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Patient-reported change of sensibility and pain after parotid and labial gland biopsy applied for primary Sjögren's syndrome diagnostics: one-year follow-up study

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Key words: Sjögren's syndrome, biopsy, pain, patient satisfaction

ABSTRACT

Objective. To assess how patients perceived pain and change of sensibility of the biopsied area after having undergone parotid and labial gland biopsy as part of the diagnostic work-up of primary Sjögren's syndrome (pSS).

Methods. Simultaneously, parotid and labial salivary gland biopsies were taken under local anesthesia. One week, 6 months and 12 months post-operatively, each patient was sent a postal questionnaire to quantify the severity of pain and change of sensibility in the biopsied areas with a visual analogue scale (VAS; range 0-100).

Results. 110 patients were included. The median age of patients was 54 years (IQR=47-65) and 92% were female. Changes in sensibility and pain in the biopsied area were significantly higher after a parotid gland biopsy than after a labial gland biopsy at one week and 6 months post-operatively, but rather minor in both areas. At 12 months post-operatively, the change in sensibility and pain level was negligible in most patients and comparable for both biopsied areas. The duration of the technique, outcome of the biopsy, exposure of nerve branches during the biopsy and bleeding during the biopsy did not affect the reported change of sensibility or pain in the biopsied area. ESSPRI was not related to pain level or change of sensibility at any time point ($r < 0.3$ and $p > 0.05$).

Conclusion. Patient-reported post-operative change of sensibility and pain in the area of the parotid and labial gland biopsy are minor and comparable. Parotid and labial gland biopsies are diagnostic techniques well tolerated by patients suspected with pSS.

Introduction

Primary Sjögren's syndrome (pSS) is a chronic, systemic autoimmune disease,

which is characterised by inflammation of the exocrine glands and prevalence of 0.05% (1). Most patients with pSS suffer from xerostomia, keratoconjunctivitis sicca and extreme fatigue (2). Currently, several criteria sets are available for the classification of pSS, with the American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) criteria being endorsed by both ACR and EULAR (3). Biopsy of the labial salivary glands is generally considered as one of the most important items of the ACR-EULAR criteria, carries a weight of 3 out of 4 and is considered the cornerstone of the diagnosis of pSS.

The diagnostic accuracy of the parotid gland biopsy is comparable to the labial gland biopsy when applied for pSS diagnostics (4). Parotid biopsy demonstrates next to the labial salivary gland biopsy a number of additional advantages, *i.e.* repeated biopsies from the same parotid gland are possible, parotid biopsy can predict patients' responsiveness to rituximab treatment (5) and since MALT lymphomas occur more frequently in parotid glands, they can be easily diagnosed by parotid gland biopsy. Additionally parotid gland ultrasound can be directly compared to parotid gland histopathology (6). Notwithstanding these aforementioned advantages, biopsies of the parotid gland have not become a common place because of concerns for damaging facial nerve branches, development of sialoceles or salivary fistulae and higher morbidity than labial gland biopsies, concerns which so far have never been confirmed or proven (7).

Therefore, the aim of this study was to assess the perceived pain and change of sensibility in the biopsied area after a parotid and labial gland biopsy performed as part of a routine diagnostic work-up of pSS.

Competing interests: none declared.

Patients and methods

Patients

This was a prospective, observational, single-centre study. Patients were recruited at the multidisciplinary Sjögren's expertise centre, University Medical Centre Groningen (UMCG), the Netherlands. All patients were ≥18 years and were clinically suspected with pSS. Patients were included if they were willing to be subjected to a complete diagnostic work-up according to the ACR-EULAR criteria including a labial and parotid biopsy. Previous radiation to head and neck area, confirmed hepatitis C infection, human immunodeficiency virus (HIV) infection, sarcoidosis, graft versus host disease (GvHD), oral cancer and pregnancy based on self-report were considered as exclusion criteria. The study protocol was approved by the ethics committee of the University Medical Center Groningen (METC approval: 2013.066). All patients provided their written informed consent.

