The First Japan-Korea Workshop on Acupuncture and EBM
Proposal of clinical trials for the future Japan-Korea collaboration
Results and issues of the clinical researches of acupuncture and moxibustion in Japan and Korea

Results obtained from multi-center RCTs on the common cold and issue to be solved

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The 53th Congress of the Japan Society of Acupuncture and Moxibusitoin 2004,Jun.11 in Chiba

Introduction

We performed clinical tests of acupuncture and moxibustion for symptoms of the common cold to obtained the high-quality evidences about “mi-byo-chi”.

In this work shop, we’ll report the progress and problems occurred in this series of clinical tests, and introduce single-case experiment design used for the clinical testl in the last year.

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Step 1
Pilot test

Effects of manual acupuncture on the symptoms of common cold

- a pilot study -

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Step 1. Effects of manual acupuncture and moxibustion on the symptoms of common cold
- a pilot study -

【Introduction】

We conducted a pilot study of the preventive and curative effects of acupuncture on the symptoms of the common cold to examine the effects of acupuncture.

【Subjects】

Twenty-four students and staffs of a Japanese acupuncture school, who gave informed consent, were registered and randomly allocated to acupuncture or control group 12 each by computer program.

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Step 1. Effects of manual acupuncture and moxibustion on the symptoms of common cold
- a pilot study -

【Experimental period】

January 20th ～ February 19th 2000. (1 month)

【Intervention】

Twice a week for 4weeks (total 8 times)

Treatment point__bilateral Y Point (extraordinary point)

→ Throat (laryngeal prominence), 1.5-2.0cm lateral of the midline

→ 0.16mm (diameter)×40mm, disposal needle, Seirin Co.Ltd.

→ sparrow pecking technique, induction of a kind of needling sensations

→ continued 15 sec

Control group__No treatment

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- a pilot study -

【Outcome】

Common Cold Diary (CCD)

→ daily condition of their common cold (binary form, yes or no)

→ daily (during experimental period), self-entry

Common Cold Questionnaire (CCQ)

→ Fifteen categorical questions with 4-5 levels

→ Four times on the days of acupuncture treatment and two weeks after the final treatment

【Data analysis】

chi-square test (χ²-test: baseline analysis)

Kaplan-Meier survival analysis (K-M test: for CCD)

General Linear Model (GLM: for CCQ)

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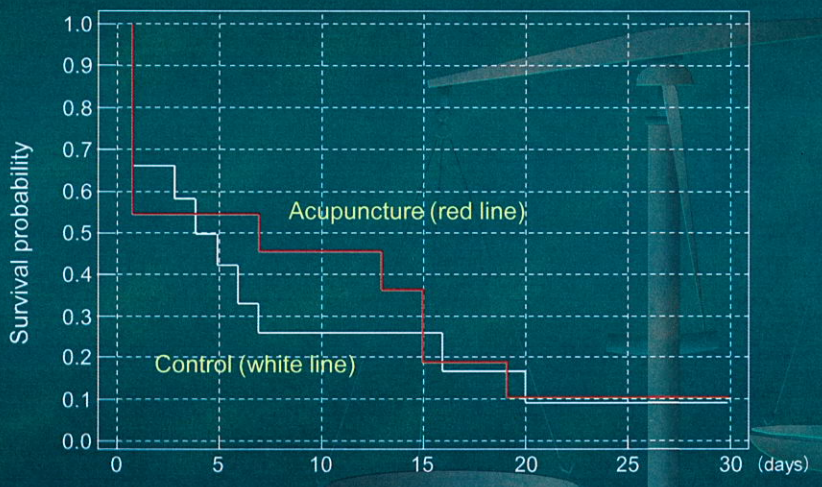
- a pilot study -

【Results: K-M test for CCD】



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Step 1. Effects of manual acupuncture and moxibustion on the symptoms of common cold
- a pilot study -

【Conclusions】

1. Preventive and curative effects of acupuncture on symptoms of the common cold was found.
2. Validity and reliability of CCD for outcome was confirmed.

【Problems】

1. Since control group had no treatment, the placebo effect was unexcludable.
2. Since it was the students and teachers of acupuncture school, the hope for a needle may have been large.

【Next step】

Based on the result of a pilot examination, sample size was computed and larger-scale enforcement of RCT was planned.

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Step 2
Multi-center randomized controlled trial

Preventive and curative effects of acupuncture on the common cold: a multi-center randomized trial in Japan

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Step 2. Preventive and curative effects of acupuncture on the common cold: a multi-center randomized controlled trial in Japan

【Objective】

Large-scale multi-center randomized controlled trial is performed to examine the preventive and curative effects of manual acupuncture on the symptoms of the common cold.

【Design】

sample size : Sixty subjects for each groups (computed from pilot test)
General design : same as the pilot test
Blood examination : carried out at one center

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Step 2. Preventive and curative effects of acupuncture on the common cold: a multi-center randomized controlled trial in Japan

【 Experimental period 】

One month from the end of January 2001.

→ the first half was treatment period (2 weeks)

→ the latter half was progress observation period (2 weeks)

【Centers】

Morinomiya college of medical arts and science; Meiji school of oriental medicine; School of nursing Tokyo-Eisei-Gakuen; School of acupuncture, moxibustion and Shiatsu Kanagawa-Eisei-Gakuen; Meiji university of oriental medicine

【 Subjects 】

A total of 326 subjects were registered then randomly allocated to the acupuncture or control group by computer program.

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Step 2. Preventive and curative effects of acupuncture on the common cold: a multi-center randomized controlled trial in Japan

【Intervention】

Same as the pilot test

【Outcome】

CCD : daily, self entry

CCQ : Four times on the days of acupuncture treatment and two weeks after the final treatment

The weather and temperature were recorded in each center during an examination period.

Adverse events were recorded

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Step 2. Preventive and curative effects of acupuncture on the common cold: a multi-center randomized controlled trial in Japan

【Blood examination】

carried out at one center

number of leukocyte, lymphocyte and granulocyte

CD4,CD8,CD14,CD19,CD56,INF-γ,IL-1β,IL4

→ before treatment period, after 2 weeks, after 3 weeks, total 3 time

【Data analysis】

chi-square test （χ^2-test: baseline analysis）

Kaplan-Meier survival analysis （K-M test: for CCD）

Cox regression analysis (Cox: for CCD)

General Linear Model （GLM: for CCQ）

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Step 2. Preventive and curative effects of acupuncture on the common cold: a multi-center randomized controlled trial in Japan

【results: summarized】

center	CCD					CCQ	
	Cox (preventive)	Cox (curative)	GLM (whole period)	GLM (treatment period)	GLM (sex)	GLM (whole period)	note
A	n.s.	n.s.	P=0.198 Sex*day : P=0.022	P=0.053 inversion	m > f	P=0.035	ACP < cont
B	P=0.0705	P=0.0097	P=0.001 sex : P=0.021	P=0.010	m > f	P<0.001	ACP > cont
C	n.s.	P=0.0059	P=0.360	P=0.071	m > f	P=0.029	ACP > cont
D	n.s.	n.s.	P=0.945	P=0.907 Sex*day : P=0.007	m > f	P=0.643	n.s.
E	n.s.	n.s.	P=0.644 Sex*day : P=0.000		m > f	P=0.218	n.s.
all	n.s.	n.s.	P=0.325 Conter*group : P=0.003	P=0.100 Center*group : P=0.002	m > f	P=0.024 sex : P=0.005 Group*sex : P=0.263	ACP > cont m > f

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Step 2. **Preventive and curative effects of acupuncture on the common cold: a multi-center randomized controlled trial in Japan**

【results: others】

1. The validity of allocation was checked by χ^2– test
2. Results of blood examination, no significant differences was found in all data, and on the center that carried out the blood examination, there was no significant differences in both preventive and curative effects.
3. No clear relevance between symptoms of common cold and the weather, temperature, etc was found.
4. Dropout was 5 and adverse events was 10 during experimental period.

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Step 2. **Preventive and curative effects of acupuncture on the common cold: a multi-center randomized controlled trial in Japan**

【The esteemed points】

1. Experimental design
   → The ideal process performed in order of pilot study, sample size compute, and Large-scale RCT was able to be taken.
2. Mental effects
   → it is the esteemed point that the treatment effect of the pure acupuncture containing the placebo effect has been examined.
3. Outcome
   → The reliability of outcome was reconfirmed.

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Step 2. **Preventive and curative effects of acupuncture on the common cold: a multi-center randomized controlled trial in Japan**

【Problems】

1. Intervention and experimental period
   - → The technical difference of acupuncture and the validity of a stimulus points and experimental period. Were these appropriate or not?
2. Subjects
   - → Subjects were students and staff of acupuncture school, so they may have the superfluous expectations to acupuncture treatment.
3. Differences between the centers
   - → The difficulty of whole management of multi-center RCT.

【Next step】

solved the technical difference, improves the experimental period, improves the management

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Step 3
Multi-center randomized controlled trial

Preventive and curative effects of indirect moxibustion on the common cold:
- a multi-center randomized trial -

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Step 3. Preventive and curative effects of indirect moxibustion on the common cold: a multi-center randomized trial

【Objective】

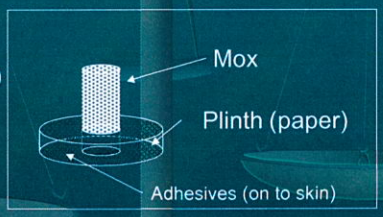
The knowledge of "mi-byo-chi" to common cold is acquired solving the problem of the preceding year.

→ indirect moxibustion was adopted

→ experimental period was extended

Indirect Moxibustion

→ 『sen-nen kyu』 (Ibuki、Senefa Co Ltd.)



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Step 3. Preventive and curative effects of indirect moxibustion on the common cold: a multi-center randomized trial

【Design】

Compared with indirect moxibustion and control group

Outcome: same as the previous research

Experimental period: extended

【Experimental period】

Six weeks from the end of January 2002

Two weeks of the beginning were treatment period

Four next weeks were progress observation period

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Step 3. **Preventive and curative effects of indirect moxibustion on the common cold: a multi-center randomized trial**

【Centers】

Morinomiya college of medical arts and science; Meiji school of oriental medicine;School of nursing Tokyo-Eisei-Gakuen; School of acupuncture, moxibustion and Shiatsu Kanagawa-Eisei-Gakuen; Meiji university of oriental medicine; Kansai College of Oriental Medicine

【Subjects】

A total of 367 subjects were registered then randomly allocated to the indirect moxibustion or control group by computer program.

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Step 3. **Preventive and curative effects of indirect moxibustion on the common cold: a multi-center randomized trial**

【Intervention】

GV14, bilateral BL12__once each, 3 times or more per week

→ In order to prevent a burn, when a subject appealed against heat full realization, it removed at the time.

【Outcome】

CCD (same as the previous study)

daily, self entry

【Data analysis】

same as the previous study

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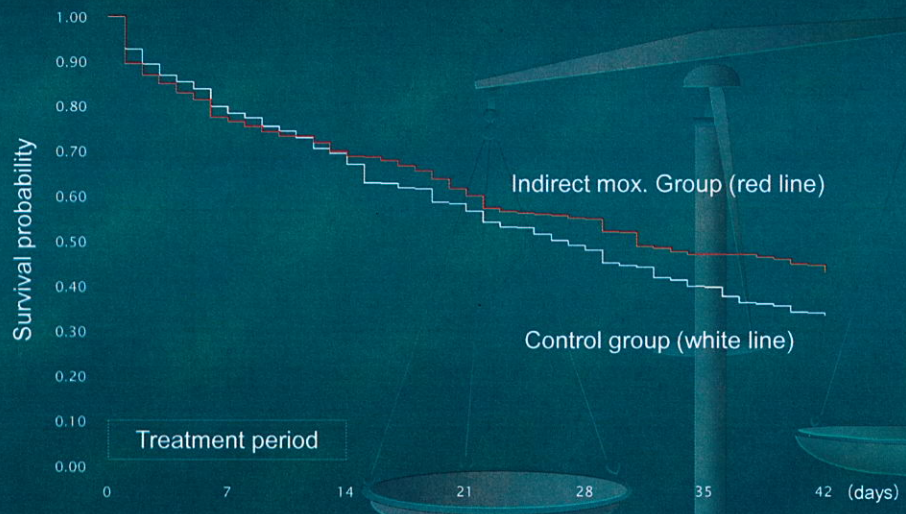
Step 3. Preventive and curative effects of indirect moxibustion on the common cold: a multi-center randomized trial

【Results：K-M test for CCD】



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Step 3. Preventive and curative effects of indirect moxibustion on the common cold: a multi-center randomized trial

【The esteemed points】

1. Intervention
   - → There were very few clinical tests about moxibustion treatment.
   - → The technical difference was abolished by having used indirect moxibustion and it was easy to obtain consent.

