THE JOURNAL OF KAMPO, ACUPUNCTURE AND INTEGRATIVE MEDICINE
Research on Theory, Practice and Integration

KAIM

The Journal of
Kampo, Acupuncture and Integrative Medicine

INTERNATIONAL INSTITUTE OF HEALTH AND HUMAN SERVICES, BERKELEY

Volume 11, Number 3 · Fall 2016

ISSN:1559-033X

The Journal of
Kampo, Acupuncture and
Integrative Medicine
(KAIM)
Research on Theory, Practice and Integration

PUBLISHER
Shuji Goto
International Institute of Health and
Human Services, Berkeley
2550 Shattuck Avenue, Berkeley
California 94704-2724, U.S.A.

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Kampo, Acupuncture and Integrative Medicine

Volume 11, Number 3 · Fall 2016

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MISSION

To disseminate peer-reviewed information on the use of acupuncture and herbs, and integration with western medicine, based on research from an international perspective; thereby stimulating further research, application of documented therapeutic measures; and facilitating dialogue among health care practitioners worldwide.

Guest Editorial

"Yasui Classification" of the Indications for Kampo Treatment

Kampo, traditional Japanese medicine, has been integrated into modern medicine in Japan, creating a unitary medical system. This system is valuable both for medical professionals and for patients. Especially, medical doctors should know the indications and limitations of Kampo medicine in daily practice. Dr. Hiromichi Yasui has a long-term clinical experience in both western and Kampo medicines, in addition to his deep insight into medical history. When we select Kampo in the decision tree of our daily practice, we should take into consideration the merits and demerits of western medicine and Kampo medicine. In modern medicine in Japan, western medicine is overwhelming, and all the medical doctors are educated with western medicine at medical school and in their residency. However, since the dawn of the 21st century, Kampo has officially been introduced into medical education system. All the medical students in Japan are supposed to learn at least the beginning of Kampo medicine. Owing to this revolutionary change, almost no sense of resistance is seen in medical doctors of young generations. On the other hand, not so many doctors prescribe Kampo medicine with Kampo diagnosis. Sometimes, misuse of Kampo happens. There are two extremes, from "no Kampo" to "only Kampo" in Japanese medical doctors. These situations are unhappy for patients. Although various mixed patterns of the above two extremes are present, we need to clarify the indications of Kampo in modern medicine. This is an essential desire of clinicians to provide the most suitable treatment to each patient, and of course, patients hope it. In this issue of KAIM, Dr. Yasui clearly classified the indications of Kampo in various situations. This is the first attempt in this field, and I would like to name this classification as "Yasui Classification" of the indication for Kampo medicine in modern medical system. I sincerely hope this classification is applied to daily practice and clinical research from now on.

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Integrating Kampo and Evidence-Based Medicine (7) – From Reports of Medical Cases from 200 Years Ago –

The Effect of Maoto on Influenza

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From medical cases about 200 years ago

This is a story of an experience by a boy born in a doctor's family in a rural area in Japan about 200 years ago.

One day, the people of the neighborhood came to this doctor's house saying they wanted him to examine a patient. At this time, the doctor was not at home, and the grandfather, who was already retired, told the doctor's younger brother to "go and examine the patient". And so the boy went and examined the patient. The grandfather asked the boy what kind of sickness the patient had, and the boy answered, "The patient's disease is Shang-han, he has splitting pain in his head, chills, fever, labored breathing, pain all over his body, and his pulse was floating and strong." To this the grandfather replied, "What kind of prescription do you think to give him?" The boy answered, "how about maoto?" Then the grandfather smiled and said, "Good job", so he prop 3 doses of maoto and ordered him to "give him these doses warm, and make him sweat a lot" and sent the messenger back. When he went back the next morning, the patient had sweat a lot and said that his suffering had quickly been alleviated. He still had a slight fever, so he changed the prescription to shosaikoto, and he recovered in barely more than a day.

This is a story experienced by Dr. Yodo ODAI (1799-1870) at age 13, who was praised as a great doctor in his later years, and he wrote of this as being his "first challenge" [1)].

These records continued to be read even to this day. Among them, the ailment that he wrote as "Shang-han lun" seems to be almost the same as the "Shang-han lun" which is listed in the " Shang-han lun", the original text in which described maoto. And seen from our modern eyes, this was probably influenza.

Maoto is currently widely used for influenza. This is because this experience of Dr. Yodo ODAI was earnestly recorded in his "Essay of Medical Technique".

The composition of maoto

"Shang-han lun" lists the compounding and dosing method of maoto as follows.

Mix ephedra (3 liang, remove stem node), apricot seed (70 pieces, remove skin tip), cinnamon twig (2 liang, remove skin), and liquorice (2 liang, scorch) with 9 sheng of water, first boil the ephedra, reduce by 2 sheng, remove foam, add the other medicines, boil down by 2.5 sheng, remove scum, and take 8 ne warm. In other words, the boiled liquid will be divided into 3 equal parts.

Currently, the following crude drugs are boiled in the following gram amounts to prepare one day's dose. The formulation divides this into 3 times.

Ephedra 3～5g, apricot seed 4～5g, cinnamon twig 2～4g, liquorice 1～1.5g

Because the amounts are slightly different at each pharmaceutical company, there is a range. Lactose is often used as an excipient, with some formulations using starch.

Maoto as a remedy for influenza

Use of maoto is generally limited to the early stages of acute fever such as influenza. As stated above, the indication is the combination of symptoms such as chills, fever, headache, joint pain, and floating pulse, with no sweating.

When administering maoto for influenza, I conduct the following dosing guidance based on the description in the "Shang-han lun".

Patients take an extract formulation of maoto in hot water. After taking, keep the body warm to help induce sweating. After the first dose, take 1 dose every 2 hours taking 1 day's worth (3 doses) in 4 hours. Subsequently, take some every 3-4 hours, and continue until sweating onsets. After sweating starts, stop taking at that point. In the original text it is stated that you must not induce too much sweating, but in actuality as long as you quickly change clothes, keep warm, and intake an appropriate amount of water.

In some cases the fever may temporarily rise before subsequently falling. For example, in some case a body temperature of 38.5℃ may rise to 39.3℃ 1 hour after dosing. Normally, the fever will go back down after this. In rare cases, palpitation or tachycardia may occur after dosing. In these cases temporary stop taking the medicine.

When the fever starts to go down, there is often large amounts of sweating, but in a few dozen percent of patients, the fever can go down with frequent urination (urination may occur about 5 times in 2 hours). In these cases, there is not much sweating. In extremely rare cases, reduction of fever may occur with nosebleeds. When effective, the fever will drop to about 37.0℃ in 18-36 hours from the start of dosing.

The amount to use for children depends on their age and body weight or body surface area

Furthermore, in the series of maoto research below, the standard method of dosing one day's worth separated into 3 times is most common.

The diseases for which maoto is indicated in the text of the "Shang-han lun" belong to taiyang diseases among diseases called "Shang-han", and they are "headache and fever, sheng teng lower back pain, bone pain, chills, and panting without sweat". Thought of in the context of modern notions of ailments, these descriptions of "Shang-han" seem to be influenza or associated ailments. In recent years, research from this point of view has progressed and there has been a great deal of clinical research produced showing that maoto is effective against influenza.

There are also many medical reports, the prototypical of which is published by Oribe in Vol.1 No. 1 of this journal.

Caution when using

Maoto is a formulation with ephedra as its main ingredient, and the main component of ephedra is ephedrine. For this reason, use in combination with other ephedra-containing compounds and catecholamine formulations requires caution. Side effects caused by ephedrine can be seen including coronary artery disease, arrhythmia, excessive perspiration and urinary retention. Also seen are digestive symptoms such as a heavy feeling in the stomach and epigastric pain.

It has also been shown that the absorption of ephedrine raises in pH of the alimentary canal, so absorption is higher when taken internally after meals, and it also has the potential to increase the likelihood of side effects due to sympathetic nerve stimulation. For the same reason, taking together with antacid drugs also requires caution [3].

Research into maoto for influenza

Influenza virus infection often shows evidence of maoto, and there have been many reports regarding the effects of administering maoto. Classified broadly, we see studies which examine the effects when adding maoto to commonly used anti-viral medicines, studies which compare maoto alone with anti-viral medicines alone, and also case series and comparative studies which investigate the side effects and administration methods in addition to what happens before and after maoto is administered.

In Japan, continuing from the rapid testing of influenza viral antigens, in February 2001 the

National Health Insurance drug prices of oseltamivir (Tamiflu®) and zanamivir (Relenza®) were listed, after which their use expanded explosively. In the case of oseltamivir especially, 70-80% of its consumption in the world is in Japan, and as a unique phenomenon in Japan it as acquired the status of the standard treatment in a short period of time. Consequently, early-stage clinical research into the results of maoto against influenza virus infection has no option to not administer the standard treatment anti-viral medicine, and has started generally as an examination of the effects of maoto on top of the other medicine.

As the use of oseltamivir expanded, in 2004 a postscript was added to the package insert of oseltamivir regarding mental and nervous disorders, furthermore about the abnormal behavior of the teenage patient, Japan's Ministry of Health, Labour and Welfare came to urgently perform a delivery of safe information in 2007, and the report that compared the independent groups given *maoto* with the oseltamivir came to attract attention. In basic researches using rats, the simultaneous administration of ethanol and oseltamivir has been reported to promote excitability, and similar phenomena are predicted in ephedrine as well [4]. For this reason there are opinions that prudence is required when using oseltamivir and maoto together.

Furthermore, in 2009 the effectiveness of maoto against new strains of influenza was investigated, and this continues today. Compared to oseltamivir, the National Health Insurance drug cost of maoto is overwhelmingly low, and it is receiving attention in terms of health economics as well regarding whether or not administering maoto alone has the same effects as oseltamivir.

Note: In Japan, the prices of medicines used with health insurance are controlled by the nation. The drug price of oseltamivir phosphate is about 640 yen per one day's worth, while maoto is about 60 yen. Arita et al. preliminarily calculated that using maoto instead of oseltamivir would result in a reduction in health care costs of 3,000 yen per person or 9 billion yen in Japan overall [5].

