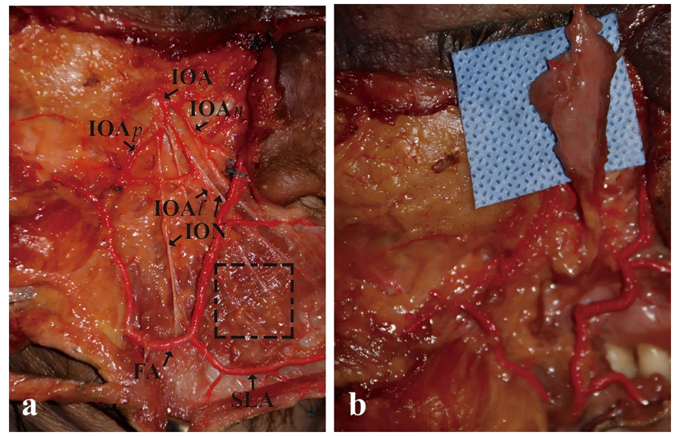

Figure 1 Anatomical diagram of the infraorbital nerve (ION) and infraorbital artery (IOA). (a) The ION and IOA emanate from the infraorbital foramen and divide into many branches. Both of them have labial branches that enter the superior labial regions (rectangle). (b) Turned the labial gland with the neurovascular pedicle upward to make the graft reach the orbit. FA, facial artery; IOA, infraorbital artery; IOAn, nasal branch of the infraorbital artery; IOAl, labial branch of the infraorbital artery; IOAp, palpebral branch of the infraorbital artery; ION infraorbital nerve; SLA, superior labial artery.

IDEAL stage 1/2a: informed consent, study population

According to the tenets of the Declaration of Helsinki, informed consent for all the investigations and surgical procedures was obtained from participants. The clinical study has been registered in the Chinese Clinical Trial Registry.

From July 2019 to March 2024, eight patients (nine eyes) were enrolled. The inclusion criteria comprised of the following: Patients were diagnosed with severe DED according to the criteria proposed by the Asia Dry Eye Society[3]; received a series of treatments such as topical medications, moisture chamber spectacles, IPL laser, and punctal plugs without improvement in signs and symptoms; maximal accumulation (MA) ≥0.5 of SMG as calculated from scintigraphy time-activity curves; ultrasound showed IOA with abundant blood flow signal; labial gland biopsy showed no atrophy and inflammatory cell infiltration.

The exclusion criteria comprised breastfeeding or pregnant women; cases with acute ocular inflammation or infection; history of eye surgery within 6 months before enrollment; Sjögren syndrome; symptoms of xerostomia or scintigraphy showing hypofunction of multiple major salivary glands.

IDEAL stage 1/2a: variables

Before surgery, each patient underwent an ophthalmologic examination, ^{99m}Tc-pertechnetate scintigraphy, vascular ultrasound, and labial gland biopsy. Best-corrected visual acuity (BCVA), Ocular Surface Disease Index (OSDI) score, tear break-up time (TBUT), Corneal

Fluorescence Staining (CFS) score, and Schirmer I test (SIT) were used as the main evaluation indices.

Ophthalmologic evaluation

A systematic ophthalmic examination was performed by the same ophthalmologist before and after surgery (1 month, 3 months, 6 months), with follow-up visits every 6 months after the sixth month of surgery. BCVA, intraocular pressure (IOP), OSDI score, TBUT, CFS score, and SIT were examined and recorded in the above order. BCVA was measured by Tumbling E Chart. IOP was measured by an Icare tonometer (Icare Finland Oy, Helsinki, Finland). In this study, TBUT was measured using fluorescein breakup time. After staining the cornea with impregnated strips, the patients were asked to blink three times, then stop blinking and observe the time of appearance of the first dry black spot under cobalt blue light. The CFS score was assessed with a 1% fluorescein solution using the 0 to 15 scoring system. Punctate epithelial erosions (PEEs) of the nasal and temporal cornea, the superior cornea, mid cornea, and inferior cornea were graded on a scale of 0 (no PEE), 1 (1–5 PEEs), 2 (6–30 PEEs), and 3 (more than 30 PEEs).[22] The SIT was performed by folding the Schirmer paper strip (5 mm*35 mm) at the notch and hooking the folded end over the temporal one-third of the lower lid margin and measuring the length of wetting from the notch after 5 min.[23]

