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Surgery of the Major Salivary Glands and Its Impact on Salivary Flow—A Review

Marc Burghartz, MD; Stephan Hackenberg, MD; Christian Sittel, MD; Rudolf Hagen, MD

Objective: The aim of this study was to bring attention to a rather unnoted side effect of salivary gland surgery—reduced salivary flow.

Methods: A systematic PubMed, Cochrane Library, LIVIVO, and Embase databases search was performed to identify relevant articles.

Results: Eight studies matched the inclusion criteria. All studies described an association between salivary gland surgery and reduced salivary flow. In five of the eight studies, patients reported on xerostomia after salivary gland surgery.

Conclusions: Head and neck surgeons should inform their patients more accurately about reduced salivary flow and possible xerostomia after salivary gland surgery, and focus more on conservative strategies and minimally invasive techniques.

Key Words: Salivary flow, salivary gland function, surgery of the salivary gland, xerostomia.

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INTRODUCTION

Surgery of the major salivary glands is a very common therapeutic procedure for a variety of different diseases. In cases involving a benign or malignant tumor, partial or complete resection of the affected gland is needed.

The amount of saliva produced by a single person averages approximately half a liter per day.1 The mean flow rate of unstimulated whole-mouth saliva ranges between 0.3 and 0.4 mL/min,2 whereas the stimulated mean flow rate of whole-mouth saliva equals up to 1.6 to 2.0 mL/min.1,2 The major salivary glands produce the majority of daily salivary secretion. The parotid glands contribute 26%, the submandibular glands 69%, and the sublingual glands 5% to unstimulated whole-mouth saliva.3 Under stimulation, the parotid glands increase their production of saliva and contribute approximately half of the total saliva volume.4

Saliva production has an enormous influence on life quality. Reduced secretion of saliva leads to dysphagia, dysgeusia, recurrent oral infections, and caries. This is a well-known phenomenon in patients receiving radiotherapy for cancer treatment, because radiotherapy in head and neck cancer often affects salivary gland function.5–7

Only a few studies have evaluated the effect of surgery on salivary flow rate. The aim of this review was to focus on an often unnoted side effect of total or partial salivary gland resection, namely reduced salivary flow, and the resulting problems for the patient.

MATERIAL AND METHODS

This systematic review was conducted according to the Preferred Reporting Items For Systematic Reviews and Meta-Analyses statement.8 Under this directive, the Participants, Interventions, Comparators, Outcomes, Study Groups criteria were defined. The intent of the systematic review was to find out if patients who had salivary gland surgery have objectively reduced salivary flow, and if those patients subjectively report about oral dryness compared to a control group or comparison group. Only studies with a prospective design had been accepted.

Therefore, a systematic literature search was conducted using the PubMed, Cochrane Library, LIVIVO, and Embase databases from their beginning until July 2017. The following key word combinations were observed: “salivary flow + submandibular gland + surgery” or “salivary flow + parotid gland + surgery” in branch 1, and “salivary gland function + gland-preserving surgery” or “salivary gland function + partial sialadenectomy” in branch 2. Furthermore, a filter was used to exclude animal studies, and only articles written in English were accepted. Selection was based on the inclusion criteria: salivary flow, submandibular gland surgery, parotid gland surgery, salivary gland function, gland-preserving surgery, and partial sialadenectomy. The first author read all articles and validated them.

The following data were extracted from each study: author and year of publication, number of participants, study design, level of evidence, randomization, postoperative measurement, and follow-up (Table I); surgery of the submandibular or parotid gland, measurement method, saliva stimulation method, sialochemistry, pathology,
intake of medication, compensatory effect, measurement of patients’ subjective evaluation/xerostomia, and objective result/salivary flow reduction (Table II).

Bias assessment in nonrandomized studies was conducted according to the Newcastle-Ottawa Scale (NOS) (Table III) and in randomized studies according to the Cochrane risk of bias (Cochrane ROB) assessment (Table IV).9 The NOS has a scoring system from zero to nine stars. No stars meaning high risk of bias and nine stars meaning low risk of bias. Cochrane ROB divides only among high risk, low risk, and unclear risk of bias.