In recent years there have also been reports of viruses that are resistant to oseltamivir, and furthermore oseltamivir-resistant viruses have shown cross-resistance with peramivir, a injectable medicine, as well. There are no reports of resistance to maoto, and viewed from the point of view of resistant virus control as well as from the point of view of drug assurance to prepare for pandemics, the significance of the existence of Kampo medicine such as maoto would seem to be great.

Studies of maoto with standard therapy

Research by Kuroki, et al.

In a comparative study by Kuroki, et al., oseltamivir was administered to 83 children with influenza, and in 44 of the 83 cases maoto 0.1-0.15g/kg/day x 3 was simultaneously administered. In the group administered oseltamivir alone, no complications were seen except 1 case of febrile convulsions. The time from the first day of fever until the alleviation of fever was 3 days in the maoto + oseltamivir group, and 2 days in the oseltamivir only administration group. The reason maoto was prescribed was not stated, and it is unclear what the fever period indicates [6].

Research by Kimoto, et al.

In an open labeled quasi-randomized-controlled trial (RCT) conducted subsequently by Kimoto, et al., with the same group, 19 patients diagnosed with influenza through clinical condition and rapid testing from January to March 2004 which did not meet exclusion criteria were divided into a group of 10 patients (4 men, 6 women, age 24.1±7.72) who were administered oseltamivir and maoto (7.5g/day×3 days) in the order of examination, and a group of 9 patients (5 men, 4 women, age 29.1±4.52) who were administered oseltamivir with Western medicine (cyproheptadine hydrochloride and clenbuterol hydrochloride or carbocysteine), and their body temperature, appetite, fatigue, and dizziness after treatment were compared via a questionnaire filled out by the patients. All of the cases were type-A influenza. 12 hours after the start of treatment, their body temperature showed a tendency to be lower in the maoto combination group than in the Western medicine combination group. The date when the maoto group's fatigue, dizziness and lack of appetite scores improved significantly compared to before treatment was sooner compared to the Western medicine group. Not examples if increased CRP were observed in the maoto group, but in the Western medicine group 3 cases of CRP increase were observed. In the Western medicine group reduced WBC, increased RBC, Hb, hematocrit and significant increase in ALT and γ-GTP were observed. A decrease in albumin was also observed in the maoto group. Including 8 weeks of follow-up observation, no serious adverse events were observed in either group [7].

Research by Fukutomi, et al.

In an open labeled RCT by Fukutomi, et al., 22 patients diagnosed with influenza through rapid testing within 24 hours of the onset of symptoms were divided into a group of 12 patients administered oseltamivir only (the single administration group) and a group of 10 patients who were administered oseltamivir with maoto (combined administration group) with the combined administration group being administered maoto (7.5g/day), and the number of days the patients continued to experience a fever of 38℃ or higher, headaches, and full-body fatigue was investigated. The method of assignment into the groups was not stated. The number of days the fever continued was 1.7±0.8 days in the single administration group and 1.9±0.6 days in the combined administration group, showing a significant difference. The number of days the headache continued was 2.4±1.0 days in the single administration group and 1.3±0.5 days in the combined administration group, while the full-body fatigue was 2.3±1.2 days in the single administration group and 1.3±0.5 days in the combined administration group, showing a significant difference. It appeared to be clinical influenza, but in the 6 cases where maoto was administered without a diagnosis via an influenza rapid testing kit, no significant difference in number of days fever, headache, and full body fatigue continued was found compared to the combined administration group. No serious side-effects were observed [8].

Research by Kubo, et al.

In an open labeled RCT by Kubo, et al., 60 case of patients (5 months to 13 years of age) experiencing fevers of 38℃ or higher, 2 or more of the symptoms headache, chills, and fatigue, and coughing and nasal inflammation all appearing within 48 hours were first classified into 2 groups: the group which was 1 year old or older with a positive rapid testing result, and the group which was 1 year or less with a positive rapid testing result or a negative rapid testing result regardless of age. Additionally, the group of 1 year and older with positive rapid testing results was further assigned randomly into 2 groups, with 19 patients being administered oseltamivir (4mg/kg/day) and 17 patients being administered oseltamivir and maoto (0.06g/kg/day). The group of 24 patients 1 year or less in age with a positive rapid testing result or a negative rapid testing result regardless of age was administered maoto only.

Antipyretics were requested not to be internally administered. The definitive diagnosis of influenza was conducted with viral culture or PCR, and among the negative rapid testing group those diagnosed with type A influenza were the only targets of analysis. The method of randomization was not stated. 3 of the patients with positive rapid testing results assigned combined administration of oseltamivir and maoto did not internally take maoto and were therefore excluded from analysis. The 2 groups which took maoto orally had significantly shorter periods of fever after examination compared to those who did not take maoto orally. All patients resumed their normal lives and no side effects from maoto were observed. No patients required hospitalization [9].

Research by Takeya, et al.

In RCT by Takeya, et al., the fever period from start of treatment until alleviation of fever was compared in two groups--a group that was administered both maoto and oseltamivir (23 type A and 17 type B) and a group that was administered only oseltamivir (59 type A and 86 type B)--targeting 185 patients (age 0-14) selected from children examined at 7 hospitals and clinics in Shimane prefecture who had not received influenza vaccination and who were shown to be type A or type B influenza virus antigen-positive in rapid testing. The results showed a shorter trend in the combined administration group compared to the oseltamivir only group, but no significant difference was observed [10].

Research by Yamamoto, et al.

In a retrospective comparative study by Yamamoto, et al., 167 cases were investigated via responses to questionnaires out of 329 cases of children where were diagnosed with new strains of influenza who were administered maoto. A questionnaire was administered to the guardians of the target patients regarding the state of oral ingestion, day of fever alleviation, and side effects or lack thereof, and the results of these were compared with the patient information in the electronic charts to confirm the patient backgrounds such as age and gender, fever period, and administration of anti-viral medicine and antibiotics or lack thereof. The results showed that in the younger ages there was more administration of maoto alone, while in the higher ages there was administration together with anti-influenza drugs. The average fever period by treatment method was 1.39±0.96 days in the maoto-only group and 1.60±1.20 days in the anti-influenza drugs combined use group, with no significant difference observed between the 2 groups. Side effects were observed in 21 patients (13.1%), and a breakdown observing duplicate responses was that 13 patients experienced lack of appetite, 5 experienced nausea/vomiting (including while taking orally), 3 experienced rashes, 2 experienced diarrhea/watery stools, and 1 each experienced bad temper and edema, respectively, with no significant difference observed between the groups [11].

Research by Tsuji, et al.

Comparative research by Tsuji, et al. targeted 81 cases of child influenza patients whose families consented in participation in the study. They were separated into 3 groups--an anti-influenza medicine only group (oseltamivir 4mg/kg/day or zanamivir 8mg/day), a maoto-only group (0.2g/kg/day), and an anti-influenza + maoto group--and investigated. The method of assignment into the groups was not stated. No significant difference was observed in the periods of fever continuation or clinical symptoms continuation among the 3 groups, however the fever continuation period and clinical symptoms continuation period were both shortest in the combined administration group. Furthermore, treatment with anti-influenza medicine, clarithromycin (10mg/kg/day), and maoto combined with clarithromycin was conducted targeting a total of 288 other child patients diagnosed with influenza (the maoto-only group and antipyretic group administered group were excluded due to a low

number of cases). The results showed no statistically significant difference between the groups in the fever continuation or clinical symptom continuation groups [12].

Studies comparing maoto administered alone and anti-viral medicines administered alone

Research by Kawamura

Although it was not random assignment, Kawamura, who is proactively proceeding with comparative research, has come to imply the possibility that the differences in results and side effects between maoto and oseltamivir are small. 139 child patients with influenza examined in the spring of 2007 were divided into a maoto (0.08 ～ 0.19g/kg/day, maximum of 7.5g in 3 divided doses) administration group and an oseltamivir (4mg/kg/day , maximum 150 ㎎ in 2 divided doses)administration group as per their parents' requests, the time of fever alleviation and fever period, etc. were investigated. The administration period was 2-8 days in the maoto group and 2-5 days in the oseltamivir group, with fever alleviation or improvement of symptoms as criterion in the case of both medicines. Antihistamine, antitussives, and expectorants were also additionally administered as necessary. In the type A patients no significant difference was observed in age, maximum body temperature, ingested dose of maoto, time from outbreak of illness to start of ingestion, time from ingestion until alleviation of fever, time from ingestion until alleviation of general symptoms, and time of continuation of general symptoms. In the type B patients, the time of starting ingestion was significantly later in the maoto group, the time from ingestion until alleviation of fever and time until alleviation of general symptoms was significantly faster in the maoto group, and the length of general symptoms was significantly shorter in the maoto group [13]. In the B group patients, the time from ingestion until alleviation of fever and time until alleviation of general symptoms was significantly shorter in the maoto group, but the time until the start of ingestion was longer, so it is difficult to come to a conclusion based solely upon this report.

In a subsequently published report by Kawamura with almost the same contents targeting 129 child influenza patients, in addition to similar contents to the preceding study, the study also investigated the time passed after onset of fever and after onset of illness until the start of ingestion, the fever period, the symptom continuation period, and the correlation between the amount of maoto ingested and the fever period and symptom continuation period. By and large no correlation was observed, but a positive correlation between the time of starting ingestion after onset of fever and fever period was observed in the type A influenza oseltamivir group and in the type B influenza maoto group. No significant difference in abnormal behavior such as sleep-talking, auditory hallucinations, and visual hallucinations was observed between these two groups [14].

