Microvascular autologous transplantation of partial submandibular gland for severe keratoconjunctivitis sicca

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ABSTRACT

Objective To evaluate the feasibility of microvascular autologous transplantation of partial submandibular gland (SMG) to prevent or reduce epiphora in severe keratoconjunctivitis sicca (KCS).

Methods A total of 39 patients with KCS, covering 42 eyes, were randomised to undergo transplantation of partial or total SMG from January 2006 to December 2009. Clinical data of survival rate of transplanted SMG, ophthalmologic features of best-corrected visual acuity, Schirmer test results, break-up time (BUT) of tear film, fluorescence staining, incidence of postoperative epiphora and frequency of subsequent surgery were compared between two groups.

Results Total SMG transplantation was performed in 22 eyes, and partial SMG transplantation was performed in the other 20 eyes. All transplanted SMGs survived. Microvascular crisis occurred in one case of partial SMG transplantation, but the gland survived after exploration to remove the venous thrombus. Obstruction of the ductal orifice in one case of partial SMG transplantation was resolved by reconstruction of the ductal orifice. Symptoms of dry eyes disappeared, and patients were able to discontinue use of artificial tears. Severe epiphora occurred in 6 eyes undergoing partial SMG transplantation and in 19 eyes undergoing total SMG transplantation ($p<0.01$). Surgical reduction was performed in 6 eyes undergoing partial SMG transplantation and 18 eyes undergoing total SMG transplantation ($p<0.01$).

Conclusions Microvascular transplantation of partial SMG is feasible and effective for severe KCS and does not decrease the survival rate of transplanted SMG. For ample SMGs with normal function, transplantation of partial SMG alleviates the symptoms of dry eye and significantly reduces the incidence of severe postoperative epiphora.

INTRODUCTION

Keratoconjunctivitis sicca (KCS) is a relatively common disease. Severe cases can lead to vision-threatening complications.[1] Routine treatments are primarily conservative to control symptoms and include use of artificial tears or occlusion of the tear drainage.[2] These treatments offer satisfactory results in mild cases but are insufficient in severe cases.[3] Autologous microvascular transplantation of the submandibular gland (SMG) was first described by Murub-del-Castillo in 1986,[4] then followed by MacLeod *et al* and MacLeod and Robbins,[5 6] Kumar *et al*,[7 8] Geerling *et al*,[9 10] Sieg *et al*,[11] Jia *et al*[12 13] and Yu *et al*[3 14] It was approved that this technique is an effective modality for severe cases. After successful transplantation, dry eye symptoms are relieved, and patients are able to discontinue use of artificial tears.[15 16] However, epiphora occurs in about half of the patients 6 months after transplantation and is more pronounced during physical exercise and in hot environments.[3 9 15 16] Severe postoperative epiphora is controlled by subsequent reduction of the transplanted gland; patients must undergo additional surgery after transplantation.[3 9 15 16]

We hypothesised that transplantation of partial SMG, not total SMG, might prevent epiphora after transplantation. Based on our anatomic study[17 18] our experimental study on transplantation of partial SMG in rabbits showed that the transplanted partial SMGs survived and secretion was lower than that in total SMG transplantation, which indicated that transplantation of partial SMG was feasible in rabbits.[19]

From these results, we designed a randomised, controlled clinical trial of transplantation of partial and total SMGs to evaluate the feasibility of microvascular transplantation of partial SMG in preventing or reducing postoperative epiphora in severe KCS.

MATERIALS AND METHODS

The study was approved by the Ethics Committee for Human Experiments of Peking University and the Beijing Bureau of Heath.

Patients

From January 2006 to December 2009, we included patients with severe KCS who were referred for treatment to the Department of Oral and Maxillofacial Surgery at Peking University School of Stomatology. All patients gave their informed consent to participate in this study.

Before surgery, each patient underwent examination of whole saliva flow rate, type-B ultrasonography, ^{99m}Tc-pertechnetate scintigraphy and ophthalmologic examination to evaluate glandular function and select suitable patients.[3 20] If the glands were ample and the function was normal, the patients were included in the study.

