

Brief History of the Japan-Korea Workshop on Acupuncture and EBM

日韓ワークショップの概略

The 1st J-K Workshop on Acupuncture and EBM at Chiba, 2004

1. Takahashi Norihito (JSAM) Results obtained from **multi-center RCTs on the common cold** and issues to be solved.
2. Seo Jung-Chul (KAMS) Is it possible to apply placebo auricular acupuncture to Korean ? – the effect of **placebo auricular acupuncture** through single-blind method and randomized controlled trial
3. Nabeta Tomoyuki (JSAM) Results obtained from **RCT of acupuncture** on the shoulder stiffness and issues to be solved.
4. Lee Sang-Hoon (KAMS) **Randomized controlled double blind study** of bee-venom therapy on rheumatoid arthritis
5. Hiroshi Tsukayama (JSAM) Results obtained from **RCT of electroacupuncture** on the low back pain and issues to be solved
6. Moon Sang-Kwan (KOMS) Antispastic effect of **electroacupuncture and moxibustion** in stroke patients

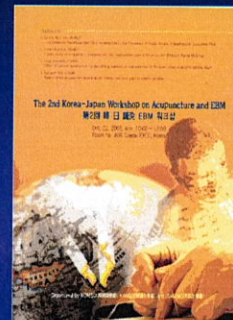


Workshop on Acupuncture and EBM in the JSAM Annual Meeting at Fukuoka, 2005

1. Lee Sang-Hoon (KAMS)
Review of **pragmatic clinical trials** of acupuncture.
2. Takahashi Norihito
Comments on the clinical trials based on the **n-of-1 RCT** research design
3. Sumiya Eiji (JSAM)
Pilot study of **multi-center N-of-1 RCTs** acupuncture on hay fever.
4. Kim Sung-chul (KOMS)
Effects of Acupuncture Treatment on the PMS: **Controlled Clinical Trial**.

The 2nd Korea-Japan Workshop on Acupuncture and EBM, at Daegu, Oct 22, 2005

1. Lee Seung-deok (KAMS)
Comparison of **superficial and deep acupuncture** in the treatment of ankle sprain: RCT
2. Kim Sung-Chul (KOMS)
A pilot study of acupuncture treatment for the **degenerative arthritis of the knee joint** on the EBM
3. Kawakita Kenji (JSAM)
Effect of indirect moxibustion on the elderly patients of **osteoarthritis of the knee-sham** controlled clinical trial-
4. Itoh Kazunori (JSAM)
Trigger point acupuncture treatment of chronic low back pain in elderly patients.





The 3rd Japan-Korea Workshop on Acupuncture and EBM



Date: June 16, 2006, 13:30-17:30
Place: Kanazawa Cyuo-koumin-kan (中央公民館)
Topics: Development of a protocol of clinical trial of acupuncture on the knee OA.
Organizer : JSAM (Japan Society of Acupuncture and Moxibustion)
Co-organizer : KAMS (Korean Acupuncture and Moxibustion Society)
 KOMS (Korean Oriental Medicine Society)

The 3rd Japan- Korea Workshop on Acupuncture and EBM

Kanazawa, July 16, 2006

Purpose (目的)

To develop a protocol of clinical trial of acupuncture on knee OA to collaborate in Japan and Korea.

日韓共同研究として、膝OAに対する鍼の効果を明らかにするための臨床研究のプロトコルを作成すること。

Themes (テーマ)

- Korean Team present four papers related to the development of protocol.
韓国チームからプロトコルに関連する4編の発表
- A protocol of clinical trials of acupuncture is proposed by the Korean team.
韓国チームから鍼の臨床試験に関するプロトコルの提案
- Based on the proposed protocol, questions and comments in each item are performed by the Japanese team, then discuss for the development of more valid protocol.
提案されたプロトコルに基づいて、各項目ごとに日本チームから質問やコメントが行われ、その後プロトコルの妥当性を高めるための討論を行う。

Proposed Protocol from Korean Team (韓国チームから提案されたプロトコル)

Multi-center, a randomized, single blind, two arms, parallel-group study to compare the effectiveness of “individualized acupuncture” with one of “standardized minimal acupuncture “ in Korean and Japanese patients with Knee Osteoarthritis (Phase IV)

多施設による、ランダム化した、患者に治療をマスクした、2群の群間比較試験-個別化した鍼治療と標準化した最小鍼刺激の韓国と日本の変形性膝関節症の患者に対する第Ⅳ相臨床試験。

The 3rd Japan- Korea Workshop Contents of presentation and comments

Presentation from Korean team

Hahn S-K: Acupuncture for tinnitus: **analysis of N-of-1 trials**
 Park, H-J: Are **sham needles** proper placebos for acupuncture research?"
 Lee S-D: Selection criteria of **local and distal** acupuncture points
 Kim Y-S: Survey of prescription of **acupuncture points for knee OA in Korea**
 Kim Y-S: Introduction of the **protocol** of acupuncture RCT of knee OA

Questions and comments from Japanese team

Takahashi N: **N-of-1 trials** for the **individualized therapy** on the knee pain
 Sumiya E: Survey of choice of acupuncture points for the **knee OA in Japan**
 Itoh K: Point selection in the **references of Knee OA** research
 Furuya E: **RCT of press tack needle** on the shoulder stiffness
 Shichidou T: Choice of **outcome measures for the knee OA**
 Yamashita H: **Safety** of acupuncture on knee OA
 Tsukayama H: **Ethical issues** in clinical trials

The 3rd Japan-Korea Workshop on Acupuncture and EBM at Kanazawa, June 16, 2006

Time	Topics of presentation	Speaker	時刻	内容	演者
1330	Opening remarks (USAM, KAMS presidents)	Yano Tadashi, Choi Do-young	1330	開会の辞ならびに挨拶 (USAM, KAMS会長)	矢野 忠, Choi Do-young
1340	Topics of this Workshop	Kawakita Kenji	1340	本ワークショップのトピックスの紹介	川喜田健司
	1 Presentation of papers from Korean team			1. 韓国チームの論文発表	
1400	Acupuncture for tinnitus: analysis of N-of-1 trials	Hahn Seo-kyung	1400	耳鳴りに対する鍼治療 n-of-1 trialsの解析	Hahn Seo-kyung
1415	Are sham needles proper placebos for acupuncture research?	Park, H-Joon	1415	鍼の研究のプラセボとしてシャム鍼は適切か?	Park, H-Joon
1430	Selection criteria of local and distal acupuncture points	Lee Seung-deok	1430	韓国における場所・遠隔の取穴方法について	Lee Seung-deok
1445	Survey of prescription of acupuncture points for knee OA in Korea	Kim Yung-suk	1445	膝OAに対する韓国のツボの選択 (アンケート報告)	Kim Yung-suk
	2 Proposal of a protocol from Korean team			2. 韓国チームの提案する共同研究のためのプロトコル	
1500	Proposal of a protocol from Korean team	Kim Yung-suk	1500	韓国チームのプロトコルの紹介	Kim Yung-suk
1530	Coffee break (10 min)		1530	休憩 (10分)	
	3 Comments on items of the protocol and discussion			3. 各テーマごとの提案ならびに討論	
1540	Research design-1 (N-of-1 trials and R statistics)	Takahashi Norihito	1540	実験デザインの提案 n-of-1 trials	高橋則人
1550	Research design-2 (RCT by real and sham superficial needle)	Shichidou Toshiyuki	1550	実験デザインの提案 RCT vs n-of-1 trials	七堂利幸
1600	Point selection-1 (literature survey by Medline database)	Itoh Kazunori	1600	膝OAに対する海外の文献にみられるツボの選択	伊藤和憲
1610	Point selection-1 (questionnaire survey using Korean prototype)	Sumiya Eiji	1610	日本鍼灸師に対する個別化治療のためのアンケート調査	角谷英治
1620	Intervention-1 (real and sham superficial acupuncture)	Furuya Eiji	1620	介入方法について 刺皮鍼による真偽の治癒RCT	古屋英治
1630	Outcome measures (literature survey, WOMAC, SF-36)	Shichidou Toshiyuki	1630	膝OAの評価方法について	七堂利幸
1640	Safety of acupuncture to the knee OA	Yamashita Hitoshi	1640	膝OAへの鍼灸治療の安全性について	山下 仁
1650	Ethical issues to be considered	Tsukayama Hiroshi	1650	臨床試験遂行上の倫理問題について	津嘉山洋
	4. Other issues to be discussed in the next meeting			4. 次回の会議で検討すべき項目	
1710	Summary and Closing Remarks	Jang Jun-Hyounk	1710	まとめと閉会の辞	Jang Jun-Hyounk

Design (実験デザイン)

Multi-center RCT with two arms (Phase IV)

多施設RCTで2群比較、第4相臨床試験

Phase IV trial is adequate?

N-of-1 trial is also applicable.

単一被験体法も適用が可能である

Fit with the individualized acupuncture

Stratification (層別化)

Severity of the knee OA strongly affect
acupuncture efficacy,

Stratification according to their severity is
important.

Kellgren - Lawrence Grade Classification

膝OAの程度によって鍼の効果は大きく異なる。
患者の症状の程度に応じた層別化が必要では？

Sample size calculation

(標本数の計算)

Sixty three in each group (63x2 groups=126)

(1群は63名、2群で合計126名)

Estimated dropout rate of 20%

(脱落者を20%と見積もり)

Intervention (介入方法)

Individualized acupuncture

(診断にもとづく個別化した鍼灸治療)

vs

Standardized minimal acupuncture

(標準化された最小鍼治療)

The minimal acupuncture is an adequate control?