In comparative research conducted by Kawamura conducted in the following season (2007/08), the time of disappearance of the influenza virus form the pharynx with maoto and oseltamivir was examined, and the study implied the efficacy of maoto. 172 patients with type A influenza in the 2007/2008 season were divided into 3 groups--64 patients with Teikoku's maoto (0.16g/kg/day, maximum 7.5g/day in 3 divided doses), 61 patients with Tsumura's maoto (0.16g/kg/day, maximum 7.5g/day in 3 divided doses), and 47 patients with oseltamivir (average 3.9 mg/kg/day, maximum 150 mg/day in 2 divided doses) by the request of the patients (their parents)--with maoto administered with 1-6 days with fever alleviation as the target, and oseltamivir administered with fever alleviation or 5 days being the criterion. The average time after ingestion until fever alleviation was 45.73±35.51 hours, 53.90±39.42 hours, and 30.36±20.96 hours, with the oseltamivir group being significantly shorter compared to the 2 companies' maoto groups. Similarly, the average fever time was average 67.27±37.88 hours,

69.57±39.76 hours, and 45.79±21.05 hours, and the time from onset of illness until disappearance of symptoms was 70.47±41.99 hours , 73.95±43.01 hours, and 48.47± 26.90 hours, significantly shorter. No significant difference was observed in the 3 groups in the time after onset of illness until the influenza virus was removed, the time from alleviation of fever was significantly shorter in the 2 companies' maoto groups compared to the oseltamivir group. In a comparison of the Teikoku and Tsumura maotos, a significant difference was observed in the fever alleviation time, fever time, general symptoms time, and elimination of A type influenza virus from the pharynx [15].

In comparative research by Kawamura, et al. conducted from January to March 2009, each subtype of influenza was investigated. 147 patients who came to a hospital within 48 hours of the onset of illness, were diagnosed with type A influenza via rapid testing kits using nasal swabs and diagnosed with a subtype (Soviet A-type H1N1, Hong Kong A-type H3N2) were divided into the symptomatic treatments of oseltamivir 4mg/kg/day and Teikoku maoto extract 0.2g/kg/day as per the request of the patients. 1-5 days of oral administration was conducted depending on the continuing time of the symptoms, and a comparative investigation of the continuation period of fever of 37.5℃ or higher and the continuation period of general symptoms such as headaches, fatigue, and lack of appetite was conducted. In Soviet A-type, there was an oseltamivir group of 15 patients (6 male patients, 9 female patients, age 11.20±16.22), an maoto group of 63 patients (33 male patients, 30 female patients, age 7.66±7.25), and a conservative of 8 patients (1male patients, 7 female patients, age 4.53±2.38), and in Hong Kong A-type there was an oseltamivir group of 18 patients (9 male patients , 9 female patients, age 12.86±16.20), an maoto group of 34 patients (18 male patients, 16 female patients, age 9.24±11.41),and a conservative of 9 patients (2 male patients, 7 female patients, age 7.86±9.40). In Soviet A-type, the conservative was significantly younger than the maoto group. Also, although the fever period was significantly longer in the conservative compared to the maoto group, there was also no significant difference observed between the groups in the time until coming to the hospital and the time until alleviation of fever after ingestion. In Soviet A-type, the time until coming to the hospital as well as the time after ingestion until alleviation of fever and fever time were all significantly shorter in the oseltamivir group compared to the maoto group. Also, although the fever period was significantly longer in the conservative compared to the oseltamivir group, there was also no significant difference observed between the groups in the time until coming to the hospital and the time until alleviation of fever after ingestion. Furthermore, the Soviet A-type had significantly longer fever time and time until fever alleviation after ingestion compared to the Hong Kong A-type. No significant difference was observed between the groups in the time until general symptoms were alleviated after ingestion [16].

Research by Fukutomi, et al.

In the preceding comparative study by Fukutomi, et al. which reported the efficacy of combined administration of maoto, 112 patients of less than 10 years of age diagnosed with influenza via rapid testing within 24 hours after the onset of illness was divided into 2 groups--54 patients (average age 4.7±2.1) administered oseltamivir and 68 patients (average age 5.2±2.7) administered Tsumura maoto extract (7.5g/day) as per the request of the patients--and their body temperatures on consecutive days were examined. In both groups, the 2nd day of illness showed a significant decrease in body temperature compared to the 1st day of illness, and no difference was observed between the groups. No serious side-effects were observed [17]. It was furthermore reported in a comparative study conducted targeting 41 cases in a different season that no difference was observed between the groups. The oseltamivir group was 20 patients (average age 4.1±1.8, 10 type A

patients/10 type B patients, fever of 39.0±0.3℃ when coming to hospital), and the maoto group was 21 patients (4.1±2.6 age, 12 type A patients・9type B patients, 39.0±0.4℃). In a questionnaire regarding the results of maoto conducted 3 days after the administration of maoto, 66% rated the results very good or good. On the other hand, a large number of respondents at 70% responded that it was difficult to drink. In spite of the common opinion that it was difficult to drink, only about 3% responded that they could not drink it [18].

Research by Mori, et al.

In a retrospective comparative study by Mori, 19 patients (12 men, 7 women, average age 11±11) out of 22 patients from amount 291 patients diagnosed with type A influenza between October and December 2009 were administered maoto extract, and the time it took for their temperature to drop to 36.9℃ from examination was investigated. They ingested 3 packets of Kampo medicine every 2 hours, and subsequently ingested every 3 hours until sweating was induced. By comparison, a group of 19 patients (7 men, 12 women, average age 16.5±16.1) administered oseltamivir and a group of 21 patients (11 men, 10 women, average age 15.4±8.7) administered zanamivir were also set up. Regarding the time for the fever to drop to 36.9℃ after administration, although the fever dropped significantly faster in the maoto group compared to the zanamivir group, no significant difference was observed between the maoto and oseltamivir groups[19].

Research by Toriumi, et al.

In the comparative research by Toriumi, et al., 86 patients (aged 5 months to 15 years) who were observed to have fevers of 37.5℃ or more and who tested positive for type B influenza were separated into 3 groups--a group between 1 and 10 years of age who desired oseltamivir, a group age 6 and older who desired zanamivir, and a group age 1 year or younger or who didn't desire neuraminidase inhibitors but desired maoto. Moreover, the patients who desired maoto from among the group which desired neuraminidase inhibitors were additionally administered maoto. Furthermore, an investigation was conducted into the patients who were administered neither anti-viral medication nor maoto. The amount of each drug administered was 4mg/kg/day for oseltamivir, 10mg/day for zanamivir, and 0.06g/kg/day for maoto. 16 patients were omitted, and only 70 patients were analyzed. No significant difference was observed in time from ingestion to alleviation of fever or time from onset of illness to alleviation of fever between the groups administered the drugs in ANOVA. The time from onset of illness to alleviation of fever was significantly shorter in all the groups administered drugs compared to the group administered no drugs.

All patients resumed their normal lives and no side effects from maoto were observed. No patients required hospitalization. Although there were 2 patients in the oseltamivir-only and zanamivir-only administration groups reported abnormal behavior respectively, no serious side effects were observed [20].

Research by Saita, et al.

In open labeled RCT by Saita, et al., 45 adult patients (average age 32.4±11.5) who tested positive for type A influenza in rapid testing were divided into 3 groups--a group of 11 maoto patients (7.5g/day), a group of 14 oseltamivir patients, a group of 9 zanamivir patients and a group of 11 patients who took maoto in combination with oseltamivir. 2 patients in the maoto and combined administration groups, 1 patient in the oseltamivir group, and 3 patients in the zanamivir group were omitted. No significant difference was observed between the groups in fever after coming to the hospital. The symptoms of joint pain, muscle pain, headache, cough, and fatigue were evaluated on a 5-point scale, with the product of the difference between the maximum and minimum values of each patient and the number of days taken to reach the minimum value from the maximum value as the

symptom score, which when compared among the groups was shown to be significantly lower in the maoto group than the oseltamivir group. 1 patient developed nausea due to the odor of the maoto, but no serious side-effects were observed [21) 22)].

Research by Nabeshima, et al.

In comparative research by Nabeshima, et al., 20 adult patients who developed a fever of 38 degrees or higher within 48h and tested positive for type A influenza in rapid testing were divided into a group of 12 patients who desired maoto (7.5g/day) and 8 patients who desired oseltamivir. No significant difference was observed between the maoto and oseltamivir groups in the fever continuation time after coming to the hospital and the symptoms continuation time. The average body temperature and headache score on the evening of the first day of treatment was significantly lower in the maoto group [23)]. In open labeled RCT subsequently conducted by Nabeshima, et al., 33 adult patients age 20-64 who developed a fever of 38 degrees or higher within 48h and tested positive in rapid testing were randomly divided into a group of 11 patients who were administered maoto (7.5g/day), a group of 10 patients who were administered oseltamivir, and a group of 12 patients who were administered zanamivir. Ischemic heart disease patients, patients with hyperthyroidism, enlargement of the prostate, and chronic infections, patients taking steroid/immunosuppressant drugs, anti-viral drugs, or Kampo medicine, and patients testing positive for new strains of influenza were excluded. 1 patient from the maoto group, and 2 patients from the oseltamivir and zanamivir groups respectively were omitted. The median value of the fever continuation time since coming to the hospital, which was the primary outcome, was 29h in the maoto group, 46h in the oseltamivir group, and 27h in the zanamivir group. A significant difference was observed between the maoto and oseltamivir groups. No significant difference was observed between the 3 groups in the influenza symptoms score. There was no significant difference in the virus isolation positive ratio or the serum cytokine concentration on the 5th day after the start of administration among the 3 groups. Mild liver dysfunction was observed in 1 patient from the maoto and oseltamivir groups respectively, but this improved quickly [24)].

Research by Yamagishi, et al.

Although retrospective, Yamagishi, et al., reported research comparing 130 pregnant women who had contracted influenza by whether they had been administered maoto or now. The assignment was by the patients' requests, with 90 patients being administered maoto and 40 patients being administered no drugs. The group administered maoto comprised 70 type A patients and 20 type B patients, while the group administered no drugs comprised 32 type A patients and 8 type b patients. The maoto was administered at 7.5g/day in 3 divided doses (administration period not stated, antitussives and expectorants administered in combination). In the maoto group, both the type A and type B patients had their fevers alleviated significantly faster than the group administered no drugs. Furthermore their symptoms such as headache, full-body fatigue and lack of appetite were observed to improve significantly faster [25)].

Research by Yaegashi, et al.