Methods

The parotid gland biopsy and labial gland biopsies were simultaneously taken under local anesthesia and with the use of loupe glass magnification (3.5x) (7, 8) as part of a routine diagnostic work up for pSS. All biopsies were performed by a single surgeon (F.K.L.S.). Pre-operatively, on the day of the biopsies, patients were asked if the sensibility of the pre-auricular and labial area was normal. Possible complications during the biopsy, e.g. bleeding, unintended exposure of nerves branches and duration of each biopsy were recorded. Additionally, the patients filled in the European League Against Rheumatism (EULAR) Sjögren's syndrome Patient-reported Index (ESSDAI) prior to the biopsies.

One week, 6 months and 12 months post-operatively, each patient was sent a postal questionnaire. The questionnaire comprised 4 questions quantifying the patient-reported severity of pain in biopsied areas and the change of sensibility (Supplementary Figure 1). Patients were asked to state their experience using a visual analogue scale (VAS; range: 0–100). Additionally, patients were asked to indicate

Fig. 1. Flowchart of patients' response to questionnaires.

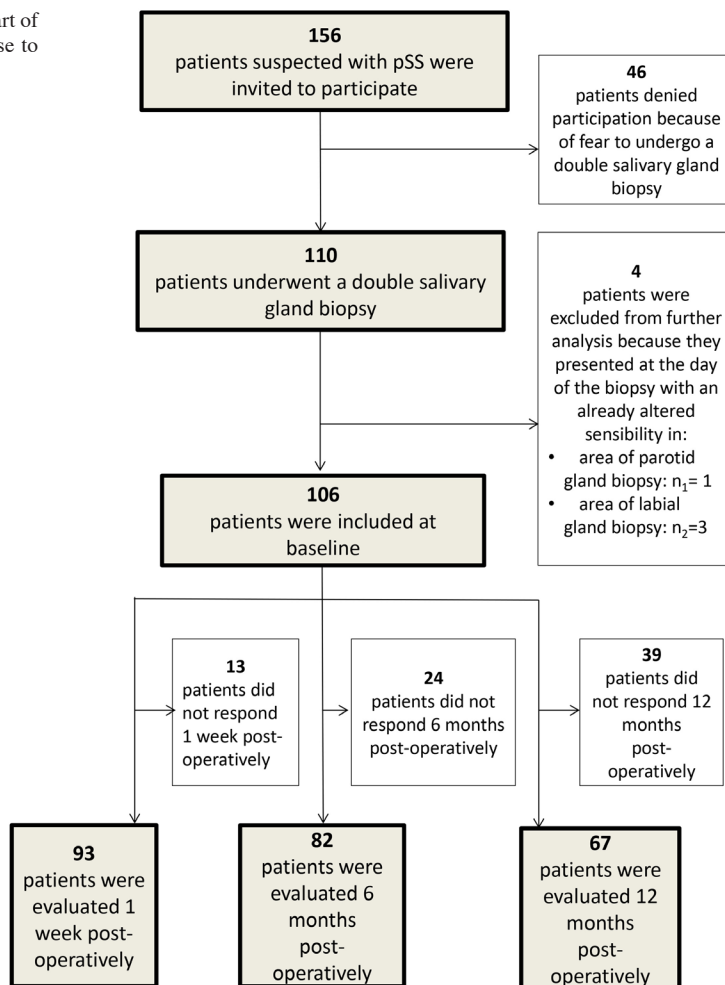
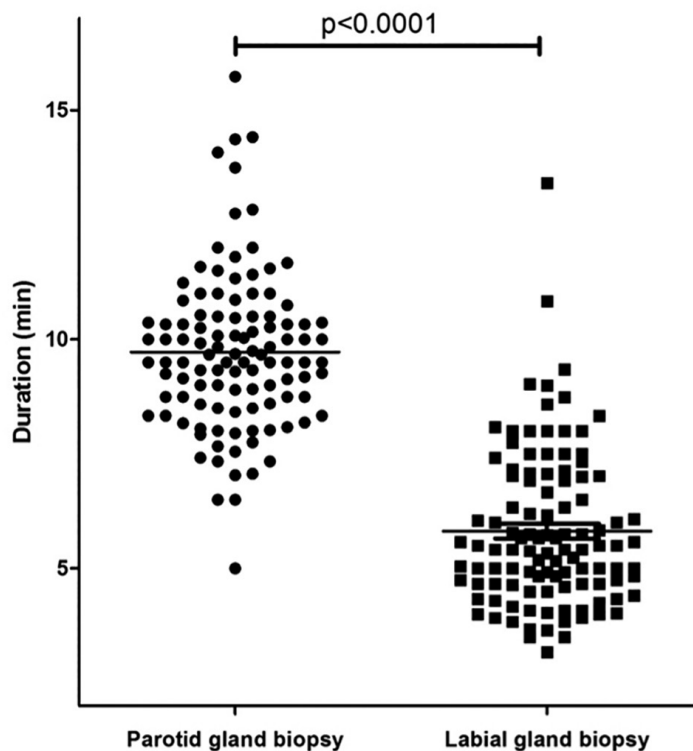


