

Treatment of Severe Keratoconjunctivitis Sicca by Parotid Duct Transposition after Tympanic Neurectomy in Rabbits

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PURPOSE. To investigate the feasibility of parotid duct transposition after tympanic neurectomy to treat severe keratoconjunctivitis sicca (KCS) in rabbits.

METHODS. Thirty rabbits were divided into three groups in experiment 1. One eye was operated on, and the contralateral eye served as the control. In the KCS group, the lacrimal gland, Harderian gland, and nictitating membrane were removed. In the group with parotid duct transposition (DT), the parotid duct was transposed into the lower conjunctival fornix. In the group with parotid duct transposition after tympanic neurectomy (DTTN), the tympanic nerve was resected in addition to parotid duct transposition. Schirmer test was performed and density of corneal staining was determined monthly after surgery, and goblet cell density was measured at postoperative month 3. In experiment 2, the tympanic nerve was resected on one side in 12 rabbits. Both sides of the parotid gland were resected for histopathology at intervals of 2 months to 1 year after surgery.

RESULTS. Tear secretion from operated eyes at rest increased significantly after surgery in the treatment groups compared with the KCS group. Tear secretion from operated eyes after chewing was significantly lower in the DTTN than in the DT group. The corneal staining scores were higher in the operated than in the control eyes of the three groups, without significant difference among the operated eyes. Parotid gland atrophy on the operated side occurred at postoperative month 4 and recovered to normal 1 year after surgery.

CONCLUSIONS. Parotid duct transposition after tympanic neurectomy could effectively reduce gustatory epiphora but may be insufficient to promote ocular surface health. (*Invest Ophthalmol Vis Sci.* 2011;52:6964–6970) DOI:10.1167/iovs.10-6459

Keratoconjunctivitis sicca (KCS), dry eye syndrome, is a relatively common disease characterized by reduced or no tears. Severe KCS leads to corneal ulceration, opacification, or even blindness. Traditional therapies for KCS are palliative and include artificial tear substitutes and occlusion of tear drainage

to replace or conserve the patient's tears. These treatment modalities give satisfactory results in mild and moderate cases but are not effective in severe cases.¹

In the early 1950s, a treatment for KCS involved transposing the parotid duct into the lateral conjunctival fornix for a natural and continuous source of tears.² However, this procedure could cause ectropion, epiphora, gustatory secretion, and traumatic keratitis because of the constant wiping of the eyes to remove excess secretion,³ and it was abandoned.

Microvascular autologous transplantation of submandibular glands with implantation of Wharton's duct into the upper conjunctival fornix to treat severe KCS was introduced by Murube-del-Castillo⁴ in 1986 and was tested by several groups.^{1,5–8} This procedure could offer a permanent autologous source of tears with the basal secretion of a transplanted revascularized but denervated submandibular gland and so overcome gustatory epiphora. However, the surgical procedure was complicated, and a perfect microsurgical technique was needed.

To overcome this problem, we hypothesized that gustatory epiphora after transposition of the parotid duct could be avoided if the parotid gland was denervated. Most of the parasympathetic nerve supply to the parotid gland is via the tympanic nerve. Parotid secretion on gustatory stimulation could decrease if the tympanic nerve were resected. Tympanic neurectomy was first used in 1962 by Golding-Wood.⁹ In this surgery, the parasympathetic nerve supply of the parotid gland is interrupted by dissecting the tympanic nerve on the promontory of the middle ear. Tympanic neurectomy has been used successfully to treat patients with drooling,¹⁰ parotid fistula,¹¹ Frey's syndrome,¹² and chronic parotitis.¹³

We aimed to investigate the feasibility of parotid duct transposition after tympanic neurectomy to treat severe KCS in rabbits. We hoped to create a new therapeutic approach for severe KCS and provide the experimental basis for its clinical application.

MATERIALS AND METHODS

The study involved 30 Japanese albino rabbits of both sexes weighing 2.0 to 3.0 kg. The rabbits were randomly divided into three groups ($n = 10$ each). All rabbits were bred by Peking University Laboratory Animal Center and treated in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. All animals were anesthetized with intravenous pentobarbital sodium (30 mg/kg). Only one eye was operated on in each animal. The contralateral eye was used as the control. All measurements and assays of eyes were performed in a masked fashion.

The KCS model was created in all rabbits by surgical removal of the lacrimal gland and the Harderian gland and nictitating membrane, as described elsewhere.¹⁴ In the parotid duct transposition (DT) group, the ipsilateral parotid duct was transposed into the lower conjunctival fornix. In the group with parotid duct transposition after tympanic