最小鍼刺激は対照刺激として適切か？

Outcome measures (評価法)

Primary outcome (主要なアウトカム)

VAS (可視的アナログ尺度)

Secondary outcome

WOMAC (Popular in knee OA research)

Other outcomes

SF-36 (QOL measurement)

LFI

HAQ

Data analysis (データ解析)

Statistical analysis by

GLM (JSAM working group recommended)

Application of Bayesian statistics to n-of-1 trials

Safety (安全性)

- Reporting the severe adverse event (SAE)

Ethical issues (倫理面の課題)

How to be approved by the IRB in Korea?

Informed consent form

Research Fund (研究資金)

JSAM project covers until 2006 program.

We need to get continuation of the support
by JSAM project in 2007-2008.

Estimation of the cost is required.

(研究費の算出が必要)

Acupuncture for tinnitus: analysis of N-of-1 trials

Seokyung Hahn

Seoul National University/Seoul National University Hospital

1

The review evidence so far...

- # “Efficacy of acupuncture as a treatment for tinnitus: a systematic review” Park et al 2000
 - “inconclusive”
- # Effectiveness Bulletin, Centre for Reviews & Dissemination, 2001
 - “ineffective”

2

Single case designs: N-of-1

- ✦ Single case designs....have the advantage of
 - "...patient acts as their own control"
 - "...adaptable to the clinical needs of the patient and ... approach of the practitioner"
 - "...do not mask individual change"
 - "...feasible", "...cheap"

Aldridge D. "Single case research designs" 1993

3

In conventional medical research:

- ✦ N-of-1 designs are usually....
 - Multiple cross-over
 - Randomised
 - Blinded
- ✦ To find out whether a particular treatment is of benefit to a particular patient in order to make a clinical decision

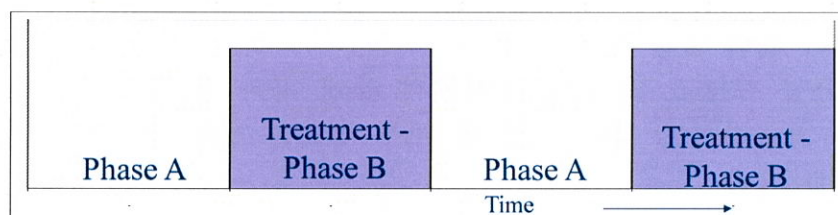
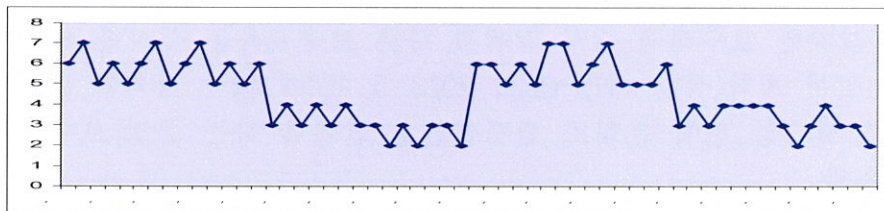
4

Conventional requirements of the N-of-1 design

- ✦ Stable baseline
- ✦ Effect of treatment should be temporary and
- ✦ Outcome measures revert to their baseline levels
 - i.e. no “carry-over effect”

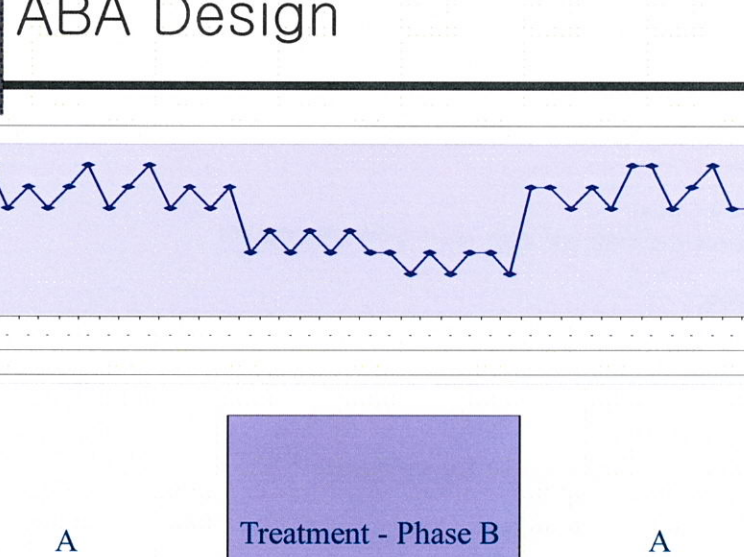
5

ABAB Design



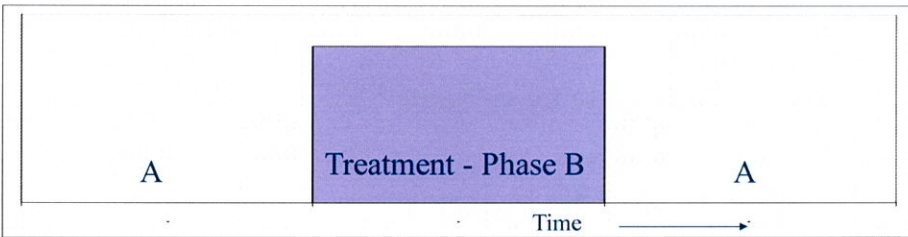
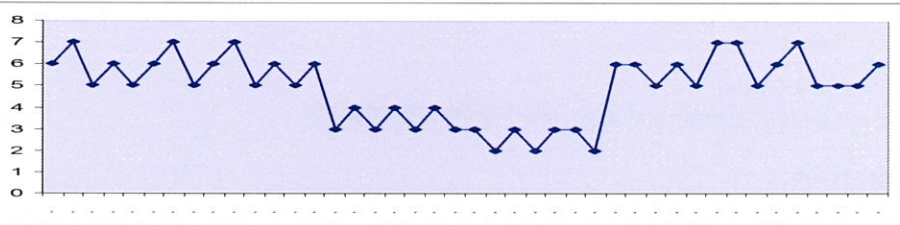
6

ABA Design



The figure consists of two parts. The top part is a line graph with a y-axis ranging from 0 to 8. The data points are connected by a blue line, showing a fluctuating pattern. The pattern starts at a level of approximately 6, drops to a level of approximately 3 during the middle section, and then returns to a level of approximately 6. The bottom part is a diagram of the ABA design. It shows a horizontal timeline with three phases: 'A' (baseline), 'Treatment - Phase B' (shaded blue), and 'A' (baseline). An arrow labeled 'Time' points to the right below the timeline.

Phase	Value (approximate)
1	6
2	7
3	5
4	6
5	5
6	6
7	7
8	5
9	6
10	7
11	5
12	6
13	5
14	6
15	3
16	4
17	3
18	4
19	3
20	4
21	3
22	2
23	3
24	2
25	3
26	2
27	3
28	2
29	6
30	6
31	5
32	6
33	5
34	7
35	7
36	5
37	6
38	7
39	5
40	5
41	5
42	6



AB Design

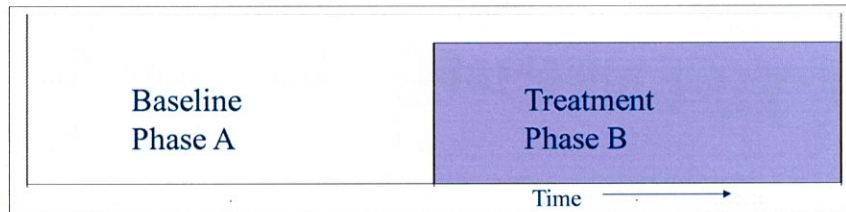
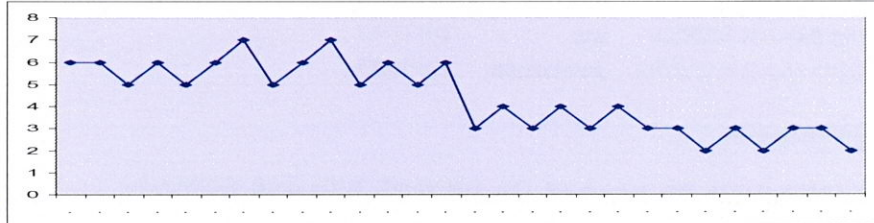
The graph illustrates the AB design, showing a baseline phase (A) and a treatment phase (B). The y-axis represents a measured variable, ranging from 0 to 8. The x-axis represents time. The data points show a general downward trend from the baseline phase to the treatment phase.

