

Original Article

Available online at

ScienceDirect

www.sciencedirect.com

submandibular glands with autologous transplantation

Elsevier Masson France



EM consulte

CrossMark

Jing-Han Wang^a, Bang Zheng^{b,c}, Lan Lv^d, Zhi-Gang Cai^a, Xiao-Jing Liu^a, Lei Zhang^a, Xin Peng^a, Chi Mao^a, Guang-Yan Yu^{a,*}, Jia-Zeng Su^{a,*}

Characteristics and management of vascular compromise after an organ

transplantation surgery of the head and neck region: Analysis of 220

^a Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, National Clinical Research Center for Oral Diseases, National Engineering Laboratory for Digital and Material Technology of Stomatology, Beijing 100081, PR China ^b Peking University School of Public Health, Beijing, 100191, China

^c Department of Non-communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, WC1E 7HT, UK

^d Department of Ophthalmology, Affiliated Beijing Tong Ren Hospital, Capital University of Medical Science, Beijing, 100730, China

ARTICLE INFO

Article History: Received 17 June 2023 Accepted 16 July 2023 Available online 23 July 2023

Keywords: Microvascular submandibular gland transplantation Severe dry eye disease Vascular compromise Hyper-secretion

ABSTRACT

Background: Microvascular submandibular gland transplantation (SMGT) for severe dry eye disease (DED) has rarely been reported in the literature. The aim of this study was to report a case series of SMGT with the special focus on monitoring and management of postoperative vascular compromise.

Methods: Using a retrospective single-cohort study design, the investigators enrolled a sample of DED patients undergoing SMGT in a Chinese university hospital during 1999 and 2021. The main outcomes were baseline and surgical data, post-operative manifestations, and surgical results. Descriptive, uni- and bivariate statistics were computed with the significant P < 0.05.

Results: During the study period, 220 DED patients (55.9% female) with a mean age of 32.66±14.47 years underwent SMGT. Vascular compromises occurred in 27 grafted glands (12.3%; 22 venous compromises and 5 arterial compromises) at a median of 27 h(range, 3.3 to 288 h) after surgery. Harden texture and swelling of the covering skin flap of the donor indicated venous compromises, while some specific sign was absent for arterial compromise. The accompanying vein of the facial artery (FAV) as a donor's vein was associated with less vascular compromise compared to the anterior facial vein (AFV). Timely reexploration was performed in 25 glands (92.6%), with a salvaged rate of 48%, and more venous compromises were salvaged compared to artery compromises (54.6% vs. 0%, P = 0.047). Temporary hypersecretion on postoperative 2-5 days was noticed in the grafted glands with no or salvaged vascular compromise (Schirmer's test, 35 mm/5 min and 37 mm/5 min, respectively, P = 0.749), while they were absent for the 15 surgically failed grands (Schirmer's test 0 mm/5 min, P<0.001).

Conclusions: Vascular compromise appears to be a common complication of SMGT. Postoperative hypersecretion of the grafted glands may indicate good circulation, and the use of FAV as the donor's vein could help to decrease the risk of vascular compromise.

© 2023 Elsevier Masson SAS. All rights reserved.

1. Introduction

Dry eye disease (DED), also known as dysfunctional tear syndrome, is a multifactorial ocular surface disease characterized by a

https://doi.org/10.1016/j.jormas.2023.101566 2468-7855/© 2023 Elsevier Masson SAS. All rights reserved.

loss of tear film homeostasis. It is accompanied by ocular symptoms (including ocular surface inflammation and damage), visual disturbance, and discomfort [1]. The prevalence of DED varies from 5.7% to 17% [2]. Conventional treatments include substituting artificial tears, occlusion of tear drainage, and applying cyclosporine; yet, these methods are useful only for mild to moderate cases. For patients with severe DED, e.g., those caused by Stevens-Johnson syndrome, toxic epidermal necrolysis syndrome, or ocular pemphigoid, where accessory lacrimal glands are damaged irreversibly, a more aggressive approach is required [3].

