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Oral leukoplakia treatment with the carbon dioxide laser: A systematic review of the literature

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ABSTRACT

We conducted a systematic review of the literature to evaluate treatment of oral leukoplakia with the carbon dioxide (CO_2) laser.

A comprehensive search of studies published between 1981 and 2015 and listed in the PubMed (National Library of Medicine, NCBI) database yielded 378 articles which were screened in detail. Relevant studies were selected according to predetermined inclusion and exclusion criteria. A total of 33 articles met the final inclusion criteria and were analysed in detail in accordance with the PRISMA-P statement. These full-text papers were classified as synopses (n = 7), recurrence and malignant transformation studies (n = 17), comparative studies between CO_2 laser and cold knife surgery (n = 3) and studies evaluating the efficacy of CO_2, Nd:YAG and KTP lasers.

According to the literature the CO_2 laser is the workhorse of oral leukoplakia treatment due to its effectiveness and low associated morbidity. However, randomized clinical trials are needed to compare CO_2 laser with other lasers. The results of our systematic review showed that there is no consensus regarding the factors involved in higher recurrence and malignization rates, so further studies are needed.

1. Introduction

Oral leukoplakia (OL) is the most common potentially malignant lesion of the oral cavity, leading, in some cases, to oral squamous cell carcinoma (OSCC). The annual rate of malignant transformation of OL into OSCC is approximately 1%–2% (Van der Waal, 2009).

Several treatment options have been used for OL, but, according to the literature, cold knife surgery and carbon dioxide (CO_2) laser surgery seem to offer better outcomes than topical or systemic medication in terms of recurrence and malignant transformation. Although there is no evidence that treatment prevents malignant transformation, it is recommended to treat OL with or without dysplasia (Horch et al., 1986; Chandu et al., 2005; Brouns et al., 2014a).

The CO_2 laser was invented in 1963 by Patel (1964), but Ben-Bassat et al. (1987) were the first to describe its use for intraoral treatment. Since then many studies have endorsed the advantages and effectiveness of the CO_2 laser as treatment not only for OL, but also for other oral and maxillofacial lesions and head and neck lesions (Chandu et al., 2005; Yang et al., 2011; Deppe et al., 2012).

The aim of the present review article was to systematically evaluate the effectiveness of CO_2 laser treatments on OL lesions.

2. Material and methods

2.1. Search strategy

A MEDLINE (PubMed) search was conducted, with studies published from 1981 to 2015 included in the systematic review (SR). The SR was updated on 16th June 2015 and conducted in accordance with the Preferred Reporting Items for Systematic

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Reviews and Meta-Analysis protocols (PRISMA-P 2015) (Moher et al., 2015). All eligible articles were manually checked for additional references.

2.2. Search terms

A combination of the following keywords was used: oral leukoplakia, vaporization, CO_2 laser, carbon dioxide laser, laser surgery, epithelial dysplasia, malignant transformation, and recurrence.

2.3. Article selection

To control for selection bias, two independent reviewers (AMV and JAHM) evaluated the titles and abstracts of retrieved articles. If it was not clear from the title and abstract whether an article met the inclusion criteria, the full text was reviewed. Expert opinions were excluded. When duplicate reports of the same study were identified, only the most recent was included. Full-text articles were then evaluated and differences between both reviewers were solved by discussion until consensus was reached.

2.4. Inclusion criteria

The inclusion criteria for the studies were as follows: studies reporting clinical series of patients with OL treated with the CO_2 laser, studies reporting clinical series of patients with OL treated with CO_2 laser compared to other surgical techniques and, finally, articles dealing with general aspects of OL treatment with the CO_2 laser.

2.5. Exclusion criteria

The exclusion criteria were as follows: duplicated studies, animal studies, experimental laboratory studies, cohort studies with less than 12 months follow-up, articles reporting leukoplakia in locations other than oral, articles published in languages other than English, French, German, Italian and Spanish and, finally, letters, editorials and abstracts.

2.6. Data collection and analysis

The following information was collected, when possible, from the selected studies: first author, year, country, number of patients treated with CO_2 laser, number of different OL lesions treated in each study, the most frequent locations for OL, recurrence rate, malignant transformation rate, type of CO_2 laser used and the complications rate. Whenever possible, data on factors affecting recurrence and malignant transformation were also collected.

3. Results

The initial MEDLINE search retrieved 378 articles. For multiple publications regarding the same group of patients, only the most recent study was included. Initial analysis of titles and abstracts eliminated 314 articles, leaving 64 articles whose full text was examined. A total of 33 studies met the inclusion criteria and so were included in the final review. Studies were classified into 4 groups (Table 1).