In open labeled RCT by Yaegashi, 14 patients aged 18 and older who had been diagnosed with type A influenza within 48 hours of developing fever were randomly divided into 2 groups--a group administered maoto and shosaikoto in combination (6 patients: 7.5g of maoto extract granules and 7.5g of shosaikoto granules/day in combination, taken for 3 days) and a group administered oseltamivir (8 patients: 150mg/day, taken for 5 days). The fever period from onset of illness, time from onset of illness until start of treatment, time from start of treatment until alleviation of fever, maximum body temperature, amount of antipyretics used, and amount of antitussives used were compared. The

method of assignment into the groups was not stated. No significant difference was observed between the groups [26].

Research by Yamauchi, et al.

In comparative research by Yamauchi, et al., child patients aged 15 and younger diagnosed with influenza were administered either anti-influenza drugs (oseltamivir or zanamivir) (166 patients) or maoto (80 patients) based mainly on the preference of their guardians, after which their frequency of follow-up treatment was investigated. The patients were administered 4mg/kg/day of oseltamivir in 2 divided doses, 20mg of zanamivir in 2 divided doses, and 0.2g/kg/day of maoto in 2-3 divided doses. The anti-viral medicine group and maoto group were further stratified by age (younger than 10, and between 10 and 15), history of bronchial asthma or lack thereof, rate of follow-up treatment for respiratory organ complications, and rate of use of concomitant drugs for respiratory organs (expectorants, bronchodilators, anti-allergy drugs, and antitussives). The rate of patients requiring follow-up treatment for respiratory organ complications was 34 out of 166 (20.5%) in the anti-viral drug group and 9 out of 80 (17.8%) in the maoto group, showing no significant difference. In the patients without a history of bronchial asthma, the rate of patients requiring follow-up treatment was 19 out of 107 (17.8%) in the former group and 4 out of 67 (6%) in the latter group, significantly higher in the anti-viral drug group. In the patients with a history of bronchial asthma younger than age 10, the rate of patients requiring follow-up treatment was 15 out of 57 (26.3%) in the anti-viral drug group and 4 out of 5 (80%) in the maoto group, showing a significantly high rate requiring follow-up treatment in the maoto group, although the number of cases was small. The rate of use of concomitant drugs for respiratory organs in all of the cases was 64 out of 166 (38.6%) in the anti-viral drug group and 12 out of 80 (15%) in the maoto group, significantly lower in the maoto group. In the patients without a history of bronchial asthma as well, the rate of use of concomitant drugs for respiratory organs was 34 out of 107 (31.8%) in the anti-viral drug group and 9 out of 13.4 (13.4%) in the maoto group, significantly lower in the maoto group. The rate of use of concomitant drugs for respiratory organs was lower in the maoto group. Furthermore, in spite of the fact that the rate of use of concomitant drugs for respiratory organs was significantly lower the maoto group in patients without a history of bronchial asthma, the need for follow-up treatment for respiratory organ complications was low [27].

Research by Suzuki, et al.

In an open labeled quasi RCT by Suzuki, et al., child patients age 1-10diagnosed with type A influenza were divided into a group administered maoto (0.15g/kg/day, in 3 divided doses) and a group administered oseltamivir (4mg/kg/day, in 2 divided doses) for 5 days in alternating order of examination. Furthermore, the subjects of the study were limited to those with a maximum body temperature of 38.4 ～40.1℃ before administration, and who also could be administered one of the drugs within 24 hours after the onset of fever. Child patients who could not be administered maoto were also excluded. A comparison of the body temperatures was conducted at each 6 hour interval. The oseltamivir group comprised 46 patients, while the maoto group comprised 40 patients. No significant differences in age, gender, rate of vaccination before contracting the illness, maximum body temperature before treatment, and body temperature at the time of starting administration were observed between the 2 groups. At 12-30 hours after the start of administration, the temperature in the maoto group was on average 0.15～0.26℃ lower, showing a significantly lower body temperature. Subsequently, the median value of the body temperatures of the two groups crossed at the 36th hour, after which the oseltamivir group's body temperature conversely became clearly lower. With having a fever is defined as "37.5℃ or higher", the average ± standard

deviation of the fever period was 84.8±36.8 hours in the maoto group and 67.0±24.4 hours in the oseltamivir group, showing a significant difference between the 2 groups. With "a fever of 37.5℃ or higher continuing for 24 hours or more after a normal temperature for between 12 and 72 hours " defined as diphasic fever, the ratio becomes 4.3% in the oseltamivir group and 20.0% in the maoto group, significantly higher in the former. The average value of the number of days of administration was 5.3±1.59 days in the maoto group and 4.6±0.75 days in the oseltamivir group. Depending on the progress, in the case of maoto, when the fever continued for 5 days or more, there were also cases where the administration was longer. Conversely, in oseltamivir, there were many cases where the fevers were alleviated quickly, with a short administration period not requiring 5 days of administration [28].

Case series and comparative studies investigating side effects, administration methods, etc.

Research by Iwaki, et al.

In a case series by Iwaki, et al., 41 patients (17 men, 24 women, age 40.5±13.6) age 20-72 diagnosed influenza positive (type A and type B) via rapid testing kits, who had fevers of 38.0℃ or higher before or when coming to the hospital, and who had been experiencing influenza symptoms for 48 hours or less were administered maoto, and the time from administration until alleviation of fever (fever alleviation time), virus survival time and transition of clinical symptoms were investigated. The results showed that the overall average fever alleviation time was 27.4 hours, of which it was 25.9 hours with type A and 33.7 hours with type B. Furthermore, the fever alleviation times of type A by subtype were 24.9 hours with H1N1 and 26.5 hours with H3N2. The survival rate of the viruses 5 days after administration was 22.6%, with type A H1N1 having a survival rate of 30.0%, type A H3N2 0%, and type B 20.0%. Regarding the progress of the clinical symptoms, upon calculating the average body temperatures and symptom scores from the patient reports, all symptoms showed improvement. Side effects appeared in 2 patients (4.9%), which were diarrhea and rashes respectively [29]. Iwaki also conducted a similar case series regarding the 2009 pandemic, in which 12 type A influenza patients (4 men, 8 women, average age 21.9±11.6) were administered Tsumura maoto extract granules in doses of 7.5g per day for adults and 0.2g/kg per day for children for a period of 5 days. Results of virus examination via viral isolation and RT-PCR using nasal swabs and throat swabs as specimens showed that all cases were the 2009 pandemic virus (H1N1). The average time from onset of illness until initial dosing was 15.7 hours, with temperatures at the time of arrival at hospital of 38.2℃ and a post-administration fever alleviation time of 18.5 hours. Regarding the symptoms, upon calculating the average symptom scores (0-3) from the patients' journals, comparing the pre- and post-administration symptoms showed significant improvement in "sore throat", "muscle and joint pain", fatigue and tiredness" and "headache". An examination of the virus survival rate conducted on average on the 5th day after the start of administration showed 6 patients positive, for a survival rate of 50.0%. Harmful events observed were 1 case each of abnormal behavior and diarrhea, with the abnormal behavior starting on the first day of administration and ending the following day and being deemed "unrelated" to the maoto [30].

Research by Ihashi, et al.

Although it is not comparative research, the case series by Ihashi et al. contains reports of results of seriously ill child patients with new strains of influenza and pneumonia requiring hospitalization who were administered maoto in combination with neurominidase inhibiters. The subjects were 70 child patients (average age: 7.3±3.7; gender: 46 male and 24 female; bronchial asthma: 25 with and 45 without; administration of anti-influenza drugs as outpatients: 21 yes and 49 no) who were hospitalized with new strains of influenza and pneumonia from

June 2009 to January 2010 with no serious underlying illnesses. The anti-influenza drugs selected for treatment after hospitalization were oseltamivir for 64 patients and zanamivir for 6 patients. Regarding the administration of maoto, the administration dose was 0.2g/kg in 3 divided doses, the administration method was every 2-3 hours on the first day and 3 divided doses from the 2nd day onwards (before or after morning, noon, and evening meals), and the administration period was 5.0 days on average (95%CI : 4.7～5.2 days). The main subject of the paper was to suggest the importance of administering neuraminidase inhibiters before hospitalization via multiple regression analysis, but even regarding treatments where maoto was administered to seriously ill patients, no side effects were observed [31].

Research by Mori

Mori's open labeled quasi RCT, which examined unique administration methods of maoto, divided cases of maoto administration from November 2007 through March 2008 into 2 groups and examined the administration methods. Group Ⅰ (group administered maoto every 3 hours): Patients with evidence of maoto up to January 31were dosed with maoto every 3 hours when the maoto administration was started (no administration during sleep). Group Ⅱ (group administered maoto every 2 hours): Patients with evidence of maoto After February 1 were dosed with maoto every 2 hours when the maoto administration was started, taking 1 day worth (3 packets) every 3 hours, and subsequently continued to take it every 3 hours until the onset of sweating (no administration during sleep). After they started sweating, the dosing was halted (Hiromichi Yasui's method). Among those treated with Kampo, group Ⅰ was 17 patients (average age 6.7) and group II was 11 patients (average age 6.7). Furthermore, 13 patients treated with oseltamivir who did not use antipyretics served as the control group. Examining group II and the group treated with oseltamivir shows that it took significantly less time for group II's fevers to drop to 36.9℃ after administration. There are no statements regarding comparisons between group Ⅰ and the control group, or between group Ⅰ and group II. No serious side-effects due to Kampo treatment were observed[32].

Research by Mori, et al.

