International Journal of Sciences & Applied Research

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NON-PHARMACOLOGICAL TREATMENTS FOR ORAL LEUKOPLAKIA: A REVIEW

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ABSTRACT

Oral leukoplakia (OLK) is one of the most typical precancerous lesions in oral striae disease, with a high incidence rate and high possibility of cancerization. At present, the clinical treatment methods for oral leukoplakia can be divided into pharmacological and non-pharmacological treatments, the latter mainly includes laser, surgery, microwave, cryotherapy, and photodynamic therapy. Compared with pharmacological treatment, non-pharmacological treatment has a wide range of indications and quicker results, so it is widely used in the clinical treatment of OLK. Of course, there are certain limitations. This article systematically organizes and reviews the non-pharmacological treatment of OLK at home and abroad, to provide relevant references for the clinical treatment of OLK.

Keywords: Oral Leukoplakia; Precancerous Lesions; Epithelial Dysplasia; Non-pharmacological Treatment;

INTRODUCTION

Oral leukoplakia (OLK) is a precancerous lesion that occurs on the oral mucosa and cannot be wiped off, nor can be diagnosed as other definable white lesions by clinical and histopathological methods(Chen et al., 2021). The majority of OLK can remain benign for a long time, and only a small proportion will develop into cancer(Villa and Sonis, 2018). The etiology of OLK is complex and the pathogenesis is unknown. The pathological changes of OLK include surface epithelial hyperplasia with hyperkeratosis, thickening of the spinous layer, and inflammatory cell infiltration in the lamina propria and submucosa, and the malignant potential of OLK increases with the degree of abnormal epithelial hyperplasia(Li et al., 2021). The most common sites of OLK are the tongue and cheek, and the disease is at high risk when it occurs in the three risk areas. It can be clinically manifested as plaque, granular, wrinkled paper, wart-like, ulcer-like, etc. Non-homogeneous leukoplakia is more closely related to abnormal epithelial hyperplasia and carcinoma(Warnakulasuriya et al., 2007). How to detect and treat OLK in time and control its cancerization is a hot issue concerned by the field of stomatology at home and abroad. Currently, the treatment methods for OLK mainly include pharmacological, and non-pharmacological treatment. Laser therapy, surgical therapy, microwave therapy, photodynamic therapy, cryotherapy, and other non-drug therapies have quick effects and wide indications, so they are widely used clinically(De Pauli Paglioni et al., 2020). This article summarizes the non-pharmacological treatment methods commonly used in clinical practice to provide some references for the treatment of OLK and subsequent clinical research.

1. Surgical Treatment

Traditional surgical treatment refers to the excision of leukoplakia with a scalpel. The traditional view is that surgical resection of lesion tissue and histopathological biopsy is the gold standard for the treatment of oral leukoplakia, and the degree of epithelial dysplasia is the most important predictor of malignant transformation in OLK(Evren et al., 2020). The risk of malignant transformation of heterogeneous OLK is higher than that of homogeneous OLK, and the risk of malignant transformation is higher in OLK occurring in the lateral edge of the tongue and the floor of the mouth.

Speight et al.(Speight et al., 2018) concluded that surgical treatment may be considered for homogeneous oral leukoplakia occurring on the laterally outer edge of the tongue and floor of the mouth without significant improvement after the removal of irritants. Sundberg et al.(Sundberg et al., 2019) collected and studied the clinical data of 180 patients with OLK, in which 57.0% of patients had oral leukoplakia lesions surgically removed and the cumulative recurrence rate was 49.0% at 5 years after surgery, so surgical treatment can not completely prevent recurrence and malignancy of oral leukoplakia. It has been suggested that the main cause of recurrence or malignancy in oral leukoplakia may be incomplete excision of the oral leukoplakia lesion and "regional carcinogenesis", where abnormal molecular alterations in the normal mucosa surrounding the epithelial tumor may occur, making the epithelial cells more susceptible to malignancy and leading to tumor development (Cai et al., 2018). Taketo et al.(Taketo et al., 2017) reported that the risk of OLK recurrence could only be reduced by complete excision of all abnormal epithelial areas. The latest version of "Evidence-Based Guidelines for the Clinical Diagnosis and Treatment of Oral Leukoplakia" in 2021 points out that clinicians should consider comprehensively before surgical treatment of oral leukoplakia: degree of abnormal epithelial hyperplasia, leukoplakia type, lesion location, lesion size, presence or absence of Candida Or human papillomavirus infection, age and sex of patients, and other systemic diseases(Chen et al., 2021).