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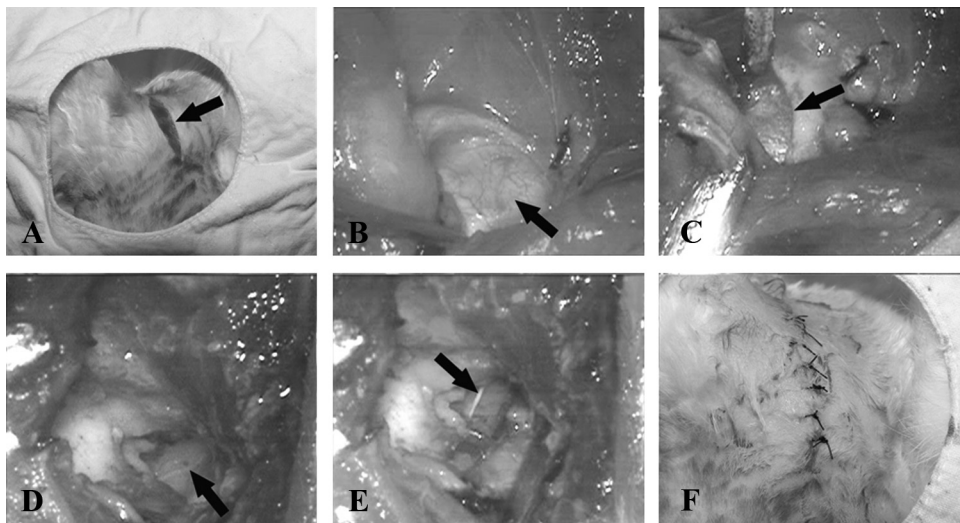


FIGURE 1. Tympanic neurectomy. (A) Surgical approach (*arrow*). (B) The cartilaginous auditory canal (*arrow*) is exposed and (C) is incised from the tragus to the origin of the bony auditory canal (*arrow*). (D) The middle ear is opened and the tympanic nerve (*arrow*) exposed. (E) The tympanic nerve is resected, and the promontory is swabbed with 50% trichloroacetic acid until the mucosa on the promontory turns black. *Arrow*: the chorda tympani nerve. (F) The skin is sutured.

neurectomy (DTTN), in addition to parotid duct transposition, the tympanic nerve was resected.

A second experiment was designed to evaluate the long-term histopathologic changes and secretion function of the denervated parotid gland. Twelve Japanese albino rabbits of both sexes weighing 2.0 to 3.0 kg were anesthetized with intravenous pentobarbital sodium (30 mg/kg). The tympanic nerve was resected on one side in each animal. The other side served as the control. Two rabbits in experiment 2 were killed at each time point at intervals of 2 months to 1 year after tympanic neurectomy.

Tympanic Neurectomy

A curve-shaped incision was made on the posterior and inferior limbus of the ear (Fig. 1A). Skin was incised and the cartilaginous auditory canal was exposed (Fig. 1B). The cartilaginous auditory canal was incised from the tragus to the origin of the bony auditory canal (Fig. 1C). Under the operating microscope, the mucosa was freed from the floor of the bony auditory canal. The middle ear was opened by inferior and posterior mobilization of the drum. In the direction of the hypotympanum, the tympanic nerve passes toward the promontory, where it usually lies in a small mucosally covered bony groove (Fig. 1D). Tympanic neurectomy was performed by subluxing the tympanic nerve from its bony groove and removing a segment of the nerve as far as possible. To coagulate any remnants of neural or mucosal tissue that

had escaped instrument destruction, the promontory was swabbed with 50% trichloroacetic acid until the mucosa on the promontory turned black (Fig. 1E). The drum and mucosa of the bony auditory canal were repositioned, and the cartilaginous auditory canal was closed in layers. The skin was sutured with 5-0 nonabsorbable sutures (Fig. 1F).

Parotid Duct Transposition

A horizontal skin incision was made in the anterior region of the cheek of rabbits (Fig. 2A). The parotid duct was located and transected in the distal end of the duct. Then, the parotid duct was freed up to the proximal end of the duct (Fig. 2B). By blunt dissection, a tunnel to the lower conjunctival fornix was made, and the duct was passed through it (Fig. 2C). Under the surgical microscope, the distal end of the duct was sutured to the margins of the conjunctival incision with 8-0 nylon sutures (Fig. 2D). The skin wound was then closed (Fig. 2E).

Postoperative Treatment

In total, 400,000 U penicillin (North China Pharmaceuticals, Hebei, China) was administered intramuscularly, twice daily for 3 days, and eye drops with 0.3% tobramycin and 0.1% dexamethasone were given three times daily for 5 days. All animals in experiment 1 were killed by intravenous pentobarbital sodium overdose at postoperative month 3.

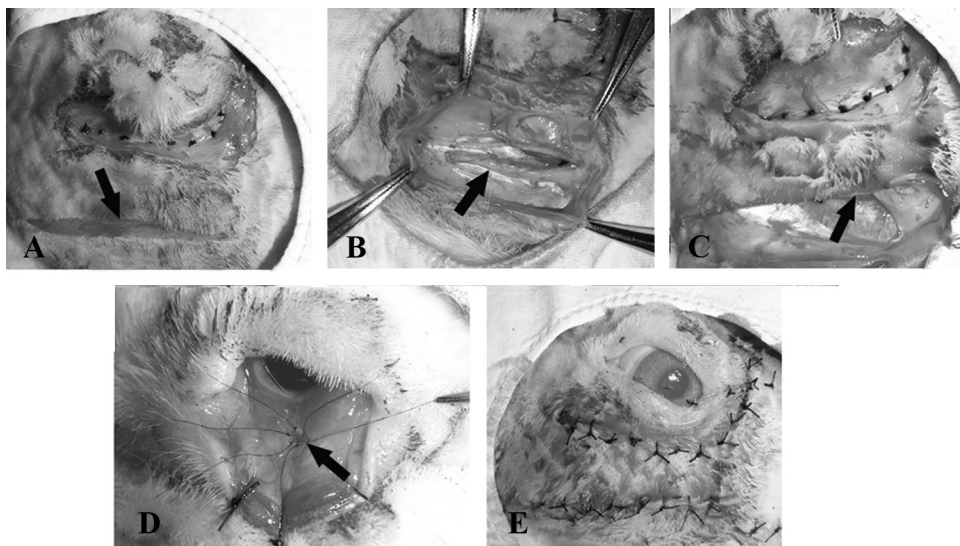


FIGURE 2. Parotid duct transposition. (A) Horizontal skin incision (*arrow*) in the anterior area of the cheek of the rabbit. (B) The parotid duct (*arrow*) is freed up to its proximal end. (C) A tunnel (*arrow*) is made to the lower conjunctival fornix, and the duct is passed through it. (D) The distal end of the duct is sutured to the margins of the conjunctival incision (*arrow*). (E) The skin wound is closed.

