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ORIGINAL ARTICLE

Patient-reported pain after surgical removal of leukoplakia – an observational 1-year follow-up study

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ABSTRACT

Objective: Oral leukoplakia (OL) presents as a white lesion of the oral mucosa and is not typically associated with the sensation of pain. OL should be surgically removed when possible because it is considered a potentially malignant oral disorder (PMOD). This study assessed the pain sensations experienced by patients in association with the occurrence and surgical treatment of OL.

Methods: Inclusion criteria were: a clinical diagnosis of OL; biopsy excision; and observation for at least 12 months in the ORA-LEU-CAN study. At the first visit, all the patients were asked about the occurrence of symptoms within the lesion. Ninety-four subjects were assessed over a period of 1 year. All patients underwent complete removal of OL. The patient cohort was divided into three sub-groups: (i) no pain before excision and at the 1-year follow-up; (ii) pain before excision; and (iii) pain at the 1-year follow-up.

Results: Overall, pain was reported by 21.3% of the patients at the study start whereas 13.8% of the patients reported pain 1 year after surgical treatment. Patient-reported pain from the lesion at study inclusion was significantly associated with lesions found on the lateral side of the tongue ($p=.002$). Pain reported by patients one year after surgery was significantly related to female gender ($p=.038$) and the presence of epithelial cell dysplasia ($p=.022$).

Conclusion: We conclude that surgical removal of OL results in a low risk of long-term post-surgical pain. However, OL located on the lateral side of the tongue and in OL with dysplasia are more likely to be associated with pain.

Introduction

Oral leukoplakia (OL) is manifested as a white lesion of the oral mucosa that cannot be scraped off and that cannot be clinically classified as any other known lesion [1–4]. OL is a potentially malignant oral disorder (PMOD) of the oral mucosa. Women and older people with OL have an increased risk of malignant transformation [3,5]. Several studies have implicated tobacco use in the aetiology of OL. In addition, excessive consumption of alcohol and infection with human high-risk papillomavirus have been proposed to play roles in the development of OL [3,6], with the latter showing different infection prevalence rates [7].

OL should be completely excised, if possible, and histopathologically analysed to evaluate the presence of an epithelial dysplasia or carcinoma [8]. If complete removal of the lesion is not possible, incision biopsies should be taken in areas with multiple reaction patterns. To date, there is a lack of consensus on the standard treatment protocol, although surgical treatment should be performed if possible, even if excision does not eliminate the risk of recurrence or the risk of malignant transformation [3,9–11].

Follow-up of patients with OL includes periodic examinations and repeated biopsies of recurrent lesions or new suspicious areas, if necessary. It is vital to reduce or eliminate the risk factors, such as alcohol and tobacco use, local traumatic and irritating factors, as well as infections [3,12]. Recurrence rates after surgical removal are high, in the range of 30–45% [4,13,14] where tongue and gingiva are the most common sites [14]. Since radical removal of the lesion does

not guarantee the elimination of OL, regular clinical check-ups are needed to ensure early detection of recurrence or malignant transformation.

Several studies have addressed treatment options for OL, such as scalpel surgery, laser surgery and cryotherapy [15]. But studies on patients' quality of life, oral pain and long-term symptoms related to surgical treatment are sparse [16–19]. It is known that patients who are treated and monitored for PMODs can develop anxiety, fear of outcome, increased pain, discomfort and symptoms, all of which can vary during treatment [20,21].

Patient-reported outcome measures (PROMs), quality of life assessments and pain scores represent accurate and reliable tools for establishing baseline values in the medical records, so as to compare pain intensity and the efficacy of pain treatment [22,23]. Pain is a sensitive and multi-dimensional individual experience that is influenced by numerous intrinsic and extrinsic factors, which means that it can be challenging to evaluate [15]. These measures represent essential tools to evaluate disease and intervention outcomes from the patients' perspectives [18].

There are studies present in the literature reporting on pain intensity and swelling directly after excision of OL, as well as comparisons of conventional knife surgery versus laser treatment [19]. Despite this there is a lack of long-term follow up. Therefore, this study aimed to assess in a 1-year time-frame patient-reported pain after surgical treatment of OL.

