

## ORIGINAL ARTICLE

# A retrospective analysis of post-operative outcomes in a series of 108 labial gland biopsies

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labial gland biopsy, lip numbness, paraesthesia, Sjogren's syndrome

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**Abstract**

**Aim:** Histopathological assessment of labial salivary glands has long been a core part of the diagnostic criteria for Sjogren's Syndrome. Biopsy of labial salivary glands is technique sensitive and has post-operative complications which can affect the patient's quality of life. Varying techniques for labial gland biopsy and associated complications are described in the literature. This article gives a step-by-step account of an effective technique for labial gland biopsy as described by Daniels in 1984 and provides a retrospective analysis of the post-operative complications in a series of 108 labial gland biopsies.

**Materials and methods:** A retrospective, post-operative telephone survey was carried out to study the post-operative complications of labial gland biopsies performed by a single operator. All consecutive patients (180) who had labial gland biopsies between October 2010 and August 2012 at the Department of Oral Medicine at Guy's Hospital were called, and 108 surveys were successfully completed. The telephone questionnaires aimed to find out medium and long-term complications of labial gland biopsies to include subjective measures of post-operative pain, swelling and paraesthesia.

**Results:** One patient out of 108 patients (0.9%) reported pain that lasted  $\geq 6$  months, and six patients (5.5%) reported swelling that lasted  $> 2$  weeks. Three patients (2.8%) reported paraesthesia lasting  $\geq 6$  months with a median bother score of 0. All biopsies provided sufficient glands to allow for histopathological diagnosis.

**Conclusions:** This article describes a safe and effective technique for labial gland biopsy. Despite a low complication rate, informed consent is essential.

**Clinical relevance****Scientific rationale for study**

Labial gland biopsy (LGB) is an important component in the diagnosis of Sjogren's Syndrome. It is technique-sensitive and has post-operative complications which can affect the patient's quality of life.

**Principal findings**

This article provides a retrospective analysis of the post-operative complications in a series of 108 LGB carried out using a technique which has proved to be effective in delivering histopathological diagnosis and has a low level of post-operative complications.

## Practical implications

This article gives a step-by-step account of an effective technique for LGB which can be used by clinicians, as well as rates of post-operative complications which are useful when obtaining informed consent from the patient.

## Introduction

Sjogren's syndrome (SS) is a systemic autoimmune disease that initially targets primarily the lacrimal and salivary glands, resulting in keratoconjunctivitis sicca (dry eye disease) and/or stomatitis sicca (dry mouth disease)<sup>1</sup>. These symptoms are caused by destruction of the exocrine glands by infiltrating lymphocytes, and patients can also develop systemic symptoms such as fatigue and arthralgia<sup>2</sup>.

The most commonly accepted international criteria are currently the American–European consensus criteria<sup>3</sup>, which requires either one of two *in vitro* tests to be positive, either extractable nuclear antigens or salivary gland investigations as well as 3/4 signs or symptoms of dry eyes or mouth. The international collaboration into SS (Sjogren's International Collaborative Clinical Alliance)<sup>3–6</sup>, which has recruited over 1700 patients from oral medicine, rheumatology and ophthalmology departments and SS clinics from around the world, has led to a detailed analysis and recently proposed new data-driven diagnostic criteria<sup>7</sup>. Case definition requires at least two of three of the following: (1) positive serum anti-SSA and/or anti-SSB or positive rheumatoid factor and antinuclear antibody titre >1:320; (2) Keratoconjunctivitis sicca with ocular staining score >3; or (3) presence of focal lymphocytic sialadenitis with a focus score >1 focus/4 mm<sup>2</sup> in labial salivary gland biopsy samples. Labial gland biopsy remains an integral component of the diagnosis of SS.

Biopsy of the labial minor salivary glands in order to diagnose Sjogren's disease was first introduced in 1968 by Chisholm and Mason<sup>8</sup>. The advantages of biopsy within the lower lip include the large number of minor salivary glands available, accessibility, ease of anaesthesia, lack of major structures susceptible to damage, avoidance of skin incisions and the relative absence of post-operative pain<sup>9</sup>.

