Kampo Medicine - Current Research

Effects of Boiogito on Osteoarthritis of the Knee

Hiromichi Yasui
Japan Institute of TCM Research

Osteoarthritis of the knee is a generative disease that occurs with age and an extremely large number of people suffer from this disease, not only in the U.S., but also in other countries. The disease is treated with many different therapies according to the severity of impairment. In recent years, herb medication has been in the spotlight as an effective treatment for the disease. In Japan, clinical research with the use of herb medicines has been carried out for several decades to treat osteoarthritis of the knee and there are some papers already released. Among the medicines studied, *boiogito,* is now gaining attention.

Boiogito is one of prescription of a holy scripture, Jin Gui Yao Lue (Essentials from the Golden Cabinet), and is described as it is effective for "Fushitsu (Wind-Damp). "Fushitu (Wind-Damp)" means a group of diseases, such as articular rheumatism and neuralgia with pain as a main symptom in the body. The book does not mention that *boiogito* is specially responsive to pain in the knee joints, but people of later age have referred to this book and used this formula for pain in knee joints.

Most recently, the research on the effect of *boiogito* on osteoarthritis of the knee has emerged, in which a clinical epidemiological method was used. The research will be introduced below with citations of preceding research.

Experience of Keisetu OTSUKA

It was Keisetsu OTSUKA (1900-1983) that used the formula of *boiogito* for knee diseases for the first time. In his paper published in 1954, "About *boiogito,*" accurate therapeutic uses of *boiogito* were mentioned, including the application to pain in knee joints. The descriptions in the paper are as follows[1]:

> The case of using *boiogito* is seen more often in "so-called" rich women of leisure than in men. This is also true of women flabby with water. Many of these women have the desire to get thinner. These women feel heavy themselves, are languid in motions, such as standing up, sitting down, etc., and do not like to do cleaning and cooking, or rather think it too much trouble to do these things. When going out, these persons use a car without physical activities and thus they gain more fat. They eat a small amount of food and can go without having one meal. Many of these persons like hot tea. They have bowel movements almost every day but often have a small amount of menstrual discharge, or complain of irregularity. They have hyperhidrosis and dripping sweat during the summer.
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> A large proportion of women of this type start complaining of pain in the knee joints when exceeding the age of 50. In the evening, they have edemas in the lower extremities and their shoes or Japanese socks become too tight. Abdominal examinations reveal swelling of the abdomen, which is flaccid with no resistance and pain.

Otsuka came to the above conclusion from his own clinical experience and used *boiogito* for many cases of osteoarthritis of the knee. In later years, he said that he found a clue in the writing of the doctor who was active 150 years ago and arrived at a conclusion, that is, "Patients have the soft and lax skin. This is not an edema but water flown into the surface of the body. [snip] Many of these patients are women who became obese before or after the age of 20 years [omit the rest.][2] Then Otsuka continued: "I interpreted this writing as "effective for women flabby with water" and used *boiogito*." He further said: "This is my own thinking and other people will get other hint from the writing. So, I want people of later days not to adhere to my interpretation and want them to find something new from the original writing."

Despite Otsuka's desire, the interpretations made later of *boiogito* have not deviated from this category. *boiogito* has been used for osteoarthritis of the knee on the basis of Otsuka's interpretation. There has been some research conducted on the effect of *boiogito* on osteoarthritis of the knee and many cases have been reported. *Boiogito* was shown to be clinically beneficial. Typical cases will be introduced below.

Sample of preceding research

Otani, et al. reported[3] that they administered *boiogito* alone to 137 patients with osteoarthritis of the knee (male 20, female 117) and followed up for 6 months. Pains were assessed in 5 stages by visual analogue scale with the results showing improvement in 45 patients (32.8%) after 4 weeks and in 59 patients (43.1%) after 6 months.