Inclusion and exclusion criteria of the study

The inclusion criteria for this study were as follows: (1) persisting symptoms of dry eyes despite previous ophthalmologic treatment including application of artificial tears and punctal plugs, (2) ophthalmologic evaluation: Schirmer test <2 mm,

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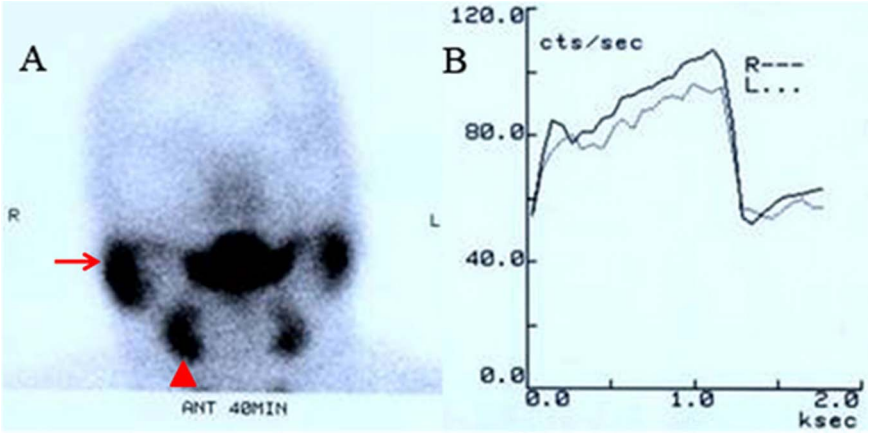

Figure 1 Scintigraphy of normal major salivary glands. (A) Parotid (arrow) and submandibular glands (SMGs) (arrowhead). (B) Time–activity curves show normal function of bilateral SMG.

break-up time (BUT)<5 s, fluorescence staining (+), (3) whole saliva flow rate >0.55 g/min, (4) SMG≥25 mm long and ≥14 mm wide as seen on type-B ultrasonography by a professional radiologist and (5) maximal accumulation (MA)≥0.5 and maximal secretion (MS) ≥0.5, as calculated from scintigraphy time–activity curves (figure 1) and described by Aung *et al* and Umehara *et al*,[21 22] respectively.

The exclusion criteria for this study were as follows: (1) Sjögren syndrome, (2) symptoms of xerostomia or whole saliva flow rate <0.3 g/min and (3) scintigraphy showing hypofunction of multiple major salivary glands (figure 2).

Treatment assignment

We randomly assigned glands (eyes) to two groups for treatment: partial and total SMG transplantation, according to the order of hospitalisation. Three patients underwent partial SMG transplantation in one eye and total SMG transplantation in the other.

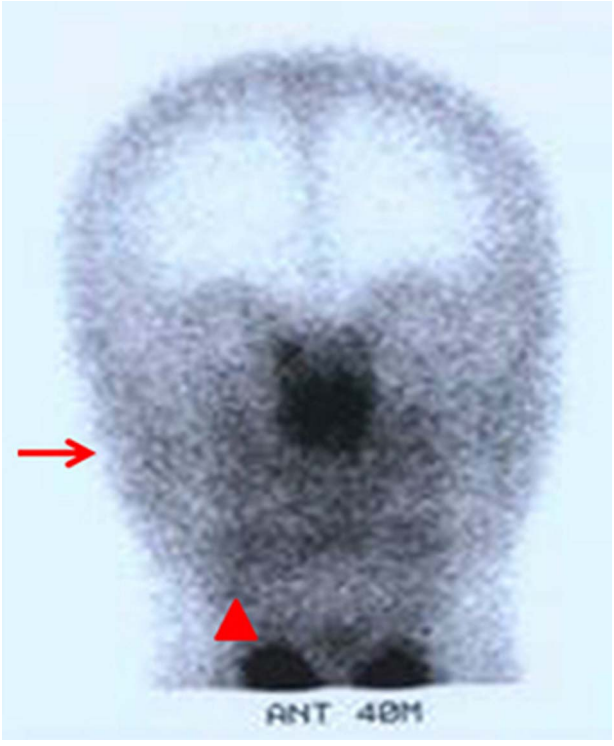

Figure 2 Scintigram of seriously damaged major salivary glands. No uptake of ^{99m}Tc-pertechnetate in parotid (arrow) and submandibular glands (arrowhead).