Table 1
Classification of analysed oral leukoplakia articles (n = 33). 1. Synopses. 2. Studies of recurrence and malignant transformation. 3. Comparative studies between CO_2 laser and cold knife. 4. Studies evaluating the efficacy of CO_2, Nd:YAG and KTP laser.

	Number of articles	Percentage
1. Synopses	7	21.21%
2. Studies of recurrence and malignant transformation	17	51.51%
3. Comparative studies between CO_2 laser and cold knife	3	9.9%
4. Studies evaluating the efficacy of CO_2, Nd:YAG and KTP laser	6	18.18%

3.1. Synopsis articles

Seven of the articles (21.21%) were synopses. Huang et al. (2015) retrospectively evaluated the safety and advantages of using CO_2 laser in the treatment of oral mucosal lesions including vascular malformations, OL and verrucous nevus in a group of 73 patients, comparing their results with a control group of 20 patients treated with the traditional scalpel. They found statistically significant ($p < .05$) better outcomes in terms of shorter operative time and less bleeding in the patients treated with the CO_2 laser. Deppe et al. (2012) prospectively evaluated recurrence rates resulting from different methods of CO_2 laser vaporization (defocused continuous wave, superpulsed mode plus scanner and continuous wave plus scanner), concluding that recurrence rates were lower to a statistically significant degree for the defocused continuous wave technique followed by the continuous wave scanner and the super pulsed plus scanner mode, in that order. Metzler (2007) reviewed the literature on surgical management of oral mucosal dysplasia, describing the technique, advantages and disadvantages of CO_2 laser for OL treatment. Colella et al. (1995) reviewing the literature on different methods of OL treatment, particularly focussing on CO_2 laser, traditional surgery and natural or synthetic retinoids. Deymes (1981) reported experiences with CO_2 laser for OL treatment and also for other intraoral benign neoplasms. Roodenburg and Horch (1993) reviewed indications for CO_2 laser in oral and maxillofacial surgery, describing advantages over other methods and concluding it to be the treatment of choice for OL. Bornstein et al. (2003) reviewed and discussed recurrence and malignant transformation rates for studies of OL treated with the CO_2 laser from 1985 to 2000, focussing especially on complications and wound healing.

3.2. Studies of recurrence and malignant transformation

Seventeen papers (51.51%) were classified as studies focussing on recurrence and malignant transformation of OL in patients treated with the CO_2 laser. These studies are summarized in Table 2 (Frame, 1985; Horch et al., 1986; Chu et al., 1988; Roodenburg et al., 1991; Chiesa et al., 1993; Huerta et al., 1999; Gooris et al., 1999; Dunsche et al., 2000; Thomson et al., 2002; Van der Hem et al., 2005; Chandu et al., 2005; Yang et al., 2011; Jerjes et al., 2012; Brouns et al., 2013, 2014; Pedrosa et al., 2015; Mogedas-Vegara et al., 2015).

All the articles were retrospective, with patients treated for different OL locations, except for one article that focused exclusively on leukoplakia of the lower lip (Gooris et al., 1999). Some studies aimed to identify the factors (epidemiological, etiological, clinical and histopathological) affecting recurrence and possibly predicting malignant transformation (Table 3).

3.3. Comparative studies between CO_2 laser and cold knife surgery

Three papers (9.9%) prospectively compared excision of OL by CO_2 laser versus traditional scalpel (Che et al., 2012; López-Jornet et al., 2013; Tambuwala et al., 2014). Table 4 summarizes these studies and the parameters used to compare the two methods ($p > .05$ was considered to be statistically significant).

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Table 2
Studies of recurrence and malignant transformation. *ni*: not indicated; sp: super pulsed; cw: continuous wave.