Post-operative complications which have been reported following labial gland biopsies include post-operative pain, paraesthesia, haematoma and swelling<sup>10</sup>. Lower lip numbness has consistently been reported as the only long-term complication of lip biopsy, occurring in 0–11.4% of patients<sup>6,10–14</sup>. Operators also often fail to sample sufficient glandular tissue



**Figure 1** Identification of biopsy site.

in order to make a pathological diagnosis<sup>15</sup>. This article gives a step-by-step account of an effective technique for labial gland biopsy as described by Daniels in 1984<sup>16</sup> and to analyse the post-operative complications.

## Clinical steps

Following are the clinical steps involved in a labial gland biopsy based on the technique described by Daniels in 1984<sup>16</sup>.

1 Ensure that the patient is sitting in a calm environment and has been adequately consented and warned of serious or frequently occurring post-operative complications. The patient should be asked to partially open their mouth, and the assistant should evert the lower lip (left or right side). Identify an area of mucosa of the lower lip that appears normal clinically and is not inflamed because mucosal inflammation will cause inflammatory cell infiltration of the salivary glands (Fig. 1).

2 Local anaesthetic is infiltrated into the sub-epithelial area that will be incised. Topical anaesthetic maybe applied prior to infiltration. The needle is inserted only once to a depth of 2 mm into the labial mucosa, just proximal to the midline as shown in the image. While slowly injecting local anaesthetic into the sub-epithelial tissues, the needle is extended laterally into the lip towards the angle of the mouth, parallel to the epithelium. Usually 1 ml of local anaesthetic is sufficient to adequately anaesthetise the tissues. Using local anaesthetic with vasoconstrictor is beneficial because it reduces bleeding (Fig. 2).

3 A no.15 blade is used to make a 1.5–2.0 cm horizontal linear incision through the epithelium and not the underlying connective tissue. The incision will be



**Figure 2** Administration of local anaesthetic.



**Figure 4** Separation of incision margins creating an elliptical shape.



**Figure 3** Incision through epithelium.



**Figure 5** Blunt dissection of lamina propria to release minor salivary glands and identify any nerve fibres.

made to the right or left of the midline, approximately halfway between the vestibule and the vermilion border and halfway between the midline and the labial commissure. This area is chosen as the biopsy site in order to avoid damage to the branches of the mental nerve and also because this is the region where numerous labial glands can be found. The depth of the incision is only through the epithelium because the glands are located within the lamina propria underneath the epithelium and will be difficult to find if the incision goes any deeper (Fig. 3).

4 Incision through the epithelium is confirmed when the incision margins separate, creating an elliptical shape (Fig. 4).

5 Use small curved dissection scissors for blunt dissection of the lamina propria adjacent to the epithelial margins to release the minor salivary glands from

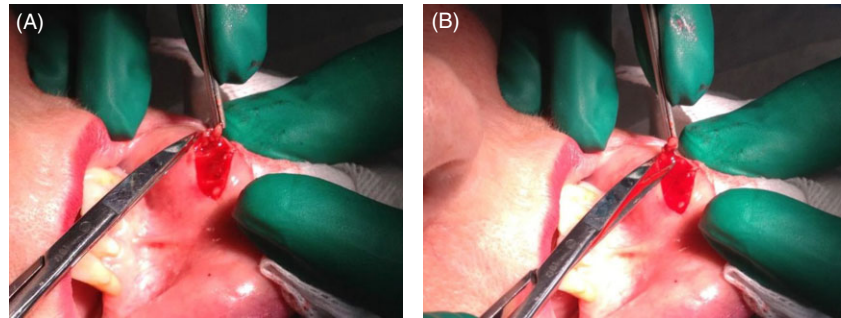
lamina propria and identify any nerve fibres passing through the surgical field. Careful blunt dissection is required in order to reduce post-operative swelling and bruising (Fig. 5).

6 Approximately 6–8 minor salivary glands should be removed, one at a time. This is done by lifting them slightly with toothed forceps, gently dissecting with the dissecting scissors, while avoiding any sensory nerves. Any additional minor salivary glands present in the field should be removed to reduce the possibility of the patient developing a mucocoele post-operatively (Fig. 6A,B).