In a case series by Mori, et al., where early-stage administration of Kampo medicine was conducted before seeing a doctor, treatment via early-stage administration of Kampo medicine was conducted on 10 patients (5 men, 5 women, average age 13.2±12.1) who exhibited flu-like symptoms between October to December 2009 and for whom treatment with the Kampo internal medicine on hand was insufficient, after which they went to hospitals and were diagnosed with type A influenza, and the results thereof were examined. Upon arrival at the hospital the evidence was reconfirmed, and in cases where it fit it was continued, while in cases where it differed the method was changed. During fevers, a dose of 1.5-2 times the normal does was administered frequently (every 2-3 hours), with the treatment being ended at the point when the fever, general condition, and respiratory tract symptoms improved. The results showed that the time from coming to the hospital until alleviation of fever was 17.0±17.0 hours, the number of days from coming to the hospital until recovery was 1.8±0.6 days, and the number of days from early-stage administration until recovery was 2.5±0.7 days. The early-stage Kampo administered before going to the hospital was keishi-to maoto for 4 patients, keishito for 3 patients, maoto for 2 patients, and saiko keishito shoken-chu-to for 1 patient, with 1-5 administrations, with 5 patients' Kampo fitting the evidence and 4 of the remaining 5 leaving early-stage administration prescriptions and combining with other compounds. Furthermore, in a comparison of the Kampo medicine/anti-viral medicine combined administration group and the Kampo-only group, no significant difference was

observed in the number of days from start of administration before going to the hospital until recovery, but the Kampo-only group had a significantly shorter fever alleviation time and number of days from going to the hospital until recovery [33].

Research by Nishimura, et al.

In a case series by Nishimura, et al., wherein there is a unique report of using a maoto suppository, a comparison is conducted on the body temperatures before administration and until 24 hours after administration of a maoto suppository in pediatrics department between June 2006 and April 2007 on 21 patients (from 10 days old to 9 years and 9 months old) with fevers of 38.9℃ or greater. There were 17 patients whose body temperature were possible to track. The temperature of these patients decreased significantly. No side-effects were observed [34].

Research by Tabata, et al.

In open labeled comparative research by Tabata, et al., in addition to the clinical results of maoto and zanamivir, the influence of interfused flavoring agent guidance by pharmacists as an idea to increase patient compliance in taking medicine was compared over 2 seasons. (1) In the 2006-2007 season, maoto was administered to 63 child influenza patients (37 type A, 26 type B). (2) In the 2007-2008 season, maoto was prescribed for all cases of children 5 years or younger, while for children of 5 years or older either maoto or zanamivir were administered after informed consent and the parents choosing one of them, with 49 patients (all type A patients) being administered maoto and 32 patients (31 type A patients and 1 type B patient) being administered zanamivir. The time until alleviation of fever was scored, and the compliance with taking the medicine was also examined split into a good group and poor group. maoto was taken 0.18g/㎏/day in 3 divided doses for 3 days, and zanamivir was inhaled 2 blisters (10mg) per time, twice per day for 5 days. In the good medication compliance group of type A influenza in (1) in the group from age 0 to 2, the good group was about 32 hours while the poor group was about 48 hours, showing a significant difference. In the type B influenza, the fever alleviation time of the good compliance group was about 28 hours while the poor compliance group was about 56 hours, showing a significant difference. In (2), the fever alleviation time of the maoto administration group was about 26 hours, which was significantly shorter than in (1) where it was about 40 hours. In the zanamivir administration group it was about 32 hours. However, in (2), a pharmacist proactively conducted interfused flavoring agent guidance for the maoto. The results were that milk coffee, cocoa, orange juice, Calpis and other flavors resulted in good medication compliance, with (2) being the good medication compliance group significantly increasing from (1)'s 69.9% to 93.9%, while in the age 0 to 5 group the good medication compliance group significantly increased from (1)'s 59.4% to 100% [35].

This concludes the discussion of the state of maoto's use in Japan as a treatment for influenza and the current state of its research. It is currently commonly used in combination with anti-viral medications, but in some circumstances it is also used alone. It is used especially often in the field of pediatrics.

The fact that the text cited in the first paragraph which was written in "Shang-han lun" is connected to the treatment by a 13 year old boy almost 200 years ago is a testament to the very high level of research that "Shang-han lun" was in Japan. The Kampo medicine of Japan even today continues to carry on this tradition.

Note: One way of looking at maoto is that veterinary surgeons are focusing on the prescription. They discovered maoto's effect on avian influenza during their research. Currently they are aggressively proceeding with the study [36]. A vast amount of research reports in future.

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Japanese Acupuncture - Current Research

Japanese Traditional Medicine Text (21)

Industrial Health Field

Kenta Sawazaki

A. Industrial Health

1. Current Status of Clinical Studies in Japan and Overseas

A search in PubMed for papers related to industrial health and acupuncture yielded 44 results as of November 2010, and indicated the existence of a small accumulation of studies. Randomized controlled trials (RCT; 4 cases) have begun to appear from around 1993, which mostly assessed rotator cuff tendinitis and apoplexy in terms of visual analog scale (VAS), Short Form 36 (SF-36), and activities of daily living (ADL), against a control group of sham acupuncture, exercise, physical therapy and occupational therapy.

A study by Szczurko et al.[1] examined and compared rotator cuff tendinitis in postal workers in a prospective RCT, by randomly dividing the subjects into an acupuncture treatment group and physical therapy group. Work-related musculoskeletal disorders have one of the highest incidence rates in the field of industrial health, and are a major cause of sick leaves[2]. Compounded with the increase in medical expenses under health insurance, establishing measures for their prevention is an important issue not only for enhancing workers' health and quality of working life (QWL), but also for preventing work loss and maintaining high productivity[2]. An economically effective means is therefore sought to address such sick leaves and increases in medical expenses. Acupuncture treatment could be one such means, as it is less expensive compared to conventional health care in terms of facilities and consumables. However, studies have hardly been made on the economic assessment of acupuncture treatment in the industrial health field.

2. Present State and Future Prospects of Clinical Studies in Japan

(a) Studies in the industrial health field in Japan

There are few full-fledged studies of the industrial health field in Japan, but a paper on "The Possibilities of Acupuncture in the Workplace"[3] was presented at the Industrial Health and Alternative Medicine symposium sponsored by the Japan Society for Occupational Health in 2003. In it, a study by Sawazaki[4] et al. is introduced in reference to the economic assessment of acupuncture treatment in the industrial health field.

In the study, acupuncture treatment was provided to 117 blue collar workers from a certain workplace who complained of pain in their neck and shoulders, lower back, or knee. The pain lessened by half in some 80% to 90% of the subjects, and the Profile of Mood States (POMS) before and after treatment also showed a significant decrease in total score. Furthermore, the numbers of subjects and the number of days that the subjects visited a medical institution due to a musculoskeletal disorder halved during the period they received acupuncture treatment, and the medical expense they paid under health insurance decreased to roughly one-third. The same examination was conducted at another similar workplace, but there was no conspicuous difference regarding the factors related to musculoskeletal disorders. In a study[5] of lumbago patients, a significant decrease was seen in their pain, POMS, and medical expenses under health insurance. These studies suggest that acupuncture treatment is effective against work-related musculoskeletal disorders in the industrial health field. Moreover, the improvement of POMS indicates the possibility of increasing QWL and productivity, and is thought to be widely economical, combined with the decrease in medical expenses.

Workers' work postures and actions are diverse. Work-related musculoskeletal disorders are a serious issue in both industrialized and

industrializing countries alike[6], and individualized approaches must be made to each work action in the workplace. In related studies, acupuncture treatment is applied based on M-Test[7, 8]. M-Test is thought to be useful as an individualized method for preventing work-related musculoskeletal disorders, as it indexes each individual's physical symptoms according to action. The M-Test is discussed in detail under "C. Special Diagnostic Techniques" in Chapter 4.

(b) Prospects of future studies (economic assessment)

1) Subjects

It is not easy to determine who shall be included among the subjects, but it is necessary to find new subjects from diverse occupations.

2) Design

Prospective studies by RCT are thought to be best at present, but as such studies are costly and take time, public investment is necessary to also ensure neutral assessment. The study by Sawazaki et al. is a case-controlled retrospective study of medical expenses under health insurance within the design of a before-and-after trial. Realistically speaking, it is most easy to set a control group, but various biases must be considered. It is ideal to conduct an economic assessment based on a perfect design, but from a practical perspective, it is also necessary to accumulate partial assessment data.

3) Assessment (Result)

In the study by Sawazaki et al., there was a decrease in medical expenses under health insurance, after applying treatment. The assessment of medical expenses may produce different conclusions depending on from whose standpoint it is analyzed, also in consideration of expenses paid by the patient and the patient's family. As the standpoints of evaluators are diverse, it is preferable to conduct an assessment from a broad social standpoint as much as possible, to ensure neutrality.

4) Analysis method

In recent years, it is considered important to have knowledge of healthcare quality, such as subjective health-related QOL and satisfaction. Therefore, proper analysis of cost effectiveness and cost utility based on patients' subjective views is expected in the future.

3. Conclusion

Studies in the field of industrial health will be needed in the future, as a means for demonstrating the roles of acupuncture treatment in society. Toward this end, a steady improvement in the quality of studies and investments in studies in this field are desired.

