

## Integrating Kampo and Evidence-Based Medicine (3) – Type 2 Case

*The Effects of Goshuyuto on Migraines*

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### Introduction

In this series, I define four types of use of Kampo medicine in daily clinical practices within Japan's unified medical system, and discuss the diseases that fall under each of these types, by respectively giving relevant case examples. In the previous issue of this journal, I introduced four episodes, and explained that they fall under the four types of use of Kampo medicine in daily clinical practices. Let me recount them below.

Type 1: Kampo treatment is better than standard modern medical treatment

Type 2: The effects of standard modern medical treatment and Kampo treatment are both strengthened when the two are used in combination

Type 3: The side effects of standard modern medical treatment can be mitigated in combination with Kampo treatment

Type 4: Circumstances prevent the application of standard modern medical treatment, but treatment is needed

In this article we shall take a look at Type 2, in which the effects of both Kampo medicine and standard treatments of contemporary medicine are strengthened when the two are used in combination. This is a type that is most commonly experienced in daily clinical practices. However, there are various types to this type. In cases where standard treatment does not have an adequate effect, standard treatment gradually loses its effect, or a presently administered standard treatment cannot be used frequently, the combined use of Kampo medicine could have a dramatic effect.

Below, I shall introduce the effects of goshuyuto on migraines. Goshuyuto is effective against certain types of migraine, but let me explain how it is used in daily clinical practices, through a number of examples.

### 1. A Certain Episode

In the latter half of the 20th century, Dr. Domei Yakazu, a prominent Kampo doctor, established a study group called Onchikai. Large numbers of researchers who hold Dr. Yakazu in high respect still gather today and hold monthly study meetings.

In the meeting that convened in October 2014, Dr. Yoshihide Yakazu presented the following case example<sup>1)</sup>.

Patient: 42-year-old woman

Chief complaint: Migraine (from the forehead to the frontal region)

History of present illness: Since a few decades ago, the woman had been receiving oral medical treatment after being diagnosed with a migraine. She had taken rizatriptan orally, but because her headache had worsened in the past few months, she took the medicine once every two days. The triptan preparation that previously had had an effect no longer alleviated her headache as it had used to, and she couldn't go to work regularly because of her serious attacks of headache.

Medical interview: Headache and vomiting appear simultaneously. She was strongly susceptible to the cold, such that air conditioners in trains and at work made her feel ill and induced a headache. Her headache also worsened with intense stress.

Kampo medical observations:

Pulse: Sunken and weak

Tongue: Pink, wet, furry, teeth marks (+)

Prescription: 3 packs/day of goshuyuto extract

Progress: A month later, she was no longer forced to be prostrated in bed, nor be absent from work. The amount of triptan she took could be reduced, and her condition could be controlled with 3 to 4 oral

tablets a month. Thereafter, she has hardly been laid up in bed with a headache—perhaps only a few times a year.

The patient started to be suffered by a migraine in her twenty. She was benefitted from triptan after it appeared on the market, but her condition worsened again to the point where she had to take it every two days. She was at a complete loss. Dr. Yoshihide Yakazu took the particular note of the fact that her “headache and vomiting appeared simultaneously,” and that she “was strongly susceptible to the cold, such that air conditioners in trains and at work made her felt ill and induced a headache.” He thus administered goshuyuto, and as a result, her migraine diminished, and her use of rizatriptan significantly decreased.

To treat migraines, we often use goshuyuto in combination with NSAIDs, triptan, or other headache prophylactic. Goshuyuto is effective in preventing certain types of migraine. For information on what types of migraine it is effective against, please see the article in the *Journal of KAIM*, Vol. 2, No. 2<sup>2)</sup>.

Goshuyuto is an effective prescription against migraines. However, its efficacy will be inconsistent for each case. While a month of taking it may completely eliminate all occurrences of the headache in some cases, it may simply decrease the frequency of occurrences and weaken the intensity of the pain without completely curing the condition, in other cases. The above example is typical of the latter. Although goshuyuto did not completely cure the patient of her migraine, it is indispensable to her. It probably also benefitted her economically, as her frequency of taking triptan was reduced. This is a successful case example in which standard treatment was combined with Kampo medicine, and can be classified as a typical Type 2 case.

Dr. Yoshihide Yakazu who presented this case example is Dr. Domei Yakazu’s grandson.