An innovative autologous organ transplantation surgery, i.e., submandibular gland transplantation (SMGT), can improve tear volume,

Abbreviations: VC, vascular compromise; AFV, anterior facial vein; DED, dry eye disease; FA, facial artery; FAV, accompanying vein of the facial artery; HV, hilum vein; SMG, submandibular gland; SMGT, submandibular gland transplantation; STA, superficial temporal artery; STV, superficial temporal vein; TBUT, tear break-up time; CT, computed tomography

^{*} Corresponding authors at: Department of Oral and Maxillofacial Surgery, Peking University School of Stomatology, 22 Zhong Guan Cun South St., Beijing, 100081, PR China

E-mail addresses: gyyu@263.net (G.-Y. Yu), sujiazeng@163.com (J.-Z. Su).

maintain stable function, and improve the life quality of patients with severe DED [4–10]. The Definition and Classification Subcommittee of the International Dry Eye Workshop II (2017) confirmed that SMGT is effective for treating dryness, photophobia, burning sensation, dependence on artificial tears, and tear film instability with potential damage to the ocular surface in severe DED patients [11]. Yet, as organ transplantation in the head and neck area, SMGT is a relatively sensitive technique. Good circulation is essential for the survival and functional exertion of the transplanted SMG. The crucial part of SMGT surgery is the procedure that anastomoses the donor (SMG) vessels with the recipient's vessels to rebuild the circulation of the transplanted gland [12]. Similar to other microvascular operations, vascular compromise (VC), which may result in the loss of the donor SMG, is one of the major complications of SMGT. The failure rates of SMGT due to VC range from 4.9% to 14.3% [7,13-15] in different centers, surpassing those of kidney transplantation or revascularized free flap transplantations in the head and neck region [16]. The clinical characteristics, risk factors, and strategies to prevent and manage VC after SMGT are still unclear.

In the present study, we collected data from 220 microvascular autologous SMGTs conducted by the same surgical team. We analyzed the incidence rate, clinical characteristics, therapies, and prognosis of VC and further discussed risk factors and prevention strategies.

2. Materials and methods

2.1. Patients

Inclusion criteria were: (1) severe DED patients who underwent SMGT at Peking University School and Hospital of Stomatology between August 1999 and June 2021 performed by the same surgical team (oral and maxillofacial surgeons: G.Y.Y and J.Z.S; microvascular surgeons: Z.G.C., X.P., and C.M.; ophthalmologist: L.L.); (2) patients with integral medical records and short-term follow-up data (10 days after the operation).

Indications for SMGT were: (1) persistent severe dry eye with general ophthalmic treatment failure; (2) Schirmer's test < 2 mm/ 5 min; (3) tear break-up time (TBUT) < 5 s; (4) corneal fluorescence staining (+). Exclusion criteria were: (1) SjÖgren's syndrome; (2) severe xerostomia or a flow rate of saliva < 0.3 g/min; (3) ^{99m}Tc-pertechnetate showed dysfunction of multiple large salivary glands [14,17].

Among 203 initially included consecutive patients, 5 were excluded due to incomplete medical records, resulting in 198 patients included in the analysis. Twenty-two patients received SMGTs for bilateral eyes. Finally, a total of 220 glands (55.9% female) with a mean age of 32.66 ± 14.47 years underwent SMGT were analyzed in this study.

The study was approved by the Ethics Committee for Human Experiments of Peking University Health Science Center (PKUSSIRB – 202,163,043) and was conducted in accordance with the Declaration of Helsinki guidelines for human research. All patients signed the informed consent.

2.2. Surgical procedures

The operation was divided into four following parts: (1) preparation of the recipient bed; (2) harvesting of the donor gland; (3) transfer of the donor gland; (4) reopening of the Wharton's duct in the eye.

2.2.1. Preparation of the recipient's bed

An incision was performed, and the recipient bed was prepared in the temporal region (Fig. 1A). The superficial temporal artery (STA) and superficial temporal vein (STV) were dissected from the distal end to the proximal end. After full exposure, they were covered by a gelatin sponge with heparinized saline for subsequent use as recipient vessels (Fig. 1A).

