Letter to Editor

Use of pure nicotine for the treatment of aphthous ulcers

Editor,

We aimed to evaluate the therapeutic effect of pure nicotine on recurrent aphthous ulcers (RAUs). These lesions are characterized by the formation of painful oral ulcers that are usually isolated, but may also be found in clusters. Cigarette smoking has been reported to be protective against RAUs.[1] These ulcers are less common among users of smokeless tobacco than non-users,[2] and among smokers than non-smokers.[3]

There are two probable theories regarding the preventive effect of smoking on RAUs:

1. Cigarette smoking prevents aphthous ulcers by causing an increase in localized keratinization of the oral mucosa; alternatively,
2. Nicotine via several possible mechanisms could modulate local immune responses, as it has been shown to induce T-cells anergy[4] and inhibits the production of pro-inflammatory cytokines, such as interleukin (IL)-2, IL-6, IL-8, IL-10 and tumor necrosis factor α.[5-7] It can also activate the release of adrenocorticotrophic hormone and cortisol,[8] leading to further suppression of inflammatory pathways.

The second mechanism is more acceptable as Bazrafshani *et al*. linked the minor aphthous ulcers to pro-inflammatory cytokines, including IL-1B and IL-6.[9] In addition, as shown in an animal study, the therapeutic role of pure nicotine can be related to the promotion of angiogenesis and wound healing via the activation of nicotinic acetylcholine receptors.[10] The theory that nicotine is known as the protective factor is also supported by three case reports, in which aphthous ulcers were prevented or healed while the patients used nicotine replacement materials.[11-13]

Nicotine replacement materials are available in various types, such as chewing gums, transdermal patches, tablets, and lozenges. It is worth mentioning that a number of studies have reported that pure nicotine (not the other components of tobacco) is a safe component, although it depends on the dose. Transdermal nicotine did not cause a significant increase in cardiovascular events in high-risk outpatients with cardiac disease.[14,15] A review of adverse effects did not find evidence of excess adverse cardiovascular events related to nicotine patches.[16] Nicotine gum used in another study,[17] appeared to be safe and unrelated to any cardiovascular illness or other serious side effects; however, about 25% of nicotine gum users reported at least one adverse effect, while most were very minor and transient. The considerable side effects mostly reported with nicotine gum, including hiccoughs, gastrointestinal disturbances, jaw pain, and oral problems (e.g., mouth or throat irritation, and excessive salivation), are not seen with transdermal patch.[18] The only side effect which appears with the use of the nicotine patch is skin sensitivity and irritation. This might affect up to 54% of patch users, but it is usually mild.[18]

Until date, tobacco has had only a prophylactic role against aphthous ulcers, therefore the role of submerged nicotine in tobacco, as a therapeutic factor should be taken into account. We tried to conduct a review about the role of pure nicotine for preventing aphthous ulcers, yet there were only three available case reports considering this issue. Initially during 1991, as part of a case report, three non-smoking patients with RAUs were prescribed to use nicotine tablets. In each case the ulcers healed and new ulcers did not appear during the nicotine therapy.[11] Afterwards, another interesting report suggested that using nicotine replacement patches may regress aphthous ulcers. This study was based on a woman suffering from Behcet's syndrome, who was a former smoker and after cessation, nicotine replacement patches were prescribed to treat her ulcers. This led to regression of all her ulcers.[13] Later, another study reported a case of complex aphthosis where the patient began to have aphthous ulcers, once she had quit smoking. This patient was treated by the use of nicotine lozenges as well.[12] The dosing was different in these reports. Bittoun prescribed up to 8 mg nicotine/day,[11] while Scheid *et al*. suggested 14 mg/day,[13] and in the study of Hill *et al*. the initial dose was 15 mg of nicotine/day, and after withdrawal of the replacement therapy, intake of only a lozenge containing 5 mg nicotine resolved the recurrent ulcers within the first 24 h.[12] Obviously, there is no consensus on the effective dose of nicotine replacement materials to prevent or cure the RAUs. It should be noticed that the dosing for aphthous treatment is lower than that used for smoking cessation; hence, the side effects could be lower, as in the study of Hill *et al*.[12] no side effects were noted when using nicotine lozenges.

To summarize, the use of pure nicotine in therapeutic forms, seems to be a proper alternative to treat aphthous ulcers; however, there has not been any evidence-based case-control study to prove such claim.

Considering all the above-mentioned points, we have two suggestions for future research:

1. Case-control studies should be performed, investigating whether the use of a nicotine replacement material upon occurrence of aphthous ulcer primary symptoms (in the first 24-48 h, inspired from Hill *et al*.'s study[12]) is efficient or not. Nicotine might be useful even after the ulcers have occurred to regress and heal the ulcers.
2. Case-control studies should be performed, determining the influence of nicotine replacement material intake for longer periods by smoking or non-smoking individuals (inspired from the latter of the three above-mentioned case reports). This long-term protocol might be useful for patients suffering from consecutive RAUs by preventing ulcer recurrence.

Conveying such studies might be helpful to reach a clinical method to cure painful aphthous ulcers using pure nicotine rather than corticosteroids, which have several side effects. In addition, more likely factors responsible for preventing or treating aphthous ulcers (keratinization or modulation of immune response) could be marked.

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