Traditional surgical treatment is indeed effective, but there are many problems and shortcomings, such as general anesthesia increases postoperative risk, a large range of lesions needs to be resected in stages, bleeding is easy during the operation, and it is difficult to repair the leftover defect with skin grafting, Primary medical institutions are difficult to promote and so on.

2. Cryotherapy

Cryotherapy refers to the use of liquid nitrogen as a cooling source to destroy or resect OLK lesion tissue in a controlled manner at a local low temperature (Yu et al., 2014). Slow degeneration and necrosis of the focal mucosa first occur on the frozen wound, followed by granulation tissue hyperplasia, and then the peripheral mucosal epithelium grows in. A sufficiently large cry surrounding area is very important in cryotherapy, and further research is needed on the recurrence and cancerization of the edge of the primary tumor. Lin et al. (Lin et al., 2012)treated 54 patients with OLK with a cryogen. After treatment, all lesions completely subsided, and all patients had hyperemia, edema, and superficial necrosis with obvious pain, and most of them healed within 2 weeks. Chen et al. (Chen et al., 2015) treated 72 patients with OLK with a cryogen, and all lesions completely disappeared after treatment. During the average follow-up period of 18 months, the recurrence rate was 11.1%, and no malignant transformation occurred, but 76.4% of the patients experienced moderate to severe pain, which could be controlled with pain medication. It can be seen that cryotherapy has the advantages of being safe and effective, good prognosis, and low recurrence rate. At the same time, there are limitations such as obvious local reactions after treatment and severe pain in patients.

Therefore, clinically, the indications for cryotherapy should be strictly selected, the number of cryotherapies should be determined according to the lesion size of oral leukoplakia patients, and pharmacological intervention should be used in time after treatment to reduce the postoperative reactions of patients.

3. Laser Treatment

The biological effect, photochemical effect, electromagnetic field effect, and thermal effect of laser technology can effectively inhibit the growth of germs and promote blood circulation. The cauterization, vaporization, and other functions of the laser have a remarkable effect on the treatment of oral leukoplakia and lichen planus. At the same time, laser therapy has the characteristics of good hemostatic effect, clear surgical field, no need for sutures, and less damage to adjacent tissues, so it has attracted much attention in the treatment of oral leukoplakia.

3.1 CO_2 Laser

The CO_2 laser is a gas laser that can cut and gasify tissues. The applied power is generally 10 W to 25 W when treating leukoplakia. It has been reported that CO_2 laser treatment has an obvious curative effect, low recurrence rate, and low malignant transformation rate(Dong et al., 2019; Mogedas-Vegara et al., 2015; Van Der Hem et al., 2005). The study by Giacomo et al. showed that CO_2 laser has a better curative effect and lower recurrence rate than Nd: YAG laser (Del Corso et al., 2015). At present, there are many cases of CO_2 laser treatment of OLK clinically, and the clinical results are relatively clear. However, factors such as the mode of laser application, the extent and depth of lesion cutting, and the nature and location of lesions can affect the recurrence of OLK after CO_2 laser treatment(De Pauli Paglioni et al., 2020). Therefore, the application of this treatment method also has certain limitations.

3.2 Nd: YAG Laser

Nd: YAG laser is a solid-state laser with a wavelength of 1064 nm. This laser can be used for the excision and coagulation of oral leukoplakia lesions in contact or non-contact mode. The appropriate treatment mode can be selected according to the location and degree of the lesion. Das et al.(Das et al., 2015) used Nd: YAG laser to treat 42 cases of OLK patients, the recurrence rate after treatment was 4.8%, and the recurrent lesions subsided after retreatment. Vivek et al. (Vivek et al., 2008) found that OLK patients had no complications such as bleeding and paresthesia after Nd: YAG laser treatment, and believed that Nd: YAG laser treatment of oral leukoplakia is a safe and effective method with good hemostatic effect and few complications, no need for anesthesia, low recurrence rate and good healing.

3.3 KTP Laser

KTP is a frequency-doubled Nd: YAG laser with a wavelength of 532 nm, which can be used for coagulation and excision of oral leukoplakia. Clinically, KTP laser treatment of oral leukoplakia has a lower recurrence rate and longer average recurrence time than CO_2 laser treatment of oral leukoplakia (Lim et al., 2010). However, the KTP laser has a short wavelength and low absorption of water, so it can penetrate water to reach deep tissues, causing greater thermal damage to surrounding tissues and increasing postoperative reactive pain (De Pauli Paglioni et al., 2020).

