



The Efficacy and Safety of Pentoxifylline in the Treatment of Recurrent Aphthous Stomatitis: A Systematic Review

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ABSTRACT

Several evidence have shown the beneficial effects of pentoxifylline in the improvement of oral aphthous ulcers. However, the data in this regard are sparse. So, the efficacy and safety of pentoxifylline in oral route was systematically reviewed to elucidate its effects on the size and number of ulcers, as well as the healing time and recurrence frequency in Recurrent Aphthous Stomatitis (RAS) patients. PubMed (Medline), Web of Science, Scopus, ScienceDirect, Cochrane Library, ProQuest, and Clinicaltrials.gov were searched for related articles. The investigated outcomes were pain level, the size and number of ulcers, the frequency of recurrence, the healing time, and finally the pentoxifylline related side effects. Only 6 related study that investigate the efficiency of Pentoxifylline on RAS (n =107) were identified. Decreasing in the pain level, improving the ulcer size and number were established in approximately all studies. Pentoxifylline established its ability to shorten the healing time of this type of mouth ulcers. However, its potential to prevent the recurrence of the disease could not establish based the data presented here. In conclusion, this systematic review suggests pentoxifylline in RAS patients because it confirmed that RAS patients who received this agent as oral administration reported suitable response. However, conducting more clinical trials with larger sample size and long follow-up time especially to efficiently judge about its ability to the recurrence prevention still is necessary to develop clinical practice guidelines for management of RAS.

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Introduction

Recurrent Aphthous Stomatitis (RAS) is one of the most common pathophysiological conditions with ulcers appeared as one or more painful red recurrent ulcers in the oral mucosa (1). The prevalence of this disease in general population is reported from 5% to 66% with an average value of 20%. This disorder is clinically divided into 3 types of major, minor, and herpetiform RAS which varies

in the number of ulcers and their size as well as their total healing time (2). This multifactorial disorder is due to the various factors leading to immune system dysfunction. They include genetic factors (24-46% of positive familial history for RAS patients), viral and bacterial infections (*Streptococcus spp.*, *Helicobacter pylori*, HSV, varicella-zoster, Cytomegalovirus, and adenoviruses), food allergies, vitamin and mineral deficiencies (especially B12, folate,

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ferritin), systemic diseases, hormonal imbalances, injuries, and stress (3). Underlying diseases, especially systemic inflammatory diseases such as Behcet's disease, inflammatory bowel disease, and celiac disease are the other most prevalent stimulators for RAS (4).

The successful treatment of RAS depends on the correct diagnosis; it is often difficult to differentially diagnose aphthous ulcers from a wide range of ulcers and injuries, such as fungal and viral lesions and Behcet's disease (5). On the other hand, because the main cause of the disease is still unknown, its treatment is based on the elimination of symptoms and empirical evidences. The final goal of the treatment is to reduce pain, stimulate ulcer healing, and prevent recurrences (6).

A wide range of local and systemic treatments are used to relieve and prevent RAS. In patients with involvement of accessible areas such as the lips and front of the tongue, local medications including topical corticosteroids and antimicrobials, analgesics, wound cleanser and dressing agents are appropriate to control the disease (7). Patients with severe RAS who have painful ulcers, may need systemic agents, including corticosteroids, colchicine, dapsone, pentoxifylline, or thalidomide (8).

Corticosteroids and analgesics are the first choices for RAS patients, but their long-term and continuous use lead to serious side effects (2).

Among the systemic treatments, pentoxifylline is an anti-inflammatory and immunomodulator that is derived from methyl-xanthine. This non-selective phosphodiesterase inhibitor, is commonly used for managing symptomatic vascular insufficiency problems, such as intermittent claudication. However, it shows many other potential uses because of its important immunomodulatory properties via inhibiting the production of TNF and other pro-inflammatory cytokines, such as IL-1 with established role in RAS. In addition, it reduces the neutrophil and T lymphocyte count and suppresses the inflammation (9)

It has been shown that the use of pentoxifylline 400 mg three times a day by RAS patients reduces the pain severity as well as the size and number of ulcers (10,11). However, there is concern about its effectiveness and side effects limits pentoxifylline administration for the management of RAS. Therefore, this study aimed to systematically evaluate the efficacy and safety of oral pentoxifylline in patients with RAS and without response to topical therapies.