For the calculation of the objective results (Table II) the data of the “last collection” of the study of Marunick et al.19 was analyzed. Whole salivary flow rates of the “unilateral” resection group were compared with the control group from the study of Jacob et al.11 For the analysis of the objective results in the study of Cunning et al.12 the “submandibular gland excision group” was compared with the control group. From the study of Chauushu et al.13 the postoperative values were compared with the preoperative values from the “involved gland”. Furthermore, from the study of Roh et al.14 the postoperative data was compared with the preoperative data from the “conventional surgery” group. From the study of Jaguar et al. the “surgery group” was compared with the “non-surgery group” for objective data evaluation.15 The group with the “gland sacrificed” was analyzed in the study of Min et al.16 Besides the data from “total sialoadenectomy” were taken for objective data calculation in the study of Ge et al.17

RESULTS

The PubMed, Cochrane Database, LIVIVO, and Embase searches detected 564 records. Duplicates were removed. Based on their relevance to the inclusion criteria, only eight publications (six publications in branch 1 and two publications in branch 2) matched all of the study criteria (Fig. 1).

In branch 1, four publications were identified in which salivary flow after surgery of the submandibular gland was described.10–12,15 as well as two publications investigating the impact of parotid surgery on postoperative salivary flow.13,14 In branch 2, both publications examined salivary flow after surgery of the submandibular gland.16,17

In two studies, sample size was borderline or below for calculating significance.10,12 In five of the evaluated articles, there were more than 30 study participants, ranging from 31 to 101 patients.11,14–17 All studies had a prospective design. Two studies included a control group,11,12 and in the other articles, patients served as their own controls or a comparison group existed.10,13–17 The level of evidence in the different studies ranged from 214,16 to 4.10–13,15,17

Missing randomization was found in six of eight studies. Only Roh et al. and Min et al. performed a randomization of their patients.14,16 Postoperative measures were performed between 0,5 month13 and 120 months11 after surgery. Follow-up was conducted in three articles.10,14,16

The so-called spitting method was used in studies investigating salivary flow after surgery of the submandibular gland.18 In contrast, Lashley cups for saliva collection were used in articles describing salivary flow after surgery of the parotid gland.19 Various methods were applied to stimulate saliva flow: parafin/parafilm was used in three studies,11,12,16 and ascorbic acid was applied by Jaguar et al.15 In one study, corn chips were given,10 and in the other three, citric acid was used.13,14,17 Sialochemistry was done in one study only.13 Two studies included patients exclusively with malignomas,10,15 four studies contained only benign lesions,12,14,16,17 and in the other two articles malignomas and benign tumors were mixed.11,12 Documentation of the medication intake of the study participants was performed in five studies,10–14 and in three publications there was no documentation of medication intake.15–17

In two articles, a compensatory activity of the contralateral gland after surgery was described.10,13 However, Jacob et al. and Jaguar et al. did not find these compensatory effects.11,15 In the other four publications, this question was not discussed.12,14,16,17

In seven articles, patients were queried for subjective evaluation of a possible xerostomia. In only one, study patients were not asked for their subjective evaluation. In five of the studies, patients reported on xerostomia11,12,15–17 whereas in the other two studies patients did not describe any xerostomia symptoms.10,13 Between 21%15 and 57%12 of the study patients suffered

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**Table I.** Study Characteristics.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>No. of Participants</th>
<th>Study Design</th>
<th>Level of Evidence</th>
<th>Randomization</th>
<th>Postoperative Measure (Months)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marunick (1993)10</td>
<td>5</td>
<td>+/CS</td>
<td>4</td>
<td>No</td>
<td>1–2</td>
<td>Yes</td>
</tr>
<tr>
<td>Jacob (1996)11</td>
<td>37</td>
<td>+/CC</td>
<td>4</td>
<td>No</td>
<td>4–120</td>
<td>No</td>
</tr>
<tr>
<td>Cunning (1998)12</td>
<td>7</td>
<td>+/CC</td>
<td>4</td>
<td>No</td>
<td>12–60</td>
<td>No</td>
</tr>
<tr>
<td>Chauushu (2001)13</td>
<td>17</td>
<td>+/OC</td>
<td>4</td>
<td>No</td>
<td>0,5</td>
<td>No</td>
</tr>
<tr>
<td>Roh (2007)14</td>
<td>101</td>
<td>+/OC</td>
<td>2</td>
<td>Yes</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Jaguar (2010)15</td>
<td>80</td>
<td>+/CP</td>
<td>4</td>
<td>No</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Min (2013)16</td>
<td>40</td>
<td>+/OC</td>
<td>2</td>
<td>Yes</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>Ge (2016)17</td>
<td>31</td>
<td>+/OC</td>
<td>4</td>
<td>No</td>
<td>12</td>
<td>No</td>
</tr>
</tbody>
</table>

