

Special Contribution

Report of the 3rd Japan-Korea Workshop on Acupuncture and EBM — Protocol development for the acupuncture trial on the osteoarthritis of the knee —

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Abstract

The 3rd Japan-Korea Workshop on Acupuncture and EBM was held at Kanazawa on 16 June. From Korea team, 4 papers were presented. Dr. Hahn introduced a new approach of data analysis on series of n-of-1 trials using the Bayesian statistics. It offered important information for the future n-of-1 trials. Dr. Park clearly demonstrated the significance of various sham devices proposed and stressed the importance of research questions when we choose the control intervention in RCT. Dr. Lee reported the results of survey in Korean Medical Doctors (KMD) for their point selection and techniques to the distal and local points. Dr. Kim presented the results of face to face survey on the KMD with 28 items for acupuncture treatment on the knee osteoarthritis(OA). Finally, a draft of protocol was introduced by Dr. Kim. The title was "multi-center, a randomized, single blinded, two arms, parallel-group study to compare the effectiveness and safety of 'individualized acupuncture' and 'standardized minimal acupuncture' in Korean and Japanese patients with knee osteoarthritis (Phase IV)".

From Japan team, 7 speakers presented their comments and proposals on the protocol. Dr. Takahashi introduced several issues regarding n-of-1 trials and pointed out the importance of obtaining generalizability from n-of-1 trials. Dr. Shichidou pointed the importance of research design, selection of outcome measures and reduction of biases. Dr. Itoh presented the results of point selection for the knee OA based on the literature survey. Dr. Sumiya introduced several differences between KMD and Japanese acupuncturists based on the questionnaire used in KMD survey. Dr. Furuya demonstrated a result of press tack needle and its sham device on shoulder stiffness. Dr. Yamashita introduced the results of literature survey regarding adverse events occurred by acupuncture on knee OA. Dr. Tsukayama stressed the importance of responsibility of Institutional Review Board (IRB) for the conduction of clinical trials. After various issues were discussed, the need of continued meeting for final protocol development was agreed, and then the workshop was closed.

Key words: acupuncture, RCT, individualized treatment, Knee OA, Japan-Korea collaboration

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I. Brief history of the workshop

Little information has been exchanged between Korea and Japan in spite of their geographical closeness and similar traditional basis on acupuncture and moxibustion. However, after 2002, the need for mutual understanding and exchange has gradually increased in the acupuncture and moxibustion research field.

A formal letter from Dr. Won-Chul Lee, then President of Korean Oriental Medical Society (KOMS) was sent to Dr. Shohachi Tanzawa, the former President of Japan Society of Acupuncture and Moxibustion (JSAM) in June 2002. Since then several activities has been conducted between the two countries. On 6 June, 2003, a preparatory meeting of Japan-Korea Workshop on Acupuncture and EBM was held in conjunction with the 52nd Annual Conference of JSAM at Takamatsu. Simultaneously, to encourage joint activities, a

memorandum of understanding (MOU) among the JSAM, the Korean Acupuncture and Moxibustion Society (KAMS) and the KOMS was developed and formally signed on 14 February, 2004 at Seoul. Based on such numerous efforts of the JSAM, KAMS and KOMS members, the first Japan-Korea workshop on acupuncture and EBM was held at Chiba on 14 June, 2004.

At the Chiba meeting, KAMS and JSAM made several agreements and the most important item among them was 'to make a small research group for real joint research in the future'. Based on that agreement, acupuncture researchers from both countries made a 'small working group' and an informal workshop held in Fukuoka, 2005. The 'small working group' met again at the 2nd Korea-Japan workshop on acupuncture and EBM on 22 October, 2005, which was held in conjunction with the 13th International Congress of Oriental Medicine (ICOM) at Daegu in Korea.

Table 1: List of speakers and titles with time schedule

ID	Topics of presentation	Speaker
I. Opening remarks and Introduction		
I-1	Opening remarks (JSAM presidents)	Yano Tadashi
I-2	Opening remarks (KAMS presidents)	Choi Do-young
II. Presentation of papers and protocol from Korean team		
II-1	Acupuncture for tinnitus: analysis of N-of-1 trials	Hahn Seo-kyung
II-2	Are sham needles proper placebos for acupuncture research?	Park, Hi-Joon
II-3	Selection criteria of local and distal acupuncture points	
II-4	Survey of prescription of acupuncture points for knee OA in Korea	Kim Yong-suk
II-5	Proposal of a protocol from Korean team	Kim Yong-suk
III. Comments on the proposed protocol from Japan team		
III-1	Research design-1(N-of-1 trials and R statistics)	Takahashi Norihito
III-2	Research design-2 (RCT by real and sham superficial needle)	Shichidou Toshiyuki
III-3	Point selection -1 (literature survey by Medline database)	Itoh Kazunori
III-4	Point selection -1 (questionnaire survey using Korean prototype)	Sumiya Eiji
III-5	Intervention-1 (real and sham superficial acupuncture)	Furuya Eiji
III-6	Outcome measures (literature survey, WOMAC, SF-36)	Shichidou Toshiyuki
III-7	Safety of acupuncture to the knee OA	Yamashita Hitoshi
III-8	Ethical issues to be considered	Tsukayama Hiroshi
IV. General discussion		
IV-1	Summary and Closing Remarks (Chairperson: KAMS)	Jang Jun-Hyouk