2.2.2. Harvesting of the donor gland

The SMG, together with Wharton's duct and all potential donor vessels, were harvested. The vessels included the proximal part of the facial artery (FA) and the accompanying vein of FA (FAV), the anterior facial vein (AFV), and the hilum vein (HV). The branches of these vessels that came from or entered the SMG were carefully protected and harvested together. Before the proximal end of the FA was severed, the AFV was cut to validate its venous outflow from the gland (Fig. 1B, 1C). In case there was no venous outflow of AFV, the FAV served as the backup of the AFV, followed by the HV. The vascular pedicle was dissected at a sufficient length to facilitate the following anastomosis. The operation was then turned intraoral. First, a nylon tube was intubated into Wharton's duct from its opening. Next, an intraoral incision was made on the mouth floor, Wharton's duct was dissected, and the main duct of the sublingual gland was reopened or ligated (Fig. 1D). A cuff of mucosa around the orifice was retained during the dissection of Wharton's duct for the next use (Fig. 1E). Herein, the donor gland, including the whole length of Wharton's duct and the vascular pedicle (FA, FAV, AFV, and HV), was fully harvested and kept free (Fig. 1E). Heparinized saline was irrigated into the gland through FA to confirm the outflow from the venous vessel.



Fig. 1. Procedures of microvascular submandibular gland transplantation. (A) Dissection of the superficial temporal artery (a) and vein (v). (B) Good outflow (*) of the anterior facial vein (v) from the gland. (C) No outflow of the anterior facial vein (v) from the gland. (D) Dissections of the Wharton's duct (single arrow) with an intubated nylon tube (double arrows) and the main duct of the sublingual gland (treble arrows). (E) The donor, including the submandibular gland (*), the facial artery (a), facial vein (v), and Wharton's duct (d) with mucosa cuff (c). (F) Anastomosis of the facial artery and superficial temporal vein (single arrow), anterior facial vein, and superficial temporal vein (double arrow). (G) The donor was completely buried under the temporal skin after surgery. (H). Temporary epiphora 3 days post-operatively (right eye)({).



Fig. 2. Venous grafting. (A) Harvesting of the cephalic vein. (B) Anastomosis of the cephalic vein with donor's vein.

2.2.3. Transfer of the donor gland

The donor gland was transferred to the recipient bed in the temporal region and prefixed. The STA was anastomosed with the FA by microvascular instruments and 8–0 suture. The STV was anastomosed with one of the donor veins, including AFV, FAV, and HV (Fig. 1F). When the STV was unavailable for anastomosis (e.g., deficiency, too small, etc.) and no other recipient veins could be utilized in the temporal site, a combined procedure of vein grafting based on using the cephalic vein in the forearm was conducted to provide a bridge connection from the vein of transplanted SMG to the external jugular vein in the neck (Fig. 2).

2.2.4. Reopening of the Wharton's duct in the eye

An intraorbital incision was made in the upper lateral conjunctival fold of the eye, and the end of Wharton's duct was transferred into the intraorbital incision through a subcutaneously prepared tunnel. Next, the mucosal cuff around the orifice of Wharton's duct was sutured with the conjunctiva to form an opening in the upper lateral conjunctival fold. Finally, the surgery was finished, with the donor gland being totally buried inside the temporal region covered by a skin flap (Fig. **1G**).

2.3. Post-operative management

After the operation, patients were asked not to lie on the operation side to protect the transplanted gland from oppression, which could compromise blood circulation to the donor gland. Intravenous infusion of antibiotics (cephalosporin) was administered for 3 days to prevent infection. Examination of the temporal site was performed 1 week after the operation (every hour in the first 4 days and once every 2 h afterward) and was crucial for monitoring possible vascular compromise. The key examination points included observing the skin color, drainage quantity, and color, and palpating the gland texture. A re-exploration surgery, with possible thrombectomy and reanastomosis of the vessels, was applied if there was any doubt about the vascular circulation of the transplanted SMG.

Schirmer's test was applied daily during the first week after the operation to determine the secretory function of the transplanted SMG (Fig. 1**H**). ^{99m}Tc-pertechnetate scintigraphy was performed on postoperative days 7–10 to finally confirm the vitality of the grafted gland [15]. The significant tracer uptake in the temporal region indicated a revascularized and viable grafted gland (Fig. 3**A**), while no or weak uptake of ^{99m}Tc-pertechnetate in the temporal region indicated failure of the transplantation surgery (Fig. 3**B**).



Fig. 3. Post-operative ^{99m}Tc-pertechnetate scintigraphy. (A) Tracer uptake (arrow) in the temporal area after successful transplantation. (B) No uptake in the temporal region after failed transplantation.

2.4. Statistical analysis

SPSS software was utilized for data analysis. Mann–Whitney U test (for continuous variables) and Fisher's exact test (for categorical variables) were used for univariate analysis. The risk factors for VC of SMGTs were evaluated using binary logistic regression. *P*<0.05 was considered statistically significant.

