Efficacy of Rikkosan For Primary Burning Mouth Syndrome: A Retrospective Study

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Short report

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Abstract

Background

Burning mouth syndrome (BMS) is a chronic condition characterized by pain in the oral cavity. Kampo medicine is a traditional Japanese medical system, which has its roots partly in ancient Chinese medicine. The purpose of this study is to evaluate the efficacy of rikkosan—a traditional Japanese herbal medicine (kampo)—in the treatment of primary BMS.

Main body:

A single-center retrospective study was conducted in 32 patients who were diagnosed with primary BMS and treated with rikkosan alone through gargling (2.5 g rikkosan dissolved in 50 mL hot water) three times daily. Patients were asked to evaluate their pain using the numerical rating scale (NRS) at first visit, after 1 month, and the end of rikkosan treatment. One patient had stomatitis as a side effect after gargling with rikkosan, however, no side effects were observed in other patients. Overall NRS scores decreased significantly between the first visit (7.6 ± 2.7) and the end of treatment with rikkosan (4.4 ± 3.3).

Conclusions

Rikkosan may be an effective treatment for primary BMS.

Background

Burning mouth syndrome (BMS) is a chronic pain characterized by a burning sensation in oral mucosal surfaces without related objective findings. Although several factors could be involved, including psychopathological factors and hormonal changes, the etiology of BMS remains unclear (1). BMS tends to be classified as primary or secondary; primary BMS is where no dental or medical cause can be identified (1).

The treatment of primary BMS is mainly based on pharmacotherapy, brief psychotherapy, and cognitive behavioral therapy (1). Previous systematic reviews have reported the efficacy of topical application of capsaicin (2), and topical and systemic administration of clonazepam (3). Randomized controlled trials have reported the efficacy of systemic administration of paroxetine, sertraline, and alpha-lipoic acid (4, 5). However, a preferred therapeutic intervention for primary BMS remains unclear, and these agents could be associated with side effects such as dizziness and drowsiness (5, 6); therefore, careful administration is required.

Kampo medicine is a traditional Japanese medical system and has its roots partly in ancient Chinese medicine. Rikkosan is a traditional Japanese herbal medicine (kampo) used to reduce oral pain caused

by tooth decay, pulpitis, dentin hypersensitivity, periodontitis, stomatitis, and pain after tooth extraction (7–9). Rikkosan consists of five crude herbs: *Asiasarum* root (saishin), *Cimicifuga* rhizome (shoma), *Saposhnikovia* root (boufu), *Glycyrrhiza* (kanzou) and Japanese Gentian (ryutan) (10). It is believed to provide analgesia through a mechanism different to that of nonsteroidal anti-inflammatory drugs (8). Although the effectiveness of rikkosan against BMS has been previously reported and several studies have addressed the efficacy of rikkosan for BMS (10, 11), few clinical studies have been conducted to evaluate its efficacy in a sufficient number of patients. This study aims to evaluate the effectiveness of rikkosan for primary BMS.

Methods

Diagnostic algorithm

Patients suspected of BMS were examined and diagnosed in our department according to the algorithm shown in Fig. 1 and the criteria of The International Classification of Headache Disorders (ICHD-3) (12). Patients were considered to have secondary BMS if any abnormalities were found during examination. Patients with residual symptoms after antifungal therapy and replacement therapy for deficiency factors such as trace metals and vitamin B12, and after blood tests were normal, were diagnosed as primary BMS.

Patients

Three hundred and forty patients who were suspected to have primary or secondary BMS were reviewed at the Department of Oral Medicine, Hokkaido University Hospital between January 2013 and July 2019 (Fig. 2). Patients with an underlying medical condition, based on interview, or any abnormalities found through our diagnostic algorithm were excluded (n = 258) because of possible secondary BMS. Patients were excluded if rikkosan was not used or they were treated with rikkosan in combination with other agents (n = 37). Patients were excluded whose treatment outcome was unclear (n = 1) or whose numerical rating scale (NRS) score was not described (n = 12). Thirty-two patients who had clear medical records of their treatment were enrolled in this study.