Surgical technique

Under general anaesthesia, the superficial temporal vessels were carefully dissected based on a temporal flap. The SMG, with its blood vessels and Wharton's duct, was harvested from the submandibular triangle through a conventional cervical approach and transferred to the temporal area. 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 using a microsurgical technique. Then, the distal end of Wharton's duct was sutured to form an opening in the upper lateral conjunctival fold with a nylon tube inserted into the duct for postoperative irrigation. The surgical process has been standardised and has been described in detail previously.[3 11]

For partial SMG transplantation, a reduction step was added to the surgery. After completion of vascular anastomosis, the blood circulation of the transplanted SMG was checked using a flowthrough technique. If the circulation was good, the gland far from the main duct and main stem of the facial artery was selected for reduction. The capsule of the SMG was opened, and blunt dissection was performed. The blood vessels and branch ducts between the lobules were cut and ligated. One-third or more of the SMG was resected. Ensuring the integrity of the blood vessel and duct system is the key point of successful transplantation (figure 3). Damage to the integrity of blood vessel may induce the destruction of blood circulation in the gland, resulting in failure of transplantation, while damage to the duct may cause saliva leakage or obstruction of the duct. The capsule could be closed to help decrease the risk of salivary fistula if it is preserved.

The other procedures were the same as for total SMG transplantation.

Evaluation of survival of transplanted SMG

Temporary epiphora (mean Schirmer test result 25 mm, range 15 to 35 mm) occurs during days 3–5 after transplantation if the transplanted gland survives. The survival of the transplanted SMG was confirmed by ^{99m}Tc-pertechnetate scintigraphy, which showed uptake of ^{99m}Tc-pertechnetate in the temporal region (Figure 4).[20]

Ophthalmologic evaluation

Patients underwent detailed ophthalmologic examinations before and after surgery (7 days, 3 and 6 months, and more

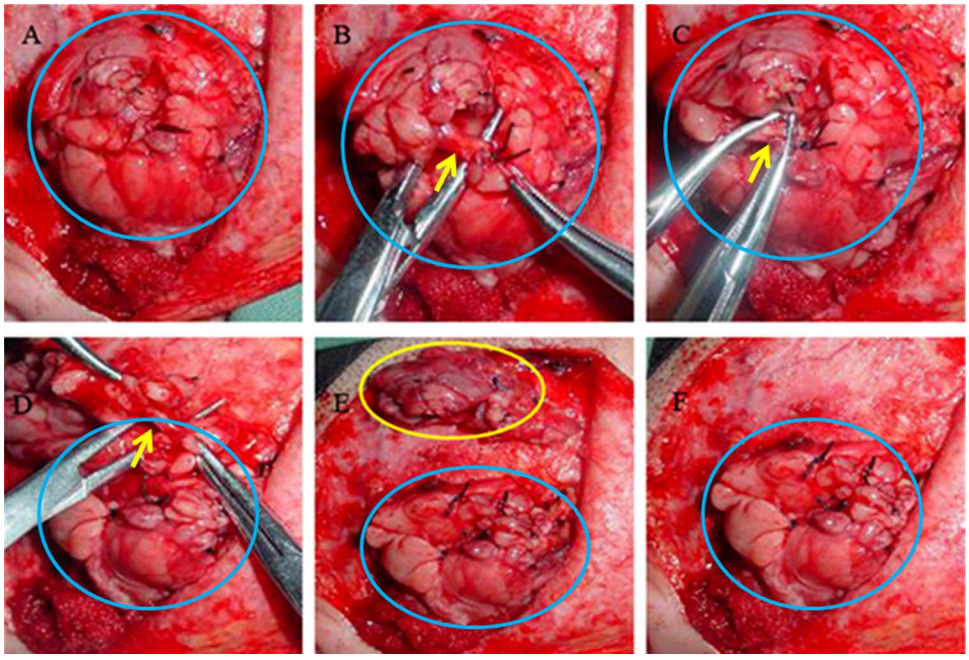

Figure 3 Surgical procedures for partial submandibular gland (SMG) transplantation. (A) Completion of vascular anastomosis of the total SMG. (B) Dissection of the branch vessels and ducts (yellow arrow) in the shallow layer of the gland. (C) Cut and ligation of the branch vessels and ducts (yellow arrow). (D) Dissection of the branch vessels and ducts (yellow arrow) in the deep layer of the gland. (E) Completed reduction of the gland and resected gland. (F) The volume of the transplanted SMG was reduced. Blue circle: border of transplanted SMG; yellow circle: resected gland.

than 1 year postoperatively) by the same ophthalmologist who was blinded to treatment to evaluate changes in ocular surface. Ophthalmologic evaluation included best-corrected visual acuity, Schirmer test without the use of local anaesthetics, BUT of tear film and fluorescence staining with standardised methods. For each patient, we calculated the parameter Schirmer test difference (△ST) as follows: △ST=postoperative Schirmer test – preoperative Schirmer test.