3. Results

3.1. Baseline data

Among the 220 cases of SMGT included in this study, Steven-Johnson syndrome was the primary cause of severe DED (59.6% of cases), followed by keratoconjunctivitis (15.9% of cases) and other causes found in 54 cases (24.6%). Left eyes (117, 53.2%) were more involved than the right eyes, and so were the left SMGs (122, 55.5%). No major intraoperative complications occurred during any of the surgeries.

3.2. Characteristics of VC

Of the 220 glands with SMGT, 191 revealed no abnormalities during the weekly monitoring. Scintigraphy showed significant tracer uptake in the temporal region (Fig. 3A) 7–10 days after surgery for those 191 glands, which were determined as viable grafted glands with successful SMGTs. Clinical signs of suspected vascular compromises, including a hard texture of the grafted gland on palpation, swollen with cyanosis of the temporal skin covering the grafted gland, increasing drainage, and blood oozing from the intraorbital incision were detected in 24 glands (Fig. 4A), all of which were managed by re-exploration surgery. Blood clots around the grafted glands without thrombosis in the anastomosed vessels were found in 2 glands, which were diagnosed as hematoma without vascular compromise. Venous congestion and thrombosis (Fig. 4B) were verified during the re-exploration of the remaining 22 glands and were identified as a venous compromise. Another five cases were re-explored due to soft texture at palpation and lack of hyper-secretion of saliva during the postoperative 2-5 days. Arterial thrombosis with pale or mottled glands and insufficient capillary refill was confirmed, and the diagnoses of arterial compromise were made (Fig. 4C). Totally 27 glands of VC were confirmed after SMGTs with an incidence rate of 12.3% (27/220); 10.0% of venous compromises and 2.3% of arterial compromises were observed.

The first sign of VC was detected at a median of 27 h (range, 3.3 to 288 h) after SMGTs. In 44.4% of glands, VC was identified within 24 h, 85.2% within 48 h, and 92.6% within 72 h post-surgery. The venous compromises were first detected 27 h post-surgery (range, 3.3 to 52 h), while arterial compromises were first detected after 84 h (range, 6 to 288 h); however, the difference was not statistically significant (P = 0.451).



Fig. 4. Manifestations of vascular compromise. (A) Cyanosis of the temporal skin (circular) and dark drainage (arrow) in venous compromise case. (B) Cyanotic, bluish, and dusky gland with enhanced turgor were noticed during re-exploration surgery. The veins (arrows) were cut, and the thrombus was cleared out (*). (C) Pale gland (arrow) with partial necrosis was detected in the arterial compromise case.

Table 1

Risk factors for vascular compromise after microvascular submandibular gland transplantation.

		No vascular compromise	Vascular compromise	OR	95% CI	P-value
Eyes		193	27			
Demographic features	Age (year)	33.28±14.79	28.33±10.94	0.972	0.940-1.005	0.097
	Gender (female/male)	108/85	15/12	0.906	0.365-2.247	0.831
Dry eye features	Detailed etiology	SJS: 117	SJS: 15	1		0.343 (overall)
		AC: 32	AC: 3	0.575	0.128-2.589	0.471
		UNK: 44	UNK: 9	1.722	0.648-4.574	0.276
Treatment parameters	Sides of the operated eye (left/right)	100/93	17/10	8.759	0.553-138.808	0.124
	Sides of graft (left/right)	106/87	16/11	0.141	0.009-2.227	0.164
Microsurgery parameters	Donor's vein	AFV: 122	AFV: 24	1		0.037* (overall)
		FAV: 65	FAV: 2	0.141	0.031-0.630	0.010*
		HV: 5	HV: 1	0.864	0.082-9.056	0.903
	Anastomosis pattern	DA: 187	DA: 23	1		
	-	VG: 6	VG: 4	6.406	1.282-32.003	0.024*

Notes: OR: odds ratio; CI: confidence interval; SJS: Stevens-Johnson syndrome; AC: acute conjunctivitis; UNK: unknown; AFV: anterior facial vein; FAV: accompanying vein of the facial artery; HV: hilum vein; DA: direct anastomosis; VG: venous graft.

* *P*<0.05, based on the multiple binary logistic regression.