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Clinical Report 1 (Acupuncture)

Post Herpetic Neuralgia

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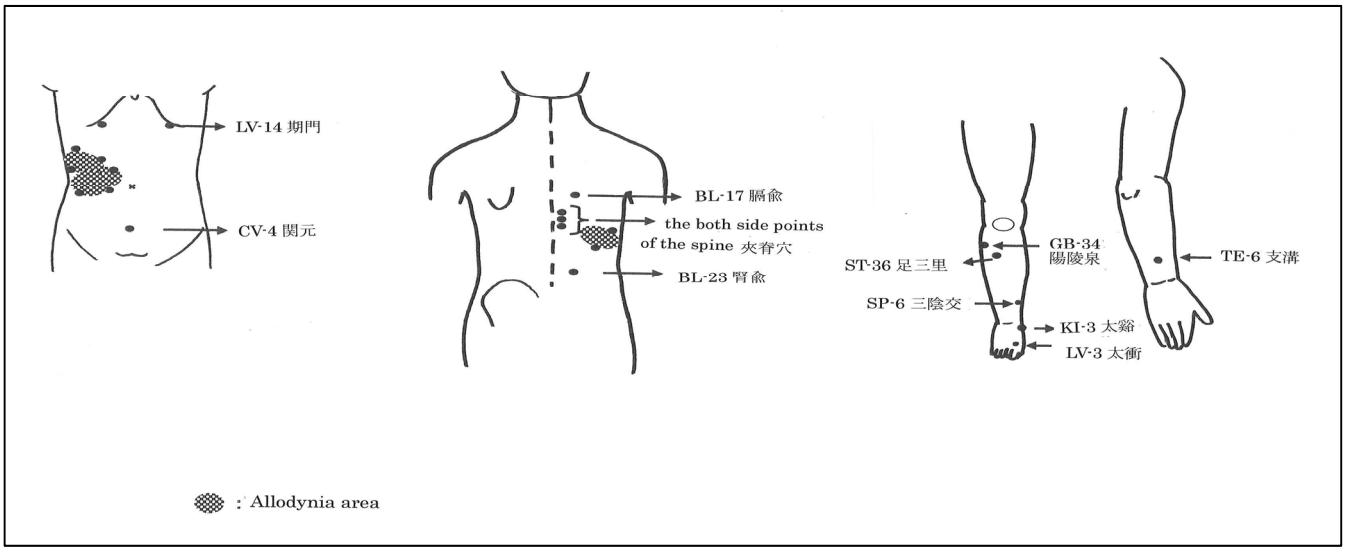
Introdution

Herpes zoster is developed through the reactivation of the varicella zoster virus and subsequent recurrent infection, which is caused by the weakened immune system of the body due to aging, strain, overstress, and/or use of immune-suppressing drugs. The varicella zoster virus is infected latently at the dorsal root ganglion or the cerebral ganglia after contracting varicella. The virus causes inflammation in the ganglion cells and/or neural fiber, and then result in exanthema on the skin. Since herpes zoster has higher incidence with aging, one out of 5-10 cases is supposedly develop the disease in the Japanese aging society of recent years. Generally, a rash appears at primary neural regions on one side. The rash can be cured by providing antiviral medication for 2-4 weeks, however the rash part may leave lingering pains. This pain is called herpes zoster pain. NSAIDs are effective to relieve the pain. However, approximately 10-15 percent of the cases of herpes zoster and herpes zoster pain can transition to post herpetic neuralgia (PHN) [1] . Many researcuuhers have reported acupuncture is effective to this pain. We have treated many cases of this kind. One case is introduced here:

[Case] 77 years old, Female, Retired
[Chief complaint] Pain in the right-side back and the right-side of abdomen
[Present Illness]
In late June this year, the patient received urgent treatment for a back pain. On the previous day, the patient felt a pain in the right-side of her back after gardening. A bladder was observed in part, so treatment by dermatologist was suggested. The dermatologist diagnosed the patient with herpes zoster, and antiviral medication was provided. Bladders disappeared two months later. However, burning and tingling ache still remains. Pain occurs when clothes rub against the affected area. The patient was diagnosed as PHN by a dermatologist. Painkiller was administered but the pain still remained. The patient wished for acupuncture treatment, and a dermatologist referred her to my acupuncture clinic.
Other symptoms include light sleep, constipation, heat, and fatigability.
[Past history]
Lumbar disc herniation (age of 50), Operation for gastric neoplasm (age of 43), Bronchial asthma (age of 55), Osteoporosis (age of 70). The patient sought medical advice for lumbago at an acupuncture clinic five years ago, and was diagnosed with kidney yin vacuity. The patient was cured after treatment. Thereafter, the patient continued therapy once a month for health maintenance.
[Present status]
Height 155cm, Weight 40kg. Pulse is deep, string-like, rapid pulse. Dark red tongue, cracked with a whitish coating. The pain VAS is 80mm. The patient has "slow smarting pain from the inside" and "superficial pain on the skin". Cutaneous discoloration is observed from the left-side back to the side abdomen. Allodynia was observed in the side abdomen. Heat in the lower legs was felt. Constipation was observed.
[TCM diagnosis]
Blood stasis, Deficiency of both Qi and yin of Kidney
[Therapeutic principle]
Active blood and resolve stasis, Nourish yin and tonify the kidney
[Acupoint selection] TE-6, GB-34, LV-14, LV-3, Ouch point (around the discolored part), SP-6, BL-17, Low-frequency waves (Low frequency 3Hz and High frequency 30Hz, for 10 minutes) are irradiated at the both side points of the spine from Left TH10-12., BL-23



[Explanation]

Pain is produced at lesser yang tripple energizer channel and reverting yin liver channel in the legs. Therefore, "clearing the liver, regulating Qi and unblocking the meridian" was done combining LV-14, LV-3, and GB-34[1]. Then purgation with twirling was practiced at the Triple Energizer Meridian (TH6) along the rib to heal the pain.[2]. Unblock the meridian by needle pricks surrounding the discolored part of the skin. Furthermore, promote blood flow and free the network vessels by purgation with twirling on SP-6 and BL-17 to strengthen “active blood and resolve stasis”. The both side points of the spine were treated in the nerve field where rash developed. I thought that this would stimulate the nerve field which is defined in Western medicine.

Needles Used: Seirin-made sterilized acupuncture needle, length 1cun6fen, No. 1

[Course] Treatments are planned twice a week.

Second session: Pain was relieved immediately after treatment, but it reoccurred in the evening of the same day.

Third, fourth and fifith session: No obvious changes were observed.

Sixth session: The pain VAS was 70mm. The slow smarting pain from the inside was gradually relieved. The area of allodynia had become 2/3.

Seventh session: The pain VAS became 60mm. The number of treatment was reduced to once a week.

Eighth session: No changes were observed. “Active blood and resolve stasis” was strengthened by practicing pricking bloodletting therapy at the point of tenderness. The patient had got a sense of relief.

Tenth session: The sense of relief continues. The pain VAS has become 30mm. The area of allodynia had become 1/3.

Twelfth session: The pain VAS became 15mm. The area of allodynia further dwindled.

Thirteenth session: Pain and allodynia almost disappeared. ST-36, KI-3, and CV-4 were added to tonify the kidney.

Fourteenth session: The pain VAS has become 0mm. The color of skin was improved. Allodynia disappeared. So treatment ended. Monthly treatment is being provided for health maintenance.

[Discussion]

Herpes zoster has been recognized from ancient times. Several different aliases exist. The representative name is "Fire Band Rash (火帯瘡)". In a book written in 1602, titled "Standards of Patterns and Treatments" (part of surgery), it says "The liver fire is overwhelming. It flows into the bladder, and it is clad with the belt vessel. Therefore it looks like bundled bands." This might have implied herpes zoster. Even in this case, a rash was observed in the

liver meridian and the belt vessel at the beginning. The case was considered to be suffering from the same disease mentioned in the old book.

A book titled "The Diagnosis and Therapy of TCM with Symptoms (Part 2)" mentioned that herpes zoster has the excess pattern of "the heat exuberance and dampness stagnation" and "the heat toxin burns the natural aspect", along with the deficiency pattern of "the spleen deficiency with dampness" and "the Qi deficiency and blood stasis." Now that two months have passed since herpes zoster developed in this case, and the acute period had passed, it is supposed that deficiency of both Qi and yin of Kidney occurred in the body and the state of blood stasis appeared. So high-frequency stimuli including the practice of "activate blood and resolve stasis" were given at the local route; thus, the symptoms were successfully relieved.

Additionally, the number of patients referred by dermatologists has increased after this case. I believe that acupuncture treatment has a considerable role within the general medicine.

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* This case study is based on the report published in the Vo. 56 No.1 2009 issue of "The Journal of Kampo Medicine" (Japanese version), and then the contents have been slightly modified and translated into English.

Clinical Report 2 (Kampo Medicine)

A Case of Acute Exacerbation of Congestive Heart Failure with Chronic Renal Failure Successfully Treated with Goreisan

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Abstract

An 85-year-old man suffered from chronic renal failure and congestive heart failure since about 2 years ago. On May 12th in 2015, he admitted to this hospital due to acute exacerbation of congestive heart failure presenting exertional dyspnea and thirst. Together with resting on bed and oxygen inhalation, a new diuretics, tolvaptan, was taken in addition to his conventional diuretic drugs. However, about 2 weeks later, tolvaptan was stopped because of worsening renal function. Then, targeting to thirst and oliguria, *goreisan* was given for relieving clinical symptoms since June 3rd. Subsequently dyspnea and poor appetite diminished at the end of June and better general condition continued more than one month around the end of July.

We report a case of congestive heart failure combined with chronic renal failure, successfully treated with *goreisan*. In this case, *goreisan* improved both acute exacerbation of the congestive heart failure and the renal dysfunction with regulating water imbalance in body. Furthermore, it is very important that his prognosis was prolonged with highly quality of life.

Keywords: congestive heart failure, chronic renal failure, *goreisan*, water balance regulation

Introduction

The pathologic condition of chronic renal failure represents "water intoxication". Regardless of whether before or after dialysis, based on clinical symptoms like edema, dry mouth, vertigo, lassitude and gastrointestinal symptoms etc. as well as abdominal diagnosis, *goreisan* is the drug of first choice[1)]. Here the formula is expected to help not only to regulate water metabolism in the body, e.g., improve the condition of water intoxication, but also blood pressure and delay the onset of dialysis[2)].

Congestive heart failure too, is also considered to represent "water intoxication". In addition to rest and restriction of salt intake western diuretics or cardiotonic drugs are used for the treatment. To rectify blood pressure or edema western diuretics (mainly loop diuretics like Furosemide or Spironolactone) are the standard therapy for congestive heart failure[3,4,5)]. However, an inattentive increase in the dosage of loop diuretics may easily lead to a deterioration of kidney function and thus adversely affect the endogenous water balance. Recently a new vasopressin receptor antagonists (a diuretic called Tolvaptan) has been added to the western diuretics, allowing to comparatively easily achieve improvements of edema and congestion[6)].

On this occasion an elderly patient treated with loop diuretics was hospitalized because of a sudden exacerbation of chronic renal failure complicated by congestive heart failure. The patient was first treated with Tolvaptan, which was expected to improve the edema and congestion, but the drug was not sufficiently effective. After switching to *goreisan*, however, the effects were even better than expected. The here presented valuable case report indicates, that the diuretic action of *goreisan* could be considered due to it correcting the endogenous water balance and thereby improving various symptoms including renal function.