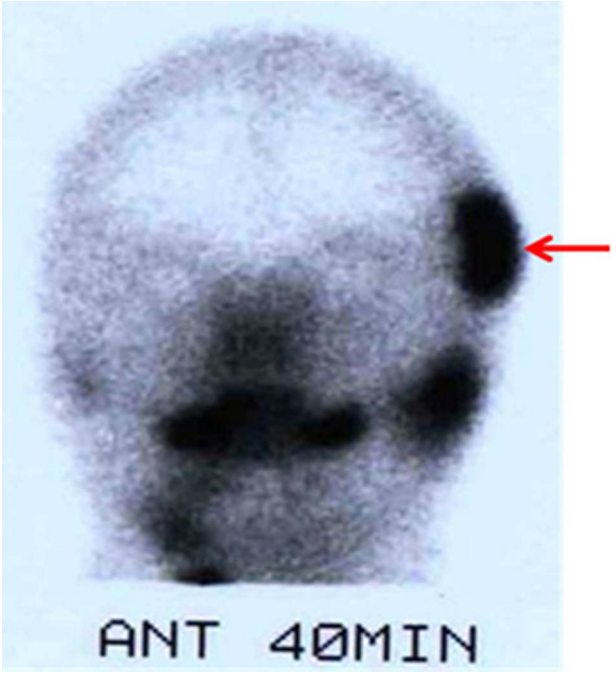

Figure 4 Uptake of ^{99m}Tc-pertechnetate in the temporal region (arrow), which indicated viable transplanted submandibular gland.

Corneal staining was assessed by a trained ophthalmologist according to the National Eye Institute/Industry Workshop on Clinical Trials for Dry Eyes. Corneal fluorescein staining was graded on a scale from 0 to 3: 0, no staining; 1, mild staining with a few disseminated stains; 2, moderate staining with a severity between grades 1 and 3; or 3, severe staining with confluent stains.

Evaluation of epiphora

All of the patients were followed-up for more than 1 year (1.5–3 years, mean 1.9 years). Patients completed a questionnaire to evaluate the degree of postoperative epiphora in different situations more than 1 year after transplantation. The severity of epiphora was divided into three levels: (1) severe epiphora: slight epiphora at rest and at room temperature but this is increased during exercise or in a hot environment; (2) moderate epiphora: no epiphora at rest and at room temperature but obvious during physical activity and localised hyperthermia; and (3) suitable: secretion of saliva tears is normal or a little more than normal, but has no effect on work or daily life.

Statistical analysis

Data are presented as number (%) or mean±SD. Comparison between two groups was performed by Student t test or χ^2 test (SPSS for Windows; SPSS Inc., Chicago, Illinois, USA). A $p<0.05$ (two-tailed) was considered statistically significant.

RESULTS

Patients

We included 39 patients (42 eyes): 20 eyes underwent partial and 22 total SMG transplantation. The two groups did not differ baseline characteristics of age and sex (table 1). Each patient was followed-up for at least 1 year.

Table 1 Baseline characteristics of patients by partial or total submandibular gland (SMG) transplantation

	Age in years, mean±SD	Male patients, n (%)
Partial SMG (n=20 eyes)	29.7±19.8	11 (55%)
Total SMG (n=22 eyes)	31.8±20.3	13 (59%)
p Value	0.34*	0.73†

*t Test.
†χ^2 Test.

The two groups did not differ in whole saliva flow rate or scintigraphy results at baseline (table 2). The function of all SMGs was normal.

Primary surgical success and postoperative complications

The surgery for all cases was successful without major complications. All transplanted SMGs survived. Microvascular crisis occurred in one case of partial SMG transplantation 1 day after surgery, which showed as obvious swelling and hard palpation. However, the gland survived after exploration to remove the venous thrombus and the glandular secretion was enough to alleviate dry eye symptoms. Scintigraphy showed positive ^{99m}Tc-pertechnetate uptake in the temporal region 1 week after transplantation in all patients.

Obstruction of the ductal orifice occurred in one case of partial SMG transplantation 8 weeks after surgery because of scar formation. The ductal orifice was reconstructed, patency was maintained, and the transplanted gland secreted well. No cases showed any complications of salivary fistula or wound infection.

The incidence of epiphora is shown in table 3. Severe epiphora occurred in 6 eyes with partial SMG transplantation and 19 cases of total SMG transplantation ($p<0.01$).