Time	Value
1	6
2	6
3	5
4	6
5	5
6	6
7	7
8	5
9	6
10	7
11	5
12	6
13	5
14	6
15	3
16	4
17	3
18	4
19	3
20	4
21	3
22	3
23	2
24	3
25	2
26	3
27	3
28	2

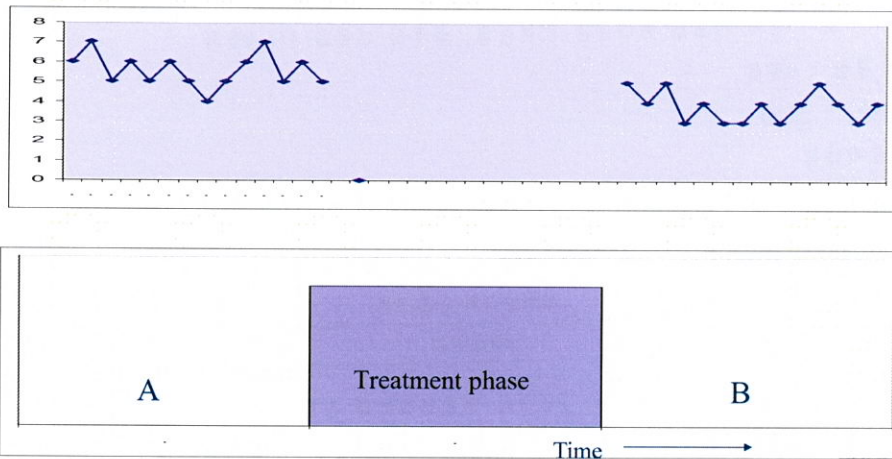
Baseline Phase A

Treatment Phase B

Time



An alternative A-B Design



9

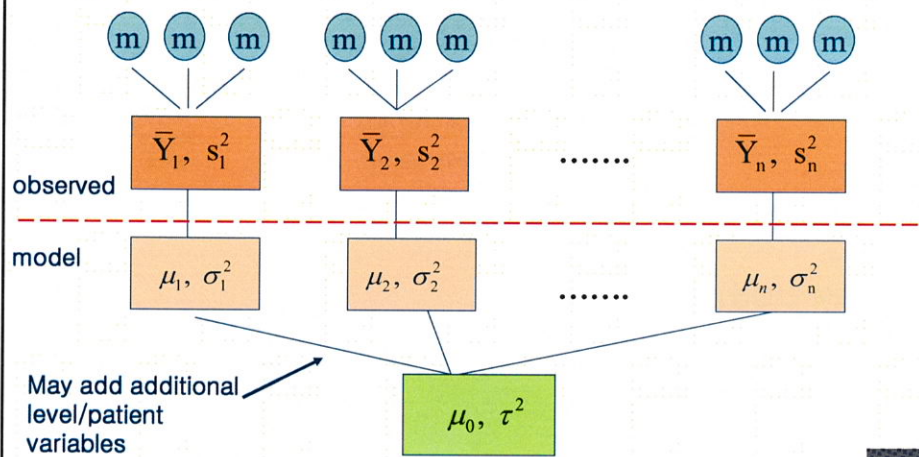
Hierarchical Bayesian meta-analysis

- # Combines results from individual patients
- # Obtains population and individual effects
- # Incorporates random variations at both levels
 - Within patients
 - Between patients

Zucker DR, Schmid CH, McIntosh RB, Agostino HP, Lau J. 1997 Combining single patient (N-of-1) trials to estimate population treatment effects and to evaluate individual patient responses to treatment. *J Clin Epidemiol.* 50(4): 401-410.

10

Hierarchical Bayesian Model



11

Model

- # Observed responses y_{ij} from the i^{th} patient at the j^{th} assessment
- # $y_{ij} = \theta_{ij} + \varepsilon_{ij} \quad \varepsilon_{ij} \sim N(0, \sigma_i^2)$
- # $\theta_{ij} = \mu_{0i} + \mu_i x_{ij}$ ← Within patient variation
- # $x_{ij} = 0$ pre-treatment, 1 post-treatment
- # μ_{0i} : pre-test mean score
- # μ_i : treatment effect in i^{th} patient
- $\sim N(\mu_0, \tau^2)$
- Overall effect ← Between patient variation (0 - ∞)

12

Procedure

- # Prior distributions are defined for μ_0, σ_i^2 and τ^2
- # Posterior distributions of μ_0 and μ_i are obtained by averaging the conditional posterior distributions of μ_0 and μ_i across the marginal posterior distributions of τ^2
- #

$\mu_0 \sim N(0, 10^6)$	}	Non-informative priors
$\sigma_i^2, \tau^2 \sim \text{IG}(0.001, 0.001)$		

13

Comparing RCTs to N-of-1

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

14

Methods in this study

- # N-of-1 case series
- # Six volunteer patients with tinnitus
- # 10 sessions of acupuncture provided
 - 5 days a week for 2 weeks
- # Diagnosed according to TCM and treated individually

15

Primary outcomes measure

- # Comparing 14 days before treatment (baseline) to 14 days after
- # Daily Diary:
 - Loudness
 - Pitch
 - Waking hours affected
 - Sleep

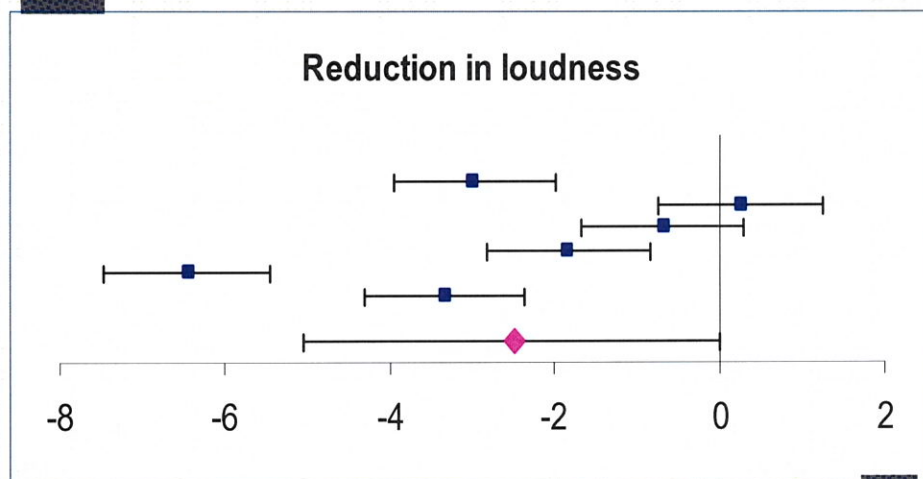
16

The patients

Patient	Age	M/F	Duration of tinnitus
A	35	M	2 years
B	79	M	Over 20 yrs
C	69	M	Over 20 yrs
D	59	M	15 years
E	32	F	12 months
F	36	M	9 years

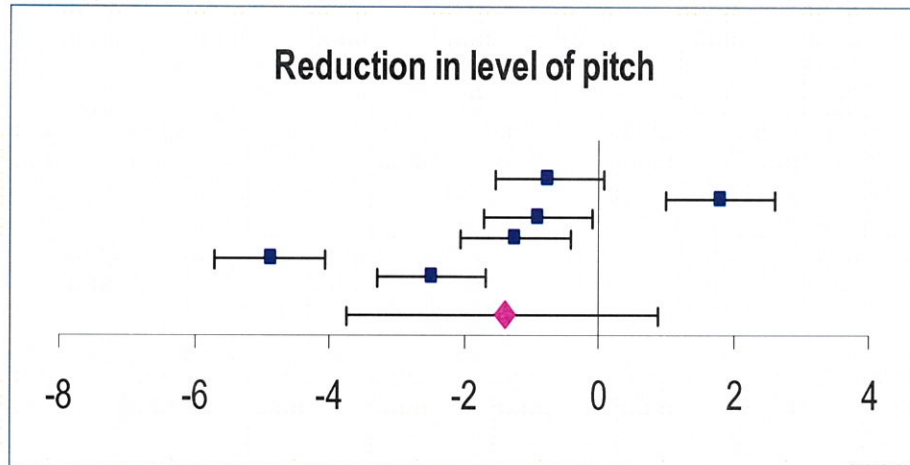
17

Daily Diary: Loudness of tinnitus



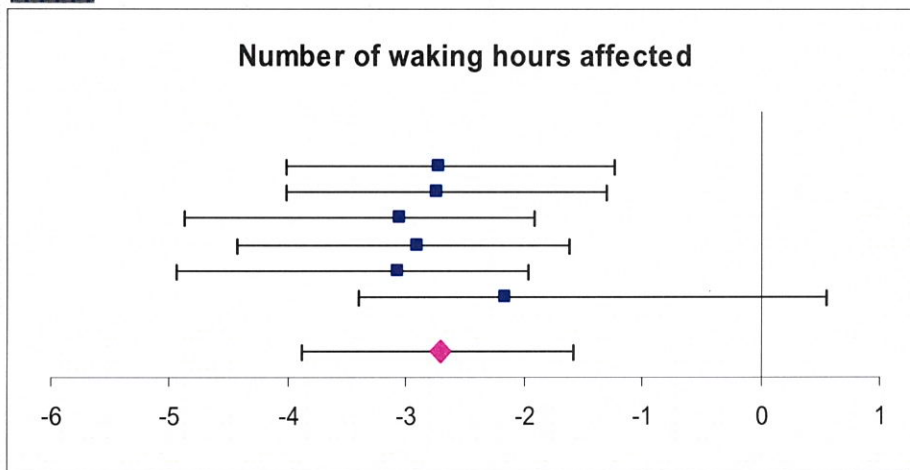
18

Daily Diary: Pitch of tinnitus



19

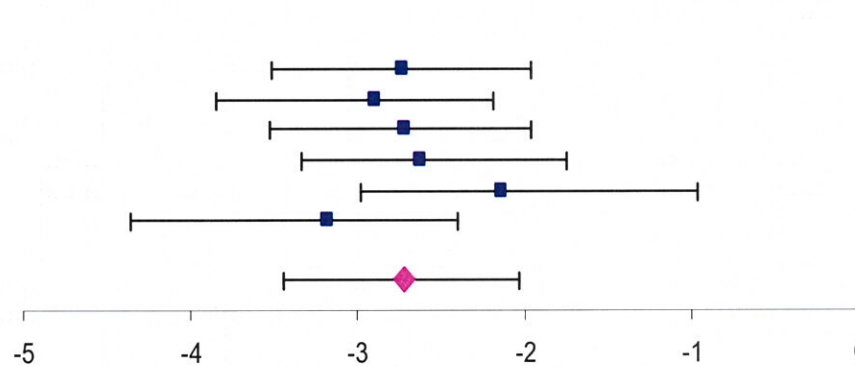
Daily Diary: Number of waking hours affected