Patients and methods

A prospective, longitudinal, multi-centre study (Gothenburg, Trollhättan and Uppsala, Sweden) in Sweden collected data from 226 patients in the period from January 2011 to December 2018. Medical and dental histories were recorded, including pain intensity and discomfort levels in the area of the lesion. Clinical classification (homogeneous/heterogeneous) and photographs were acquired, and the histopathological diagnosis was recorded. In patients who were eligible for surgery, OL was removed utilizing conventional scalpel technique with a 2-mm surgical margin and sent for histopathological examination. All patients received treatment according to the standard of care, which consisted of surgical excision when possible and follow-up protocols.

Inclusion criteria for the participants in this study were: (i) clinical diagnosis of OL, (ii) complete surgical removal of OL either by excision at first surgery (69 patients) or an incisional biopsy (25 patients) followed by complete surgical removal after histopathological analysis of primary biopsy, (iii) a histopathological diagnosis of benign hyperkeratosis or hyperkeratosis with dysplasia and (iv) follow-up for at least 12 months according to the ORA-LEU-CAN study protocol. Grading of epithelial dysplasia was done according to WHO Classification of Head and Neck Tumours [24].

Patient-reported symptoms were assessed before surgery and at 12 months postsurgery. Post-operative signs and symptoms immediately after surgery were not an objective in the study and therefore not registered in the study protocol. Patients were recalled 3 months after inclusion for the 2nd study visit. Exclusion criteria were missing data or oral squamous cell carcinoma in the primary biopsy.

From the ORA-LEU-CAN data-base medical history, gender, age, medication, tobacco and alcohol habits, and patients' symptoms associated with the mucosal condition were collected. Data on clinical diagnosis (homogeneous or non-homogeneous OL), location, lesion size and presence of multiple OL were also retrieved.

In the database, 94 out of 226 patients met the inclusion criteria for this study. The study cohort was divided into three groups: (i) patients who did not report any pain either at inclusion or one year after surgical treatment; (ii) patients who reported pain at inclusion; and (iii) patients who reported pain one year after surgical treatment.

Pain was evaluated with a Visual Analogue Scale (VAS) [25] before surgery and 12 months after surgical excision. Each patient was informed on how to use the VAS and was asked to grade the intensity of their pain, where VAS $= 0$ meant no pain and VAS $= 10$ indicated extremely severe pain [26]. For patients who reported VAS-values with decimals, the values were rounded up to whole numbers. The VAS data were grouped as follows: no pain (VAS $=$ 0); low pain (VAS $=$ 1–3); moderate pain (VAS $=$ 4–6); and severe pain (VAS $=$ 7–10).

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden (Dnr. 673-10) and was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all patients.

Statistical analyses

The obtained data were saved in Microsoft Excel for Office 365, ver. 1908 (Redmond, WA). Statistical analysis was performed with the IBM SPSS Statistics ver. 25 software (IBM, Armonk, NY). Fisher's exact test was used to analyse differences between the groups. Uni- and multivariable logistic regression analyses were used to demonstrate the risk factors at baseline for pain at 1-year post surgery. A p value $<.05$ was considered statistically significant for the primary outcome.

Results

Ninety-four subjects were included in this study. The study cohort consisted of 48 men (51.1%) and 46 women (48.9%), with a mean age of 60.5 years (median: 62; range: 28–81 years; Table 1). Fifty-six patients (59.6%) had homogeneous OL, while 38 patients (40.4%) had non-homogeneous OL. In this group, 63 (67.0%) of the removed lesions had an area of $<200 \, mm^2$ and 31 (33.0%) had an area $\geq 200 \, mm^2$. OL lesions were registered on the lateral side of the tongue ($N = 26$, 27.7%); in the gingiva ($N = 33$, 35.1%); and other distinct oral sites ($N = 35$, 37.2%): in the buccal mucosa ($N = 10$, 10.6%); in the hard palate ($N = 10$, 10.6%); on the ventral side of the tongue ($N = 7$, 7.4%); in the floor of the mouth ($N = 4$, 4.3%); on the lips ($N = 3$, 3.2%); and in the soft palate ($N = 1$, 1.1%). Nineteen patients (20.2%) had OL with an

Table 1. Characteristics of the study cohort.