Schirmer Test

Strips of filter paper 5 mm in width were folded at the 5-mm notch and placed into the lower mediolateral third of the conjunctival fornix of both eyes for 5 minutes without anesthesia before and after the rabbits chewed food pellets. The rabbits were strapped down and fixed in the wooden box, and the eyes were closed with hands after the strips were inserted, to avoid their scratching their eyes to remove the test strips. The length of moisture on the paper was measured. The test was repeated three times, and the mean value was obtained. The test was performed before surgery and monthly for 3 months after surgery.

Assessment of Amylase Activity of Tears

The tear samples were collected by a microcapillary tube placed near the lacrimal lacus on the operated eyes of the DT and DTTN groups. Normal tear samples were obtained by stimulating the conjunctiva with a microcapillary tube before surgery. The tear specimens were collected monthly after surgery after the rabbits chewed food pellets. All the tear samples were collected between 9 and 11 AM and immediately stored in 0.5-mL vials (Eppendorf, Fremont, CA) at -80°C until analysis. Amylase activity of the tear was measured using ethylidene-4-nitrophenyl- α -D-maltoheptaoside (Leadman Group Co., Ltd., Beijing, China) as a substrate. Bichromatic readings were made at 405 and 546 nm on an automatic biochemical analyzer (LX20; Beckman, Fullerton, CA).

Fluorescein Test

The eyes of all animals were checked monthly after surgery for 3 months with instillation of 1 drop of 1% fluorescein solution. Corneal staining was assessed by a trained ophthalmologist (YJ). The modified scoring system was used according to the National Eye Institute/Industry Workshop on Clinical Trials for Dry Eyes.¹⁵ 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.

Rose Bengal Test

With rabbits under surface anesthesia, both eyes were checked after instillation of 1 drop of 1% solution of rose bengal on day 2 after each fluorescein staining. The scoring method was the same as that used for fluorescein staining.

Measurement of Goblet Cell Density

Bulbar conjunctival biopsy was performed on both eyes after animals in experiment 1 were killed at postoperative month 3. The conjunctival goblet cell density depends on the topographic location within the conjunctival field.¹⁶ Therefore, we obtained conjunctival biopsies superior to the cornea between the musculus rectus lateralis oculi and medialis oculi. Specimens were processed by routine techniques. The sections (6 μm) perpendicular to the conjunctival surface were rehydrated and stained with periodic acid Schiff (PAS). Conjunctival goblet cells were counted in five sections at $\times 40$ magnification under an optical microscope.¹⁷ The mean value was recorded as the number of goblet cells per field.

Histopathologic Examination

All the rabbits for the histopathologic examination in experiment 1 were killed at postoperative month 3. The parotid gland and bulbar conjunctival and corneal biopsies were taken from the operated and control sides. Tissue samples were processed by routine techniques. The sections were stained with hematoxylin and eosin and observed under an optical microscope.

In experiment 2, two rabbits were killed at each time point at intervals of 2 months to 1 year after tympanic neurectomy. Both sides of the parotid gland were removed from each animal. Half the tissue samples were fixed in formalin and stained with hematoxylin and eosin

(H&E) for routine histopathologic study. The other half of the sample were cut into small cubes and fixed in 2.5% glutaraldehyde with phosphate-buffered saline (0.1 M; pH 7.2–7.4) for 2 hours, postfixed in 0.1% OsO_4 in the same buffered solution for 1 hour, and then dehydrated and embedded in epoxy resins. Ultrathin sections were counterstained with uranyl acetate and lead citrate and observed under a transmission electron microscope (400S; Philips, Eindhoven, The Netherlands).

Statistical Analysis

Data are presented as the mean \pm SD. The tear secretion at rest in each group was analyzed before and after surgery by univariate ANOVA. The tear secretion in the DT and DTTN groups was analyzed, before and after chewing, by paired Student's *t*-test each month after surgery. The tear secretion of the DT and DTTN groups after chewing was compared by independent-samples *t*-test at each time point after surgery. Amylase activity in the DT and DTTN groups was compared before surgery and after surgery by univariate ANOVA. The Kruskal-Wallis test was used to compare corneal staining in operated and control eyes. One-way ANOVA was used to compare goblet cell density in operated and control eyes. Multiple comparison was performed by Bonferroni tests. $P < 0.05$ was considered statistically significant (SPSS ver. 11.5; SPSS Inc., Chicago, IL).

RESULTS

Tear Secretion at Rest

For the KCS alone group, tear secretion from the operated eyes was significantly lower at all postoperative time points than before surgery ($P = 0.000$), indicating that the KCS model was established successfully.

