Brief Report

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Analgesic effects of Goreisan in patients with glossodynia: A preliminary exploratory study

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SUMMARY: Glossodynia-related pain refers to persistent, chronic pain occurring on the oral mucosal surface. Various medications are prescribed depending on symptom profiles and have demonstrated therapeutic benefits; however, these agents are often associated with adverse effects such as drowsiness or dizziness. Goreisan, a traditional Japanese Kampo medicine, has long been used empirically for glossodynia-related pain, particularly in patients reporting symptom fluctuation associated with weather changes. Nevertheless, high-quality clinical evidence supporting its efficacy remains limited. This multicenter, randomized, open-label preliminary exploratory study enrolled patients receiving treatment for glossodynia-related pain. Participants were assigned to receive either Goreisan (7.5 g/day for 12 weeks) in addition to standard therapy or standard therapy alone. Pain intensity was assessed using the visual analog scale (VAS) at baseline and at 4, 8, and 12 weeks. Salivary amylase activity was measured as an exploratory stress-related biomarker, and atmospheric pressure was recorded at each outpatient visit. Owing to insufficient enrollment, all analyses were descriptive and exploratory. Pain intensity improved from baseline in both groups. However, the proportion of patients achieving ≥ 20% improvement in VAS at week 12 was not higher in the Goreisan group than in the control group. Weak negative correlations between VAS scores and barometric pressure were observed in both groups ($r \approx -0.2$). No clinically relevant adverse events or hepatic dysfunction related to Goreisan were identified. This preliminary exploratory study did not confirm a clear analgesic efficacy of Goreisan for glossodynia. However, the findings provide descriptive data on pain trajectories, safety, and potential meteorological associations, supporting the need for future large-scale, double-blind, placebo-controlled trials.

Keywords: glossodynia, burning mouth syndrome, Kampo medicine, Goreisan, exploratory study

1. Introduction

"Glossodynia (tongue pain)," synonymous with burning mouth syndrome, refers to persistent, chronic pain occurring on the oral mucosal surface and is often accompanied by burning sensations in the oral cavity. According to the International Classification of Headache Disorders, 3rd edition, glossodynia is defined as a prickling sensation or unpleasant tingling that recurs daily for more than 2 h per day for over 3 months.

Because the etiology of glossodynia remains unclear, no curative treatment exists, and current management relies on symptomatic therapy. Various pharmacological agents—including pregabalin, antidepressants, anticonvulsants, duloxetine, amitriptyline, *N*-methyl-D-aspartate receptor antagonists, and tramadol—are prescribed depending on clinical presentation. Although these agents may alleviate pain, they are frequently associated with adverse effects such as drowsiness and dizziness, limiting long-term use.

Goreisan, a Kampo medicine, has been used empirically for pain management in glossodynia and other oral and maxillofacial pain conditions, particularly when symptoms are perceived to fluctuate with meteorological changes such as barometric pressure variations (*1-5*). The tongue and surrounding oral tissues are richly supplied with capillaries and lymphatic vessels, rendering them potentially sensitive to changes in fluid balance. Goreisan is thought to improve local tissue metabolism, alleviate congestion, and enhance lymphatic

flow, with relatively few central nervous system–related adverse effects.

However, according to current chronic pain treatment guidelines, the level of evidence supporting Kampo medicines for chronic pain remains low (2C–2D), and well-designed clinical studies are lacking. Therefore, this study was conducted as a preliminary exploratory randomized trial to descriptively evaluate the efficacy and safety of Goreisan in patients with glossodynia.

2. Methods / Design

2.1. Study design

This multicenter, randomized, open-label exploratory trial enrolled patients undergoing treatment for glossodynia-related pain. After providing written informed consent, participants were randomly assigned (1:1) to receive either Goreisan in addition to standard therapy or standard therapy alone. The study was registered in the Japan Registry of Clinical Trials (jRCTs071200017) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice in Japan. The research protocol was approved by The Clinical Research Review Board in Nagasaki University.

2.2. Participants

Participants were recruited and treated at Nagasaki University Hospital, Aichi Medical University Hospital, and Tokyo Medical and Dental University. Clinical research coordinators explained the study details to all participants, after which written informed consent was obtained. This study included patients undergoing treatment for glossodynia.

