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REVIEW ARTICLE

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Doxycycline: An option in the treatment of ulcerated oral lesions?

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Abstract

What is known and objectives: In addition to its antimicrobial effect, doxycycline has potent anti-inflammatory activity. In view of these pharmacological characteristics, its use in the management of inflammatory, autoimmune and granulomatous diseases has been proposed. The objective of this study was to investigate, through a systematic literature review, the effect of doxycycline on pain and healing of ulcerated lesions of the mouth.

Methods: An electronic search was performed in accordance with PRISMA guidelines in PubMed, Cochrane Central Register, Web of Science, Bireme/LILACS and Scopus databases. Controlled, randomized clinical trials were selected. The concentration of doxycycline, frequency of application, pain relief and clinical remission of the lesions were analysed.

Results and discussion: According to the inclusion criteria, five articles were selected. In four of these studies, doxycycline was used in the treatment of aphthous stomatitis, and in one study, it was used in the treatment of herpes labialis. In all studies, the drug was used topically, both as a hydrogel and as a crushed tablet (along with a prosthetic adhesive). The groups treated with doxycycline showed faster healing of lesions and lower pain scores compared to placebo.

What is new and conclusion: The present study suggests that topical doxycycline has a positive effect on the treatment of recurrent aphthous ulceration and herpes labialis. Experimental animal studies and double-blind randomized clinical trials should be performed on other oral lesions, such as traumatic ulcers and mucositis.

KEYWORDS
aphthous stomatitis, doxycycline, herpes labialis, oral ulcer

1 | WHAT IS KNOWN AND OBJECTIVES

Ulcerated lesions are frequent in the oral mucosa and can be caused by trauma, drugs, chemicals, hypersensitivity reactions, autoimmune disorders and infectious processes, among others.[1-3] Usually, they are covered by a yellowish-white pseudomembrane and surrounded by erythematous halo, and they can cause substantial painful symptomatology. According to duration and frequency, oral ulcers are classified as acute, chronic and recurrent, and may be single or multiple.[3] The variety of aetiological factors often makes its

clinical management challenging.[4] The time of repair is variable and dependent on the aetiological nature. However, continuing trauma and secondary infections may exacerbate the inflammatory condition and make it persistent.[3] Interventions to prevent such clinical episodes are necessary. Drugs such as corticosteroids, antibiotics, anaesthetics, anti-inflammatories, antihistamines and antiseptics have been used topically and/or systemically to promote the healing process and decrease the painful symptoms of patients.[5-8]

Doxycycline is an antibiotic chemically derived from 1st generation tetracyclines. It has broad-spectrum bacteriostatic action, inhibiting bacterial protein synthesis by binding to the 30S ribosomal subunit of both gram-positive and gram-negative bacteria.[9] This drug also acts on the 40S ribosomal subunit, which is specific to mammalian cells, implying lack of specificity.[10] In 1983, Golub et al[11] demonstrated that tetracyclines possess potent anti-inflammatory activity independent of their antimicrobial action, inhibiting collagenase activity in rat gingival tissue. Since then, studies on these mechanisms have been conducted, demonstrating that doxycycline at sub-antimicrobial doses, from 20 to 40 mg per day, has anti-inflammatory activity. Thus, this drug is now prescribed in the treatment of inflammatory, autoimmune, periodontal, granulomatous and acne diseases. Some properties such as regulation of cytokines, antioxidation, inhibition of protease-activated receptor 2 (PAR2), inhibition of matrix metalloproteinases (MMPS), inhibition of collagen breakdown and chemotaxis of leucocytes have been reported as being responsible for its anti-inflammatory effect.[12]

Some studies have suggested the use of doxycycline in the treatment of ulcerated lesions of the mouth, but a consensus has not yet been reached on its efficacy on this type of lesions.[13,14] We carried out a systematic review to investigate the effect of doxycycline on pain and clinical remission of ulcerated lesions of the mouth.

2 | METHODS

We carried out a systematic review on studies investigating the effect of topical and systemic use of doxycycline in the treatment of oral lesions such as traumatic ulcers, herpes simplex, erosive lichen planus, recurrent aphthous stomatitis, oral mucositis, benign mucosal pemphigoid and pemphigus vulgaris. An electronic search was conducted according to PRISMA guidelines in the PubMed, Cochrane Central Register of Controlled Clinical Trials, Web of Science, Bireme/LILACS and Scopus databases. We used the MeSH terms: 'Doxycycline' AND 'Oral Ulcer' OR 'Stomatitis, Aphthous' OR 'Lichen Planus, Oral' OR 'Oral Mucositis' OR 'Stomatitis, Herpetic' OR 'Pemphigus' OR 'Pemphigoid, Benign Mucous Membrane'.