Author, year, country	Patients	Lesions	Location	Recurrence rate	Malignant transformation rate	Laser/Wattage	Complications	Follow-up
Mogedas 2015, Spain	65	65	Tongue 32.3%	33.8%	15.4%	Lumenis sp/15 W	7.7% Pain	15 months
Pedrosa 2015, Portugal	59	59	*ni*	40.7%	10.2%	*ni* cw/6–15 W	0%	43.75 months
Brouns et al., 2014, 2013, Netherlands	35	35	Tongue 25.7%	40%	14%	Visor 40′ sp cw/4–8 W	2.85% Mental nerve paraesthesia	61.5 months
Jerjes 2012, UK	77	123	Tongue 37.4%	19.5%	10.4%	Sharplan sp cw/2–15 W	0%	6.4 years
Yang 2011, Taiwan	114	114	Cheek 53.5%	17.5%	11.4%	Lumenis cw/12–15 W	0%	3.4 years
Van der Hem, 2005 Netherlands	200	282	Tongue 22.7%	9.9%	1.1%	Sharplan 791, Cavitron, Sharplan 40C/15–20 W	*ni*	52 months
Chandu 2005, Australia	43	73	*ni*	28.9%	7.3%	Sharplan 743/10–15 W	6.9% Temporary mental nerve paraesthesia, headache, pain	47.2 months
Thomson 2002, UK	57	62	Floor of mouth 42%	24%	7%	Ultrapulse 1000/10–15 W	7% (4/57) Sialadenitis, lingual nerve paraesthesia	18 months
Dunsche 2000, Germany	91	168	Floor of mouth 41.7%	4.9%	1.5%	*ni*/3–5 W	*ni*	35.2 months
Gooris 1999, Netherlands	23	27	Lips 100%	14.8%	0%	Sharplan 791, Cavitron 33A, Sharplan 1025 (defocused)/8–10 W	*ni*	3–192 months
Huerta 1999, Spain	34	34	Tongue 26.5%/ Buccal mucosa 26.5%	25.8%	X	10 W	*ni*	12 months
Chiesa 1993, Italy	167	167	Buccal mucosa 59.2%	34.73%	3%	Continuous wave/9–12 W	*ni*	52 months
Roodenburg 1991, Netherland	70	103	Buccal mucosa 28%	9.7%	0%	Sharplan 791, Cavitron 300A defocused/15–20 W	*ni*	5.3 years
Chu 1988, USA	29	38	Floor of mouth, ventral tongue 36.8%	10.8%	2.6%	Coherent 450/451 XLG/3,5–20 W	13.8% Granuloma, bleeding,	5 years
Horch 1986, Germany	32	50	Cheek 64%	22%	*ni*	Defocused/15–20 W	*ni*	37 months
Frame 1985, UK	63	75	*ni*	3.1%	0%	Coherent 450, Sharplan 733/10 W	*ni*	29 months

Table 3
Factors related to recurrence and malignant transformation.

Author, year	Factors affecting recurrence	Factors predicting malignant transformation
Mogedas-Vegara, 2015	Gingiva vs. tongue ($p = .032$)	X
Pedrosa et al., 2015	Moderate to high-grade dysplasia ($p = .006$)	X
Brouns, 2013b	*Not reported*	Size 4 cm or more ($p = .034$)
Jerjes, 2012	Erythroleukoplakia ($p < .001$) Non-homogeneous OL ($p < .001$) Heavy life-long smokers ± heavy life-long alcohol consumers ($p < .001$)	Erythroleukoplakia ($p < .001$) Non-homogeneous leukoplakia ($p < .001$) Heavy life-long smokers ± heavy life-long alcohol consumers ($p < .001$)
Yang, 2011	Smoking continuation after laser treatment ($p = .008$) Multiple-focus OL ($p = .006$) Non-homogeneous OL ($p = .04$) High-grade displasia ($p = .012$)	*Not reported*
Chandu, 2005	Alcohol consumption ($p = .034$) Previous malignancy ($p = .018$)	*Not reported*
Thomson, 2002	X	X

3.4. Studies evaluating the efficacy of CO_2, Nd:YAG and KTP laser

Six articles (18.18%) retrospectively evaluated OL management with the CO_2 laser, KTP laser or Nd:YAG laser. Del Corso et al. (2015) compared the CO_2 and Nd:YAG lasers OL treatment, finding no statistical differences in terms of recurrence or malignant transformation rates. However, CO_2 laser excision resulted in better outcomes than Nd:YAG laser evaporation for non-homogeneous OL ($p = .04$) and OL with mild dysplasia ($p = .03$). Lim et al. (2010) compared CO_2 and KTP laser treatment in cohorts of 45 and 30 patients, respectively, finding a statistically significant reduction in terms or recurrence ($p = .049$) for patients treated with the KTP laser, hypothesizing that the KTP laser may be more effective owing to deeper tissue penetration and thermal scatter. Ishii et al. (2004) evaluated treatment with CO_2, Nd:YAG and KTP lasers of 116 patients presenting with 154 OLs, observing a recurrence rate of 29.3%

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Table 4
Comparative studies between CO_2 laser and cold knife surgery.

