Effects of berberine gelatin on recurrent aphthous stomatitis: a randomized, placebo-controlled, double-blind trial in a Chinese cohort

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Objective. Recurrent aphthous stomatitis (RAS) is a common oral mucosal disease, yet effective therapeutic approaches are lacking. This study aimed to determine the effects of application of berberine gelatin in the treatment of minor RAS (MiRAS).
Methods. A randomized, double-blind, placebo-controlled, clinical trial was performed. The gelatin containing berberine (5 mg/g) or vehicle only was applied 4 times per day for 5 days. Clinical evaluation included pain level, size, erythema, and exudation of certain ulcers on days 1, 2, 4, and 6.
Results. A total of 84 subjects fulfilled the study without obvious side effects. Berberine gelatin treatment reduced the ulcer pain score compared with placebo gelatin ($P < 0.05$). Ulcer size was significantly reduced ($P < 0.05$) and lower erythema ($P < 0.05$) and exudation ($P < 0.05$) levels were associated with berberine treatment.
Conclusions. Berberine gelatin may be a safe and effective treatment for MiRAS. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:212-217)

Recurrent aphthous stomatitis (RAS), which clinically manifests as distinct and shallow ulceration with a necrotic center covered by a pseudomembrane and surrounded by an erythematous halo, is among the most prevalent oral mucosal lesions affecting the general population.[1] Minor RAS (MiRAS) is the most common form, consisting of 70% to 87% RAS.[2,3] Although RAS is an episodic and self-limited affection, the ulceration usually severely interferes with eating, speaking, and swallowing. Because no definitive etiology has been identified, there is no uniformly effective and reliable therapy in the termination of this potentially debilitating disorder.[3] Available systemic or topical treatments currently are aimed at alleviating pain, decreasing functional disability, and promoting ulcer healing. Some systemic medications, although effective, have side effects that limit their extensive or long-term application. Therefore, topical agents (including glucocorticoids, antibiotics, analgesics, astringents, and laser therapy) remain the mainstay of therapy.[3]

Competing interests. The authors state that they have no conflict of interest.
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Berberine, an isoquinoline alkaloid originally isolated from medicinal herbs, such as *Hydrastis canadensis, Coptidis rhizoma*, and *Berberis vulgaris*, is an antimicrobial drug routinely prescribed in traditional Eastern medicine.[4] Recently, several investigations have suggested that berberine possesses a wide range of pharmacologic and biological activities, including anti-inflammatory,[5-7] antimicrobial,[8] antitumor,[9] and antipyretic[10] properties. We hypothesized that berberine may be an effective and favorable treatment candidate for MiRAS because of its multiple bioactivities. The objective of this randomized, double-blind, placebo-controlled clinical trial was to investigate the efficacy and safety of berberine gelatin in the treatment of MiRAS.

MATERIAL AND METHODS

Materials

Berberine gelatin (10 g) containing 50 mg berberine (98% HPLC, Biopurify Science and Technology Development Co. Ltd., Chengdu, China), hydroxypropyl methyl cellulose, polyethylene glycol 400, glycerine, and flavoring additives was used. The placebo agent (10 g) contained the above-mentioned excipients with

Statement of Clinical Relevance

In this placebo-controlled, double-blind trial, berberine gelatin was effective in alleviating pain intensity and promoting oral aphthous healing without notable side effects.

the exception of berberine and had a similar shape, color, and flavor. All gelatin, packed in soft tubes, was produced by the pharmaceutical department of the First People's Hospital of Chenzhou, University of China South.