## 2. Oral Instruction Regarding Goshuyuto

Dr. Yoshihide Yakazu prescribed goshuyuto for the above case for a number of reasons, but the most important was the following oral instruction given by Dr. Keisetsu Otsuka, who was a contemporary of Dr. Domei Yakazu <sup>3)</sup>.

“Use Goshuyuto for severe paroxysmal headaches. Most occur as a migraine. In cases of severe attacks, vomiting also occurs. Attacks commonly occur when one is tired, has eaten excessively, or before menstruation among women. They may occur once or twice a month, or even five, six times a month. When an attack occurs, the muscles of the neck contract and cause extreme stiffness from the shoulders to the neck. [...]. The degree of stiffness of the neck serves as an indicator for using goshuyuto. When a patient is examined during an attack, an inflation of the epigastric area is observed, and the patient frequently claims a feeling of having a clogged stomach. This abdominal condition is also an important indicator for using goshuyuto. [...]. Also during an attack, the feet become extremely cold, and the pulse tends to become sunken and slow. This is sometimes accompanied by a type of agitated condition in which the patient cannot remain relaxed but tends to agonize over repeatedly getting up and going to sleep. Vomiting bile with strong nausea occurs during strong attacks, but not necessarily..

Patients who have such headaches would no longer experience attacks if they are prescribed with goshuyuto when they are not experiencing an attack. They should continue to take the prescription for at least two to three months, although it depends on the patient. When they take goshuyuto during an attack, their headache will disappear almost immediately.

[...]. Based on the above indicators, it can be said that goshuyuto has a marked effect on migraines. Additionally, goshuyuto can be used for headaches other than migraines. [...]. Additionally, patients who display types of goshuyuto sometimes develop a flushed face and complain of their head feeling hot. This was called “true cold and false heat” by ancient

people, and is not real heat. In my experience with goshuyuto, there were two patients who complained that cooling their head made them feel ill no matter how painful their headache was.

Goshuyuto is effective against cold headaches and not thermal ones. Therefore, it is best not to cool the head even if feels burning hot.”

The above oral instruction contains many hints for using goshuyuto against migraines. Some may say that it is simply a narrative and does not contain anything trustworthy according to EBM. However, from the perspective that “no evidence means that validity has not yet been proven, which differs from being ‘not valid,’” it could be a subject of research as clinically useful information.

It must be noted, however, that symptoms specific to migraines and the indications of goshuyuto are mixed in the instruction, and that if they are confused, the prescription will not be able to be used properly. For instance, about the passage, “In cases of severe attacks, vomiting also occurs. Attacks commonly occur when one is tired, has eaten excessively, or before menstruation among women. They may occur once or twice a month, or even five, six times a month,” these are general symptoms of migraines, and not indications of goshuyuto.

On the other hand, the passages, “When a patient is examined during an attack, an inflation of the epigastric area is observed, and the patient frequently claims a feeling of having a clogged stomach” and “Also during an attack, the feet become extremely cold, and the pulse tends to become sunken and slow,” refer to indications specific to goshuyuto.

Let us take a look at the results of clinical tests that were performed to prove this.

### 3. Clinical Studies of Goshuyuto on Headaches

In a sense, it is common understanding in Japan that goshuyuto is effective against migraines.

However, it is not clear to what percentage it is effective against what conditions of headaches in what types of people. Thus, a number of researchers have conducted clinical studies to find the answer to these questions. The scope of these studies includes not only migraines, but also tension headaches. Therefore, they do not reveal to what percentage goshuyuto is effective against migraines in it, but nevertheless provide a clinically significant reference. A couple of representative studies are introduced below.

#### 1) Study on the uniform administration of Goshuyuto to chronic headache patients by Odaguchi et al.<sup>4)</sup>

The subjects of the study were 49 people (men/women = 6/43, age 43+/-14) who use medicine for their attacks of chronic primary headache once a month in principle. According to the improvement of the intensity and frequency of their headaches, chills, menstrual cramp, and stiff shoulders, they were divided into a Responder group (R group; 36 people) and Non-responder group (N group; 13 people) based on a certain set of criteria, and were uniformly administered 7.5g of Tsumura goshuyuto extract 3 times a day for a month. A contingency table examination was then performed.