2. Control group
   - → The treatment effect of the pure indirect moxibustion containing the placebo effect has been examined.

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Step 3. Preventive and curative effects of indirect moxibustion on the common cold: a multi-center randomized trial

【Problems】

1. Inter-center difference
   - → In spite of having abolished the technical difference, the results of every center differed.
   - → The difference may have been in the motivation and the enforcement method for subjects for every center.
2. No clear results
   - → A significant difference is not accepted statistically.
   - → There was the possibility for which the clinical test design using indirect moxibustion was not appropriate.

【Next step】

- → improve the treatment, more prolonged examination

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Step 4
Pilot test

Preventive effects of long term acupuncture and moxibustion treatment on the common cold:
- a pilot test -

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Step 4. Preventive effects of long term acupuncture and moxibustion treatment on the common cold: a pilot test

【Objective】

Investigate that the effects of various acupuncture and moxibustion treatment for symptoms of common cold in long term.

【Design】

Intervention was determined with each center which participated.

An experimental period was set as a long period.

→ Ten to 12 weeks for treatment period, after 4 weeks for progress observation period.

Outcome was the same in all centers (same as previous study).

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Step 4. Preventive effects of long term acupuncture and moxibustion treatment on the common cold: a pilot test

【The outline of each center】

center	Subjects	Intervention	Treatment period	Observation period
A	46	Subcutaneous acupuncture (once a week) bilateral BL11,BL12,Tei-Zen	12 weeks	4 weeks
B	42	Indirect moxibustion (two Pieces at once, once a week or more) GV14	10 weeks	4 weeks
C	72	Direct moxibustion (half-Mox corn, three pieces at once, two time a week) bilateral ST36	12 weeks	4 weeks
D	72	Indirect moxibustion (one piece at once, three times a week or more) bilateral BL12, GV14	8 weeks	4 weeks

In all centers, subjects were students and staffs of school.
Allocated by computer program.

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Step 4. Preventive effects of long term acupuncture and moxibustion treatment on the common cold: a pilot test

【Results: summarized】

center	baseline	K-M test	GLM	Cox regression
A	equality	p=0.648	n.s.	Significant tendency (however, inversion)
B	Non-equality	p=0.259	n.s. (slightly significant tendency)	n.s.
C	equality	p=0.042	n.s.	n.s.
D	equality	p=0.876	n.s. (significant tendency in sex)	n.s. (also sex)

No preventive effects on the common cold were found in all centers.

In center B, allocation problem was found.

In center A, the preventive effect was seen in the control group.

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Conclusion so far

Although the fixed result was obtained as a result of the multi-center RCT to a series of common cold carried out so far, an effective cure was not able to be found out especially.

【Problems so far】

1) The difference of the result seen between centers
2) Subjects bias (students and staffs in a school)
3) The placebo effects in control group (they had no treatment)
4) Validity of a stimulus part and the amount of stimuli

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Next step

Obtain the subject who is inexperienced in acupuncture treatment

→ It's difficult to excluded the various placebo effects and bias from students and/or staffs of acupuncture school.

→ On another side, it is difficult to assemble many patients .

Thinks over the clinical design fundamentally

→ The design which does not need many numbers of subjects be adopted.

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Step 5
Pilot study

Proposal of new test design for acupuncture and moxibustion clinical research:
The trial of the large-scale case accumulation using the single case experimental design

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Step 5. Proposal of new test design for acupuncture and moxibustion clinical research:
The trial of the large-scale case accumulation using the single case experimental design

【Objective】

We used the single case experimental design (n of 1) that the evidence hierarchy has been raised recently.

【Design】

1) Use the n of 1 experimental design
2) The acupuncture and moxibustion treatment effects on pollinosis was examined.
3) The preventive effects of common cold was examined at 1 center.
4) Intervention was determined with each center which participated.
5) Subject was inexperienced in acupuncture treatment.

【Data analysis】

Randomization test (R-test)

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Step 5. Proposal of new test design for acupuncture and moxibustion clinical research:
The trial of the large-scale case accumulation using the single case experimental design

【Progress situation】

In the center which participated in RCT to last time, the examination to pollinosis was carried out separately. It ends and results were under analysis now.

The examination that indirect moxibustion treatment effects on symptom of common cold was carried out at one center with elderly subjects. It ends and results was under analysis now.

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Conclusion

In this workshop, we could not report the result of n-of-1 trials. Based on the previous results and problems of RCT we found, our expectation on the n -of-1design is getting great. We will continue to accumulate the data using n-of-1 experimental design as a useful tool.

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Acupuncture on the neck and shoulder stiffness

-Results and issues found in three successive RCTs from 1995 to 1999-

Tomoyuki Nabeta

JSAM EBM Working-groupOsaka College of Medical Technology

The First Trial in 1995

Patients with complains of neck and shoulder stiffness

↓

Dropout ← I.C.(informed consent)

↓

Random allocation

Real acupuncture group	Minimum acupuncture group
[Needle inserted to the muscle (BL10) and sparrow pecking for inducing de-qi and retained for five minutes.]	[Needle penetrated the skin and removed immediately and simulated as the real acupuncture. (BL10)]

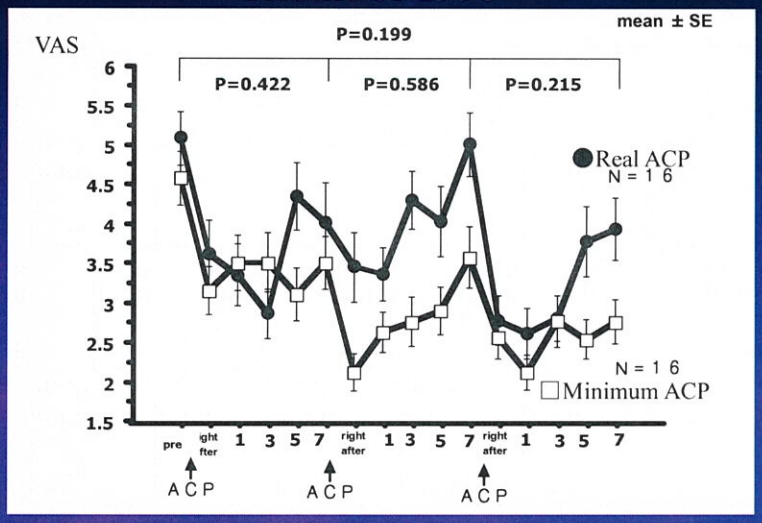
↓

Once a week for 3 session and evaluate by VAS

↓

Assessment of blinding technique

Result of 1995



		anser for patients		
		insert to muscle	penetrate to skin	could not discriminate
allocate group	insert to muscle	26	6	7
	penetrate to skin	15	11	16

Problems extracted from the trial in 1995

Why was real ACP less effective than minimum ACP ?

↓

1)Technique of real ACP was not adequate as used treatment point was fixed in all patients.

2)Minimum ACP was not adequate as control intervention as it decreased VAS score effectively after treatments.

↓

The patients' sensitivity to acupuncture between the groups should be similar uniformly in the next trial.

The Second Trial in 1997

patients complain of neck and shoulder stiffness

↓

Dropout ← I.C. → Beforehand search

↓

Penetrate the skin (BL10 or G12) on once a week for 2 session

↓

VAS decrease more than 50% — VAS decrease less than 50%

↓

I.C. → Dropout ← I.C.

↓

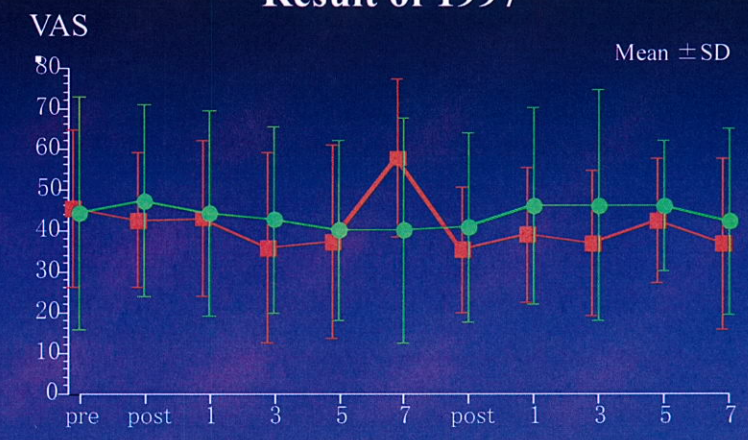
Random allocate — Random allocate — Main trial

Real acupuncture group (BL10 or G12)	Minimum acupuncture group (BL10 or G12)
[Needle inserted to the muscle and sparrow pecking for inducing de-qi]	[Needle penetrated the skin and was removed immediately and simulated as real ACP.]

↓

Once a week for 2 session and evaluate by VAS

Result of 1997

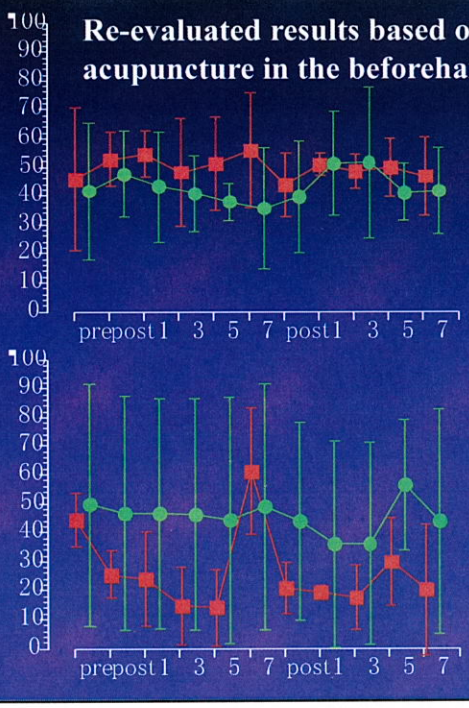


Penetrated the skin n=9 (5men & 4women)

inserted to the muscle n=8 (4men & 4women)

There was no difference between two groups.

Re-evaluated results based on the sensitivity to acupuncture in the beforehand search



Less than 50 % group

- Penetrate the skin
  n=6 5men & 1women
- insert to the muscle
  n=5 3men & 2women

Women/patients=27%

More than 50% group

- Penetrate the skin
  n=3 3women
- insert to the muscle
  n=3 1men & 2women

Women/patients=83%

Problems extracted from the trial in 1997

Why did we not obtain more positive results in the real ACP than the minimum ACP ?

↓

There was sensitivity differences to acupuncture among the patients. Many of women were sensitive.

↓

The fixed technique of real acupuncture in all subjects was not adequate.

↓

Treatment method (points, technique, frequency, etc) must be selected appropriately in each patient in the next trial.

The third trial in 1999

Patients with complains of neck and shoulder stiffness

↓

Distinction of sex

↓

Random allocation

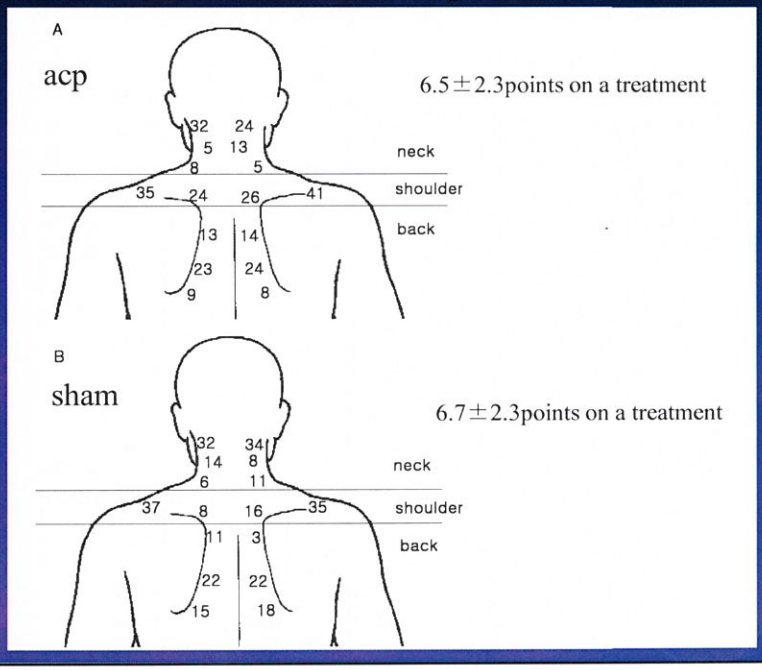
Real acupuncture group [Needle insert to the muscle and sparrow pecking for inducing de qi (tender points) and retained for five minutes.]	Sham acupuncture group [Sham needle with blunt tip was used with gesture of insertion to the muscle but not penetrated the skin (tender points).]

