Daisaikoto for shoulder stiffness and related changes in stool condition: Retrospective study

Minoru Ohsawa,1,2,3 Shin Takayama,∗1,2,3* Akiko Kikuchi,1,2,3 Ryutaro Arita,1,2 Natsumi Saito,1,2 Yuka Ikeno,1 Hitoshi Nishikawa,1 Hiroyo Sasaki,1 Michiyo Kojima,1 Masayuki Shimizu,1 Takehiro Numata,1 Kota Ishizawa2 & Tadashi Ishii1,2,3

1 Department of Kampo Medicine, Tohoku University Hospital, Sendai, Japan
2 Department of Education and Support for Regional Medicine, Tohoku University Hospital, Sendai, Japan
3 Department of Kampo and Integrative Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

ABSTRACT
Aim: Daisaikoto has been used for the treatment of shoulder stiffness and abdominal distention with constipation, which makes stool changes associated with the prescription a concern. The aim of this retrospective observational study was to investigate the effect of daisaikoto on shoulder stiffness and the relation between its effects on stiffness relief and stool condition.

Methods: We reviewed the medical records of middle-aged women who were treated with daisaikoto for menopause-like symptoms and shoulder stiffness from December 2014 through November 2015 at Red Cross Maebashi Hospital. Two or 4 weeks after the prescription of daisaikoto, symptoms were evaluated and categorized as improved, no change, or worse. Stool condition was also evaluated and categorized as constipation, normal, or diarrhea. Change in symptoms from before to after treatment was analyzed using the Wilcoxon signed-rank test. The relationship between symptom changes and stool condition was analyzed using Spearman’s rank correlation coefficient.

Results: Of 24 patients who received daisaikoto, shoulder stiffness was relieved in 79% (P < 0.05). Diarrhea was reported in 8% of patients, all of whom were classified in the non-improvement group, which included depressed patients. Improvement of shoulder stiffness and stool condition had a correlation coefficient of 0.542. Daisaikoto did not worsen stool condition in the patients in whom it was effective.

Conclusion: Daisaikoto effectively relieves shoulder stiffness in middle-aged women, and did not worsen stool condition in those with improvement in shoulder stiffness. Daisaikoto without Rhubarb or other formulas may be an alternative treatment choice for diarrhea patients with shoulder stiffness.

KEY WORDS: constipation, daisaikoto, diarrhea, kampo, stool

INTRODUCTION
Shoulder stiffness is one of the most common conditions seen in Japanese clinics. Once organic disease has been ruled out, treatment such as medication, physical therapy, exercise, or acupuncture is selected for symptom relief. Often, traditional Japanese (kampo) medicine is recommended. There are 19 kampo formulae, which are covered by the Japanese health insurance system, for stiff shoulders and muscle pain, such as kakkonto, keishibukuryogan, daisaikoto and so forth in Japan. Of these, daisaikoto, which consists of Japanese Pharmacopoeia (JP) [1] JP Bupleurum root, JP Pinellia tuber, JP Scutellaria root, JP Peony root, JP Jujube, JP Immature Orange, JP Ginger, and JP Rhubarb, is generally used for patients with abdominal distention and constipation [1,2]. JP Rhubarb (hereafter called Rhubarb) contains sennoside A, a laxative, which means that practitioners should be aware of the effects of daisaikoto on stool condition. The effectiveness and safety of daisaikoto for the treatment of shoulder stiffness, however, have not been studied.

The aim of this study was to investigate the association between the effects of daisaikoto on shoulder stiffness and stool condition.

METHODS
In this retrospective observational study, we reviewed the medical records of middle-aged women treated with daisaikoto for shoulder stiffness from December 2014 through
November 2015 at the Department of Gynecology, Red Cross Maebashi Hospital.

The dosage of daisaikoto extract granules for clinical use (Tsumura, Tokyo, Japan; Table 1) varied according to major symptoms (except constipation). Patients were given 2.5–7.5 g/day, which corresponds to 0.3–1.0 g Rhubarb, depending on the severity of shoulder stiffness.