	No. of patients N (%)[a]	Pain at baseline N (%)[b]	p Value[c]	Pain at 1-year post surgery N (%)[b]	p Value[c]
Study cohort	94 (100%)	20 (21.3%)		13 (13.8%)	
Gender			.32		**.038**
Male	48 (51.1%)	8 (16.7%)		3 (6.2%)	
Female	46 (48.9%)	12 (26.1%)		10 (21.7%)	
Age (at first appointment)			.62		.55
≤62 years	48 (51.1%)	9 (18.8%)		8 (16.7%)	
>62 years	46 (48.9%)	11 (23.9%)		5 (10.9%)	
Clinical appearance			.071		.36
Homogeneous	56 (59.6%)	8 (14.3%)		6 (10.7%)	
Non-homogeneous	38 (40.4%)	12 (31.6%)		7 (18.4%)	
Size of OL			.59		1.00
≥200 mm^2	31 (33.0%)	8 (25.8%)		4 (12.9%)	
<200 mm^2	63 (67.0%)	12 (19.0%)		9 (14.3%)	
Dysplasia			.11		**.022**
Yes	19 (20.2%)	7 (36.8%)		6 (31.6%)	
No	75 (79.8%)	13 (17.3%)		7 (9.3%)	
Smoking			1.00		.71
Yes	18 (19.1%)	4 (22.2%)		3 (16.7%)	
No	76 (80.9%)	16 (21.0%)		10 (13.2%)	
Snuff			.12		.35
Yes	10 (10.9%)	0 (0%)		0 (0%)	
No	82 (89.1%)	19 (23.2%)		13 (15.8%)	
No data	2	1			
Alcohol consumption			.80		.38
Yes	41 (43.6%)	8 (19.5%)		4 (9.8%)	
Rarely/never	53 (56.4%)	12 (22.6%)		9 (17.0%)	
Site			**.002**		.096
Gingiva	33 (35.1%)	3 (9.1%)		3 (9.1%)	
Lateral side of the tongue	26 (27.7%)	12 (46.2%)		7 (26.9%)	
Other	35 (37.2%)	5 (14.3%)		3 (8.6%)	
Pain at baseline			–		**.006**
Yes	20 (21.3%)	20 (21.3%)		7 (35.0%)	
No	74 (78.7%)	0 (0%)		6 (8.1%)	

[a]Column percent.
[b]Row percent.
[c]Fisher's exact test.
The bold values are statistically significant.

Table 2. Levels of pain reported by patients at baseline and at 1-year follow-up.

Level of pain (VAS)	No. of patients at baseline (%)				No. of patients at 1-year follow-up (%)			
	0	Low (1–3)	Moderate (4–6)	Severe (7–10)	0	Low (1–3)	Moderate (4–6)	Severe (7–10)
Group (i)	68 (100)	–	–	–	68 (100)	–	–	–
Group (ii)	–	14 (70.0)	4 (20.0)	2 (10.0)	13 (65.0)	6 (30.0)	1 (5.0)	–
Group (iii)	6 (46.2)	6 (46.2)	1 (7.6)	–		10 (76.9)	3 (23.1)	–

epithelial cell dysplasia. Patients' characteristics for the study cohort in detail are presented in Table 1.

All patients underwent surgical removal of their OL either by excision (69 patients) or preceded by an incisional biopsy (25 patients).

Sixteen patients (23%) of the 69 who underwent excision of OL reported low to severe pain at inclusion and prior to surgery. Four patients in this group reported low to moderate pain one year after excision. Fifty-three patients did not report any pain at baseline. Out of these 53 patients, three patients reported low-moderate pain at 1-year follow-up. Pain levels are described in Table 2.