Subjects and study design

This randomized, double-blind, placebo-controlled clinical trial was conducted under the approval of the Institutional Ethics Committee/Institutional Review Board of the First People's Hospital of Chenzhou, University of South China. The clinical diagnosis was based on the patients' medical history and clinical appearance.[11] To exclude potentially confounding systemic diseases, all patients underwent careful examination by dermatologists, gastroenterologists, ophthalmologists, and hematologists before enrollment. All patients were selected according to inclusion and exclusion criteria. The inclusion criteria were as follows: (1) male or female individuals aged 18 to 50 years, who could exactly follow the study protocol and sign the informed consent form voluntarily; (2) a history of RAS for a minimum of 6 months with an average of 1 to 2 outbreaks per month and 1 to 5 minor aphthae per outbreak; (3) agreement not to use analgesics or other drugs curing oral ulcer during the study; (4) 1 to 3 aphthous ulcerations with a size >5 and <10 mm in diameter; for more than 1 ulceration, a distance between ulcerations of more than 1 cm; (5) time of ulceration onset within 48 hours; and (6) ulcers in locations that are easily accessible for evaluation and treatment. Exclusion criteria were as follows: (1) history of allergies to berberine; (2) pregnancy or lactation; (3) ulcers as a manifestation of a systemic disease process such as Behçet's disease, ulcerative colitis, Crohn's disease, or acquired immune deficiency syndrome; (4) taking systemic nonsteroidal anti-inflammatory drugs, immunomodulatory agents, or systemic antibiotics within 2 weeks; (5) treatment with any oral topical medication or invasive dental procedures within 2 weeks; (6) normal resolution of aphthous ulcers expected in <5 days without any treatment; (7) use of toothpaste containing anti-inflammatory drugs; (8) ulceration secondary to hematinic deficiency, vitamin deficiency, or nutritional deficiency; and (9) ulceration caused by drugs such as nicorandil or methotrexate. Patients were then assigned to a berberine group or a control group using a computer-generated random numbers list. Both the investigators and the participants were blind to the group assignment until study completion.

In this trial, only 1 ulcer was selected for analysis. For patients with more than 1 ulcer, the most recent ulcer was selected. The pain level was evaluated by the subjects following instructions by the investigators, and the size of the ulcers and the erythema and exudation were measured and recorded by the investigator before the first administration and at each evaluation thereafter. To evaluate pain, a visual analog scale consisting of a 100-mm horizontal line between the poles of "no pain" to "unbearable pain" was used. Subjects were instructed to mark the line with a vertical line at the point that best represented the present pain level of the appointed ulcer. Then, the length between the vertical line and the pole representing no pain was measured and recorded to represent the ulcer pain score. To measure the size of the ulcers, the investigators measured the distance between 2 opposite outside edges of the ulcer border with millimeter markings on a calibrated dental probe. The 2 measurements approximately 90 degrees from each other were obtained 3 times, and the largest distance was used as 1 of the measurements. The 2 measurements were then multiplied to represent the cross-sectional area of the ulcer. The degree of erythema and exudation was evaluated and recorded by the investigators on a 4-point scale (Table I) ranging from 0 to 3 based on the methods of Liu et al.[12] and Babaee et al.[13]

Table I. Classification of erythema and exudation levels

Classification	*Erythema*	*Exudation*
0	No erythema	No exudation
1	Light red/pink	Light exudation
2	Red but not dark in color	Moderate exudation
3	Very red, dark in color	Heavy exudation, with pseudomembrane

All subjects were instructed to dry the ulcer by patting it with clean gauze, squeeze 1 cm of the drug onto a sterile cotton swab, and dab the gelatin onto the ulcer. They were observed for 30 minutes for any possible signs of acute hypersensitivity reactions or other adverse events at the first administration and advised to avoid drinking or eating in the 30 minutes after each administration. The subjects were requested to apply the drug 4 times a day (after meals and before bedtime) for 5 days. The baseline parameters were taken and recorded at the first visit (day 1). The evaluations were made at the same time on the morning of days 2, 4, and 6 before gelatin administration. Participants were requested to bring the soft tube containing the gelatin to every visit to ensure the drugs were used properly. Further, periodic telephone interviews were made to supervise the administration on schedule. Side effects after gelatin administration were recorded, and the oral mucosa was inspected by the investigator at each visit. Subjects were also informed that possible side effects may occur, at which time they should