Konari, et al. reported as follows[4]: They performed an analysis of 2,886 patients out of 7,088 patients with osteoarthritis of the knee that visited Konari's medical institution during January 2001 to March 2006. *Boiogito* was used in 1,009 patients. The breakdown of these patients was 330 females and 679 males with an age range from 25 to 95, an average of 64.1 years old. The duration of the use of *boiogito* was 0.5 to 75 months with an average of 4.4 months. The treatment effects showed improvement in 753 cases (74.6%), remained unchanged (7.5%) and not-known (10.6%). There was no difference in the improvement ratio among age, sex and duration.

Noguchi, et al. reported the following[5]. They made a controlled study with the subjects being 84 patients with primary osteoarthritis of the knee who were diagnosed as having edemas and whose roentogenographic images within 6 months after the enrollment were assessed as not over Stage III using the Hokudai Scale. The subjects were divided into the following three groups and administered the assigned medication for a period of 8 weeks: a group of *boiogito*, a group of *boiogito* in combination with NSAIDs, and a group of NSAIDs.

Improvements in floating patella were observed with 80.0% in the *boiogito* group, 96.4% in the *boiogito* and NSAIDs group, and 57.9% in the NSAIDs. The concomitant group of *boiogito* with NSAIDs showed a better improvement ratio than the NSAIDs alone group. Similar levels of improvement were shown in swelling in soft parts of the knee and a sensation of heat.

There was a study conducted on the use of *boiogito* for knee disease other than osteoarthritis of the knee. Otsuka, et al. released a report that they performed arthroscopic meniscectomy for symptomatic discoid lateral meniscus and used *boiogito* for the patients who then had hydrarthrosis, and the results were favorable[6].

New study by Mizuno, et al.

With the above studies of the past, Mizuno et al. conducted an epidemiological study using multivariate analysis in order to objectively grasp the effects of *boiogito* on osteoarthritis of the knee. The results were quite different from common knowledge and had clear indicators that can be used directly at clinical sites.

1. Subjects and methods

The subjects of the study were patients aged 60 or above who were complaining of persistent knee pain for 3 months or more, diagnosed as having osteoarthritis of the knee, and started the therapy of *boiogito*. The period of the treatment was four weeks.

With consent from each patient prior to the commencement of the treatment, questions were asked about patients' living habits, general symptoms before and after the treatment, and symptoms of the herb medicine to make investigations of symptoms and signs. General questions asked of patients (general questionnaire sheet) included 66 items about systemic condition: mood, sleep, cephalic symptom, thoracic symptom, dermal condition, dietary habit, oral condition, drinking and eating, hand and feet, lumbar, shoulders, muscles, abdominal symptom, urine and stools, and menopausal syndrome. And 24 questions were made to the attending physicians concerning physical findings, pulsation, abdominal findings, tongue condition, complexion, and complications.

Before and after the treatment, semiquantitative questions specific to the knee condition were provided to the patients, using a written questionnaire. The questions covered 11 items: severity of pain (visual analog scale: VAS), region of pain, duration of pain, presence of swelling, history of drainage of fluid from the knee, motion to cause pain, whether to able to sit on the heels or not, walking distance, necessity of supporting tool for walking, whether able to descend steps, analgesic now in use, etc.

The attending physicians made semiquantitative examinations (4 steps) on the five items, i.e., presence

of a sensation of heat, presence of edema, varus deformation (distance between both knees), and angle of knee extension.

Treatment was performed with *boiogito* at 7.5g / day in two doses in principle. Antiphlogistic analgesic was used as needed as far as possible. For serious cases, regular administration of NSAIDs was given orally, for which case the evaluation of the herbal effect was focused on whether the amount of NSAIDs could be reduced or not. Before the start of the administration (within a month) and during the course of the herb administration, new therapy had not been given (cool compress, rehabilitation, manipulative treatment, intraarticular injection, etc.).

The subjects were 64 patients (male 7, female 57) with a larger proportion of female (89.1%). Patient profile is shown in Table 1 below. With regard to BMI, the values before and after the administration were indicated.