This retrospective study was conducted with the approval of the Hokkaido University Hospital Independent Clinical Research Review Committee (Approval No. 019-0044).

Treatment algorithm for primary BMS

We first explained to each participant the pathology of primary BMS. After explaining that there is no need for immediate surgical treatment and that the disease is non-fatal, we initiated pharmacotherapy according to each patient's preference and follow-up once or twice a month. In our department, we often choose Japanese kampo medicines as initial pharmacotherapy because they have relatively few side effects and are easy to introduce (13).

Treatment dosage and administration

In this study, we administered single-agent rikkosan as a mouthwash for gargling (2.5 g rikkosan [Tsumura, Tokyo, Japan] dissolved in 50 mL hot water) three times daily (7.5 g/day). Treatment was continued until the final visit or the therapeutic agent was changed.

Study variables

Various factors, such as patient characteristics (age, gender) and clinical parameters (duration of illness, site of BMS, dosing period, treatment outcome, and side effects), were retrospectively examined. The duration of the disease was defined as the time from when the patient became aware of the symptoms to when the patient visited our department.

Evaluation criteria of the therapeutic effects

The effectiveness of the treatment was assessed by referring to changes in NRS scores. NRS scores were evaluated by asking patients to assess the degree of pain they were currently experiencing, with 0 being no pain and 10 being the worst possible pain. NRS scores were measured at the time of the first visit, at 1 month after the initiation of gargling with rikkosan, and at the end of treatment of rikkosan.

2.6 Statistical analysis

Statistical analyses were performed using JMP Pro Version 14.0 (SAS Institute, Cary, NC) and included Wilcoxon rank test. Wilcoxon rank test was performed to assess significant differences in mean NRS scores at different time intervals. $P < 0.05$ was considered statistically significant.

Results

Thirty females out of the 34 patients with primary BMS were included in this study (mean age, 56 years; median, 55 years; range, 35–75 years). The mean duration of illness was 25 months (median, 7 months; range, 4–252 months). All patients had BMS that occurred on the tongue. The overall mean dosing period of rikkosan was 89 days (median, 85 days; range, 14–246 days).

The outcomes of the treatment are shown in Fig. 3. Although one patient had stomatitis as a side effect after gargling with rikkosan, no other side effects were observed in patients. Thirteen patients also dropped out of the study at the 1-month visit because of lack of efficacy, which caused the patients to want to change medication. However, the overall NRS scores significantly reduced, from 7.6 ± 2.7 at the first visit to 5.6 ± 2.8 at the 1-month visit ($P < 0.05$), and to 4.4 ± 3.3 at the final visit ($P < 0.05$).

Discussion

This is the first study to assess the efficacy of rikkosan for primary BMS using NRS scores. Rikkosan treatment showed a significant reduction in NRS scores for primary BMS, and no serious side effects. These results indicate that gargled rikkosan could be a potential therapeutic option for primary BMS.

Anti-anxiety and antidepressant medications have been used for the treatment of BMS and their efficacy has been reported (2–4). However, these agents are often associated with side effects such as dizziness and drowsiness (5–6). Side effects of medications must be considered when administering pharmacotherapy for BMS. In the present study, no obvious side effects were observed with rikkosan. In addition, since it is used as a gargle, it can be used as an alternative for patients who are resistant to the use of anxiolytics and antidepressants, and even for the elderly.