As a result, the subjective symptom “being immune to motion sickness” (R group 34 people, N group 8 people:  $P = 0.01$ ) and the objective finding “para-umbilical tenderness and resistance” (R group 15 people, N group 1 person:  $P = 0.04$ ) were significantly frequent in the R group. Other tendencies of the R group included some items, namely, chills, hypochondriac discomfort and distension, without flushed face, and without sigmoid colon tenderness. Additionally, items with sensitivity and specificity exceeded 0.5 were chills, menstrual cramps, epigastric discomfort and resistance, and abdominal tenderness, without sweating, without menstrual irregularity, without abdominal deficiency, and without weakness of the lower abdominal region.

This study examined the differences in symptoms between a group of patients who were sensitive to goshuyuto (Responder group) and a group of patients who were not susceptible to goshuyuto (Non-responder group), and is a groundbreaking study that marks the first step toward revealing the facts of goshuyuto pattern. The results are clearly evident in subjective symptoms and abdominal examination findings, and have provided a hint to the future application of goshuyuto.

## 2) Study by Hayashi et al.: Clinical study of Goshuyuto against chronic headaches<sup>5)</sup>

Goshuyuto was administered to 32 chronic headache patients, and was effective at a rate of 34.4%. However, there were no factors that had a significant relevance to the effectiveness of goshuyuto ( $p < 0.05$ ). Goshuyuto was neither particularly effective against either migraines, tension headaches, or combined headaches.

To reveal the types of goshuyuto, this study also examined more than 100 subjective symptoms in a multivariate analysis. The methodology was highly subjective, and excluded the perspective of Kampo medicine as much as possible. As a result, there were hardly any symptoms that were related to goshuyuto. This result was obtained, because the study eliminated any partiality to Kampo medicine as much as possible, in contrast to the Kampo-oriented study by Odaguchi et al.

Normally, an efficacy rate of around 30% in the field of pain can be construed as being the same as a placebo. In this respect, this study suggested that goshuyuto is in no way a special medicine. However, many physicians who were involved in the study say that patients who benefitted from goshuyuto became dramatically better. This is a characteristic of goshuyuto that cannot be ignored from the standpoint of narrative medicine.

## 4. Goshuyuto in Integrated Medicine

When treating migraines in general practice, it is important to alleviate the pain that has developed,

but more important is to prevention. Some studies have been conducted on the effects of goshuyuto in preventing migraines. I shall introduce two such studies below. One is a study by Dr. Koji Maeda et al., in which the frequency of administering triptan could be reduced by the combined use of goshuyuto. The other is a study of combined therapy using lomerizine hydrochloride and goshuyuto, by Dr. Tetsuhiro Katayama.

### Dr. Maeda's study<sup>6)</sup>

Dr. Koji Maeda administered goshuyuto to patients who took Triptan to treat their migraine, experienced an attack more than four times a month, and continued to require 5 Triptan tablets or more per month although they saw no change in the frequency of their attacks of headache (12 patients: 2 male, 10 female). He then examined the number of occurrences and frequency of their headache, the number of times they took Triptan, associated symptoms, the effects of reducing medical expenses, effectiveness, and side effects. As a result of taking Goshuyuto in combination, their attacks lessened to about two times a month roughly three months after taking goshuyuto.

At the same time, 9 out of 12 patients became able to reduce their dose of goshuyuto from 7.5g to 5.0g. Goshuyuto was also effective against stiff shoulders and stiff nape in 5 out of 8 patients, and effective against chills in 7 out of 10 patients. Nausea and vomiting during an attack were mitigated in 7 out of 10 patients. The combined use of goshuyuto reduced medical expenses compared to using triptan alone (Triptan: approx. ¥1,000/tablet; goshuyuto: approx. ¥100/day; lomerizine hydrochloride: approx. ¥140/day), and was judged to be effective in 75% of cases.

Dr. Maeda states that the combined use of triptan and goshuyuto helped control the headache attack, lowered the occurrence of attacks, and produced satisfactory results in preventing headaches, as well as improved other associated symptoms and reduced

the number of Triptan tablets that need to be taken. He gives high marks to goshuyuto, as having freed patients from the anxiety of anticipating migraine attacks that were apt to occur at any time, and making it possible to fully control migraines.

### **Dr. Katayama's study<sup>7)</sup>**

Dr. Tetsuhiro Katayama examined the effect of the headache prophylactic lomerizine hydrochloride and goshuyuto in preventing migraines in a crossover comparative study.