After parotid duct transposition, tear secretion from the operated eyes increased significantly at all postoperative time points in both groups, with or without tympanic neurectomy, compared with the KCS group ($P = 0.000$; Fig. 3A).

Tear secretion from the operated eyes in the DTTN group was similar compared with that in the DT group at postoperative months 1 and 2, but was higher in the DTTN group at postoperative month 3 than in the DT group (DTTN group versus DT group at postoperative month 3, $P = 0.037$).

Tear Secretion after Chewing

For the DT group, tear secretion from the operated eyes significantly increased after chewing than at rest at postoperative months 1 to 3 ($P = 0.001$, $P = 0.001$; and $P = 0.015$ respectively; Fig. 3B).

Furthermore, tear secretion from the operated eyes after chewing was significantly lower in the DTTN group than in the DT group at all postoperative time points ($P = 0.000$; Fig. 3B), suggesting that the gustatory reflex was effectively controlled after tympanic neurectomy.

Amylase Activity of Tears

For the DT and DTTN groups, the amylase activity of tears in the operated eyes significantly increased at all postoperative time points compared with before surgery ($P = 0.000$; Table 1). The amylase activity of tears in the operated eyes was significantly higher only at postoperative month 3 in the DTTN group than in the DT group ($P = 0.012$).

Ocular Surface Changes

At monthly examination during the first 3 months after surgery, slit lamp examination showed abnormal fluorescein and rose bengal staining of the cornea in the operated eyes of the three groups (Fig. 4). Compared with the mean scores for contralateral control eyes, the mean corneal fluorescein staining scores

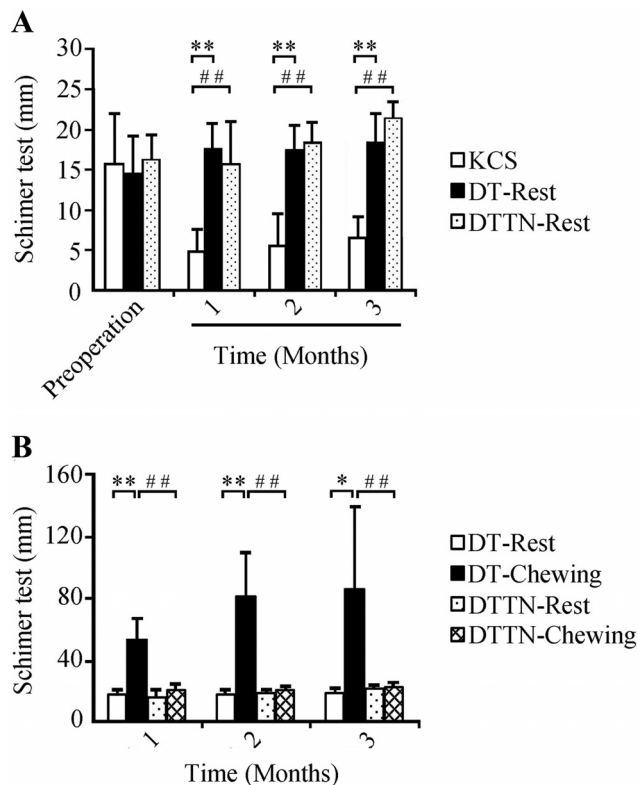


FIGURE 3. Tear secretion from the operated eyes, at rest and after chewing. Tear secretion was measured by Schirmer test, at rest and after chewing food pellets. (A) Tear secretion from the operated eyes at rest. Tear secretion from the operated eyes significantly increased in the treatment groups compared with that in the KCS group after surgery. ** $P < 0.01$ compared with KCS group. *** $P < 0.01$ compared with KCS group. (B) Effect of tympanic neurectomy on tear secretion after chewing. Tear secretion from the operated eyes was significantly higher after chewing than at rest in the DT group and higher than after chewing in the DTTN group at all postoperative time points. * $P < 0.05$ and ** $P < 0.01$ compared with DT group at rest. *** $P < 0.01$ comparing DT with DTTN groups after chewing. $n = 10$ at each time point in each group. KCS, keratoconjunctivitis sicca; DT-Rest, parotid duct transposition at rest; DT-Chewing, parotid duct transposition after chewing; DTTN-Rest, parotid duct transposition after tympanic neurectomy at rest; DTTN-Chewing, parotid duct transposition after tympanic neurectomy after chewing.

and the mean rose bengal staining scores in the operated eyes increased significantly in the three groups at all postoperative time points ($P = 0.000$), with no significant difference in the operated eyes between the three groups. Meanwhile, the extent of the corneal staining did not change with time in the three groups.

Goblet cell density was significantly lower in the operated eyes in the KCS group than in the DTTN group ($P = 0.010$;

Figs. 5, 6), but without significant difference compared with the control eyes and the operated eyes in the DT group (the operated eyes in the KCS group versus control eyes, $P = 0.099$; the operated eyes in the KCS group versus the DT group, $P = 0.100$). The operated eyes of the two groups did not differ significantly in goblet cell density ($P = 1.000$).

Histopathology

A large quantity of basophilic secretion granules were observed in normal acinar cells of the parotid gland. The DT group showed many secretion granules in acinar cells of the parotid gland on the operated side at postoperative month 3, but the secretion granules decreased in the DTTN group. Neither control nor operated eyes of all three groups showed inflammatory pathologic changes of cornea and conjunctiva.