Two or 4 weeks after the prescription of daisaikoto, symptoms were evaluated and classified as improved or not improved. The degree of stiffness was evaluated using a numerical rating scale (NRS; range, 0–10); all patients had a score >5 before treatment. Patients whose NRS score decreased by half or more were categorized as improved, and the others were categorized as not improved. Stool condition was also evaluated and classified as constipation, normal, or diarrhea. In the present study, ‘constipation’ refers to difficult bowel movements for >2 days, ‘normal’ refers to daily defecation, and ‘diarrhea’ refers to frequent bowel movements with watery stools and bowel pain.

**Statistical analysis**

Change in shoulder stiffness (from before to after treatment) was analyzed using the Wilcoxon signed-rank test. The relationship between changes in shoulder stiffness and stool condition was analyzed using Spearman’s rank correlation coefficient. *P < 0.05* was considered statistically significant. After the overall analysis, patients were classified into an improvement group and non-improvement group.

**Ethics**

This study was approved by the ethics review board of Red Cross Maebashi Hospital (IRB no. 28–40), and the study design conforms to the provisions of the Declaration of Helsinki. Given the retrospective nature of the study, the requirement for informed consent was waived.

**RESULTS**

Patient characteristics and changes in symptoms and stool condition are listed in Table 2. The records of 24 patients (all female; average age, 49.8 ± 11.6 years) were analyzed in the study. Overall, shoulder stiffness was relieved in 79% of patients (improvement, *n = 19*; no improvement, *n = 5*, *P < 0.05*; Table 2). Diarrhea was reported as a side-effect in 8% of patients (*n = 2*). In the improvement group (patients A–S), nine patients (47.4%) reported a change in stool condition from constipation to normal. The remaining 10 reported no stool change. Accompanying symptoms such as headache, irritation, numbness in the right leg, and chest tightness improved in nine patients whose shoulder stiffness improved. In the non-improvement group (patients T–X), two patients (40.0%) had diarrhea. Diarrhea spontaneously recovered after stopping treatment in the non-improvement group. The accompanying symptom of depression did not improve with daisaikoto in four non-improved patients. Spearman’s rank correlation coefficient for the improvement of shoulder stiffness and stool condition was 0.542.

**DISCUSSION**

In this study, daisaikoto relieved shoulder stiffness in 79% of patients, and was associated with diarrhea in 8%. A moderate relationship between the improvement of shoulder stiffness and stool changes was observed. Daisaikoto did not worsen stool condition in the patients in whom it was effective. The patients who reported diarrhea as a side-effect were all in the non-improvement group.

In this study, the subjects had menopausal symptoms. In the menopausal period, patients complain of hot flashes, headache, neck and shoulder stiffness, edema, palpitation, joint pain, or constipation due to a decrease in estradiol [3]. Daisaikoto is an effective treatment for neck stiffness that spreads to the shoulder blade or oppressive pain around the diaphragm. It is also useful as a treatment for irritation. These characteristics of daisaikoto make it ideal for menopausal women experiencing irritation.

Although the mechanism by which daisaikoto relieves shoulder stiffness remains unclear, a combination of the crude drugs bupleurum root, pinellia tuber, scutellaria root, peony root, jujube, immature orange, ginger, and rhubarb

---

**Table 1** | Daisaikoto extract granules (Tsumura): Effects, application, and crude drugs [2]

| Kampp medicine | Effects | Application for symptom | Crude drugs in daisaikoto |
|----------------|---------|-------------------------|--------------------------|
| Daisaikoto     | Improvement of muscle stiffness, peristalsis of gastrointestinal tract, and emotional stability | Shoulder stiffness and pain | 6.0 g JP Bupleurum root |
|                |         | Abdominal distention    | 4.0 g JP Pinellia tuber  |
|                |         | Nausea                  | 3.0 g JP Scutellaria root|
|                |         | Headache                | 3.0 g JP Peony root      |
|                |         | Constipation            | 3.0 g JP Jujube          |
|                |         | Irritation              | 2.0 g JP Immature Orange |
|                |         |                         | 1.0 g JP Ginger          |
|                |         |                         | 1.0 g JP Rhubarb         |