+= prospective, CC = case-control study; CP = comparison group; CS = case series; OC = patients served as their own control.
from xerostomia symptoms. Significant xerostomia was only measured in three studies.\textsuperscript{12,16,17} The other studies did not calculate significance.\textsuperscript{10,11,13,15}

Due to a larger number of patients, statistical evaluation regarding salivary flow was possible in seven publications. In the unstimulated setting, salivary flow reduction ranged from 28.0\%\textsuperscript{10} to 50.0\%\textsuperscript{11,12} and under stimulation from 12.6\%\textsuperscript{17} to 84.2\%.\textsuperscript{13} Four studies reported on statistically significant unstimulated postoperative hyposalivation.\textsuperscript{11,12,15,17} Under stimulation, statistically significant results were only reported in three studies.\textsuperscript{11,13,14} In only one article, significance for both unstimulated and stimulated flow were described.\textsuperscript{11}

Risk of bias could be found in every nonrandomized study.\textsuperscript{10–13,15,17} Only the study of Cunning et al. has a relatively low risk for bias.\textsuperscript{12} The risk of bias in the nonrandomized studies was mostly unclear; only in the study of Min et al.\textsuperscript{16} was a low risk for selection and attrition bias detected.

DISCUSSION

Head and neck surgery includes several procedures of partial or complete resection of one of the major salivary glands. Because the main salivary glands, namely the submandibular, parotid, and sublingual glands, are responsible for 96\% of saliva production,\textsuperscript{4} it is not surprising that resection of a larger amount of salivary gland tissue affects saliva production. Unfortunately, however, reduced salivary flow after surgery of the salivary glands and possible xerostomia seems to be a problem that is rarely discussed.

In all studies screened in this review, a negative impact of salivary gland surgery on objectively measurable salivary flow was described. In four of the studies dealing with the impact of submandibular gland surgery, a significant reduction in unstimulated saliva production was found.\textsuperscript{11,12,15,17} Under stimulation, there was no significant reduction described except for one study.\textsuperscript{11} This corresponds to the fact that the submandibular gland is mainly responsible for basal unstimulated secretion, whereas the parotid gland covers the peak demand (e.g., during food intake). Furthermore, both studies dealing with the impact of parotid surgery reported significant reduction in saliva flow postoperatively.

In five studies, a xerostomia within the patient collective was documented.\textsuperscript{11,12,15–17} Only two studies found no xerostomia.\textsuperscript{10,13} But evaluation methods differed substantially. Chaushu et al. and Ge et al. just asked their patients if they had dry mouth symptoms.\textsuperscript{13,17} Jacob et al. and Cunning et al. asked their patients to describe a pattern concerning oral dryness (e.g., nocturnal dryness).\textsuperscript{11,12} Marunick et al. used a grading system from zero to three,\textsuperscript{10} and Jaguar et al. used the grading system\textsuperscript{15} according to Eisbruch et al.\textsuperscript{20} Standardized questionnaires on quality of life, which would make results comparable, were only applied by Min et al.\textsuperscript{16}

Additionally, a compensatory effect was described in two studies (i.e., the remaining gland increased its saliva production),\textsuperscript{10,13} but in two articles this phenomenon was not found.\textsuperscript{11,15} In the remaining articles, there was no
comment on this point. The time of postoperative measurement ranged between 0.5 month\(^{13}\) and 120 months.\(^{11}\)

If a compensatory mechanism exists, it presumably needs some time to arise. In animal studies it could be demonstrated that after removal of one salivary gland, a compensatory process in the contralateral gland was apparent.\(^{21,22}\)

For reproducible and reliable salivary flow measurements, the testing method should be standardized as well. In all studies that included salivary flow measurements after resection of a salivary gland, the same approach was used, the so-called spitting method.\(^{10-12,15-17}\) This technique was described by Bucher et al., and is an easy-to-use testing method that requires little time, effort, and knowledge.\(^{18}\)

