



## Efficacy of *Kampo* medicine *Kakkonto* as acute medication to treat tension-type headache among musculoskeletal pain patients using regular analgesics

Masahito Katsuki, M.D.<sup>1)\*</sup>, Yasuhiko Matsumori, M.D., Ph.D.<sup>2)</sup>, Kenta Kashiwagi, M.D.<sup>3)</sup>,  
Shin Kawamura, M.D.<sup>1)</sup> and Akihito Koh, M.D.<sup>1)</sup>

**Abstract:** Objectives: Tension-type headache (TTH) is the most prevalent type of primary headache disorder. Its acute pharmacotherapy is acetaminophen or non-steroidal anti-inflammatory drugs based on the Japanese Clinical Practice Guideline for Headache Disorders 2021. With Japan's aging population, however, the number of TTH patients with comorbidities that have been treated by analgesics is increasing. Under this context, it is sometimes difficult to select an acute pharmacotherapy for TTH. *Kakkonto*, Japanese traditional herbal *kampo* medicine, is empirically used for TTH. We hypothesized that *kakkonto* has efficacy for TTH with painful comorbidities. Materials and Methods: We prospectively collected 10 consecutive TTH patients who had already taken analgesics for comorbidities. We prescribed 2.5 g of *kakkonto* (TJ-1), and patients took it. A numerical rating scale for pain before and 2 hours after *kakkonto* intake was evaluated. Results: Eight women and 2 men were included. The mean age was  $71.0 \pm 13.4$  years old. Four patients had lower back pain, 2 had lumbar spinal stenosis, 2 had knee pain, 1 had neck pain, and 1 had shoulder myofasciitis. Celecoxib was used for 4 patients, acetaminophen for 3, loxoprofen for 2, and a combination of tramadol and acetaminophen for 1, as routinely used analgesics. The median numerical rating scale statistically improved from the median of 4 to that of 0. There were no side effects of *kakkonto*. Conclusion: *Kakkonto* showed efficacy as an acute medication for TTH with comorbidities that have been treated by analgesic.

**Key words:** acute medication, analgesic, *kakkonto*, tension-type headache (TTH), Japanese herbal *kampo* medicine

### Introduction

Headache is a widely spread public health problem. Migraine, tension-type headache (TTH), and trigeminal autonomic cephalalgias are included as representative primary headaches in the International Classification of Headache Disorders 3rd edition (ICHD-3)<sup>1)</sup>. In Japan, migraine prevalence is 0.9–9.5%<sup>2)–5)</sup>, that of TTH is 15–20%<sup>6)</sup>, and that of MOH is 2.3%<sup>5)</sup>. About 22.4–29.2% of TTH sufferers complained that TTH disturbed their performances<sup>6)</sup>. The prophylactic and acute treatment of headache disorders depends on the type of primary headache disorders and requires proper diagnosis based on ICHD-3<sup>1)</sup>.

The treatment strategies for TTH, the most prevalent type

of primary headache disorder, are described in the Clinical Practice Guideline for Headache Disorders 2021<sup>1)</sup>. Acute pharmacotherapy consists of acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). Prophylactic pharmacotherapy for frequent episodic and chronic TTH includes amitriptyline. As non-pharmacotherapy, psychiatric treatment, psycho-behavioral treatment, physical therapy, and acupuncture should be considered for all TTH patients.

With Japan's aging population, it is expected that the number of TTH patients with comorbidities that have already been treated by analgesics will increase. For example, the prevalence of lower back pain is 24.3%, and that of knee pain is 10.4%<sup>7)</sup>. Also, some study showed that the prevalence of oncologic pain without cognitive impairment was 64% among stages I and II,

\*Corresponding author: Department of Neurosurgery, Itoigawa General Hospital [457-1, Takehana, Itoigawa, Niigata 945-0006, Japan]

<sup>1)</sup> Department of Neurosurgery, Itoigawa General Hospital

<sup>2)</sup> Sendai Headache and Neurology Clinic

<sup>3)</sup> Department of Neurology, Itoigawa General Hospital

(Received October 18, 2022; Accepted November 17, 2022; Published online in J-STAGE on January 31, 2023)

Rinsho Shinkeigaku (Clin Neurol) 2023;63:73-77

doi: 10.5692/clinicalneurol.cn-001812

and 84% in stages III and IV of the patients in the surgical ward<sup>8)</sup>. Under this context, it is sometimes difficult to select an acute pharmacotherapy for TTH because some TTH patients may have already taken analgesics for comorbidities with pain. However, there are basically no other acute treatments for TTH than acetaminophen and NSAIDs recommended in the guideline.

