

# *Kampo* (Japanese herbal) medicine for primary headache as an acute treatment –a retrospective investigation in Kesennuma City Hospital during 5 years-

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## Research Article

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# Abstract

Kampo (Japanese herbal) medicine for primary headaches as an acute treatment has been empirically prescribed, but the evidence is insufficient. Therefore, we retrospectively investigated kampo medicine's efficacy for primary headaches at 1 week and discussed how kampo medicine works for headaches, referring to previous articles. We prescribed, as needed, kakkonto (TJ-1) for 223 tension-type headaches, goshuyuto (TJ-31) for 93 migraines with or without aura and those with the menopausal disorder, goreisan (TJ-17) for 71 migraines with edema, dehydration (Sui-doku), or associated with weather conditions, and non-steroidal anti-inflammatory drugs (NSAIDs) for 162 primary headaches between 2015 and 2019 in Kesenuma City Hospital. As a total, 92.0% of the patients' subjective symptoms improved after 1 week. The ratio of improvement was not significantly different between each kampo medicine and NSAIDs. The follow-up period is short as 1 week, and it is difficult to judge whether the improvement is due to medication, the placebo effect, or spontaneous remission. However, our results suggested that kampo medicine could be an alternative medication as an acute treatment for primary headaches, and our strategy would be applicable to the clinical practice of primary headaches. (187/250 words)

## Introduction

Headache is a public health problem worldwide.<sup>[7]</sup> Migraine and tension-type headache (TTH) are included as primary headaches in the International Classification of Headache Disorders (ICHD), and they are the main types of primary headaches. In Japan, the overall prevalence of migraine is 8.4%, and 74.2% of them complain that migraine headache disturbs their daily lives.<sup>[3, 17]</sup> Also, about 15–20% of Japanese people have TTH, and 22.4–29.2% complained that TTH impairs their performances.<sup>[3, 14, 21]</sup> However, only 2.7% of the migraine patients consult a doctor regularly,<sup>[17]</sup> and 59.4% of the primary headache patients had never consulted a physician about their headaches.<sup>[21]</sup> Therefore, most of the headache patients presumably manage the pain by using over-the-counter (OTC) medications.<sup>[3]</sup> Besides, if the headache patients consult doctors, only neuroimaging is performed to exclude emergent or organic diseases, and the appropriate diagnosis for primary headache and its treatment are insufficient, leading to patient dissatisfaction.<sup>[3]</sup>

Of course, we should treat primary headache according to the Japanese Clinical Practice Guideline for Chronic Headache 2013.<sup>[3]</sup> However, some elderly patients have already taken non-steroidal anti-inflammatory drugs (NSAIDs) for other orthopedic diseases, so it is difficult to add other medications for headaches. Such elderly patients sometimes take multiple medications as polypharmacy, so side effects and drug interaction can also occur when we add other medications. Furthermore, some busy young patients have suffered medication overuse headache (MOH) overusing OTC NSAIDs. While it is important to spread the warning about MOH, drugs with less dependent and fewer side effects are desirable.

To solve these problems, we herein focused on and retrospectively investigated the effects of kampo medicine (traditional Japanese herbal medicine) as an acute treatment for primary headaches. Kampo medicines have been used empirically for headaches and have shown therapeutic effects.<sup>[3]</sup> We use kampo medicine as the first-choice acute treatment for primary headaches, considering the side effects and costs of NSAIDs or triptan as well as the aging population around our hospital.<sup>[19]</sup> Kampo medicine contains a wide variety of substances, and each substance acts comprehensively on the entire body to safely produce a therapeutic effect.<sup>[8, 16]</sup> Therefore, kampo medicine, especially for the elderly, is attractive and can reduce the number of drugs and medical costs and has less possibility of side effects for the elderly.<sup>[22]</sup> Furthermore, kampo medicine is available as OTC, so it would be used instead of OTC NSAIDs to avoid MOH development. Regarding primary headache, this is a relatively large retrospective study on kampo medicine as an acute treatment.

## Materials And Methods

The study was approved by our hospital's research ethics committee (KCHE-2020-3) on September 27th, and we gained written informed consent for this study from all of the patients, the legally authorized representative of the patients, or next of kin of the deceased patients. All methods were carried out in accordance with relevant guidelines and regulations (Declaration of Helsinki). All personal patient information was deleted from the database for this study to protect patient privacy.

