The Efficacy of Japanese Herbal Kampo Medicine as an Acute and Prophylactic Medication to Treat Chronic Daily Headache and Medication Overuse Headache:—Single Arm Retrospective Study

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Abstract

Introduction

A chronic daily headache (CDH) comprises a group of headaches occurring at least 15 days per month for three or more consecutive months. We retrospectively investigated the effectiveness of the hybrid treatment strategy for CDH using Kampo medicine combined with Western medication.

Methods

We retrospectively investigated 43 consecutive first-visit CDH patients. In addition to Western acute and prophylactic medications, we prescribed three types of Kampo medicines: goreisan, goshuyuto, and kakkonto depending on the patients’ symptoms. Headache impact test-6 (HIT-6), monthly headache days (MHD), monthly migraine days (MMD), and monthly acute medication intake days (AMD) before, 1- and 3-months after starting the hybrid medications were assessed as outcomes.

Results

Thirty-six women and seven men were included. The median age was 51 years old. Nine were chronic migraine (CM), 22 were episodic migraine and tension-type headaches (EM+TTH), and 12 were chronic TTH. Twenty-seven patients also had medication overuse headaches (MOH). The medians of HIT-6 before, one and three months after treatment were 63, 48, and 40, respectively. Those of MHD were 20, 5, and 2. Those of MMD were 2, 0, and 0. Those of AMD were 15, 0, and 0. Significant reductions in HIT-6, MHD, MMD, and AMD were observed one and three months after starting Kampo treatment. Similar trends were observed in the EM+TTH and MOH patients as subgroup analyses.

Conclusion

The hybrid medication strategy of Kampo and Western medicines for CDH is safe and effective in terms of both acute and prophylactic medications with rapid efficacy.

Introduction

A chronic daily headache (CDH) comprises a group of headaches occurring at least 15 days per month for three or more consecutive months. About 5% of the normal population suffers from CDH [1]. The treatment for CDH is difficult because (1) acute medications are ineffective in 25% of patients, which can cause a transformation from episodic to chronic headache [2], medication-overuse headache (MOH) [3,4], and other side effects [5], and (2) prophylactic medications are ineffective in about 50% of patients and have side effects, leading to poor patient adherence, with more than half of the patients stopping treatment within two months [6]. In this context, alternative acute and prophylactic medications for CDH are needed. The ideal medication is a drug that can be used for headache attacks, may not lead to chronic headache and MOH, and can also be used prophylactically with rapid effectiveness.

In Japan, to solve these problems of Western medicine, Japanese traditional herbal Kampo medicine can be used for headache treatment and is also described in the Japanese Clinical Practice Guideline for Headache 2021 [7]. Kampo medicine can be used as both acute [8] and prophylactic therapy [9-12] for headaches. In our hospital, we treated CDH patients with the so-called “hybrid medication strategy of Kampo and Western medicines” [13]. We retrospectively investigated the effectiveness of the CDH treatment strategy using
Kampo medicine, including goreisan, goshuyuto, and kakkonto, combined with Western medication.

Materials And Methods

Study population

From the medical records between October 2021 and May 2022, we retrospectively investigated 43 consecutive first-visit CDH patients who presented at our headache-specialized outpatient. All the patients suffered from headaches at least 90 days before the first visit and the Kampo treatment. The headache diagnosis was based on the International Classification of Headache Disorders, 3rd edition (ICHD-3) [14]. Chronic migraine (CM), episodic migraine with tension-type headache (EM+TTH), chronic TTH (CTTH), and MOH were diagnosed.

The hospital’s research ethics committee approved this study (approval number 2021-4), and we gained written informed consent for this study from all the patients or patients’ families. This retrospective study was performed following the Declaration of Helsinki.

Treatment strategy

After diagnosing the headache based on the ICHD-3, we treated the patients by referring to the Japanese Clinical Practice Guideline for Headache 2021 [7]. Depending on the severity, we prescribed acute medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and triptans. In addition, we also prescribed prophylactic medications, such as lomerizine, propranolol, angiotensin receptor blockers, valproic acid, antidepressants, monoclonal calcitonin gene-related peptide antibodies (CGRP mAbs), and muscle relaxants. If specific prophylactic medications had been used in the past and were ineffective or had side effects, they were not to be prescribed aggressively.