As an alternative therapy, we focused on *kakkonto*, one of the Japanese traditional herbal *kampo* empirically used for TTH. Japanese traditional herbal *kampo* medicine can be used for headache treatment in Japan and is also described in the Japanese Clinical Practice Guideline for Headache 2021<sup>1)</sup>. *Kampo* medicine can be used as both acute<sup>9)10)</sup> and prophylactic therapy<sup>11)–13)</sup> for headaches. Therefore, we hypothesized that *kakkonto* could be an alternative acute treatment for TTH patients with comorbidities that have already been treated with analgesics. Here, we prospectively investigated the effectiveness of the *kakkonto* for TTH with comorbidities that have already been treated by analgesics.

## Materials and Methods

### Study population

From April 2021 to August 2022, we prospectively collected 10 consecutive TTH patients who had already taken analgesics for comorbidities. All the patients visited our hospital's outpatient. The TTH diagnosis was based on the ICHD-3, the clinical history, and appropriate radiological examination. Intracranial and cervical lesions were ruled out for all patients by performing computed tomography or magnetic resonance imaging. The inclusion criteria: 1) patients aged 20 or older, 2) patients diagnosed as TTH (ICHD-3 code 2.1, 2.2, 2.4.1, and 2.4.2), 3) patients who had already taken analgesics for comorbidities, such as NSAIDs, acetaminophen, and opioids, and 4) patients who had now TTH attacks and wanted to solve them as soon as possible. Patients with any of the following will not be included in this study: 1) patients at risk of adverse reactions (pseudoaldosteronism, aspiration, history of allergy in the past) to herbal medicines, 2) patients with a history of psychiatric disorders, 3) patients with chronic TTH (ICHD-3 code 2.3 and 2.4.3), and 4) patients with both migraine and TTH.

### Treatment and efficacy evaluation

After patients fulfilled the criteria above, we evaluated the patients' pain severity by numerical rating scale (NRS). Then, we prescribed 2.5 g of *kakkonto* (TJ-1), and patients took it once. After 2 hours, we reevaluated patients' pain severity by NRS. The primary outcome was the presence of improvement in NRS 2 hours after taking *kakkonto*. The 2-hour evaluation time point was determined because previous reports of placebo for TTH

have also been 2 hours interval<sup>14)</sup>, and because the evaluation time for acute medications for migraine is also 2 hours interval<sup>15)</sup>. We also collected patients' characteristics, such as age, sex, comorbidities, and other medications.

### Statistical analysis and sample size calculation

Variables with normal distribution are shown by mean  $\pm$  standard deviation. Those without normal distribution are shown by median (interquartile range). Shapiro-Wilk test was performed to check the normal distribution. The difference between NRS before and after *kakkonto* intake was tested by Wilcoxon signed-rank test. We also calculated Cohen's *d*. Cohen's *d* indicated the effect size, and it was interpreted as "small effect" for  $d = 0.21$ – $0.50$ , "medium effect" for  $d = 0.51$ – $0.80$ , and "large effect" for  $d > 0.81$ <sup>16)</sup>. A one-tailed  $P < 0.05$  was defined as statistically significant. We used SPSS 28.0.0 (IBM, New York, USA),

The sample size was determined by G\*Power (<https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower>). We set the effect size of Cohen's *d* as 1.0, alpha error as 0.05, and power as 0.80. The needed sample size was 9, and we decided on a sample size of 10, considering the dropout cases. As ad-hoc analysis, a statistical power analysis was also performed.

### Ethics

The hospital's research ethics committee approved this study (approval number 2021-10, 4/8/2021 approved), and we gained written informed consent for this study from all the patients. This single-arm prospective study was performed following the Declaration of Helsinki.