II. Purpose and themes of the workshop

The purpose of this workshop was to develop a protocol of clinical trial of acupuncture on knee osteoarthritis(OA) for the Korea-Japan collaboration of clinical trials in the future. For the purpose, this workshop consisted of three themes. First, the Korean team presented four papers related to the development of protocol, and then, a draft of the protocol of clinical trials of acupuncture on knee OA was proposed by Korean team. Second, based on the proposed protocol, questions and comments in each item were performed by the Japanese team. Finally, researchers of both countries discussed the development of more valid protocols.

III. Contents of the workshop

The 3rd Japan-Korea workshop on acupuncture and EBM was held at Kanazawa on 27 June, 2006. Thirteen members of the KAMS and KOMS joined the workshop and about 30 members of the JSAM audience participated. All of the presentations were prepared in English, even though both members had several difficulties in understanding of complicated discussions in each theme. One of the aims of the agreement was to improve English presentation and discussion skills of the researchers in both countries. At the beginning of the workshop, the chairpersons, Dr. Kawakita (JSAM) and Dr. Jang (KAMS), briefly introduced by themselves, then the presidents of JSAM (Prof. Yano) and KAMS (Prof. Choi) made opening greetings.

Speakers and their titles of presentation are listed in Table 1. Five presentations from Korean team including proposal of a protocol of J-K collaboration of clinical trial and 8 presentations of comments from Japanese team on the draft protocol. In the general discussion, several issues were discussed and finally both Japan and Korea members agreed with the necessity of further meeting for the development of the protocol in near future.

1. Presentation of papers from the Korean team

Topics of the 1st paper

Dr. Hahn briefly reported an 'acupuncture for tinnitus: analysis of N-of-1 trials'. The aim of this study was to explore patient perceived benefits of acupuncture for tinnitus. The design was controlled N-of-1 trials, with two phases A and B. Primary outcome measures were the Daily Diary records relates to four tinnitus symptoms; loudness of tinnitus, pitch of tinnitus, number of waking hours affected and quality of sleep. Secondary outcomes were Tinnitus Handicap Inventory (THI) and Measure Your Outcome Profile (MYMOP). Patients received a course of 10 acupuncture treatments over a 2-week period. Daily Diary entries related to the four tinnitus symptoms, THI, MYMOP were recorded at pre-treatment and post-treatment.

A hierarchical Bayesian model was used to combine the results from the individual patients to obtain estimates of the population and individual patient treatment effects, incorporating random

	RCT	N-of-1	Series of N-of-1 in Bayesian model
Population estimate	○		○
Individual estimate		○	○

Figure 1. Comparison of RCT, N-of-1 and Bayesian model

variations at both levels (between patients and within patients).

Prof. Hahn presented about N-of-1 single case design first and explained Hierarchical Bayesian meta-analysis. Finally, methods, outcome measure, results were presented.

The results obtained are very clear. Primary outcome measures of 4 items were clearly reduced by acupuncture treatment. According to her presentation, this approach has two kind of potential advantages. One is population benefits: Data can be accumulated as part of everyday practice and may induce better representation of "effectiveness" in usual clinical setting. The other is patient benefits: Better understanding of patient variability and ability to predict individual responses.

Usefulness of research design of N-of-1 trials in the individualized treatment such as acupuncture has been well recognized^{1,2)}, however, its lack of generalizability is always severe issue of discussion. In the present presentation she clearly demonstrated a possible solution of such problem (Figure 1). However, in the discussion, importance of consideration for auto-correlation of time series data was pointed out.

Topics of the 2nd paper

Dr. Park presented the issue of "sham needles: proper placebos for acupuncture research?".

Randomized, double-blind, placebo-controlled trials are generally considered as the best tool to separate the 'specific' and the 'unspecific' or 'placebo' effects of a therapy. If the intervention is a drug, the 'specific' component is the pharmacologically active agent while the placebo is an inert substance. The issue becomes more complicated if the therapy under test is a complex physical intervention such as physiotherapy, chiropractic manipulation, or acupuncture. Because of complex situation, there is a variety of sham techniques that have been used in clinical trials of acupuncture^{3,4)}. Figure 2 summarizes various sham interventions used in the clinical trials.

A validated sham acupuncture device has a greater placebo effect on subjective outcomes than oral placebo pills. Streitberger & Kleinhenz introduced a placebo needle into acupuncture research in 1998. The needle is not fixed inside the copper hand. Its tip is blunt, and when it touches the skin pricking sensation is felt by the patient, simulating the puncturing of the skin. The needle moves inside the handle, and appears to be shortened.

