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The therapeutic effect of systemic (oral) corticosteroids on the recurrent aphthous stomatitis: A systematic review

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Review Article

Abstract

BACKGROUND AND AIM: Recurrent aphthous stomatitis (RAS) is the most common chronic disease of the oral cavity with 5-25% morbidity. Etiopathogenesis is still unclear and there is no certain cure for the disease. This study was conducted systematically to access the therapeutic effects of systemic (oral) corticosteroids on oral aphthae.

METHODS: This systematic review study was conducted according to the Cochrane's recommended manual, and clinical trial studies that compared oral systemic corticosteroids with placebo or other drugs, were considered eligible to include. For this purpose, keywords were determined using Mesh system and were searched through the Boolean searching method using "and" and "or" in the PubMed, Cochrane Library, Scopus, Web of Science, and Google Scholar databases. In order to increase sensitivity, time and language limitations were not implemented. Afterwards, all of the searched studies were evaluated and the required information was obtained.

RESULTS: In this systematic review, only five clinical trials were involved. In all of the studies, prednisone or prednisolone (the active form of prednisone) was used as a systemic corticosteroid, rather than systemic drugs such as colchicine, sulodexide, montelukast, levamisole, and placebo. In general, this drug was effective in healing aphthous symptoms.

CONCLUSION: There were few clinical trials using systemic corticosteroids. The results of this study showed that low prednisolone dosage combined with levamisole was effective in curing aphthae with no serious side effects.

KEYWORDS: Aphthous Stomatitis; Aphthous Ulcers; Aphthae; Corticosteroid

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Recurrent aphthous stomatitis (RAS) is one of the most frequent cases in clinics.[1,2] The morbidity rate of these ulcers has been reported to be 5-50% at different intervals. Aphthae is characterized by painful multiple or solitary recurrent ulcers in non-keratinized oral mucosa. RAS ulcers are usually completely distinctive, round, or oval-shaped, and are surrounded by an inflammatory areola. They are usually 1 cm in size (minor aphthae), but some patients have deeper or bigger ulcers (major aphthae) that take weeks to heal, and also have scarring.[3]

RAS etiology remains unclear, but the most mentioned factor in these studies is heredity. Aphthae-like ulcers can be associated with mineral deficiencies such as lack of folic acid, iron, zinc, or B1, B2, B6, and B12 vitamins, digestive tract disorders (Crohn's disease or Celiac disease), immunodeficiency [human immunodeficiency virus (HIV) infection], stress, trauma, stopping smoking, menstruation, and allergy.[4,5]

A variety of cures have been suggested for aphthae, although considering the multiple

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etiological factors associated with aphthae and their ambiguity, curing this disease is a complicated matter. The cures are mostly alleviative, reducing pain and sensitivity, and accelerating healing.[6-13]

A variety of drug classifications such as local anesthetics, antiseptics, steroids, and immunosuppressants have been suggested for aphthae. Nevertheless, none of them are considered to be a definitive cure for aphthae. Steroids are one of the drug types that can reduce symptoms and cause early healing, and are used in different local and systemic forms.[14] However the degree to which the systemic use of steroids is useful, and whether their effects are beneficial for the patients considering their side effects, have not yet been determined because there has not been any organized review study on the effects of systemic steroid in curing RAS, except for a few clinical trial studies. Thus, conducting an organized review study and meta-analysis to investigate the effects of systemic steroids on curing aphthae is highly essential and can be an essential guide for physicians to prescribe these drugs for the afflicted patients. Thus, this study was conducted to systematically review the effectiveness of systemic corticosteroids (oral) in curing oral aphthae.

Methods

In this systematic review, which was based on the recommended guide of Cochrane information bank, the research question was determined based on Population, Intervention, Comparison, and Outcome (PICO) as the following:

Population: Patients with non-syndromic RAS.

Intervention: In this study, pharmaceutical interventions included systemic glucocorticoids given to the intervention group in the clinical trial studies.

Comparison: A category that included placebo group, control group, or other drug groups.

Outcomes: Improvement of the patient's clinical condition, including healing period, as well as severity and repetition rate of the ulcers.