Although there are few studies on the pharmacological effects of rikkosan, some reports are available. Horie et al (14) suggest that rikkosan inhibits prostaglandin E_2 (PGE-2) production by selectively inhibiting cyclooxygenase-2 (COX-2) activity in activated macrophages in vivo. However, the pharmacological mechanism of pain control by rikkosan is still unclear; therefore, its mechanism of action in BMS remains unclear. Some of the crude herbs in rikkosan, particularly, *Asiasarum* root (saishin), are thought to have surface anesthetic action (11). In BMS patients, transient receptor potential vanilloid 1 (TRPV1), a capsaicin receptor that responds to nociceptive stimulation, such as thermal stimulation, is upregulated in the lingual mucosal epithelium (15). The components of saishin include agonists of TRPV1, such as methyl eugenol and higenamine (an alkaloid). It is our firm belief that some of the components of saishin bind to the TRPV1 receptor and produce an efficacy similar to topical capsaicin (2), although this is difficult to identify.

This study has several limitations. The number of overall cases and agents administrated was limited, in part because the target population was selected from patients with a diagnosis of primary BMS, rather than from a population who had used rikkosan. Definitive criteria for diagnosis of primary BMS have not yet been standardized; the definition used in this study may differ. Furthermore, this study is not a randomized controlled trial but a retrospective study. It is necessary to further continue this study while taking these factors into consideration.

Conclusions

In summary, the results of our study suggest that rikkosan, a Japanese traditional kampo medicine, can be effective in reducing symptoms in patients with primary BMS.

Abbreviations

NRS
numerical rating scale; BMS:burning mouth syndrome; ICHD-3:The International Classification of Headache Disorders; PGE2:prostaglandin E2; TRPV1:transient receptor potential vanilloid 1

Declarations

Ethical approval and consent to participate

This retrospective study was conducted with the approval of the Hokkaido University Hospital Independent Clinical Research Review Committee (Approval No. 019-0044) and waived the requirement for informed consent owing to the retrospective design.

Consent for publication

Not applicable

Availability of data and materials

We are not able to share our data because sharing data is not permitted by our hospital or the ethics committee.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Conceptualization: HH, KS. Methodology: HH, KS, JS, AT, NO. Investigation: HH, KS. Formal Analysis: HH, KS. Writing - Original Draft: HH. Writing - Review & Editing: KS, JS, YY. Supervision: YK.