3.4 Semiconductor Laser

The semiconductor laser is a soft tissue laser located in the infrared band, which mainly produces thermal effects on biological tissues. The laser is widely used in oral and maxillofacial surgery because of its high cutting efficiency, good coagulation effect, and less damage to surrounding tissues. Kharadi et al. (Kharadi et al., 2016)treated 10 patients with homogeneous OLK with a semiconductor laser, and the clinical complete remission rate was 100.0%, and no complications occurred during the 1-month follow-up. When a semiconductor laser is used to treat leukoplakia of oral mucosa, the thermal penetration to the surrounding tissue is large, so the recurrence rate and cancerization rate after treatment are relatively lower than those of water laser and CO_2 laser(De Pauli Paglioni et al., 2020). However, there are few clinical reports on semiconductor laser treatment of oral leukoplakia, and its long-term efficacy needs further observation and research.

3.5 Er: YAG LASER AND Er, Cr: YSGG Laser

Er: YAG laser is a solid-state laser with a wavelength of 2940 nm, which can be used for soft tissue ablation; Er, Cr: YSGG laser has a wavelength of 2780 nm, which can use high-speed kinetic energy to cut tissue. These two lasers have a high absorption rate to water, cause little thermal damage to surrounding tissues, and have little impact on pathological diagnosis, so they can be applied not only to soft tissues but also to hard tissues. Monteiro et al.(Monteiro et al., 2017) found that Er: YAG laser treatment of OLK has a high recurrence rate, so further clinical verification is needed for its efficacy. According to Arduino et al. (Arduino et al., 2018), The Er: YAG laser treatment of OLK has the same curative effect as a traditional scalpel, the recurrence rate in the past 5 years is the same, and the postoperative wound heals well without obvious complications. Matuliĉ et al. (Matulić et al., 2019) applied Er: YAG laser and Er, Cr: YSGG laser to treat OLK, and found that the degree of a residual lesion in the Er: YAG laser group was significantly higher than that in the Er, Cr: YSGG laser group and there was no recurrence within 1 year after the second treatment, without scar formation.

In summary, laser treatment of OLK has a significant curative effect and has the advantages of a low recurrence rate, good hemostatic effect, relatively small tissue damage, and simple operation. The CO_2 laser is the most widely used, and its curative effect is generally recognized; Nd: YAG laser treatment has a low recurrence rate and excellent hemostatic effect; KTP laser treatment is effective, but the tissue thermal damage is large, and it is easy to increase reactive pain; the reports of semiconductor laser treatment of OLK are limited, and its effectiveness is unclear; The Er: YAG laser treatment and the Er, Cr: YSGG laser treatment is effective, and there is no obvious postoperative complication. However, there is currently a lack of high-quality prospective randomized controlled clinical trials comparing the efficacy of various lasers on oral leukoplakia, and the research on the recurrence rate and malignant transformation rate of laser treatment of OLK is still shallow.

4. Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) is a new type of non-invasive treatment method, whose three elements are photosensitizer, light of appropriate wavelength, and oxygen dissolved in cells. PDT can use its cytotoxic and vascular toxic effects on diseased tissues to treat oral mucosal lesions. It has achieved certain curative effects in the treatment of cancer recurrence or elderly cancer patients who cannot tolerate surgery, radiotherapy, and chemotherapy(Simple et al., 2015). The first generation of photosensitizers is porphyrins, which have more affinity for tumor tissue than normal tissue, but they have low chemical purity, low tissue penetration depth, and highly toxic side effects(Obaid et al., 2016). Thesecond-generation photosensitizers mainly include porphyrin derivatives, bacteriochlorophylls, dihydro porphyrins, phenothiazines, phthalocyanines, etc. They have high chemical purity, high single-linear oxygen generation rate, and can penetrate deep tissues, but poor water solubility limits the route of administration(Kwiatkowski et al., 2018), and are mainly used for deep tumor therapy. Third-generation photosensitizers mainly increase tissue targeting based on the second-generation, which have a higher affinity for tumor tissues and higher selectivity, reducing the damage to healthy tissues during PDT treatment, such as glycosylated photosensitizers, activated photosensitizers, and polymeric photosensitizer nanoparticles(Kwiatkowski et al., 2018; Obaid et al., 2016). 5-Aminolevulinic acid is the most widely used photosensitizer in PDT for OLK due to its low molecular weight, short phototoxicity, good tissue permeability, and high singlet oxygen production(Chen et al., 2019). Exogenous 5-aminolevulinic acid (5-ALA)-mediated PDT has been used in a variety of oral and cervical tumors, including early-stage oral squamous carcinoma, with a good prognosis. Figueira JA et al. found good clinical results with topical application of 20% 5- ALA as a photosensitizer, using LED lights for 15 minutes at 7-day intervals(Figueira and Veltrini, 2017). However, some clinical reports have shown the recurrence of head and neck tumors after PDT treatment, suggesting some limitations of this therapy(De Visscher et al., 2013).