Once a week for 3 session and evaluate by VAS

↓

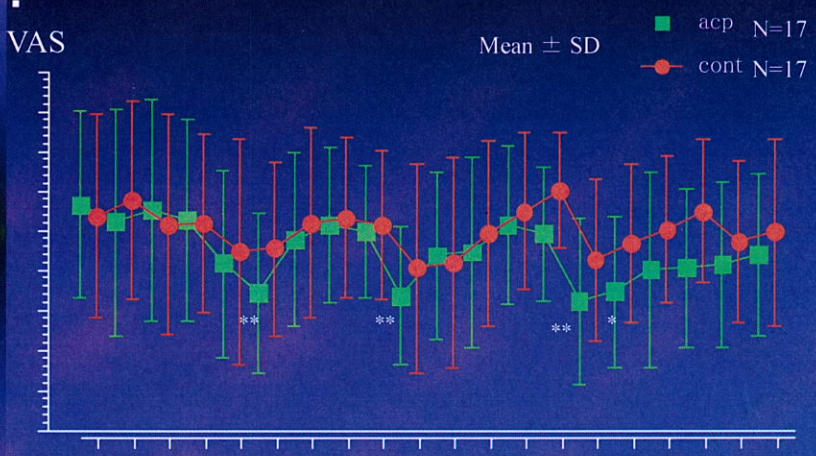
Assessment of blinding technique

Number of tender points



Result of 1999

Dunnett's multiple test * $p<0.05$ ** $p<0.01$



Result of blind technique

chi-square=0.6 p=0.74

	inserted to muscle	not penetrated skin	could not discriminate
AG	11	4	2
SG	9	6	2

Sham needle in this trial was effective.

Result of 1999 and Conclusions from three trials

Acupuncture treatment in 1999 trial was effective for improve quality of life of patients because there was statistical difference after treatment in real ACP.

↓

If researchers design the clinical trial of acupuncture it must select the most appropriate method of treatment for a patient.

Design of pollinosises trial in 2004

Recruit subjects that have not experience acupuncture treatment
(except for acupuncture students, medical school students ,these friends and these families)

↓

informed consent→ drop out

↓

prescription

↓

Random allocate

↓ ↓

having only tea — tea and moxibustion treatment

↓ ↓

having tea every day — subjects distribute three treatment type from prescription

treatment1 treatment2 treatment 3

↓ ↓ ↓

moxibustion treatment
(more than twice a week and having tea everyday)

diary record

← symptom examination every two week
← if symptom change others type, teach treatment again

send diary and final examination

Learning from the multi-center randomized controlled trial on acupuncture for lumbago

Tsukuba College of Technology Clinic
Hiroshi TSUKAYAMA

Aim of this presentation

- Introducing the first multi-center randomized controlled trial (RCT) for lumbago in Japan supported by "*Foundation for Training and Licensure Examination In Anma-Massage-Acupressure, Acupuncture and Moxibustion*".
- Illustrating requirement for conducting multi-center acupuncture trials in Japan.
  - We call this study "AHAKI Foundation lumbago study" in this presentation.

June-11 / 2004

AHAKI Foundation lumbago study

- AHAKI Foundation lumbago studies were planned as a model case of multi-center randomized controlled trial in Japan by the Foundation.
- These studies were performed at clinical facilities in 4 universities or colleges in Japan from 1995 until 1999.
- The studies consisted of two trials.
  - Study I (1995 - 1996)
  - Study II (1996 - 1999)

Study I – research organization

- The foundation asked researchers of 4 research institutions to conduct “high quality clinical study of acupuncture for lumbago”.
  - Tadasu MATSUMOTO
    - School of Acupuncture and Moxibustion, Meiji University of Oriental Medicine (MUOM)
  - Masazumi KAWAMOTO
    - Department of the Clinic of Acupuncture, Kansai College of Oriental Medicine (KCOM)
  - Koji ITO
    - Department of Medicine and Physical Therapy, Faculty of Medicine, University of Tokyo (UT)
  - Tomomi SAKAI
    - Department of Acupuncture, Tsukuba College of Technology (TCT)

Study I – basic design

- Objective
  - To compare semi-standardized acupuncture with other conservative treatment
- Design
  - Multi-center parallel RCT
- Schedule
  - Two weeks treatment period
  - No follow-up observation
- Subject
  - Non-specific low back pain patients (without sciatica)
  - Target sample size: 100 subjects

Study I – characteristics

- A brief preparation period (2 months)
- Consideration for practicability.
  - Subjects selection
    - No limitation about duration from onset or age
  - Intervention
    - Acupuncture stimulation technique and detail was undefined.
    - Control interventions were chosen in each institution
  - Design
    - Room to choice design depending on the environments of each institution
    - A short-term working scheme
      - No follow-up observation

Study I – implementation (design)

- Failed to conduct uniformed multi-center RCT.
  - The protocol was implemented into different procedure by each institution.
    - Difference in design, intervention and randomization process

Institution	Design	Acupuncture	Control	Allocation	Result
MUOM	no control	manual Ac.	no control	no	
KCOM	two independent studies without control	electro Ac.	poultice	no	favor to acupuncture
UT	parallel comparison	Manual or electro Ac.	drug Tx. (include Kampo)	random (envelop method)	no difference
TCT	parallel comparison	manual Ac.	traction hot-pack	quasi-random (alternation)	favor to acupuncture

Study I – implementation (subject)

- The number of subject recruited did not reach the target.
  - Because of difficulty in taking informed consent, including possibility of non-acupuncture intervention, from outpatients at acupuncture clinic.
- Subject were heterogeneous among institutions.
  - Difference in age, stage, level of disability or population.

	Group	No.	Age	Mean duration from onset (months)	Informed Consent	population
MUOM	Ac.	10	46-86 years	50.9±153.2	oral	outpatient
KCOM	Ac.	12	19-36 years	31.3±35.9	written	student
	Cont.	6	19-48 years			
UT	Ac.	14	14-79 years	45.5±92.5	oral	outpatient
	Cont.	12	34-66 years	11.0±25.5		
TCT	Ac.	8	18-60 years	1.6±3.0	oral	applicant
	Cont.	9	18-66 years	3.9±5.1		

Study II – research organization

- The Foundation organized a working committee, which included clinical trial expert, orthopedists and acupuncture researchers from the following institutions:
  - Tsukuba College of Technology
  - Meiji University of Oriental Medicine
  - Kansai College of Oriental Medicine
  - University of Tokyo
  - Tokyo Medical and Dental University
- The member's commitment to the study did not seemed to be spontaneous or based on own interest.
  - Financial support should be one of incentives to commitment.

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Study II – research organization

- The committee was managed under strong leadership of the clinical trial expert.
  - The working group held meeting for designing protocol frequently.
    - It functioned as a training program for acupuncture researchers.
    - The meetings made common knowledge among the members.
  - The committee clearly defined role and responsibility of each member
    - Chair
    - Writing protocol
      - setting endpoint, making procedure of intervention and supervision
    - Designing informed consent form and explanatory leaflet
    - Designing of leaflet for patient recruitment
    - Research coordinate in each institutions
    - Monitoring and data management
    - Allocation (Controller)
    - Data analysis

Study II – basic design

- Objective
  - To compare electro-acupuncture with transcutaneous electrical nerve stimulation (TENS) as different type of electrodes
- Design
  - Multi-center parallel RCT
- Schedule
  - One week run-in period
  - Two weeks treatment period
  - No follow-up observation
- Subject
  - Non-specific low back pain patients (without sciatica)
  - Recruit applicants by public information
  - Target sample size: 80 subjects

Study II – characteristics

- Introducing the methods of quality management
  - Concealed allocation
  - Monitoring and data management
  - Trial coordination
- Simple interventions
  - Treatment regimen: twice a week for two weeks
  - Electro-acupuncture: Semi-standardized procedure
    - Two needling points were chosen bilaterally around predefined 3 points in lumbar part by palpation.
  - Control: TENS in the same manner as electro-acupuncture
- Outcomes
  - Evaluate by independent investigator

Study II – implementation

- Implementation of the protocol was fully controlled.
  - Powerful leadership and clear concept led the study.
    - Clear definition of the role and responsibility of each working group member.
    - Training and education of clinical trial by frequent meeting.
  - The introduction of quality management was success.
    - Monitoring for allocation, research setting and implementation process in each institutions
    - Trial coordination in each institution
    - Data management
    - Concealed allocation

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Study II – implementation

- Multidisciplinary collaboration supported quality of trial
  - Clinical trial expert
  - Clinical medicine expert
  - Acupuncture researchers
    - But luck of collaboration with trial statistician
      - Statistical flaw was pointed out.
- Support for research money made easy to conduct multi-center trial
  - Conducting multi-center RCT need a lot of money.
  - Financial support could be one of incentives to researchers.

Study II – problems

- Failed to confirm the hypothesis.
  - There was no significant difference in any of the outcomes.
    - Appropriate acupuncture procedure should be based on
      - Pre-existing evidence
      - Review of standard texts
      - Research of usual practice in reality
    - Flaw in outcome measurement tool was pointed out.
      - Standard measurement tools in conventional medicine were not always based on evidence.
      - Measurement tools should be validated in each language
- The number of subject recruited did not reach the target.
  - Difficulty of patient recruitment from outpatient of acupuncture clinic has not been solved in Japan.
    - Collaboration with conventional medical system
    - Advertising of patients recruitment
      - Research money may aid to solve this problem.

Requirement for conducting multi-center trial -1

- Clear concepts which are really accepted and shared by all of the working group member are needed in acupuncture multi-center trial.
  - Top-down model need powerful leadership, clear strategy and incentive for researchers.
  - Training of clinical trial is needed.
    - Convincing meeting aid to make common knowledge.
  - Spontaneous commitment to study group is desirable.
- Conducting RCT need a lot of cost.
  - Financial support is needed to conduct multi-center RCT in multi-disciplinary collaboration.

Requirement for conducting multi-center trial - 2

- Multidisciplinary collaboration is recommended in phase III RCT
  - Clinical trial expert
  - Clinical medicine expert
  - Bio-statistics expert
  - Acupuncture researchers
- Clear definition of the role and responsibility of each working group member were needed in multi-center trial
- Concept of quality control is useful in multi-center trial
  - Monitoring for allocation, research setting and implementation process in each institutions (monitor)
  - Trial coordination in each institution (coordinator)
  - Data management (data manager)
  - Concealed allocation (independent controller)

Requirement for conducting multi-center trial - 3

- Requirement in trial design
  - Appropriate acupuncture procedure should be based on
    - Pre-existing evidence
    - Review of standard texts
    - Research of usual practice in reality
  - Outcome measurements should be validated in each language
- Difficulty of patient recruitment from outpatient of acupuncture clinic has not been solved in Japan.
  - Collaborations with conventional medical system
  - Advertising of patients recruitment
- Consideration for the ethical issue
  - An approval from ethical committee

Is It possible To Apply Our Placebo Auricular Acupuncture Device to Korean?
<Preliminary study>

-The Effects of Placebo Auricular Acupuncture through Single-blind Method and Randomized Controlled Trial-

Seo Jung-chul

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College of Oriental Medicine,
Dae-Gu Haany University, Korea

Purpose

1. To find out whether our placebo auricular acupuncture device is able to be applied as an appropriate control group for needle insertion.

