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

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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 consequences. 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 α1- 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

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from epiphora in the long term after surgery\textsuperscript{10,12,13}. The second problem was that half of the patients suffered a low flow rate may lead to the obstruction of Wharton’s duct. The Schirmer’s test, with a mean of 5 mm. Such a low flow rate may lead to the obstruction of Wharton’s duct. 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 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 latent period, usually the first 3 months after surgery, 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 tears\textsuperscript{10}.

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\%\textsuperscript{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\textsuperscript{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.

\alpha\textsuperscript{-}Adrenoceptors

Using a rabbit submandibular gland transfer model, the expression of the \(\alpha\textsubscript{1}\)-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 blot\textsuperscript{14}.

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 \(\alpha\textsubscript{1A}\), \(\alpha\textsubscript{1B}\), and \(\alpha\textsubscript{1D}\)-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 \(\text{C}_\alpha\) (phospho-PKC\(\text{C}_\alpha\)) and PKC\(\text{C}_\alpha\) in the transferred gland\textsuperscript{15}.

These results indicate that phenylephrine treatment moderates structural injury and improves secretory function in the transferred submandibular gland through promoting \(\alpha\textsubscript{1}\)-AR expression and post-receptor signal transduction.

\beta\textsuperscript{-}Adrenoceptors

The expression and function of \(\beta\)-AR subtypes was investigated in normal rabbit submandibular glands. Both \(\beta\textsubscript{1}\) and \(\beta\textsubscript{2}\)-ARs, but not \(\beta\textsubscript{3}\)-AR, were expressed in rabbit submandibular glands. \(\beta\textsubscript{1}\)-AR proteins were widely expressed in acinar and ductal cells, whereas \(\beta\textsubscript{2}\)-AR proteins were mainly expressed in ductal cells. Perfusion with the \(\beta\)-AR agonist isoproterenol induced a significant increase in saliva secretion, which was eliminated by pretreatment with the nonselective \(\beta\)-AR antagonist propranolol and \(\beta\textsubscript{1}\)-AR-selective antagonist CGP
secretion. These findings indicate that functional VR1 inhibited the increase in intracellular calcium and saliva glands. However, capsazepine, a VR1 antagonist, eliminated the increase in intracellular calcium in neonatal rabbit submandibular gland cells. Saliva secretion was significantly increased after infusion of capsaicin in isolated submandibular gland cells. Saliva secretion was further investigated. The results showed that capsaicin could stimulate the secretion of the transferred submandibular gland in patients.

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 weather. 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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References