## Study population and treatment strategies

This retrospective study included 988 consecutive new patients aged over 15 years of age at our neurosurgical outpatient who were revealed as a primary headache after neurological examination, personal interview, laboratory tests, head computed tomography, and magnetic resonance angiography between 2015 and 2019. The primary headaches were defined in the ICHD 3rd edition (beta version) (ICHD-3 beta).<sup>[15]</sup> Initially, we explained to the patients that their headaches were the primary ones. Then, we asked them whether they hoped for medical treatment. When the patients hoped specific medications from their experience, we prescribed NSAIDs, triptans, and other medicines, taken as needed. If not, we prescribed kampo medicine as the first choice.<sup>[3]</sup>

The choice of kampo medicine was based on the Japanese Clinical Practice Guideline for Chronic Headache 2013,<sup>[3]</sup> expert's opinion,<sup>[8]</sup> our experience, and a few previous reports in Japanese.<sup>[3]</sup> When the patients had TTH (Part I, 2. in ICHD-3 beta), we prescribed kakkonto (TJ-1).<sup>[20]</sup> When the patients had a migraine (Part I, 1. in ICHD-3 beta), we used two different drugs. We prescribed goshuyuto (TJ-31) for patients with migraines with or without aura (Part I, 1.1 or 1.2 in ICHD-3 beta),<sup>[13, 24]</sup> or those with the menopausal disorder.<sup>[11]</sup> We prescribed goreisan (TJ-17) for those with edema or dehydration (Sui-doku; unbalance of water distribution in kampo medicine theory)<sup>[12]</sup> or migraines associated with weather conditions.<sup>[25]</sup> Hochuekkito (TJ-41), yokukansankachimpihange (TJ-47), or chotosan (TJ-83) was also

prescribed if dementia, depression, or irritation was present. All medicine was taken as needed depending on the patients' symptoms.

All patients who were prescribed medication were followed up at 1 week, and we asked them whether their headache improved or not. The outcomes were defined as the improvement of subjective symptoms at 1 week. (Fig. 1) The chi-square test evaluated the difference of the improvement ratio between each kampo medicine and NSAIDs.

## Statistical analysis

Results are shown as median (interquartile range). Chi-square test performed using SPSS software version 24.0.0. (IBM, New York, USA). A two-tailed  $p < 0.05$  was considered statistically significant.

## Results

Clinical characteristics of the 988 patients (574 women and 414 men) with primary headaches are summarized in **Table 1**. The median (interquartile range) age was 60 (41–75). Conservative treatment was applied for the 399 patients, and the others were treated by medications. Kakkonto (TJ-1) was prescribed for 223 patients, goshuyuto (TJ-31) for 93 patients, and goreisan (TJ-17) for 71 patients. NSAIDs were prescribed for 162 patients. As a total, 92.0% of the patients' subjective symptoms improved after a week. The ratio of improvement was not significantly different between each kampo medicine and NSAIDs by chi-square test (All kampo medicines vs. NSAIDs;  $p = 0.25$ , kakkonto (TJ-1) vs. NSAIDs;  $p = 0.73$ , goshuyuto (TJ-31) vs. NSAIDs;  $p = 0.074$ , goreisan (TJ-17) vs. NSAIDs;  $p = 0.12$ , respectively.) (**Table 1**)

## Discussion

We herein report 988 primary headache patients who came to our hospitals. About 90% of patients' symptoms improved after a week in both those treated by kampo medicine and those by NSAIDs. This report is important because there are few reports on the kampo medicine as an acute treatment for primary headache.

## Kampo medicine for TTH

TTH is the most prevalent form of primary headache in the general population, but the least studied headache. Peripheral factors have traditionally been considered important in TTH, and many studies have reported increased tenderness and hardness of pericranial myofascial tissues in TTH patients. In addition, the increased myofascial pain sensitivity in TTH could also be caused by central factors; (a) sensitization of second-order neurons at the level of the spinal dorsal horn/trigeminal nucleus; (b) sensitization of supraspinal neurons; and (c) decreased antinociceptive activity from supraspinal structures. Furthermore, increased excitability of the central nervous system generated by repetitive and sustained pericranial myofascial input may be responsible for the transformation of non-chronic TTH

into the chronic one.<sup>[2]</sup> Appropriate exercise, bathing, and massage are alternative therapies, and NSAIDs are used as acute treatment.<sup>[3]</sup>

Kakkonto (TJ-1) is composed of 7 herbal components. It is available as OTC drugs in Japan and is often used to treat common cold at the early stage. Empirically, kakkonto is effective for headache, shoulder stiffness, muscle pain, and pain in hands and shoulder, presumably because its herbal components perform each effect; mao has adrenergic effects improving capillary circulation in the muscles, shakuyaku has an analgesic effect, kanzo has an anti-inflammatory effect, and keihi warms up the body. Also, some of these effects are basically studied and revealed in animal and in vitro experimental models.