2. To find out whether acupuncture experience affects acupuncture sensation

Design

- RCT (Randomized Controlled Trial)

1. Randomization

- Acupuncture order
  - A : right real – left placebo
  - B : left placebo – right real
  - C : left real – right placebo
  - D : right placebo – left real

block randomization

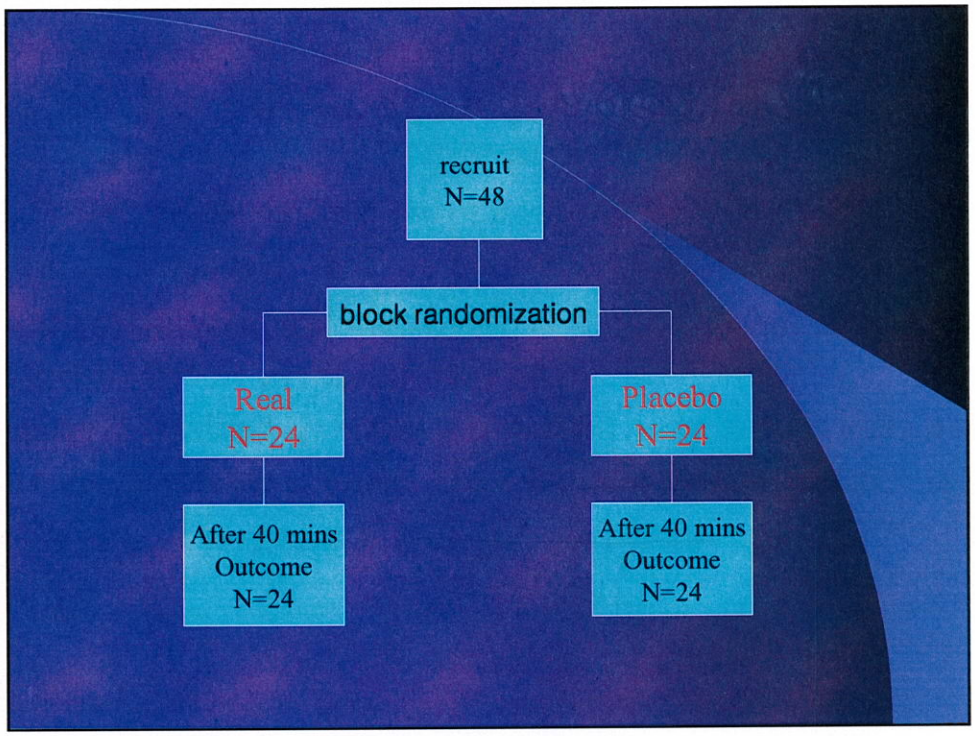
A;B;C;D=1;1;1;1

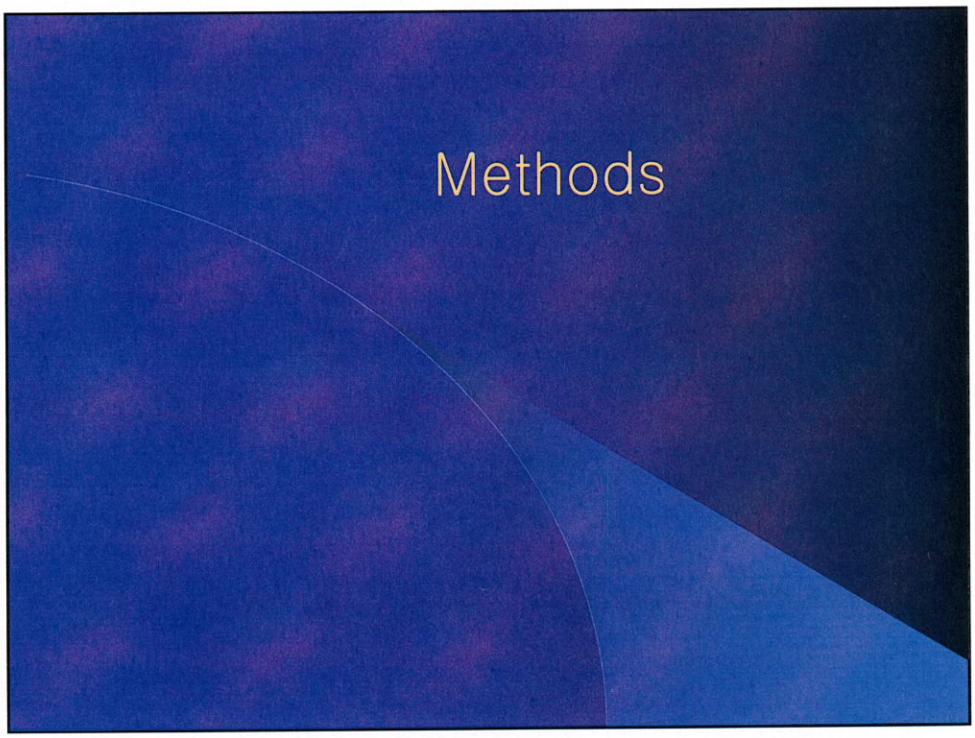
- block size ; 4
- permutation ; 4! = 4×3×2=24
- ABCD, ABDC, BACD, ...total 24 block
- using table of random numbers
- sampling 12 blocks without replacement
- matching with each subject's ID number
- ABDC, ABCD,.....BACD
- 1.....48

2. Single-blind method

→ Only physician knows

→ Subjects or other investigators doesn't know


recruit
N=48
block randomization
Real
N=24
Placebo
N=24
After 40 mins
Outcome
N=24
After 40 mins
Outcome
N=24


Methods

Subjects

- 48 individuals recruited from the staffs of Oriental Medical hospital of the Daegu Haany University.
- They had no sign of disease and felt healthy.

→ men 21, women 27
average age 29.1±6.7

Pilot study

1. Test of acupuncture points
- According to Margolin's study,
- : sympathetic, lung, liver and shen men.
- After pressed in sympathetic, every subjects correctly identified which ear received real acupuncture.
- → exclude sympathetic
- : lung, liver and shen men.

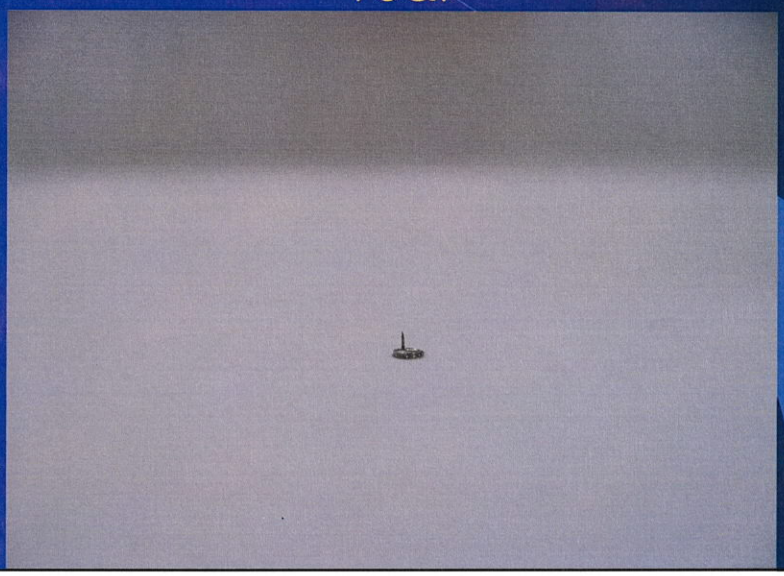
2. Test of acupuncture press strength

- When pressed in strong strength degree, all subjects correctly identified which ear received real acupuncture.
- Weak strength degree – no insertion
- medium strength degree – 8 subjects correctly identified which ear received real acupuncture.
- → with pressure strength in medium degree

Intervention

1. Real auricular acupuncture device
   : manufactured in Heng-lim Acupuncture Inc., Korea.
→ sharp tip of needle, needle is 2mm long,
→ can be inserted when pressed.

real



2. Placebo auricular acupuncture device

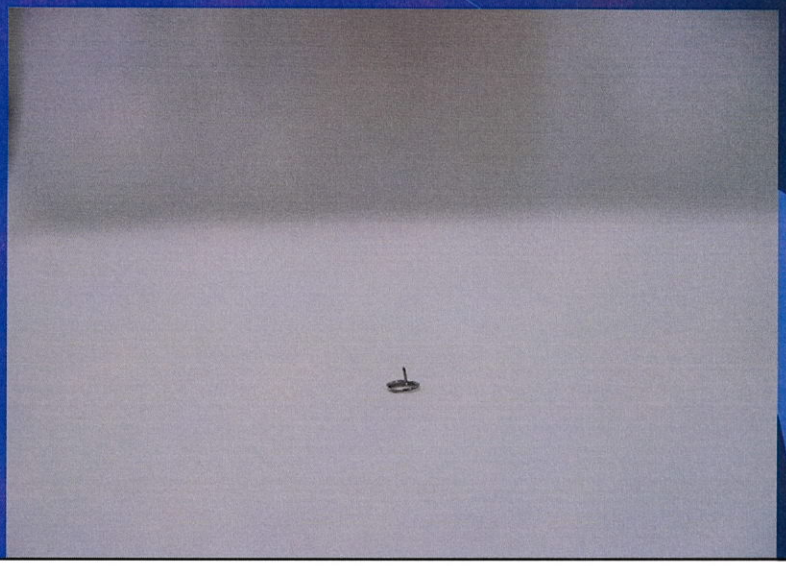
: cut real auricular acupuncture by scissors.

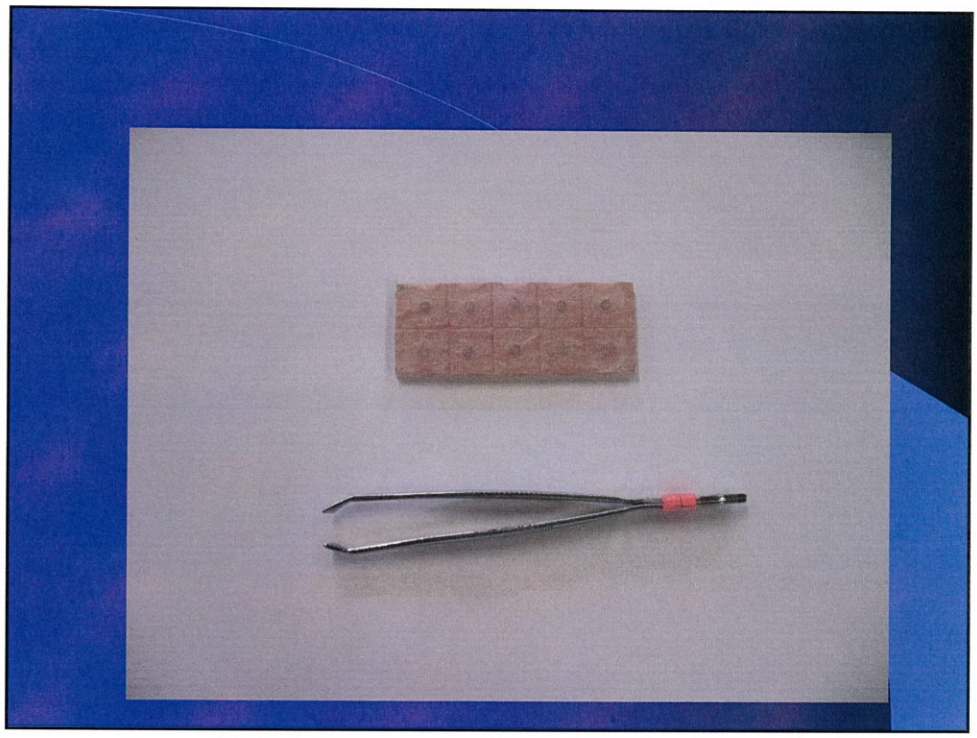
devices were performed by one person, to be the consistency of study.