Methods

Seven electronic databases were searched for Randomized

Clinical Trials (RCTs), Controlled Clinical Trials (CCTs), and Case Reports, focusing on pentoxifylline usage for the treatment of RAS, from 1990 until Dec 2020. They included PubMed (Medline), Web of Science, Scopus, Science Direct, Cochrane Library, ProQuest, and ClinicalTrials.gov. The search terms used individually or combined included "recurrent aphthous ulcer", "recurrent aphthous stomatitis", "recurrent oral ulcer", "recurrent oral ulceration "Pentoxifylline", "Oxpentifylline", "Trental", and "Pentoxil". Two of the authors performed the literature review independently and a third author participated in data collection according to the inclusion and exclusion criteria. The information of each study including authors name, publication year, journal name, and the type of study, duration of intervention and follow-up, number of participants, type of interventions, evaluated parameters in each study, the age range of study population, and the established adverse effects. The inclusion criteria for the studies were: 1) confirmed diagnosis of RAS and 2) use of pentoxifylline with the dose of 400 mg orally three times a day. Of note, because of the few number of clinical trials in this regards, case reports, letters to the editor, and uncontrolled clinical trials were also included in this review. The exclusion criteria were: 1) studies on other types of mouth lesions (i.e., non-aphthous ulcers), and 2) in-vitro and animal studies.

Results

As shown in the Figure 1, a total of 107 articles were found during the initial search. Based on the exclusion and inclusion criteria, 101 studies were excluded due to not fulfilling the criteria, while 6 studies were deemed suitable for this review. Among the included studies, one of them was a randomized clinical trial (RCT), one was a case report, three were open-trials, and one a letter to the editor. From the total of 6 included studies, 78 patients were treated by pentoxifylline or its placebo. The age range of the patients was 10 to 78 years. The evaluated outcome measures were pain, the number and size of ulcers, the probability of recurrence, the duration of recovery or healing time, and related adverse effects. Among these variables, the number of ulcers and the recurrence rate were analyzed in all studies. The incidence of various side effects was also surveyed in all studies except for the case report which used pentoxifylline for the treatment of aphthous ulcers in a HIV-positive patient (12).

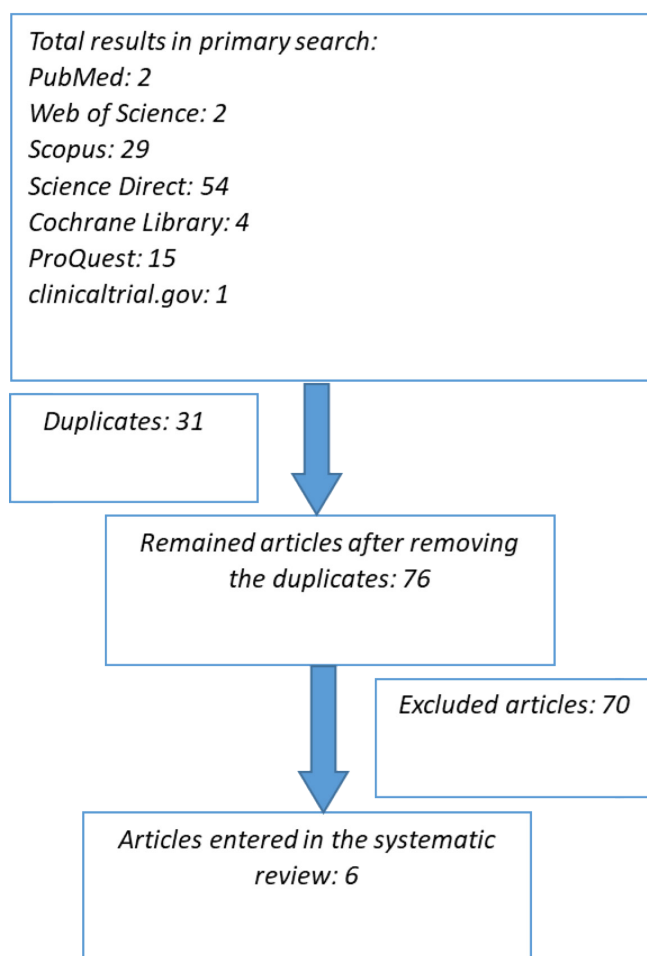


Figure 1. The algorithm of search study results.

For the severity of pain, as the first investigated parameter, all studies that surveyed this variable showed that pentoxifylline 400 mg three times daily led to pain relief in RAS patients. However, it seems that the decrease in the pain level of patients is related to the decrease in number and size of ulcer. Based on the Thornhill clinical trial, the pain intensity was higher in placebo group compared to pentoxifylline group (10).