7 Closure is achieved with two to four simple interrupted resorbable sutures (Fig. 7).

8 Pressure is applied to the biopsy site to achieve haemostasis, and post-operative instructions are given.





**Figure 6** Careful dissection of minor salivary glands.



**Figure 7** Closure of biopsy site.

### Post-operative morbidity and paraesthesia survey

We carried out a post-operative telephone survey to study the medium and long-term complications of labial gland biopsies, performed as described previously. All consecutive patients (180) who had labial gland biopsies between October 2010 and August 2012 at the Department of Oral Medicine at Guy's Hospital for the diagnosis of SS were called, and 108 surveys were successfully completed. The minimum length of time between the biopsy and the survey was 6 months, and the maximum time was 25 months (mean length of time between biopsy and telephone call was 20 months). These biopsies had been carried out under local anaesthetic by a single operator. The telephone questionnaire aimed to find out the medium and long-term complications of labial gland biopsies to include subjective measures of post-operative pain, swelling and paraesthesia. Patients were verbally consented to participate in the telephone questionnaire and were

asked to rate pain scores on a VAS scale for any pain they continued to experience *beyond* 2 weeks post-biopsy and the duration for which it lasted. Pain that lasted >2 weeks, but <6 months was defined as a medium term or temporary post-operative complication, and any pain that lasted  $\geq$ 6 months was defined as long term or a permanent complication. Similarly, patients were also asked to give a bother score (a score for how much these symptoms bothered them on a scale of 0–10) for any symptoms of swelling and paraesthesia that they may have continued to experience *beyond* 2 weeks post-biopsy.

### Results

Out of the 108 patients that completed the survey, six patients (5.5%) reported post-operative pain that lasted > 2 weeks with an average VAS pain score of 5. For five out of the six patients, the pain resolved within 1 month post-biopsy, but one patient reported that her pain had lasted for 6 months. This particular patient also reported symptoms of swelling and paraesthesia that lasted for 6 months with a bother score of 9. Six out of the total 108 patients (5.5%) complained of post-operative swelling that lasted > 2 weeks. Four of these patients reported the swelling to be mild, and two reported it to be moderate in severity. The average bother score for the swelling was 5.

Eight out of the 108 patients (7.4%) reported some paraesthesia following biopsy. Five of these patients (4.6%) reported temporary localised paraesthesia (lasting < 6 months), average time of paraesthesia being 3 months post-biopsy with an average bother score of 5.8. Three patients (2.8%) reported permanent localised paraesthesia that lasted  $\geq$  6 months, and the bother scores for these patients were 0, 0 and 9 respectively.

### Discussion

This article gives a step-by-step account of a safe and effective technique for labial gland biopsy as described

originally by Daniels in 1984<sup>16</sup> and demonstrates a low incidence of medium and long-term complications in our survey of 108 patients. Only one patient out of 108 patients (0.9%) reported pain that lasted  $\geq 6$  months, and only six patients (5.5%) reported swelling that lasted  $>2$  weeks. Permanent localised paraesthesia occurred in three out of the 108 patients (2.8%), but the bother score for two of these patients was 0 (i.e. the localised paraesthesia did not bother the patient at all and it would not have been reported if not for the telephone survey). Only one patient who had paraesthesia in the form of tingling that lasted  $\geq 6$  months was adversely affected by it, with a bother score of 9. This particular patient was a 53-year-old female patient who also reported during the survey that she had pain and mild swelling that lasted 6 months after the biopsy with a VAS pain score of 8 (the only patient in the survey that had pain that lasted  $>1$  month) and a bother score of 9 for the swelling. However, this patient had not complained of symptoms of pain and swelling when seen for a post-operative review on clinic prior to the survey, and on examination, there was no evidence of any swelling present.

A major advantage of a telephone survey to assess patients post-operatively is that it allows a large number of patients to be assessed in a short space of time<sup>17</sup>. Furthermore, it saves patients having to attend a hospital appointment which may require time off work and having to travel. The use of telephone questionnaires in exploring the post-operative symptoms of a patient is a simple and convenient method, and studies which directly compare telephone and face-to-face interviewing tend to conclude that telephone interviewing produces data which are at least comparable in quality with those attained by the face-to-face method<sup>15</sup>. All our patients were reviewed on the clinic after their biopsies in order to be given their results and diagnoses and form a management plan. All patients who participated in the telephone interview were also offered an additional face-to-face review if they wished.