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Figures

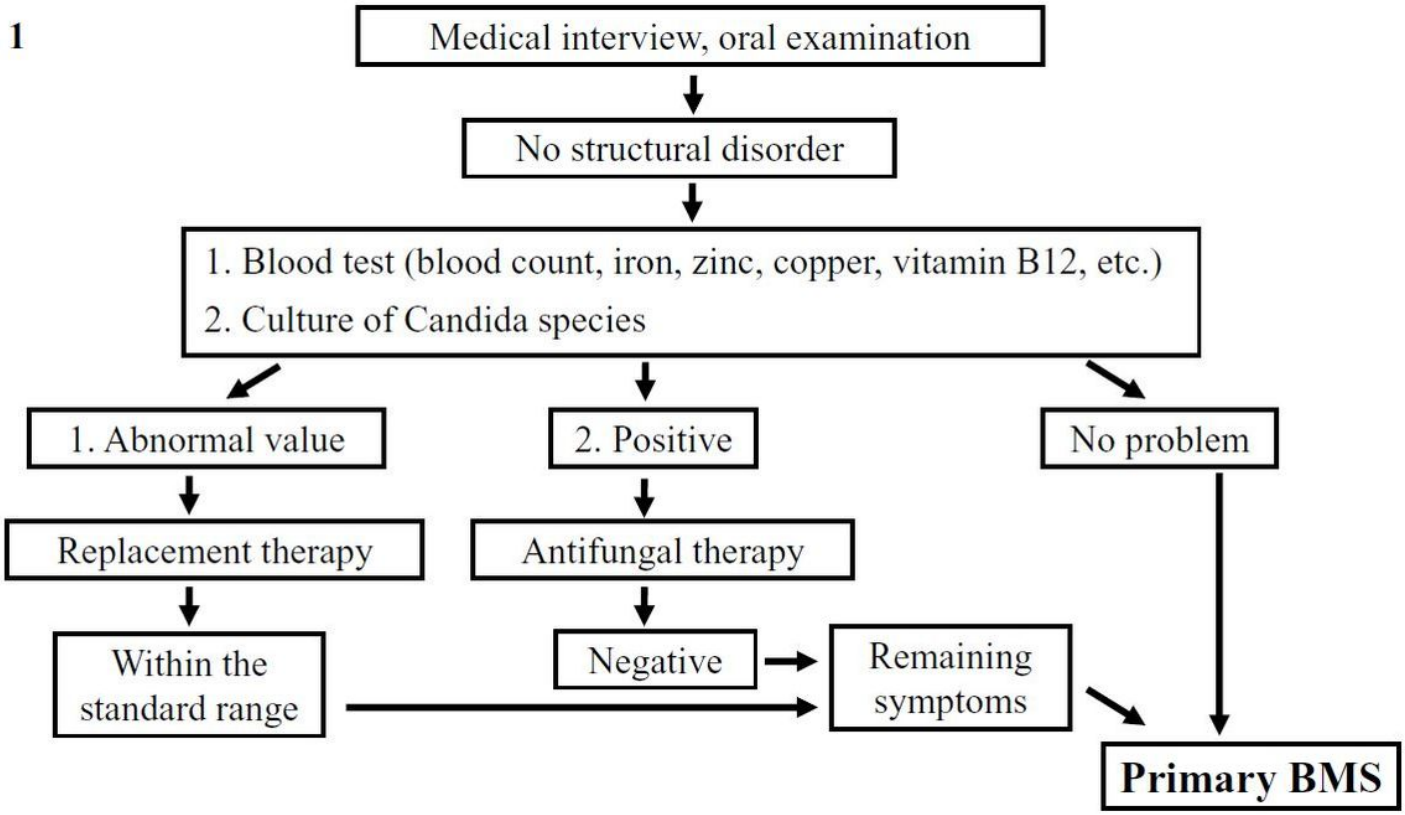


Figure 1

Our department's diagnostic algorithm for primary burning mouth syndrome (BMS) Patients were diagnosed with primary BMS if they had residual symptoms after antifungal therapy, replacement therapy for deficiency factors, such as trace metals and vitamin B12, and after blood tests were normal.