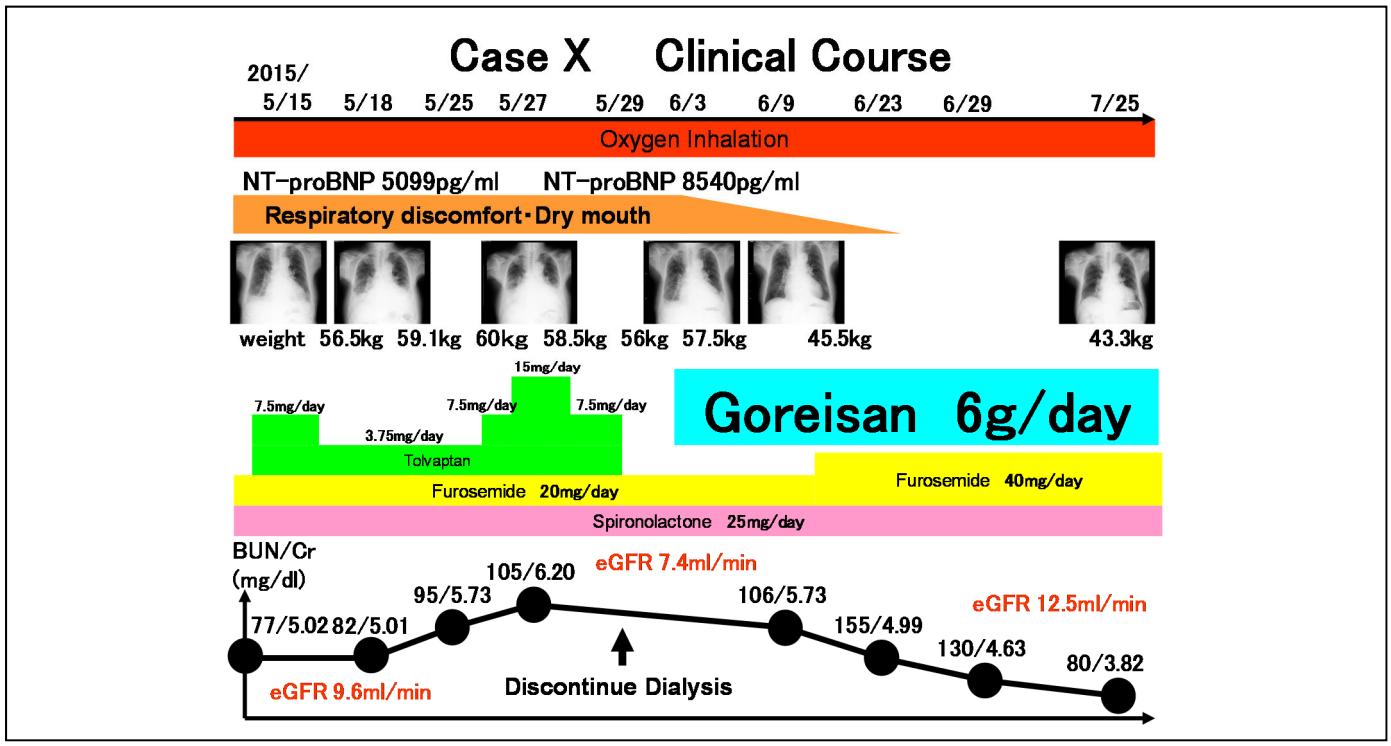
Case: age 85, man
Chief complaint: exertional dyspnea, dry mouth
Past history: in 2002: fracture of left tibia and right ankle
Clinical course 1 (until admission):
Treatment for chronic renal failure complicated by congestive heart failure on an outpatient basis was initiated approximately 2 years earlier. On May 12, 2015 exertional dyspnea developed. On May 15 he visited our hospital and was admitted for treatment because of an acute exacerbation of the chronic renal failure complicated by congestive heart failure.

Western medical findings:
Alert, height: 153 cm, weight: 56.5 kg, facial edema, body temperature: 36.4°C, SpO_2: 91%, BP: 137/71, HR: 101/min, regular, cardiopulmonary: systolic murmur, pulmonary rales, abdomen: flat, soft; edema of the legs;

Oriental medical findings:
Subjective symptoms: exertional dyspnea, dry mouth; Objective signs: inspection: poor complexion, earthen colored; edema of face and lower extremities; pulse diagnosis: deep, thin, weak; tongue diagnosis: thin white coat with dental impressions and engorged sublingual veins; abdominal diagnosis showed lack of strength and softness of the lower abdomen. Hyochondrial fullness and tenderness as well as epigastric clapotage.
Examination results:
Blood examination:
white count: 3,500, hemoglobin: 7.4 g/dl, CRP: 0.61 mg/dl, urea nitrogen: 77 mg/dl, creatine: 5.02 mg/dl, eGFR: 9.3 ml/min/1, NT-proBNP 1,383 pg/ml, albumin: 3.3 g/dl;
chest x-ray: enlarged cardiac shadow, bilateral pleural effusion, pulmonary congestion

Clinical course 2 (after admission): Figure 1

After admission the medication, including the western loop diuretics (Furosemide and Spironolactone) prescribed during the treatment as an outpatient were continued. In conjunction with rest and initiation of oxygen inhalation the diuretic Tolvaptan was added to the regimen on May 16, the day following admission. Yet, the dyspnea continued and renal function deteriorated further. On May 29 administration of Tolvaptan was discontinued. After consultation with the patient and his family it was decided not to initiate dialysis and instead conservative treatment, including palliative care, chosen. From June 3 *goreisan* (Kotaro Pharmaceutical Co., Ltd., 6 g/day) was added to the otherwise unchanged regimen in order to improve the subjective symptoms of dyspnea, dry mouth and lack of appetite, targeting the dry mouth and decreased urine volume. Later, body weight gradually decreased and the pleural effusion decreased too. By the end of June the dyspnea, dry mouth and lack of appetite had improved. After a while, over a period of about 1 month until the end of July, the general condition stabilized. By the end of August the patient's general condition deteriorated because of an infection and he died of multiple organ failure.



Discussion

Goreisan is comprised of the five crude drugs Alisma rhizome, Polyporus umbellatus, Poria cocos, Atractylodes lancea rhizome and cassia bark. It is widely used as a diuretic for intermediate conditions between deficiency and excess with water intoxication as its indication. In the classic Shan Han Lun the pathologic condition is specified as the lesser yang disease state and the formula widely used for dry mouth, diabetes, acute or chronic nephritis, nephrosis, edema, uremia etc.[1,2].

On the other hand, western diuretics are used to reduce the preload, but even increase urine volume when there is edema in the presence of dehydration. In case of elderly people dehydration, electrolyte anomalies, hypotension and similar conditions can easily complicate the situation, so that the administered dose must be carefully considered[3].

Taking the side effects of western diuretics like Furosemide into account, in particular in case of long-term administration, the dehydration may possibly lead to renal dysfunction or cerebrovascular disorders. Short-term combination with *goreisan* while carefully observing the pathologic condition, or else switching to *goreisan* to increase the diuretic effect, is also considered to be effective. When taking the side effect dehydration into account, it is possible to optimally utilize the advantage of *goreisan* to promote diuresis only in the presence of edema, possibly decreasing the side effects of western diuretics.

Moreover, if a dose increase of the western diuretics is in certain cases difficult due to the general condition, combination with diuretic Kampo formulas like *goreisan* can be effective. However, recently the western diuretic Tolvaptan has made its debut on the clinical scene. Edema and congestion can now comparatively easily be alleviated, the drug causes only minor blood pressure fluctuations and is said to be safer than western loop diuretics[6]. Some reports have described the ease of water control during the initial stage of dialysis[7].

The pathologic condition of chronic renal failure is precisely the manifestation of water intoxication. Endogenous water balance in renal failure is marked by an imbalance between the water of the blood and the water compartment outside of blood vessels. In other words, the equilibrium between tissues and body cavities has been disrupted. Moreover, while there is excess water in the tissues and body cavities, it cannot moisten the blood. *goreisan* adjusts this condition, supplies cells and the blood with water and since it lowers osmotic pressure, during strong inhibition of the diuresis, it ameliorates the disrupted water equilibrium in the body and should therefore be understood not to be simply a diuretic. Regarding this property its effect can be expected to delay the the timing of dialysis initiation in cases of renal failure complicated by congestive heart failure. Also, in cases of organic renal diseases it is by virtue of its properties given priority over treatment with western diuretics and the guidelines pertaining chronic renal failure as a chronic renal disease have been adjusted[8].

Then again, congestive heart failure as a pathologic condition too represents a true form of water intoxication. It is marked by progressive intravascular dehydration and an excess of water in the alimentary tract.

In case of organic disease, similar to organic renal diseases, based on its properties, this formula should be given priority over western diuretics. The details have been arranged in form of the treatment guidelines divided into acute and chronic cardiac insufficiency[6,7]. Cardiac diseases that are indications for Kampo medicines are functional disorders associated with cardiac neurosis. Again, not so much the acute phase but rather the chronic phase is the disease stage at which treatment is administered. In case the western diuretics are insufficiently effective, Kampo formulas are often administered as required to alleviate symptoms, promote diuresis and stabilize the general condition.

Moreover, in case a right heart insufficiency is observed when considering Kampo treatment

mokuboito (Mu Fang Yi Tang[9]) may be one of the choices that can be used. To alleviate the symptoms of edema or cold pattern Kumibinroutou[10] is also said to be useful. *Goreisan* is often used in cases of heat pattern associated with a decrease in urine volume and edema. It can also be used for anasarca caused by cardiac insufficiency as well as a diuretic in cases of pleural effusion due to congestive heart failure during the still comparatively acute phase. It is considered to correct the intravascular dehydration and reduce the amount of excessive water within the alimentary tract[11,12].