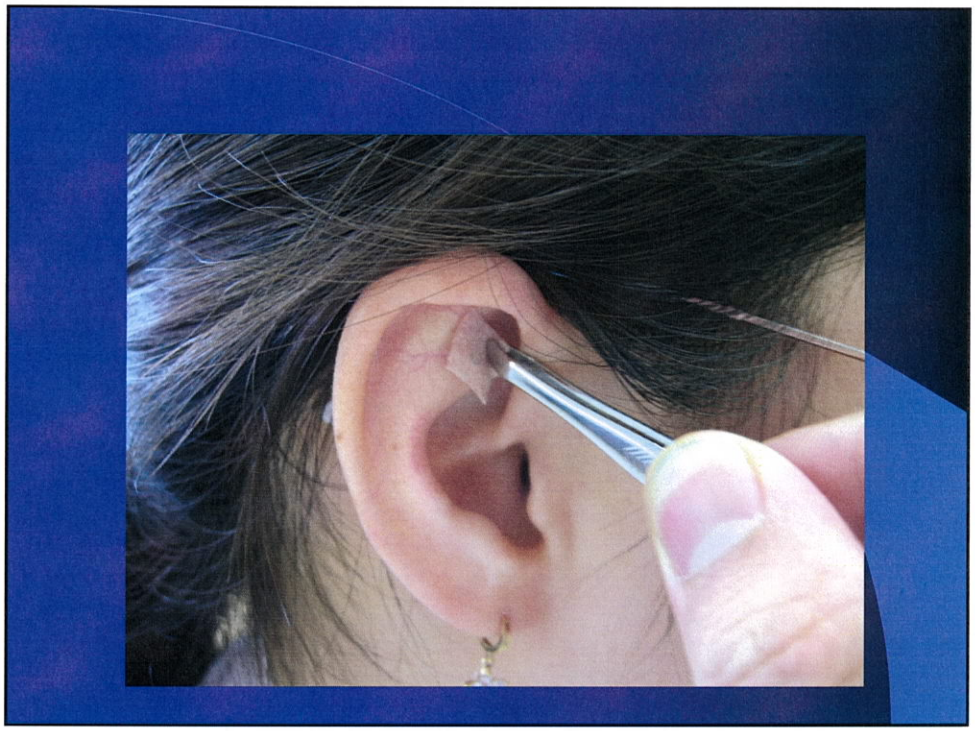
→ dull tip of needle, needle is 1mm long,

→ can't be inserted when pressed,

placebo







Outcome

Item of Questionnaire & Results Variable

Five dependent measures
- warmth,
- fullness,
- pain,
- activity,
- radiating sensation

Sensation degree points
: ① nothing = 0 ② a little =1 ③ so so =2
④ a lot =3 ⑤ much =4

Statistics

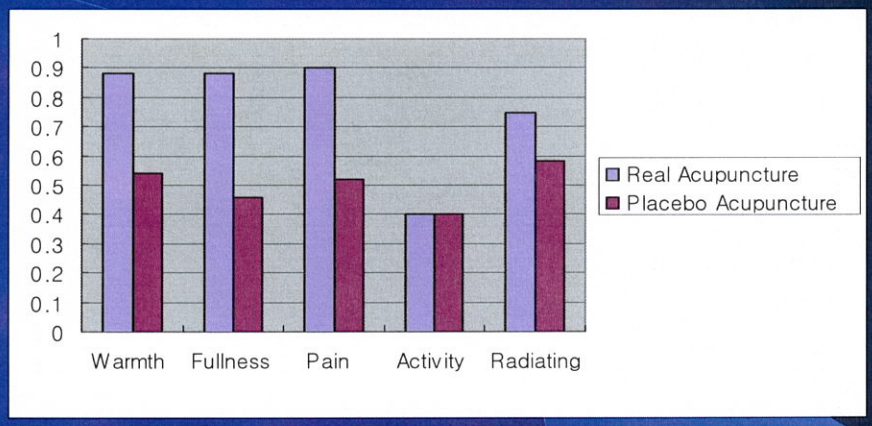
SAS(version 8.1),

paired two-tailed *t*-test
Chi-square
Pearson's correlation

the summary of data is described and proved by the mean and standard deviation,
$p < 0.05$.

Results 1
- placebo recognition

The Acupuncture Sensation of Real and Placebo Acupuncture on Each Item

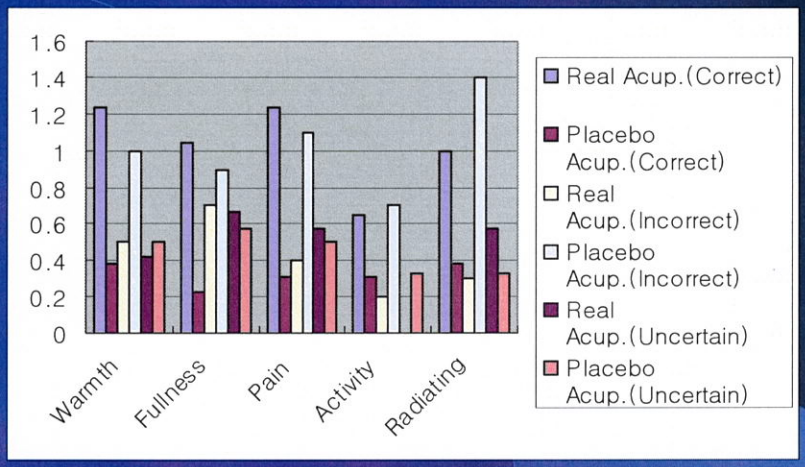


Ability to Differentiate Real and Placebo Acupuncture

	Real Acup.	Placebo Acup.	Total
Thinking it as the real	26	10	36
Thinking it as the placebo	10	26	36
Uncertain	12	12	24
Total	48	48	96

P-value, Pr>chi^2 = 0.0008

The Acupuncture Sensation **for Subjects** who could and could not Differentiate between Real and Placebo Acupuncture and those who were uncertain



Correlation Matrix between the Items on the Acupuncture Effects

		Real Acupuncture					Placebo Acupuncture				
		W	F	P	A	R	W	F	P	A	R
Real Acupuncture	W	1.00									
	F	0.57**	1.00								
	P	0.38*	0.24	1.00							
	A	0.66**	0.43*	0.40*	1.00						
	R	0.48**	0.41*	0.43*	0.55**	1.00					
Placebo Acupuncture	W	0.12	0.04	−0.23	−0.20	−0.02	1.00				
	F	−0.09	0.15	−0.10	0.02	0.18	0.37	1.00			
	P	−0.23	−0.13	0.02	−0.11	0.05	0.22	0.16	1.00		
	A	−0.11	0.01	0.09	0.09	0.27	0.36	0.67**	0.30	1.00	
	R	−0.21	0.17	−0.17	0.03	0.03	0.15	0.40**	0.41*	0.28	1.00

W: Warmth, F: Fullness, P: Pain, A: Activity, R: Radiating
Values are Pearson's correlation coefficients.
* P<0.01, ** P<0.001

Results 2
– acupuncture experience

Experienced Acupuncture Recipients (N=23)

→ people who had little or no previous acupuncture experience

: under 2 times

average time 0.3±0.62

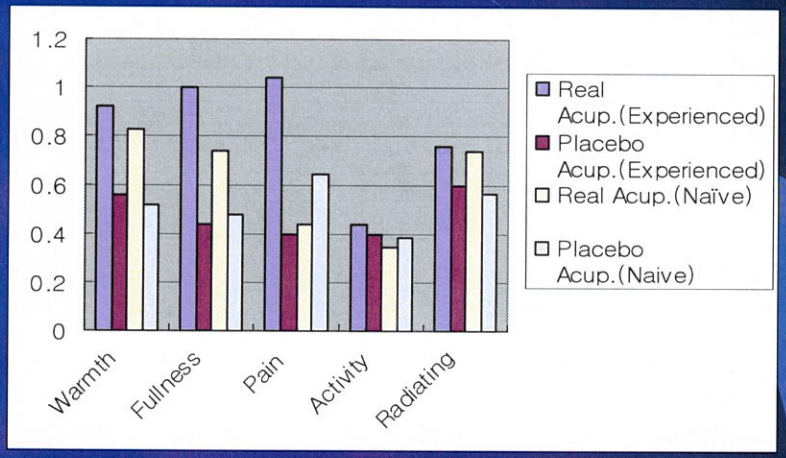
Naive Acupuncture Recipients (N=25)

→ people who had previous acupuncture experience

: more than 3 times

average time 23.4±25.2

The Acupuncture Sensation for Experienced and Naive Acupuncture Recipients.



Ability to Differentiate Real and Placebo Acupuncture for Naive and Experienced Acupuncture Recipients

	Correct	Incorrect	Uncertain	Total
Naive	9	6	8	23
Experienced	17	4	4	25
Total	26	10	12	48

P-value, Pr>chi^2 = 0.128

Discussion

Placebo

- 1. Must be Indistinguishable from the real treatment.
- 2. Must be Inactive
- -psychological effect ; Yes !
- -physiological effect ; No !

cf. But some one says it is impossible in acupuncture

The Need of Placebo Acupuncture

For the proof of effects of acupuncture

- without satisfactory placebo to acupuncture
- it is difficult to differentiate the effect of acupuncture.

→To measure the effect, a placebo method of needling is required.

with the same psychological impact as actual needling.

Methods of placebo acupuncture -1

- <points>
- Sham point
- Needling at inappropriate points

- → easy to make placebo
- → but not so satisfactory investigation

Methods of placebo acupuncture -2

- <stimulation>
- Sham TENS
- Sham electrostimulation
- Pricking with blunt needle
- Blunted needle with a foam to position the needle
- Minimal acupuncture

- → satisfactory investigation
- → but difficut to make placebo

Our Method of placebo acupuncture

- <stimulation>

- Blunted needle acupuncture

Investigations of Placebo Auricular Acupuncture -1

- Margolin's Investigation in 1993 :
- For the sham acupoint
- with the same acupuncture needle,

Ability to Differentiate Real and Placebo Acupuncture

-sham acupoint - Margolin, 1993

	Real Acup.	Placebo Acup.	Total
Thinking it as the real	14	22	36
Thinking it as the placebo	22	14	36
Uncertain	12	12	24
Total	48	48	96

Investigations of Placebo Auricular Acupuncture – 2

- Park's Investigation in 2002 :
- For the same acupoint
- with the placebo acupuncture needle
- just press instead of penetrating the skin,

Ability to Differentiate Real and Placebo Acupuncture – placebo acupuncture needle, Park, 2002, English

	Real Acup.	Placebo Acup.	Total
Thinking it as the real	11	9	20
Thinking it as the placebo	0	0	0
Uncertain	18	20	38
Total	29	29	58

Ability to Differentiate Real and Placebo Acupuncture – our placebo acupuncture needle, Korean

	Real Acup.	Placebo Acup.	Total
Thinking it as the real	26	10	36
Thinking it as the placebo	10	26	36
Uncertain	12	12	24
Total	48	48	96

P-value, Pr>chi^2 = 0.0008

WHY different results ?

- 1. Difference of device ?
- 2. Racial or cultural difference ?

Limitation

- 1. selection bias
- – subjects in the same office
- – need to be selected in multi center
- 2. Irregular device
- – not by scissors
- – need to be made in factory
- 3. sample size
- – small
- – need to be calculated and large

Conclusion

- **1. We found that our placebo auricular acupuncture device is not able to be applied**
- **2. We found that acupuncture experience affected acupuncture sensation response.**
- **3. We found that acupuncture experience didn't affected placebo**

Suggestion

- 1. Further study is needed for new placebo auricular acupuncture device.
- 2. About placebo recognition racial or cultural difference between Korean and English needs to be considered.
- 3. Need to consider acupuncture experience

Randomized Controlled Double Blind Study of Bee Venom Therapy on Rheumatoid Arthritis

Lee Sang-hoon. Hong Seung-jae. Kim Su-young
Yang Hyung-in, Choi Do-young, Lee Doo-ik
Lee Yun-ho, Lee Jae-dong

Research Group of Pain and Neuroscience
East-West Medical Research Institute
Kyung Hee University, Seoul, Korea

Background (1)

1) The history of bee venom therapy

- *The tomb of Mawangdui, BC 168*

  Collected bee venom was used as a ***skin patch*** to enhance the vitality.

- *Hippocrates (460-377 BC)*

  He used bee venom and called it ***Arcanum*** - a very mysterious remedy.

Background (2)

2) Animal study of bee venom therapy

- *Acute arthritis model study*

  Bee venom injection at specific acupoint had *anti-inflammatory effects* on adjuvant-induced arthritis rats.

  (Lee JD et al., Pain, 2001)

- *Collagen-induced chronic arthritis model study*

  Bee Venom injection at specific acupoint showed significant *reduction of arthritic changes* in collagen-induced arthritis mice.