Author, year	Study	Laser (n)/scalpel (n) (patients)	Outcomes for laser vs cold knife ($p < .05$)	Outcomes for laser vs cold knife ($p > .05$)
Tambuwala, 2014	Non-randomized	25/25	Less bleeding Less oedema Scarring distribution after 1 month ($p = .045$)	Postoperative pain ($p = .208$, 1st post-op day, and $p = .533$, 2nd post-op day)
Chee and Sasaki, 2013	Randomized	24/23	Less bipolar cautery per square cm Less blood loss Less margin needed to clear specimens by frozen section ($p = .03$)	Excision time
López-Jornet, 2013	Randomized	20/28	Less pain ($p = .021$) and swelling ($p = .019$) 12–48 h after surgery	

and a malignization rate of 1.2%. Excision with the CO_2 or KTP laser was preferred for non-contact application for non-keratinized epithelium OL. Non-contact CO_2 laser and contact Nd:YAG laser vaporization approaches were used for OL located on the gingiva or hard palate. Schoelch et al. (1999) reported OL management of 55 patients based on combining CO_2 and Nd:YAG lasers. In follow-up for more than 6 months (range 6–176 months), 29 patients obtained complete control of their lesions, 19 patients obtained control after small recurrences treated with subsequent laser surgery, 2 patients had full recurrence and 5 patients developed squamous cell carcinoma. White et al. (1998), for 39 patients with OL, reported recurrence rates of 27% and 24% in patients treated with the Nd:YAG laser and the CO_2 laser, respectively. Gendelman et al. (1993) found no significant differences in a sample of 8 patients with OLs treated with the Nd:YAG and CO_2 lasers.

4. Discussion

Oral leukoplakia is considered to be the most potentially malignant lesion of the oral cavity and is associated with the development of OSCC with an annual malignant transformation rate of 1% (Van der Waal, 2009). Therefore, early recognition, management and follow-up should be performed in order to improve long-term survival rates and minimize treatment. Clinical suspicion of oral leukoplakia, should eliminate possible etiological factors (smoking, Candida, dental restorations or mechanical friction) and a subsequent evaluation in 2 weeks is needed. If after this time the injury persists a biopsy is recommended. Incisional biopsy and histopathological examination are the gold standard in the diagnosis of OL although, there may be discrepancies between the results for incisional biopsy compared to excisional biopsy, producing a potential underdiagnosis of dysplastic lesions by 28% and masking an OSCC diagnosis in 9% of the cases (Mogedas-Vegara et al., 2015; Brouns et al., 2014; Goodson et al., 2012; Van der Waal, 2009). Regarding follow-up examinations in patients with OL, there are authors that recommend a tight follow-up every 3 months in the first year, every 6 months in the second year and annually for life thereafter, but there is currently no evidence about the possible value of follow-up (Mogedas et al., 2015; Kumar et al., 2013; Van der Waal, 2009). To our knowledge this is the first systematic review of OL treatment with the CO_2 laser.

CO_2 laser has been used for OL excision or evaporation for more than 30 years. Given that it is a very precise tool associated with minimal complications and good disease control, it has become a common procedure for OL treatment worldwide.

One of the most important issues relating to CO_2 laser treatment is recurrence and malignization rates, reported in the literature as ranging between 3 and 1% and 40.7% and between 0% and 15.4%, respectively, for follow-up from 1 to 6.4 years. Some authors have used the term cumulative disease-free survival (DFS) in order to avoid confusion in reporting recurrence rates per lesion or per patient. Chiesa et al. (1993) reported DFS rates of 70.7% and 51.5% at 3 and 5 years, respectively; Chandu and Smith (2005) reported DFS rates of 55.4% (95% CI; 38.3–72.5) after 3 years and of 33.9% (95% CI; 10.2–57.5) after 5 years; Pedrosa et al. (2015) reported an overall DFS rate of 88% after 1-year follow-up. Since it seems that recurrence is unavoidable due to field cancerization, tight follow-up is advisable (Slaughter et al., 1953; Yang et al., 2011; Mogedas-Vegara et al., 2015). The treatment of other oral lesions such as erosive lichen planus with CO_2 laser, appears to influence the recurrence rate, as well as the malignant transformation to oral OSCC, but further randomised prospective clinical trials are needed (Mücke et al., 2015).

Although several studies have shown that certain factors (high-grade dysplasia, erythroleukoplakia, smoking, alcohol, non-homogeneous or multiple-focus OL, 4-cm or larger lesions, previous malignancies) may be related to higher recurrence and malignant transformation rates, consensus is still lacking so further studies are needed. On the other hand, although there is no evidence that treatment prevents OL developing into OSCC, the transformation rate can be significantly decreased with CO_2 laser treatment (Yang et al., 2011; Jerjes et al., 2012; Brouns et al., 2013, 2014; Pedrosa et al., 2015; Mogedas-Vegara et al., 2015).