Regarding the number of ulcers, on the other hand, most studies established the decrease in this parameter in patients treated with pentoxifylline. In Asher et al., study, in which the pentoxifylline was used in six patients with RAS, the results showed that the number of aphthous ulcers decreased after the treatment in all assessed patients. This result was repeated in Pizarro et al. study which investigated 22 patients with various types of aphthous ulcers (14). In another study on 24 participants, exactly 14 patients showed decrease in the ulcers number (58% of total) (15). Finally, the results of the RCT showed that the median of ulcer numbers recorded at the peak of each RAS

episode decreased in the active treatment group, whereas in the placebo group, worsening or no improvement in this outcome occurred (10). In the open-trial conducted by Mimura et al., the decrease in the number of ulcers was established in 60% of patients treated by pentoxifylline (11).

A critical parameter for evaluating the effectiveness of pentoxifylline in the treatment of various types of aphthous ulcers is the rate of wound recurrence, which has been evaluated in all studies. Over various follow-up durations ranging from 2.5-24 months, the results have shown that, overall, pentoxifylline leads to the inhibition of ulcer recurrence. Indeed, of 58 patients underwent the treatment with pentoxifylline for their aphthous ulcers, only 19 patients (33%) showed recurrent ulcers and the frequency of episodes decreased in all studies. However, in the mentioned RCT, there was no significant difference between the case and control groups in episode frequencies (10). Finally, according to the results of Mimura et al., study, one patient from a total of five volunteers treated by pentoxifylline showed no episodes of ulcers during 12 months of follow-up. Furthermore, two patients showed decreased recurrence of ulcers in this study (11).

Regarding the healing time, although this variable was not evaluated in all surveyed studies, in general, it seems that pentoxifylline leads to the decrease in the duration required for ulcer healing. According to the case report, the single ulcer healed after 10 days (12). In Pizarro et al., study, the duration of ulcer healing time reduced in six of 22 patients (14). Furthermore, in the study of Chandrasekhar et al. on 24 RAS cases, the healing time reduced in 22 patients (15). Also, in the RCT, the duration of ulcer healing in pentoxifylline group was significantly shorter than in placebo group (10). Finally, in the study of Mimura et al., shorter healing time was observed in 40% of patients treated by pentoxifylline (11).

Another important parameter investigated in the patients under the treatment with pentoxifylline, was the rate of adverse events. Generally, analysis of the results of studies showed no serious adverse effects related to pentoxifylline. The incidence of side effects associated with this drug has been investigated in almost all evaluated studies. Out of 57 patients, only five (8.8%) showed various side effects. Based on the results of the RCT, there was no significant difference between pentoxifylline and placebo in terms of side effects including dizziness, headache, nausea, and other gastrointestinal symptoms (11). Surprisingly, the results of this study also showed that from six participants excluded from the study because of drug discontinuation

due to the intolerable adverse effects, four cases were in placebo group. So, it seems that pentoxifylline is free of serious side effect leading to the discontinuation by the patient.

Table 1. Included studies in the review.

| Author | date | Number of participants | Type of study | Evaluated outcomes |
|--------------------------|------|------------------------|---------------------------|---|
| Slayter KL, et al (12) | 1998 | 1 | Case report | Pain level number of ulcers recurrence frequency |
| Wahba-Yahav, et al(13) | 1995 | 6 | Letter to the editor | Number of ulcers Adverse effects Recurrence frequency |
| Pizarro, et al (14) | 1995 | 22 | Open clinical trial | Number of ulcers Pain level Recurrence Frequency Adverse effects |
| Chandrasekhar, et al(15) | 1999 | 24 | Open clinical trial | Number of ulcers Size of ulcers Recurrence Frequency Adverse effects |
| Thornhill, et al(10) | 2007 | 20 | Randomized clinical trial | Pain level Number of ulcers Size of ulcers Recurrence Frequency Healing time Adverse effects |
| Mimura, et al(11) | 2009 | 5 | Open clinical trial | Type of ulcers Number of ulcers Healing time Size of ulcers Recurrence Frequency Adverse effects |

Discussion

Over the years, there has been a great challenge in RAS treatment. However, there is no appropriate management for this condition (16). On the other hand, this clinical condition affects the patient's quality of life because of its severe pain as well as eating and talking interference.