JP, Japanese Pharmacopoeia.
Daisaikoto for shoulder stiffness

has been shown to be effective. Daisaikoto contains 1 g/day Rhubarb. Sennoside A, an ingredient of Rhubarb, is metabolized to rheinanthrone by \( \beta \)-glucosidase, and its laxative effect is induced by gut microbiota. The dosage of Rhubarb may contribute to changes in stool condition. Usually, the laxative effect of Rhubarb is observed with doses \( >1.0 \) g/day. Beubler and Kollar reported that sennoside increased intraluminal prostaglandin E2 and resulted in water and electrolyte secretion [4]. Rhubarb has been reported to inhibit cholera toxin activities, including adenosine diphosphate (ADP)-ribosylation and the accumulation of intraluminal fluid [5]. Changes in stool condition after daisaikoto treatment depend on the Rhubarb dosage and are based on the enhancement of gut motility, secretion of water and electrolytes, and an antibacterial effect.

In conclusion, daisaikoto can effectively relieve shoulder stiffness in middle-aged women, and a relationship between change in stool condition and improvement of shoulder stiffness was observed in this study. Daisaikoto did not worsen stool condition in patients whose shoulder stiffness improved. After daisaikoto treatment, diarrhea occurred in some patients whose shoulder stiffness did not improve. Daisaikoto without Rhubarb or other formulas may be an alternative treatment

Table 2  | Patient characteristics and changes in stool and shoulder stiffness

| Patient | Sex | Age (years) | Prescription (TJ-8) | Stool condition before treatment | Stool condition after treatment | Change in stool condition | Shoulder stiffness | Major symptoms except for bowel movement |
|---------|-----|-------------|---------------------|---------------------------------|---------------------------------|---------------------------|------------------|------------------------------------------|
| A       | F†  | 42          | 7.5 g/day, t.i.d.   | Constipation                    | Constipation                    | No change                 | Improved         | Irritation and headache                  |
| B       | F   | 35          | 7.5 g/day, t.i.d.   | Constipation                    | Constipation                    | No change                 | Improved         | Numbness of right leg                     |
| C       | F   | 76          | 7.5 g/day, t.i.d.   | Constipation                    | Constipation                    | No change                 | Improved         | Chest tightness                           |
| D       | F   | 32          | 7.5 g/day, t.i.d.   | Constipation                    | Normal                          | Improved                  | Improved         | Chest tightness                           |
| E       | F   | 45          | 7.5 g/day, t.i.d.   | Constipation                    | Normal                          | Improved                  | Improved         | Headache                                  |
| F       | F   | 42          | 7.5 g/day, t.i.d.   | Constipation                    | Normal                          | Improved                  | Improved         | Headache                                  |
| G       | F   | 53          | 7.5 g/day, t.i.d.   | Constipation                    | Normal                          | Improved                  | Improved         | Headache                                  |
| H       | F   | 43          | 7.5 g/day, t.i.d.   | Normal                          | Normal                          | No change                 | Improved         | Irritation                                |
| I       | F   | 47          | 7.5 g/day, t.i.d.   | Normal                          | Normal                          | No change                 | Improved         | Irritation                                |
| J       | F   | 51          | 7.5 g/day, t.i.d.   | Normal                          | Normal                          | No change                 | Improved         | Headache                                  |
| K       | F   | 43          | 7.5 g/day, t.i.d.   | Normal                          | Normal                          | No change                 | Improved         | Headache                                  |
| L       | F   | 51          | 7.5 g/day, t.i.d.   | Normal                          | Normal                          | No change                 | Improved         |
| M       | F   | 36          | 5.0 g/day, b.i.d.   | Constipation                    | Normal                          | Improved                  | Improved         | Irritation                                |
| N       | F   | 44          | 5.0 g/day, b.i.d.   | Constipation                    | Normal                          | Improved                  | Improved         | Irritation and headache                  |
| O       | F   | 53          | 5.0 g/day, b.i.d.   | Constipation                    | Normal                          | Improved                  | Improved         | Irritation and headache                  |
| P       | F   | 80          | 5.0 g/day, b.i.d.   | Constipation                    | Normal                          | Improved                  | Improved         | Headache                                  |
| Q       | F   | 52          | 5.0 g/day, b.i.d.   | Normal                          | Normal                          | No change                 | Improved         | Headache and dizziness                    |
| R       | F   | 50          | 2.5 g/day, q.d.     | Constipation                    | Normal                          | Improved                  | Improved         | Headache                                  |
| S       | F   | 58          | 2.5 g/day, q.d.     | Normal                          | Normal                          | No change                 | Improved         | Tinnitus                                  |
| T       | F   | 66          | 7.5 g/day, t.i.d.   | Constipation                    | Diarrhea                        | Worse                     | Not improved   | Depression and chest oppression           |
| U       | F   | 44          | 7.5 g/day, t.i.d.   | Normal                          | Diarrhea                        | Worse                     | Not improved   | Depression and chest oppression           |
| V       | F   | 44          | 5.0 g/day, b.i.d.   | Constipation                    | Constipation                    | No change                 | Not improved    | Depression                                |
| W       | F   | 58          | 2.5 g/day, q.d.     | Normal                          | Normal                          | No change                 | Not improved    | Depression                                |
| X       | F   | 49          | 2.5 g/day, q.d.     | Normal                          | Normal                          | No change                 | Not improved    | Depression                                |
| n = 24  |     | 49.8 ± 11.6 | 7.5 g/day (n = 14), | Constipation                    | Constipation                    | Improved                  | Improved         | Depression and chest oppression           |
|         |     |             | 5.0 g/day (n = 6),  | Normal                           | Normal                          | Improved                  | Improved         | Depression                                |
|         |     |             | 2.5 g/day (n = 4)   | Normal                          | No change                       | Not improved              | Not improved    |