Of the 25 patients (36%) who underwent incision biopsy before excision, 21 patients did not report pain at baseline. Four patients reported a low level of pain at baseline and three of these patients reported low-moderate pain at 1-year follow-up.

The study cohort was divided into three groups based on absence or presence of pain: (i) patients who did not report any pain either at inclusion or one year after surgical treatment, (ii) patients who reported pain at inclusion and (iii) patients who reported pain one year after surgical treatment.

Group (i) patients who did not report any pain either at inclusion or 1 year after surgical treatment

Group (i) comprised 68 patients (72.3% of the study cohort; 29 women, 39 men) who had asymptomatic OL (VAS = 0) before excision and who were still asymptomatic one year after surgical removal of the OL. Forty-five patients (66.1%) in group (i) were diagnosed with homogeneous OL and 23 (33.8%) patients had non-homogeneous OL. Forty-eight patients (76.2%) had lesions with area <200 mm^2 and 20 patients (64.5%) had lesions with area ≥200 mm^2. The most common sites for the lesions were the gingiva (28 patients, 84.8%) and the lateral side of the tongue (11 patients, 43.3%). Eight patients (42.1%) had OL with an epithelial cell dysplasia: six with mild dysplasia (two OL on the ventral and

one on the lateral tongue; two in the gingiva and one in the buccal mucosa) and two with moderate dysplasia both located on lateral border of the tongue. Smoking was reported by 12 patients and 10 patients reported the use of Swedish snuff. Thirty-seven patients reported never or rarely consuming alcohol.

Twenty-six patients of the 68 patients (38.2%) in this subgroup had recurrence during the 1-year observation period.

Group (ii) patients who reported pain at inclusion

Group (ii) comprised 20 patients with pain at inclusion (21.3% of the study cohort; eight men, 12 women), with the majority 11 being >62 years of age (Table 1). The levels of pain at inclusion were low in 14 patients (70.0%), moderate in four patients (20.0%) and severe in two patients (10.0%) (Table 2). Eight patients (14.3%) were diagnosed with homogeneous OL and 12 patients (31.6%) had non-homogeneous OL (Table 1). Twelve patients (19.0%) had lesions with an area <200 mm^2 and eight (25.8%) had lesions with an area ≥200 mm^2 (Table 1). The lateral side of the tongue was the most common lesion site, observed in 12 patients (46.2%) and in the gingiva in three patients (9.1%) (Table 1). Dysplasia was registered in seven (36.8%) of these patients: one patient diagnosed with mild dysplasia (lateral tongue), five patients with moderate dysplasia (lateral tongue: 4; buccal mucosa: 1) and one patient with severe dysplasia (lateral tongue) (Table 1). Smoking was reported by four patients and no patients reported the use of Swedish snuff (Table 1). Twelve patients reported having never or rarely used alcohol (Table 1).

Eight patients of the 20 patients (40%) in this subgroup had recurrence during the 1-year follow-up.

Seven patients out of 20 patients reported pain also at the 1-year follow-up: six with low-level pain, and one with moderate pain. Five of the patients were female. Thus, 13 out of 20 patients (65.0%) in group (ii) were free of pain at the 1-year follow-up (Table 2).

Group (iii) patients who reported pain at 1-year of follow-up

Thirteen patients (13.8% of the study cohort; three men, 10 women) (Table 1) reported pain one year after surgery. Ten patients (76.9%) experienced low-level pain and three (23.1%) reported a moderate level of pain (Table 2). Six patients (10.7%) had homogeneous and seven (18.4%) had non-homogeneous OL (Table 1). Furthermore, in this subgroup of the study cohort, four patients (12.9%) had a lesion size ≥200 mm^2, while nine patients (14.3%) had a lesion size <200 mm^2 (Table 1). Six patients (31.6%) had OL with dysplasia, i.e. two patients had mild dysplasia (lateral tongue and floor of the mouth), three patients had moderate dysplasia (lateral tongue: 2 and buccal mucosa: 1) and one patient had severe dysplasia (lateral tongue) (Table 1). Three patients reported smoking habits, no patient reported snuff use. Nine patients reported never or rare alcohol use (Table 1).