Age	72.9±8.9 years
Height	152.7±7.5 c m
Weight before	58.1±9.1 k g
Weight after	57.9±9.1 k g
BMI-before	24.9±3.2kg/㎡
BMI-after	24.8±3.2kg/㎡
Systolic BP	132.9±15.2mmHg
Diastolic BP	76.3±9.7mmHg
Pulse	72.8±9.5/min

Table 1 Patients Profile

2. Efficacy Assessment and rates

Similarly with general accumulation case studies, one of the objectives of this study was to see the efficacy rates of *boiogito* in osteoarthritis of the knee. The other objective was to identify the effectiveness.

Effectiveness was graded as “markedly effective”, “moderately effective”, “slightly effective”, and “poor.” This was administered by persons who were not involved in the treatment on the following three points: 1) Visual Analog Scale (VAS) records taken by the patient for the knee pains before and after the treatment, 2) self-assessment on improvements in the knee condition, and 3) physician’s assessment.

The results are shown in Table 2. Moderately effective or above was 31.3% with 57.8% indicating slightly through markedly effective. These results are not greatly different from those of other studies above and it has been confirmed that this medication has certain levels of effects on this disease that occurs with age.

Markedly effective	9.3%
Moderately effective	21.9%
Slightly effective	26.6%
Poor	42.2%

Table 2 Efficacy ratio of *boiogito* in osteoarthritis of the knee

3. Effective factors and ineffective factors

The other purpose of the study was to identify the factors that allow effective functioning or ineffective functioning of the medication using a multivariate analysis. The materials used for the analysis were vast volumes of investigational items, VAS recorded by patients, degree of improvement in subjective symptoms, and findings of physical examinations by the attending physicians. These symptoms and signs were investigated to find the factors in the group with effectiveness and the group without effectiveness.

The items in Table 1 were divided into an effective group of markedly effective + moderately effective (20 patients, 31.2%) and an ineffective group of slightly effective + poor (44 patients, 68.8%) for statistical analysis. The results indicated that effective factors of significance were “less than 1 year of pain duration” (odds ratio 3.2) and “presence of swelling in the knee joints” (odds ratio 3.2). Although significant differences were not observed statistically, the effective factors had a tendency of “**supporting tool is necessary for walking”** (odds ratio 8.0) and “free from insomnia” (odds ratio 4.2) (Table 3).

Study items	p value	Odds ratio	95% confidence interval
Duration of knee pains - less than one year	0.037	3.2	1.08～9.81
Presence of swelling in knee joints	0.037	3.2	1.07～9.62
Supporting tool necessary for walking	0.054	8.0	0.96～65.87
Can sleep	0.078	4.2	0.85～20.61

Table 3 Effective factors
(Markedly effective + Moderately effective vs. Slightly effective + Ineffective)

Meanwhile, ineffective factors of significance were "no sensation of heat" (odds 0.19), "BMI 25 or above before the treatment" (odds ratio 0.25), "have nocturnal urine" (odds ratio 0.28), "fatigable" (odds ratio 0.3), "BMI 25 or more after the treatment" (odds ratio 0.3). (Table 4)

Study items	p value	Odds ratio	95% confidence interval
No sensation of heat	0.009	0.19	0.06～0.66
BMI25 or more before treatment	0.023	0.25	0.08～0.82
Have nocturnal urine	0.024	0.28	0.09～0.84
Fatigable	0.037	0.3	0.10～0.93
BMI25 or more after treatment	0.047	0.3	0.09～0.98
Stomach feels heavy r stuck	0.069	0.14	0.02～1.17
Not have dry mouth	0.081	0.33	0.10～1.15
Often eat miso-soup	0.094	0.35	0.10～1.19

Table 4 Ineffective factors
(Markedly effective + Moderately effective vs. Slightly effective + Ineffective)

Conditions of age, pulsation, tongue and abdominal did not work either as an effective factor or an ineffective factor.

Table 5 shows symptoms associated with osteoarthritis of the knee that develops with the probability of 40% or above. Many of these symptoms are the targets of *boiogito*. "Feeling short of breath" and "getting hot flashes in hands and feet" accounted for 70% of all the patients. Accounting for 60% were "hands and legs/feet become numb", "sensitive to heat and cold", "mouth gets dry", "shoulders get stiff easily", "muscles cramp", "have nocturnal urine", "have a chill in the lower back", etc. Analysis was carried out on these factors, but the result showed that they are neither effective factors nor ineffective factors.