Salivary gland scintigraphy

The patient was placed in a supine position, and the field of view included the salivary glands and part of the thyroid gland. After intravenous administration of 50 MBq 99mTc-pertechnetate, dynamic scintigraphy was performed and time-activity curves were generated over a period of 30 min (1 frame/min, matrix 128*128, zoom factor 1.3). Salivary excretion of 99mTc-pertechnetate was stimulated by subcutaneous administration of 0.2 mg carbachol at 20 min.[24]

Oval-shaped regions of interest were drawn over the four major salivary glands (figure 2a). The following points were designated on the schematic presentation of the glandular time-activity curve (figure 2b): point A, the initial shoulder; point B, the maximum activity point. The counts at points A and B were shown as V1 and V2. MA was quantified according to the following formula: MA=(V2−V1)/V2*100 (%).

Vascular ultrasound

Ultrasound was performed on the patients preoperatively and at 6 months postoperatively. The room temperature was 25°C. The patient was placed in a supine position, the pillow removed, and the examination site was fully exposed. The appropriate image depth was adjusted, from near to far. The best section of the long axis of the IOA was displayed under the guidance of color Doppler flow imaging mode, and then the pulsed wave Doppler to confirm the artery.[25] Blood flow parameters measured were peak systolic velocity (PSV) in centimeters per second (cm/s), end-diastolic velocity (EDV) in centimeters per second (cm/s), and Resistivity Index (RI).

Histopathologic examination

Labial gland biopsy was performed within 1 week after salivary gland scintigraphy. After disinfection of the lower lip, local anesthesia was applied. An incision of 3–5 mm was made and the labial gland tissue containing at least four glandular lobules was removed and placed in formalin solution.[21] After dehydration, the specimens were embedded in paraffin, cross-sectioned, and stained with hematoxylin-eosin. The sections were observed under an optical light microscope.

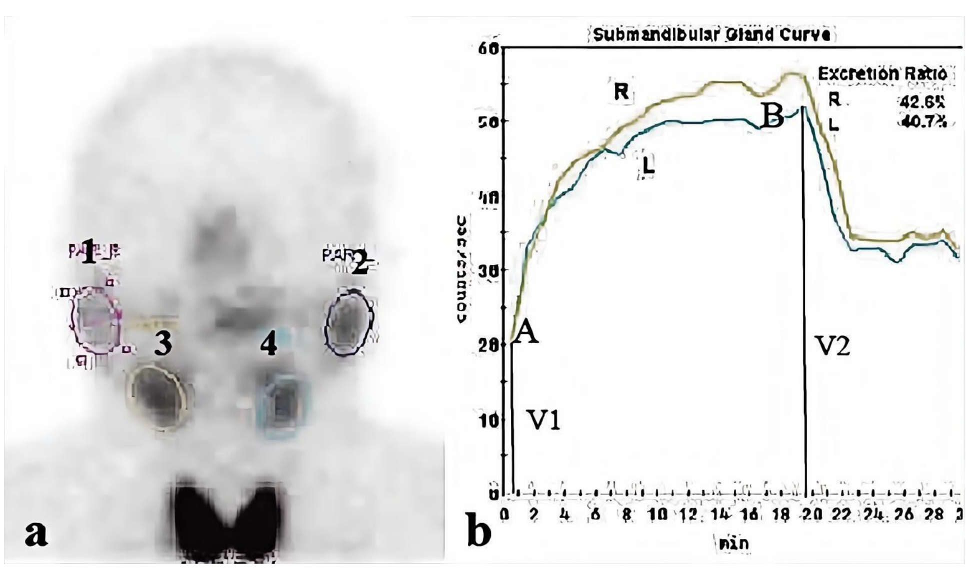

Figure 2 Scintigraphy of salivary glands. (a) Oval-shaped regions of interest on scintigraphic image: areas 1 and 2, parotid glands; areas 3 and 4, submandibular glands. (b) Time-activity curves of submandibular glands. A=initial shoulder; B=maximum activity point; V1 and V2=counts at A and B, respectively.