Inclusion criteria include: (1) Patients receiving treatment for chronic pain in the oral and maxillofacial region; (2) Adults aged ≥ 20 years at the time of informed consent; (3) No sex restrictions; (4) Outpatient only; (5) Patients who received sufficient explanation of the study, demonstrated understanding, and provided informed consent. Exclusion criteria include (1) Patients currently taking Kampo medicines containing kakkonto; (2) Patients with severe hypertension (systolic blood pressure ≥ 120 mmHg); (3) Patients with severe hepatic or renal dysfunction; (4) Patients with drug hypersensitivity; (5) Pregnant women, women who may be pregnant, and breastfeeding women; (6) Patients who participated in another clinical trial within the past 4 months; (7) Individuals deemed inappropriate for participation by the principal investigator.

2.3. Intervention

After consent, baseline assessments of pain intensity and salivary flow were performed. The intervention group received Goreisan at 7.5 g/day for 12 weeks in addition to ongoing standard therapy. Standard therapy consisted of Western pharmacological treatments selected by the treating physician, including antidepressants, anticonvulsants, and non-opioid analgesics, with stable dosing during the study period. The control group continued standard therapy alone without Kampo medicine.

Meteorological data, including temperature, humidity, and barometric pressure, were recorded during each outpatient visit. Patients also recorded self-assessed pain intensity at home.

2.4. Endpoints

The primary exploratory endpoint was defined as ≥ 20% improvement in VAS score from baseline to week 12. Secondary exploratory endpoints included changes in VAS score at weeks 4 and 8, salivary amylase activity, tongue findings, and safety outcomes.

2.5. Sample size

This study aimed to enroll 90 patients undergoing treatment for glossodynia. A preliminary study showed that 8 of 14 cases (57%) experienced ≥ 20% improvement in VAS scores after 2 weeks of Goreisan. Assuming a 10% improvement rate in the standard therapy group and a 40% expected improvement rate in the Goreisan group, with $\alpha = 0.05$, power = 0.9, and a 10% anticipated dropout rate, a target sample size of approximately 90 patients (41 per group) was required. Therefore, 45 patients were included in each group.

2.6. Randomization

Participants were registered and randomized using REDCap. Stratified block randomization was used to allocate participants in a 1:1 ratio to the Goreisan or control group.

2.7. Statistical analysis

The primary endpoint was defined as a ≥ 20% reduction in VAS score from baseline. This study aimed to statistically confirm whether the Goreisan group showed a higher response rate than the standard therapy group. However, due to insufficient enrollment, formal hypothesis testing was not feasible. Therefore, an estimation of endpoints and confidence intervals was performed instead. Baseline characteristics were expressed as medians and interquartile ranges for continuous variables and counts and percentages for categorical variables. Correlation between barometric pressure and VAS scores was also evaluated. All statistical analyses were performed using R version 4.4.0.

3. Results and Discussion

Twenty-six patients were enrolled, and 25 completed the study. Baseline characteristics, including pain severity and disease duration, were comparable between groups (Table 1). Pain location was predominantly the tongue in both groups (Goreisan: 12/13; Control: 10/13). Gingival or palatal pain was less frequently reported, and no marked imbalance in pain distribution between groups was observed at baseline. Initial pain severity evaluated by VAS score was identical in both group. Estimated disease duration with pain was identical in both group of several months.

Both groups demonstrated improvements in VAS scores over time. However, the proportion of patients achieving ≥ 20% improvement at week 12 was numerically higher in the standard therapy group than in the Goreisan group (Table 2). Figure 1 illustrates changes in VAS scores from baseline.

Salivary amylase levels showed variability during follow-up, with transient elevations observed in the control group at week 4 (Figure 1). Pearson's correlation analysis revealed weak negative correlations between VAS scores and barometric pressure in both groups (Goreisan group: $r = -0.19$; control group: $r = -0.22$).

No serious adverse events occurred. Liver function parameters remained within normal ranges throughout the study (Table 3).

This randomized, open-label exploratory study evaluated the efficacy and safety of Goreisan in patients receiving treatment for glossodynia. Although the originally planned sample size was not achieved, the present study provides preliminary descriptive information regarding pain trajectories, stress-related biomarkers, safety, and potential associations between pain perception and meteorological factors in this patient population.