After initial assessments, the main important keywords were determined using Mesh system (Table 1). The keywords were searched by the Boolean searching method using "and" and "or" in the PubMed, Cochrane Library, Scopus, Web of Science, and Google Scholar databases. In order to increase sensitivity, time and language limitations were not implemented. The primary and secondary searches were performed by two reviewers (B.M. and R.M.) independently.

Table 1. List of Mesh standard keywords

RAS	Corticosteroid
Aphthous stomatitis	Steroid
Aphthous stomatitides	Glucocorticoid
Aphthous ulcer	Dexamethasone
Aphthae	Triamcinolone
Canker sore	Prednisone
	Prednisolone
	Methylprednisolone
	Fluocinolone
	Betamethasone

RAS: Recurrent aphthous stomatitis

The search results of the above-mentioned databases (2,652 articles in total, including Cochrane Library: 22, PubMed: 145, Google Scholar: 84, Web of Science: 371, and Scopus: 1829) were entered into EndNote X8 software. In addition, a manual search (article references and reference books) was also performed. EndNote X8 has a tool to find repeated articles. The unrelated articles were eliminated through the following steps. First, using EndNote tools, repeated articles were found, the ones with the most complete data were kept, and all the other corresponding articles were deleted. In the next step, the articles were evaluated based on the title, and then, the abstract; finally, 16 articles remained. Finally, the remaining articles were assessed accurately. Then, the articles with completely related subjects that were conducted as a clinical trial study and had the criteria to enter a systematic review were chosen. To assess the articles' quality, a numerical scale editing (the presented checklists on www.equatornetwork.org) was used. All the articles were scored according

to these checklists, and then, weighted based on the scores. The full texts of all studies were assessed by two authors (A.E. and B.M.) separately. In case of disagreement between the two researchers, an agreement was reached in consultation with the third reviewer/epidemiologist and statistical consultant (R.M.). The selected articles' data including original article researcher names and publication dates, study type, sample size, steroid drugs used, age, gender ratio, and treatment results in the groups, were individually entered into Microsoft Office Excel 2016. In this stage, all five articles were entered into the systematic review (Figure 1). Due to assessment shortage and the fact that different drugs were used in these five studies compared to others, meta-analysis was not performed.

Results

7 out of 16 studies with fully assessed texts were systematic reviews about local treatments and systemic aphthae,[14-20] and the local form of corticosteroids was used in 4 articles.[21-24] In a clinical trial article that studied the effects of different systemic treatments, prednisolone was prescribed for all the afflicted patients for two weeks to put all the patients in the same basic state. After that, the patients were divided into multiple different groups and each group was prescribed one of the following drugs: thalidomide, dapsone, colchicine, and pentoxifylline.[25] The aforementioned article was also removed from the study. Thus, only five clinical trial studies compared systemic corticosteroids with other drugs (Table 2), more detailed information of which is shown in table 3.[26-30]

Discussion

Oral aphthae treatment still remains unspecific and the treatment goals include controlling pain and functional disorder due to inflammatory response, reducing recurrence, or preventing the development of new aphthae. Standard local treatment options for common aphthae forms that induce symptomatic sedation include analgesics, anesthetics, disinfectants, anti-inflammatory agents, steroids, sucralfate, and tetracycline suspension. Dietary changes could also support treatment efforts. In treatment-resistant cases, appropriate systemic treatment could be chosen from the wide variety of drugs that balance the immune system, including colchicine, prednisolone, cyclosporine A, interferon, antimetabolites, and alkylating agents.[14] There are few available clinical trials regarding the use of systemic steroids in aphthous ulcer cases, and steroid-related information is provided by case reports and case series.[9]