In seven out of 13 patients (53.8%), OL recurrences were registered. Patient-reported symptoms other than pain at 1-year follow-up included: difficulty with speaking, a stinging and burning sensation, and numbness at the site of surgery.

Statistical calculations

Statistical comparison between group (ii), where patients reported pain on the first visit before lesion excision, and the study cohort, showed a significant correlation between lesion site and pain. Patients with OL located on the lateral tongue reported significantly more pain in comparison with other locations ($p=.002$; Table 1).

Group (iii), reporting pain one year after complete removal of the lesion, was characterized by a significant correlation between gender ($p=.038$; Table 1), cell dysplasia ($p=.022$; Table 1) and pain at baseline ($p=.006$; Table 1).

Univariable logistic regression analysis for risk factors at baseline associated with pain at one year after surgery, showed a significant difference for gender, where the occurrence of pain in females was significantly more frequent than in males ($p=.040$; odds ratio 4.2 (1.1–16); Table 3). Presence of cell dysplasia at baseline significantly correlated with pain one-year post surgery ($p=.018$; odds ratio 4.5 (1.3–16); Table 3). Pain at baseline constituted also a significant risk factor for pain after one year ($p=.004$; odds ratio 6.1 (1.8–21); Table 3).

Multivariable logistic regression showed pain signification ($p=.014$; Table 3) and statistical tendencies for gender ($p=.056$; Table 3) and an epithelial dysplasia ($p=.051$; Table 3) as risk factors for pain one year after complete lesion removal.

Discussion

To date, it has not been established whether surgical treatment of OL improves prognosis and prevents cancerous transformation of the OL [15,19]. The choice of therapy depends on the clinical picture of the lesions, appropriate therapeutic options and prognosis, including risks and complications [27]. Recurrence rates after excision are high, with several studies reporting recurrence in 30–45% of patients [4,15,16]. The gold standard, in most centres, is considered to be surgical removal when possible and follow-up [3]. When considering surgical treatment, it is of importance to consider patient-reported symptoms. In patients who have symptoms, surgery may alleviate pain in addition to removing a potentially malignant lesion. Few studies have addressed these aspects, although OL-related pain can have an impact on patients' quality of life [17,28]. Many studies have investigated patients' perceptions in the diagnostic-therapeutic process for oral lesions, focussing often on the pathogenesis and therapy of the disease, without addressing what that process means for the individual patient [16–18].

Measuring pain is challenging, as it is difficult to interpret the physical and mental aspects. The collection of subjective data that affect the patients' quality of life relies heavily on patient communication and professional perception skills

Table 3. Risk factors at baseline for pain at 1-year post surgery.

	Univariable logistic regression		Multivariable logistic regression	
	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value
Gender		**.040**		.056
Male	1.0 (Ref.)		1.0 (Ref.)	
Female	4.2 (1.1–16)		4.2 (1.0–19)	
Age (at first appointment)		.29		
≤62 years	1.0 (Ref.)			
>62 years	0.5 (0.1–1.8)			
Clinical appearance		.29		
Homogeneous OL	1.0 (Ref.)			
Non-homogeneous OL	1.9 (0.6–6.1)			
Size of OL		.86		
≥200 mm^2	1.0 (Ref.)			
<200 mm^2	1.1 (0.3–4.0)			
Dysplasia		**.018**		.051
Yes	4.5 (1.3–16)		3.8 (1.0–15)	
No	1.0 (Ref.)		1.0 (Ref.)	
Smoking		.70		
Yes	1.3 (0.3–5.4)			
No	1.0 (Ref.)			
Snuff				
Yes	–			
No	–			
Alcohol consumption		.32		
Yes	1.9 (0.5–6.6)			
Rarely/never	1.0 (Ref.)			
Site				
Gingiva	1.0 (Ref)			
Lateral side of the tongue	3.7 (0.8–16)	.08		
Other	0.9 (0.2–5.0)	.94		
Pain at baseline		**.004**		**.014**
Yes	6.1 (1.8–21)		5.2 (1.4–19)	
No	1.0 (Ref.)		1.0 (Ref.)	