We also prescribed three types of Kampo extract formulations considering the patients’ symptoms. The choice of a specific Kampo medicine was based on the guidelines [7], experts’ opinions [15], and previous Japanese reports [7,8,16-18]. For CDH patients with mainly TTH, we prescribed kakkonto [19]. In the case of CDH with migraine, we used two different drugs: goshuyuto for migraines with or without aura [9,20], or for those with sensitivity to cold or the menopausal disorder [21], and goreisan for patients with edema or dehydration (sudoku status; unbalance of water distribution in Kampo medicine theory) [22] or migraines associated with weather conditions [23,24]. All Kampo medications were taken as needed, depending on the patients’ symptoms. Multiple Kampo medicines were sometimes prescribed, and patients were given a choice depending on the characteristics of their headaches.

Notably, we instructed that the Kampo medicine could be taken prophylactically before a headache occurs or during prodrome symptoms. Besides, Kampo medicine could be taken daily against a headache as a prophylactic medication, with a maximum of three packets per day, in addition to the prescribed Western medicines. We also told the patients that Kampo medicine could be used as an acute medication when the headache was present but not so severe as to use NSAIDs or triptans. When a single Kampo intake could not resolve the headache, Kampo medicine could be used in combination with NSAIDs and triptans. This prescription policy, for Kampo medicine as both acute and prophylactic medication, was based on the fact that Kampo medicine contains a wide variety of substances, not a single active ingredient, and each component acts comprehensively on the entire body to safely produce a therapeutic effect [15]. Such a prescription policy of Kampo medicine as both acute and prophylactic medication is beginning to be widely practiced in Japan [13].

Clinical variables and outcomes

We collected patients’ characteristics, such as age, sex, comorbidities, and the onset of the headache (years ago). Clinical data reported by paper-based or electronic headache diaries were used. Monthly headache days (MHD), monthly migraine days (MMD), and monthly acute medication intake days (AMD) were defined as the monthly values over the respective observation period of 30 days. A headache day was defined as a day with any kind of headache; a migraine day was defined by patients when they had severe pain, migraine pain characteristics (pulsating, one-sided pain), aura symptoms, vegetative symptoms like phono- or photophobia, nausea, vomiting, need for rest, or when triptans were taken [25]. Headache impact test-6 (HIT-6) [26] was also investigated over the respective observation period. Monthly use days of acute medication and Kampo medicine were also collected from the headache diary. The prescribed prophylactic medications we started with Kampo medicine as the hybrid treatment were also checked. The outcomes were defined as the changes in HIT-6, MHD, MMD, and AMD before treatment and after one or three months.

Statistical Analysis

Results were presented as the median (range). A Friedman’s test and a subsequent Wilcoxon’s test were performed to compare HIT-6, MHD, MMD, and AMD before treatment and after one or three months. We conducted these analyses using version 28.0.0 of SPSS software (IBM, NY, USA). A two-tailed p<0.05 was considered statistically significant. Bonferroni’s correction for multiple comparisons in each test was applied, but we did not apply it throughout the study [27].
Results

General characteristics

Table 1 shows the characteristics of 43 CDH patients. Thirty-six women and seven men were included. The median age was 51 (15-99) years old. Of the 43 patients, 9 were CM, 22 were EM+TTH, and 12 were CTTH. Twenty-seven patients also had MOH. The median past years from the first repetitive headache was 20 (1-70) years. Goreisan, goshuyuto, and kakkonto were prescribed depending on the patients' headache characteristics. Twenty-six patients also had prophylactic medications. The median use days of goreisan in the first month of treatment were 15 (0-30) days, those of goshuyuto were 4 (0-30) days, and those of kakkonto were 5 (0-30) days, with a maximum intake of three packets per day. Other details and characteristics of each headache type were also described in Table 1.