Fourteen patients (all women, average age 28.4 $\pm$ 3.8) diagnosed as a migraine, as defined by the International Classification of Headache Disorders, were divided into two groups. One group (7 patients) was first administered 10mg/day of lomerizine hydrochloride for 28 days, followed by 7.5g/day of goshuyuto extract for the next 28 days. The other group (7 patients) was first administered goshuyuto extract for 28 days, followed by lomerizine hydrochloride for the next 28 days. The effect of preventing migraines in the two groups was then evaluated by examining the number of times a migraine attack occurred and its intensity evaluated via visual analogue scales prior to and during the 28 days of taking the preventive drugs. The patients were allowed to take Triptan if they experienced an attack during the test period. All 14 patients completed the 56-day clinical test, with the result that the group that was first administered goshuyuto experienced a significant decrease in the frequency of their migraine attack and headache intensity. In the group that was first administered lomerizine hydrochloride, 2 patients experienced sleepiness, but none of the patients in the group that was first administered goshuyuto experienced any such adverse event. Goshuyuto also controlled the frequency of nausea as a secondary effect.

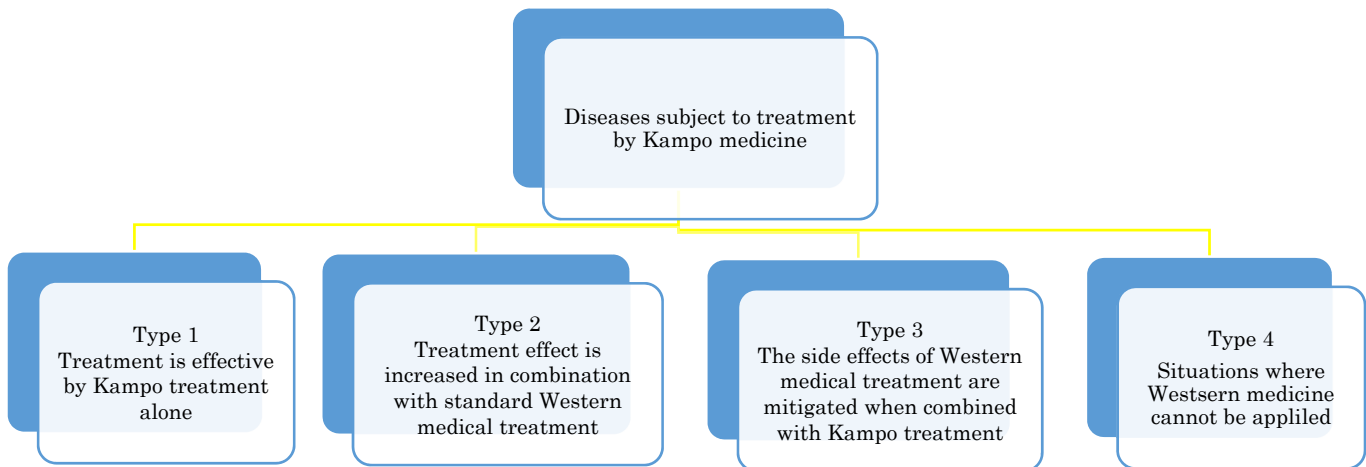
This study examined the combined effect of goshuyuto and lomerizine hydrochloride in preventing migraines, and showed goshuyuto's significant power.

Such studies as the above have clarified the effect of combining goshuyuto with Triptan or lomerizine hydrochloride in treating migraines. The studies by Drs. Maeda and Katayama, in particular, showed that Dr. Yoshihide Yakazu's case example that was introduced at the beginning of this article is not a special case, but a common one.

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## The four types and their characteristics



Other Type 2 pathologies and prescriptions are as follows.

- Example 1: Combined use of carbamazepine and goreisan for trigeminal neuralgia
- Example 2: Combined use of MTX and Kampo prescriptions for rheumatoid arthritis
- Example 3: Combined use of an antibacterial agent and daiokanzoto for colonic diverticulitis
- Example 4: Combined use of kakkontokasenkyushini and standard treatment for purulent rhinorrhea
- Example 5: Combined use of steroid and Kampo for bronchial asthma and COPD
- Example 6: Administration of daikenchuto for bowel movement after an intra-abdominal surgery