20

Daily Diary: Quality of sleep

Reduction in impact of tinnitus on sleep



Potential advantages of this approach

- ✦ Population benefits:
 - Data can be accumulated as part of everyday practice
 - May better represent “effectiveness”
 - Generalisable to clinical setting
- ✦ Patient benefits:
 - Better understanding of patient variability
 - More able to predict individual responses

Discussion

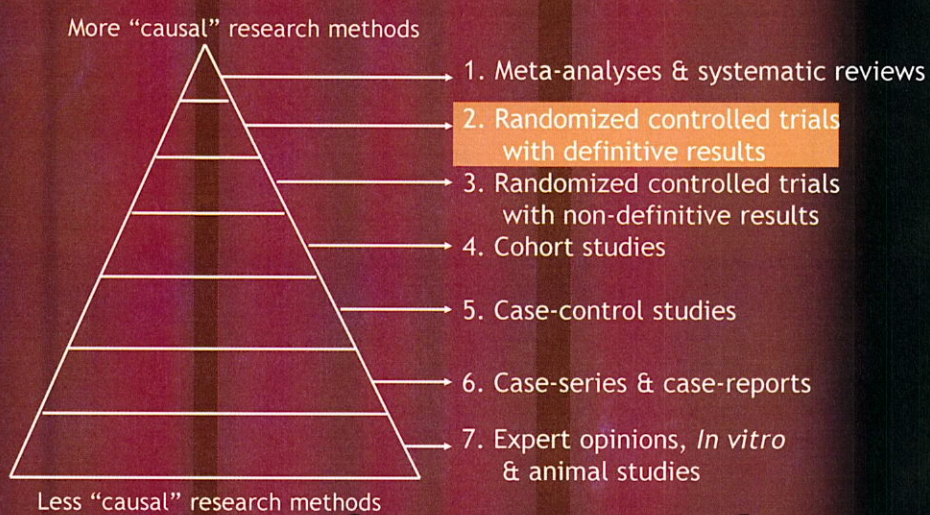
- # Yet, consideration for auto-correlation (the data within each phase should be independent) need to be resolved
- # May include additional level/patient variables

Sham needles: proper placebos for acupuncture research?

Hi-Joon Park, KMD, PhD

*Department of Meridian & Acupunture
College of Korean Medicine
Kyung Hee University*

Hierarchy of evidence



www.cebm.net/levels_of_evidence.asp

A spectrum of treatment factors

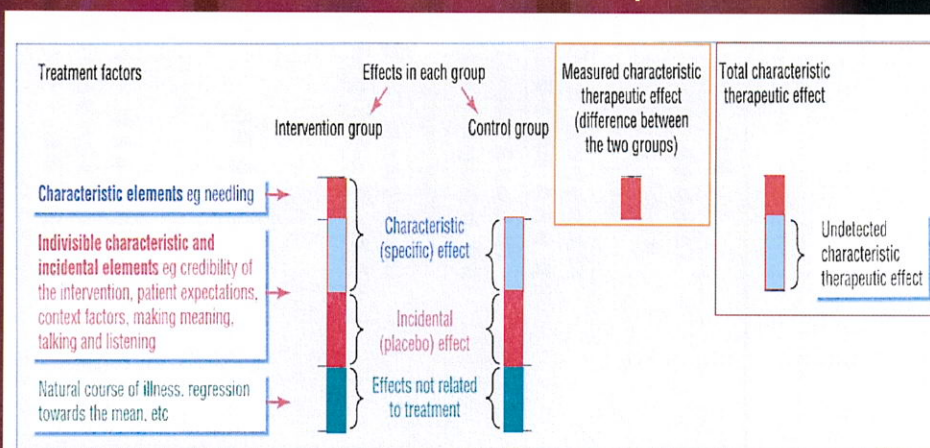
Characteristic effects (specific effects of the intervention)

+

Incidental effects (placebo, non-specific, context effects)

3

Application of randomized controlled design to trial of non-pharmaceutical intervention such as acupuncture



Paterson & Dieppe. BMJ 2005;330:1202-5.

Sham needle vs. inert pill?

- A validated sham acupuncture device has a greater placebo effect on subjective outcomes than oral placebo pills.

Kaptchuk et al. BMJ 2006;332:391-7.

5

Types of placebo techniques used in acupuncture RCTs

- 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

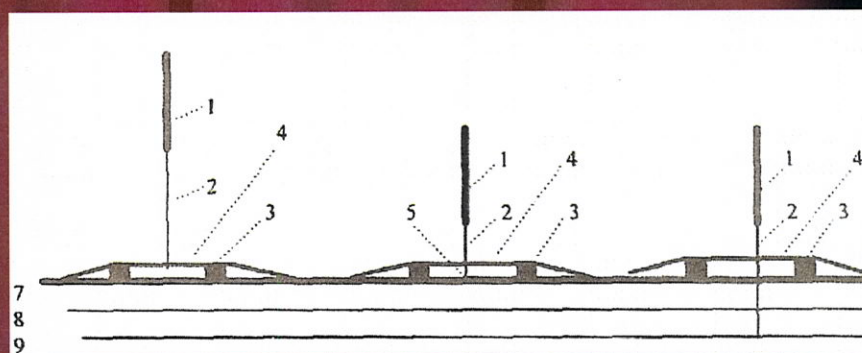
Vickers. Eval Health Prof 2002;25:421-35.

6

Appropriateness of controls ?

- It depends on
“What is your research question?”
- Then, choose the type of controls that has;
 - No physiologic effect
 - Identical appearance
 - No different credibility between groups

Streitberger's placebo needle



1, needle handle; 2, needle; 3, plastic ring; 4, adhesive plaster;
5, blunt tip of the placebo needle; 6, sharp tip of acupuncture needle;
7, skin; 8, dermis; 9, muscle.

Streitberger & Kleinhenz. Lancet 1998;352:364-5.

Streitberger's placebo needle; validation study

- 60 acupuncture naïve healthy volunteers (F:M=29:31)
- In a cross-over design, 90% of volunteers felt penetration with real needle and 79% did so with placebo needle.
- 22% of volunteers felt a dull sensation with placebo, while 57% did so with real needle.
- VAS score for pain was not significantly different between real and placebo acu punctures.

Streitberger & Kleinhenz. Lancet 1998;352:364-5.

9

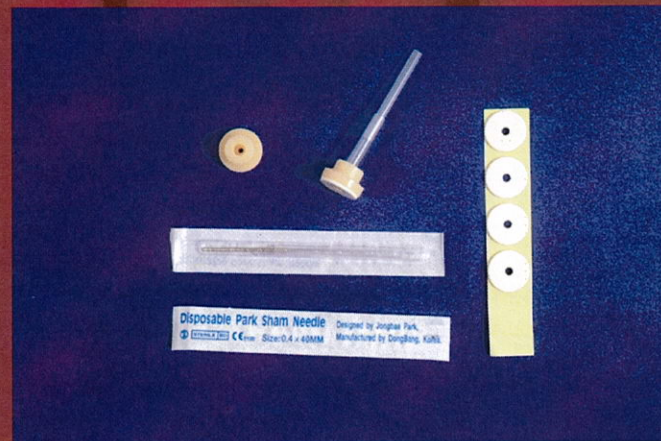
Streitberger's placebo needle; RCTs

Author (yr)	Condition	n	Results
Kleinhenz (1999)	Rotator Cuff Tendonitis	52	A superior to S in Constant-Murley score ($p = 0.014$)
Streitberger (2003)	Chemotherapy-Related Nausea & Vomiting	80	NS, 61% failure in A, 64% in S ($p = 0.82$)
Streitberger (2004)	PONV (gynaecological or breast surgery)	220	NS, 43.4% failure in A, 50.9% in S ($p = 0.27$) NS between application before ($p = 0.56$) and after ($p = 0.44$) induction of anaesthesia A superior to S in vomiting within 24 hr ($p = 0.03$)
Linde (2005)	Menstrually Related Migraine	28	NS

Lee H, Kor J Meridian & Acupoint, 2006: 23, 95-110

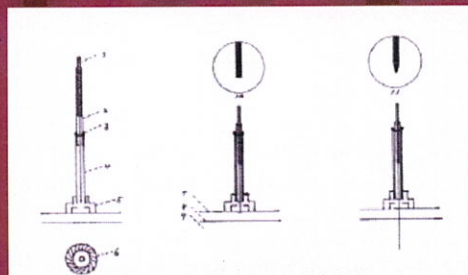
10

Park Sham Device



Park et al. Acupunct Med 1999;17:110-2.

Park sham needle vs. real needle



Before Insertion

After Insertion

Park Sham Needle; Credibility study 1;

-Is sham needle indistinguishable from real one?
 “Did you receive real or sham acupuncture?”

Needle \ Guess	Real	Sham	Total
Real	11	9	20
Sham	0	0	0
Don't know	18	20	38
Total	29	29	58

Park et al. Acupunct Med 2002;20:168-74.

Park Sham Needle; Credibility study 2

“does sham needle elicit *de-qi* sensation?”

Judgment \ Needle	<i>de-qi</i>	No <i>de-qi</i>	Total
Real	22 (71%)	9 (29%)	31
Sham	6 (21%)	23 (79%)	29
Total	28 (47%)	32 (53%)	60

Park et al. Acupunct Med 2002;20:168-74.

