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PERSPECTIVE

Cryogun cryotherapy is the first-line treatment of choice for oral leukoplakia

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Oral leukoplakia (OL) is the most common oral precancerous lesion. Histologically, approximately 90% of OL lesions show hyperkeratosis and/or epithelial hyperplasia, 5% show epithelial dysplasia or carcinoma *in situ*, and another 5% show invasive carcinoma. The malignant transformation rates of OL lesions have been reported to be 1–7% for homogenous thick leukoplakia, and 4–15% for granular or verruciform leukoplakia.[1–3] The relatively high malignant transformation rates of OL lesions highlight the importance of early detection and treatment of OL lesions.

Although OL lesions can be eradicated by surgical excision, laser surgery, and photodynamic therapy, cryotherapy is also an effective and alternative treatment modality for OL lesions.[1–5] Cryotherapy is a method that locally destroys lesional tissues by freezing *in situ*. It has several advantages including being a bloodless treatment, has a very low incidence rate of secondary infections, and has a relative lack of scarring and pain.[1–3] Cryotherapy can be carried out with either a "closed" or an "open" system.[1–3] Closed-system cryotherapy offers a greater degree of temperature control but requires complex, delicate, and expensive equipment. Open-system cryotherapy involves directly applying the cryogen to the lesion with either a cotton swab[2] or a portable spray apparatus such as a cryogun (Brymill Corp., Ellington, CT, USA).[3] When performing open-system cryotherapy, it is more difficult to maintain a constant lower temperature in the lesional tissues during the whole treatment period. However, it does not require expensive equipment. Cotton-swab cryotherapy is suitable for the treatment of small OL lesions,[2] but cryogun cryotherapy can be used for the treatment of medium and large OL lesions with either smooth or rough surfaces.[3]

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The mechanisms for cell destruction after cryotherapy are complex, involving a combination of both direct and indirect effects.[1–3] Direct effects consist of extracellular and intracellular formation of ice crystals which in turn disrupt cell membranes, cellular dehydration, toxic intracellular electrolyte concentration, inhibition of enzymes, protein damage, thawing effects that cause the cell to vacuolate, swell, and rupture, and thermal shock injury to cells.[1–3] Indirect effects include vascular changes that lead to ischemic necrosis of the treated tissue and immunological responses that cause cell damage through a cytotoxic immune mechanism.[1–3]

Our previous study used the cotton-swab cryotherapy to treat 60 OL lesions and found complete regression of all OL lesions after an average of 6.3 treatments.[2] For comparison, we used the liquid nitrogen spray with a cryogun (cryogun cryotherapy) to treat 60 OL lesions and discovered complete regression of all OL lesions after an average of 3.1 treatments.[3] Cryogun cryotherapy seems more efficient than cotton-swab cryotherapy for the treatment of OL lesions, because the former needs approximately half the number of treatments to achieve complete regression of nearly equal-sized OL lesions compared to the latter. In fact, the cotton swab carries only a small amount of liquid nitrogen that cannot maintain a constant low temperature in the treated OL lesional tissues. On the contrary, cryogun can deliver onto the OL lesional surface a relatively large amount of liquid nitrogen that can maintain a more constant, lower temperature in treated OL lesional tissues. This can further explain why the cryogun cryotherapy is more efficient in the treatment of OL lesions than the cotton-swab cryotherapy. In addition, we also discovered that when OL lesions are treated by either cotton-swab or cryogun cryotherapy, those OL lesions on oral mucosal sites other than the tongue, smaller than 2 cm,[2] with epithelial dysplasia, or with a surface keratin thickness < 55 μm require significantly fewer cryotherapy treatments to achieve complete regression of the OL lesions than the corresponding OL lesions.[2,3] Recently, we used cryogun cryotherapy to treat 72 OL and adjacent smoking-induced melanosis (OLM) lesions. We found that complete regression was achieved in all 72 OLM lesions after a mean of 3.3 ± 1.3 cryogun cryotherapy treatments. OLM lesions in patients without smoking habit, with the greatest diameter < 2.8 cm, with epithelial dysplasia, or with a surface keratin thickness ≤ 50 μm needed significantly fewer cryogun cryotherapy treatments to achieve complete regression of the OLM lesions than the corresponding OLM lesions.[4] Therefore, we suggest that cryogun cryotherapy is also an effective treatment modality for OLM lesions.

Our previous studies found that topical 5-aminolevulinic acid-mediated photodynamic therapy (topical ALA-PDT) is very effective for oral erythroleukoplakia and oral verrucous hyperplasia lesions, but is less effective for OL lesions.[5] However, when topical ALA-PDT is combined with cryotherapy, the combination therapy may be an effective treatment modality for OL lesions.[5] Chang and Yu[6] used topical ALA-PDT and then cryogun cryotherapy to treat a large oral verrucous hyperplasia lesion in the same treatment and achieved complete regression of the lesion after six treatments of combination therapy. Actually, cryogun cryotherapy can also be used before topical ALA-PDT in the same treatment to facilitate the diffusion of ALA into the precancerous epithelial cells and to improve the clinical outcome of topical ALA-PDT.[5,7] The efficacy of topical ALA-PDT can also be enhanced by pretreatment with methotrexate. Pretreatment of SCC4 cells with 0.001 mg/L methotrexate for 72 hours results in a significant increase in methotrexate-ALA-PDT-induced killing of SCC4 cells.[8] In addition, topical methotrexate pretreatment can increase intracellular protoporphyrin IX production in hamster buccal pouch precancerous lesions and significantly improves the outcomes of the precancerous lesions treated with topical ALA-PDT.[9] The aforementioned findings suggest that topical ALA-PDT combined with either cryotherapy or methotrexate pretreatment has a high potential to be used for treatment of OL lesions.

Compared to topical ALA-PDT or combination therapy, cryogun cryotherapy is a simple, easy, cheap, less-painful, effective, and acceptable treatment modality for OL lesions.[1–3] Therefore, we conclude that cryogun cryotherapy can serve as the first-line treatment of choice for OL lesions. Moreover, cryogun cryotherapy is also an effective treatment modality for OLM lesions.[4]

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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