

Microvascular Autologous Submandibular Gland Transfer in Severe Cases of Keratoconjunctivitis Sicca: A 10-year Experience

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Keratoconjunctivitis sicca, characterized by reduction or lack of tears with the resulting consequences, is a relatively common disease. The current therapeutic options are largely symptomatic and insufficient in severe cases. During the last 10 years, 141 cases (150 eyes) of severe keratoconjunctivitis sicca have been treated by autologous submandibular gland transfer. It has been shown that autologous submandibular gland transfer is a lasting and effective solution for the severe cases. However, there are two main problems with this method that need to be resolved. One is that a lower flow rate leads to the obstruction of Wharton's duct in the early stage after transfer. The other is that half of the patients suffer from epiphora in the long term. In order to resolve the two problems, both clinical and basic research were performed to modify surgical procedures and to understand the mechanisms underlying the secretion of the transferred submandibular gland. We found that partial submandibular gland transfer could prevent or alleviate epiphora and that α 1- and β -adrenoceptors and vanilloid receptor 1 were involved in the secretion by normal and transferred submandibular glands. The agonists of these receptors could moderate structural injury and improve secretory function in the transferred submandibular gland.

Key words: keratoconjunctivitis sicca, dry eye syndrome, autologous submandibular gland transfer, receptor, surgery

Keratoconjunctivitis sicca, known as dry eye syndrome, is a relatively common disease. According to the literature, the incidence of this condition is 2.7% of the population¹. In other words, there are roughly 30 million patients suffering from keratoconjunctivitis sicca in China. Keratoconjunctivitis sicca is characterized by reduction or lack of tears with the resulting con-

sequences. The current therapeutic options are largely symptomatic, including artificial tear substitutes, tarsorrhaphy or occlusion of tear drainage. These treatment modalities give satisfactory results in mild cases. However, they seem to be insufficient in severe cases. Submandibular gland transfer was first described and successfully performed by Murube-Del-Castillo in 1986². Since then, several doctors, including MacLeod^{3,4}, Geerling^{5,6}, Sieg⁷ and Jia^{8,9}, have reported their clinical or research work on submandibular gland transfer.

The present clinical work on submandibular gland transfer was started in 1999 based on a series of animal experiments, collaborating with ophthalmologists from Beijing Tong Ren Hospital. Between August 1999 and August 2009, 141 cases (150 eyes) diagnosed as severe keratoconjunctivitis sicca were treated with microvascular autologous submandibular gland transfer in the Department of Oral and Maxillofacial Surgery, Peking

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University School of Stomatology. Among them, 69 cases were males and 72 cases females. Their ages ranged from 9 to 69 years, with a mean of 33.2 years.

Surgical Procedure

Under general anaesthesia, the submandibular gland, including Wharton's duct and its related blood vessels, was isolated and transferred to the temporal area. The blood vessels of the submandibular gland were anastomosed with temporal blood vessels. The distal end of Wharton's duct was sutured to form an opening in the upper lateral conjunctiva fold. The secretion from the transferred submandibular gland supplements the insufficient natural tears¹⁰.

Clinical Outcome

The transfer was successful in 133 glands (88.7%) and failed in 17 glands. Among the unsuccessful cases, four cases were due to anatomical abnormality of blood vessels, seven cases due to venous thrombosis, two cases due to arterial thrombosis, and another four cases due to obstruction of Wharton's duct.

In the patients with successful transfer, their symptoms of xerophthalmia were relieved or disappeared. The discomfort resulting from bright light and wind was also relieved. These patients could stop applying artificial tears. Visual acuity improved in some patients. Reduced staining spots and intensity in fluorescent staining, and reduced cornea capillary formation and turbidity could be detected in post-operative ophthalmologic examination. The results of a subjective satisfaction questionnaire in 50 patients showed a satisfaction rate of 90%¹¹.

Ten years of clinical experience with severe keratoconjunctivitis sicca suggested that microvascular autologous submandibular gland transfer is a lasting and effective solution for the severe cases.

However, during long-term follow up, it was found that there were two main problems for this relatively new technique. The first problem was that during the latent period, usually the first 3 months after surgery, the saliva flow ranged from 0 to 11 mm measured by Schirmer's test, with a mean of 5 mm. Such a low flow rate may lead to the obstruction of Wharton's duct. The second problem was that half of the patients suffered from epiphora in the long term after surgery^{10,12,13}.

In order to resolve the two problems, some clinical and basic research work was conducted on surgical procedure modification and secretion regulation of the transferred submandibular gland.

Studies on Secretion Regulation of the Transferred Submandibular Gland

Since the chorda nerve and sympathetic nerve were cut off during the transfer, the submandibular gland was completely denervated after surgery. The secretion mechanism was changed. Some basic research was then conducted on the roles of receptors related to saliva secretion in the regulation of secretion of both normal and transferred submandibular glands.

α -Adrenoceptors

Using a rabbit submandibular gland transfer model, the expression of the α_1 -adrenoceptor (AR) subtype was evaluated by reverse transcription polymerase chain reaction, the translocation of aquaporin-5 (AQP5) was identified by confocal microscope, the proliferating cell nuclear antigen-positive cells in the submandibular gland was detected by immunohistochemical staining and the expression of extracellular signal-regulated kinase (ERK) was evaluated by Western blot¹⁴.

