ADA CE Program ARTICLE 2

Efficacy and safety of Chinese patent medicines in the treatment of recurrent aphthous stomatitis

A systematic review

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ABSTRACT

Background. Recurrent aphthous stomatitis (RAS) is the most common chronic oral mucosal condition of the oral cavity. Investigators in clinical trials have evaluated the effectiveness of Chinese patent medicines in the treatment of RAS. However, the results are conflicting rather than conclusive. To evaluate the efficacy and safety of Chinese patent medicines for the treatment of RAS, the authors conducted a systematic review.

Types of Studies Reviewed. The authors searched 9 electronic databases to identify randomized controlled trials (RCTs) or potential clinical controlled trials (CCTs), published in any language, in which the investigators compared Chinese patent medicines with vitamin tablets or placebos for the treatment of RAS.

Results. The authors included 11 RCTs and 1 CCT in the review. Results showed that Chinese patent medicines were beneficial for patients with RAS in relieving ulcer pain and reducing the duration and frequency of attacks. The reported adverse effects of Chinese patent medicines included stomachache, abdominal distention, diarrhea, mild nausea, and gastrointestinal discomfort, which were either self-limiting or could be relieved by treatment cessation.

Conclusions and Practical Implications. Chinese patent medicines may be effective for treatment of RAS by means of relieving pain and reducing ulcer size and episode duration and frequency.

Key Words. Recurrent aphthous stomatitis; Chinese patent medicine; systematic review; efficacy; safety.
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Recurrent aphthous stomatitis (RAS), also called *recurrent aphthous ulcer*, is the most common chronic oral mucosal condition of the oral cavity, which affects 5% to 25% of the population.[1-3] The age of onset of RAS is usually between 10 and 19 years, with no sex predilection,[4] but it can persist into adulthood and throughout life.[4] The underlying cause is not clear,[5] although several factors are known to predispose a person to RAS, including local, systemic, immunologic, genetic, allergic, nutritional, and microbial factors,[1] as well as local trauma.[6]

The typical minor type of RAS lesion is most common and manifests with a painful, rounded or oval ulcer less than 1 centimeter in diameter with a gray-white pseudomembrane and an erythematous halo, which heals within 7 to 14 days. Although minor RAS is common, major RAS also can occur in 10% of patients with RAS.[1] It is more severe, with a diameter greater than 1 cm. Major RAS ulcers can last from weeks to months. Herpeslike RAS is characterized by numerous small ulcers that coalesce, and it is the rarest form of the condition.[7,8] Diagnosis of RAS usually is based on previous or current history of RAS and clinical manifestations; however, it should be differentiated carefully from manifestations of systemic diseases such as Behçet

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syndrome, Reiter syndrome, Crohn disease, celiac disease, ulcerative colitis, inflammatory bowel disease, erythema multiforme major, vitamin and mineral deficiencies, hematologic disorders, gastrointestinal diseases, and cyclic neutropenia immune deficiencies.[9]

The primary aim of treatment is to reduce pain and promote healing, as well as to reduce RAS episode duration and recurrence rate. For severe RAS cases that are characterized by major type or frequent recurrence, immunosuppressants (for example, colchicines, pentoxifylline, dapsone, azathioprine, hydroxychloroquine, and cyclosporine) might be necessary; however, the widespread use of such agents is limited because of potential adverse events. No satisfactory curative treatment exists for RAS.[10] Traditional Chinese herbs are becoming increasingly popular and accepted worldwide. In China, topical and systemic patent medicines made of traditional Chinese herbs commonly are prescribed—for example, Liuwei Dihuang pills generally are considered safe and can be effective. However, to our knowledge, no meta-analyses or systemic reviews have been published on the effects of Chinese herbal medicines for treatment of RAS. Therefore, we conducted a systematic review to assess the existing randomized controlled trials (RCTs) and clinical controlled trials (CCTs) that included Chinese patent medicines for the treatment of RAS and to provide an up-to-date evidence-based evaluation of the effectiveness and safety of Chinese patent medicines for RAS treatment.

METHODS

Databases and search strategies. We searched 9 electronic databases for RCTs or CCTs focusing on Chinese patent medicines for treatment of RAS: China National Knowledge Infrastructure database (1979-2015), VIP China Science and Technology Journal Database (1989-2015), Chinese Biomedical Literature Database (1977-2015), Wanfang Data (1985-2015), Embase (1966-2015), PubMed (1949-2015), Science Citation Index (1900-2015), and current controlled trials and the Cochrane Central Register of Controlled Trials in the Cochrane Library (search date: March 15, 2015). We used hand searching as a complement. We used no restrictions for language or type of publication. All the searches ended in March 2015. We included in this review all clinical trials in which the investigators compared the use of Chinese patent medicines with vitamin tablets or placebos for RAS treatment. The search terms used individually or combined included "Chinese patent medicine," "Chinese patent drugs," "traditional Chinese medicine," "Chinese herbology," "Chinese medicine," "Chinese material medica," "Chinese herbs," "Chinese herbal medicine," "herbal medicine," "Chin Tradit Pat Med," "recurrent aphthous ulcer," "recurrent aphthous stomatitis," "recurrent oral ulcer," and "recurrent oral ulceration."

Inclusion and exclusion criteria and outcomes. We included in this review studies that met the following inclusion criteria:

- Participants had to be patients with a confirmed diagnosis based on previous or current history of RAS or clinical examination who sought care for RAS-like lesions. Exceptions were patients with Behçet syndrome, Reiter syndrome, erythema multiforme, viral infections, celiac disease, Crohn disease, ulcerative colitis, vitamin- and mineral-deficiency anemia (vitamin B_{12}, folic acid, and serum iron), and other systemic diseases.
- Interventions in the treatment group were orally administered Chinese patent medicines with or without vitamin tablets, with no restrictions on the types or doses.
- Control groups received placebos or vitamin tablets.
- Investigators had to report at least 1 of the primary or secondary outcomes. Primary outcomes included ulcer pain, ulcer size, episode duration, and episode frequency associated with RAS; secondary outcomes included patients' quality of life.
- The studies had to be RCTs or CCTs.

We excluded the following types of studies:

- duplicate publications reporting the same groups of participants;
- studies that lacked basic information regarding the participants or interventions;
- studies with inconsistencies in the duration or frequency of interventions between the treatment and control groups;
- studies in which the investigators used only topical formulations of Chinese patent medicines;
- case reports, reviews, workshop summaries, and studies about clinical observations.

Data collection and analysis. Two of the authors (P.Z., Q.M.) performed the literature searches independently. In addition, both authors were responsible for selection of studies and data collection. We conducted the literature search by using the following criteria from the *Cochrane Handbook for Systemic Reviews of Interventions*, Version 5.1.0.[11] We imported the search results from the 9 databases into reference management software (NoteExpress 3.0.4, Beijing Aegean Sea

ABBREVIATION KEY. bid: Twice a day. **CBM:** Chinese Biomedical Literature Database. **CCT:** Clinical controlled trial. **CD:** Cluster of differentiation. **CNKI:** China National Knowledge Infrastructure. **Cochrane:** Cochrane Central Register of Controlled Trials in the Cochrane Library. **qd:** Once a day. **RAS:** Recurrent aphthous stomatitis. **RCT:** Randomized controlled trial. **SCI:** Science Citation Index. **TCM:** Traditional Chinese medicine. **tid:** 3 times a day. **VIP:** VIP China Science and Technology Journal Database. **Wanfang:** Wanfang Data.