In a cross-over experiment with 60 volunteers they tested whether needling with the placebo needle feels any different from real acupuncture. Of 60 volunteers, 54 felt a penetration with acupuncture and 47 felt it with the placebo. 34 felt a dull pain sensation (De-qi) with acupuncture and 13 with the placebo.

- Needling of true acupoints that are inappropriate for the condition being studied
- Needling of non-acupoints
- Noninsertion of needles
- Sham acupressure
- Sham electrical stimulation
- Minimal acupuncture
- Sham needles

Figure 2. Types of placebo techniques used in acupuncture RCTs

Park et al.³⁾ designed a placebo needle (Park sham needle: PSD) similar to Streitberger's⁵⁾. They used a flange and guide tube to place the needle instead of a plastic ring covered with plastic sheet in Streitberger's placebo needle. In a credibility study, PSD is indistinguishable from real needles and cannot elicit De-qi sensation. In another 2 credibility studies to experienced subjects, the results were different. But, it seems to be capable to use it as sham needle for blinding in acupuncture RCTs.

Fink et al.⁶⁾ designed modified Streitberger's sham needle which uses a sponge instead of a plastic ring covered with plastic sheet. In a validation study of 68 patients with tension-type headache, patients unable to discriminate sham from real acupuncture and 84% of patients felt De-qi while 34% of the sham group did. Effectiveness of acupuncture for various conditions was tested using these needles in 10 RCTs. They have been adequately validated and usually successful in achieving patient-blinding. However, the results from the RCTs so far support the skeptics who believe that the clinical effects of acupuncture are no more than a placebo response.

She pointed out several disadvantages to sham needle as follows: needling technique is significantly interfered, accurate point location is difficult or almost impossible, and attaching the device to keep the needle in place is time consuming and may lessen the effect of verum treatment. The device is not applicable to all acupuncture points.

Finally, she emphasized that appropriateness of controls depends on "what your research question is?"

Topics of the 3rd paper

Dr. Lee reported similarities and differences in the selection criteria and technique between local and distal acupuncture points in Korean medical doctors (KMD). It is very important to select the adequate acupuncture points, needling technique and other factors related to acupuncture stimulation. Figure 3 summarizes various factors which may influence the clinical efficacy of acupuncture treatment.

He tried to investigate and characterized perceptions of acupuncture point selection, especially similarities and differences between the distal and local points in the experts of KMD. He designed a self-administered questionnaire and performed during the annual acupuncture conference of KAMS. 91 (79.8%) of 114 subjects were responded and 88 (77.2%) respondents were analyzed.

In the survey, KMDs recognized that disease of locomotor system (27.7%), regional disease (26.0%), sprain / contusion / trauma (14.0%) is effective conditions to select the local points. On the other hand, they usually select distal points in meridian disorder (19.0%), Zang-fu viscera disease (18.6%), non-regional disease (17.7%), etc. In a symptom of indeterminate origin (30.2%) and

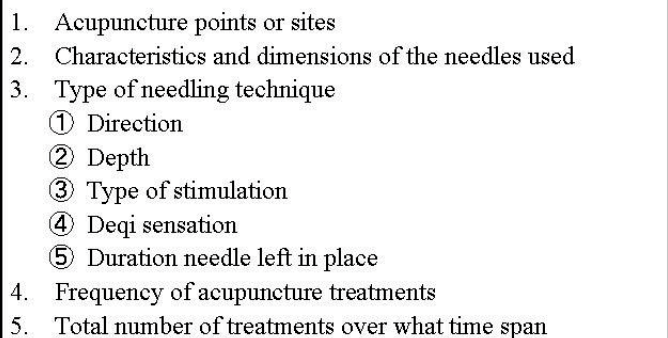
- 
1. Acupuncture points or sites
 2. Characteristics and dimensions of the needles used
 3. Type of needling technique
 - ① Direction
 - ② Depth
 - ③ Type of stimulation
 - ④ Deqi sensation
 - ⑤ Duration needle left in place
 4. Frequency of acupuncture treatments
 5. Total number of treatments over what time span

Figure 3. Factors influencing effectiveness of acupuncture

chronic disorders (25.4%), they recognized that selection of local points is ineffective. Erroneous syndrome differentiation (41.4%) was understood to be the most ineffective condition to select distal points. In the survey, they usually select local points in the case of response points such as pressure pain and follow the western medicine diagnosis.

However, in the case of selecting distal points, mostly they followed traditional theory of meridian (88%). This survey implies the real acupuncture practice may be different from those of reported in the research papers.

Topics of the 4th paper

Dr. Kim reported a face-to-face survey of Korean oriental medical doctors: How do they prescribe the acupuncture points for knee osteoarthritis patients? This survey was performed for the development of

new clinical research design suitable for the individualized procedures because survey can reflect real common clinical practice.