For patients suffering from the severe RAS, systemic medication could be a suitable treatment option (11). Pentoxifylline is one of these systemic agents with several sparse evidence for beneficial effects on RAS. According to our review, overall, patients taking pentoxifylline showed beneficial changes in RAS

parameters including ulcer-free days, pain severity, and ulcer size and number. However, most evaluated studies in this review were open-trials without any placebo/control group, so that the final outcomes in these studies were evaluated based on the patient's baseline condition before receiving pentoxifylline. This could have an obvious effect on the reliability of data. Furthermore, some studies have had several confounding factors complicating the results. For example, in the open-trial of Pizarro et al., on 22 RAS patients, five cases of participants suffered from various systemic diseases such as rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis, and so on, which forced them to use some systemic immunomodulatory agents (e.g., corticosteroids), probably influencing the study outcomes (14). Also, the probable contribution of HIV drugs to the oral ulcers (12) and lack of serum B12 and folic acid assessment (as the possible risk factors of RAS) could be other confounding factors among the studies (17). Moreover, some surveyed parameters (e.g., pain severity and ulcer size) were not quantified and were reported only qualitatively, making it more difficult to judge about the results.

The found clinical trials as well as the number of participants in each study were few. The main reason seems to be the refusal of patients to receive systemic medication to treat a simple disease such as RAS. However, in major RAS or cases which topical agent do not act well, systemic pentoxifylline could be an appropriate choice. As mentioned, other systemic therapies currently used in the treatment of RAS, especially corticosteroids, show many side effects that are more serious than the adverse effects of oral pentoxifylline. Generally, pentoxifylline is a safe drug with GI symptoms (e.g., diarrhea, nausea, vomiting, and epigastric pain) being the most commonly reported side effects occurring in a few cases (18). Remarkably, in the surveyed RCT, fewer patients in pentoxifylline group versus placebo group discontinued the intervention due to the side effects (10). Furthermore, most patients showed an obvious preference for systemic pentoxifylline instead of previous topical treatments they used for RAS (10).

It can be suggested that the topical formulations of pentoxifylline be evaluated as a potential appropriate treatment for patients who refuse to take oral medication, to increase their compliance for milder cases of RAS; however, taking a tablet may seem simpler than using topical medications in the oral cavity.

In one study, involved in the present review, four systemic agents including dapsone, thalidomide, colchicine, and

pentoxifylline were used for RAS treatment and compared in terms of efficacy and safety profiles (11). Although thalidomide was reported as the most effective agent with more than 87% of complete remission, it showed high rate of adverse effects (e.g., drowsiness and constipation). On the other hand, in another study with a larger population, the obtained healing rate with thalidomide was lower than that in the above-mentioned study (19,20) while the observed side effects were more (21). Furthermore, thalidomide is an established agent for its teratogenicity and categorized as "X" in pregnancy. Dapsone, the second systemic agent used in the mentioned open-trial, resulted in the efficacy rate of 90% in RAS patients. However, the drug was discontinued in six participants (among a total of nine cases) due to moderate-to-severe side effects such as anemia, hemolysis, and jaundice. Also, colchicine showed benefits in 90% of consumers and its healing rate was calculated as about 40%. The efficacy of colchicine in RAS treatment has also been reported in other studies (22). However, it has serious adverse effects, including lower limbs paresthesia, neuropathy, and myopathy (23), precluding its general use. Pentoxifylline, the other evaluated drug in the trial (only prescribed for five participants due to its cost), led to reduction of the healing time and recurrence rate in 60% of consumers, while the other 40% showed no positive outcome (11). However, few side effects were observed in the consumers. Although pentoxifylline is somewhat more expensive than colchicine because of three-times-daily vs. once-daily dosing, it acts more successfully than colchicine in preventing RAS recurrences after drug withdrawal. Dapsone and thalidomide led to no recurrences after their withdrawal; however, for both agents, the adverse events were more problematic than for pentoxifylline (11). Moreover, among these three systemic agents, pentoxifylline can be prepared in lower costs.

In general, RAS patients who received pentoxifylline reported lower pain severity, decrease in the size and number of mouth ulcers, healing time reduction, and inhibition of recurrence after drug withdrawal. So, it is concluded that pentoxifylline may be successfully used for RAS in the cases that other treatments have failed or as an adjunctive therapy along with the other drugs. However, yet there is no sufficient evidence to recommend it as the first choice for RAS treatment. Therefore, according to this review, the researchers are advised to consider this drug as an effective, safe, and inexpensive treatment for RAS, so that in the future, a better decision can be made about the place of pentoxifylline in the treatment of this disorder.

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