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Management of duct obstruction in transplanted submandibular glands

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ABSTRACT

Background: Submandibular gland (SMG) transplantation is a successful treatment approach for patients with severe dry eye. However, duct obstruction can occur post-transplant.
Methods: We studied nineteen patients with duct obstruction of transplanted SMGs, including five interventional modalities: stone removal; secretory stimulation (to mimic "internal irrigation" with substantial secretory flow); irrigation; surgical opening of stenosis and orifice reconstruction; cephalic vein bypass and Wharton's duct reconstruction.
Results: A solitary stone was found and removed in one patient. Duct blockages like mucus plug were cleared by secretory stimulation in three patients, and by normal saline irrigation in two grafts. In the remaining 13 patients, irrigation failed and surgical opening was performed. Orifice reconstruction succeeded in six of the eight patients, whose stenosis was near the orifice. Wharton's duct reconstruction was successful in two of the five cases where stenosis was located in the middle segment of the duct.
Conclusion: Transplanted SMGs obstruct for various reasons. Stone, which is easy to diagnose and treat, should be excluded first. Non-organic blockage and stenosis were semblable in clinic. Therefore, subsequent steps should be a diagnostic/therapeutic trial of secretory stimulation, followed by irrigation; failure of these interventions suggests the diagnosis of duct stenosis, necessitating surgical recanalization.

1. Introduction

Dry eye, or keratoconjunctivitis sicca (KCS), is a relatively common ocular disease. It presents as discomfort, visual disturbances, and tear-film instability, with potential damage to ocular surfaces (Lemp et al., 2007). Patients with severe dry eye, for whom conventional therapeutic options are insufficient (Geerling et al., 1998), may benefit from autologous microvascular submandibular gland (SMG) transplantation. This procedure, which was recommended by the International Dry Eye Workshop for patients with end-stage dry eye (Pflugfelder et al., 2007), enables permanent autologous substitution of tears generated by secretions from the transplanted and revascularized SMG. The procedure has proven to be effective in selected patients (Schroder et al., 2003; Yu et al., 2004, 2013; Paniello, 2007; Jacobsen et al., 2008; Geerling et al., 2008; Borrelli et al., 2010; Qin et al., 2013).

During the transplantation procedure, the SMG, Wharton's duct, and the facial artery and vein are harvested and transplanted to the temporal region. Wharton's duct is reopened into the upper conjunctival fornix of the eye through a subcutaneous tunnel (Geerling et al., 1998; Sieg et al., 2000; Yu et al., 2004). The transplanted SMG is completely disconnected from its normal nerve supply, therefore it displays a unique secretory pattern after transplantation. The most noticeable alteration is a 3-month period of low-level secretions, known as the latent period. The transplanted gland generates nearly zero secretions during this period (Yu et al., 2004). Because of low-level secretions introduced by the latent period, as well as because of surgical trauma to the

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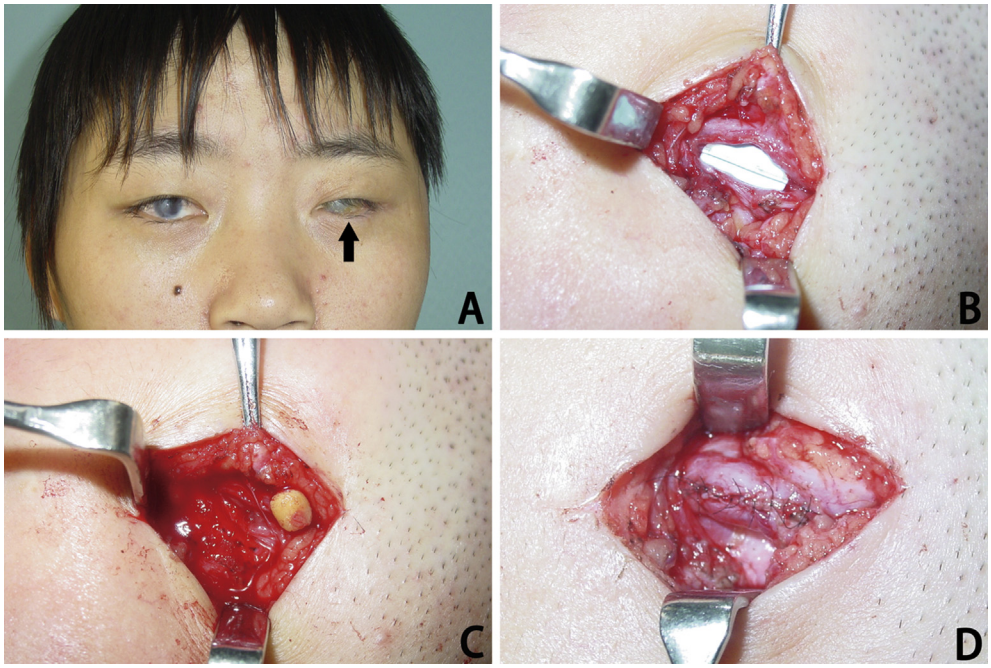