3.1. Association between Goreisan and pain perception

Pain intensity, assessed using self-reported VAS scores, improved over time in both the Goreisan and control groups. However, contrary to the initial hypothesis, the proportion of patients achieving a ≥ 20% improvement in VAS at week 12 was not greater in the Goreisan group than in the standard therapy group. Given the exploratory nature of this study and the insufficient sample size, these findings should not be interpreted as evidence against the efficacy of Goreisan, nor do they support a definitive analgesic benefit.

Several factors may have contributed to the observed pattern. First, the open-label design may have introduced expectation bias. Patients allocated to the Goreisan group (standard therapy + Goreisan) may have anticipated a marked therapeutic effect, potentially influencing their subjective pain ratings. Conversely, patients in the control group may have experienced reassurance or therapeutic benefit from continued standard care and repeated clinical encounters, resulting in apparent pain improvement. Such bias is particularly relevant for subjective endpoints such as pain intensity and may partly explain the unexpectedly greater improvement observed in the control group.

From a mechanistic perspective, prior case reports and small observational studies have suggested that Goreisan may exert anti-inflammatory effects through modulation of aquaporin function and regulation of glymphatic flow, particularly in conditions associated with fluid imbalance or meteorological changes (*6*). However, the present study was not designed to test these mechanisms, and the current findings should be interpreted as hypothesis-generating rather than confirmatory.

Table 2. The proportion of patients who achieved ≥ 20% reduction in pain (VAS) from baseline at each time point

Group	Week	Event/Total	Proportion % (95%CI)
Goreisan	4	3/13	23.1 (8.2 to 50.3)
	8	4/13	30.8 (12.7 to 57.6)
	12	4/13	30.8 (12.7 to 57.6)
Standard treatment	4	6/12	50.0 (25.4 to 74.6)
	8	6/12	50.0 (25.4 to 74.6)
	12	6/12	50.0 (25.4 to 74.6)

Abbreviations: CI, confidence interval.

Table 1. Demographic data

Characteristic	Goreisan (n = 13)	Standard treatment (n = 12)
Female, n (%)	9 (69%)	11 (92%)
Age, median (IQR)	59 (39, 75)	66 (40, 78)
Height, median (IQR)	156.7 (150.0, 175.0)	155.0 (149.0, 170.0)
Weight, median (IQR)	56 (40, 78)	52 (39, 69)
Initial VAS score	4.0 (2,4, 5.7)	4.3 (2.5, 6.0)
Primary pain site (Tongue)	12	10
Primary pain site (Gingiva)	1	2
Primary pain site (Palate)	1	0

Abbreviations: IQR, interquartile range. The definition of primary pain site (Tongue) is as follows: Tongue refers to all areas including the tongue itself; Gingiva refers to areas including the gums; Palate refers to areas including the palate.

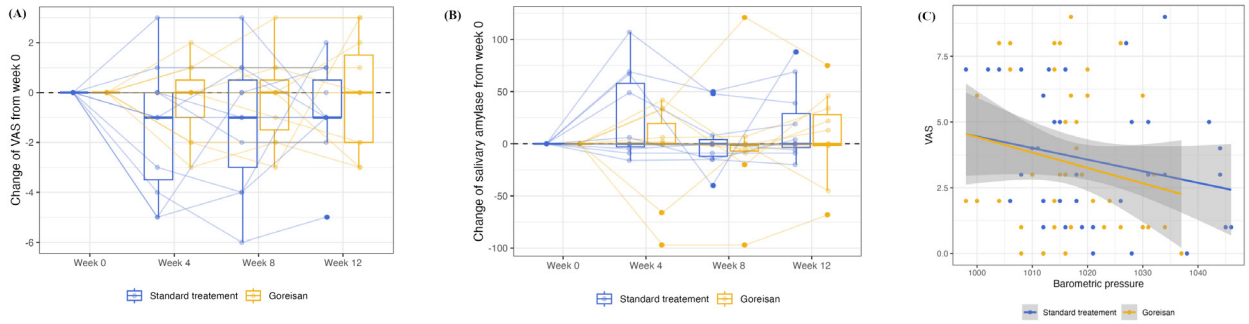

Figure 1. (A) The change in VAS from week zero. (B) The change in salivary amylase from week zero. There is slight increase in amylase level at week four in control group. (C) The correlation between VAS and barometric pressure.