The most frequent OL sites in the reviewed articles were the tongue (4 articles) and the cheek (4 articles). Huerta et al. (1999) reported the same percentage of lesions (26.5%) on the tongue and on the cheek. Only one article focused on patients with lesions located only on the lips (Gooris et al., 1999).

The CO_2 laser is a versatile instrument and not only allows vaporization and excision, but also reparation of diseased tissue with also obtaining a satisfactory effect and low complication rate (Huang et al., 2015). In implementing OL treatment with the CO_2 laser, there is no standardized protocol of how to carry out the procedure. While some authors excised the lesion (Del Corso et al., 2015), there are others that vaporized the lesion (Huerta et al., 1999; Gooris et al., 1999; Dunsche et al., 2000; Van der Hem et al., 2005; Chandu et al., 2005; Deppe et al., 2012; Brouns et al., 2013; Pedrosa et al., 2015; Mogedas-Vegara et al., 2015) and yet others combined both approaches (Thomson et al., 2002; Yang et al., 2011). The need for an accurate pre-operative biopsy specimen which is as representative as possible of the lesion as a whole, to ensure ablation of a carcinoma is not occurring, is mandatory. This is especially important if only vaporization of the OL is performed due to the impossibility of examining the whole lesion histologically (Goodson et al., 2012; Chandu, 2005). Del Corso et al., were the first group that compared the excision and the vaporization of OL, but this study was made with different lasers (the CO_2 and the Nd:YAG respectively) (Del Corso et al., 2015). It seems that

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small lesions may be successfully treated either by excision or vaporization, whereas larger, multiple and not well circumscribed lesions may be better treated with vaporization in order to avoid retractions and functional problems in large lesions and minimize postoperative pain. Multifocal cases of OL seems that are at more risk of recurrence due to the "field of cancerization" and multiple biopsies ("field mapping") should be considered, but there is no special protocol for treating this situation. There is a low level of evidence regarding this topic and further studies comparing the two techniques, with the CO_2 laser, in terms of effectiveness and whether they affect recurrence and malignancy rates, should be conducted (Del Corso et al., 2015; Mogedas et al., 2015; Yang et al., 2011; Chandu et al., 2005).

Although different CO_2 laser methods have been used, the classical defocused continuous wave technique seems to be the most effective in terms of minimizing the risk of recurrence, probably because it penetrates deeper and destroys more dysplastic cells (Deppe et al., 2012).

The complications rate — only reported in 8 studies and mostly pain-related — ranged from 0% to 13.8%. Apart from pain, other complications reported were mental nerve paraesthesia, lingual nerve paraesthesia, headache, sialadenitis, granuloma formation and bleeding (Chu et al., 1988; Thomson et al., 2002; Chandu et al., 2005; Yang et al., 2011; Jerjes et al., 2012; Brouns et al., 2013; Pedrosa et al., 2015; Mogedas-Vegara et al., 2015).

For postoperative care most studies recommended a 0.12% chlorhexidine mouthwash and non-steroidal anti-inflammatory drugs or paracetamol (Roodenburg et al., 1991; Huerta et al., 1999; Van der Hem et al., 2005; Jerjes et al., 2012; Brouns et al., 2013; Mogedas-Vegara et al., 2015).

Only 3 articles compared the CO_2 laser and cold knife surgery for OL treatment, but it seems advisable to recommend the former as it is associated with less postoperative pain, swelling and scarring and also leads to better intraoperative haemostasis control. The margins needed to clear a specimen is also better for the CO_2 laser. The reviewed literature contained no randomized trials that compared traditional scalpel and CO_2 laser in terms of recurrence and malignant transformation.

Although other laser systems (Nd:YAG and KTP) have also been proposed for OL treatment, few studies have directly compared their efficacy. Since there is still no consensus on their superiority, the CO_2 laser continues to be the workhorse for OL treatment.

5. Conclusions

Treatment of OL with the CO_2 laser is a reliable, reproducible technique associated with low complications and morbidity rates and suitable for routine practice. Because of the high recurrence and malignant transformation rates, tight follow-up and patient education to eliminate risk factors are recommended. Randomized controlled trials are needed to establish indications and effectiveness of the different surgical methods for treating OL, especially in terms of recurrence and malignant transformation.

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