Fig. 1. Stone removal from a 14-year-old female patient. (A) Secretion in the transplanted gland decreased substantially 16 months after surgery. (B) The stone was located and the lesion was exposed via blunt dissection. (C) The stone was removed via an incision along the duct. (D) The incision of the Wharton's duct wall was closed with interrupted suture.

Wharton's duct and its opening, there is a markedly increased incidence of duct obstruction in transplanted SMGs. This complication, known as obstructive sialadenitis, gives rise to insufficient ocular lubrication and even transplant failure (MacLeod and Robbins, 1992; Yu et al., 2004).

Previously, we documented the pathological, clinical and imaging manifestations of this complication (Su et al., 2014). Treatment of this type of obstructive sialadenitis differs substantially from treatment of "normal" (non-transplanted) SMG complications. In the current study, we detail our approach to management of obstructive sialadenitis in transplanted SMGs.

2. Materials and methods

2.1. Patients

This study was approved by the Ethics Committee for Human Experiments of Peking University Health Science Centre, and was conducted in accordance with the Declaration of Helsinki guidelines for human research. All patients provided informed consent prior to treatment. We retrospectively evaluated all patients with severe dry eye undergoing successful SMG transplantation between August 1999 and May 2017 at Peking University School and Hospital of Stomatology. Out of 182 eyes, a total of 19 eyes (10.4%) in 19 patients were diagnosed with obstructive sialadenitis. Most of the obstructions (17/19) were diagnosed in the "latent period", the first 3 months, with a median time of 28 days after operation (range, 10–90 days). In 2 cases, onset of this complication was in the long term after transplantation (8 and 12 years, respectively). Diagnostic criteria were as follows: viable transplanted SMG confirmed by ^{99m}Tc scintigraphy; viscous secretions and recurrent swelling of the transplanted SMG; no improvement in secretion following stimulation (massage, hot compress, or exercise); Schirmer's test value < 3 mm; or irregular main duct dilation on sialography (Su et al., 2014).

Ductal stone, the most common cause of obstructive sialadenitis of "normal" SMG, was excluded by palpation. In the absence of stone, subsequent treatments included non-invasive interventions by intensive stimulation and irrigation. Failing this, we performed invasive surgical procedures including Wharton's duct reconstruction or simple orifice reconstruction.

2.2. Stone removal

The stone was located through palpation. A 2 cm skin incision was made above the stone and along the duct. The duct containing the stone was exposed via blunt dissection. An incision was made along the duct, a little longer than the major diameter of the stone, and the stone was removed (Fig. 1). The incision in Wharton's duct wall was closed with interrupted suture. A polyethylene tube was inserted in the duct and left in place for 2 weeks.

2.3. Intensive secretory stimulation

Mucus plugging is often the cause of transplanted SMG duct obstruction. Early stage obstruction, by definition, occurs during the first 3 months post transplantation (the latent period). The transplanted gland produces very little secretion, leading to mucus plug formation and duct blockage (Harbison et al., 2011).