<sup>[1]</sup> These effects may have favorable effects on TTH, but further basic studies are desired.

## **Kampo medicine for migraine**

There are some hypotheses of the pathogenesis of migraine; vascular, neural, and trigeminovascular theory. In the vascular theory, platelet hyper-aggregation may be caused by collagen, thrombin, adenosine diphosphate, serotonin, thromboxane A<sub>2</sub>. Serotonin is excessively released from platelets, and the elevation of cerebral blood levels of serotonin is thought to cause the aura of the first stage of migraine by contracting the cerebral blood vessels with cortical spreading depression. Furthermore, it is thought that because the excessive serotonin released is immediately metabolized, the second stage of migraine with severe headache is due to the relaxation of the cerebral blood vessels. Also, in the trigeminovascular theory, it has been postulated that the release of inflammatory neuropeptides such as calcitonin gene-related peptide and substance P by trigeminal nerve fibers causes neurogenic inflammation and subsequent sensitization.<sup>[9]</sup> Therefore, serotonin, vascular constriction, and inflammation seem important.

Goshuyuto (TJ-31) is composed of 4 herbal components. In basic research, goshuyuto inhibits platelet aggregation in guinea-pig whole blood,<sup>[5]</sup> constricts the isolated rat aorta.<sup>[4]</sup> These findings suggested that goshuyuto decreases platelet hyper-aggregation, preventing the excess serotonin release, and it constricts vessels appropriately, avoiding acute relaxation of the blood vessel constriction. In clinical research, after 12 weeks of treatment by goshuyuto for its responder with chronic headache, the blood serotonin level increased<sup>[13]</sup> and lateralization of the pupillary dynamics decreased.<sup>[23]</sup> These findings suggest that raising serotonin levels beforehand by goshuyuto may suppress the hyper-reactivity of serotonin receptors for serotonin, and goshuyuto would maintain the appropriate autonomic nerve conditions.

Goreisan (TJ-17) is composed of 5 herbal components and is used to adjust the water balance of the body, both edema and dehydration, by inhibiting mainly aquaporin 4 (AQP4)<sup>[10]</sup> channels as well as other AQP subtypes. AQP 3, 4, and 5 enhance chemokine production,<sup>[18]</sup> and goreisan has a potential of anti-inflammatory effect through inhibiting AQPs<sup>[6]</sup> as well as adjusting water balance. These two mechanisms would contribute to migraine relief by goreisan.

## **Limitation of this study**

First, the number of the sample was small, and this study performed in a single hospital. Other home doctors or internal medicine hospitals also treat headaches, so not all headache patients in the Kesenuma area could necessarily be studied. Second, we did not separate chronic migraine and TTH (15 or more days per month) and those non-chronic (less than 15 days per month). Its mechanism and efficacy of the medication are supposed to be different in each type.<sup>[3]</sup> Therefore, we should have investigated the frequency per month and use it to make prediction models. Third, the follow-up period is short as 1 week, and it is difficult to judge whether the improvement is due to medication, the placebo effect, or spontaneous remission. We also should have investigated the number of intake of prescribed medication and the change of severity, frequency, or duration of the headache. Fourth, the effect of comorbidities, such as orthopedic diseases treated by analgesic or psychotic drugs, should be considered in detail.

## Conclusions

About 90% of the primary headache patients' symptoms could improve at 1 week using kampo medicine, so our study suggested that kampo medicine could be an alternative medication as an acute treatment for primary headache.

## Declarations

### Acknowledgments

Not applicable.

### Declaration of Conflicting Interests

The authors declare that there is no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Author contributions

MK and NN: drafting article. MK, NN, NI, OW, and SC: data acquisition. YM: critical advice about headaches. TT: supervision.

## References

1. Ara T *et al*: Studies on shokyo, kanzo, and keihi in kakkonto medicine on prostaglandin E2 production in lipopolysaccharide-Treated human gingival fibroblasts. *Int Sch Res Not* 2016: 9351787, 2016.