Some patients with severe epiphora had to undergo subsequent reduction surgery: 6 eyes with partial and 18 eyes with total SMG transplantation underwent repeat surgery once; 3 of the total SMG transplantation patients underwent repeat surgery twice ($p<0.01$) (table 4).

Ophthalmologic evaluation

For the 20 eyes that underwent partial SMG transplantation, questionnaire results showed that the symptoms of dry eye disappeared, and patients were able to discontinue use of artificial tears. The mean secretion from transplanted glands increased from 1.52±1.05 mm preoperatively to 21.65±11.61 mm more than 1 year after surgery ($p<0.01$). In total, 15 cases showed no tear film preoperatively to uneven tear film postoperatively. Postoperatively, for 14 cases, the intensity of fluorescent staining was reduced and the score of fluorescent staining was diminished (9.80±1.45 preoperatively to 4.70±1.55 more than 1 year postoperatively, $p<0.05$)

Table 2 Whole saliva flow rate and scintigraphy results at baseline

	Whole saliva flow rate, g/min	MA (%)	MS (%)
Partial SMG (n=20 eyes)	0.67±0.27	57.6±8.3	51.5±7.1
Total SMG (n=22 eyes)	0.64±0.23	54.2±8.7	51.7±7.5
p Value	0.68*	0.43*	0.65*

Normal values of saliva flow rate: 0.46±0.05 g/min. Normal values of scintigraphy results: MA: 50%, MS: 50%.
*t Test.
MA, maximal accumulation; MS, maximal secretion; SMG, submandibular gland.

Table 3 The incidence of epiphora

	Severe epiphora	Mild epiphora	Suitable
Partial SMG (n=20 eyes)	6	6	8
Total SMG (n=22 eyes)	19	3	0

Rank-sum test, $p<0.01$. Mild epiphora was combined with suitable for analysis.
SMG, submandibular gland.

The preoperative and postoperative Schirmer test results are shown in table 5. Schirmer test results were lower for partial than total SMG transplantation more than 1 year postoperatively (21.65±11.61 vs 36.60±14.02 mm, $p<0.01$). The △ST was significantly lower for the partial than total SMG transplantation (20.63±11.98 vs 35.15±13.74 mm; $p<0.01$).

DISCUSSION

Treatment of KCS, especially severe cases, is a global refractory problem.[1] Routine treatments do not yield satisfactory results. Because of similarities in the composition, Filatov and Cheraljer, in 1951, treated KCS by transferring the parotid duct into the conjunctival sac.[2,3] The patients who had been treated reported their dry eye symptoms were relieved, but this procedure may cause epiphora, gustatory secretion and traumatic keratitis due to constant wiping of the eye to remove excessive secretions. Autologous microvascular transplantation of the SMG was introduced into the clinical treatment since 1986[4] and has been carried out in several research centres in the past 30 years.[5–16] With the technique, the free SMG is transferred to the temporal region, related blood vessels are anastomosed and the Wharton duct is inserted into the upper conjunctival fornix, replacing natural tears with saliva secreted by the transplanted SMG. Gustatory secretion is avoided because of the denervation of the transplanted gland.[15 16]

For patients with severe KCS, microvascular autologous transplantation of total SMG has been effective. Obstruction of the Wharton's duct of transplanted SMGs may occur, which could be prevented or lessened by promoting the secretion of transplanted SMG during the early stage of transplantation.[3 17] Another common complication is epiphora, which may occur in about half of the patients 6 months after transplantation. Severe epiphora affects daily life and can damage patients' vision because of osmotic oedema.[24] Research data has shown that the incubation of corneal tissue in parotid saliva does not result in histologically detectable enzymatic digestion. It was confirmed that amylase is not harmful to the cultured corneal epithelial cells. The low osmolality of natural saliva was the major factor contributing to its toxicity.[24] Routine management for severe

Table 4 Frequency of subsequent reduction operation

	Twice	Once	0
Partial SMG (n=20 eyes)	0	6	14
Total SMG (n=22 eyes)	3	15	4

Rank-sum test, $p<0.01$. The 'twice' group was combined with the 'once' group for analysis.
SMG, submandibular gland.

Table 5 Preoperative and postoperative Schirmer test results

	Preoperative (mm)	Postoperative (mm)	△ST (mm)
Partial SMG (n=20 eyes)	1.52±1.05	21.65±11.61	20.63±11.98
Total SMG (n=22 eyes)	1.45±0.74	36.60±14.02	35.15±13.74
p Value	0.63*	0.01*	0.01*

△ST=postoperative Schirmer test – preoperative Schirmer test.
*t Test.
SMG, submandibular gland.

epiphora is reduction of the transplanted SMG. However, patients may have to undergo additional surgery. We wondered whether the reduction procedure could be performed during rather than after SMG transplantation.