Symptoms	Symptom ratio (%)
Get short of breath	76.6
Get hot flashes in hands and feet	76.6
Hands and legs/feet become numb	68.8
Sensitive to heat and cold	67.2
Mouth gets dry	64.1
Shoulders get stiff easily	64.1
Muscle cramp	62.5
Have nocturnal urine	60.9
Have a chill in the lower back	60.9
Prefer something cold	56.2
Fatigable	54.7

Table 5 Rates of symptoms associated with osteoarthritis of the knee (40% or more)

4. Discussion by Mizuno, et al.

Gaining the results above, Mizuno, et. al. have added the following considerations: Efficacy rates of *boiogito* in osteoarthritis of the knee in this study were 57.8% for slightly effective or above and 31.3% for moderately effective or more. These results were similar to those reported in the past, not greatly different from those of other clinical studies. What was made clear in this study we4.re effective factors and ineffective factors.

In Kampo therapy of osteoarthritis of the knee, bibliographic effective factors of *boiogito* were: traditionally fair-complexioned, soft flesh, obesity trend or so-called flabby with water, fatigable, and

tend to perspire a lot. This study, however, has revealed that *boiogito* is less responsive to obesity with BMI25 or above. This result is decisively different from what was believed to be effective in patients with the constitution of flabby-with-water. It has also been revealed that it is difficult to get effectiveness of the medication in patients with the condition of lack of qi, such as fatigue and nocturnal urine. On the contrary, since either of "no mouth dry" or "no sensation of heat" are a significant ineffective factor, condition with heat could be considered as an effective factor.

It is reasonable to consider from the above results that effective factors of *boiogito* are symptoms peculiar to osteoarthritis of the knee and not *boiogito* itself.

It was also revealed that *boiogito* is effective if the duration of the disorder is within one year. If the duration becomes longer, it is less responsive. In short, *boiogito* is effective in the case of osteoarthritis of the knee with a short duration and mild severity, whereas the medication is less effective in the case of the disease which becomes serious in a short period. This is probably because joint destruction progresses and great organic changes take place.

As far as knee conditions are concerned, swelling and heat sensation are greatly benefited by *boiogito*, whereas conditions without heat were less responsive. In other words, it has clearly been shown that only swelling, like hydrarthrosis, is less effective and obvious heat conditions such as heat in joints and dry mouth are more responsive.

It has been said that weight loss can be expected as *boiogito* has an aquaretic function. In fact, there were some cases that weight was lost together with an increase in urine volume after the administration[7]. However, it is not clear if there were variances in weight before and after the use of the medication. It seems difficult to expect strong aquaretic function.

In regard to the profiles of pulsation, tongue and abdomen, effective factors or ineffective factors of significance were not observed. Age was neither an effective factor nor an ineffective factor.

What can be derived from the study

From the above, prediction can easily be made if *boiogito* is beneficial or not, from the following elements: "duration of the disease is within one year" and "BMI is 25 or below" (these were from the interview with the physician), and "a sensation of heat and swelling in knee joints" from findings of physical examinations. As the author, et al. say, the results of this study will offer substantial benefits to the scenes of actual clinical practice that have time constraints.

At the clinical sites, there are many cases in which this formula is used with an addition of prepared aconite tuber or ephedra, or in combination of Cassia Twig Tuckahoe Pill. Many clinicians say that the combination use of *boiogito* brings excellent benefits. Especially an addition of prepared aconite tuber gives further effects[8]. Nagao, et al. reported that *boiogito* added by prepared aconite tuber showed an efficacy ratio of 87.8% and is a safer and effective therapy, compared to the results of nonsteroid anti-inflammatory agents[9].

It is expected that further research on *boiogito* will be conducted. With the use of the methodology of clinical epidemiology in the research of Kampo medicine, this paper has opened a new page to clinical applications of the formula of *boiogito*. This research will greatly contribute to future development of this field.

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