The 12 rabbits killed for histologic examination showed many secretion granules in normal acinar cells of the parotid gland and some fatty tissue in the lobes of the parotid gland (Figs. 7A, 7B, 8A). The secretion granules decreased in acinar cells of the parotid gland on the operated side at postoperative month 4 (Figs. 7C, 8B). Fatty tissue had infiltrated in the lobes of the parotid gland on the operated side at postoperative month 6 (Fig. 7D). The histopathologic changes of the parotid gland on the operated side recovered to normal 1 year after surgery, the fatty tissue in the lobes of the parotid gland decreased (Fig. 7E), and the secretion granules increased in acinar cells of the parotid gland (Fig. 7F, 8C), compared with that at postoperative months 4 and 6.

DISCUSSION

During the 1950s and 1960s, severe KCS was treated by transferring the parotid duct into the conjunctival sac.¹⁸⁻²⁰ However, patients could not endure the gustatory epiphora, and this technique was discarded. To overcome this problem, several researchers tried to reduce the secretion of the operated parotid gland, but they failed to control the gustatory epiphora successfully without serious complications.^{3,21} Keegan et al.²² reported that intraglandular and periglandular injection of botulinum toxin might be useful to treat hyperlacrimation secondary to “crocodile tearing” or submandibular gland transplantation, but it was temporary. The saliva secretion from the parotid gland is predominantly regulated by the tympanic nerve. Since 1962, tympanic neurectomy has been successfully applied to reduce saliva secretion of the parotid gland in treating drooling, parotid fistula, Frey’s syndrome, and chronic parotitis.²³⁻²⁶ It is a relatively mature technique for the otolaryngologists without serious complications.¹³ We hypothesized that gustatory epiphora with parotid duct transfer to treat KCS might be controlled by resecting the tympanic nerve. Therefore, we designed a protocol of transferring the parotid duct into the inferior conjunctival fornix after tympanic neuroectomy to treat severe KCS in rabbits. Our results indicated that

TABLE 1. Comparison of Pre- and Postoperative Amylase Activity of Tears in the Surgically Altered Eyes in the DT and DTTN Groups

Group	Preoperative	Postoperative			P
		Month 1	Month 2	Month 3	
DT	82 ± 54	44,098 ± 9,888*	40,060 ± 2,263*	28,505 ± 13,092*	0.000
DTTN	48 ± 79	69,025 ± 54,072†	53,950 ± 24,285†	57,225 ± 24,975†	0.000

Data were expressed as mean IU/L ± SD. $n = 10$ at each time point.

* $P < 0.01$ compared with before surgery in the DT group.

† $P < 0.01$ compared with before surgery in the DTTN group.

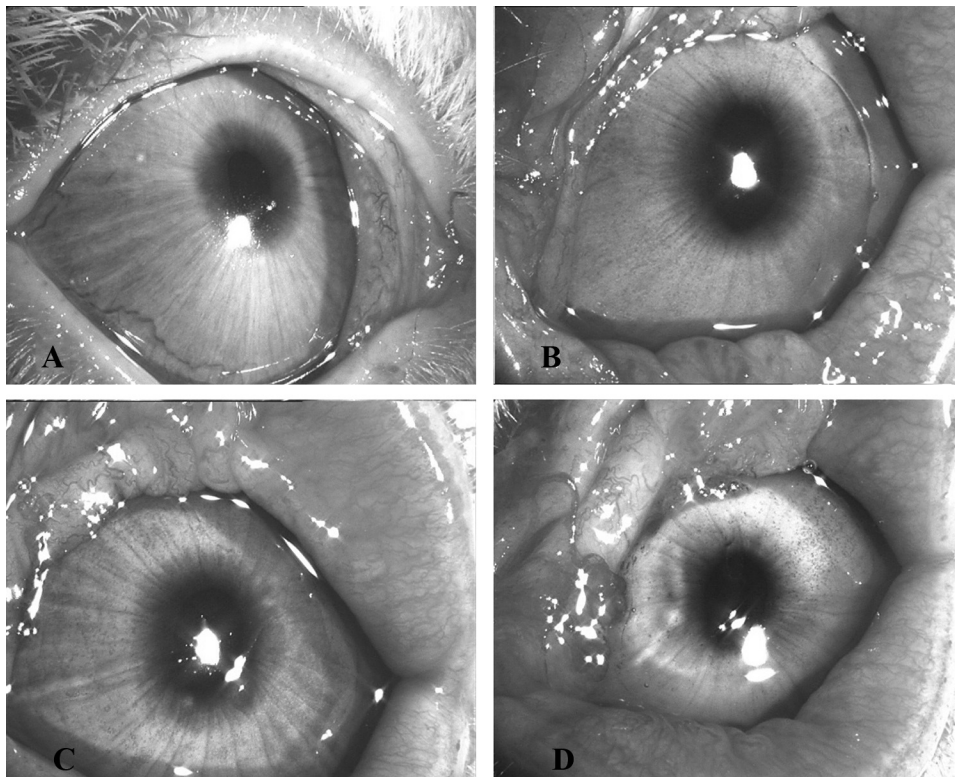


FIGURE 4. Rose bengal staining of the cornea after surgery. (A) control eye. Eyes with (B) KCS alone, (C) parotid duct transposition, and (D) parotid duct transposition after tympanic neurectomy. Diffuse staining was observed in the operated eyes. The control eye showed a normal-appearing cornea.

there was a significant decrease in the quantity of tear secretion in the operated eyes after chewing at all postoperative time points in the DTTN group compared with that in the DT group. The tear secretion from the operated eyes after chewing was much higher than secretion at rest in the DT group, while the tear secretion after chewing was similar to secretion at rest in the DTTN group. Therefore, gustatory epiphora after parotid duct transposition could be controlled by tympanic neuroectomy.