## Results

### General characteristics

Table 1 shows the characteristics of 10 TTH patients treated by *kakkonto*. Eight women and 2 men were included. The mean age was  $71.0 \pm 13.4$  years old. Four patients had lower back pain, 2 had lumbar spinal stenosis, 2 had knee pain, 1 had neck pain, and 1 had shoulder myofasciitis. Celecoxib was most used for 4 patients, acetaminophen for 3, loxoprofen for 2, and a combination of tramadol and acetaminophen for 1, as routinely used analgesics. Hypertension, dyslipidemia, diabetes mellitus, cancers, stroke, and interstitial pneumonia were confirmed as comorbidities. Nobody had ever been prescribed *kakkonto* as a treatment for headaches.

### Treatment response

Of all the 10 TTH patients treated by *kakkonto*, the median NRS before treatment was 4 (1), and that 2 hours after

Table 1 Characteristics of the patients.

Patient number	Age (y.o.)	Sex	Comorbidities	Medication	NRS before <i>kakkonto</i> intake	NRS 2 hours after <i>kakkonto</i> intake
1	51	W	lower back pain	celecoxib	4	0
2	55	W	shoulder myofasciitis, HT	loxoprofen, amlodipine	5	0
3	57	W	neck pain	celecoxib	4	2
4	67	W	lower back pain	loxoprofen	4	0
5	68	W	lower back pain, HT, DL, DM	celecoxib, amlodipine, bezafibrate, depagliflozin	4	0
6	76	W	lumbar spinal stenosis	celecoxib	4	1
7	79	M	lumbar spinal stenosis, liver cancer, bladder cancer, HT, constipation	tramadol, acetaminophen, nifedipine, lactulose, temocapril	4	2
8	83	W	knee pain, HT, DL	acetaminophen, amlodipine, rosuvastatin	6	0
9	86	M	knee pain, HT, DL, stroke	acetaminophen, amlodipine, olmesartan, rosuvastatin, aspirin	6	0
10	88	W	lower back pain, interstitial pneumonia	acetaminophen	5	0
Mean or Median	71 ± 13.4				4 (1)	0 (1)

The results are shown with the mean ± standard deviation or the median (interquartile range). Abbreviations: DL, dyslipidemia, DM, diabetes mellitus, HT; hypertension, NRS; numerical rating scale.

treatment was 0 (1). There were no side effects of *kakkonto*. Wilcoxon signed-rank test showed the statistical improvement of NRS ( $P = 0.005$ ). Cohen's  $d$  was 2.829 (95%CI 1.391–4.242). The statistical power was 0.99999998.

## Discussion

We performed the pilot study and described the prospective results of 10 TTH patients treated by *kakkonto*. *Kakkonto* showed efficacy as an acute medication for TTH. In addition, there were no side effects of *kakkonto*.

### Pathophysiology of TTH

The mechanism and pathophysiology of TTH have not been unclear. Peripheral sensitization has been considered important in episodic TTH and central sensitization in chronic TTH. Many studies have reported increased tenderness and rigidity of pericranial myofascial tissues in TTH patients<sup>17)</sup> and decreased pressure pain thresholds over the craniocervical area<sup>18)</sup>. As muscle tone increases, neurotransmitters such as substance P and glutamate are released. This stimulates N-methyl-D-aspartate receptors, activating inducible nitric oxide synthase and cyclooxygenase. Finally, pain-producing substances such as bradykinin, serotonin, and prostaglandin E2 are induced. This chronic stimulation increases myofascial pain

sensitivity, making patients aware of pain even with weak stimuli<sup>19)</sup>.

Considering these mechanisms, in the case of episodic TTH, abnormal muscle tone and accumulation of pain substances in the craniocervical area are related to acute TTH attacks. As an acute care drug, it is expected to relieve muscle contractions and eliminate pain substances as soon as possible.

### *Kakkonto* for TTH

*Kakkonto* is composed of seven herbal components. Tsumura *kakkonto* (TJ-1) 2.5 g in granular form is a galenic preparation containing: *kakkon* (pueraria root, 1.3 g), *taisou* (jujube, 1.0 g), *mao* (ephedra herb, 1.0 g), *kanzo* (glycyrrhiza, 0.7 g), *keihi* (cinnamon bark, 0.7 g), *shakuyaku* (peony root, 0.7 g), and *shoukyou* (ginger, 0.7 g).