Patients were instructed to perform glandular massage, apply local hot compresses, and exercise as much as possible. Simultaneously, patients were treated with capsaicin and carbachol. Zostrix cream (Medicis Pharmaceutical Corp. Phoenix, AZ, USA) containing 0.075% capsaicin was topically applied to a 2 × 2 cm^2 region of the skin covering the transplanted SMG (0.5 g, 4–6 times a day). Carbachol was purchased from Freda Biotechnology Corp. (Jinan, Shandong, China). Adult patients received subcutaneous injections of 0.2 mg carbachol to the abdominal wall near the navel, while children (<16 years old) received 0.1 mg. Carbachol was administered once every two days. These stimulations were expected to induce a substantial flow rate in the transplanted SMG

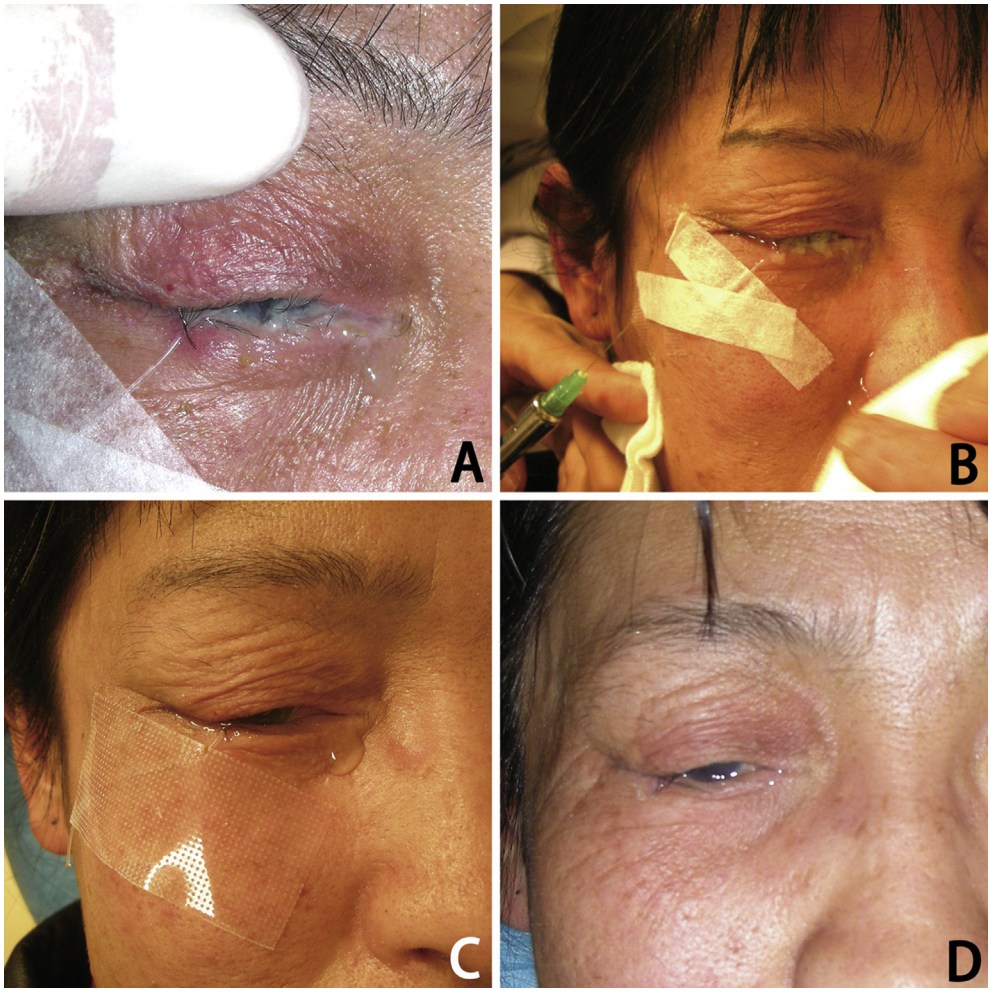

Fig. 2. Intubation and irrigation in a 38-year-old female patient. (A) Secretion diminished severely and became thick 8 years after submandibular gland transplantation. (B) Normal saline was irrigated in retrograde fashion through a polyethylene tube. Thick secretions and deposits were cleared out. (C) The transplanted gland produced spontaneous normal secretions 6 days after treatment. (D) Secretion was normal at 1 month follow-up.

and to mimic an "internal irrigation" effect, to clear the mucus plug from the duct (Su et al., 2016; Wang et al., 2016). Stimulations were continued until the resting secretions from the transplanted gland recovered to >5 mm/5 min.