3.3. Management and outcomes of vascular compromise

All suspected VC instances were re-explored. The median time between finding vascular compromises and re-exploration surgery was 1 hour (0.5 to 192 h). After thrombectomy and re-anastomosis of vessels, 12 of 22 glands with venous compromise were salvaged, and significant tracer uptakes in scintigram were confirmed after re-exploration. Yet, among the 5 cases with an arterial compromise, no cases were salvaged (no tracer uptakes were shown in glands of failed re-exploration) (Fig. **3B**). The overall salvage rate of vascular compromises after SMGTs was 44.4% (12/27); the salvage rate of venous compromise (54.5%, 12/22) was significantly higher compared to arterial compromise (0%, 0/5) (P = 0.047).

Nine glands were removed by reoperation after failed re-exploration in the early stage of our study, whereas 6 glands were treated with antibiotics, following which no symptoms of infection were found.

3.4. Influence of VC on the secretory function of the grafted glands

Two to five days following surgery, all transplanted SMGs without VC showed very strong secretory functions, with a median Schirmer's test of 35 mm/5 min (7–125 mm/5 min), named "temporary epiphora" (Fig. 1H). Initially, the temporary epiphora was missing in all 27 transplanted SMGs with vascular compromise. After re-exploration of vascular compromise, temporary epiphora was detected in 11 eyes (median Schirmer's test: 37 mm/5 min) of the 12 salvaged glands. Temporary epiphora did not occur in the 15 transplanted SMGs with VC, where re-exploration failed. Schirmer's test values of these 15 eyes (median Schirmer's test: 0 mm/5 min) were significantly lower compared to the eyes without VC (P<0.001).

3.5. Risk factors for the incidence and salvage of vascular compromise

The influence of age, sex, pathogeny, side of the operated eye, side of SMGs, donor vein, recipient vein, and anastomosis patterns (direct anastomosis or venous graft) on the occurrence of VC were analyzed (Table 1). Our results showed that age, sex, pathogeny, side of the operated eye, and side of SMGs were not associated with VC (P>0.05).

Of the 220 glands, AFVs were employed as donor veins in 146 glands (66.36%), followed by FAVs (68 glands, 30.9%) and HVs (6 glands, 2.7%). The incidence rates of VC were different when different donor veins were used for the anastomosis (P = 0.037): FAV (4.41%), AFV (17.1%), and HV (16.7%) (Table 1).

The donor's vein was anastomosed with the STV directly in 210 glands (95.5%), while a venous graft was utilized in 10 cases (4.6%). The incidence rate of VC was significantly higher for venous graft cases (40%) compared with cases of direct anastomosis (10.9%) (P = 0.024) (Table 1).

When the VC was suspected after SMGTs, most cases (25/27, 92.6%) accepted re-explorative surgery within 4 h, and 48% (12/25) of them were successfully salvaged. However, 2 instances were re-explored after a relatively long time (24 and 192 h after suspicion of the vascular compromise, respectively). These two glands failed to be salvaged and were ultimately lost. The success rate of salvage was higher when re-exploration was timely performed; however, there was no significant difference between an early and late intervention (P = 0.483).

4. Discussion

4.1. DED management and SMGT

A logical and evidence-based management algorithm has been proposed by the Tear Film and Ocular Surface Society's Dry Eye Workshop II (TFOS DEWS II) to assist in choosing the best DED treatment for different-stage patients [11]. Therapy strategies start with conventional, low-risk, and widely accessible treatments before moving on to more advanced treatments. We basically complied with this management algorithm in practice. For the severe DED, healthy education and lid hygiene are still the preconditions for all the following treatments. Artificial tear substitutes are recommended as a primary, convenient, and non-invasive therapy. For severe DED, very frequent application of artificial tear substitutes is always required, which could interfere with the patient's daily activities, amounting to quite a financial expense. Tear conservation strategies such as punctual occlusion or moisture chamber spectacles/goggles are suggested for indicated cases to retain patient's original tears, with possible complications including infection, pyogenic granuloma, et al. Prescription drugs such as cyclosporine are considered for more severe patients. Topical cyclosporine could reduce the inflammation of the ocular surface and elevate tear osmolarity in some cases of severe dry eyes [11].