Empirically, *kakkonto* is effective for headaches, shoulder stiffness, muscle pain, and hand and shoulder pain. *Kakkonto* is reimbursed for these diseases in Japan. *Kakkon* (pueraria root) contains flavonoids, such as daidzein and isoflavone, and has a papaverine-like antispasmodic effect. *Mao* (ephedra herb) contains ephedrine and exerts an adrenaline-like effect, improving muscle capillary circulation. In addition, *mao* has anti-inflammatory, analgesic, and antispasmodic effects. *Kanzo* (glycyrrhiza) has an anti-inflammatory effect. *Keihi* (cinnamon bark) increases the body temperature and inhibits the

overproduction of interleukin-1alpha. *Shakuyaku* (peony root) has an analgesic effect<sup>20,21</sup>. Also, *Shoukyou* (ginger) plays a key role in inhibiting nerve conduction related to pain alleviation<sup>22</sup>. Furthermore, *kakkonto* elevates body temperature and phagocytic activation of macrophages<sup>23,24</sup>, and inhibits cytokine production<sup>25</sup>. These anti-inflammatory and analgesic components may act synergistically and complementary to relieve muscle tension and pain and improve peripheral sensitization, acting as an acute treatment for TTH.

*Kampo* medicine has side effects. The major side effects are pseudoaldosteronism, interstitial pneumonia, liver dysfunction, and allergy. *Kakkonto* contains *kanzo* (glycyrrhiza), 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 should be considered appropriately.

#### Limitations of this study

First, the sample size was small as 10, and this study was performed in a single hospital with a single arm, although the sample size was calculated and confirmed as ad-hoc and post-hoc statistical analysis. Second, we did not compare to the control arm, so the actual therapeutic effects of *kampo* medicine were unknown. The placebo effect of spontaneous remission could be considered. Third, *kakkonto* contains multiple ingredients, so it is unclear which components functioned as a therapeutic effect. Also, the patients took *kakkonto* 2.5 g as a single dose, but the dose-dependent or frequency-dependent therapeutic effect is also unknown. Fourth, we did not have a detailed understanding of the patients' usual headaches. To investigate what kind of headache *kakkonto* is effective for, it is necessary to check the frequency and nature of the patients' daily headaches by keeping a headache diary<sup>26</sup>. Fifth, we did not evaluate the consistency of response because our study was based on single doses of *kakkonto* in a single arm. In modified-design crossover randomized control trials with a placebo-control, namely multiple attacks with random insertion of placebo, the consistency of response should be assessed. A further prospective study using a control arm and placebo will be considered in future research, in accordance with the guideline for controlled trials of drugs in tension-type headache: Second edition<sup>26</sup>.

#### Conclusions

We prospectively used *kakkonto* for 10 TTH patients who had already been treated with analgesics for their comorbidities. *Kakkonto* showed efficacy as an acute medication for TTH. In addition, there were no side effects of *kakkonto*.

※The authors declare there is no conflict of interest relevant to this article.