2.4. Intubation and irrigation

If the patients failed to respond to the stimulations, irrigation was performed next. A polyethylene tube was inserted into the duct opening in the lateral upper conjunctive fold, and normal saline irrigation was performed three times per day (Fig. 2). The irrigation continued until resting secretion from the transplanted gland recovered to >5 mm/5 min (Fig. 2).

2.5. Wharton's duct orifice reconstruction

If irrigation failed, we proceeded to surgical removal of the presumed organic stenosis. For the majority of patients, the stenosis was located at the end of the duct. Therefore, our skin approach began from the lateral orbital wall and continued to approximately 3 cm superior to the duct (Fig. 3). The end of the duct was then isolated with blunt dissection. If, under direct vision, the stenosis was confirmed to be near the orifice of the duct, the stenosis and distal part of the duct would be removed. The remaining part of the duct was re-opened in the conjunctival fold. A polyethylene tube was inserted and left in the duct for about 1 month to prevent new stenosis formation (Fig. 3).

2.6. Wharton's duct reconstruction

If the stenosis was in the middle or the proximal part of the duct, the remaining part of the duct would not be long enough to be re-opened in the eye following stenosis removal. The length from the end of the duct to the eye was measured and the desired length of vein was harvested from the cephalic vein in the left forearm. The distal end of the cephalic vein was anastomosed end-to-end with the remaining duct, and the wall of the proximal end of the vein was sutured to the conjunctival mucosa to form a new opening (Fig. 4). A polyethylene tube was inserted and left in the duct for about 1 month. A pressure dressing above the grafted vein was applied for 10 days.

3. Results

Ten patients (52.6%) were women and nine (47.4%) were men, with a mean age of 30 (17–62) years. The mean follow-up time was