Four professors of the Oriental Medical College and 10 resident doctors of the Oriental Medical Hospital developed the questionnaires which consist of 28 items (Table 2). Seventy two KMDs who preferred to answer the remote acupuncture prescription at previous telephone survey responded the entire questionnaires which took ten to fifteen minutes to complete. In the survey, Korean medical doctors preferred to use the five shu acupuncture points, especially 'hyung' or 'shu' points, on the contra-lateral side of lesion and that the first target organ is the liver. Five element points theory was mainly based on 'Nanjing' and 'Hwangdi Nejing'. The De-qi sensation of both doctor and patients were emphasized.

This study showed that Korean medical doctors prefer to follow the Korean traditional acupuncture

Table 2. Items of Questionnaire

1.	How many years have you been treating patients for osteoarthritis of knee?
2.	When diagnosing OA of knee, which standard symptom(s) do you look for?
3.	When you treat patients with knee pain or osteoarthritis of knee, by what criterion do you select the needle insertion points?
4.	When you use local point selection pattern, by what criterion do you select the needle insertion points? [☞ Check no more than two.]
5.	When you use distant point selection pattern, what examination procedures do you follow?
6.	When using distant point selection method, what differential symptom characteristics do you look for?
7.	In distant point selection, Which Five Zang Organs and Six Fu Organs symptom differentiations do you look for?
8.	In distant point selection, which side of the body do you prefer?
9.	In distant point selection, which needle insertion points do you prefer to use?
10.	In distant point selection, which of the five-shu points do you prefer?
11.	In distant point selection, what is your preferred standard for choosing among five-shu points?
12.	In distant point selection which are the specific preferred points other than five-shu points?
13.	Of the available methods for reinforcing and reduction of manipulation, which do you most prefer to use with five-shu point and Sa-an acupuncture methods?
14.	In five-shu point or Sa-an acupuncture method, what is your preferred standard channel or meridian?
15.	In Sa-an acupuncture method, which meridian do you mainly prefer?
16.	In Sa-an acupuncture method*, what is your preferred standard for choosing among reinforcing and reducing manipulations?
17.	Approximately how many needles do you use with local point selection method?
18.	Approximately how many needles do you use with distant point selection method?
19.	When inserting needles, how do you determine the arrival of qi?
20.	When inserting needles, which method of confirming arrival of qi do you prefer?
21.	How do you determine the duration of needle retention?
22.	When treating OA patient, how many treatments weekly do you consider optimal?
23.	How much time usually elapses between treatment onset and appearance of observable change in osteoarthritis of knee condition?
24.	How long is it expected to accomplish a cure of osteoarthritis of knee condition?
25.	Which evaluation criterion do you prefer in making a determination whether a patient's osteoarthritis of knee condition is improved?
26.	When treating osteoarthritis of knee with acupuncture, which other therapy(ies) might you sometimes use?
27.	Which treatment or therapy other than acupuncture/moxibustion do you prefer for osteoarthritis of knee?
28.	From your experience treating osteoarthritis of knee, describe the representative case where your treatment was considered most effective.

methods respecting the old classic principles. And these results can guide to develop advanced clinical trial protocols more closely to real acupuncture practice.

2. Proposal of a protocol from the Korean team

Dr. Kim from the Korean team proposed a draft of the protocol. The title was "multi-center, a randomized, single blinded, two arm, parallel-group study to compare the effectiveness and safety of 'individualized acupuncture' and 'standardized minimal acupuncture' in Korean and Japanese patients with knee osteoarthritis (Phase IV)".

This protocol plans to include 126 subjects and divided into two arms. 126 volunteers with knee osteoarthritis will be recruited from the community and then randomized to one of the two study arms in a ratio of 1:1. One arm participants will receive individualized acupuncture twice a week, the other arm participants will receive standardized acupuncture twice a week. Each patient will

participate in this study for a maximum of 8 months. The study consists of a screening visit, baseline assessment visit (day 1), a treatment period (week 3-week 9), and a six month follow-up visit (week 35). The total duration of the study will be approximately one and half years and will include a total of twelve study visits.

Assessment of pain and function of the knee joint will take place at the baseline and at the 26 week (6 months) interval throughout the follow-up period. The primary objective of this protocol was to determine whether individualized acupuncture provides greater pain relief compared with standardized minimal acupuncture in patients with osteoarthritis of the knee. Therefore, the primary outcome measure is participant pain rating based on a 100mm VAS.