Park Sham Needle; Credibility study 3

“Which factors influence the applicability of sham needle?”

- 2 randomised, assessor-blind, cross-over trials in acupuncture experienced subjects.
- LI4 trial; significant difference between real and sham needles in terms of perceiving penetration and *de-qi* sensation
- BL23 trial; sham indistinguishable from real
- Potential factors that influence the applicability of placebo needling include patient's knowledge and experience of acupuncture, acupuncture point selection, the visual impact of needling.

Tsukayama et al. Clin J Pain 2006;22:346-349

15

Park Sham Needle; Credibility study 4

“Is Park sham needle good enough to blind acupuncture naïve and experienced Chinese subjects?”

- Randomized, subject and data collector blind controlled trial
- Sham needle seems to be capable of blinding both acupuncture naïve and experienced subjects.
- Subjects' experience and even indirect knowledge of acupuncture sensation may reduce the degree of blinding of the sham needle.

Zhang et al. from the 11th Annual symposium on complementary health care 2004 Nov.

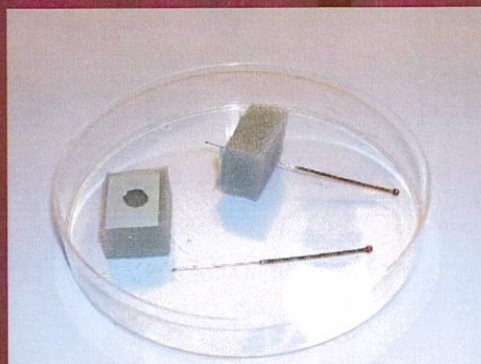
Park Sham Needle; RCTs

Author (yr)	Condition	n	Results
Park (2005)	Acute Stroke	116	NS More severely disabled had more significant benefit from real acupuncture ($p = 0.034$)
Yin (in press)	Hypertension	41	A superior to S in both systolic ($p = 0.013$) and diastolic ($p = 0.049$) blood pressure at 8 weeks

Lee H, Kor J Meridian & Acupoint, 2006: 23: 95-110

17

Fink's sham needle



18

Fink's sham needle; validation study

- 68 patients with tension-type headache
- Patients unable to discriminate sham from real acupuncture
- 84% of patients felt *de-qi* while 34% of sham group did ($p < 0.001$).

Fink et al. *Forsch Komplementarmed Klass Naturheilkd* 2001;8:368-72.

19

Fink's sham needle; RCTs

Author (yr)	Condition	n	Results
Karst (2000)	Chronic tension-type headache	39	NS at any measurement
Karst (2001)	Chronic or episodic tension-type headache	69	NS at any measurement
Karst (2002)	Alcohol withdrawal	34	NS Fewer withdrawal symptoms on day 14 in A ($p = 0.045$)
Karst (2004)	Chronic post-stroke leg spasticity	25	NS

Lee H, Kor J *Meridian & Acupoint*, 2006: 23, 95-110

20

Conclusion

- Streitberger, Park and Fink sham needles have been adequately validated and usually successful in achieving patient-blinding.
- The results from the RCTs so far support to sceptics who believe that the clinical effects of acupuncture are not more than a placebo response.

21

Sham needles, what are they controlling for?

- They control for needling (insertion) *per se* but nothing else.
- Several disadvantages to sham needles include;
 - needling technique is significantly interfered.
 - accurate point location is difficult or almost impossible and the device is not applicable to all acupoints.
 - attaching the device to keep the needle in place is time consuming and may lessen the effect of verum treatment.

22

Appropriateness of controls ?

- It depends on

“What is your research question?”

- Then, choose the type of controls that has;
 - No physiologic effect
 - Identical appearance
 - No different credibility between groups

23

Other considerations

- The use of placebo or sham controlled trial design will not therefore detect the whole characteristic effect and may generate false negative results.
- Other approaches such as randomized pragmatic designs may be more appropriate and rigorous.

Paterson & Dieppe. BMJ 2005;330:1202-5.

24

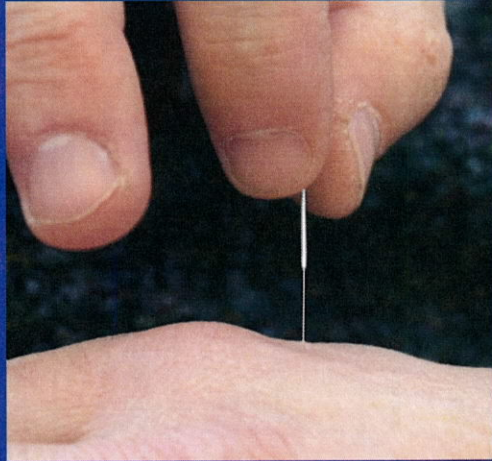


Similarities and differences in selection criteria and technique between of local and distal acupuncture points

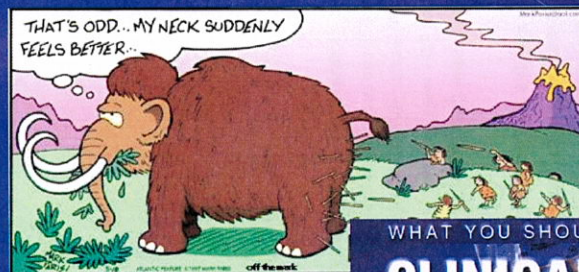
- Lee Seung-deok, KMD, PhD,
- Assistant Professor of Acupuncture & Moxibustion, Department of Acupuncture & Moxibustion, Division of Neuromuscular Diseases, Dongguk University School of Korean Medicine; Gangnam Korea-medicine Hospital

Background

Acupuncture

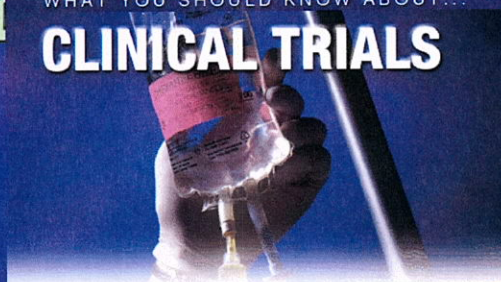


Clinical trial



WHAT YOU SHOULD KNOW ABOUT...

CLINICAL TRIALS

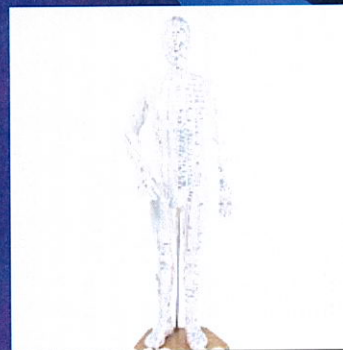


Factors influencing effectiveness of acupuncture

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

Acupuncture points

- Three categories
 - Meridian acupuncture points
 - Extraordinary points
 - *Ashi* points



Function of acupuncture points

- Three categories
 - Proximal curative effect
 - Distal curative effect
 - Special curative effect

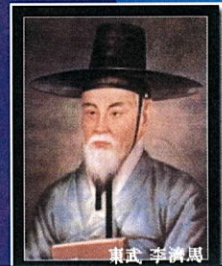


Selection of acupuncture points

- Three categories
 - Local points selection
 - Distal points selection
 - Symptomatic points selection

Objective

- Investigate and characterize perceptions
 - Selection of acupuncture points
 - Among expert of KMD(Korean Medical Doctor)
 - Similarities and differences
 - Distal points
 - Local points



Method

Questionnaire

- Background of experts
- Type of acupuncture practice
- Local points vs Distal points
 - ① Effective conditions
 - ② Ineffective conditions
 - ③ Criteria of selection
 - ④ Effective acupuncture points
 - ⑤ Effective acupuncture technique
 - ⑥ Depth of needle insertion
 - ⑦ Confirmation of *Deqi* sensation
 - ⑧ Method of Confirmation of *Deqi* sensation

Design & Setting

- Design
 - Self-administered questionnaire
- Setting
 - Annual acupuncture conference of Korea Acupuncture and Moxibustion Society (KAMS)
- Participants
 - 114 Members of KAMS
 - Korean Medical Doctors
 - KMDs with a acupuncture practice in Korea
 - Residents and specialists in acupuncture
 - Residents in other practice specialties

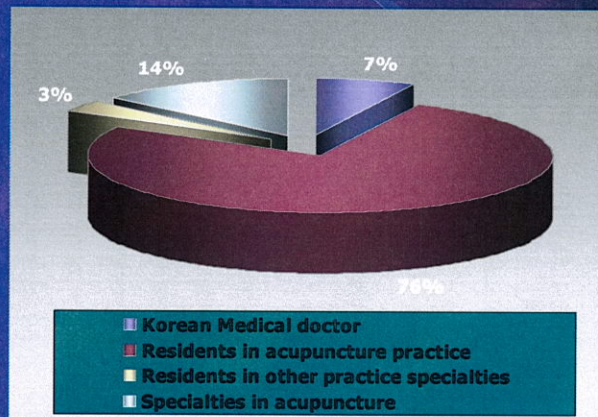
Response Rate & Analysis

- 114 Questionnaires
 - Response Rate
 - 91(79.8%)
 - Analysis
 - 88 (77.2%)