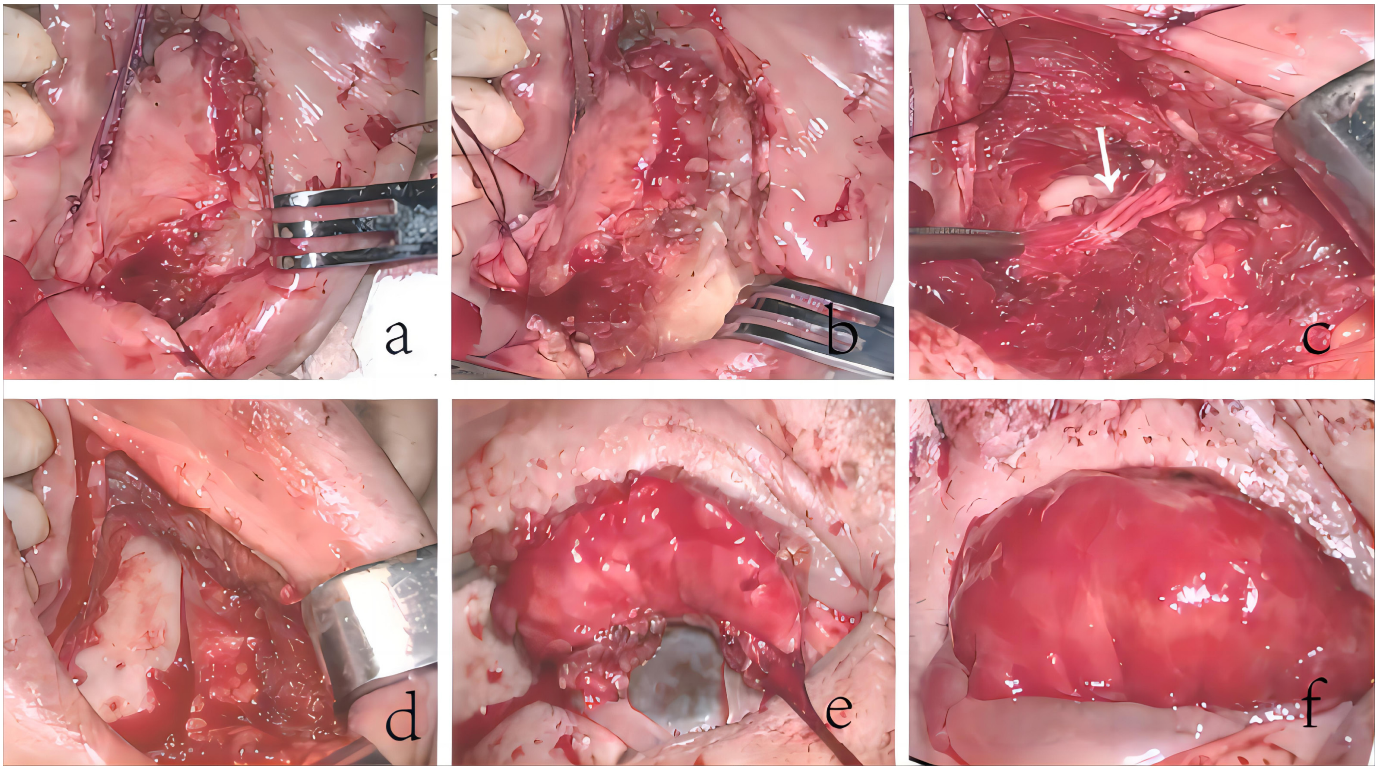

Figure 3 Intraoperative appearance of insular infraorbital neurovascular pedicle labial salivary gland transplantation. (a) Incise the mucosa of the upper lip along the markings. (b) Separate the labial gland. (c) Separate the infraorbital artery and infraorbital nerve (arrow). (d) Turn over the gland with neurovascular pedicle to the orbit and the maxillary bone wall is exposed. (e) Cut the lower lid conjunctival sac and transplant the labial gland into the recipient bed. (f) Suture the labial gland to the surrounding conjunctival.