The secondary objective included four items. First, to determine if individualized acupuncture has more change in pain, stiffness, physical function of the knee (WOMAC) compared to standardized minimal acupuncture at 6 weeks and 6 months. Second, to

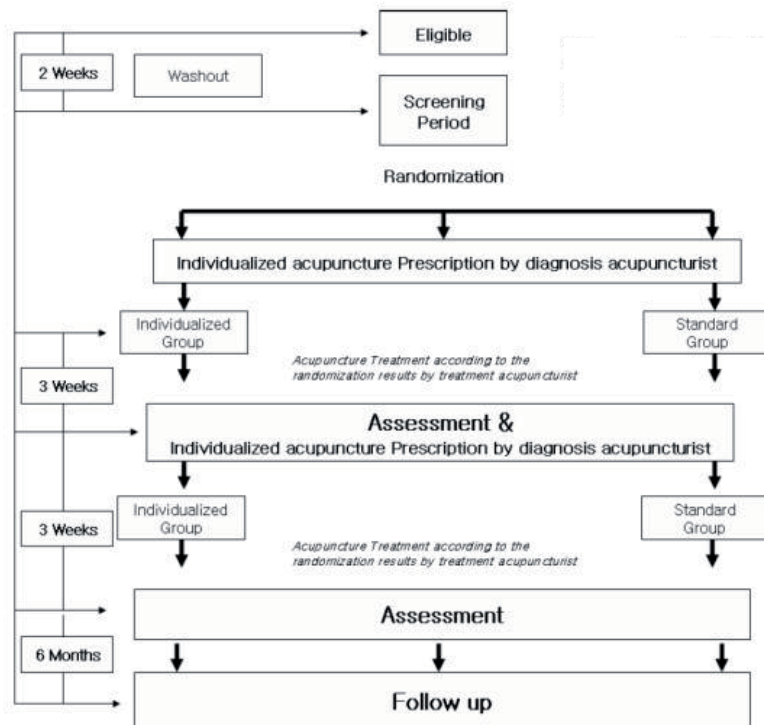


Figure. 4. Outline of the protocol.

determine if individualized acupuncture increases average quality of life (SF-36) compared to standardized minimal acupuncture at 6 weeks and 6 months. Third, to determine if individualized acupuncture increases average joint function (LFI score) compared to standardized minimal acupuncture at 6 weeks and 6 months. Fourth, to determine if individualized acupuncture increases average physical function (HAQ) compared to standardized minimal acupuncture at 6 weeks and 6 months.

Thus, the secondary outcome measures are Western Ontario McMaster Questionnaire (WOMAC), Quality of Life (SF-36), Lequesne Functional Index (LFI) score, and physical function was evaluated by the Health assessment Questionnaire (HAQ).

The scheme of this study is shown in Figure 4.

3. Comments on the proposed protocol and discussion from Japan team

1) Comments on the research design-1

Dr. Takahashi commented on the issue of clinical trial design. In his presentation 'N-of-1 trials for the individualized therapy on the knee pain', he proposed to use the n-of-1 design for the Japan-

Korea cooperated clinical trial for acupuncture and moxibustion treatment of knee pain. The reason is that RCT is difficult to recruit enough subjects in the same time and difficult to manage many subjects with many institutions.

He showed the difference of RCT and integrates N-of-1. Then, he questioned whether meta-analysis of various N-of-1 trials can be generalized?(Figure 5).

In addition, he pointed out problems in N-of-1 trials. N-of-1 trial may incline toward the patient who is likely to be effective (selection bias). Therefore, we have to recruit a patient so that there may be no deviation. Another problem is that we need methods to integrating the result of the trials for an individual and to generalization. Statistics may be a solution. Finally, he concluded that if problems were solved using N-of-1 trials may be released from the difficulty which manages many patients simultaneously. Furthermore, more clearly curative effect of acupuncture and moxibustion may be discovered.

2) Comments of research design-2

Dr. Shichidou showed his expertise about RCT designing and planning order for the Korea/Japan joint research as research adviser. He explained four items about research design and planning order

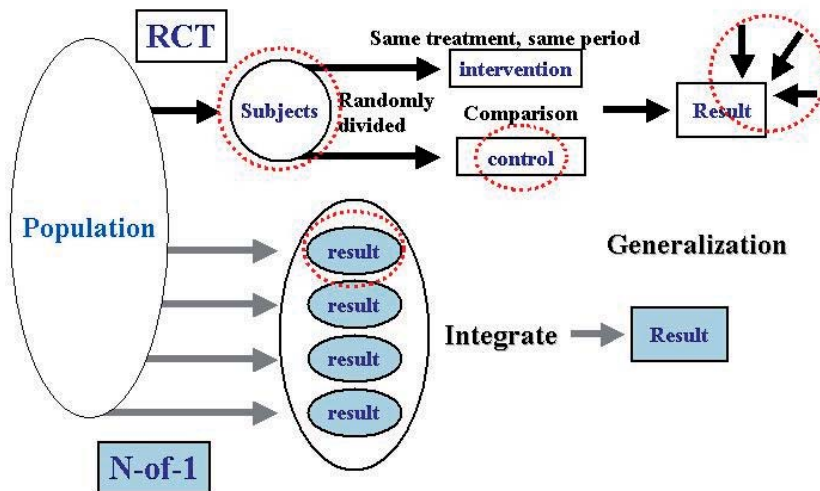


Figure 5. Comparison of RCT and n-of-1 trials

such as examination in questionnaires, planning control group, feasibility, and data analysis methods.