| Variables | Total (n=43) | CM (n=9) | EM+TTH (n=22) | CTTH (n=12) | MOH (n=27) |
|-----------|--------------|---------|---------------|-------------|------------|
| Age (years old) | 51 (15-99) | 48 (15-57) | 43 (15-74) | 79 (40-99) | 52 (15-99) |
| Women: men (%women) | (83.7%) | (100%) | (77.3%) | (66.7%) | (85.2%) |
| With medication overuse headache | 27 (62.8%) | 7 (77.8%) | 11 (50.0%) | 9 (75.0%) | 27 (100%) |
| Monthly acute medication intake day before Kampo treatment | | | | | |
| Triptan | 2 (0-30) | 7 (0-30) | 0 (0-8) | - | 3 (0-30) |
| NSAIDs | 7 (0-30) | 12 (0-30) | 2 (0-30) | 0 (0-30) | 9 (0-30) |
| Combination analgesic (most over-the-counter drugs containing two types of NSAIDs and caffeine) | 7 (0-30) | 4 (0-30) | 0 (0-20) | 13 (0-30) | 10 (0-30) |
| Comorbidities | | | | | |
| Hypertension | 7 (16.3%) | 0 | 3 (13.6%) | 4 (33.3%) | 6 (22.2%) |
| Diabetes | 2 (4.7%) | 0 | 1 (4.5%) | 1 (8.3%) | 0 |
| Dementia | 4 (9.3%) | 0 | 0 | 4 (33.3%) | 3 (11.1%) |
| Back pain and knee pain | 3 (7.0%) | 0 | 2 (9.1%) | 1 (8.3%) | 1 (3.7%) |
| Premenstrual syndrome | 3 (7.0%) | 2 (22.2%) | 1 (4.5%) | 0 | 2 (7.4%) |
| Psychological disorders (depression, anxiety) | 7 (16.3%) | 2 (22.2%) | 1 (4.5%) | 4 (33.3%) | 5 (18.5%) |
| Others (asthma, Basedow's disease, epilepsy, irritable bowel syndrome) | 4 (9.3%) | 3 (33.3%) | 1 (4.5%) | 0 | 3 (11.1%) |
| Onset (years ago) (n=39) | 20 (1-70) | 25 (5-45) | 18 (1-48) | 30 (1-70) | 20 (1-70) |
| Kampo medicine (use days in the first month after starting Kampo treatment) | | | | | |
| Goreisan | 15 (0-30) | 20 (0-30) | 16 (0-30) | 9 (0-30) | 16 (0-30) |
| Goshuyuto | 4 (0-30) | 6 (0-30) | 0 (0-30) | 2 (0-30) | 4 (0-30) |
| Kakkonto | 5 (0-30) | - | 0 (0-30) | 5 (0-30) | 3 (0-40) |
| Prophylactic medications except for Kampo medicine | | | | | |
| Nothing | 17 (39.5%) | 0 | 10 (45.5%) | 7 (5.8%) | 6 (22.2%) |
| Lomerizine | 3 (7.0%) | 1 (11.1%) | 1 (4.5%) | 1 (8.3%) | 3 (11.1%) |
| Treatment response of *Kampo* medicine for CDH |
|---------------------------------------------|
| Of all the 43 CDH patients, the median HIT-6 before, one and three months after treatment were 63 (44-78), 48 (36-78), and 40 (36-78), respectively. MHD before, one and three months after treatment were 20 (15-30), 5 (0-30), and 2 (0-30), respectively. Those about MMD were 2 (0-16), 8 (2-30), and 0 (0-7). Those about AMD were 15 (0-30), 15 (0-30), and 15 (0-30). |
| Regarding all the 43 CDH patients, significant reductions in HIT-6, MDH, MMD, and AMD were observed one month after starting *Kampo* treatment. These trends were also confirmed after three months. Similar
trends were observed in the 22 EM+TTH patients and 27 MOH patients. In the 9 CM patients and 12 CTTH patients, a significant decrease in AMD at one and three months were observed, but those of HIT-6, MDH, and MMD were confirmed only at three months (Figure 1). Laboratory tests and physical examinations over three months confirmed no side effects of Kampo medicines, such as liver dysfunction, interstitial pneumonia, and pseudoaldosteronism.

**FiGURE 1: Treatment response**

Treatment response of Kampo medicine for chronic daily headache containing all the types of headaches, chronic migraine (CM), episodic migraine with tension-type headache (EM+TTH), chronic tension-type headache (CTTH), and medication-overuse headache (MOH). Boxplots of the headache impact test-6 (HIT-6), monthly headache days (MHD), monthly migraine days (MMD), and monthly acute medication intake days (AMD) (y-axis) before treatment (0 month), after one and three months of treatment (x-axis) were shown. HIT-6, MDH, MMD, and AMD were significantly improved after treatment (*; significantly decreased compared to 0 month adjusted by the Bonferroni’s correction, p < 0.01).

**Discussion**

We herein describe the results of our hybrid therapy for CDH using Kampo and Western medicines. Kampo medicine may act as both acute and prophylactic medications, leading to the rapid decrease of HIT-6, MHD, MMD, and AMD, especially in EM+TTH and MOH patients. In addition, there were no side effects from Kampo medicine.