  (Lee JD et al., Acup.&Mox., 2002)

Background (3)

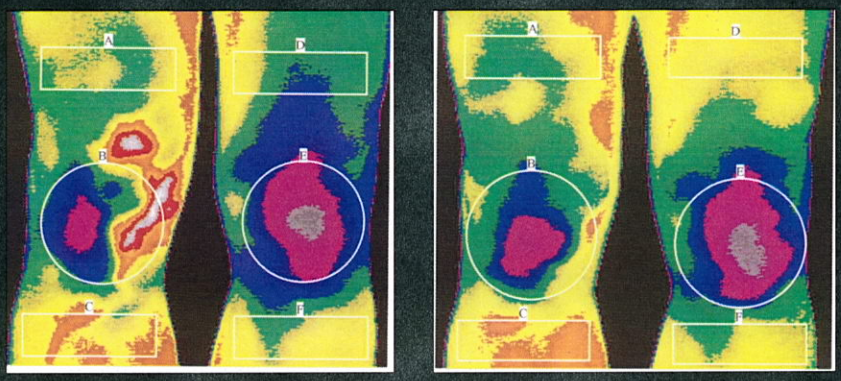
3) Human study of bee venom therapy

- Bee venom therapy has been used to *relieve pain* and to *control inflammatory diseases* such as *rheumatoid arthritis.*

  (Billingham et al., Nature, 1973)

■ Bee venom therapy has an ***analgesic effect*** on ***knee osteoarthritis.***

(Lee JD et al., Am J Chin Med, 2001)



Before

After

5

❑ Objective

▪ In order to evaluate the effects of bee venom therapy on the ***symptoms*** and ***quality of life*** in rheumatoid arthritis patients as a ***randomized controlled trial.***

6

Methods - Subjects

- Subjects : Rheumatoid arthritis patients
- Recruited by newspapers and internet
- Confirmed by Rheumatologist
- Randomized by Coordinator
- Grouping : Bee venom treated group (BVT) (n=50)
  Control group (n=50)
- Randomized Controlled Trial

Methods - Exclusion Criteria

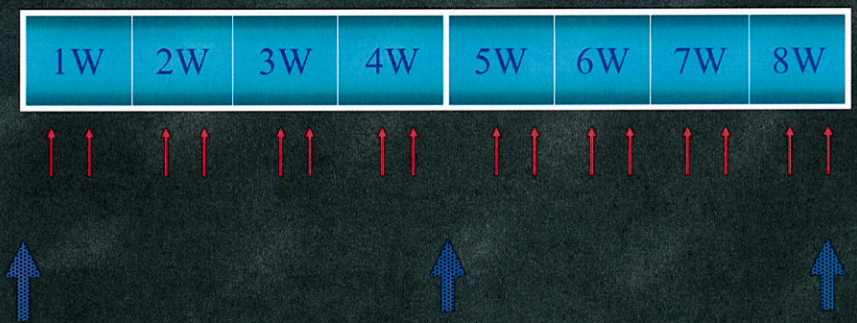
- Allergy to bee venom
- Other advanced systemic diseases
  (Cardiovascular, DM)
- Infection
- Abnormal lab findings (LFTs, CBC, BUN/Cr, UA)
- Other connective or periarticular diseases
- Intraarticular steroid injections within the last 6 weeks.

Methods - Treatment

- Treatment
  - BVT group
    Bee venom (0.1~1cc, 1:3000 dilution)
    Acupoints around the involved joints area
  - Control group
    Normal saline (0.1~1cc)
    Acupoints around the involved joints area

9

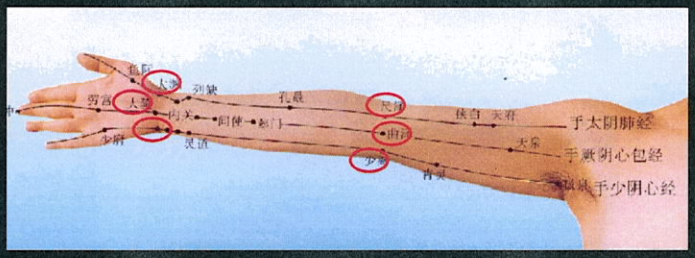
Subjects were treated twice a week for 8 weeks

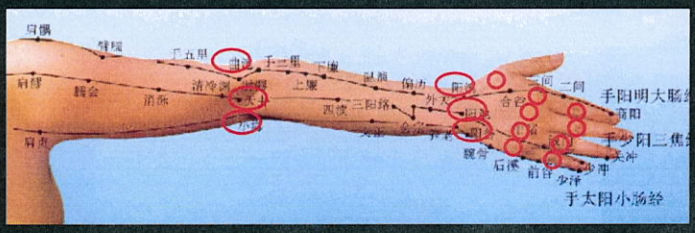


Clinical and Laboratory Assessments

10

❑ Major Acupoints of Upper Extremities





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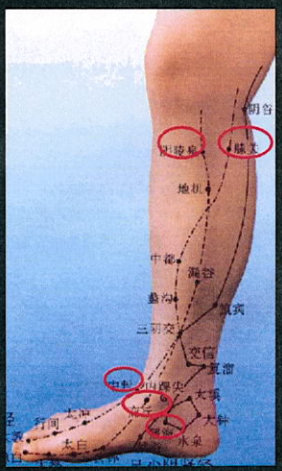
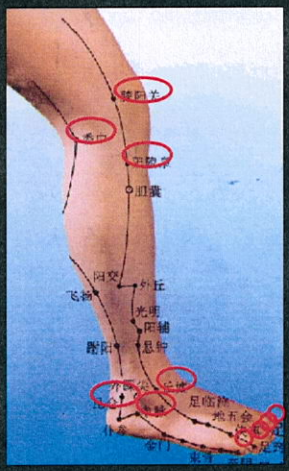
❑ Major Acupoints of Lower Extremities





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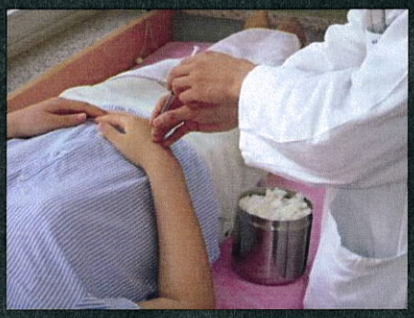
Treatment by KMD



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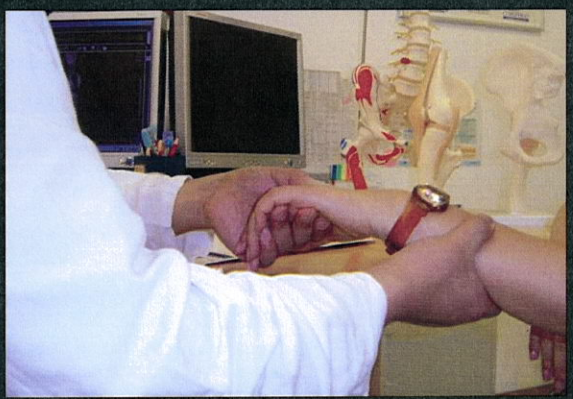
Assessment by Rheumatologist



14

- **Clinical Assessment**
  - Tender Joint Count
  - Swollen Joint Count
  - Morning Stiffness
  - Pain (Visual Analog Scale)
  - Health Assessment Questionnaire (HAQ)
- **Laboratory Assessment**
  - Erythrocyte Sedimentation Rate
  - C-Reactive Protein

15

Demographic and Clinical Characteristics of Patients at Baseline

	BVT group (N=37)	Control group (N=32)
Age (yr)	49.2 ± 9.6	47.3 ± 8.9
Female (%)	90.3	89.7
Disease duration (yr)	9.2 ± 7.0	7.3 ± 4.6
Pre-treatment DMARDs	2.0 ± 0.7	2.1 ± 0.7
Tender Joint Count	5.2 ± 3.3	4.8 ± 2.7
Swollen Joint Count	4.7 ± 3.3	4.5 ± 2.6
Morning Stiffness (Gr0-5)	3.6 ± 4.8	3.4 ± 1.7
Pain (VAS 0-100)	65.5 ± 20.1	64.3 ± 28.6
HAQ	1.2 ± 0.7	0.9 ± 0.5
CRP (mg/dl)	1.7 ± 3.4	1.5 ± 1.3
ESR (mm/h)	31.6 ± 14.4	30.9 ± 17.7

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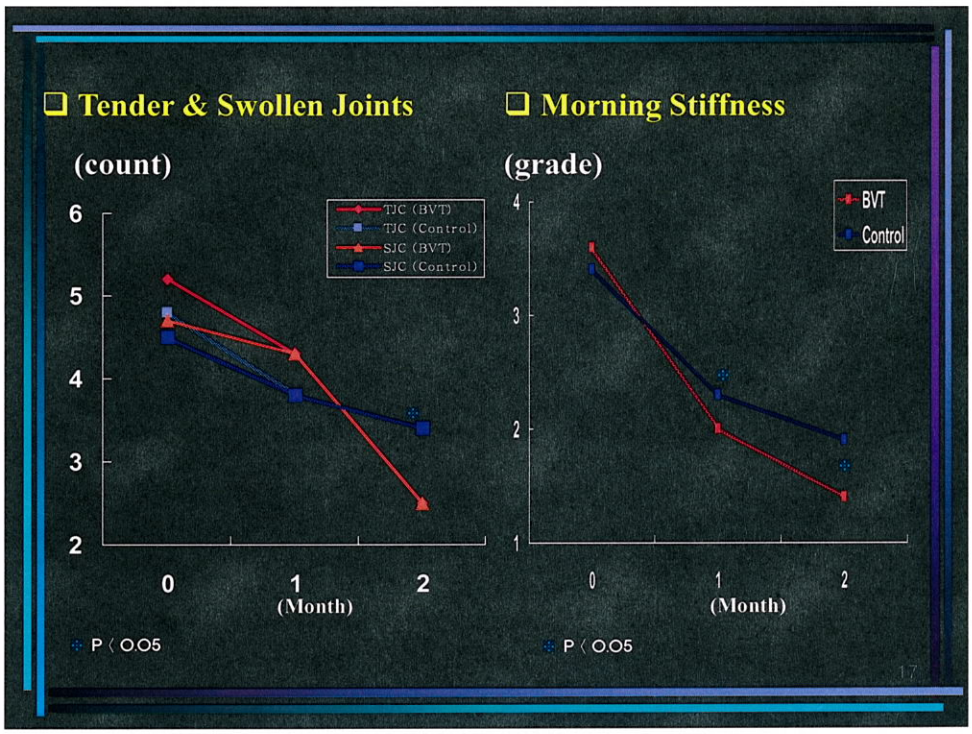
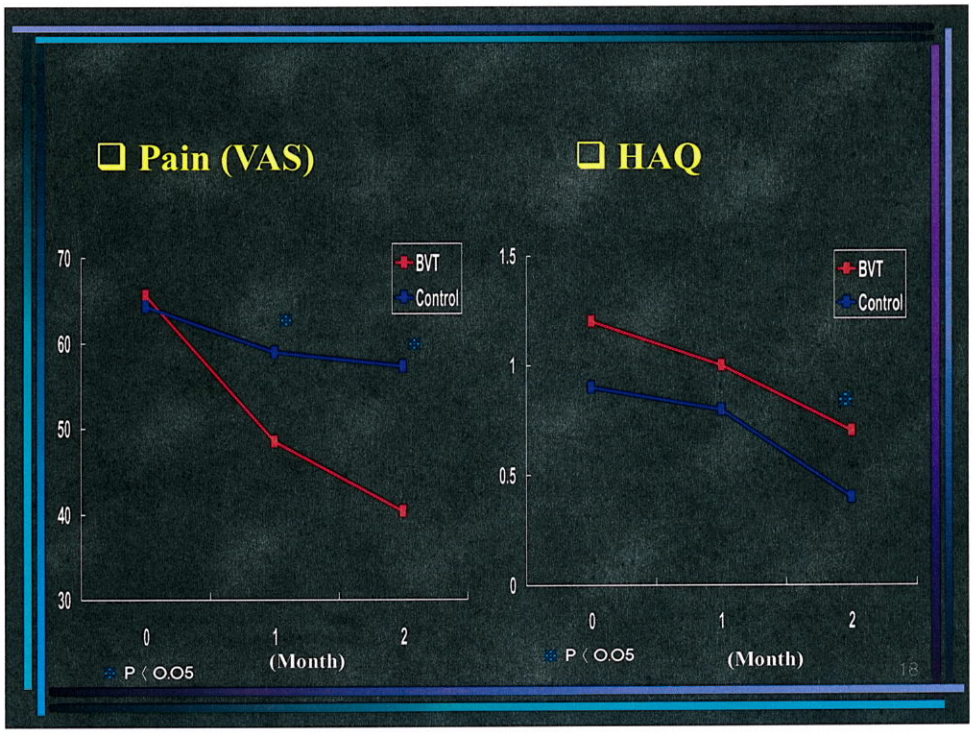
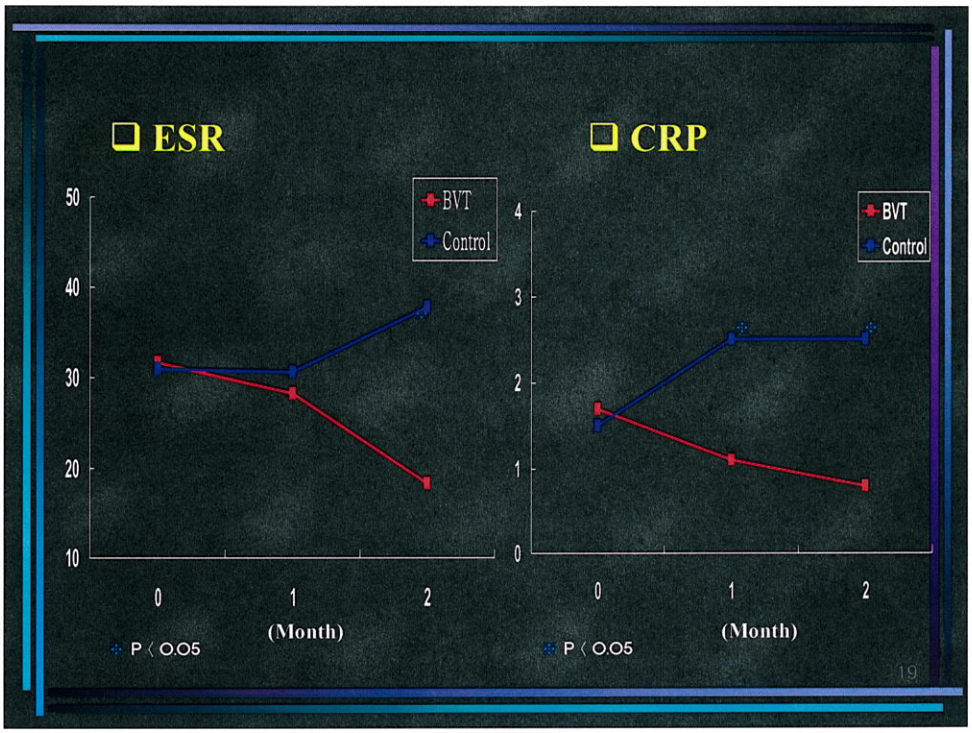