Fig. 2. Duration of salivary gland biopsies. Horizontal lines indicate median values.



which biopsied area caused more post-operative complaints. Detailed written instructions were given to patients on how complete the questionnaire.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 23 (SPSS, Chicago, IL, USA). Descriptive parameters were expressed as number of patients (%) and median (Interquartile range (IQR)=Q1-Q3) when appropriate. Mann-Whitney U-test was used to evaluate differences in VAS scores between the parotid and labial gland biopsy. Wilcoxon signed-rank test was used to compare differences over time. Spearman's correlation coefficient (r) was used to analyse the relationship between ESSPRI and the VAS scores. P-values<0.05 were considered statistically significant.

Results

One hundred and fifty-six patients suspected with pSS were invited to participate, of which 110 consented to undergo both parotid and labial gland biopsy as part of a routine diagnostic pSS work-up. Four patients had to be excluded from further evaluation for the purposes of this study because they presented at the day of the biopsy with an already altered sensibility of the biopsied area. The median age of patients was 54 years (IQR=47-65) and 92% were female. A flowchart of patients' response to questionnaires is shown in Figure 1. Analysis of missing data did not detect a pattern on patients response, indicating a completely random type of missing data.

The median duration of the surgical procedure (from incision to complete closure of the wound) of parotid gland biopsy was significantly longer than of the lip (9.5 min (IQR=8.6-10.5) vs. 5.4 min (IQR=4.7-7.0), $p<0.001$; Fig. 2). Bipolar electrocautery was needed to control bleeding during 4 (4%) parotid and 2 (2%) labial gland biopsy procedures, while exposure of sensory nerve branches was detected in 5 (5%) parotid (branches of the auricular temporal nerve, no branches of the facial nerve) and 68 (64%) labial (branches of the mental nerve) gland biopsies. None of