Bernard demonstrated that a denervated salivary gland maintained a basal secretion after an initial lag period (see review by Kumar et al.²⁷). Yu et al.¹ reported that the secretion of the denervated autotransplanted submandibular gland, which was attributed to basal secretion from the transplanted gland, could lubricate the ocular structures in patients with severe KCS. Geerling et al.²⁸ found that free submandibular autografts remained viable in the long term due to substantial survival of parasympathetic ganglia and

sympathetic reinnervation in transplanted gland tissue. In the present study, tear secretion in the operated eyes with KCS alone significantly decreased within 3 months. The tear secretion from the operated eyes did not decrease after surgery in the DTTN group. Therefore, the denervated parotid gland did not lose the function of the secretion and maintained a basal secretion. In our study, tear secretion from the operated eyes did not significantly decrease at rest in the DTTN group compared with that in the DT group. As we know, saliva secretion is lower at rest in the parotid gland than in the submandibular gland, but significantly increases under stimulus. We speculated that the tympanic nerve predominantly regulates the saliva secretion of the parotid gland in response to stimulus, but not at rest. The mechanism of increased secretion at rest in the DTTN group at postoperative month 3 is not clear. Whether it was due to “paralytic” secretion needs further investigation. In the parotid gland on the operated side, the secretion granules

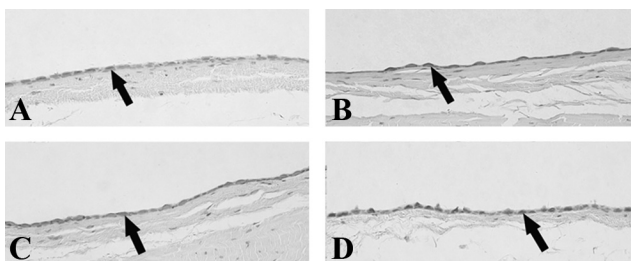


FIGURE 5. Histologic examination of conjunctival goblet cell after surgery. (A) Control eye. eyes with (B) KCS alone, (C) parotid duct transposition, and (D) parotid duct transposition after tympanic neurectomy. Arrow: the goblet cell. The goblet cells decreased in the operated eye compared with those in the control eye in the KCS group, and the density of cells in the operated eyes was close to that in the control eyes in the other two groups. Periodic acid Schiff staining; magnification, $\times 40$.

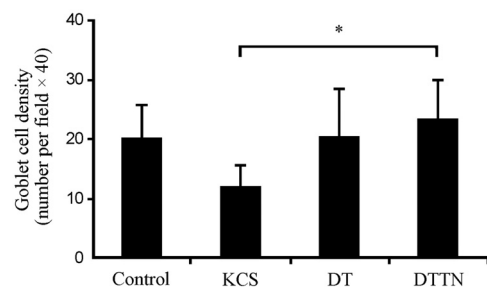


FIGURE 6. Comparison of postoperative mean conjunctival goblet cell density in the control eyes and the operated eyes of the three groups. Goblet cell density was significantly lower in the operated eyes in the KCS group than the DTTN group, but without significant difference compared with control eyes and the operated eyes in the DT group. * $P < 0.05$ compared with the operated eyes of the DTTN group. $n = 10$ in each group.

FIGURE 7. Histologic examination of the parotid gland after tympanic neurectomy. (A) There were many secretion granules (*arrow*) in normal acinar cells of the control parotid gland. (B) The fatty tissue (*arrow*) presented in the lobes of the control parotid gland. (C) The secretion granules decreased in acinar cells of the operated parotid gland at postoperative month 4. (D) The fatty tissue obviously infiltrated the lobes of the operated parotid gland at postoperative month 6, but (E) decreased at 1 year after surgery. (F) The secretion granules (*arrow*) recovered to normal in the acinar cells of the parotid gland 1 year after surgery. H&E staining; magnification: (A, C, F) $\times 100$; (B, D, E) $\times 25$.