This patient was a case of acute deterioration of chronic renal failure complicated by congestive heart failure and not a single organ acute exacerbation like acute exacerbation of congestive heart failure or acute exacerbation of chronic renal failure alone. The heart and the kidneys maintain a close correlation called cardiorenal coupling. In spite of the presence of edema or pulmonary congestion the diuretic Tolvaptan was probably due to the decreased renal function not very effective.

Goreisan on the other hand does not only improve the edema and congestion, but also renal function. Since it promotes the inflow of unevenly distributed excess water into the blood vessels, it increases renal blood flow, which can be interpreted as helping making it easier for western diuretics to recover their effects. Thus, the diuretic effect of *goreisan* improves the responsiveness to western loop diuretics through its regulation of the water balance and was therefore considered to contribute to improvements of clinical symptoms, ADL as well as delaying the timing of initiation of dialysis. We are hoping that the comparatively early addition of *goreisan* to the regimen in this kind of acute exacerbation of chronic renal failure complicated by congestive heart failure will be a promising therapy.

Isohama is conducting research indicating that *goreisan* regulates water balance via aquaporin[13,14,15]. Similarly, the diuretic Tolvaptan is also said to exert its effects via aquaporin[6]. In this case Tolvaptan could not sufficiently exert its effects because of the deteriorating renal function, but *goreisan* was conceivably effective because of differences between the two agents on the molecular level. A new disease concept "aquaporin disease" has been proposed and *goreisan*, unlike western diuretics, seems to be a formula with bright prospects regarding its ability to prevent "water moving into directions generally not allowed".

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Conference Report

A Letter from the 67th General Assembly of The Japan Society for Oriental Medicine

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Key words: The Japan Society for Oriental Medicine (JSOM), The 67th General Assembly of the Japan Society for Oriental Medicine, *Kampo* medicine, International Organization for Standard (ISO)

1. Introduction

Kampo medicine is a medical system that has been traditionally practiced in Japan, based on ancient Chinese traditional medicine. The Japan Society for Oriental Medicine (JSOM) is the largest and one of the most active medical societies on *Kampo* medicine in Japan. As of June, 2016, the JSOM has a total of more than 9000 members. It was established to improve the quality of life (QOL) of the people by sharing research results on health, welfare, and medical science, functioning as a worldwide network to realize the aim. It became a member of the Japanese Association of Medical Sciences in 1991[(1)].

The 67th General Assembly of the JSOM took place June 3-5, 2016 at Sunport Hall Takamatsu, Kagawa International Conference Hall, and JR Hotel Clement Takamatsu in Takamatsu, Japan[(2)]. The General Assembly was organized by JSOM and supported by the Japan Medical Association, the Japan Dental Association, the Japan Pharmaceutical Association, the Japan Acupuncture and Moxibustion Association, the Japan Society of Acupuncture and Moxibustion, Tokushima Medical Association, Kagawa Medical Association, Kochi Medical Association, Ehime Medical Association, Tokushima Pharmaceutical Association, Kagawa Pharmaceutical Association, Kochi Pharmaceutical Association, and Ehime Pharmaceutical Association. The conference was attended by 2509 researchers, acupuncturists and physicians from all over the world – primarily from Japan – who exchanged opinions and presented studies on diverse *Kampo* medical research fields in over 100 sessions including 14 symposiums, 13 training sessions, 5 workshops and 25 seminars[(3)].

2. Sessions

This General Assembly is designed for researchers and scholars to present various studies on its theme, which is "The inheritance of *Kampo* paradigms and its paradigm-shift --- Bridging *Kampo*, Science, and Practice". The conference was a great success with some standees on the section of general lectures and of acupuncture and moxibustion. There were some educational seminar on *Kampo* for physicians, acupuncturists and pharmacists.

In the afternoon session on June 3rd, there was a clinical symposium on traditional medicine, which theme was "The *Kampo* paradigms and its paradigm-shift from the standpoint of history". Dr. Tatsuhiko SUZUKI (Teikyo Heisei Univ, Chiba, Japan / Oriental Medicine Research Center, Kitasato University, Tokyo, Japan) has given a speech on "From *Sanki TASHIRO* to *Dosan MANASE*--- The dawning of *Kampo* medicine (of *Goho-ha* school) from the view point of the inheritance of the drug theories for the diagnosis and use of crude drugs". Dr. Masakazu YAMASAKI (Kampo-Kyoguchimon Clinic, Hiroshima, Japan) has made a lecture on "On a Paradigm Shift of Kampo Medicine by *Todo YOSHIMASU*". Dr. Yoshihide YAKAZU (Department of Anesthesiology, Tokyo Medical University, Tokyo, Japan) has made a presentation on "On a Paradigm Shift of *Kampo* Medicine by Dr. Domei YAKAZU and Dr. Keisetsu OTSUKA". There were some meetings including the annual general meeting of members.

In the morning session on June 4th, there was a presidential lecture on traditional medicine, which theme was "The effectiveness of *Kampo* medicine for extension of healthy life expectancy and anti-unhealthy-aging. --- focusing especially on

experimental research---". Prof. Hiroshi SHIMIZU (The University of Tokushima, Tokushima, Japan / Toyo Hospital, Tokushima, Japan) has given a lecture on the relation between kidney deficiency (腎虚) and hypothalamo-pituitary-adrenal system.

At "The Japan-Korea academic symposium on *Kampo* medicine and traditional Korean medicine", which theme was clinical use of *goshakusan* (五積散<jp>, Powder of five kinds of Stagnations, Wu-Ji-San), Dr. Takashi SEKI (Division of Geriatric Behavioral Neurology, Tohoku University CYRIC, Sendai, Japan) has made a lecture on "*Kampo* and traditional Korean medicine extract formulation for prescription in Japan and Korea", and Prof. Dongwoo NAM (Depertment of Acupuncture and Moxibustion Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Korea) has made a presentation on "Introduction of Ojeoksan usage in Korean clinics". Furthermore, Prof. Sung-Yoon Kim (Depertment of Acupuncture and Moxibustion Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Korea) has given a speech on "Introduction of Ojeoksan studies in Korean", and Dr. Masao OGAWA (Kanazawa Medical University, Uchinada, Ishikawa, Japan) has presented on "On *goshakusan* (五積散<jp>, Powder of five kinds of Stagnations, Wu-Ji-San) configuration and on the history of the change of secret oral teachings in the *Kampo*-sects by the masters".

In the afternoon session on June 4th, there was a symposium, which theme was "Who is 'the Globalization of Traditional Medicine' for? (What Kind of Traditional Medicine do Patients Desire in globalism?)", by the International Committee and the Terminology Committee of the JSOM. Prof. Shuji YAKUBO (Department of Medicine, Nihon University School of Medicin, Tokyo, Japan) has introduced on "Who is 'ICD-11' for?", and Prof. Yukihiro GODA (National Institute of Health Sciences, Tokyo, Japan) has presented on "Activity of the Western Pacific Regional Forum for the Harmonization of Herbal Medicines (FHH)". Furthermore, Prof. Takao NAMIKI (Department of Japanese-Oriental (*Kampo*) Medicine, Chiba University Graduate School of Medicine, Chiba, Japan) has given a speech on "Status Quo and prospect of ISO/TC 249", and Dr. Maiko TANOUE (School of Law, Senshu University, Tokyo, Japan) has made a presentation on "International trends with respect to protection of the traditional intellectual property and impact on Japanese traditional medicine".

In the morning session on June 5th, there was an invited lecture. Prof. Carl-Hermann HEMPEN (the Technical University Munich for Traditional Chinese Medicine, Munich, Germany) has introduced on "Education and practice of Traditional Chinese Medicine in Europe".

In the afternoon session on June 5th, there were some *Kampo* seminars for medical instructors in *Kampo* medicine, residents who were going to be board certified specialties of *Kampo* medicine, and pharmacists who specialize in *Kampo* medicine. And there was a symposium, which theme was "Restoration of acupuncture and moxibustion". Dr. Kazu MURAI (Kazu clinic, Wakayama, Japan) has presented on "Personal clinical experience on the marvelous clinical effects of acupuncture and moxibustion", and Prof. Hitoshi YAMASHITA (Morinomiya University of Medical Sciences, Osaka, Japan) has introduced on "Evidence Based Medicine and Acupuncture and Moxibustion: the Status Quo and Problems". Furthermore, Prof. Akira KAWASHIMA (Tokyo Ariake University of Medical and Health Sciences, Tokyo, Japan) has given a speech on "How can we save Japan by prevention of disease?: the Status Quo and Problems of Acupuncture and Moxibustion in Medical Environments", and Prof. Ikurou WAKAYAMA (Kansai College of Oriental Medicine, Osaka, Japan) has made a presentation on "Future Approaches of Acupuncture and Moxibustion".

In the morning session on June 4-5th, there were four acupuncture and moxibustion seminars for physicians.

3. Concluding remarks and about the upcoming congresses.

All the participants agreed that the General Assembly was an academic event of *Kampo* medicine with high level and standard. The researchers, pharmacists, acupuncturists and physicians of the *Kampo* Medicine have obligation to improve the quality of life (QOL) of people all over the world by sharing study results on health, welfare, and medical science.

There will be the 68th General Assembly of The Japan Society for Oriental Medicine (JSOM) in Nagoya, Japan (June 2-4, 2017) [4]. The theme of this future conference will be "Establishment of *Kampo* medicine. --- Strive for development of *Kampo* medicine and cooperation among *Kampo*-sects". In view of JSOM's long experience in organizing important events and of the city's main congress facilities, the 68th General Assembly of the JSOM 2017 will be sure not to disappoint.

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[1] Homepage of the Japanese Association of Medical Sciences. http://jams.med.or.jp/members-s/87.html [the last date of access September18, 2016]

[2] Homepage of the 67th General Assembly of the Japan Society for Oriental Medicine. http://www.pcojapan.jp/jsom67/ [the last date of access September18, 2016]

[3] Abstracts of the 67th General Assembly of the Japan Society for Oriental Medicine. Kampo Medicine (extra issue), 2016; 67: 1-394.

[4] Homepage of the 68th General Assembly of the Japan Society for Oriental Medicine. http://www.ccs-net.co.jp/touyo68/ [the last date of access September18, 2016]