Regarding examination in questionnaire, he mentioned three important things. First, we have to consider the questionnaire and scale. That means we have to pretest the reliability (reproducibility) and validity of the questionnaire. Second, we must choose and use the scales (ratio, interval, ordinal, nominal) accurately. Third, if we use a translated overseas questionnaire, we need to conduct a reliability/validity test as well. It is very common to use an overseas questionnaire, however, we should concern about the fact that it is made under different culture. And we have to confirm its frequency and reliability and validity test in foregoing papers.

WOMAC, VAS, SF 36, etc. are used for pain/function scale of the knee OA in the foregoing research. For example, the gonarthrosis questionnaire made by Japan Orthopedic association (JOA) has no reliability and validity test. Now, JOA is making new score named JKOM.

About planning control group, he introduced several sham acupuncture and research papers

which used it. Feasibility is also important in the research. Adequate number of subjects, adequate technical expertise, affordable in time and money, manageable in scope are essential items for feasibility. Data analysis methods are emphasized by as well.

Finally, he wanted to touch other important items such as randomization, allocation concealment, treatment term & frequency, eligibility criteria. But he could not because of shortage of presentation time.

3) Point selection-1

Dr. Itoh reported point selection in the references of knee OA research. In the evaluation of the efficacy of acupuncture, important parameters were the stimulation site, intensity and modality of stimulation of the points. For the assessment of stimulation site, one can indicate certain variable, numbers of stimulation sites, and the location of stimulation sites. On the other hand, the location of the stimulating site in the knee OA patients was a traditional acupuncture point around the knee in most previous studies.

The main aim of this study was to review the

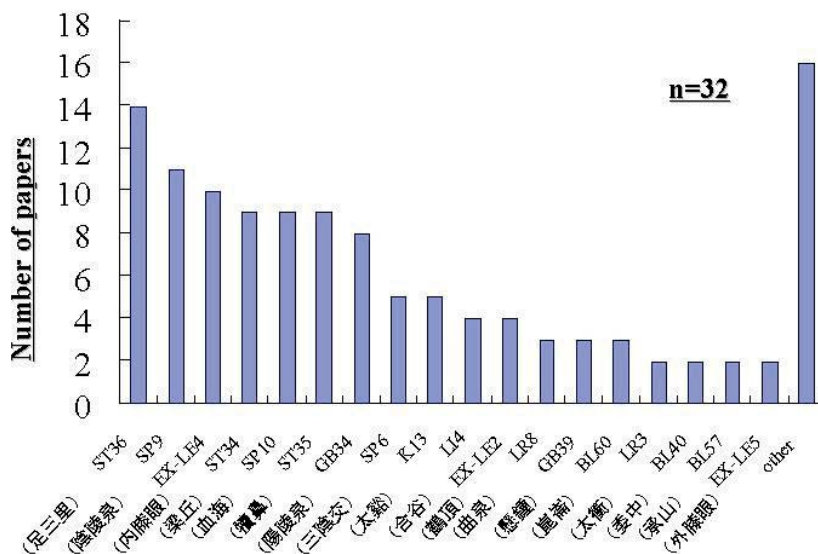


Figure 6. Frequency of use on treatment point

widely used and effective stimulation sites of the knee OA in the recent clinical trials. He used Medline (from 1996 to 2005) as a search database and search terms; 'acupuncture' and 'moxibustion', 'osteoarthritis of knee', 'knee arthritis' or 'knee pain'. The search was also limited to 'humans' and 'English'. On the other hand, he searched the references of each paper. As the result of literature survey, VAS and WOMAC were the most frequently used outcome measures and ST36 (足三里) and SP9 (陰陵泉) were the most frequently used acupuncture points. Figure 6 summarizes the number of papers which used each acupuncture point listed. ST36 was the most frequent choice among the papers searched.

On the other hand, he calculated effect size of each paper as well. Effect size is the change in endpoint divided by standard deviation (SD). However, it was not possible to calculate formal effect size, because few authors reported standard deviation. In the effect size calculated, WOMAC was used in 7 papers and their effect size was the biggest. HSS (Hospital special surgery knee score) used in 2 papers, and the effect size was the second. VAS used in 5 papers and the effect size was the third. In the effect size of treatment points, ST34 (梁丘) was the biggest, ST35 (犢鼻), GB34 (陽陵泉), SP9 (陰陵泉), LR3 (太衝) were about the same each other, and it should be noticed that it also varied with the control interventions.

In conclusion, SP9 (陰陵泉), GB34 (陽陵泉), EX-LE4 (外膝眼), ST35 (犢鼻), ST36 (足三里) were more useful and effective points than the other points for treatment of the knee OA.

4) Point selection-2

Dr. Sumiya reported the problems of questionnaire survey using Korean prototype. His title was "The problems in carrying out the questionnaire in Japan, which had carried out in Korea". He used the similar questionnaire that carried out by Korea team, but it was slightly modified in order to adjust for the present acupuncture treatment style in Japan. The questionnaires were just sent to 1,000 members that were chosen randomly from about 6,000 registered members of the Japan Society of acupuncture & Moxibustion by computer.

