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Report

Clinical Response to Premonitory-Phase Goreisan Therapy in Migraine with Weather- and Barometric Pressure-Related Headache

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Goreisan has long been prescribed for weather- and barometric pressure-related headache. However, its efficacy when initiated during the premonitory phase of migraine has not been systematically evaluated. We retrospectively reviewed 81 patients diagnosed with migraine (mean age: 41.7 ± 11.5 years; 14.8% male). Subtypes included migraine with aura (MA, n = 1), without aura (MO, n = 72), and combined type (MA + MO, n = 8). Patients who received Goreisan monotherapy during the premonitory phase were categorized as consistent responders (CRs) or inconsistent responders (IRs). Clinical characteristics and treatment responses were compared between the two groups. The overall response rate to Goreisan was 61.7% (n = 50). Headache profiles and the efficacy of triptans did not differ significantly between CRs and IRs. However, psychiatric comorbidities were more frequent in IRs than in CRs (p = 0.011). Initiating Goreisan during the premonitory phase appears to be an effective therapeutic approach for migraine patients with weather- and barometric pressure-related headache. Clinical background, including psychiatric history, may influence treatment outcomes and should be considered when selecting patients for this strategy.

Key words migraine, goreisan, premonitory period, psychiatric disorders, weather

INTRODUCTION

Migraine is a common neurological disorder that causes substantial disability and significantly impairs quality of life. In Japan, the prevalence of migraine is estimated to be 8.4–8.6%.[1,2] Various triggers, including stress, irregular diet, sleep disturbance, menstruation, and changes in weather and barometric pressure, have been identified.[3–5] While some of these triggers can be managed by patients themselves, weather- and barometric pressure-related headaches remain difficult to control.

Japanese herbal Kampo medicines, such as Goreisan, Goshuyuto, and Kakkonto, are listed as empirically effective options in the Japanese Clinical Practice Guidelines for Headache 2021.[6] Goreisan, a formula composed of Alismatis rhizoma, Atractylodis lanceae rhizoma, Polyporus, Poria, and Cinnamomi cortex, is widely used for migraines, tension-type headaches, and secondary headaches. Experimental studies suggest that Goreisan modulates water metabolism by inhibiting aquaporin-4 activity, thereby reducing cerebral edema in animal models.[7] Clinically, it is used both prophylactically and as needed for headaches related to weather and barometric pressure.[6]

The time course of migraine attacks includes premonitory, aura, headache, and postdrome phases.[8,9] Premonitory symptoms such as stiff neck and shoulders, photophobia, and phonophobia often precede migraine onset.[9] Our previous survey showed that many patients with weather- or barometric pressure-related headache reported premonitory symptoms, particularly neck and shoulder stiffness.[10] These observations suggest that early intervention at the premonitory phase could allow patients to mitigate the onset or severity of attacks. Some of these patients used Goreisan at the onset of such symptoms, suggesting the potential of a premonitory-phase treatment strategy. However, the clinical efficacy of initiating Goreisan during the premonitory phase has not been systematically investigated, and factors associated with treatment response remain unclear.

Therefore, the aim of the present study was to evaluate the efficacy of Goreisan initiated during the premonitory phase in migraine patients with weather- and barometric pressure–related headache, and to identify clinical factors, including premonitory symptom recognition, that may predict treatment response.

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METHODS

Subjects The cohort consisted of 81 patients with migraine as their initial headache who were prescribed Goreisan (TJ-17, 2.5 g/time, 7.5 g/day) as short-term preventive therapy for weather- and barometric-induced headache by specialists in the Japanese Headache Society. Patients were admitted to the outpatient clinic of Kuramae Kato Medical Clinic, Tokyo between June 2017 and April 2022. The patients took Goreisan from the premonitory period. Headache was diagnosed according to the International Classification of Headache Disorders, Third Edition criteria.[11] Patients with medication-overuse headache (MOH) or with chronic migraine (CM) were asked about their initial headache by specialists, who also confirmed the initial headache and type of episodic migraine after treating the patients for MOH or CM. MOH patients were included if they had migraine as their initial headache. Although the cohort included patients with migraine and those with both migraine and tension-type headaches, patients with tension-type headache were excluded from this study.

