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Long-term results of autologous submandibular gland transfer for the surgical treatment of severe keratoconjunctivitis sicca

Hans-Christian JACOBSEN[1], Samer G. HAKIM[1], Isabel LAUER[2], Andreas DENDORFER[3], Thilo WEDEL[4], Peter SIEG[1]

[1] *Department of Maxillofacial Surgery (Chairman: Prof. Dr. Dr. P. Sieg), University of Luebeck, Germany;* [2] *Department of Radiology and Nuclear Medicine (Chairman: Prof. Dr. T. Helmberger), University of Luebeck, Germany;* [3] *Institute of Pharmacology and Toxicology (Chairman: Prof. Dr. P. Dominiak), University of Luebeck, Germany;* [4] *Institute of Anatomy (Chairman: Prof. Dr. J. Westermann), University of Luebeck, Germany*

SUMMARY. Aim: **The aim of this study was to assess the long-term results of autologous submandibular gland transfer for surgical correction of severe keratoconjunctivitis sicca.** Patients and methods: **A survey was undertaken of 32 patients who had undergone submandibular gland transfer (42 glands) and by following up 11 patients (15 glands) for 5–10 years. Subjective benefit was evaluated as well as clinical findings at the ocular surface. The biochemical consistency of the secreted "saliva-tear" was analysed and compared with natural submandibular saliva of a matched control-group. The vitality and function of the transplants was tested by means of sialoscintigraphy. Immunohistochemical investigations were carried out in specimens of submandibular tissue, gained during reduction procedures of the transplants to correct secretory excess.** Results: **Patient evaluation and clinical assessment revealed a long-lasting subjective benefit in 2/3 of the patients and a stabilisation at the ocular surface in all cases. The secretion remained as highly concentrated submandibular saliva. Glandular vitality and function was shown scintgraphically. Immunohistochemical investigations revealed no progressive atrophy after transplantation, the ability of cell division remained intact and there was still neuronal tissue in all transplants, even several years after transfer. As all transplants responded well to parasympathomimetic drugs, this might be an indication of re-innervation of the gland.** © **2008 European Association for Cranio-Maxillofacial Surgery**

Keywords: **submandibular gland transfer, keratoconjunctivitis sicca, long-term results, microvascular surgery, sialoscintigraphy**

INTRODUCTION

Dry eye syndrome is one of the most frequently occurring ophthalmological conditions. Its prevalence lies between 5 and 58% depending on selection of study groups and criteria recommended for diagnosis (*Schaumberg* et al., 2003; *Moss* et al., 2004). The development of keratoconjunctivitis sicca is proven to be associated with increasing age and female gender; alone in China about 30 million people suffer from this disorder (*Yu* et al., 2004).

From a biological point of view, dry eye and the resulting keratoconjunctivitis is produced by the inadequate interrelation between lacrimal film and ocular surface epithelium, caused by quantitative and qualitative deficits in one or both of them.

Without adequate treatment this chronic condition almost always produces permanent discomfort for the patient and is followed by a progressive destruction of the corneal surface leading to recurrent infections and visus restriction or even loss of the eye. Symptomatic treatment includes the application of tear substitutes first of all, surgical corrections such as tarsorrhaphy or implantation of oral mucosal grafts into the conjunctival fold and/or obliteration of the lacrimal drainage pathways. A further therapeutic option was first suggested by Murube-del-Castillo in 1986, who described the microvascular autologous submandibular gland transfer for surgically correcting severe keratoconjunctivitis sicca. For complicated cases, this has been the common procedure in Luebeck for more than 10 years. This procedure requires extensive interdisciplinary coordination and is currently clinically established in only a few centres in Australia, China, the UK and Germany.

Very few publications are available on the follow-up of these patients. They all describe the results within the first 2 years postoperatively (*Murube-del-Castillo*, 1986; *Kumar* et al., 1991; *Sieg* and *Schirner*, 1995; *Geerling* et al., 1998; *Sieg* et al., 2000; *Yu* et al., 2004). There remain several questions regarding the long-term follow-up of keratoconjunctivitis as well as the long-term stability of the function and morphology of the revascularised gland. As far as we know this paper is the first to report the long-term follow-up after submandibular gland transfer.

PATIENTS AND METHODS

Patients

The aim was to revaluate patients who had undergone submandibular gland transfer more than 5 years ago. Out of 11 such patients, four underwent a bilateral procedure in two steps, so the total number of transferred glands was 15. The mean time between operation and evaluation was 6.4 + 0.8 years. The mean age was 53.4 + 19.4 years and eight of the 11 were female. The underlying pathology causing keratoconjunctivitis sicca was heterogeneous (Table 1).