2. Ashina S *et al*: Pathophysiology of tension-type headache. *Curr Pain Headache Rep* 9: 415–422, 2005.
3. Chronic Headache Clinical Practice Guideline Development Committee: Clinical Practice Guideline for Chronic Headache 2013: Online 2015; Available: <https://www.neurology-jp.org/guidelinem/ch/index.html>.
4. Hibino T *et al*: Goshuyuto, a traditional Japanese medicine, and aqueous extracts of *Evodiae Fructus* constrict isolated rat aorta via adrenergic and/or serotonergic receptors. *Biol Pharm Bull* 32: 237–241, 2009.
5. Hibino T *et al*: Goshuyuto, a traditional Japanese medicine for migraine, inhibits platelet aggregation in guinea-pig whole blood. *J Pharmacol Sci* 108: 89–94, 2008.
6. Inada R *et al*: Oryeongsan (Goreisan) ameliorates experimental autoimmune encephalomyelitis. *Intern Med* 59: 55–60, 2020.
7. Jensen R *et al*: Epidemiology and comorbidity of headache. *Lancet Neurol* 7: 354–361, 2008,
8. Kawamura T. [Kampo medicine in neurosurgery] (Japanese). *No Shinkei Geka* 48: 267–274, 2020.
9. Nagata E. [Recent advances in the elucidation of migraine pathophysiology] (Japanese). *Clin Neurol* 60: 20–26, 2020.
10. Nakano T *et al*: Goreisan prevents brain edema after cerebral ischemic stroke by inhibiting aquaporin 4 upregulation in mice. *J Stroke Cerebrovasc Dis* 27: 758–763, 2018.
11. Nakayama T *et al*: [Aiming of higher-rank of treatment with Kampo medicine, toward the female medicine (Sterility, hyperemesis gravidarum and climacteric symptom)] (Japanese). *J Japan Soc Menopause Women's Heal* 23: 371–374, 2016.
12. Noguchi T. [Therapeutic effect of Goreisan for headache accompanying hemodialysis] (Japanese). *Sci Kampo Med* 34: 182–183, 2010.
13. Odaguchi H *et al*: The efficacy of goshuyuto, a typical Kampo (Japanese herbal medicine) formula, in preventing episodes of headache. *Curr Med Res Opin* 22: 1587–1597, 2006.
14. Okuma H *et al*: [Epidemiology of headache] (Japanese). *Nippon rinsho Japanese J Clin Med* 63: 1705–1711, 2005.
15. Olesen J *et al*: The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 33: 629–808, 2013.
16. Osawa S-I *et al*: [Safety and efficacy of keishi-bukuryo-gan in patients with spontaneous intracerebral hemorrhage during the acute period: CT image-based analysis of the clearance of hematoma] (Japanese). *No Shinkei Geka* 46: 763–770, 2018.
17. Sakai F *et al*: Prevalence of migraine in Japan: A nationwide survey. *Cephalalgia* 17: 15–22, 1997.
18. Sakamoto Y *et al*: Aquaporin 5 increases keratinocyte-derived chemokine expression and NF- $\kappa$ B activity through ERK activation. *Biochem Biophys Res Commun* 448: 355–360, 2014.
19. Shibahara I *et al*: Increase in the number of patients with seizures following the Great East-Japan Earthquake. *Epilepsia* 54: e49–e52, 2013.

20. Shibata Y. [Clinical analysis of the patients with tension-type headache in whom kakkontou is effective] (Japanese). *J Neurosurg kampo Med* 5: 16–18, 2019.
21. Suzuki N *et al*: Prevalence and characteristics of headaches in a socially active population working in the Tokyo metropolitan area -surveillance by an industrial health consortium. *Intern Med* 53: 683–689, 2014.
22. Takayama S *et al*: Systematic review of traditional Chinese medicine for geriatrics. *Geriatr Gerontol Int* 17: 679–688, 2017.
23. Wakasugi A *et al*: Effects of goshuyuto on lateralization of pupillary dynamics in headache. *Auton Neurosci Basic Clin* 139: 9–14, 2008.
24. Yarnell E. Herbal medicine and migraine. *Altern Complement Ther* 23: 192–201, 2017.
25. Yasui H. [Efficacy of “Poria Powder with Five Herbs” for Headache: An epidemiological research study on the relationship between chronic headache and atmospheric depression] (Japanese). *J Kampo, Acupunct Integr Med* 1: 7–11, 2006.

## Tables

Table 1 is not available with this version.