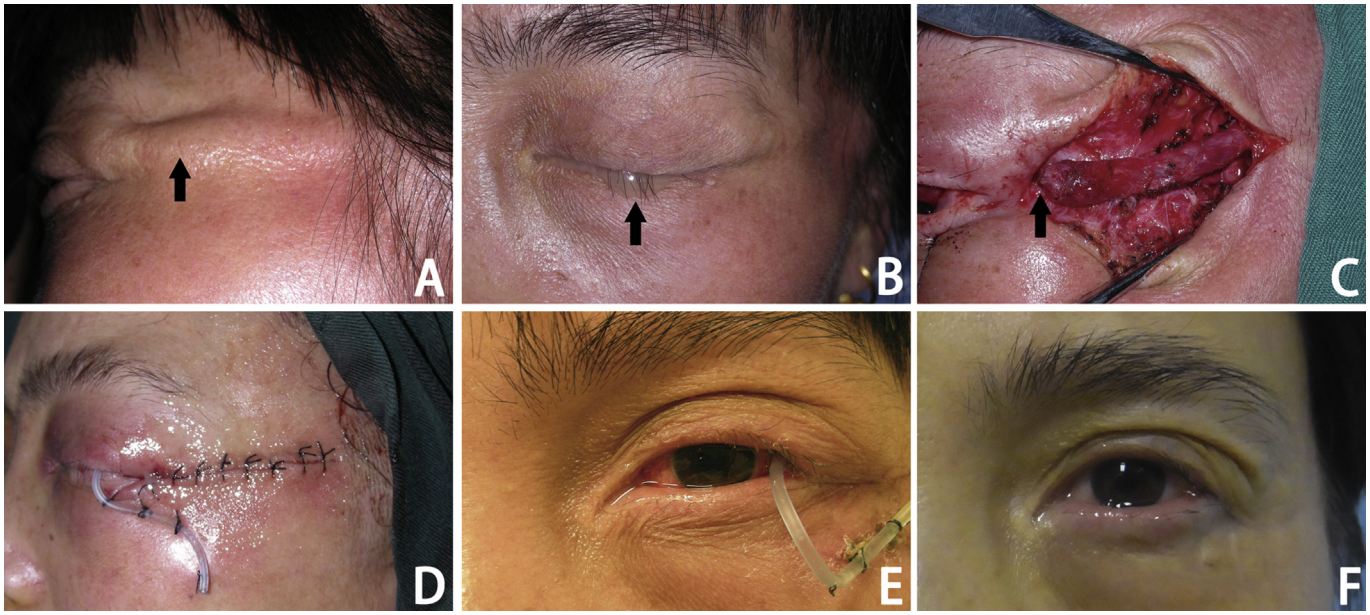

Fig. 3. Wharton's duct orifice reconstruction in a 34-year-old female patient. (A, B) The transplanted gland was swollen (arrow) and secretions became scant and thick (arrow) 8 months after surgery. (C) The end of the duct was isolated via a skin approach, and the stenotic portion of the duct near the orifice was identified (arrow). (D) The stenosis and distal part of the duct were removed and the remaining part of the duct was re-opened. (E) The transplanted gland gave spontaneous normal secretions 1 month after treatment. (F) Secretion was normal at 2 years follow-up.

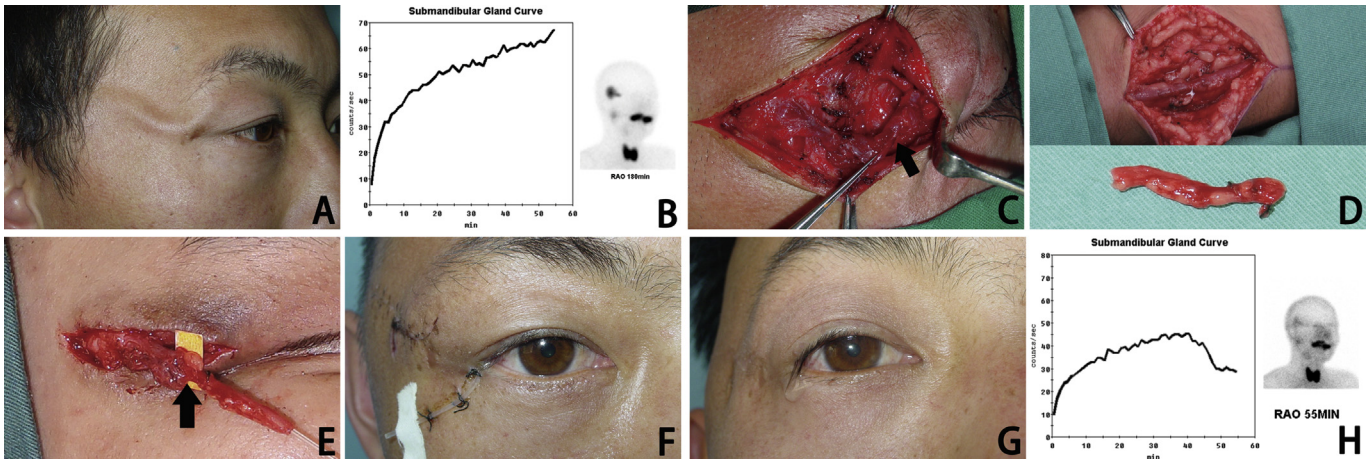

Fig. 4. Wharton's duct reconstruction in a 38-year-old male patient. (A) The transplanted gland was swollen with no secretion 4 months after surgery. (B) ^{99m}Tc-pertechnetate concentrated in the proximal portion of the duct and showed no drainage even at 180 min after injection. (C) The duct was exposed via a skin approach and the lesion was identified in the middle part of the duct (arrow). (D) The cephalic vein was harvested from the left forearm. (E) The stenosis and distal part of the duct were removed, and the cephalic vein was anastomosed end-to-end with the remaining duct. (F) The incision healed well at 2-week follow-up. (G) The transplanted gland gave spontaneous normal secretion at 1 year follow-up. (H) The gland showed normal uptake and drainage of ^{99m}Tc-pertechnetate on scintigraphy.