Table 3. Evaluation of liver function at week 12

Characteristic	Goreisan (n = 13)	Standard treatment (n = 12)
AST	20.4 (4.9)	19.1 (5.3)
ALT	19.2 (8.0)	18.1 (7.9)
γ-GTP	46.1 (88.4)	32.2 (47.9)

AST: Alanine transaminase; ALT, Aspartate aminotransferase; γ-GTP, gamma-glutamyl transpeptidase.

3.2. Stress evaluation using salivary amylase

Patients with glossodynia frequently experience psychological stress related to chronic pain, anxiety, and frustration due to the absence of identifiable organic pathology. This study is, to our knowledge, the first to explore changes in salivary amylase activity during Goreisan treatment in patients with glossodynia.

Salivary amylase levels demonstrated variability during follow-up, with transient elevations observed in the control group at week 4. Salivary amylase is considered a surrogate marker of sympathetic nervous system activity and acute stress responses. The observed elevation in control group may reflect fluctuations in stress levels associated with changes in pain perception, adaptation to treatment, or comorbid psychological factors. However, because other stress-related biomarkers such as cortisol were not measured, and because salivary amylase is sensitive to multiple confounding factors, these findings must be interpreted cautiously. Further studies incorporating comprehensive psychophysiological assessments are warranted to clarify the relationship between glossodynia, stress, and treatment response.

3.3. Relationship between pain perception and barometric pressure

This study also explored the association between pain perception and barometric pressure changes. Weak negative correlations between VAS scores and barometric pressure were observed in both treatment groups, suggesting that pain perception may increase slightly as atmospheric pressure decreases. However, the magnitude of these correlations was small ($r \approx -0.2$), indicating limited explanatory power.

These findings should therefore be regarded as preliminary observations rather than evidence of a clinically meaningful relationship. Correlation does not imply causation, and numerous confounding factors—such as temperature, humidity, psychological state, and individual sensitivity to environmental changes—may influence pain perception. Nevertheless, the results are consistent with previous reports that certain chronic pain conditions, including trigeminal pain and meteorological headaches, may be influenced by barometric pressure fluctuations (*7,8*).

From the perspective of traditional East Asian medicine, meteorological factors have long been considered relevant to symptom fluctuation, and Goreisan has historically been prescribed for conditions thought to be associated with fluid imbalance. Although the present study does not establish a causal link between barometric pressure changes and glossodynia-related pain, it supports further investigation into whether specific subgroups of patients—such as those reporting weather-sensitive symptoms—may respond differently to treatment.

3.4. Limitations and future directions

The most fundamental limitation of this study is the insufficient sample size relative to the original study design, which precluded formal hypothesis testing and definitive conclusions regarding efficacy. The insufficient sample size is a fundamental flaw of this study, and the true efficacy of Goreisan cannot be confirmed or refuted based on these findings.

Additional limitations include the open-label design, heterogeneity of concomitant standard therapies, and reliance on subjective pain assessments. The use of an "open-label" design (non-blinded), where both patients and researchers are aware of the group allocation, introduces expectation bias and assessment bias. The anomalous finding of a higher VAS improvement rate in the control group strongly suggests the presence

of such bias in this study. Therefore, future studies should prioritize a double-blind, placebo-controlled design to minimize expectation and assessment bias. The development of a placebo formulation identical in appearance and taste to Goreisan appears feasible and should be considered a core design element for future clinical study. Larger sample sizes would also allow stratified analyses to explore whether specific patient subgroups, such as those with meteorologically sensitive symptoms, derive greater benefit from Goreisan.

4. Conclusion

In summary, this exploratory study did not confirm a clear analgesic advantage of Goreisan over standard therapy in patients with glossodynia. However, it provides valuable descriptive data on safety, pain trajectories, stress-related biomarkers, and potential meteorological associations. These findings underscore the need for well-designed, adequately powered randomized controlled trials to clarify the therapeutic role of Goreisan in glossodynia.

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