As the last step of the management algorithm of DED, salivary gland transplantations are recommended for the severe refractory DED when all other treatments are inadequate. Three surgical modalities have been proposed to provide endogenous lubrication with saliva as a tear substitute. The first one is parotid duct transposition, where the original innervation of the parotid gland is preserved; however, the gustatory reflex epiphora with excessive low-osmolarity pure serous secretion makes blepharitis, keratitis, and epithelial edema the unbearable complications [11]. In contrast, SMGT, which is a free organ graft, is a denervation procedure where gustatory reflex epiphora is absent. Besides, compared with the pure serous secretion of the parotid gland, the secretion of the submandibular gland contains both mucous and serous components, thus making it more similar to tears. Nevertheless, epiphora induced by high ambient temperature or body exercise is still a main complication after SMGT, which may require subsequent treatments, including surgical reduction of the gland size, topical application of atropine gel, or local Botulinum toxin A injection [14]. Transplantation of minor salivary glands (usually the labial glands) has gained popularity over the last two decades. Compared with the other two modalities, this procedure is simple with minimal surgical risk, and postoperative epiphora is rare. Yet, the secretory flow rate of transplanted minor salivary glands is limited. For the end-stage dry eye, it may not offer enough lubrication [18].

SMGT is the most commonly reported and used salivary gland transplantation surgery for severe DED patients. The transplanted gland could maintain baseline secretion in the long term, and reflex secretion induced by high ambient temperature or body exercise is observed for most of the grafts. According to our previous study, the transplanted gland was reinnervated by autonomic nerves as early as 4 months after transplantation. The sympathetic plexus around the supplying arteries and the parasympathetic fibers contained in the auriculotemporal nerve may be the sources of these autonomic nerves [9]. The lubrication collected from the eye after SMGT is known as "saliva tear". The saliva tear differs from natural submandibular gland saliva or natural tear regarding electrolyte, osmotic pressure, amylase, and total protein. When compared to natural submandibular gland saliva, saliva-tear has a rise in sodium, chloride, osmotic pressure, and total protein, making it more similar to natural tears. However, the contents of these biochemical components are still lower in saliva-tear than in natural tears [14].

One of the most important complications that may lei o oad to the failure of SMGT is VC [19–22]. Thus, a better understanding of the characteristics of VC after SMGT is of crucial importance for further improving the success rate of this technique-sensitive treatment modality. For the 220 glands of SMGT in this study, 27 glands (12.3%) were confirmed as VC at a median of 27 h after the operation. There were more venous compromises (10.0%) than arterial compromises (2.3%). The salvage surgery of thrombectomy and re-anastomosis was performed on time (≤ 4 h) for most vascular compromises (92.6%); yet, only 44.4% of the cases were successfully salvaged. The final survival rate of transplanted SMG was 93.2%, which was lower than that of free flap transplantations in the head and neck region

(>95%) performed by the same team in other studies [16]. We believe that difficulty in the early detection of VC, and mismatch between the donor and recipient's veins, were 2 key points for this difference in success rate and 2 key issues to be resolved for further improvement of SMGTs.

4.2. Early detection of VC

Like a buried free flap, transplanted SMGs lack an external component, making the early detection of VC more complex and likely to be delayed [23]. In the present study, only 44.4% of the vascular compromises were identified within 24 h for SMGTs, while 82.3% of this complication could be identified within 24 h for free flap transplantations [24]. Early finding of VC is a precondition of timely salvage surgery for vascular compromises. According to our study, the hardened texture of the grafted SMG by palpation, skin ecchymosis in the temporal region, and blood oozing from the intraorbital incision indicated vein compromise, while the sign of hardened texture of the grafted SMG was absent in artery compromise. The texture of the grafted gland was kept soft because no vein stasis developed in artery compromise. Thus, finding the artery compromises in the early stage was more challenging.

SMG is an independent functional organ, and SMGT is a minor organ transplantation surgery. The most significant difference of SMGT compared to vascularized free flap transplantation surgery is that vital transplanted SMG could independently function to secrete saliva after the transplantation surgery. An important finding of this study was that all transplanted SMGs with good circulation had a high flow rate of secretion (35 mm/5 min) during postoperative days 2 - 5, which may be used as a significant marker of vital grafted SMG. At the same time, this sign of strong functional secretion was missed for the transplanted SMGs with non-treated VC. Measurement of the secretory flow rate of the transplanted SMG is essential for monitoring the condition of circulation and the viability of the grafted glands. Postoperative Schirmer's test could be used as an important observed indicator for VC, especially for artery compromises lacking other signs. This post-transplantation organic function monitoring is also used in kidney transplantation. Oliguria or anuria is one of the manifestations of VC after kidney transplantation [25].