A PICO was stablished:

P—Patients with oral ulcers.
I—Topical and/or systemic doxycycline.
C—*Sham* or other drug.
O—Pain relief, clinical remission.

The last search was conducted on May 2019.

2.1 | Inclusion and exclusion criteria

The software EndNote 7 was used to aid in the selection of articles. We included controlled studies that used doxycycline topically or systemically for the treatment of ulcerated oral lesions. The concentration of doxycycline, the frequency with which it was applied, the substance used as control, pain relief, and clinical remission had to be described. Case reports, reviews, case series, author comments and letters to the editor were excluded.

2.2 | Study design

Initially, the search for articles was carried out by two independent authors in the databases described. After the initial search, the exclusion of articles was carried out by reading the titles and abstracts. At this point, duplicate articles were also removed. If there was not enough information in the abstract, or if there was a divergence in the inclusion and exclusion criteria among the researchers, the article was 7yu66read completely until a consensus was reached.

Data extraction was then performed independently and duplicated by the two reviewers. The following data were collected: study groups, drug concentrations, route of administration, type of oral lesion, duration of follow-up and outcomes. Figure 1 shows the flow chart of the search strategy and the selection of articles.

3 | RESULTS

Five controlled clinical trials were included. In four of these, doxycycline was used in the treatment of minor recurrent aphthous stomatitis [14,15,16,17] and one in the treatment of herpes labialis.[18] No studies were found in which doxycycline had been used for the treatment of oral traumatic ulcers, mucositis, erosive lichen planus, pemphigus vulgaris or benign mucosal pemphigoid. Although it was proposed as an inclusion criterion, we found no study that used doxycycline systemically in the treatment of ulcerated lesions of the oral mucosa.

The quality of clinical trials was assessed by two independent researchers (Table 1). Table 2 describes the selected clinical trials. In these studies, doxycycline was used topically in the form of crushed tablet or hydrogel. Of the five articles selected, three used conventional doses of doxycycline (100-150 mg), [14,16,17]and two used subdoses (1.5 mg/g-0.05%) [15,18]They showed positive results for doxycycline, with faster clinical remission [15-18]and lower pain scores than placebo[14-18].Two studies were randomized single-blind. [14,16]In contrast, the other two selected studies were randomized double-blind. [15,18]Patients with systemic comorbidities were excluded.

Sharma et al[16] compared the clinical efficacy of topical doxycycline, amlexanox, triamcinolone acetonide, benzocaine and placebo on recurrent aphthous stomatitis. Doxycycline was more efficacious in reduction of size and pain compared to placebo, and it was less efficacious than amlexanox and triamcinolone acetonide. These authors describe a double-blind study; however, doxycycline was administered as a powder mixed with denture adhesive and saline in a single application. The