One disadvantage of a telephone survey is that results are purely a subjective measure of the patient's reported symptoms, and physical examination cannot be conducted. In particular, paraesthesia is most reliably tested using an objective method of using a pin prick test or two-point discrimination, which would not be possible without a clinical exam<sup>18</sup>. Furthermore, telephone surveys can introduce some responder bias in that patients may overstate a problem if they are dissatisfied with treatment or underplay a post-operative complication in an attempt to please the telephone investigator.

The bother index<sup>19</sup> is a valuable prognostic aid and is based on what the patient believes would be his or her ability to tolerate his current level of symptoms for the rest of his life. It has widely been used as a subjective measure of the effect of a symptom on the patient<sup>20</sup>. However, the use of analgesia and non-steroidal inflammatory drugs as well as other medication that may affect post-operative pain and swelling was not taken into account. Furthermore, the interval between date of biopsy and date of telephone questionnaire varied from 6 months to 25 months and could have been standardised to ensure more accurate results.

A number of varying techniques for labial gland biopsy and complications are described in the literature (Table 1). Several studies involve the use of a horizontal incision with the rate of post-operative paraesthesia ranging from 1 to 11%<sup>16,21–28</sup>. Greenspan *et al.*<sup>21</sup> used a technique very similar to that used in this study, with a 1.5–2 cm linear incision of mucosa parallel to the vermilion border and lateral to midline, and the incidence of long-term paraesthesia in 75 patients was reported to be 1%. Pijpe *et al.*<sup>23</sup> used a technique involving a horizontal incision of 3 cm and reported the incidence temporary paraesthesia to be 11% and long-term paraesthesia to be 6% ( $n = 35$ ). Santiago *et al.*<sup>22</sup> used a 2–3 mm horizontal incision, reporting a 7% incidence of post-operative pain and 3% incidence of temporary paraesthesia but no permanent paraesthesia. ( $n = 186$ ). However, only 90.9% of the biopsy material obtained using this technique was useful for histopathological diagnosis.

Some studies have made use of a vertical incision. Gorson and Ropper used a 1 cm vertical incision behind the wet line through mucosa and submucosa and reported one case of persistent numbness (2%)<sup>29</sup>. Berquin *et al.* used an oblique incision, 1.5 cm from the midline proceeding lateroinferiorly, avoiding the glandular free zone in the centre of the lower lip, with a 4% incidence of paraesthesia<sup>11</sup>. Other techniques included sampling glands through punch biopsy<sup>30</sup> or through removing an ellipse of mucosa<sup>8</sup> with no reported long-term complications. A novel method described in a technical note by Peloro *et al.* outlined an X-mark procedure. This involved marking the yellow papules of the salivary glands with a surgical pen, then a superficial stab incision of 1.5–2 mm was made through the area identified, and a second stab incision was then made perpendicular to the first incision marking an 'X' overlying the gland. However, no details were given regarding the rate of complications<sup>31</sup>.

Minor gland biopsies have also been performed in the hard palate, using the technique of a punch biopsy<sup>32</sup>. However, haemostasis can be difficult to