IDEAL stage 1/2a: surgical technique and postoperative medication

Preoperatively, levofloxacin eye drops were used in the operated eye four times a day and the mouth was rinsed with compound chlorhexidine by gargling three times a day for 3 days.

Under general anesthesia, a 20 mm*15 mm incision was made on the mucosa of the root of the upper lip on the same side as the operative eye (figure 3a). A block of tissue containing oral mucosa and submucosal connective tissue (including the labial glands) was carefully separated along the deep mucosal surface against the bony surface of the anterior wall of maxillary sinus (figure 3b). ION and IOA branches associated with the labial glands were preserved and continued to be separated approximately 15 mm toward the infraorbital foramen (figure 3c). Levator labii superioris muscle above the neurovascular pedicle was detached from the maxillary tonally up to the inferior orbital margin to expose the infraorbital space. Conjunctival fornix of the lower lid was incised and the orbital septum was bluntly dissected to the inferior orbital margin. The labial tissue with the neurovascular pedicle was turned upward through the infraorbital space and passed out of the orbital septum to the conjunctival sac. Maxilla was fully exposed within the upper lip incision (figure 3d), indicating that the graft was separated and turned tightly against the bone wall. The labial gland was placed on the recipient bed with the mucosa oriented toward the surface (figure 3e). After checking that the neurovascular pedicle was not twisted, the upper lip incision was closed with 3-0 sutures. The edges of the graft were sutured to the surrounding conjunctiva and Tenon's s tissue using 8-0 polylactic acid (figure 3f).

Postoperatively, intravenous ornidazole 25 mg two times e a day for 7 days, intravenous dexamethasone sodium phosphate injection 5 mg and cefotaxime 50 mg once a day for 3 days were applied. Tobramycin and dexamethasone eye drops (Alcon, Couvreur, Belgium) four times a day and tobramycin and dexamethasone eye ointment (Alcon, Couvreur, Belgium) once per night were used for 7 days. Then, 0.1% fluorometholone eye drops (Santen, Japan) three times a day after 1 week postoperatively, tapered, and stopped after 6 weeks. Recombinant bovine basic fibroblast growth factor eye drops (Essex Bio-Technology, China) four times a day for 1 month. Depending on the patient's symptoms, preoperative lubricant eye drops and ointments can be continued.

Statistical analysis

Data are presented as mean±SD. Due to the small sample size, normality tests were conducted on the data of OSDI, CFS, SIT, etc. For normally distributed data, paired t-tests were used to compare preoperative and postoperative differences. For non-normally distributed data, the Wilcoxon signed-rank test was used to assess. Statistical analysis was carried out using SPSS V.26.0 (SPSS, Chicago,

Table 1 Patient characteristics

Patient	Age	Eye	Etiology	Duration of disease (years)	MA of left SMG (%)	MA of right SMG (%)	Follow-up (months)
1	40–50	OD	SJS	40	61.5	66.7	13
2	50–60	OS	LG injury	0.5	67.3	59.8	12
3	20–30	OS	SJS	0.75	75	80	13
4	40–50	OD	SJS	40	60	63.6	41
		OS					32
5	20–30	OD	Dacryoadenectomy	2	55.6	51.1	12
6	50–60	OS	SJS	35	53.1	50.9	21
7	<20	OD	SJS	6	64.3	63.5	8
8	30–40	OD	SJS	20	51.8	61.7	6

LG, lacrimal gland; MA, maximal accumulation; OD, right eye; OS, left eye; SJS, Steven-Johnson syndrome; SMG, submandibular gland.

Illinois, USA). A two-tailed p value <0.05 was considered statistically significant.

RESULTS

Eight patients (nine eyes) with severe DED who underwent insular infraorbital neurovascular pedicle LSGT were enrolled. The preoperative medical history of DED spanned 0.5–40 years. The baseline characteristics are summarized in table 1. The age ranged from 17 to 60 years (mean 43.40±13.39 years). Clinical outcomes were reported for at least 6 months (mean 17.56±11.72 months) follow-up.