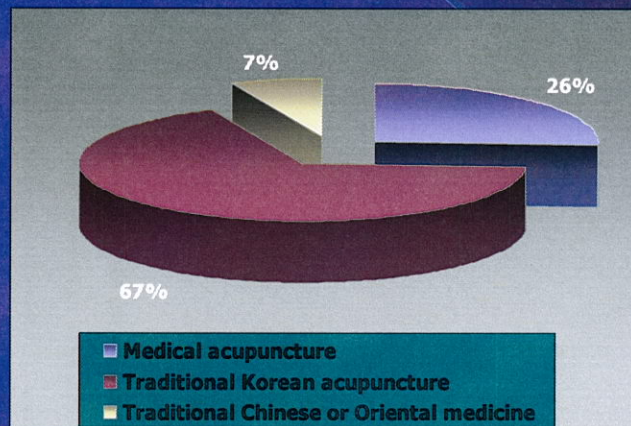


Results

Background of respondents



Type of acupuncture practice



Effective conditions -Local points-

Regional disease	26.0
Disease of locomotor system	27.7
Neuralgia or Palsy	11.1
Chronic . non-inflammatory disease	1.3
Acute inflammation disease	6.0
Aponeurotic channel or meridian disease	3.8
Disease of ear, nose and throat	1.7
Disease of digestive system	1.3
Sprain, contusion, trauma	14.0
Uncured by treatments of basic cause	2.6
All kinds of disease	1.7
Local acupuncture points not used	3.3
Total	100

Effective conditions -Distal points-

Non-regional disease	17.7
Non-locomotor system disease	4.8
Locomotor system disease	3.9
Painful disease	6.1
Meridian disorder	19.0
Zang-fu viscera disease	18.6
Central nervous system disease	10.8
Uncurable disorder using local points	8.2
All kinds of disease	10.8
Total	100.0

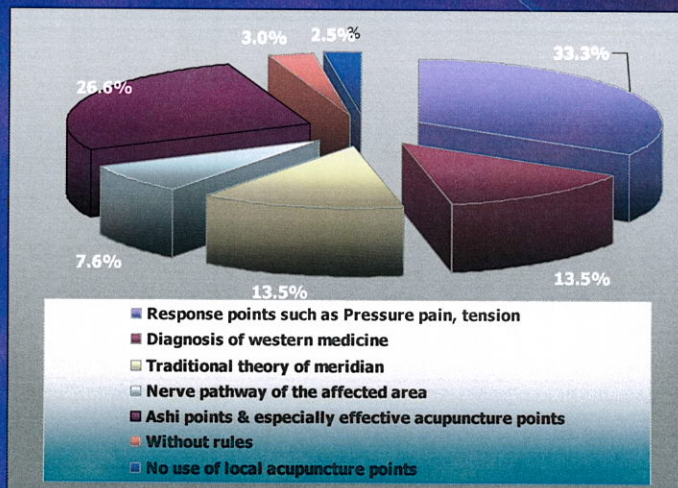
Ineffective conditions -Local points-

Other disease except for locomotor disorders	4.8
Severe injury or inflammation	15.1
Symptom of indeterminate origin	30.2
Chronic disorders	25.4
Fearfulness	13.5
None	4.8
Don't know	5.6
Etc	8
Total	100.0

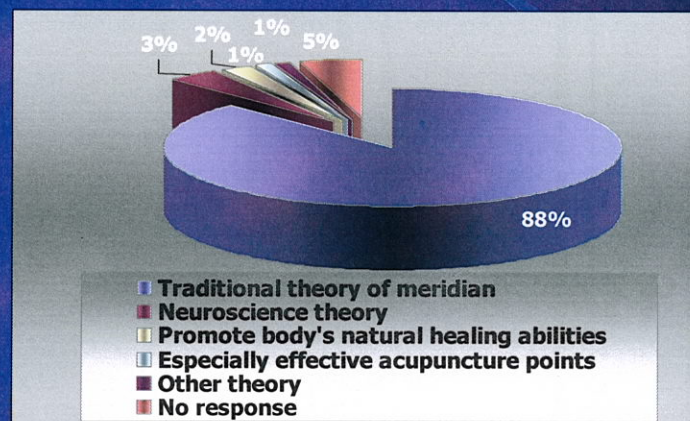
Ineffective conditions -Distal points-

Contusion, Sprain or Trauma	2.6
Severe deformity or injury	17.2
Chronic regional inflammation	5.2
Static blood	5.2
Symptoms of Insensitivity or paralysis	3.4
Erroneous syndrome differentiation	41.4
Lack of explanation	1.7
Non-immediate effect	1.7
All cases of disorder	21.6
Total	100.0

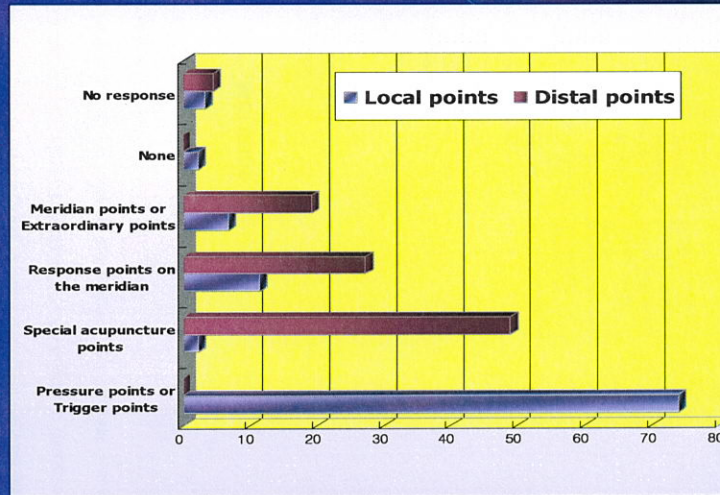
Criteria of selection -Local points-



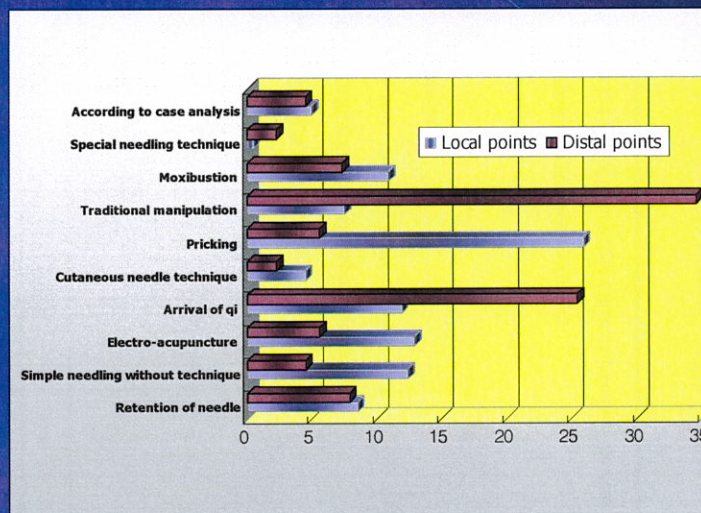
Criteria of selection -Distal points-



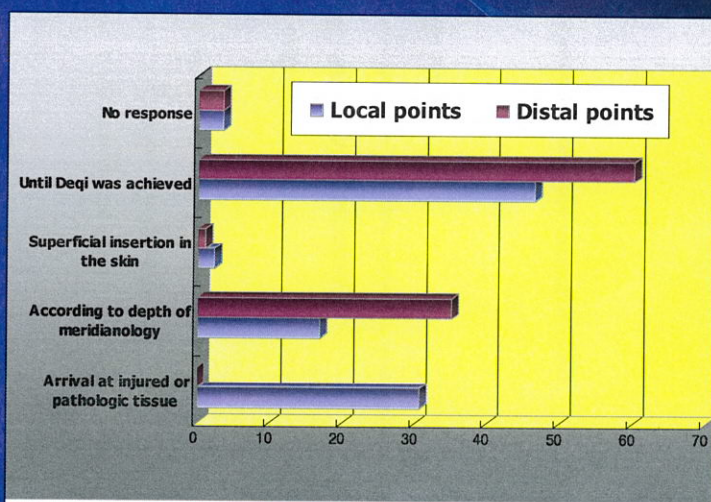
Effective acupuncture points -Local vs Distal points-



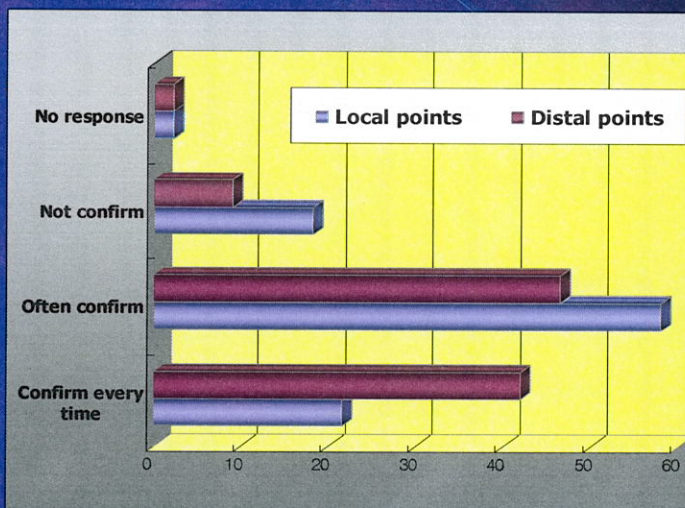
Effective acupuncture technique -Local vs Distal points-



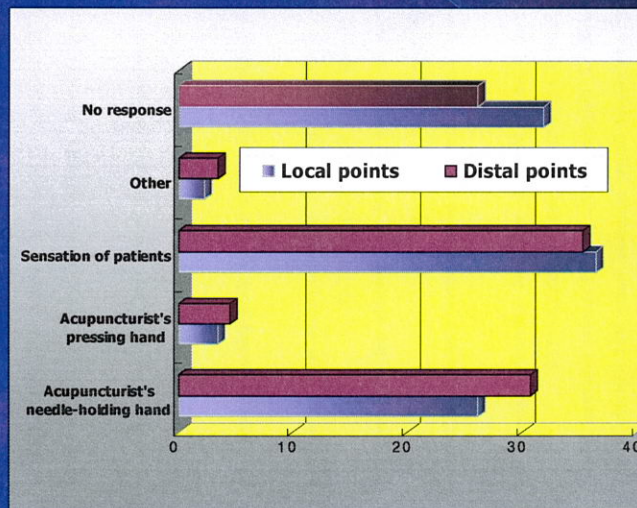
Depth of needle insertion -Local vs Distal points-



Confirmation of *deqi* sensation -Local vs Distal points-



Method of Confirmation of *Deqi* -Local vs Distal points-



Other consideration

- Local points vs distal points
 - The greatest differences
 - Effective conditions
 - Ineffective conditions
 - Criteria of point selection
 - Use-technique
 - Depth of needling
 - Some difference
 - Frequency of *Deqi* sensation
 - No difference
 - Method of detection of *Deqi* sensation

Conclusion

- Effective conditions
- Points selection
- Techniques

Acknowledgment

- This research was supported by a grant from Japan Society of Acupuncture and Moxibustion (JSAM).