Regarding questionnaire used in Korea, he found several issues to be modified. In Japan at present, there are 4 main acupuncture and moxibustion treatment styles. They are treatments based on 1) western medicine, 2) traditional Chinese medicine, 3) meridian and 4) eclectic style. However, many acupuncturists using the Western medicine style do not understand the reinforcing and reducing manipulations and arriving qi as well. Moreover, acupuncturists who do not know about the theory of meridians and collaterals or the theory of Yin and Yang organs are not rare.

The treatment effect of acupuncture and

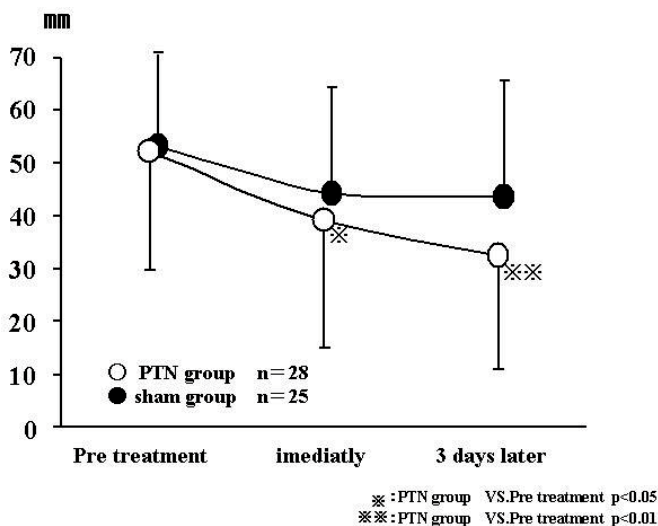


Figure 7. The degree of shoulder stiffness using VAS

moxibustion on the osteoarthritis might be influenced by the degree of seriousness of knee OA symptoms, however, the Japanese acupuncturists can not legally allowed to diagnose the patients as having knee OA. And now in Japan, acupuncturists are prohibited to use pricking and cupping therapy causing hemorrhage on the law. These situations of Japanese acupuncturists make it difficult to conduct the survey using the same questionnaire with Korean team. The results of this survey will be collected, analyzed and reported in near future.

5) Intervention-1

Dr. Furuya of the Tokyo therapeutic institute reported "The effect of press tack needle (PTN) treatment on shoulder stiffness". Shoulder stiffness is defined as unpleasantness and a strained trapezius muscle. This symptom is improved by a rubbing or slight pressure, and frequently treated with acupuncture and moxibustion. It is caused by psychological, physical and social factors. Shoulder stiffness is caused by a reduction of pain threshold and is related to autonomic nerve dysfunction as well. Before treatment, he did a physical

examination for the differential diagnosis of other disease such as herniated nucleus pulposus, thoracic outlet syndrome, etc. PTN is used for the purpose of pain reduction or prolongation of the effects of regular acupuncture and moxibustion treatment. For example, PTN is used for relaxation of shoulder stiffness in chronic symptoms. However, there are few reports that inspected the effectiveness of PTN itself⁴⁾.

Therefore, this study was planned to inspect curative effect of PTN. A change of subjective symptoms after PTN treatment was compared with that of sham needle using volunteers with shoulder stiffness. This study was designed as a randomized controlled trial (RCT). Fifty six volunteer subjects who aware of shoulder stiffness were treated with 0.6mm length PTN for 3 days. The subjects were the staff and students of Tokyo Therapeutic Institute.

The number of the volunteers reporting awareness of shoulder stiffness after 3 days decreased from 28 to 12 in the PTN group and from 25 to 23 in the sham group ($p < 0.01$). As shown in Figure 7, VAS value of shoulder stiffness decreased immediately

Table 3. Adverse events reported in the literatures

First author (Year)	Acupuncture group	Sham or no treatment group
Christensen (1992)	3 patients: worsening of pain, nausea, or dizziness. 1 patient: a large hematoma (no sequela). 1 patient: vaso-vagal attack (of 32 treated: cross-over)	
Sangdee (2002)	1: joint swelling 21 (46x45%): local contusion (of 46 patients treated)	2: joint swelling (dummy EA: patch electrodes and sound) (of 45 patients treated)
Tukmachi (2004)	"No side effects...were noted" (of 9 patients treated)	"No side effects...were noted" (of 10 patients treated)
Vas (2004)	3: bruising at acupoint (of 48 patients treated)	No events (of 49 patients treated)
Berman (2004)	"subjective symptoms... (dizziness, nausea, and numbness)... did not statistically significantly differ... and incidence... was quite low" (of 190 patients treated)	(no specific description) (of 189 patients treated)
Witt (2005)	18 events: small hematoma/ bleeding 6 events: others (ex. needling pain) (of 150 patients treated)	9: small hematoma/bleeding 1: local inflammation (minimal acupuncture) 6: others (of 74 treated)

($p < 0.05$) after PTN treatment and it continued and increased 3 days later ($p < 0.01$). These results suggested that PTN treatment on the tender points improved shoulder stiffness. The sham device of PTN used in this study seems to be very excellent for its purpose. The Japanese team has planned to conduct a RCT using real PTN and sham PTN, however, the efficacy of PTN alone on the symptoms of knee OA has not known, so an exploratory study should be conducted using n-of-1 research design.