8.5 years (1–18 years). Among 19 patients, 14 achieved a satisfactory result. In five patients, the treatments failed and the transplanted glands lost secretory function (Fig. 5). A solitary stone in Wharton's duct was found in one patient and was removed successfully without complications (Fig. 1). Intensive stimulation of secretions was applied in 12 of the remaining patients (six early patients did not receive this treatment). In three of these patients, the obstructing substance was successfully cleared. Polyethylene tube intubation was attempted in nine patients, with success in two patients. Resting Schirmer's test values recovered to >5 mm/5 min following 5 and 6 days of normal saline irrigation, respectively (Fig. 2). No complications or duct obstruction recurrences were found in the five patients successfully managed by “internal” or external irrigation.

Surgical exploration was performed in 13 patients. In nine patients, a stenosis was found in the orifice of the duct. The duct was successfully re-opened in six patients and secretion returned to normal without any complications or recurrence (Fig. 3). Surgery failed in two patients. For the remaining patient, a new stenosis was found in the middle part of the duct 4 months following orifice reconstruction surgery. This patient, along with four other patients with middle duct obstruction, underwent Wharton's duct reconstruction surgery. Cephalic vein grafting was successful with no complications or recurrence in two patients (Fig. 4).

In all, there were five patients for whom surgical explorations failed, with resulting loss of secretions in the transplanted SMGs. For four patients, the remaining Wharton's duct was extremely distended and the duct wall was too fragile to be re-

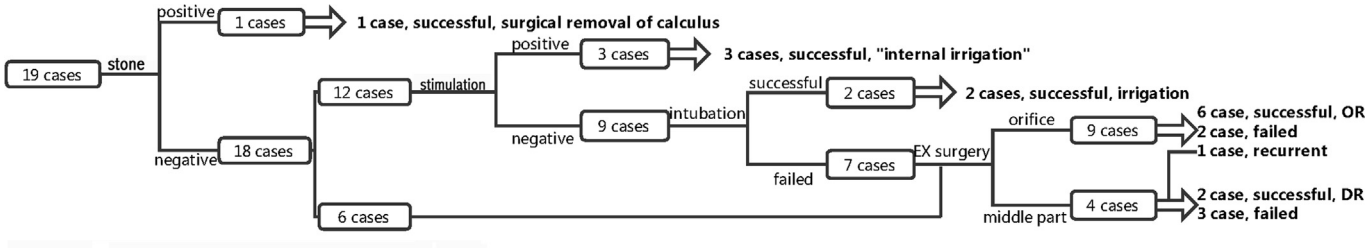

Fig. 5. Flow chart outlining diagnostic/therapeutic protocol for 19 patients. EX: exploration. OR: orifice reconstruction. DR: duct reconstruction.

opened or anastomosed. For one patient, the cephalic vein was successfully anastomosed with the duct, but the gland produced no secretion after surgery, suggesting that the graft might not have survived.

4. Discussion

Obstructive sialadenitis is the most common inflammatory disorder of the major salivary glands. The main cause is stone, especially in the submandibular gland. In most cases, sialoendoscopy permits minimally-invasive surgical treatment (Witt et al., 2012). However, this technique is not applicable for transplanted SMGs for severe dry eye patients, since even flexible endoscopes cannot traverse the sharp rigid angel of Wharton's duct where it passes the lateral orbital wall. In addition, stone only accounts for a very small percentage of blockages in transplanted SMGs. Therefore, the treatment strategies for normal SMG obstruction are not applicable to obstructive sialadenitis in transplanted SMGs. In the present study, we describe treatment of 19 such patients, and offer a step-wise clinical protocol to manage this complication (Fig. 5).