#### References

- 1) Headache Clinical Practice Guideline Development Committee. [Clinical Practice Guideline for Headache Disorders 2021] (Japanese). Japanese Society of Neurology J, Japanese Headache Society J, Japanese Society of Neurological Therapeutics J, editors. Tokyo: Igaku-Shoin; 2021. p.494.
- 2) Katsuki M, Kawahara J, Matsumori Y, et al. Questionnaire-based survey during COVID-19 vaccination on the prevalence of elderly's migraine, chronic daily headache, and medication-overuse headache in one Japanese city—Itoigawa Hisui Study. *J Clin Med* 2022;11:4707.
- 3) Katsuki M, Matsumori Y, Kawahara J, et al. School-based online survey on chronic headache, migraine, and medication-overuse headache prevalence among children and adolescents in Japanese one city -Itoigawa Benizuwaigani Study. PREPRINT. 2022. DOI:10.13140/RG.2.2.19532.49283
- 4) Sakai F, Igarashi H. Prevalence of migraine in Japan: a nationwide survey. *Cephalalgia* 1997;17:15-22.
- 5) Katsuki M, Yamagishi C, Matsumori Y, et al. Questionnaire-based survey on the prevalence of medication-overuse headache in Japanese one city-Itoigawa study. *Neurol Sci* 2022;43:3811-3822.
- 6) Suzuki N, Ishikawa Y, Gomi S, 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* 2014;53:683-689.
- 7) Suka M, Yoshida K. The national burden of musculoskeletal pain in Japan: projections to the year 2055. *Clin J Pain* 2009;25:313-319
- 8) Iritani S, Tohgi M, Miyata H, et al. Impact of dementia on cancer discovery and pain. *Psychogeriatrics* 2011;11:6-13.
- 9) Katsuki M, Narita N, Matsumori Y, et al. *Kampo* (Japanese herbal) medicine for primary headache as an acute treatment—a retrospective investigation in Kesenuma City Hospital during five years—. *J Neurosurg Kampo Med* 2022;7:1-7.
- 10) Katsuki M, Kashiwagi K, Kawamura S, et al. 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. *Cureus* 2022;14:e25419.
- 11) Ishida K. *Kampo* medicines as useful therapeutic agents in clinical practice of neurology: case reports & representative medicines. *Clin Neurol* 2013;53:938-941.
- 12) Sanno N, Kawashima A, Ishii Y, et al. [Efficacy of the *Kampo* medicine in prevention of classical migraine] (Japanese). *J Neurosurg Kampo Med* 2016;2:41-46.
- 13) Katsuki M, Kawamura S, Kashiwagi K, et al. Medication overuse headache successfully treated by Japanese herbal *kampo* medicine, *yokukansan*. *Cureus* 2021;13:8-11.
- 14) van Gerven JM, Schoemaker RC, Jacobs LD, et al. Self-medication of a single headache episode with ketoprofen, ibuprofen or placebo, home-monitored with an electronic

- patient diary. *Br J Clin Pharmacol* 1996;42:475-481.
- 15) Sakai F, Takeshima T, Homma G, et al. Phase 2 randomized placebo-controlled study of lasmiditan for the acute treatment of migraine in Japanese patients. *Headache* 2021;61:755-765.
  - 16) Cohen J. *Statistical Power Analysis for the Behavioral Sciences* Routledge; 2013.
  - 17) Mørk H, Ashina M, Bendtsen L, et al. Induction of prolonged tenderness in patients with tension-type headache by means of a new experimental model of myofascial pain. *Eur J Neurol* 2003;10:249-256.
  - 18) Castien RF, van der Wouden JC, De Hertogh W. Pressure pain thresholds over the cranio-cervical region in headache: a systematic review and meta-analysis. *J Headache Pain* 2018; 19:9.
  - 19) Fumal A, Schoenen J. Tension-type headache: current research and clinical management. *Lancet Neurol* 2008;7:70-83.
  - 20) Ara T, Sogawa N. Studies on shokyo, kanzo, and keihi in kakkonto medicine on prostaglandin E2 production in lipopolysaccharide-Treated human gingival fibroblasts. *Int Sch Res Not* 2016;2016:9351787.
  - 21) Nakae H, Saito Y, Okuyama M, et al. A case of tetanus treated with Kampo medicines such as Kakkonto and Shakuyakukanzoto. *Acute Med Surg* 2017;4:217-220.
  - 22) Matsushita A, Fujita T, Ohtsubo S, et al. Traditional Japanese medicines inhibit compound action potentials in the frog sciatic nerve. *J Ethnopharmacol* 2016;178:272-280.
  - 23) Muraoka K, Yoshida S, Hasegawa K, et al. A pharmacologic study on the mechanism of action of Kakkon-to: body temperature elevation and phagocytic activation of macrophages in dogs. *J Altern Complement Med* 2004;10:841-849.
  - 24) Kitamura H, Urano H, Ara T. Preventive effects of a kampo medicine, kakkonto, on inflammatory responses via the suppression of extracellular signal-regulated kinase phosphorylation in lipopolysaccharide-treated human gingival fibroblasts. *ISRN Pharmacol* 2014;2014:784019.
  - 25) Saito N, Kikuchi A, Yamaya M, et al. Kakkonto inhibits cytokine production induced by rhinovirus infection in primary cultures of human nasal epithelial cells. *Front Pharmacol* 2021;12: 687818.
  - 26) Bendtsen L, Bigal ME, Cerbo R, et al. *Guidelines for controlled trials of drugs in tension-type headache: Second edition.* *Cephalalgia* 2010;30:1-16.