Fig. 2

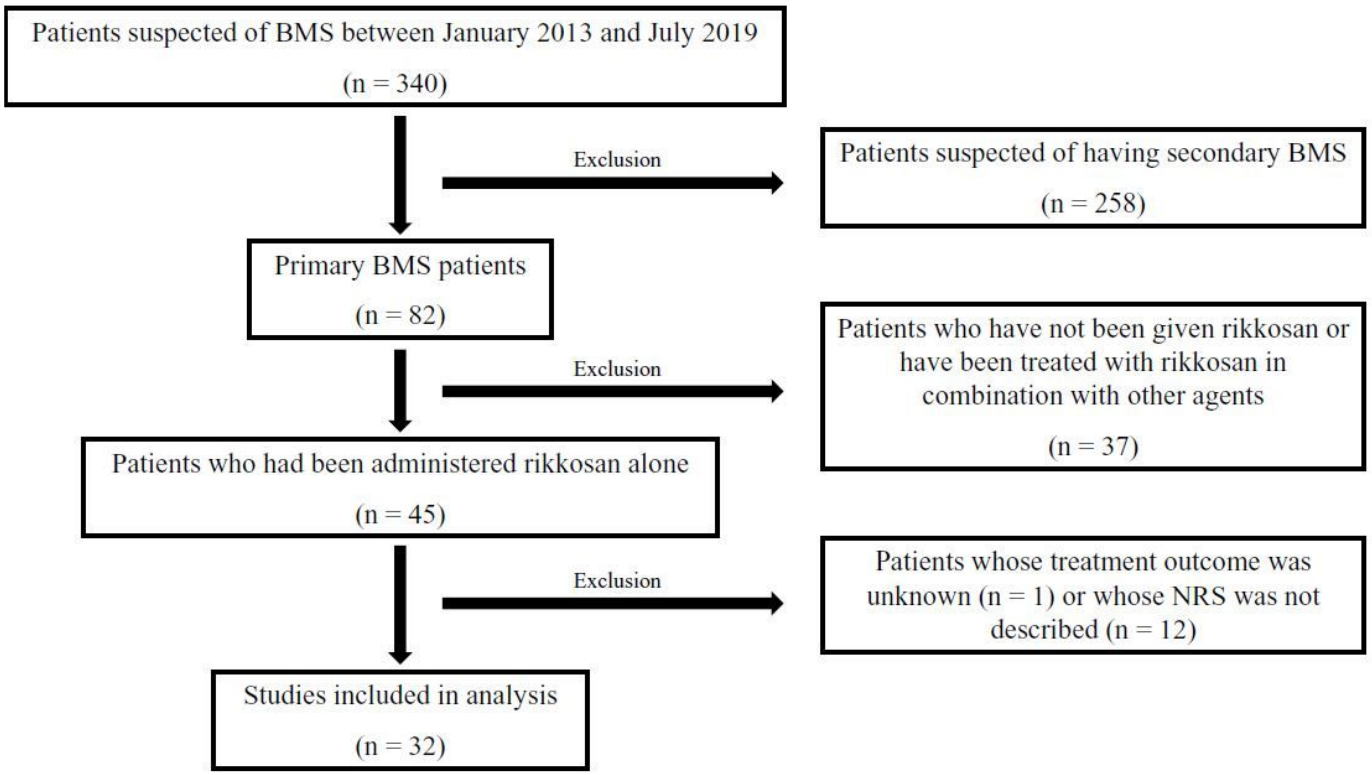


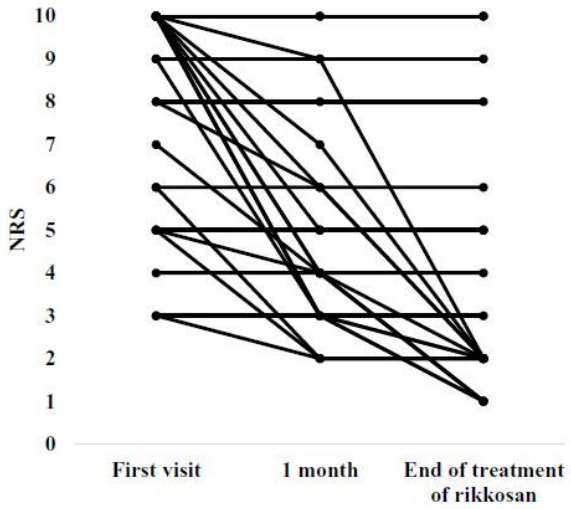
Figure 2

The inclusion and exclusion criteria The study included 32 patients.

Fig. 3

Patients	First visit	1 month	End of treatment of rikkosan
1	4	4	2
2	10	9	2
3	10	6	2
4	10	3	2
5	10	7	2
6	5	2	2
7	9	3	2
8	6	2	2
9	10	3	1
10	10	4	1
11	6	6	2
12	7	4	1
13	5	4	1
14	10	3	1
15	10	5	5
16	10	4	4
17	5	5	5
18	8	6	6
19	3	2	2
20	8	8	8
21	3	3	3
22	3	3	3
23	10	10	10
24	9	9	9
25	5	5	5
26	10	10	10
27	3	3	3
28	5	5	5
29	10	10	10
30	10	10	10
31	10	10	10
32	10	10	10

A.



B.

Figure 3

Changes in NRS scores between first visit, at 1 month after the initiation of gargling with rikkosan, and at the end of treatment of rikkosan (A) and (B) show the changes in pain scores for each patient treated with rikkosan.