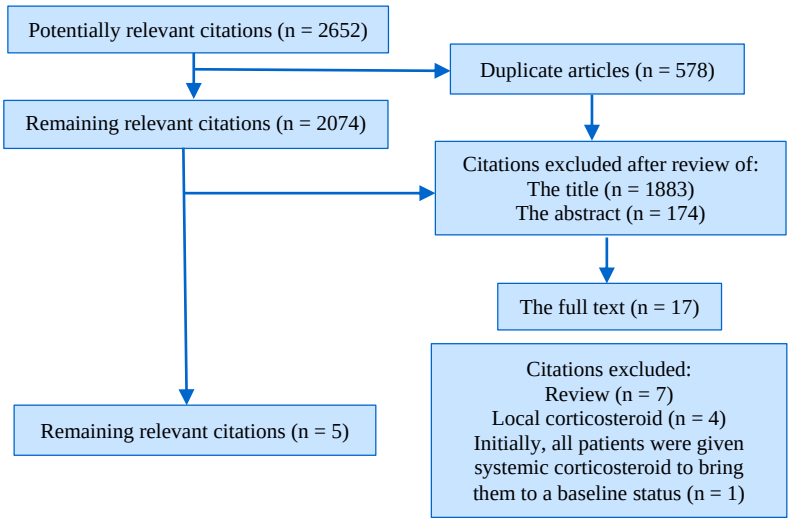

Figure 1. Studies considered for inclusion in this systematic review

Table 2. Basic information on studies entered the systematic review

Study	Country	Type of study	Sample size	Age (Mean or range)	Sex
Femiano et al.[26]	Italy	Double-blind clinical trial	30	21-48	F (n = 24) M (n = 6)
Pakfetrat et al.[27]	Iran	Double-blind clinical trial	34	31.50 (11.90)	F (n = 22) M (n = 12)
Femiano et al.[28]	Italy	Double-blind clinical trial	60	18-48	F (n = 38) M (n = 22)
Sharda et al.[29]	India	Single-blind randomized placebo-controlled trial	50	18-53	F (n = 26) M (n = 24)
Xue et al.[30]	China	Randomized clinical trial	300	Groups*: L = 27.93 (2.42) P = 28.86 (3.03) L + P = 29.18 (2.81)	F (n = 143) M (n = 57)

*Group L = Levamisole, Group P = Predinisolone, Group L+P = Levamisole + Prednisolone; F: Female; M: Male

In this assessment, only five clinical trial studies entered the systematic review. Prednisone (prednisolone) was the systemic corticosteroid throughout the study, compared to other systemic drugs. In general, low dosages of this drug were effective in the healing process and did not cause any serious side effects.

Local corticosteroids are the most frequently used drugs in immune-mediated oral mucosa diseases. The purpose of such treatment is to remove symptoms so that the patient can eat, speak, and maintain routine oral hygiene because local corticosteroids reduce or even suppress pain and reduce aphthae healing time.[14,19] Oral aphthae are generally treated using local treatments. In some cases, these efforts are inadequate due to lesions or unknown reasons and in such cases, the second wave of treatment is performed using systemic drugs.[14]

Corticosteroids are the primary choice for systemic treatment and are usually used for patients with treatment-resistant and severe aphthae.[14] In the five articles reviewed, prednisolone was the oral corticosteroid, which started with a 25 mg per day dosage in two of the five studies and gradually decreased in the next two months.[26,28] In a study by Femiano et al., the effects of prednisolone and sulodexide (a type of heparin with low molecular weight with immunosuppressive characteristics but few side effects) on local corticosteroid-resistant aphthae treatment were compared. The prednisolone dosage was 25 mg per day in the first 7 days of the treatment course, but it was later reduced gradually. The results showed that systemic prednisolone had a better effect than sulodexide given the duration of drug consumption before the pain was relieved, and the time it took to heal the ulcers. After using the drug for a month, epithelization and ulceration were observed; however, the patients who had received sulodexide had less ulceration in a 3 to 4-month period compared to the systemic prednisolone. Two side effects were reported in both the prednisolone-treated group (one case of gastritis and one case of hypertension) and the sulodexide-treated group (one case of hypotension and one case of emesis). In general, prednisolone had more serious side effects.[26]

In another study, Femiano et al. compared the effects of systemic prednisolone (initial dose of 25 mg per day for 15 days, then reduced gradually) and systemic montelukast (leukotriene receptor antagonist as an anti-asthma drug) in curing local treatment-resistant aphthous ulcers. The results showed that prednisolone and montelukast were able to control RAS significantly in contrast to placebo. The researchers introduced montelukast as a better option for treating RAS because it has fewer side effects than prednisolone, although prednisolone had a better performance concerning pain reduction and speeding up ulcer healing.[28]