Ophthalmologic evaluation

The preoperative and final follow-up results are summarized in table 2 and figure 4. At the last follow-up, BCVA improvement ≥20/200 was observed in four eyes and remained stable in five eyes. Dry eye symptoms were relieved in all patients, the frequency of artificial tears was reduced, and the OSDI score decreased from 59.33±14.37 to 26.27±10.14 (t=7.183, p<0.001). Mean TBUT increased significantly from 0.23±0.48 s to 5.48±4.67 s (Z=−2.666, p=0.008). Mean CFS dropped from 12.56±2.65 preoperatively to 7.56±3.09 postoperatively (t=6.882, p<0.001). Tear secretion was improved in all patients, with mean SIT from 0.00±0.00 mm preoperatively to 5.44±2.01 mm postoperatively (t=−8.138, p<0.0001). The surface of the oral mucosa exposed in the conjunctival sac was ruddy in all patients. Figure 5 shows the slit-lamp photographs of the right eye of case 4 at different postoperative times.

Vascular ultrasound

Preoperative and postoperative hemodynamic indices are summarized in online supplemental table S1 and figure S1. PSV of IOA was 22.78±3.67 cm/s preoperatively and 24.24±9.21 cm/s postoperatively (t=−0.557, p=0.593). EDV decreased from 7.85±2.08 cm/s to 5.95±1.30 cm/s (t=2.419, p=0.042). RI increased from 0.70±0.10 to 0.72±0.05 (t=−3.105, p=0.015). Online supplemental figure S2 shows the preoperative and 6-month postoperative color Doppler flow imaging of the right eye in case 4.

Complications

Complications such as surgical site infections, decreased visual acuity, diplopia, ocular proptosis, ocular motility disorders, ptosis, and epiphora were not observed in the operated eyes of all participants. Patients will experience facial edema for 1–2 months after surgery. Temporal local hypaesthesia of the operated cheek and upper lip occurred in all patients and was relieved by oral administration of vitamin B_1 10 mg and methylcobalamin 0.5 mg three times a day for 2 weeks to 3 months, with no cosmetic problems such as abnormal facial appearance or activity.

DISCUSSION

Treatment of severe DED is a global challenge that often requires surgery such as salivary gland transplantation to resolve. SMG transplantation humidifies the cornea and conjunctiva by draining saliva into the conjunctival fornix, which relieves patients' symptoms and improves Schirmer test results.[13 14] However, the surgical procedure for SMG transplantation is complex, requiring harvesting of the SMG, blood vessels, and Wharton's duct, and microsurgical techniques for vascular anastomose.[10] Meanwhile, the frequent postoperative epiphora seriously affects the results and needs subsequent gland reduction surgery.[15 26 27]

LSGT seems to be a new treatment option for severe cases of DED. There are estimated to be 600–1000 minor salivary glands in humans. These glands are located in the palatal, buccal, labial, and lingual parts of the mucosal membrane in the oral cavity and consist of small clusters of secretory cells with a short excretory duct that transports saliva to the surface of the mucosa.[28] The location of the minor salivary glands is shallow and the salivary secretion is small, accounting for approximately 8% of the total stimulated and unstimulated salivary secretion in humans.[29] In addition, proteomic analysis revealed

Table 2 Outcomes of insular infraorbital neurovascular pedicle labial salivary gland transplantation in severe dry eye disease

Case	BCVA		IOP (mmHg)		OSDI score		TBUT (s)		CFS score		SIT (mm)		Frequency of artificial tears	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
1	20/333	20/100	12	15	43	29.17	0	2.17	13	4	0	3	10–15	1–5
2	FC/30 cm	FC/30 cm	11	12	59.75	34	0	5.03	15	12	0	3	15–20	5–6
3	20/50	20/50	12	14	83.33	47.73	0	5	13	6	0	7	25–30	8–10
4	20/100	20/33	14	16	64	18	0	15.52	13	7	0	8	20–25	1–2
	20/100	20/40	15	14	56.25	15.91	0	10.81	12	6	0	7	20–25	1–2
5	20/32	20/32	16	15	43	24.63	1.31	2.2	7	4	0	3	15–20	5–8
6	FC/BE	20/133	14	18	59.38	29	0	4.15	15	12	0	6	20	2–3
7	20/1000	20/1000	10	11	78.27	20	0	2.22	15	10	0	5	20–30	4–5
8	20/200	20/200	12	15	47	18	0.78	2.19	10	7	0	7	15–20	5–6