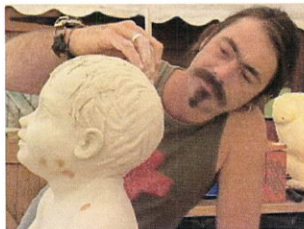
*Thank you
for
your attention*

**An Face-to-face Survey of Korean
Oriental Medical Doctors:**
*“How do they prescribe the acupuncture
points for knee osteoarthritis patients?”*

Yong-Suk Kim, Sang-Hoon Lee,
Jung-Chul Seo, Seung-Deok Lee,
Sun-Woong Kim and Sun-Mi Choi

This study was supported by the Korea Institute of Oriental Medicine, 2005.

*Acupuncture is
the Art of Healing*



*RCT's are about 50 years old, while
acupuncture is 5000 years old.*

*The development of
new clinical research design
suitable for
the individualized procedures*

*How do treatments reflect
common practice?*

- Literature reviews
- Reviews of clinical records
- Surveys of practitioners



Surveys are best at *telling us*
what is there *rather than*
how or why it got there

E-mail survey (self-completion questionnaires)



Telephone interviews



Face-to-face interviews



Methods

- **The questionnaires development**
 - 4 professors and 10 resident doctors
 - 28 items
- **Subjects**
 - 72 KMDs, who answered to prefer remote acupuncture prescription at previous telephone survey
- **Face-to-face survey**
 - Responses were used only for the purpose of completing this research, and were completely anonymous and confidential
 - The entire questionnaire took ten to fifteen minutes to complete.

Questionnaires

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?

Questionnaires

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?

Questionnaires


13. Of the available methods for reinforcing and reduction of manipulation, which do you most prefer to use with five-shu point and Sa-am acupuncture methods?
14. In five-shu point or Sa-am acupuncture method, what is your preferred standard channel or meridian?
15. In Sa-am acupuncture method, which meridian do you mainly prefer?
16. In Sa-am 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?

Questionnaires

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?

Questionnaires

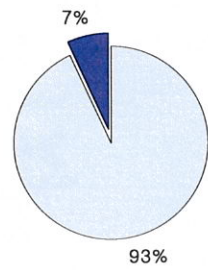
25. Which evaluation criterion do you prefer in making a determination whether a patient's osteoarthritis of knee condition is improved?
26. When treating osteoarthritis of knee with acupuncture, which other therapy(ies) might you sometimes use?
27. Which treatment or therapy other than acupuncture/moxibustion 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.



Result

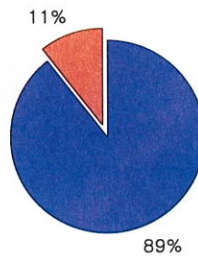
Subject

Response Ratio



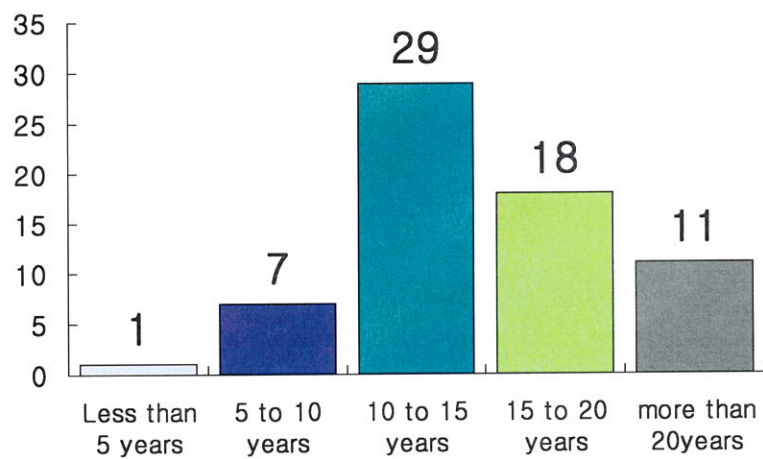
□ Response ■ Nonresponse

Sex Ratio



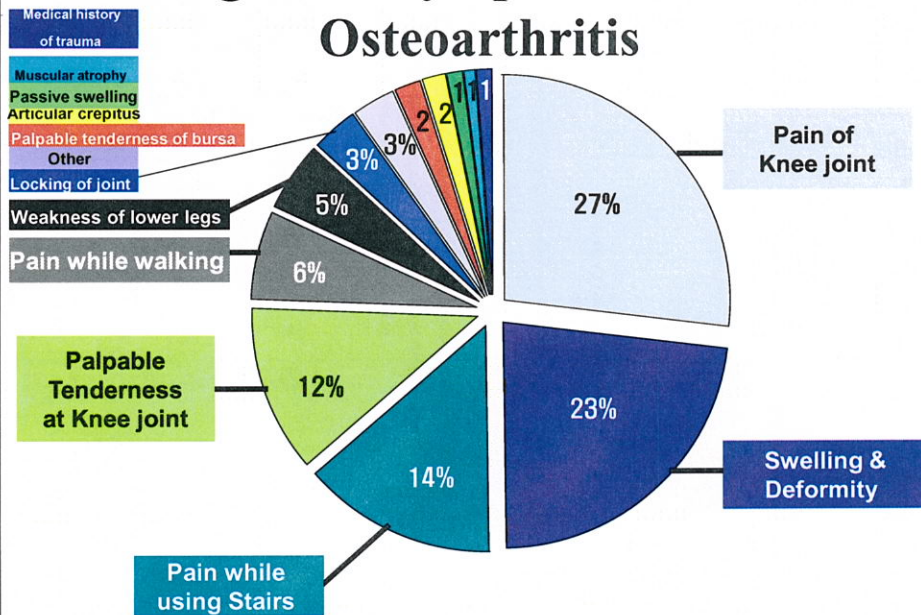
■ Male ■ Female

Experience Duration

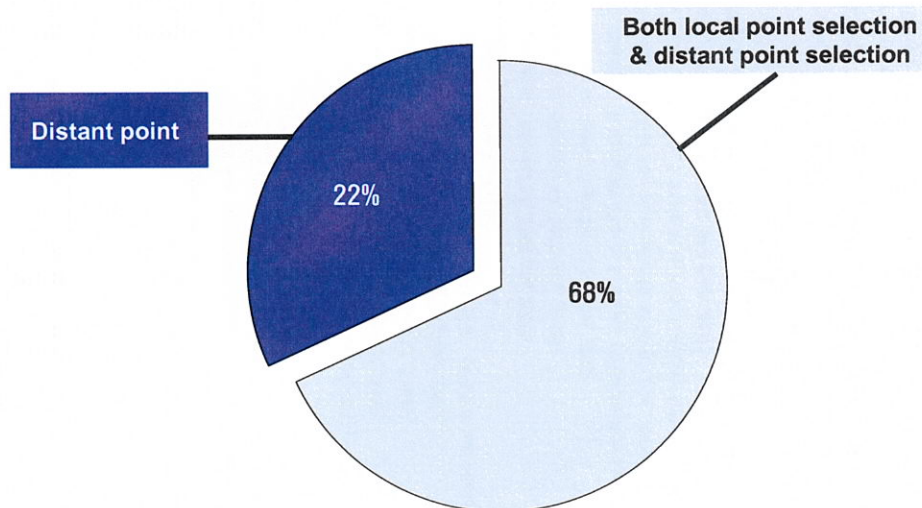


Average duration : 13.5 years

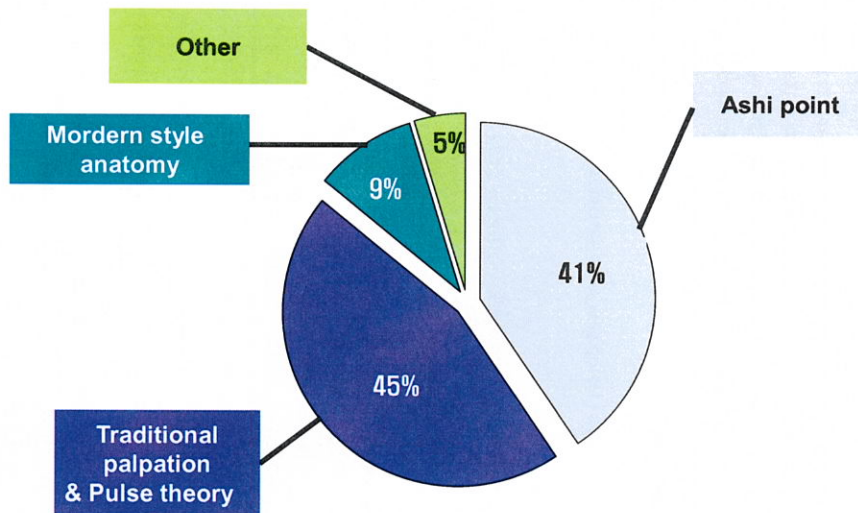
Diagnostic Symptoms of Knee Osteoarthritis