❑ Tender & Swollen Joints
(count)
TJC (BVT)
TJC (Control)
SJC (BVT)
SJC (Control)
6
5
4
3
2
0
1
2
(Month)
P < 0.05
❑ Morning Stiffness
(grade)
BVT
Control
4
3
2
1
0
1
2
(Month)
P < 0.05
17


❑ Pain (VAS)
BVT
Control
70
60
50
40
30
0
1
2
(Month)
P < 0.05
❑ HAQ
BVT
Control
1.5
1
0.5
0
0
1
2
(Month)
P < 0.05
18



Side-effects

- Minor side effects
  Localized edema, erythema, itching, dizziness, etc.
- No significant generalized side effect
  Anaphylaxis

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❑ Conclusion

- Bee venom therapy can improve the *clinical symptoms* and *signs* as well as *quality of life* in RA patients more than control group.
- *Further studies* of a variety of bee venom effects are necessary in the future.

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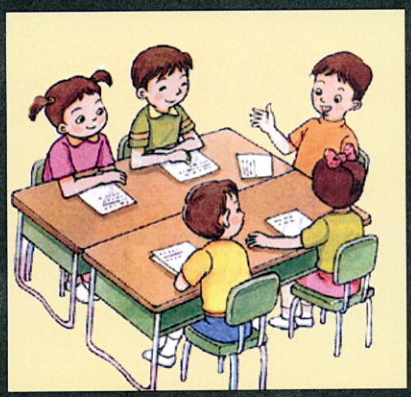
❑ Discussion



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❑ Difficulties in Clinical Studies of Acupuncture

- Low Compliance & Many Dropouts
  - Reasons: Frequent Visits, Long Distance…
    → **Multi-Center Trial**
- Needling Pain & Minor Side-Effects
  → **Development of Safer and More Comfortable Method**

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Thank you !!!

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Antispastic Effect of Electroacupuncture and Moxibustion in Stroke Patients - *AJCM 2003, 31(3)* -

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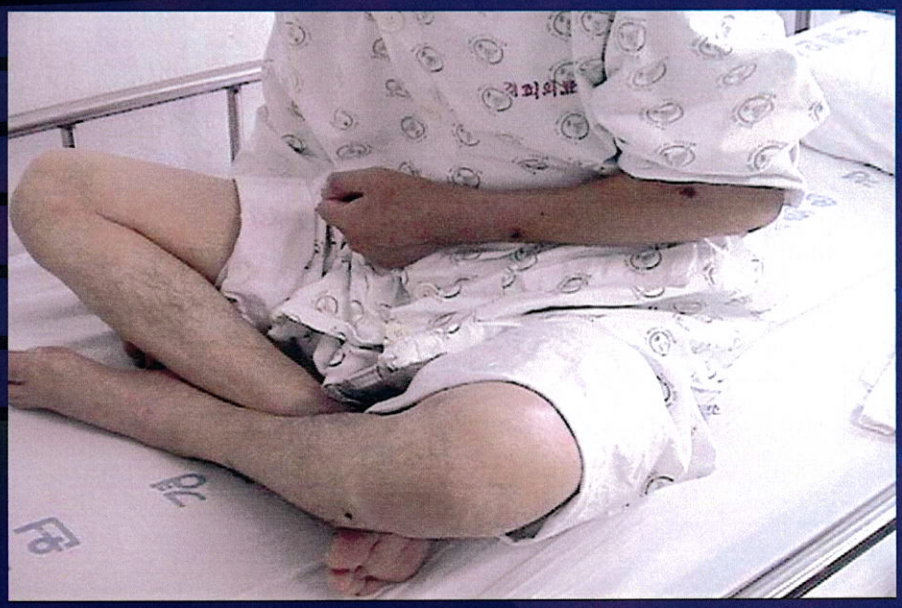


Spasticity in Patients with Stroke

- Common complication
- May interfere with voluntary motor function in patients with residual muscle power
- Causes difficulties with activities of daily living and muscle pain or discomfort

Acupuncture & Moxibustion vs. Spasticity

◆ Acupuncture & electroacupuncture have effectiveness in treating spasticity

- Paek et al. 1997, *J. Korean Acad. Rehab. Med.*
- Yu et al. 1995, *Chin. Med. J.*
- You et al. 1999, *J. Korea Acupuncture & Moxibustion Society*
- Kim. 2000, *J. Korea Acupuncture & Moxibustion Society*

- Arguments as to whether they have cumulative effect

◆ Few data about the effect of Mosibustion on spasticity

Objectives

- To determine if Electroacupuncture and Moxibustion can reduce spasticity due to stroke, if so then for how long it can continue
- To determine if they can maintain reduced spasticity when they were applied repeatedly

Study design

- Assessor-blind
- Randomized (by table of random numbers)
- Controlled (no intervention control)
- Trial

Subjects

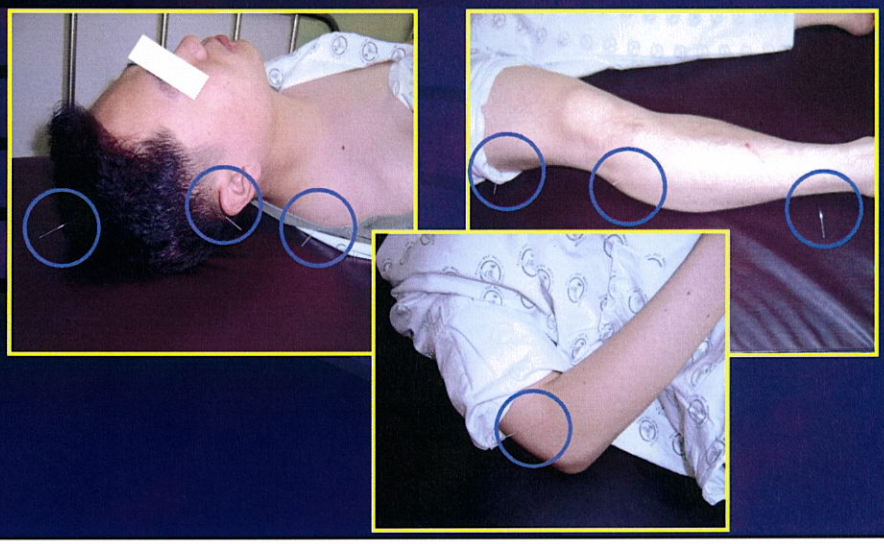
- 35 stroke patients with elbow spasticity
- At least 5 weeks after the onset of stroke
- ≥ 2 on Modified Ashworth Scale

- Randomized & allocated to 3 groups
  - Electroacupuncture (EA) group
  - Moxibustion (Mox) group
  - Control group

Common Treatment for 3 groups

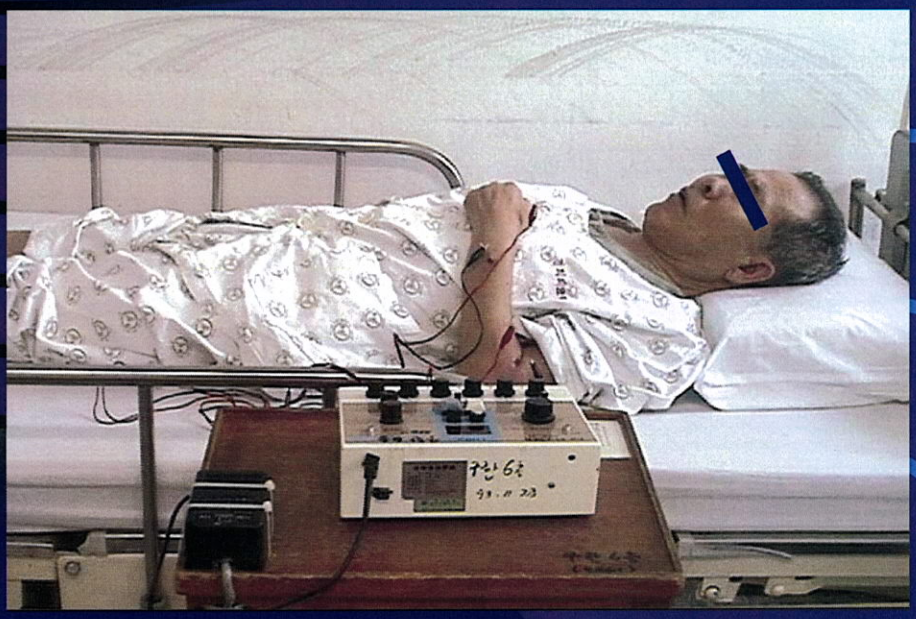
- All of 3 groups
  - Routine acupuncture therapy for stroke once a day
  - Conventional stroke rehabilitation
  - Not allowed nerve block or surgical operation
- Control group was given only these treatments
  - no special treatment for spasticity