Table 3. Comparison of the effects of systemic corticosteroids with the effects of control drugs in the selected trials

Study	Intervention (Sample size)	Comparison (Sample size)	Treatment duration	Outcome	Side effects
Femiano et al.[26]	Prednisone for months 1 and 2, initially with a 25 mg dosage daily in the morning for 7 days, with dose reduction[10]	Sulodexide ULS 250[10] Control group (cellulose starch) 100 mg[10]	2 months	The effectiveness of systemic sulodexide was almost comparable with systemic prednisone in patients with frequent RAS.	Sulodexide showed less serious adverse effects than prednisone.
Pakfetrat et al.[27]	Prednisolone 5 mg[17]	Colchiciine 0.5 mg[17]	3 months	Both colchicine and prednisolone significantly reduced RAS. There were no significant differences in the size and number of ulcers, recurrence and severity of pain, and duration of pain-free period between the two groups.	Colchicine (52.9%) had significantly more side effects than prednisolone (11.8%).
Femiano et al.[28]	Prednisone 25 mg orally daily for 15 days, 12.5 mg daily for 15 days, 6.25 mg daily for 15 days, then, 6.25 mg on alternate days for 15 days[20]	Montelukast 10 mg orally every evening, and then, on alternate days for the second month[20] Cellulose (placebo) 100 mg	2 months	Both prednisone and montelukast were effective in reducing the number of lesions and improving pain relief and ulcer healing compared with placebo. Prednisone was more effective than montelukast in pain cessation and in accelerating ulcer healing.	Adverse drug reactions were more common in the prednisone group (30%) compared with montelukast (10%) and placebo (10%).
Sharda et al.[29]	Levamisole 50 mg and low-dose Prednisolone 5 mg[20]	Placebo[10] Levamisole 50 mg[20]	3 weeks	A statistically significant improvement was found in all parameters except for the size of ulcers in patients treated with levamisole alone and with the combination of levamisole and low-dose prednisolone. There was no statistically significant improvement in the placebo group.	Any reported side effects were recorded.
Xue et al.[30]	1- Prednisolone 15 mg/day (100) 2- Levamisole 150 mg/day + Prednisolone 15 mg/day (100),	Levamisole 150 mg/day (100)	6 months	All patients showed reductions in ulcer sizes and pain. Levamisole and prednisolone monotherapy for patients with RAS were similar in terms of safety and efficacy. Combination therapy and monotherapies showed similar efficacy.	Combination therapy was associated with more non-serious adverse events.

RAS: Recurrent aphthous stomatitis

Drug dosage was reduced in two other studies. In a study, Pakfetrat et al. compared prednisolone (5 mg) and colchicine (a drug that interferes with different inflammatory pathways) (0.5 mg), which were prescribed for three months, and it was found that both prednisolone and colchicine could control RAS significantly. There was no significant difference between the individuals of each group regarding lesion size and quantity, pain and twinge severity, and the pain absence duration; however, colchicine was reported to have more (52.9%) side effects than prednisolone (11.8%). Although both drugs were able to control RAS well, it seems that a low dosage of prednisolone is a better option for treating RAS since it has fewer side effects.[27] In the second study, prednisolone had been used in combination with levamisole. In a study by Sharda et al., levamisole (50 mg, antiparasitic drug) and the combination of prednisolone (5 mg) and levamisole (50 mg) were compared, and it was found that after three weeks, the groups treated with medication were in a much better state compared to the placebo group concerning pain, lesion size and quantity, ulcer healing time, and ulceration frequency; however, there was no significant difference between the group that received levamisole and the one which received a combination of prednisolone and levamisole.

In the latest study conducted by Xue et al.,[30] levamisole and prednisolone solitarily and their combination were compared. Drug dosages were fixed during the study period (6 months), and they were as follows: prednisolone 15 mg (three 5 mg pills per day) and levamisole 150 mg (three 50 mg pills per day), which were prescribed for three groups including prednisolone group, levamisole group, and prednisolone + levamisole group. This study showed that the lesion size and pain had a meaningful decline in all patients, and levamisole and prednisolone monotherapy were the same, considering safety and effectiveness. The combination therapy (levamisole and prednisolone) showed a better performance compared to the other groups; pain severity had a more significant decline. In general, monotherapy and combination therapy almost had the same effectiveness. Unserious side effects significantly increased in the combination therapy.