BCVA, best-corrected visual acuity; BE, before eye; CFS, corneal fluorescence staining; FC, finger count; IOP, intraocular pressure; OSDI, Ocular Surface Disease Index; Post-op, postoperative; Pre-op, preoperative; SIT, Schirmer I test; TBUT, tear break-up time.

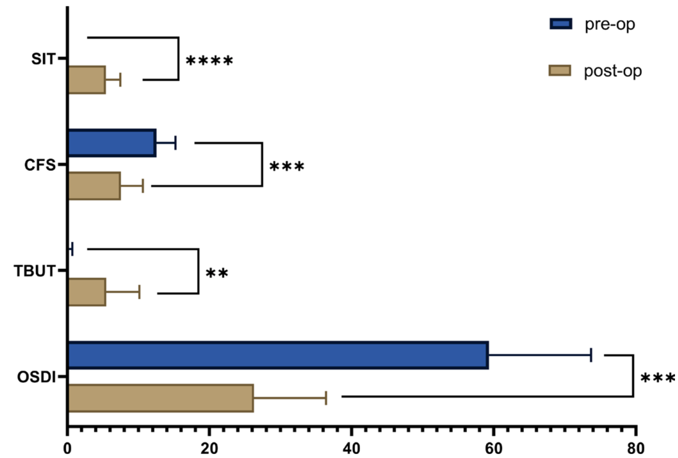

Figure 4 Outcomes of insular infraorbital neurovascular pedicle labial salivary gland transplantation in severe dry eye disease. **0.05<p<0.01; ***0.01<p<0.001; ****0.001<p<0.0001. CFS, Corneal Fluorescence Staining score; OSDI, Ocular Surface Disease Index; TBUT, tear break-up time; SIT, Schirmer I test.

that salivary tears contained almost all the proteins abundant in tear fluid and had highly active antibacterial proteins such as SIgA, and lysozyme, which may protect ocular structures.[30] Moreover, the saliva flow rate of minor salivary glands is 2.1–2.9 µL/min/cm^2, which is of the same order of magnitude as the tear flow rate of around 0.6–1.4 µL/min.[31] The secretion from the minor salivary gland accounts for most unstimulated saliva and is less affected by eating, so the ocular surface can remain continuously moist after transplantation.

Traditionally, a 1.5*2.5 cm mucosa graft with labial glands is harvested from the lower or upper lip. An incision of approximately 2.5 cm is made along the posterior edge of the tarsal plate, and the conjunctiva is dissected posteriorly for approximately 1.5 cm to prepare the recipient bed. The graft is sutured to the recipient bed with 7.0 or 8.0 sutures.[32] Sant' Anna *et al*[18] performed LSGT on 19 patients. A significant improvement in Schirmer scores, conjunctival and corneal staining scores, as well as grades of corneal neovascularization and opacification was observed. However, other studies revealed that grafts cannot remain viable in the long term after LSGT due to the absence of blood supply. Qin *et al*[19] assessed the efficacy of LSGT in eight rhesus monkeys with severe DED. Then, 24 weeks after surgery, the conjunctival epithelium showed squamous metaplasia with inflammatory cell infiltration. Wakamatsu *et al*[20] performed a histopathologic examination of transplanted labial gland tissue several months after surgery and showed varying degrees of fibrosis, acinar atrophy, and lymphocytic infiltration.