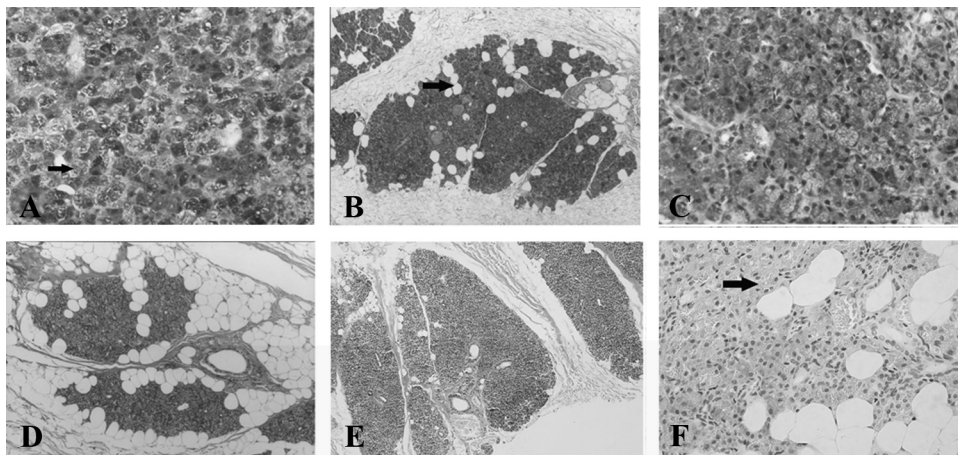
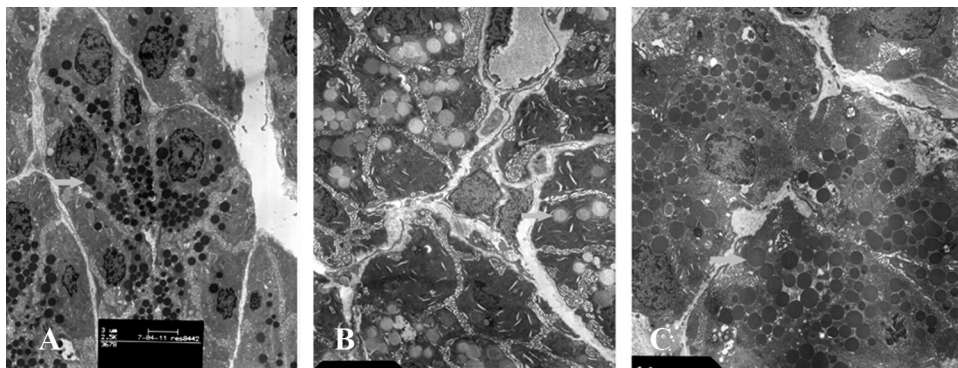


FIGURE 8. Ultrastructure of the parotid gland after tympanic neurectomy. (A) Many secretion granules (*arrow*) were observed in the acinar cells of the control parotid gland. (B) The secretion granules (*arrow*) decreased in the acinar cells of the parotid gland at postoperative month 4 and (C) increased to normal 1 year after surgery. Magnification, $\times 2500$.



decreased in the acinar cells 4 months after tympanic neurectomy, the fatty tissues infiltrated in the lobes of the gland 6 months after surgery, whereas the morphology of the gland became normal 1 year after surgery, which suggested that no persistent atrophic changes would occur in the denervated parotid gland.

Kumar et al.,²⁷ in studying autologous submandibular gland transfer to treat KCS, found that the amylase activity of tears was significantly higher in successful cases than in unsuccessful cases. The authors considered that the amylase activity of tears could be an indicator of the successful transfer of submandibular gland. We found that the amylase activity of tears in the operated eyes was significantly higher at all time points after than before surgery in the DT and DTTN groups. The result indicates that the transferred parotid duct had not been obstructed and the amylase activity of tears could also be an indicator of successful parotid duct transposition.

In our study, goblet cell density measured at postoperative month 3 was lowest in the operated eyes of the KCS group compared with control eyes and the operated eyes of the DT group, especially significantly lower than that in the operated eyes of the DTTN group. Goblet cells synthesize, store, and secrete large gel-forming mucins that play an important role in keeping the tear film stable.²⁹ Goblet cell density is a critical variable that reflects the overall health of the ocular surface. Our results suggest that continuous secretion from the operated gland was helpful for the recovery of conjunctival goblet cells in KCS. However, mean corneal fluorescein and rose bengal staining scores were significantly higher in the operated than in the control eyes during the first three postoperative months in the three groups. The secretion of the parotid gland being purely serous and tenous (it can stay in the ocular surface only for a relatively

short time) may have led to abnormal staining of the cornea in the operated eyes in these two treatment groups.

The quality of saliva tears can be responsible for ocular surface changes. Several groups have performed autologous submandibular gland transfer to treat severe KCS successfully in the past 20 years.^{1,4-6,30} However, some problems were revealed after surgery. A low osmolality relative to tears may result in corneal epithelial microcystic edema in patients with excessive saliva tears.^{31,32} An *in vitro* study showed that natural saliva from the submandibular gland had a severe cytotoxic effect on corneal epithelial cells.³³ Its low osmolality was thought to be the major factor contributing to its toxicity. Zhu et al.³⁴ compared the quality of tears with that of saliva from the human parotid and submandibular glands. Their results demonstrated that the osmolality of saliva from the parotid gland was higher than that of the saliva from the submandibular gland, and the other results were consistent with those in a previous study.³¹ Our previous study showed that the composition of saliva secreted by the denervated parotid gland with duct transposition was very close to that of normal tears.³⁵ However, the quality of saliva from the denervated parotid gland and its secretion mechanism must be further investigated.

In conclusion, gustatory epiphora could effectively be reduced after parotid duct transposition with tympanic neurectomy. However, saliva from the denervated parotid gland may be insufficient to warrant ocular surface health.