Selective submandibular saliva was collected from a matched control-group of healthy patients in order to investigate the biochemical quality of the secretion and the response to pain sympathetic stimulation of the gland.

Surgical technique

The surgical procedure consisted of harvesting the submandibular gland with its supplying blood vessels and the excretory duct from a combined cervical and intra-oral approach (Fig. 1). The gland was transferred into a preformed pocket in the temporal muscle (Figs. 2 and 3). The blood vessels were anastomosed microsurgically to the temporal vein and artery (Fig. 4). The excretory duct was led subcutaneously to the lateral canthus and implanted into the upper lateral fornix of the conjunctiva. The key points of the procedure have already been described in detail (*MacLeod* et al., 1990; *MacLeod* and *Robbins*, 1992; *Sieg* and *Schirner*, 1995; *Sieg* et al., 2000; *Yu* et al., 2004).

Methods

Evaluation included a subjective assessment using a questionnaire, a clinical examination of the ocular surfaces and conjunctivae, a biochemical analysis of the "saliva-tears" in comparison with regular submandibular saliva collected from the matched control-group, and sialoscintigraphy for functional assessment of the gland. To gain more information about the structural changes in the transplants, specimens were examined from tissue taken during reduction procedures of transplanted glands. These procedures became necessary due to epiphora or persisting excessive secretion and were carried out 9−88 months (mean 26.5 months) after transplantation. Specimens from 11 cases were investigated immunohistochemically and compared with six specimens of non-transplanted submandibular tissue, removed during neck dissection procedures.

Patient questionnaire and clinical evaluation

The patients were sent a questionnaire including the question whether they would undergo the procedure again considering the present result. Further questions evaluated factors such as physical activity, warm temperature, and the effect of wind or chewing on the secretion as well as the changes of secretion during the daytime. These questions had to be rated semi-quantitatively with values from 0 to 10 points.

Clinical evaluation consisted of measuring the basal secretion using Schirmer's test (*Collins* and *Augustin*, 1997). In order to evaluate the stimulation of secretion, a parasympathetic drug (0.2 mg Carbachol) was administered subcutaneously and Schirmer's test was repeated after 10 min. The ocular surfaces were evaluated by slit-lamp examination after rose Bengal staining. These results were compared with the findings made prior to transplantation.

Biochemical analysis

The saliva-tears were collected before and after medical parasympathetic stimulation. They were examined for sodium, chloride, calcium phosphate and the whole protein content; and the osmolality was also evaluated. Specific proteins like kallikrein, peroxidase and secretory immunoglobulin A (sIgA) were analysed to show the function of relevant cell-types in the transferred glands.

Sialoscintigraphy

Salivary gland scintigraphy was performed using a double head gamma camera (Picker/Marconi Prism 2000 S, Marconi Medical Systems, Cleveland, USA) with low energy ultra high resolution collimator. Directly after administering 50 MBq ^{99m}Tc-pertechnetate intravenously, dynamic scintigrams of the head (lateral views) were acquired over a period of 45−50 min (1 frame/min, matrix 128 × 128, zoom factor 1.3). Salivary excretion was stimulated by subcutaneous administration of 0.2 mg Carbachol after 20 min. In order to analyse the scintigrams, regions of interest (ROIs) of the transplants were marked and time activity curves were generated (Figs. 9 and 10). Percentage tracer uptake before and after administration of Carbachol was calculated using an additional background ROI (Uptake before Carbachol Up_{before}, Uptake after Carbachol Up_{after}). The salivary excretion fraction (EF) was quantified according to the following formula (*Liem* et al., 1996; *Bohuslavizki* et al., 1997): $EF(\%) = (Up_{before} - Up_{after}/Up_{before}) \times 100$. The EF of the parotid gland and, if possible, of the submandibular gland of the opposite side was calculated in the same way.

Histology and immunohistochemistry

The existing biopsy samples were cut at 2−6 μm and dewaxed. The amount of fat and fibrosis was measured (in %) in all sections after digital binary separation using the soft-imaging system ANALYSIS®. Standardised immunohistochemical staining with monoclonal antibodies (Dako™, Glostrup, Denmark) was performed. The staining with alpha smooth muscle actin (ASMA) for the myofilaments in smooth muscle cells was an indicator for degenerative processes in salivary gland tissue (*Hakim* et al., 2002). Monoclonal Ki 67 antibodies (clone MIB 1) were applied to find proliferating cells in the (transferred) gland parenchyma. The reaction to protein gene product (PGP) 9.,5 and protein S-100 antibody showed the presence of neuronal ganglionic cells and nerve fibres, respectively. As chromogen a commercial