6) Outcome measures

This presentation was performed in the session of general discussion because of the shortage of time. Please refer to the general discussion for the detailed comments about this issue.

7) Safety of acupuncture to the knee OA

Dr. Yamashita, the chief investigator of the Committee for Safe acupuncture in JSAM, presented his report "Safety of acupuncture for knee OA".

He mentioned that there are four published case reports on acupuncture adverse events in treating knee OA⁷. The reported adverse events were

acupuncture mycobacteriosis, pseudoaneurysm of the popliteal artery, necrotising fasciitis, and candida arthritis of the knee. Regarding these reports, however, two questions may arise; "How often does it happen?" and "Is a causal relationship well established?". Since case report is in low level in the hierarchy of clinical evidence, he reported a review of safety information from acupuncture RCTs on knee OA. He searched in PubMed and Igaku Chuo Zasshi (Japan Centra Revuo Medicina) as a data base. Search keywords are "acupuncture, electroacupuncture, osteoarthritis, knee, gonalgia and gonarthrosis", and search limits are "randomized controlled trial", and he found 11 papers which reported adverse events in acupuncture RCTs.

Table 3 summarizes the adverse events reported in the literatures⁸⁻¹³. There were some adverse events such as joint swelling, bruising and small hematoma. Several subjective symptoms were dizziness, nausea and numbness, but it did not significantly differ and their incidences were quite low. Finally he recommended two things for establishing safety information on adverse events in acupuncture RCTs. First, calculate each event's

Table 4. Responsibilities of IRB/IEC in clinical trials

3	INSTITUTIONAL REVIEW BOARD / INDEPENDENT • ETHICS COMMITTEE (IRB/IEC)
3.1	Responsibilities
3.1.1	An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.
3.1.2	The IRB/IEC should obtain the following documents: trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g.advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator' s current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfill its responsibilities.
3.1.3	The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.
3.1.4	The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

incidence (frequency). Second, classify the events caused by acupuncture with avoidability and severity.

8) Ethical issues to be considered

Dr. Tsukayama presented "Ethical consideration on conducting and publishing randomized controlled trial". He introduced ethical standards and international guidelines for ethics in the biomedical field¹⁴⁾.

There are three ethical standards in the biomedical field, which is the Nuremberg Code (1947), Helsinki declaration (1964) and the Belmont Report (1974). The Belmont Report is ethical principles and guidelines for the protection of human subjects of research and standards for Institutional Review Board. Also, there are three international guidelines for ethics in biomedical field as follows. (1) Good Clinical Practice guidelines (GCP) are developed by International Committee on Harmonization (ICH), (2) International ethical guidelines for biomedical research involving human subjects is developed by Council for International Organization of Medical Sciences (CIOMS) and (3) Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication made by the international committee of medical journal editors.

He used most of his time to introduce important thing about Institutional Review Board/Independent Ethics Committee (IRB/IEC) in ICH/GCP. Table 4 summarizes the responsibilities of IRB/IEC closely related to the protocol development for the clinical trials. These issues are also important to develop a final protocol and actual conduction of clinical trials.

IV. General discussion

During the general discussion session, question from the floor was not allowed because we need much time to discuss about the protocol which already presented by Korean team.

Because shortage of time, Dr. Shichidou asked several questions as a representative of the Japanese team as they had another workshop for discussion of the protocol.

VAS is used as the primary outcome measure and secondary outcome measures are WOMAC, Quality of Life (SF-36), Lequesne Functional Index (LFI) score, and physical function was evaluated by the Health assessment Questionnaire (HAQ). He suggested that WOMAC includes pain, stiffness and

physical function items, so it is better to use WOMAC. Other measures are not necessary. In case of contradictory results obtained among the outcome measures, it is very difficult to explain the results. Repeated measurements of similar items in different questionnaires may also induce severe statistical errors. Another important point he mentioned was issues of individualized and standard interventions¹⁵⁾. In the protocol, de-qi is required in the individualized intervention, whereas no de-qi in the standard group. There are two factors included in the interventions, the location difference of acupuncture points and induction of de-qi or not. If we got the significant result among the two groups, we have no idea which is the cause of the results. This is also important issue to be considered.

Finally all of members of both countries agreed to reconsider the protocol based on the discussion today, and to have a next meeting in the near future.

Appendix

All six speakers kindly agreed to exhibit their slides to the members of the JSAM, KAMS and KOMS for promoting the clinical research in both countries. It is allowed for the personal use only, so please do not use for other purposes. You can see these slides at the homepages of the JSAM, KAMS and KOMS soon.

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