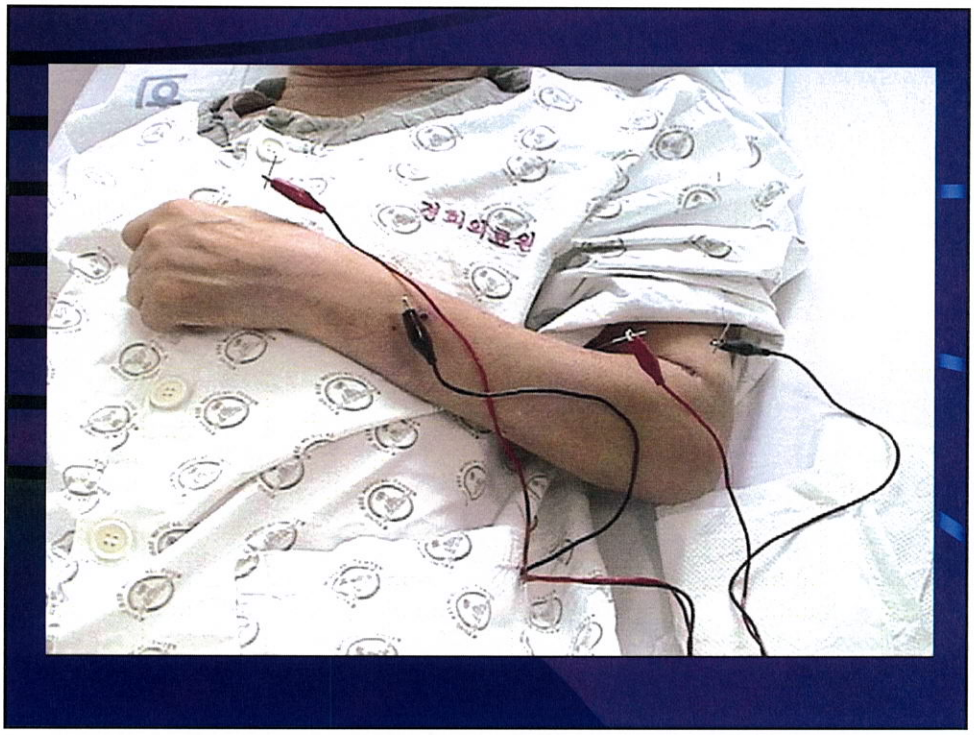
Routine acupuncture therapy for stroke



Electroacupuncture Treatment for EA group

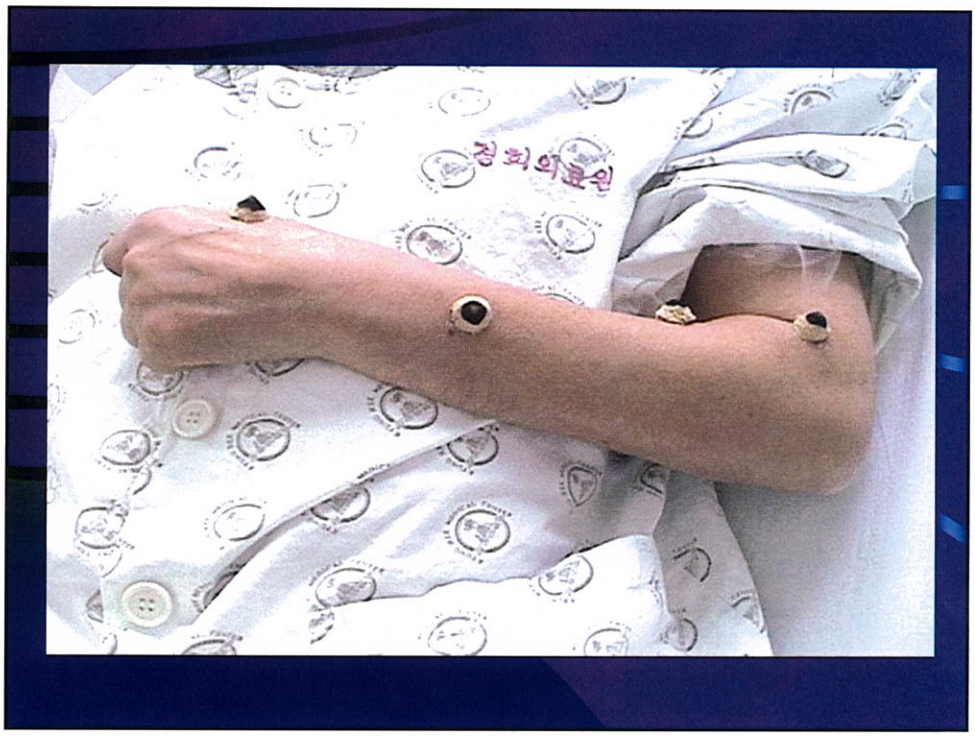
- **Electrical stimulation**
  - LI11(曲池)-LI10(手三里), TE5(外關)-LI4(合谷) of the paretic side
  - For 30 min each time, every two days
  - For 15 days (8 treatment sessions in total)
- **Frequency, Intensity & Wave form**
  - 50Hz
  - Feel, but no muscle contraction
  - Intermittent wave





Moxibustion Treatment for Mox group

- Cone shape moxa
  - 1.4cm diameter, 1.6cm height
- Direct moxibustion
  - at LI11(曲池), LI10(手三里), TE5(外關), LI4(合谷)
- Three times a day, every two days
- For 15 days (8 treatment sessions in total)

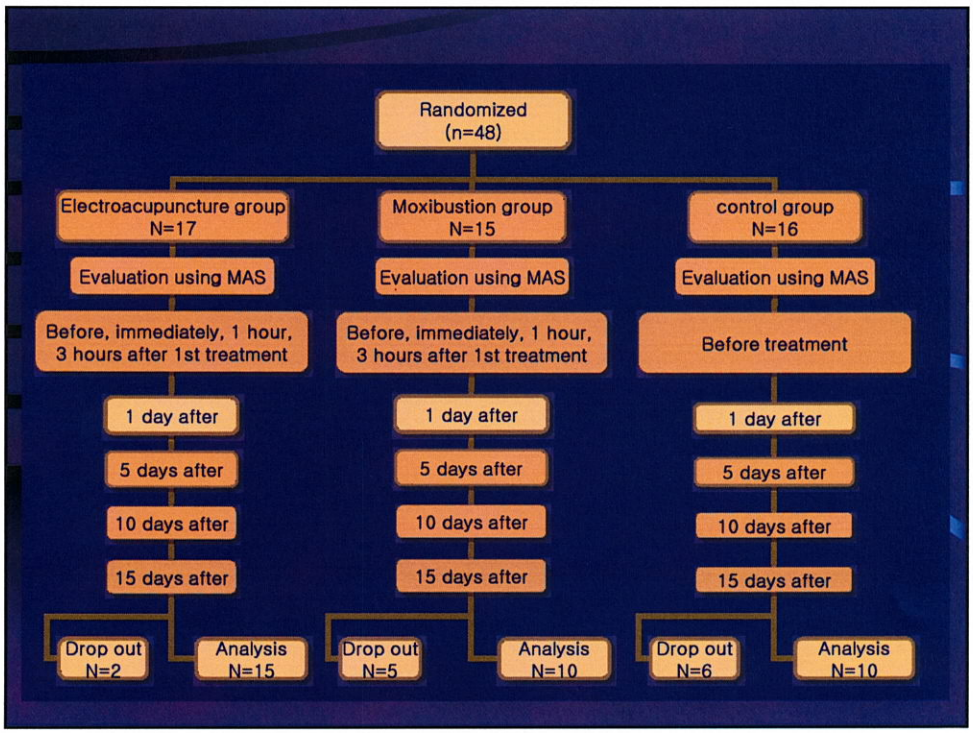


Assessment for spasticity

All assessments were performed by the same investigator who didn't know the allocation of patient's group.

Modified Ashworth Scale (MAS)

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end
2	Slight increase in muscle tone, manifested by a catch followed by minimal resistance throughout the remainder(less than half) of the ROM.
3	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved.
4	Considerable increase in muscle tone, passive movement difficult
5	Affected part(s) rigid in flexion or extension



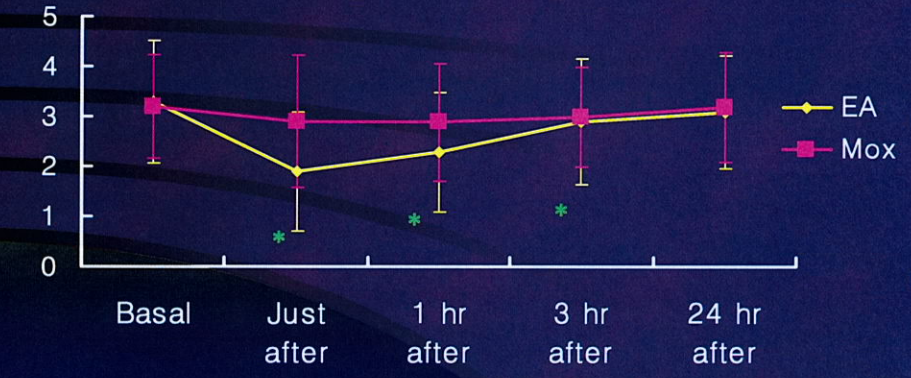
Statistical analysis

- SPSS version 7.5
- Compare MAS measured before treatment with those after treatment using the Wilcoxon signed ranks test
- Statistical significance was set at $p < 0.05$

Characteristics of Subjects

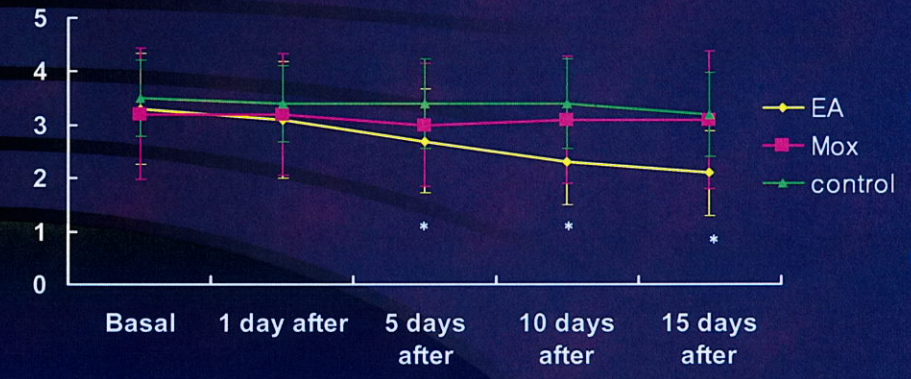
	EA (n=15)	Mox (n=10)	Control (n=10)
Age (years)	58.2±10.8	63.9±9.2	65.1±7.9
Male sex, n(%)	7(47)	5(50)	4(40)
Duration of stroke (months)	3.7±3.7	2.5±1.8	2.7±1.4
Right side of spasticity, n(%)	8(53)	5(50)	4(40)
Stroke type, n			
Hemorrhage	6	4	3
Infarction	9	6	7
Brain lesion, n			
Cortex	2	3	3
Subcortex	10	6	7
Brainstem	3	1	0

Changes of MAS after the First Treatment



*, $p < 0.05$ vs. basal state

Changes of MAS according to Treatment Period



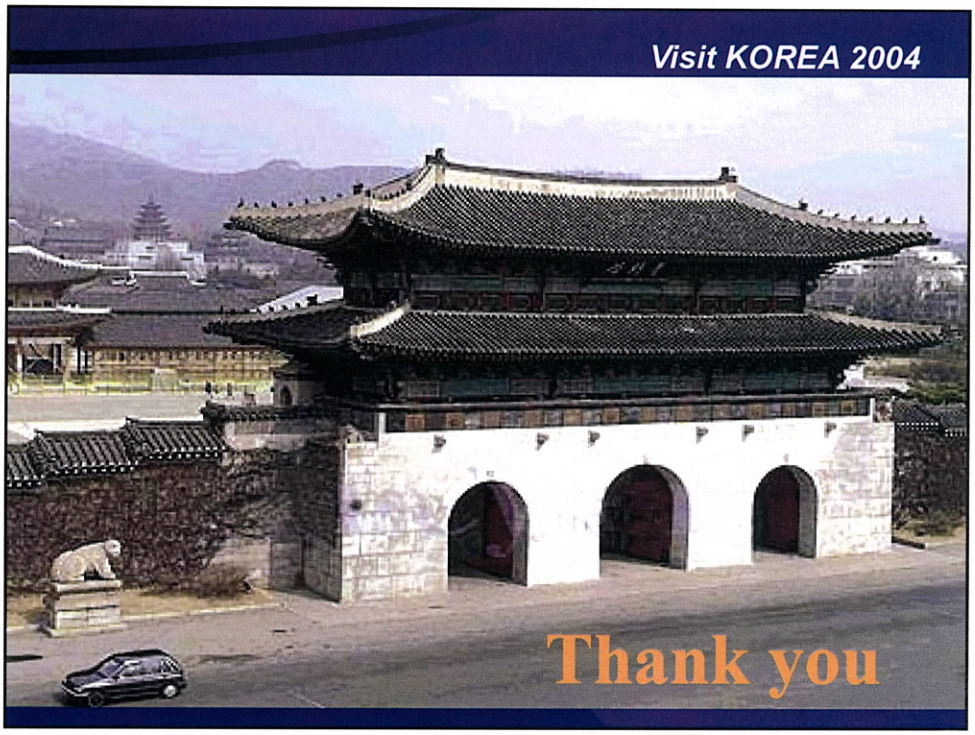
*, $p < 0.05$ vs. basal state

Limitations & Suggestions

- Issue of Control
  - vs. standard treatment control (ex. Antispasticity drugs)
  - vs. placebo control (placebo acupuncture)
- Issue of Blinding
  - patient-blind using *placebo acupuncture*
- Issue of the Traditional Concept of Oriental Medicine
  - Treatment according to pattern identification (differentiation)
  - Objective method of pattern identification

Conclusions

- Electroacupuncture(EA) can temporarily reduce spasticity due to stroke.
- EA can maintain reduced spasticity when applied repeatedly.
- Further studies are needed to show the mechanism of effect of EA on spasticity due to stroke.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Thank you