In the two studies dealing with the surgery of the parotid gland, salivary flow was determined using a Lashley cup,\(^{15,14}\) which is directly placed on Stenson’s duct to collect saliva.\(^{19}\) The handling of the Lashley cup is more complex than the spitting method, but, if correctly used, is more reliable. However, Lashley cups do not allow the measurement of whole saliva. Two articles\(^{23,24}\) complied with the inclusion criteria of this review but salivary flow was tested using the so-called biscuit test. During this test, the time a patient needs to swallow a cracker biscuit is determined. However, this is only an indirect method to quantify hyposalivation, and an exact quantification of the saliva production is not possible with this procedure.

Although the testing methods for salivary flow measurements did not differ extensively, some modifications became apparent in the different approaches to stimulate saliva. Gustatory stimulation with ascorbic acid\(^{15}\) or citric acid\(^{13,14,17}\) does not guarantee a constant flow rate, because saliva dilutes the stimulation agents. Furthermore, analysis of saliva buffering capacity can be disturbed by citric acid or ascorbic acid. Mechanical stimulation with paraffin gum\(^{11,12,16}\) or corn chips\(^{10}\) does not interfere with saliva composition, but it is difficult for the patient to chew with a constant force during the collection period.

Heterogeneity between the analyzed studies was found in many fields due to mixed groups of malignant and benign tumors,\(^{11,13}\) or to different localizations of the tumors. Marunick et al. and Jaguar et al. included patients with a tumor in the oral cavity and the oropharynx.\(^{10,15}\) Patients with a tumor in the floor of the mouth could have impaired salivary flow simply due to the localization of the tumor, plus a malignant process is likely to influence salivary flow due to other reasons. Even if the study population consisted only of patients with a benign tumor, the underlying diseases were very different, such as benign neoplasms, chronic sialadenitis, or symptomatic sialolithiasis.\(^{12}\) The articles of Min et al. and Ge et al. were the only publications with a homogeneous study population, meaning that all patients had a benign neoplasm of the submandibular gland.\(^{16,17}\)

The composition of saliva (e.g., amylase, sodium, potassium, calcium, pH) is characterized by sialochemistry. It can be applied for diagnosis and treatment response analysis in salivary gland diseases.\(^{25}\) It is presumable that partial or total resection of a salivary gland does not change the composition of the remaining saliva. However, the buffering capacity of saliva, for example, could be insufficient such that neutralization of dietary acid is no longer assured. Only Chaushu et al. performed sialochemistry in their collective. They tested for potassium, sodium, and amylase, and found no differences between pre- and postoperative values.\(^{13}\)

Jaguar et al., Min et al., and Ge et al. additionally performed a salivary gland scintigraphy for evaluation of salivary gland function.\(^{15-17}\) However, it may be questioned whether the use of a radioactive tracer (\(^{99}\)Tc-pertechnetate) is justified in this incidence. Furthermore, there are other technically complex methods available for testing salivary flow rate, like the time-
Surgeons should keep in mind to preserve as much of salivary gland tissue as possible. In cases of a tumor of the tongue or the floor of the mouth located in the midline, it should be carefully balanced whether a submandibullectomy on both sides is necessary. From an oncological perspective, there is ever-increasing evidence indicating that it is possible to preserve the submandibular gland when doing neck dissection in cases of an oral squamous cell carcinoma. Furthermore, there is ongoing research investigating a partial submandibulectomy in selected patients with a benign tumor to preserve saliva production. Concerning benign tumors of the parotid gland, surgeons should focus on partial parotidectomy or extracapsular resection, thus preserving as much glandular tissue as possible, because the superficial lobe makes up 80% of the total gland volume. Finally, minimally invasive gland-preserving techniques, such as sialendoscopy, shock-wave lithotripsy, and transoral and cervical salivary stone removals, have also reduced the need for gland resection in cases involving salivary stones.

CONCLUSION
There are indications that salivary gland surgery leads to reduced salivary flow, which may result in xerostomia. Head and neck surgeons should keep that in mind while planning salivary gland surgery and inform the patient about possible side effects. Further well-planned studies are needed to further elucidate the impact of salivary gland surgery on salivary flow and quality of life.

BIBLIOGRAPHY