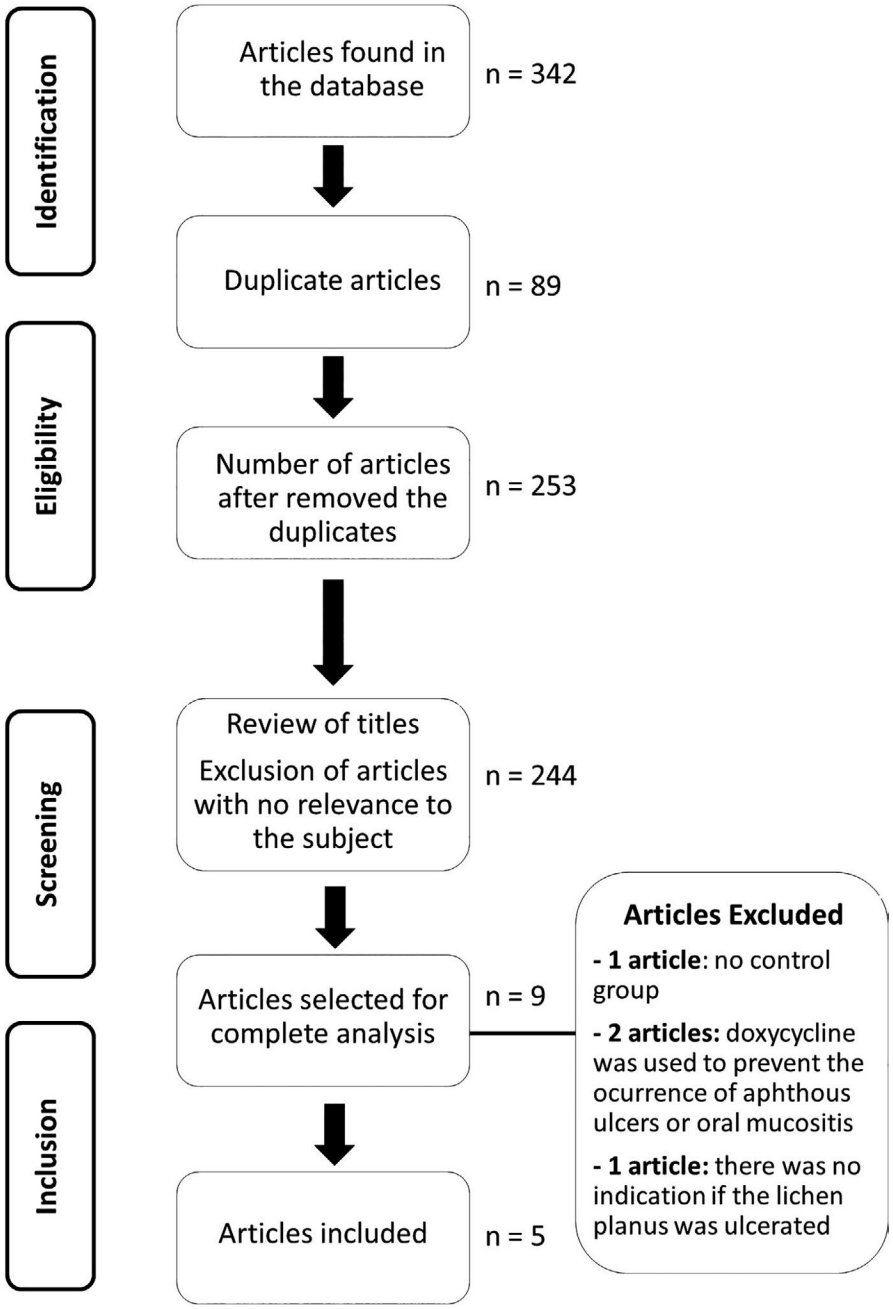

FIGURE 1 Flow chart of selection of articles

other agents were applied 4 times a day, which represents an important bias and may explain the differences between the effects of doxycycline compared to amlexanox and triamcinolone acetonide.

The diagnosis of aphthous stomatitis was established by well-defined clinical criteria. [14-17]The pain scores were evaluated by visual numerical scale[14,15] or by visual analogue scale,[16-18] which are

TABLE 1 Assessment of quality of the studies

Author/year	Randomized	Description of randomization	Patient blind	Observer blind	Description of withdrawals	Total score
Ylikontiola et al. 1997[14]	1	1	0	1	0	3
Skulason et al. 2009[15]	1	1	1	1	1	5
Skulason et al. 2012[18]	1	1	1	1	1	5
Vijayabala et al. 2013[17]	1	1	0	0	0	2
Sharma et al. 2018[16]	1	1	0	1	1	4

Note: 1 = Yes; 0 = Not or no informed.

TABLE 2 Controlled randomized clinical trials investigating the topical use of doxycycline for treatment of oral ulcerated lesions

Author/year	Sample	Type of lesion	Drug used/concentration/frequency of use	Follow-up	Outcomes
Ylikontiola et al. 1997[14]	31 patients	Minor aphthous stomatitis	- Crushed tablet of 150 mg doxycycline + prosthetic adhesive - Placebo + prosthetic adhesive Single application	10 d	The pain was significantly less in the doxycycline group ($P < .05$) compared to placebo. Variables of clinical improvement were not described in this study. Pain was measure by VAS
Skulason et al. 2009[15]	49 patients	Minor aphthous stomatitis	-1.5 mg/g doxycycline hydrogel -Placebo 4 times a day	3 d	68% of ulcers healed in 3 d of treatment in the doxycycline gel group, while in the placebo group, 25% of lesions regressed in this period ($P < .05$). Pain scores (VAS) were also significantly lower in the doxycycline group ($P < .05$). Healing was determined by the subjects as the time when they no longer aware of the presence of the ulcer
Vijayabala et al. 2013[17]	50 patients	Minor aphthous Stomatitis	- Crushed tablet of 100 mg doxycycline + prosthetic adhesive - Placebo + prosthetic adhesive Single application	10 d	Patients treated with doxycycline had less pain at day 1 ($P < .001$) and more rapid involution of lesions ($P < .001$) compared to placebo. Pain also measure by VAS. A graduated periodontal probe was used to measure the ulcer size on its maximum diameter
Skulason et al. 2012[18]	75 patients	Herpes labialis	- 0.5% monocaprin hydrogel - 0.5% monocaprin hydrogel + 0.15% doxycycline - Placebo 5 times a day for 5 d	2 wk	The mean healing time of the lesions was significantly shorter in the monocaprin + doxycycline group in relation to the placebo ($P < .05$). Pain relief (VAS) was significantly greater in the monocaprin + doxycycline group when compared to monocaprin alone and placebo ($P = .0114$). Clinical evaluation was determined by the subjects as the time when they no longer aware of the presence of the lesion
Sharma et al. 2018[16]	50 patients	Minor aphthous Stomatitis	- 5% amlexanox -0.1% triamcinolone acetonide - 20% benzocaine gel - 100 mg doxycycline + prosthetic adhesive - Placebo gel 4 times a day, except for doxycycline (single application)	10 d	0.1% triamcinolone acetonide and 5% amlexanox were more efficacious in reduction of size and pain (VAS) at day 8 ($P = .000^*$) and at day 10 ($P = .000^*$) as compared to single application of 100 mg doxycycline, 20% benzocaine gel and the placebo. Doxycycline was more efficacious in reduction of size and pain (VAS) at day 10 ($P = .000^*$) compared to placebo