## Figures

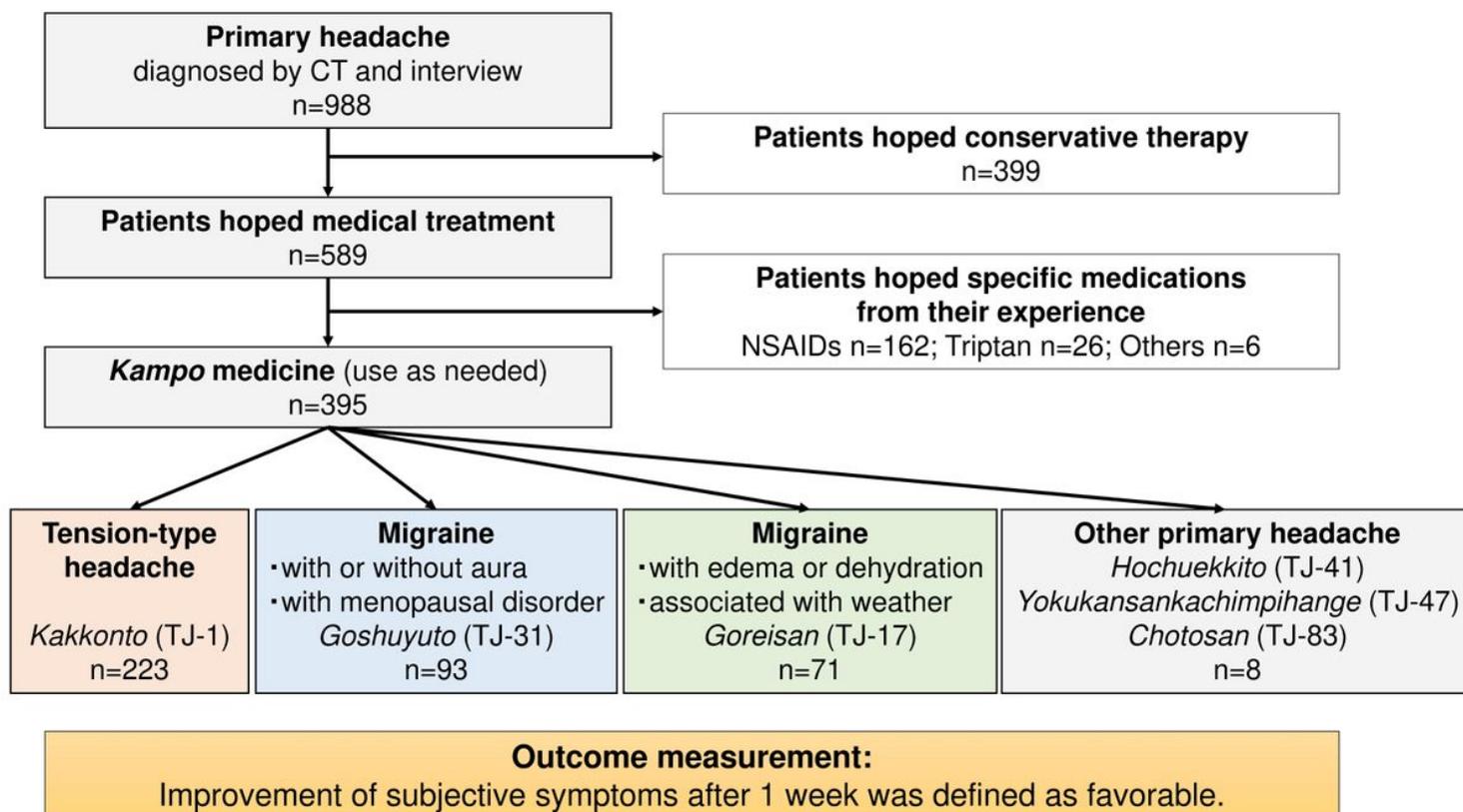


Figure 1

Chart of our treatment strategy for primary headache. After diagnosing primary headaches, we explained to the patients that their headaches were primary ones. Then, we asked them whether they hoped for medical treatment. When the patients hoped for specific medications from their experience, we prescribed them as they want. If not, we prescribed kampo medicine as the first choice. When the patients had tension-type headaches, we prescribed kakkonto (TJ-1). We prescribed goshuyuto (TJ-31) for patients with migraines with or without aura, or those with the menopausal disorder. We prescribed goreisan (TJ-17) for those with edema or dehydration or migraines associated with weather conditions. Hochuekkito (TJ-41), yokukansankachimpihange (TJ-47), or chotosan (TJ-83) was also prescribed if dementia or irritation was present. All medicine was taken as needed depending on the patients' symptoms. All patients who were prescribed medication were followed up at 1 week. The outcomes were defined as the improvement of subjective symptoms at 1 week. Abbreviations: CT; computed tomography, NSAIDs; non-steroidal anti-inflammatory drugs.