**Treatment strategy for CDH**

The standard CDH treatment is not established. However, the main treatment strategies are (1) to discontinue the current regimen of analgesic medications, (2) to rotate and select appropriate analgesic medicine specific to the headache characteristics, and (3) to initiate a prophylactic medication regimen to reduce the frequency and intensity of both the chronic headaches and the acute exacerbations [28].

About (1) and (2), in approximately 77% of CDH patients, discontinuation of the overused medication alone will result in the return to an episodic form of headache that can then be more easily managed [29]. However, some patients have withdrawal headaches or continuous headaches during this process, and bridging analgesics are needed [7,30]. Therefore, our results show that AMD and HIT-6 decreased rapidly by using Kampo medicine as an alternative acute medication [8] can help resolve the withdrawal headache or continuous headache and stop the medication overuse.

About (3), the consideration of the duration of prophylactic therapy as well as tapering and discontinuation of the therapy also depends on the severity of headache-induced disability before the prophylactic therapy, and no uniform criteria can be applied. However, it takes at least two months before the effectiveness of prophylactic therapy can be evaluated [7,31]. While determining efficacy during the two months, it is possible that CDH could recur. Some medications act rapidly, such as amitriptyline [32] and CGRP mAbs.
Kampo medicine can be a prophylactic medication that rapidly acts [7,18] and has long-term effects [10]. Furthermore, Kampo medicine does not have a side effect of drowsiness, which is often confirmed by using amitriptyline. Also, Kampo medicine is not as expensive as CGRP mAbs. Our results showed the possibility that Kampo medicine can be prescribed as a prophylactic medication for CDH.

**Kampo medicine for headache**

*Kampo* medicine is empirically used for headache treatment. However, it cannot be denied that scientific evidence, such as basic and clinical research, remains insufficient. In addition to goreisan, goshuyuto, and kakkonto, keishininjinto, and chotosan are introduced in the Japanese guidelines [7]. Many other *Kampo* medicines are also prescribed for headache treatment. Therefore, further studies with a strong evidence level should be needed, using placebos or case cross-over studies. There are some studies with strong evidence of *Kampo* medicines’ utility in other clinical faculties. Yokukansan is effective for the behavioral and psychological symptoms of dementia [34]. Daikenchuto prevents postoperative ileus after abdominal surgery [35]. Goreisan prevents postoperative recurrence of some types of chronic subdural hematomas [36]. Like these clinical trials, a large prospective study for headache treatment using *Kampo* medicine is needed.

*Kampo* medicine has side effects. The major side effects are pseudoaldosteronism, interstitial pneumonia, liver dysfunction, and allergy. Of the three types of *Kampo* medicines we used, kakkonto contains kanzo, which sometimes causes pseudoaldosteronism. Since long-term use of kakkonto may result in pseudoaldosteronism, other appropriate treatment modalities, such as physical therapy for TTH, are essential. Also, laboratory tests, X-rays, and physical examinations should be considered appropriately.

**Limitation of this study**

First, the sample size was small, and this study was performed in a single hospital with a single arm. Second, we did not compare to the control arm, so the true therapeutic effects of *Kampo* medicine were unknown. Third, the follow-up period differed for each patient, and side effects can occur in the long term. Therefore, we should follow up with the patients carefully. Fourth, we could not check the medication compliance rate of *Kampo* medicine other than the first month because some patients’ headache diaries became less accurate as their symptoms improved. Finally, it was difficult to assess whether the improvement was due to the Western medication, a placebo effect, or spontaneous remission. Further studies using a control arm and placebo are considered in future research.

**Conclusions**

The hybrid medication strategy of *Kampo* and Western medicines for CDH is safe and effective in terms of both acute and prophylactic medications with rapid efficacy. The decrease of HIT-6, MHD, MMD, and AMD, especially in EM+TTH and MOH patients, was observed. Goreisan, goshuyuto, and kakkonto can be used as alternative medicines for CDH treatment combined with Western medicine. Further studies are needed to establish the efficacy of *Kampo* medicine for headaches.

**Additional Information**

**Disclosures**

**Human subjects:** Consent was obtained or waived by all participants in this study. Itoigawa General Hospital Ethics Committee issued approval 2021-4. The hospital’s research ethics committee approved this study (approval number 2021-4), and we gained the written informed consent for this study from all the patients or patients’ families. This retrospective study was performed following the Declaration of Helsinki.

**Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue.

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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