Uni- and multivariable logistic regression.
The bold values are statistically significant.

[19,28,29]. A feeling of pain or discomfort and its severity is difficult for the patients to repost accurately. Patients' experiences of low-level of pain or slight discomfort may be due to the physical presence of the lesions, as well as the patient's mental approach to accepting that the localized oral mucosal lesion has the potential for malignant transformation.

In this observational study, we analysed three sub-groups in a cohort of patients from whom OL was removed in toto and whose pain sensation or absence was observed one year after lesion excision. The study shows that complete surgical removal of OL can be achieved without long-term side-effects, such as pain or discomfort, in 72.3% of patients. Patients who reported pain at the start of the study comprised 21.3% of the cohort, and their pain was significantly associated with a specific lesion site: the lateral side of the tongue. The last group of patients, who reported pain 1-year post surgery (13.8%) showed statistically significant correlation between pain at baseline, gender and cell dysplasia. Most of the cases of OL were asymptomatic, although this study shows that a non-negligible number of patients report pain from their OL.

The largest sub-group (72.3%) consisted of patients who did not report pain from their OL at the baseline visit and were free of pain one year after treatment. Thus, surgical excision of OL can be performed with the expectation of few side-effects, at least in the 1-year time-frame.

The second sub-group (21.3% of the study cohort) consisted of patients who reported pain at inclusion. The

reported levels of pain were low to severe at baseline. One year after lesion removal, a small number of patients described their pain level as low. The third subgroup (13.8% of the studied cohort) included patients who reported pain one year after surgery. Reported pain levels were low to moderate initially, and these levels remained at 1-year follow-up. No severe pain level was reported by patients in any of the analysed subgroups. This justifies complete removal of OL from a risk of pain perspective.

Recurrence rates were between 38% and 53% in the subgroups. Since recurrence is an event occurring after baseline pain registration this parameter cannot be included in the statistical analysis in this study.

One of the main findings of the present study is that symptoms were reduced after surgery in patients who entered the study with symptoms. Of 20 patients (21.3%), who had pain before surgery, 13 patients did not report any pain 1-year post surgery. Only six patients who entered the study without pain, reported pain after excision at the 1-year follow-up, and all of these patients experienced pain at a low or moderate level (maximum VAS of 4). In patients who reported symptoms other than pain 1-year after surgery, hyposensitivity, hypersensitivity, tingling sensations and difficulty in speaking were registered and consistent with the surgical sequelae. This highlights the importance of information to patients before excision about the risk of side-effects such as described above.

Incision biopsies before complete lesion removal were performed on 36% of the study patients. Only 4% reported

pain at the 1-year follow-up. Thus, incision biopsy *per se* does not seem to create an increased risk for pain.

A limitation of this study is that the number of patients in subgroups (ii) and (iii) with pain is limited. This is an effect of OL being a mucosal disorder often presenting without symptoms. Despite the limited number of subjects in these groups some important conclusion can be drawn from the present study.

The surgical protocol used in this study involved conventional surgical scalpel excision of OL lesions. The scalpel technique is widely used and already consolidated in the literature [11–14]. Compared to conventional surgical treatment with a scalpel, the use of lasers, including CO_2, has increased significantly and shows advantages during the operative moment and in term of reduced oral bleeding, reduced contamination by microorganisms, and preservation of healthy surrounding tissues [30,31].

Studies of patient-reported outcomes for surgery types other than the conventional surgery would be of importance.

Conclusions

Our present study shows that the majority of patients with OL do not have pain related to the disorder at baseline. Most patients do not experience pain from their OL; pain was reported by only 21.3% of patients at the study start and only 13.8% of the patients reported pain one year after surgical treatment. Female gender, OL localization on the later side of the tongue and the presence of dysplasia were factors significantly associated with pain. Therefore, surgical removal of OL can be performed with a low frequency of pain complications and should be recommended to patients.

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Disclosure statement

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