According to their clinical response to Goreisan, patients were divided into consistent responder (CR) and inconsistent responder (IR) groups. The patients were asked whether their headaches diminished following Goreisan therapy from the premonitory period. Patients whose pain score improved to 50% or less compared to before treatment were judged to have received effective treatment, whereas those whose pain score was less than 50% were judged to have received ineffective treatment. Pain scores were assessed using a numerical rating scale (NRS), where 0 indicated no headache and 10 represented the maximum pain ever experienced by the patient. Consistent responders were defined as patients who experienced a ≥50% reduction in average NRS score across multiple migraine attacks. Attack frequency was not considered in this definition. Patients who did not meet this threshold were categorized as inconsistent responders. Patients who used Goreisan in combination with Goshuyuto (n = 92) and those who did not return for follow-up visits (n = 17) were excluded from the study, resulting in a final enrollment of 81 out of 190 patients.

Clinical responses to triptans were determined according to the responses of the responders and non-responders. Responders treated with triptans were defined as those with diminished pain described as either “mild” (within 4 h of oral or nasal administration) or “none” (within 2 h of oral or nasal administration) in at least 2/3 attacks.[12-14] Patients whose pain was not alleviated in three consecutively treated migraine attacks were defined as non-responders.

This clinical research was conducted after obtaining approval from the Human Subject Research Ethics Committee of Teikyo Heisei University (approval number: 30-115-1). The patients were informed that they are able to opt out from the use of their data for research purposes at the bulletin board in the clinic. This study was performed in accordance with the principles of the Declaration of Helsinki.

Clinical Parameters For medical examinations, we used headache diaries and/or headache questionnaires to obtain pain location, headache characteristics, and frequency of headache and associated symptoms, and confirmed these by interview. In the case of MOH, we confirmed the initial headache and type of episodic migraine after curing the patients of MOH or CM.

The data collected from all patients were as follows: age, sex, current type of headache being treated, initial headache, type of episodic migraine, trigger of migraine, and history before the commencement of Goreisan treatment. In addition, we collected data on headache characteristics and frequency, location of pain, and associated symptoms before treatment. We investigated the use of prophylactic drugs and use of acute treatment drugs, such as triptans, when using Goreisan. Furthermore, we investigated the reduction of headache by Goreisan.

Statistical Analysis For continuous variables, statistical analyses were conducted with F test followed by Student’s *t* test. For categorical variables, χ^2 test or Fisher’s exact test was conducted. Fisher's exact test was utilized when the sample size was small with expected frequency less than five in one cell. $p < 0.05$ was considered significant. The statistical software used was Excel Statistics ver. 3.21 (Social Information Service).

RESULTS

Patient Characteristics The study population consisted of 81 patients with migraine as their initial headache (age, 41.7 ± 11.5 years), consisting of 12 (12.1%) men and 69 (87.9%) women. In total, 81 individuals had migraines with the following characteristics: one patient with aura (MA), 72 patients without aura (MO), and 8 patients with combined type (MA + MO). The efficacy of Goreisan (CR ratio) was 61.7% (n = 50) for these 81 patients (Table 1).

Factors Associated with Clinical Response to Goreisan The frequencies of past histories of psychiatric disorders was significantly different between the CR and IR groups ($p = 0.011$, Table 1). The clinical profile of headache was not different between the CR and IR groups (Table 2). No intergroup difference was detected for the use or efficacy of triptans (Table 3). Edema was observed in three patients in the CR group and three patients in the IR group when Goreisan was prescribed ($p = 0.670$, data not shown).