4.3. Mismatching between the donor and recipient's veins

The most commonly used donor vein in SMGT, not only in this study but also in previous literature reports [5-7,10,13,15], is AFV, which has an average caliber of 3.12 ± 0.25 mm [26], while the recipient vein for SMGT, which is STV, has an average caliber of 1.79 ± 0.54 mm in the temporal region [27]. Large caliber mismatch between bigger donor and smaller recipient veins is a crucial factor in thrombosis [28].

The risk factors for the incidence of vascular compromise were analyzed, revealing that when the FAV, which is much smaller than AFV and better matching with STV, was used as the donor's vein, the incidence rate of vascular compromise significantly declined. Accordingly, we proposed that the FAV, instead of the AFV, should be used as the first choice of donor's vein to prevent postoperative VC.

In summary, the hardened texture of grafted glands, swelling with cyanosis of the temporal skin covering the gland, and lack of hypersecretion of saliva during the postoperative 2–5 days were typical clinical signs of vascular compromises. The mismatch of vessel calibers between donor and recipient veins is an important factor influencing vein compromise, and the FAV should be the first choice of donor's vein. Early detection and timely management of vascular compromises are essential for improving the survival rate of transplanted SMGs.

4.4. Study limitations

We proposed using FAV as a donor's vein. However, FAV was sometimes very small, and the anastomosis was challenging. The technical sensitivity is much higher for the anastomosis of FAV than that of AFV. The ideal method should include finding a better (bigger and well-match AFV) recipient vein than STV. Preoperative computed tomography venography is a useful way for predicting the calibers of AFV and STV. Thus, a gland with more matchable AFV (with STV) might be chosen between the bilateral sides before operation [29]; however, the well-matched AFV and STV may not be available for all the patients. Another possible solution is using vein grafting to provide a bridge connection from AFV to the external jugular vein in the neck. However, the risk factors analysis indicated that vein grafting increased vascular compromise risk. Thus, further studies should identify another recipient vein from the temporal region that could match the AFV.

Author contribution

J.H.W. participated in collecting data, all the analyses, and writing the manuscript B.Z. participated in performing analyses and revising the manuscript. L.L., Z.G.C., X.J.L., L.Z., X.P., and C.M. participated in designing the study and revising the manuscript. J.Z.S. and G.Y.Y. participated in designing study, collecting data, performing analyses, and revising the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China [82170977, 81974151].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- Lemp MA, Baudouin C, Baum J, et al. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 2007;5:75–92.
- [2] Akpek EK, Amescua G, Farid M, et al. Dry eye syndrome preferred practice pattern. Ophthalmology 2019;126:286–334.
- [3] Geerling G, Sieg P, Bastian GO, Laqua H. Transplantation of the autologous submandibular gland for most severe cases of keratoconjunctivitis sicca. Ophthalmology 1998;105:327–35.
- [4] Su JZ, Zheng B, Liu XJ, et al. Quality of life and patient satisfaction after submandibular gland transplantation in patients with severe dry eye disease. Ocul Surf 2019;17:470–5.
- [5] Sieg P, Geering G, Kosmehl H, Lauer H, Waenecke K, Domarus HV. Mirovascular submandibular gland transfer for severe cases of keratoconjunctivitis sicca. Plast Reconstr Surg 2000;106:554–60.