4.1. Management protocol

4.1.1. First step

Stones may form in transplanted SMGs. As Wharton's duct is located immediately subcutaneously after transplantation, stone is easily diagnosed via palpation, and is easily removed via a skin approach. For every patient with obstructive sialadenitis of transplanted SMGs, exclusion of a stone should be the first step.

4.1.2. Second step

When there is no evidence of stones, blockage may be due to either abnormal viscus secretions (mucus plug) or to duct stenosis (the former may be an early stage and may lead to the latter) (Harbison et al., 2011). These two mechanisms cannot be differentiated via history or physical examination. Therefore, we suggest that the second step should be non-invasive methods of intensive secretion stimulation. Transplanted SMGs are denervated, and thus they respond much more strongly to stimulation, especially to carbachol, than do “normal” SMGs. Substantial flow rates may be expected from these stimulations, and may produce an “internal irrigation” effect.

4.1.3. Third step

Grafts failing to respond to stimulation are either hypofunctioning or have become stenotic. Polyethylene tube intubation should be the next step for these patients. Successful intubation provides a pathway for retrograde irrigation, a proven remedy for early stage obstructive sialadenitis in normal SMGs (Antoniades et al., 2004). If, however, intubation fails, duct stenosis should be highly suspected, and surgical exploration should be considered.

4.1.4. Fourth step

The final step is surgical exploration with stenosis removal or Wharton's duct reconstruction. In the current study, organic stenosis was diagnosed in all patients undergoing surgical exploration. Most stenoses were located near the orifice of the duct, which might have been caused in part by the surgical trauma of transplantation. This kind of stenosis was managed by a re-opening procedure, with a relative high successful rate of 66.7% (6/9). Treatment of stenosis in the middle part of the duct was complicated and had a successful rate of only 40% (2/5).

For six early cases in our study, experience was lacking and treatment was not given promptly. All six developed duct stenosis. Surgical reconstruction of the orifice or Wharton's duct failed in three (50%). Excluding these six patients, the success rate of treatments following the protocol described above was 84.6% (11/13). Therefore, early diagnosis and timely treatment of obstructive sialadenitis of transplanted SMGs is essential. On the other hand, Wharton's duct management should be emphasized as one of the most demanding surgical steps during transplantation. To avoid any possible injury and the following scarring and stenosis, careful blunt dissection should be applied when harvesting the Wharton's duct. Besides, to prevent scar formation in the ductal orifice, it is essential to harvest the mucosal cuff around the Wharton's duct orifice. Then after the duct was transferred, the mucosal cuff, instead of the duct wall, could be sutured with the conjunctiva.

5. Conclusion

We review our experience with obstructed submandibular glands that had been transplanted for the treatment of dry eye, and described a step-wise approach to management of this complication. Stone, which is easy to diagnose and treat, should be excluded first. Non-organic blockage and stenosis were semblable in clinic. Therefore, subsequent steps should be a diagnostic/therapeutic trial of secretory stimulation, followed by irrigation; failure of these interventions suggests the diagnosis of duct stenosis, necessitating surgical reconstruction of the orifice or Wharton's duct. Reconstruction carries a measurable failure rate.

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Authors' contributions

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Acquisition, analysis and interpretation of data: Jia-Zeng Su, Zhi-Gang Cai, Xiao-Jing Liu, Lan Lv, Guang-Yan Yu.

Drafting the article: Jia-Zeng Su, Guang-Yan Yu.

Revising the article: Jia-Zeng Su, Zhi-Gang Cai, Xiao-Jing Liu, Lan Lv, Guang-Yan Yu.

Final approval of the version to be published: Jia-Zeng Su, Zhi-Gang Cai, Xiao-Jing Liu, Lan Lv, Guang-Yan Yu.

Agreement to be accountable for all aspects of the work: Jia-Zeng Su, Zhi-Gang Cai, Xiao-Jing Liu, Lan Lv, Guang-Yan Yu.

All authors have read and approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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