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References

1. Yu GY, Zhu ZH, Mao C, et al. Microvascular autologous submandibular gland transfer for severe cases of keratoconjunctivitis sicca. *Int J Oral Maxillofac Surg*. 2004;33:235-239.
2. Filatov VP, Chevaljev VE. Untitled letter. *J Ophthalmol (Odessa)*. 1951;55:893.
3. Bennett JE. The management of total xerophthalmia. *Arch Ophthalmol*. 1969;81:667-682.
4. Murube-del-Castillo J. Transplantation of salivary gland to the lacrimal basin. *Scand J Rheumatol Suppl*. 1986;61:264-267.
5. Geerling G, Sieg P, Bastian G-O, et al. Transplantation of the autologous submandibular gland for most severe cases of keratoconjunctivitis sicca. *Ophthalmology*. 1998;105:327-335.
6. Sieg P, Geerling G, Kosmehl H, et al. Microvascular submandibular gland transfer for severe cases of keratoconjunctivitis sicca. *Plast Reconstr Surg*. 2000;106:554-560.
7. Paniello RC. Submandibular gland transfer for severe xerophthalmia. *Laryngoscope*. 2007;117:40-44.
8. Jacobsen HC, Hakim SG, Lauer I, et al. Long-term results of autologous submandibular gland transfer for the surgical treatment of severe keratoconjunctivitis sicca. *J Craniomaxillofac Surg*. 2008;36:227-233.
9. Golding-Wood PH. Tympanic neurectomy. *J Laryngol Otol*. 1962;76:683-693.
10. Goode RL, Smith RA. The surgical management of sialorrhoea. *Laryngoscope*. 1970;80:1078-1089.
11. Edussuriya B. Parotid fistulae treated by tympanic neurectomy. *Ceylon Med J*. 1994;39:86-87.
12. Van Dishoeck HAE. The auriculo-temporal or Frey syndrome and tympanic neurectomy. *Laryngoscope*. 1968;78:122-131.
13. Vasama JP. Tympanic neurectomy and chronic parotitis. *Acta Otolaryngol*. 2000;120:995-998.
14. Chen ZY, Liang QF, Yu GY. Establishment of a rabbit model for keratoconjunctivitis sicca. *Cornea*. 2011;30:1024-1029.
15. Lemp MA. Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes. *CLAO J*. 1995;21:221-232.
16. Gilbard JP, Rossi SR, Gray KL. A new rabbit model for keratoconjunctivitis sicca. *Invest Ophthalmol Vis Sci*. 1987;28:225-228.
17. Driot JY, Bonnet C. Beneficial effects of a retinoic acid analog, CBS-211A, on an experimental model of keratoconjunctivitis sicca. *Invest Ophthalmol Vis Sci*. 1992;33:190-195.
18. Bennett JE, Bailey AL. A surgical approach to total xerophthalmia: transplantation of the parotid duct to the inferior cul-de-sac. *AMA Arch Ophthalmol*. 1957;58:367-371.
19. Ashley FL, Schwartz AN, Straatsma BR, et al. Transplantation of the parotid duct for xerophthalmia. *Am Surg*. 1959;25:815-818.
20. Shanon E, Lazar M, Redianu C. Surgical treatment of xerophthalmia. *Laryngoscope*. 1973;83:1999-2002.
21. Nicholas JP, Brown FA. Management of the epiphora following parotid duct transposition for xerophthalmia. *Arch Ophthalmol*. 1962;68:529-531.
22. Keegan DJ, Geerling G, Lee JP, et al. Botulinum toxin treatment for hyperlacrimation secondary to aberrant regenerated seventh nerve palsy or salivary gland transplantation. *Br J Ophthalmol*. 2002;86:43-46.
23. Mullins WM, Gross CW, Moore JM, et al. Long-term follow-up of tympanic neurectomy for sialorrhoea. *Laryngoscope*. 1979;89:1219-1223.
24. Mandour MA, Helmi AM, El-Sheikh MM, et al. Effect of tympanic neurectomy on human parotid salivary gland: histopathologic, histochemical, and clinical study. *Arch Otolaryngol*. 1977;103:338-341.
25. Friedman WH, Swerdlow RS, Paharico HM. Tympanic neurectomy: a review and additional indication for this procedure. *Laryngoscope*. 1974;84:568-577.
26. Motamed M, Laugharne D, Bradley PJ. Management of chronic parotitis: a review. *J Laryngol Otol*. 2003;117:521-526.
27. Kumar PA, Macleod AM, O'Brien BM, et al. Microvascular submandibular gland transfer for the management of xerophthalmia: an experimental study. *Br J Plast Surg*. 1990;43:431-436.
28. Geerling G, Garret JR, Paterson KL, et al. Innervation and secretory function of transplanted human submandibular salivary glands. *Transplantation*. 2008;85:135-140.
29. Inatomi T, Spurr-Michaud S, Tisdale AS, Zhan Q, Feldman ST, Gipson IK. Expression of secretory mucin genes by human conjunctival epithelia. *Invest Ophthalmol Vis Sci*. 1996;37:1684-1692.
30. Kumar PAV, Hickey MJ, Gurusinge CJ, et al. Long term results of submandibular gland transfer for the management of xerophthalmia. *Br J Plast Surg*. 1991;44:506-508.
31. 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.
32. 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.
33. Geerling G, Daniels JT, Dart JK, et al. Toxicity of natural tear substitutes in a fully defined culture model of human corneal epithelial cells. *Invest Ophthalmol Vis Sci*. 2001;42:948-956.
34. Zhu ZH, Yu GY, Li XX. A comparison between the quality of tears with saliva (in Chinese). *J Modern Stomatol*. 2003;17:26-28.
35. Chen ZY, Liu XY, Yu GY. A study on the quality of saliva secreted by the denervated parotid gland with duct transposition in the rabbits (in Chinese). *J Modern Stomatol*. 2007;21:361-363.