The blood supply of the glands is important for their survival. In SMG transplantation, the anterior facial vein or venae comitantes of the facial artery in the SMG were anastomosed with the temporal vein, and the facial artery in SMG was anastomosed with the temporal artery to maintain the long-term blood supply to the graft.[33] Postoperative follow-up revealed that atrophy of the gland

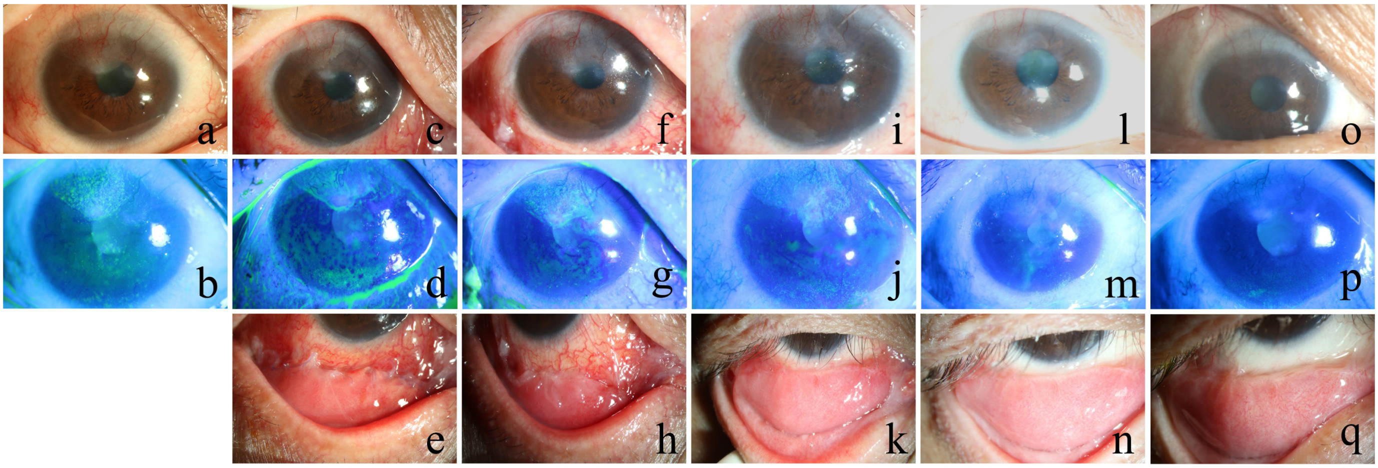

Figure 5 Slit-lamp photographs of the right eye of case 4 at different times after surgery. (a, b) Preoperatively, the patient's upper corneal epithelial defect with neovascularization growing 4 mm into the corneal limbus to the pupil margin. Fluorescence staining revealed corneal epithelial erosion and partial fusion. (c–e) At 1 month postoperatively, the punctate epithelial erosions reduced. (f–h) At 3 months postoperatively, the mucosal of the graft was ruddy. (i–k) 6 months postoperative. (l–n) At 1 year postoperatively, the corneal epithelium was smooth. (o–q) At 3 years postoperatively, the corneal epithelium was smooth with punctate staining only on the lower part, and the graft was ruddy.

was associated with microvascular crisis, confirming the significance of blood supply.[13 15] Vazirani *et al*[34] also realized the importance of the blood supply, so they modified LSGT by securing the gland directly to the superior rectus muscle in order to provide a robust source for the vascularization of the graft. However, this approach still cannot provide direct blood flow to the gland. Besides, innervation also plays an important role in the survival of the gland. To study the innervation of the gland after surgery, Zhang *et al*[35] established a rabbit SMG transplantation model. They found the acinar area or the secretory flow rate of the transplanted glands was statistically correlated with the cholinergic axon density, the transplanted SMGs are reinnervated by autonomic nerves, and the cholinergic nerves play a role in the morphological and functional restoration of the glands. Based on these findings, we modified the LSGT to preserve the nerves and blood vessels connected to the glands.