- [6] Jia G, Wang Y, Lu L, Wang X, Li Z. Reconstructive lacrimal gland with free submandibular gland transfer for management of xerophthalmia. Chin J Ophthalmol 1998;34:388–90.
- [7] Paniello RC. Submandibular gland transfer for severe xerophthalmia. Laryngoscope 2007;117:40–4.
- [8] Geerling G, Honnicke K, SchrÖder C, et al. Quality of salivary tears following autologous submandibular gland transplantation for severe dry eye. Graefes Arch Clin Exp Ophthalmol 2000;238:45–52.
- [9] Zhang XM, Yang NY, Liu XJ, et al. Autonomic reinnervation and functional regeneration in autologous transplanted submandibular glands in patients with severe keratoconjunctivitis sicca. Int J Oral Sci 2018;10:14.
- [10] Jacobsen HC, Hakim SG, Lauer I, Dendorfer A, Wedel T, Sieg P. Long-term results of autologous submandibular gland transfer for the surgical treatment of severe keratoconjunctivitis sicca. J Craniomaxillofac Surg 2008;36:227–33.
- [11] Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. Ocul Surf 2017;15:575-628.
- [12] Yu GY, Zhu ZH, Mao C, et al. Microvascular autologous submandibular gland transfer in severe cases of keratoconjunctivitis sicca. Int J Oral Maxillofac Surg 2004;33:235–9.
- [13] Borrelli M, Schröder C, Dart JK, et al. Long-term follow-up after submandibular gland transplantation in severe dry eyes secondary to cicatrizing conjunctivitis. Am J Ophthalmol 2010;150:894–904.
- [14] Zhang L, Su JZ, Cai ZG, et al. Factors influencing the long-term results of autologous microvascular submandibular gland transplantation for severe dry disease. Int J Oral Maxillofac Surg 2019;48:40–7.
- [15] Wang DK, Zhang SE, Su YX, Zheng GS, Yang WF, Liao GQ. Microvascular Submandibular Gland Transplantation for Severe Keratoconjunctivitis Sicca: a Single-Institution Experience of 61 Grafts. J Oral Maxillofac Surg 2018;76:2443–52.
- [16] Liu S, Zhang WB, Yu Y, et al. Free flap transfer for pediatric head and neck reconstruction: what factors influence flap survival? Laryngscope 2019;129:1915–21.
- [17] Su JZ, Liu XJ, Zhang L, Yu GY. Schirmer test in transplanted submandibular gland: influencing factors and a modified measurement method. Cornea 2013;32:419– 22.
- [18] Su JZ, Zheng B, Wang Z, et al. Submandibular gland transplantation vs. minor salivary glands transplantation for treatment of dry eye: a retrospective cohort study. Am J Ophthalmol 2022;241:238–47.
- [19] Su JZ, Cai ZG, Yu GY. Microvascular autologous submandibular gland transplantation in severe cases of keratoconjunctivitis sicca. Maxillofac Plast Reconstr Surg 2015;37:5.
- [20] Yu GY, Zhu ZH, Mao C, Cai ZG, Zou LH, Lv L. Microvascular submandibular gland transfer for severe keratoconjunctivitis sicca: operation key points, prevention and management of complications. Chin J Stomatol 2002;37:353–5.
- [21] Yu GY, Wu LL, Cai ZG, Lv L, Cong X. A 20-year study on microvascular autologous transplantation of submandibular gland for treatment of severe dry eye. J Peking Univ Health Sci 2018;1:1–4.
- [22] Mao C, Zhang L, Yu GY, Zhu ZH, Cai ZG, Zou LH. Management of blood vessels in the vascularized autogeneous submandibular gland transfer for severe keratoconjunctivitis sicca. Chin J Stomatol 2005;5:370–2.
- [23] Disa JJ, Cordeiro PG, Hidalgo DA. Efficacy of conventional monitoring techniques in free tissue transfer: an 11-year experience in 750 consecutive cases. Plast Reconstr Surg 1999;104:97–101.
- [24] Chen KT, Mardini S, Chuang DCC, et al. Timing of presentation of the first signs of vascular compromise dictates the salvage outcome of free flap transfers. Plast Reconstr Surg 2007;120:187–95.
- [25] Keller AK, Jorgensen TM, Jespersen B. Identification of risk factors for vascular thrombosis may reduce early renal graft loss: a review of recent literature. J Transplant 2012;2012:793461.
- [26] LI L, Gao XL, Song YZ, et al. Anatomy of arteries and veins of submandibular glands. Chin Med J (Engl) 2007;120:1179–82.
- [27] Lee HJ, Choi YJ, Lee KW, Kim HJ. Superficial temporal vein for use in decompression treatments for migraine. Sci. Rep. 2018;8:16539.
- [28] Mao C, Yu GY, Peng X, Guo CB, Huang MX. Postoperative vessel thrombosis and its management after free flap transfers in head and neck region. Chin J Otorhinolaryngol Head Neck Surg 2005;40:415–8.
- [29] Su JZ, Yu HK, Sun ZP, et al. Effect of computed tomographic venography on donor selection in submandibular gland transplantation in patients with severe dry eye. J Craniomaxillofac Surg 2017;45:1692–7.