PDT has a broad anti-tumor spectrum, high target specificity, low damage to normal cells and organs, low systemic toxic side effects, and can be repeatedly treated. Li et al. (Li et al., 2019) conducted a meta-analysis on PDT treatment of OLK, including a total of 352 OLK patients, and the statistical results showed that the overall remission rate was 76.1%, and the recurrence rate was 0-60.0%. Han et al. (Han et al., 2019)found that PDT using aminolevulinate in the treatment of oral leukoplakia patients with moderate to severe dysplasia was more effective than patients without abnormal hyperplasia, and the treatment time required per square centimeter of the lesion was less. Wang(Wang et al., 2019)et al. suggested that for OLK patients with epithelial hyperkeratosis, Plummer acupuncture with PDT could be effective.

To sum up, PDT has the advantages of high efficiency, minimal invasiveness, fewer adverse reactions, and good selectivity in the treatment of oral leukoplakia. However, the application of PDT in the field of the oral cavity is still short, and there are still some problems and challenges, such as the clinical treatment standard of PDT is not unified and standardized, the selection of indications is not clear, the use of photosensitizers and the adjustment of treatment parameters are relatively difficult. Therefore, future clinical trials still need to expand the sample size, clarify the mechanism of its treatment of OLK, and conduct long-term follow-up observations.

5. Microwave Treatment

Microwave is a high-frequency electromagnetic wave with a wavelength of 1 mm to 1000 mm and a frequency of 300 MHz to 300000 MHz. Due to the polarity of water molecules in human tissue, when a microwave antenna is placed in a diseased tissue to emit electromagnetic waves, the oscillating charge generated by the microwave radiation will cause the water molecules to flip, and the violent movement of the water molecules will generate friction and heat, thereby inducing coagulation necrosis. Tissue cell death is widely used clinically in the treatment of benign tumors(Du et al., 2018; Jingjing et al., 2010). At present, the research on microwave treatment of oral leukoplakia is still insufficient, and its long-term efficacy remains to be observed.

SUMMARY

The clinical treatment methods for oral leukoplakia mainly include drug therapy and non-drug therapy. The relative advantages of non-drug therapy make it the main choice for the clinical treatment of OLK. However, there is no unified opinion on the treatment of OLK in the field of stomatology.

Surgical resection is currently one of the more commonly used methods for the treatment of OLK. However, surgical excision is more traumatic, and scarring may occur after surgery. Sometimes general anesthesia or even skin grafting is required, which has a certain impact on patients' oral function and is difficult to promote at the grassroots level. Some scholars believe that too frequent surgical excision may induce malignant transformation of leukoplakia, so it is not always the first choice for treatment. Laser therapy is more and more widely used in clinical practice due to its advantages of simple operation, less blood loss during operation, good field of view, less pain for patients, and smaller postoperative scar. Sufficient, so its long-term efficacy needs to be clinically verified. Cryotherapy is also a treatment for oral leukoplakia. Cryotherapy and laser therapy are more minimally invasive than surgical resection and can be used to treat leukoplakia that is not suitable for surgical resection, but these treatments cannot mobilize the body's immune response, nor do they have the property of selectively targeting abnormally proliferating cells.PDT treatment of OLK is more targeted, minimally invasive, and less toxic than laser, freezing, and other methods, so it can effectively reduce the recurrence of leukoplakia. In addition, its therapeutic effect is relatively certain, and it has the advantages of fewer adverse reactions, safety and effectiveness, and repeatable treatment in clinical practice, so it has been paid more and more attention and application. However, the indications and long-term efficacy of PDT need further study.

To sum up, from the perspective of evidence-based medicine, there are many options for the treatment of oral leukoplakia (OLK), but there is still a lack of standard and effective treatment methods. When choosing a treatment method for OLK, we should maximize our strengths, avoid weaknesses, and use them in combination if necessary. In addition, once oral leukoplakia is diagnosed, no matter whether the patient has any high-risk factors for cancer, whether to take active treatment or choose what kind of treatment method, you should have Regular follow-up and close observation.

Conflict of interest statement

The authors report no conflicts of interest.

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