**Bold**: improvement with daisaikoto. b.i.d., twice per day; F, female; q.d., once per day; t.i.d., three times per day; TJ-8, daisaikoto extract granules (Tsumura, Tokyo, Japan).
choice for these patients. Regular daisai-koto, which contains Rhubarb, can be recommended for use by middle-aged and elderly women with stiff shoulders.

ACKNOWLEDGMENTS

This study was presented at the 67th annual meeting of the Japan Society of Oriental Medicine in 2016. This study was funded by the Tohoku University Hospital administration fund. Author contributions are as follows: M.O. planned this study and performed statistical analysis. M.O. and S.T. wrote the manuscript. A.K., R.A., N.S., Y.I., H.N., H.S., M.K., M.S., T.N., K.I., and T.I. gave advice on revision.

CONFLICT OF INTEREST

M.O., A.K., S.T., and T.I. belong the Department of Kampo and Integrative Medicine at Tohoku University School of Medicine, which received a grant from Tsumura, a Japanese manufacturer of kampo medicine, but the grant was used as per Tohoku University rules. Potential conflicts of interests were addressed by the Tohoku University Benefit Reciprocity Committee and were managed appropriately. The other authors declare no conflicts of interest.

REFERENCES

1. Ministry of Health, Labour and Welfare. Japanese Pharmacopoeia, 17th edn. Tokyo: Ministry of Health, Labour and Welfare of Japan, 2016. [Cited 26 Dec 2018.] Available from URL: https://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-lyakushokuhinkyoku/JP17_REV_1.pdf.
2. Department of Pharmacognosy, Phytochemistry and Narcotics (DPPN), National Institute of Health Sciences (NIHS) of Japan and National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN). Table of the Links of Kampo Product Informations in Japanese Pharmacopoeia (JP) and/or Package Insert. [Cited 9 May 2019.] Available from URL: http://mpdb.nibiohn.go.jp/stork/
3. Ushiroyama T. Menopausal symptom. J. Ther. 2004; 86: 650–653 (in Japanese).
4. Beubler E, Kollar G. Prostaglandin-mediated action of sennosides. Pharmacology 1988; 36: 85–91.
5. Oi H, Matsuura D, Miyake M et al. Identification in traditional herbal medications and confirmation by synthesis of factors that inhibit cholera toxin-induced fluid accumulation. Proc. Natl. Acad. Sci. U. S. A. 2002; 99: 3042–3046.