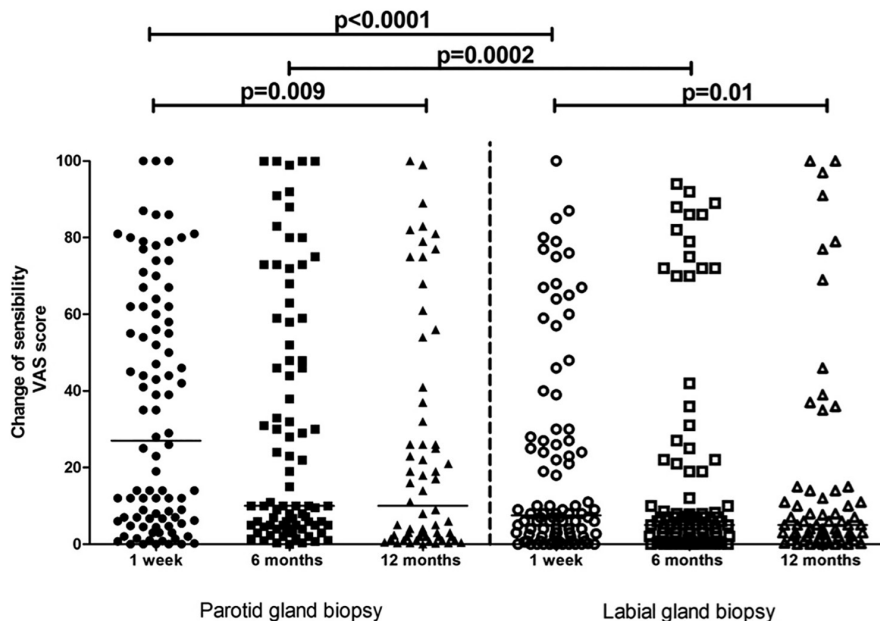


Fig. 3A. Change of sensibility VAS score of patients after biopsies. Horizontal lines indicate medians.

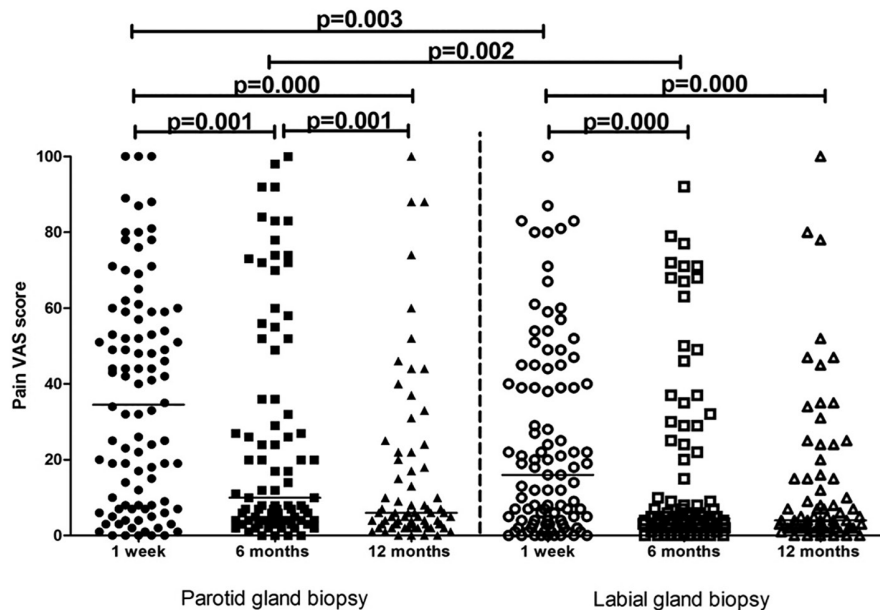


Fig. 3B. Pain VAS score of patients after biopsies. Horizontal lines indicate medians.

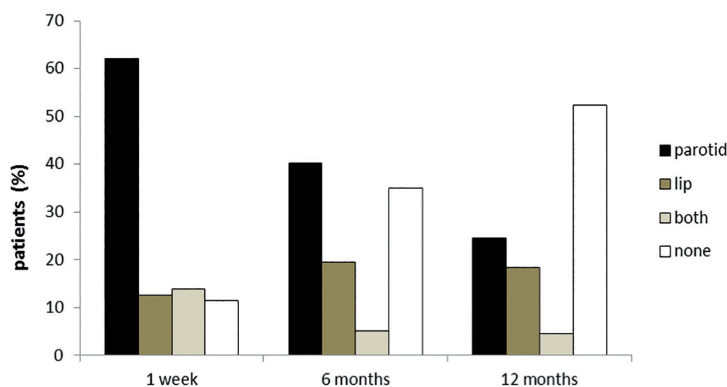


Fig. 4. Type of biopsy perceived by patients (%) as most bothersome.

the patients experienced post-operative bleeding, paresis of the facial nerve, fistula or sialoceles formation.