Normally, retaining the integrity of the vascular and ductal system of the transplanted gland is crucial for successful treatment outcome. Therefore, we investigated the microanatomy of human SMG by perfusing methacrylate to form resin casts of blood vessels and ducts, and found a treelike structure with structures of blood vessels and ducts similar at each level in the lobules. This characteristic treelike structure provided a solid anatomical basis for transplantation of partial SMG.[17 18] Then, we performed experimental transplantation of partial SMG in rabbits. Results showed that transplantation of partial SMG was feasible in rabbits.[19] Based on our human anatomical and rabbit experimental studies,[17–19] we successfully devised a new technique, transplantation of partial SMG, and tested it in a clinical trial of 42 eyes with severe KCS.

All of the 20 glands undergoing partial SMG transplantation survived, which indicated successful transplantation, although microvascular crisis occurred in one case 1 day after operation. Therefore, partial SMG transplantation is safe if the key points of the surgery are followed.

Postoperative ophthalmologic evaluation showed relief of dry eye symptoms, increased Schirmer test values, improved formation of tear film and reduced intensity of fluorescent staining and number of stained spots. Therefore, partial SMG transplantation was as effective as total SMG transplantation for severe KCS.

One of the main purposes of partial SMG transplantation is to prevent or reduce the postoperative epiphora. The incidence of severe epiphora with partial SMG transplantation was significantly lower than that with total SMG transplantation (6/20 vs 19/22). Fewer patients with partial than total SMG transplantation underwent subsequent reduction surgery (6/20 vs 18/22).

Steven–Johnson syndrome is one of the main causes of severe KCS. The major salivary glands may also be involved in the syndrome.[20] Therefore, not all patients who undergo SMG transplantation will have postoperative epiphora and need partial SMG transplantation. Partial SMG transplantation is suggested for patients with ample size and normal function of glands. Therefore, preoperative assessment of the size and function of SMG is crucial. The function of SMG may be well evaluated by scintigraphy with ^{99m}Tc-pertechnetate, and the size of SMG may be assessed by type-B ultrasonography. In this study, suggested parameters for partial SMG transplantation are whole saliva flow rate ≥0.55 g/min, SMG≥25 mm long and ≥14 mm wide by type-B ultrasonography and MA≥0.5 and MS≥0.5 by scintigraphy time–activity curves.

Maintaining the integrity of the vascular and ductal system of the transplanted gland is paramount. Attention should be paid to the following key points during the operation. (1) The selection of the location of the gland to be resected. The stem vessel of the facial artery and the main duct of the gland should not be damaged. The former enters the gland at the posterior area of SMG, and the latter originates from the hilus of SMG. The anterior superficial area, the area far from the main stem of the facial artery and the main duct, is the most suitable part of the SMG to be resected. (2) Dissection of the gland by lobectomy. Each lobule of the gland is independently supplied by a subtree of arteries, veins and ducts originating from the stem vessels.[17 18] Therefore, although lobectomy is performed during partial SMG transplantation, the integrity of the vessel system and blood supply could be achieved if each lobule is kept intact. (3) The size of the gland to be resected. According to our previous experience of reducing the size of transplanted SMG for the patients with severe epiphora, secretion from one-third of normal SMG could relieve dry eye symptoms. However, resection of two-thirds of the gland would damage the integrity of the blood vessel and duct systems. In general, one-third of the gland can be resected. Resection of two-fifths of the gland can be safe if performed carefully. (4) While resecting, the capsule of the SMG should be preserved. When the reduction is completed, the capsule can be closed to help decrease the risk of salivary fistula. If these key points are followed, primary success can be guaranteed and further postoperative complications may be prevented.

In summary, microvascular transplantation of partial SMG is feasible and effective for severe KCS. For ample SMGs with normal function, transplantation of partial SMG can alleviate dry eye symptoms and reduce the incidence of severe postoperative epiphora, which showed better results than total SMG transplantation without further complication.

Contributors JQ, LZ and GY: participated in all of the work. ZC, CM, LL and XP: participated in the performance of the research. XL and JS: participated in the data collection. LL and JW: participated in the ophthalmologic research.

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Competing interests None.

Patient consent Obtained.

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