DISCUSSION

Katsuki *et al*. reported an 83.1% efficacy rate for acute treatment using Goreisan in 71 cases of weather-related migraine.[15] However, the proportion of female subjects was 50.7%, and the criteria for judging efficacy were not provided. On the other hand, in the present study, efficacy was 61.7% and 85.2% of subjects were women who took Goreisan upon experiencing premonitory symptoms. The difference in responder rates between this study (61.7%) and the previous report by Katsuki *et al*. (83.1%) may be due to methodological differences, including the timing of Goreisan administration, the definition of efficacy, and population characteristics such as sex distribution. This difference in diagnostic inclusion criteria may also have contributed to the discrepancy in responder rates. Although the overall efficacy rate was lower than previously reported, this study suggests a potential clinical value of initiating Goreisan during the premonitory phase, as an association was observed between early administration and improved management of migraine attacks. However, given the retrospective nature of the study, causality cannot be established.

Migraine patients are known to be particularly prone to

Table 1. Background of Patients

	CR		IR		*p* value
	n = 50	%	n = 31	%	
Age (mean ± SD)	40.9 ± 11.8		43.0 ± 11.1		0.425
Sex					
Men	5	10.0	7	22.6	0.197
Women	45	90.0	24	77.4	
Type of headache (headache during treatment)					
Migraine	38	76.0	28	90.3	0.344
Migraine + TTH	5	10.0	2	6.5	
Migraine + MOH	4	8.0	1	3.2	
Chronic migraine	3	6.0	0	0.0	
Primary headache					
MA	0	0.0	1	3.2	0.329
MO	44	88.0	28	90.3	
MA + MO	6	12.0	2	6.5	
Association with menstruation	n = 45		n = 24		
Menstrual-related migraine	28	62.2	16	66.7	0.715
Triggers of migraine					
Changes in weather and barometric pressure	50	100.0	31	100.0	(-)
Temperature difference	2	4.0	3	9.7	0.366
Crowd of people	4	8.0	4	12.9	0.474
Past history					
Hypertension	3	6.0	3	9.7	0.670
Hyperlipidemia	15	30.0	11	35.5	0.607
Diabetes	3	6.0	0	0.0	0.282
Epilepsy	2	4.0	1	3.2	1.000
Bronchial asthma	0	0.0	1	3.2	0.383
Sinusitis	1	2.0	3	9.7	0.154
Psychiatric disorders	1	2.0	6	19.4	0.011 *
MOH	8	16.0	2	6.5	0.303
Insomnia	2	4.0	4	12.9	0.196
Hay fever	18	36.0	10	32.3	0.731
Prophylactic drugs					
Yes	33	66.0	20	64.5	0.891
No	17	34.0	11	35.5	
Prescribed prophylactic drugs					
Lomerizine	25	50.0	13	41.9	
Valproate	19	38.0	11	35.5	
Clonazepam	12	24.0	10	32.3	
Amitriptyline	7	14.0	4	12.9	
Topiramate	3	6.0	4	12.9	
Propranolol	1	2.0	1	3.2	
Galcanezumab	1	2.0	0	0.0	

*: $p < 0.05$, CR vs. IR

CR: consistent responder, IR: inconsistent responder, TTH: tension-type headache, MOH: medication overuse headache, MA: migraine with aura, MO: migraine without aura

developing MOH as a comorbidity.[16] We previously reported that the incidence of depression is significantly higher in MOH patients than migraine patients.[17] Moreover, we reported that the complication of depression caused by another psychiatric disorder, such as panic disorder or personality disorder, contributed to the negative response to prophylactic therapy using valproate in migraine patients.[18] In the present study, psychiatric comorbidities were associated with a reduced response to Goreisan; however, this trend is consistent with other migraine treatments and should be considered a general limitation rather than a specific drawback of Kampo therapy.