**Table 1** Literature review of labial gland biopsy techniques and complications

Paper	Sample	Technique	Number of patients with short-term complications <i>n</i> (%)	Number of patients with long-term complications <i>n</i> (%)
Santiago <i>et al.</i> 2012 <sup>22</sup>	186	2–3 mm incision on inner surface of lower lip	Haematoma: 5 (3) Pain: 12 (7) Inflammation: 6 (3) Granuloma: 2 (1) Temporary Numbness: 5 (3)	0
Pijpe <i>et al.</i> 2007 <sup>23</sup>	35	Lower lip mucosal incision 3 cm parallel to vermilion border, lateral to midline.	Temporary paraesthesia: 2 (6)	Permanent paraesthesia >1 year: 2 (6)
Richards <i>et al.</i> 1992 <sup>24</sup>	58	Horizontal mucosal incision	Temporary paraesthesia: 1 (2)	Permanent paraesthesia >1 year: 1 (2)
Caporali <i>et al.</i> 2008 <sup>25</sup>	502	2–3 mm incision on inner surface of lower lip.	Temporary paraesthesia: 57 (11) Haematoma: 8 (2) Swelling: 27 (5) Bleed/scar: 5 (1)	0
Chisholm and Mason 1968 <sup>8</sup>	40	Ellipse of mucous membrane down to muscle	0	0
Greenspan <i>et al.</i> 1974 <sup>21</sup>	75	1.5–2 cm linear incision incision of mucosa, parallel to vermilion border and lateral to midline		Paraesthesia for several months: 1 (1)
Daniels 1984 <sup>16</sup>	362	Single 1.5–2 cm horizontal incision through mucosa	Temporary paraesthesia: 3 (1)	
Marx <i>et al.</i> 1988 <sup>26</sup>	77	3 × 0.75 cm horizontal mucosal incision	Temporary paraesthesia: 2 (3)	Permanent paraesthesia >2 years: 1 (1)
Delgado and Mosqueda 1989 <sup>37</sup>	19	Longitudinal incision 1 cm in labial mucosa in front of lower first premolar.	0	0
Pennec <i>et al.</i> 1990 <sup>27</sup>	50	Single 1.5–2 cm horizontal incision through mucosa	0	0
Guevara-Gutierrez <i>et al.</i> 2001 <sup>30</sup>	50	4 mm punch biopsy just penetrating epithelium between midline and commissure	Temporary paraesthesia: 2 (4)	
Friedman <i>et al.</i> 2002 <sup>38</sup>	118	5–7 mm incision on inner surface of lower lip.	Pain: 3 (3) Swelling: 5 (4) Infection: 2 (2) Suture failure: 4 (3) Cheloid formation: 1 (1) Paraesthesia >3 weeks: 2 (2)	Paraesthesia >3 weeks: 2 (2)
Gorson and Ropper 2003 <sup>29</sup>	54	1 cm vertical incision behind wet line through mucosa and submucosa	0	Permanent paraesthesia: 1 (2)
Smith <i>et al.</i> 2004 <sup>39</sup>	11	Vertical incision made on mucosal surface lateral to midline	0	0
Berquin <i>et al.</i> 2006 <sup>11</sup>	24	Oblique incision, 1.5 cm from midline proceeding lateroinferiorly, avoiding the glandular free zone in the centre of the lower lip.		Permanent paraesthesia: 1 (4)
Teppo and Revonta 2007 <sup>28</sup>	191	2–3 mm horizontal incision	Pyogenic granuloma in wound: 1 (1)	0

Table 1 shows a review of the literature published between December 1960 and December 2012 regarding techniques and complications of labial salivary gland biopsy for diagnosis of Sjogren's syndrome. Databases searched included MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. Sixteen studies were found which gave details of technique and any complications encountered.

achieve, and also primary closure is not possible, leading to possible increased post-operative pain and discomfort. Apart from post-operative complications, the other factor that determines the effectiveness of a labial gland biopsy technique is also whether the technique yields enough glands for diagnosis. Techniques that involve the use of a punch biopsy<sup>33,34</sup> usually provide little glandular tissue for examination and do not allow for visual identification of sensory fibres, which may lead to increased incidence of post-operative paraesthesia<sup>16</sup>. Removing an ellipse of mucosa as described in several studies<sup>35,36</sup> can also lead to damage of unidentified sensory nerves, and also, the epithelium is unnecessarily lost<sup>16</sup>. Moreover, as the glands are attached to the epithelium, they are at different levels, which could make diagnosis and focus scoring inaccurate and difficult<sup>16</sup>. All biopsies carried out in this study provided sufficient glands to allow for histopathological diagnosis and focus score calculation.

## Conclusion

Labial gland biopsy has played an important role in SS because of its disease specificity, wide availability, minimal invasiveness and opportunity to assess autoimmune disease-active cells within a Sjogren's target organ<sup>4</sup>. It also remains part of the new American College of Rheumatology criteria for diagnosis of SS. Labial gland biopsy remains a safe procedure with low complication rates. Despite a low complication rate, patients must be fully informed of possible risks associated with the procedure, especially that of long-term paraesthesia. Furthermore, because of the technique-sensitive nature of labial gland biopsy, it is essential that the surgeon has experience with the procedure and that sufficient glands are sampled to avoid a repeat operation. This article outlines a technique for labial gland biopsy which has proved to be effective in delivering histopathological diagnosis and has a low level of post-operative complications.

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