It was found that, during the first week after transfer, salivary flow of the transferred submandibular gland was significantly decreased. Atrophy of acinar cells was shown in transferred glands. Phenylephrine treatment reversed the decrease in saliva secretion after transfer, enhanced the expressions of α_{1A} , α_{1B} , and α_{1D} -AR mRNA, and ameliorated atrophy of acinar cells. Furthermore, phenylephrine also induced translocation of AQP5 from the cytoplasm to the apical membrane, and increased the levels of phospho-ERK1/2, ERK1/2, phosphoprotein kinase C ζ (phospho-PKC ζ) and PKC ζ in the transferred gland¹⁵.

These results indicate that phenylephrine treatment moderates structural injury and improves secretory function in the transferred submandibular gland through promoting α_1 -AR expression and post-receptor signal transduction.

β -Adrenoceptors

The expression and function of β -AR subtypes was investigated in normal rabbit submandibular glands. Both β_1 and β_2 -ARs, but not β_3 -AR, were expressed in rabbit submandibular glands. β_1 -AR proteins were widely expressed in acinar and ductal cells, whereas β_2 -AR proteins were mainly expressed in ductal cells. Perfusion with the β -AR agonist isoproterenol induced a significant increase in saliva secretion, which was eliminated by pretreatment with the nonselective β -AR antagonist propranolol and β_1 -AR-selective antagonist CGP



20712A¹⁶. The expression and secretion of α -amylase were significantly stimulated by isoproterenol, which was eliminated by propranolol and CGP 20712A.

The results indicate that both β_1 and β_2 -ARs are expressed in rabbit submandibular glands. β_1 -AR is the predominant subtype and may play an important role in regulating saliva and α -amylase secretion.

In a rabbit submandibular gland transfer model, the expressions of β_1 and β_2 -AR and their maximum binding capacity markedly decreased in the transferred gland. Isoproterenol significantly reversed the decreasing secretion, enhanced the expressions of β_1 and β_2 -AR, and ameliorated the atrophy of acinar cells. The contents of cAMP and phospho-ERK1/2 were increased after isoproterenol treatment. These results indicate that lack of β -AR stimulation is involved in early dysfunction of the transferred gland¹⁷.

Vanilloid Receptor

In clinical observations, it was found that the transferred submandibular gland seemed to secrete more saliva after the patients had a spicy diet, suggesting that spicy food might have a role in secretion promotion. After carefully investigating the components of capsicum, the vanilloid receptor was selected for additional research.

Vanilloid receptor 1 (VR1) is a polymodal receptor originally found in sensory neurons of the central nervous system. Recent studies indicate that VR1 is also expressed in non-neuronal tissues¹⁸. The endogenous expression of VR1 was investigated in rabbit submandibular glands. The results showed that there was expression of VR1 mRNA and protein in the rabbit submandibular gland; VR1 was mainly localised in the basolateral membrane of duct cells and the cytoplasm of acinar cells¹⁹.

The function of the vanilloid receptor on regulating saliva secretion was further investigated. The results showed that capsaicin induced a significant increase in intracellular calcium in neonatal rabbit submandibular gland cells. Saliva secretion was significantly increased after infusion of capsaicin in isolated submandibular glands. However, capsazepine, a VR1 antagonist, eliminated the increase in intracellular calcium and saliva secretion¹⁹. These findings indicate that functional VR1 is expressed in submandibular glands and plays an important role in regulating saliva secretion.

Based on the rabbit experiment, 0.075% capsaicin cream (Medicis Canada Ltd/Ltee) was applied topically on the superficial skin of the transferred submandibular gland during the latent period. The results

showed that capsaicin could stimulate the secretion of the transferred submandibular gland in patients²⁰.

Surgical Modification

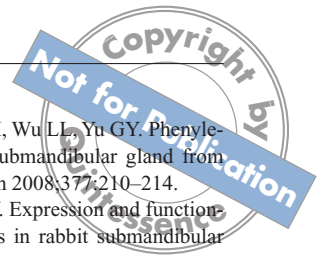
Secretion of the submandibular glands is much greater than that of lacrimal glands. According to the present authors' experience, secretion of one-third of a normal submandibular gland is enough for lubrication of the ocular surface structures. More than half of the patients who had successful transfer with an intact submandibular gland suffered from epiphora, especially during physical activity or in hot weather¹⁰. This problem was addressed by gland reduction surgery, removing part of the transferred submandibular gland to decrease the glandular secretion. However, the patients had to suffer through secondary or even more operations. Therefore, the surgical technique of glandular transfer was modified. For those patients with ample and good function in the submandibular gland, serious epiphora would be expected to occur. Hence, a partial submandibular gland transfer, which means the combined techniques of transfer and reduction of the gland, was performed. The secretion of a partial transferred submandibular gland was much lower than that of an intact transferred submandibular gland. These results indicate that partial submandibular gland transfer is an efficient technique to prevent or alleviate epiphora.

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