The overuse of acute treatment drugs, such as NSAIDs and triptans, has become a concern; however, there have been no reports of MOH caused by Kampo such as Goreisan. MOH is an intractable headache that recurs repeatedly,[19] and most MOH patients initially had migraine.[16] Ishikawa *et al*. reported that the combined use of Western prophylactics and Kampo, such as Goreisan, contributes to successful withdrawal from causative drugs.[20] In Japan, Teirakku, an over-the-counter drug of Goreisan, is taken when the patient feels unwell such as when the weather turns bad (Kobayashi Pharmaceutical Co.).[21] The recommended timing of administration of Goreisan is the same as in this study, in which it is taken from the premonitory period. These findings indicate that premonitory-phase Goreisan therapy was associated with reduced migraine frequency and may help prevent MOH, particularly in patients who are able to recognize early premonitory symptoms. However, this association should be interpreted with caution due to

Table 2. Clinical Profile of Headache

	CR		IR		*p* value
	n = 50	%	n = 31	%	
Age at onset of migraine (mean ± SD)	21.1 ± 8.0		23.4 ± 10.5		0.257
Duration of migraine history (mean ± SD)	19.9 ± 13.2		19.6 ± 13.7		0.935
Pain location					
Occipital/accipitocervical	9	18.0	7	22.6	0.615
Frontal	5	10.0	1	3.2	0.399
Temporal/temple	24	48.0	15	48.4	0.973
Pariental	1	2.0	1	3.2	1.000
Whole head	15	30.0	10	32.3	0.831
Periobital	14	28.0	7	22.6	0.589
Characteristics					
Throbbing	27	54.0	19	61.3	0.520
Feeling of heaviness	31	62.0	19	61.3	0.949
Tightness	7	14.0	4	12.9	1.000
Others	3	6.0	3	9.7	0.670
Frequency (before treatment with Goreisan, day/month)					
0~5	27	54.0	13	41.9	0.236
6~10	13	26.0	13	41.9	
11~14	4	8.0	4	12.9	
Over 15	6	12.0	1	3.2	
Associated symptoms					
Nausea/vomiting	41	82.0	26	83.9	0.693
Photophobia	39	78.0	24	77.4	0.951
Phonophobia	18	36.0	11	35.5	0.419
Osmophobia	16	32.0	10	32.3	0.981
Aggravation of headache by physical activity	45	90.0	27	87.1	0.726
Allodynia	18	36.0	11	35.5	0.962
Vertigo, dizziness	10	20.0	9	29.0	0.327

CR: consistent responder, IR: inconsistent responder

Table 3. Use of Triptans

	CR		IR		*p* value
	n = 50	%	n = 31	%	
Use of triptan					
Yes	46	92.0	31	100.0	0.292
No	4	8.0	0	0.0	
Prescribed triptans					
Sumatriptan	8	16.0	2	6.5	
Rizatriptan	15	30.0	6	19.4	
Eletriptan	19	38.0	12	38.7	
Naratriptan	2	4.0	3	9.7	
Zolmitriptan	2	4.0	8	25.8	
Response to triptans	n = 46		n = 31		
Responder	46	100.0	31	100.0	1.000
Nonresponder	0	0.0	0	0.0	

CR: consistent responder, IR: inconsistent responder

the retrospective design of the study.

The most important contribution of the present study is the demonstration that initiating Goreisan during the premonitory phase can be an effective therapeutic strategy for weather- and barometric pressure-related migraine. This study had several limitations. First, the sample size was small, and it was conducted at a single clinic; therefore, a multi-institutional approach is needed for validation of our findings. Second, the study had a retrospective design. Future studies with a larger sample size are warranted to confirm the reproducibility of our findings and allow for more robust statistical modeling. Third, pain reduction was assessed using NRS, rather than a formally validated tool such as the Visual Analogue Scale (VAS). This may raise concerns regarding reproducibility. However, NRS is widely used in clinical practice due to its simplicity and ease of understanding for patients, and was considered appropriate for this real-world study. In future studies, it will be important to stratify patients based on psychiatric comorbidities and to evaluate whether combining Goreisan with other Kampo medicines can further enhance therapeutic outcomes.

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Conflict of interest The authors declare no conflict of interest.

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