Abbreviation: VAS, Visual Analogic Scale.

validated instruments to measure this outcome. Sharma et al[16] evaluated the ulcer size using a millimetre dental probe. On the other hand, in the studies of Skulason et al[15] and Vijayabala et al [17]clinical remission was assessed by self-report of the participants. Ylikontiola et al[14] did not evaluate the clinical remission of the lesions.

Ninety-six participants with herpes labialis met the eligibility criteria and were assigned to the treatment arms in the study of Skulason et al [18]Twenty-one patients dropped out or were excluded from the trial on account of various reasons not related to the drugs. Pain was also evaluated by analogue visual scale and clinical remission by self-report of the participants.

The selected studies totalled a sample of 255 participants, 180 with recurrent aphthous ulceration and 75 with herpes labialis. In the studies that used crushed doxycycline along with prosthetic adhesive, the drug was applied by the healthcare professional in a single dose [14,16,17]This form of application may entail some difficulty in performing the treatment, as well as caution regarding the adhesiveness of the pharmaceutical formulation. On the other hand, in the studies that used the drug in the form of a hydrogel, the applications were performed by the patients themselves four to 5 times a day[15,18].

4 | DISCUSSION

Studies show that in addition to the antimicrobial effect, doxycycline has a potent anti-inflammatory effect. In view of these pharmacological characteristics, some authors have suggested the use of topical and/or systemic doxycycline for the treatment of inflammatory, autoimmune and granulomatous diseases.[11-22] Based on these properties, the present study aimed to review the literature investigating doxycycline as a therapeutic option in the management of ulcerated oral lesions.

In oral medicine, the anti-inflammatory properties of doxycycline have been investigated in periodontal diseases, demonstrating effectiveness as a complementary therapy to conventional scaling treatment.[11,22-25] In this study, nine articles were found in which doxycycline was used in ulcerated oral lesions, with four being excluded because they did not meet the inclusion criteria adopted. Of the selected studies, four evaluated the effect of doxycycline in patients with recurrent aphthous ulceration [14-17]and one in patients with herpes simplex, [18]showing that doxycycline has been little explored in the management of ulcerated oral lesions. Due to the heterogeneity of the studies regarding the duration of treatment, application and concentration of doxycycline, it was not possible to meta-analyse the data.

Skulason et al[18]proposed the combination of monocaprin, a monoglyceride of capric acid capable of inactivating HSV in vitro, with doxycycline to block viral replication and to optimize tissue repair. In one group, the anti-viral was used alone, and in the other, it was associated with doxycycline to evaluate the effect of this drug in the healing. This combination promoted pain relief and reduced healing time.

Studies point to glucocorticoids as the first-line treatment for recurrent aphthous ulceration.[6,26,27] However, there is some concern about the use of medium and high potency corticosteroids in the oral cavity due to the risk of causing mucosal atrophy and predisposing to proliferation of opportunistic microorganisms if they are used extensively.[6,27] Four of the studies analysed were performed on aphthous lesions and all showed promising results; however, in none of these was the effect of doxycycline compared to that of corticosteroids.

Despite the properties of doxycycline, which have already been established in the literature, its use is still little explored in acute, chronic and recurrent ulcerative lesions of the oral mucosa. The selected studies suggest a positive effect in the treatment of recurrent aphthous ulceration and herpes labialis. Experimental animal studies and double-blind, randomized clinical trials are needed with regard to other lesions, such as traumatic ulcers and oral mucositis, to provide evidence that doxycycline may be an option in the treatment of ulcerated lesions that occur in the mouth.

5 | WHAT IS NEW AND CONCLUSION

Although the scientific evidence is based on few clinical trials, the present study suggests that topically used doxycycline may be a therapeutic option in the management of ulcerated oral lesions. The antibiotic effects of doxycycline and also its anti-inflammatory properties are probably responsible for the beneficial effects of this drug in the treatment of ulcerated lesions of mouth.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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