Patient-reported changes in the sensibility of the biopsied area were more common after a parotid biopsy than after a labial salivary gland biopsy at one week and 6 months post-operatively. Although significantly different, the change of sensibility in the area of the labial and parotid gland was minor for both types of biopsy. At 12 months post-operatively, the change in sensibility of the biopsied areas was minor and comparable in both biopsied areas (Fig. 3A; Supplementary Table I).

Patients experienced significantly more pain in the area of the parotid gland biopsy than in the area of the labial gland biopsy at one week and 6 months post-operative visits, but again pain in both areas was at the low levels. At 12 months postoperatively, pain level was very low in most patients and comparable for both biopsied areas (Fig. 3B; Supplementary Table II).

Figure 4 shows which biopsied area was perceived as the most bothersome at each time-point. Labial biopsies were experienced as less bothersome than parotid biopsies by the majority of patients one 1 week and 6 months post-operatively (12.7% and 19.5%, respectively). Twelve months post-operatively, half of the patients did not report any of the biopsied areas as annoying. The duration of the technique, outcome of the biopsy, exposure of nerve branches during the biopsy and bleeding during the biopsy did not affect the reported change of sensibility or pain in the biopsied area. ESSPRI and ESSPRI-pain domain did not correlate with the pain level or change of sensibility at any time point ($r < 0.3$ and $p > 0.05$).

Discussion

This study showed that at 12 months post-operatively pain was very low and comparable in both biopsied areas. These results are in agreement with the study of Pijpe *et al.* (4), who assessed the post-operative pain in a study including 15 patients with pSS and 20 healthy controls. Pijpe *et al.*

(4) reported, however, a similar pattern also at one week and six months post-operatively, while in the present study patients reported significantly less pain in the area of the labial gland biopsy compared to the parotid at these time points. Number of patients participating in the studies and the fact that we included patients suspected with pSS, while Pijpe *et al.* (4) included patients already diagnosed with pSS and compared them to healthy controls, might explain to some extent the discrepancy between both studies.

As far as sensibility is concerned, this study showed that one week post-operatively patients reported less change in the area of the labial gland biopsy compared to the parotid and that 12 months post-operatively change of sensibility was comparable in both biopsied areas. Likewise, Pijpe *et al.* (4) reported that at one week post-operatively fewer patients had paresthesia in the area of the lip biopsy compared to the parotid, *i.e.* 11% versus 26%, respectively. At 6 months post-operatively, however, in our study change of sensibility, although still at the lower levels, was significantly higher in the area of the parotid gland biopsy compared to the lip, *i.e.* VAS for change of sensibility was 25.7 versus 7.0, respectively, while Pijpe *et al.* (4) showed that none of the patients had any complaints of paresthesia at the area of the parotid gland biopsy. All the reasons mentioned in the aforementioned paragraph could justify the difference again. Additionally, it has to be acknowledged that in the present study, change of sensibility was assessed and quantified by the patients themselves, based on the questionnaire sent to their home, while in the study of Pijpe *et al.* (4) change of sensibility was assessed by physical testing of the sensibility and was not based on a questionnaire. Whether physicians' assessment reflects patients' perception of loss of sensibility remains questionable (9). On the other hand, patients' understanding of questionnaires is also questionable, since even the apparently most simple questions are subject to misinterpretation (10).

Conclusion

Post-operative patient-reported change of sensibility and pain in the area of the parotid and labial gland biopsy are minor and comparable. Labial and parotid gland biopsies are diagnostic techniques both well tolerated by patients suspected with pSS.

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