Through pre-anatomical studies, we found that the labial glands at the root of the upper lip are supplied by the IOA and innervated by the ION. The IOA is a terminal branch of the maxillary artery, which emanates from the infraorbital foramen and is divided into three main branches—palpebral, nasal, and labial branches.[36] The ION is a fully sensory nerve that is the terminal branch of the maxillary nerve, the second branch of the trigeminal nerve. It travels with the IOA and passes through the infraorbital foramen to the face.[37] The ION is accompanied by the IOA beneath the levator labii superioris within the infraorbital space. The superior labial branches supply the cheek, upper lip, associated oral mucosa, and labial glands.[38] The key to the new procedure was to maintain the integrity of the neurovascular pedicle and transpose it to the lower lid conjunctival sac. Then, experimental transplantation of modified LSGT in cadavers was performed to confirm the feasibility of the procedure. We named this new procedure as insular infraorbital neurovascular pedicle LSGT. Based on our anatomical studies, a clinical trial was conducted in eight patients (nine eyes) with severe DED.

To evaluate the labial gland adequately, preoperative labial gland biopsy and scintigraphy are necessary. Patients with inflammatory cell infiltration or fibrosis of the labial glands and hyposecretion of salivary glands were contraindicated for this approach. However, there is no standardized method for measuring the secretory capacity of the minor salivary glands. Previous studies have shown that major salivary gland flow rate is positively correlated with minor salivary glands.[39 40] Moreover, the MA of the SMG is statistically significant with the severity of the disease, which was 52.8±15% in normal subjects.[26] In this study, suggested parameters for insular infraorbital neurovascular pedicle LSGT were MA of SMG ≥0.5.

The key to assessing the success of the procedure was the improvement of the patient's symptoms and signs, as well as the long-term blood supply to the labial glands. During our follow-up, we found that the patients' OSDI scores in the operated eye decreased significantly and the frequency of artificial tear dosing was reduced. A number of patients described feeling an increase in ocular wetness while eating or exercising. In addition to symptom relief, objective indicators such as TBUT, SIT, and CFS scores in the patient's operated eye were also significantly improved. To assess the blood supply to the transplanted gland, ultrasound was performed at 6 months postoperatively. Previous studies reported that the mean PSV of IOA was 15.55±13.06 cm/s and the RI was 0.75±0.10.[41] Our results showed a decrease in EDV and a significant increase in RI in all patients. A higher RI suggested narrowing of the anterior vessels or an increase in vascular resistance, which indicated a decrease in diastolic function of the IOA and a decrease in vascular elasticity after surgery. However, the patient's hemodynamic parameters were still within the normal range. Therefore, we concluded that intraoperative operations do cause vascular damage, but not vascular crises that result in inadequate blood supply to the gland. Based on clinical signs and symptoms, hemodynamic parameters of IOA, and color of the glands, it was shown that grafts supplied by ION and IOA could maintain secretion for a long term after surgery.

The postoperative hypaesthesia on the operated side, which occurred in all cases, is related to the constriction of the ION and other branches of the maxillary nerve by straining. ION is a cardinal cutaneous nerve that provides a general sensation to the mid-face. Its twigs are vulnerable to iatrogenic damage during medical manipulations.[42] Although the superior labial branch of the ION associated with the labial gland is finely separated during surgery, damage to other terminal branches is inevitable. We used vitamin B_1 and methylcobalamin (vitamin B_{12}) to treat postoperative hypaesthesia. According to previous studies, B vitamins present neuroprotective effects and combined application of B vitamins may prevent the development of heat hyperalgesia after infraorbital nerve injury.[43 44] Patient's symptoms were relieved after treatment, and long-term postoperative follow-up revealed that the patient had no obvious sensory and motor deficits, indicating the high safety of the procedure.

CONCLUSIONS

In conclusion, insular infraorbital neurovascular pedicle LSGT is an innovative surgical approach for the treatment of severe DED. For ample labial glands with normal function, transplantation of partial glands with a neurovascular pedicle could alleviate patient signs and symptoms. One year after surgery, the gland remained viable and had a good blood supply. Since experience with this technique is still very limited, large-sample studies need to be performed.

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Ethics approval Three embalmed cadavers were autopsied with the approval of the ethics committee of Capital Medical University of Beijing Tongren Hospital (TRECKY2016-010). This clinical study was approved by the Ethics Committee of Capital Medical University of Beijing Tongren Hospital (TRECKY2020-018). Participants gave informed consent to participate in the study before taking part.

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