Hence, by reviewing these five clinical trials, it can be concluded that although 25 mg dosage of prednisolone caused some side effects, low dosages of this drug (5 mg), as monotherapy[27] and in combination with levamisole[29] were effective in treating aphthae and had no serious side effects. In the study done by Xue et al.,[30] prednisolone was prescribed with a dose of 15 mg per day for six months and the results support the effectiveness and safety of this dosage over a long period of time. These studies indicated that although the combination of prednisolone and levamisole was effective in healing aphthae, it caused more side effects, though they were not serious. Prednisolone monotherapy has fewer unserious side effects compared to combination therapy.

However, other review studies show that there is no standard treatment in this area. A study conducted by Deepak and Sharma[19] included a comprehensive review of aphthae treatment methods and suggested that the systemic treatment of prednisone should be started with a 1.0 mg/kg per day dosage in patients afflicted with severe aphthae, and should be reduced during the next two weeks due to its side effects such as hyperglycemia, lipodystrophy, depression, moon facies, and adrenal suppression. In order to provide effective treatment, it can be prescribed with other immunosuppressants such as azathioprine (AZA). However, these studies did not mention prescribing low dosages of this drug or any studies on this subject.

A review study conducted by Sabbagh and Felemban indicated that oral prednisolone, or its equivalent, can be prescribed 10-30 mg per day for a month, and higher prednisolone doses up to 40-60 mg as a morning dose in lower periods of 10-12 days.[16]

Challacombe et al.[18] carried out an

evidence-based study to cure aphthae and concluded that although various treatment methods and standard treatment methods such as local steroids have been suggested for aphthae, there are few clinical trials. Non-standard clinical diagnoses and defects in evaluating ulcer severity have resulted in reporting different clinical results, affecting the treatment choice. According to the researchers, these are the reasons why an evidence-based review is not possible. From their perspective, another important issue in treating aphthae is the inability to determine whether we need a treatment method for curing current ulcers or we need a method for the very difficult challenge of preventing future ulcers. Almost every antibacterial or anti-inflammatory agent can help to heal and relieve pain, but few are expected to prevent ulcerations. It seems that local steroid mouthwashes are an effective choice and there are pieces of evidence suggesting that steroid mouthwashes can reduce ulceration frequency and heal current ulcers. Therefore, considering this study, preventing new ulcerations usually needs systemic treatment. The researchers have reported effectiveness of colchicine (despite the many gastric conditions that happened in the dosages taken) in most studies. However, they stated that most of these studies were conducted for a short period of time (3-6 months) and there were not enough accidental clinical trial studies with an adequate amount of samples in this field. In addition, thalidomide and AZA have also been mentioned, but they were not the primary choice. In addition, pentoxifylline and dapsone need more trial studies. This evidence-based study has not mentioned systemic steroids as recommended drugs in curing aphthae.[18]

In another evidence-based review study by Patel and Peter about aphthae, corticosteroids were mentioned as the first line of treatment to be used locally and injected into the lesion. Drugs like dapsone, thalidomide, and colchicine have been suggested for systemic treatment as well. However, this study has not mentioned systemic corticosteroids.[20] This study has propounded the need for more evidence-based studies.

It seems as though more clinical trial studies are needed, since only a few exist, to examine whether prednisolone is effective in low dosage, side effects of other systemic drugs, recommendation of review and evidence-based studies for conducting more studies, and the absence of a standard protocol regarding severe and treatment-resistant aphthae. So that we might be able to answer this question: should corticosteroids be only used as basic and short-term drugs? Or can we use them in low dosages as the main drug?

Conclusion

There are few clinical trial studies regarding systemic corticosteroids. The present study showed that using prednisolone as monotherapy in low dosage or in combination with levamisole is effective in curing aphthae and has no serious side effects. However, further studies are recommended to compare this drug to other drugs and to determine an appropriate dose for long-term treatment considering the effectiveness of corticosteroids.

Conflict of Interests

Authors have no conflict of interest.

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