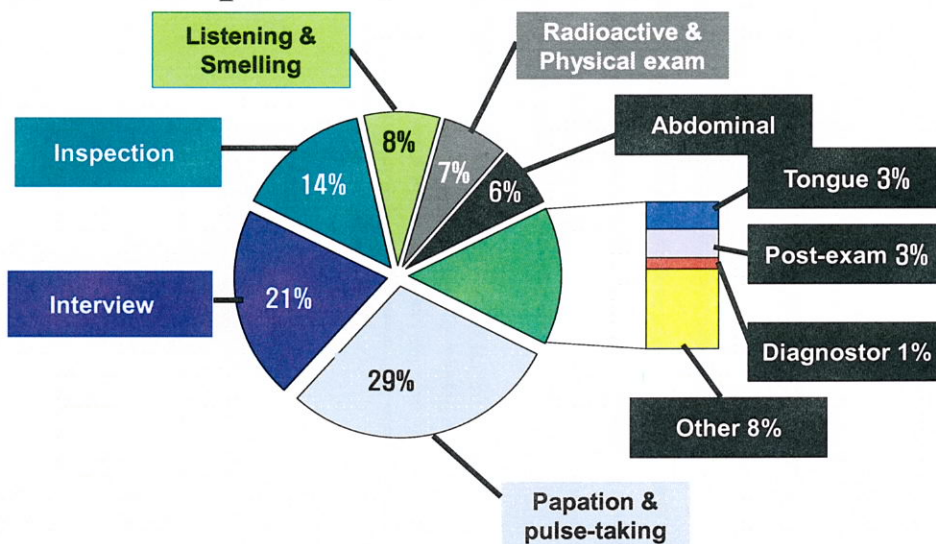
Needle Insertion Points



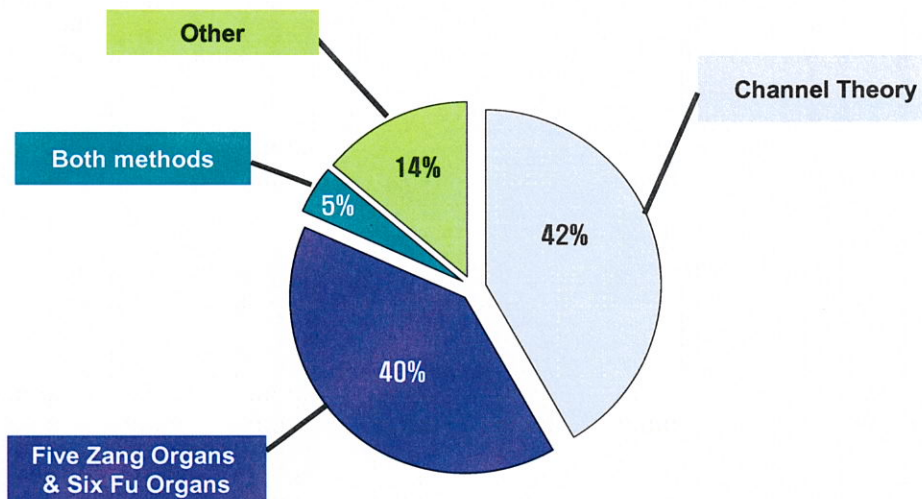
Principle for Local Acupuncture Points Selection



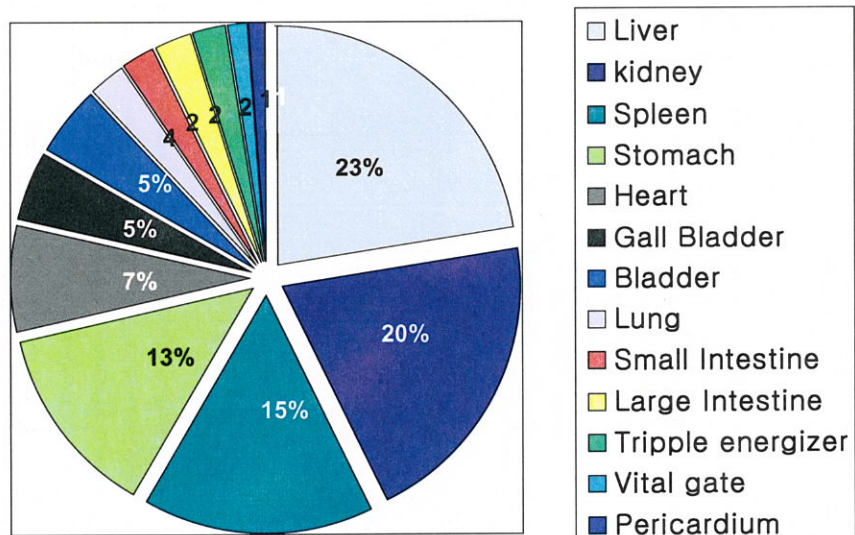
Diagnostic Method for Remote Acupuncture Points Selection



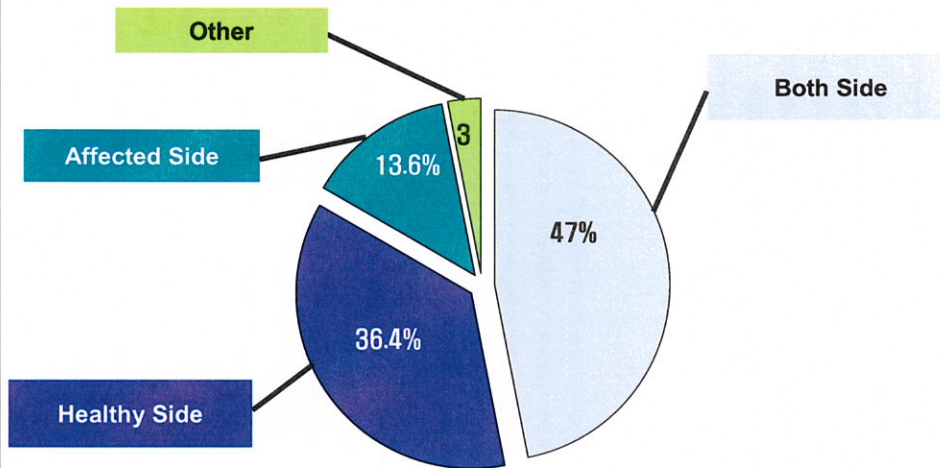
Principle for Distant Acupuncture Points Selection



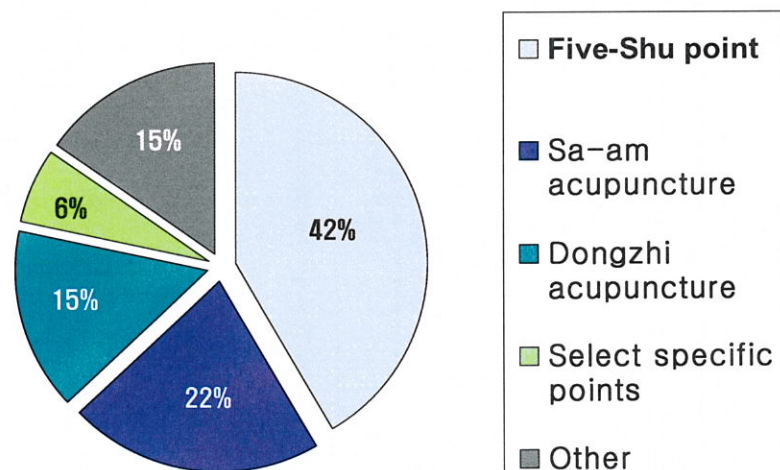
Taget Organ



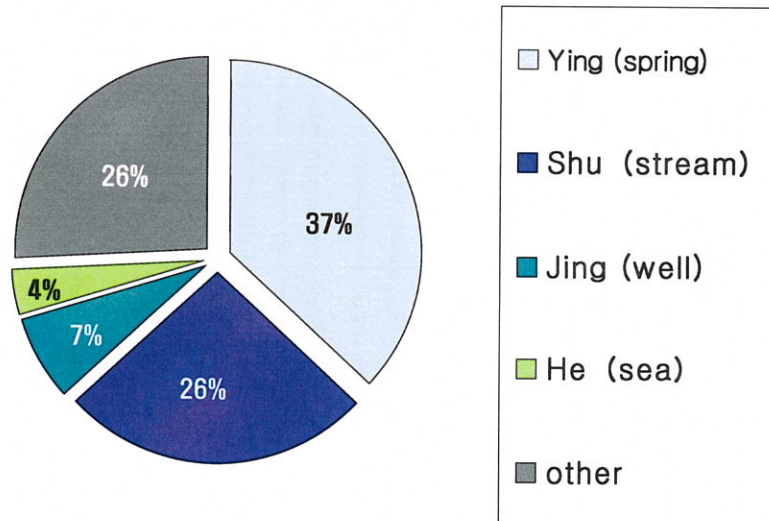
Side Selection for Distant Acupuncture



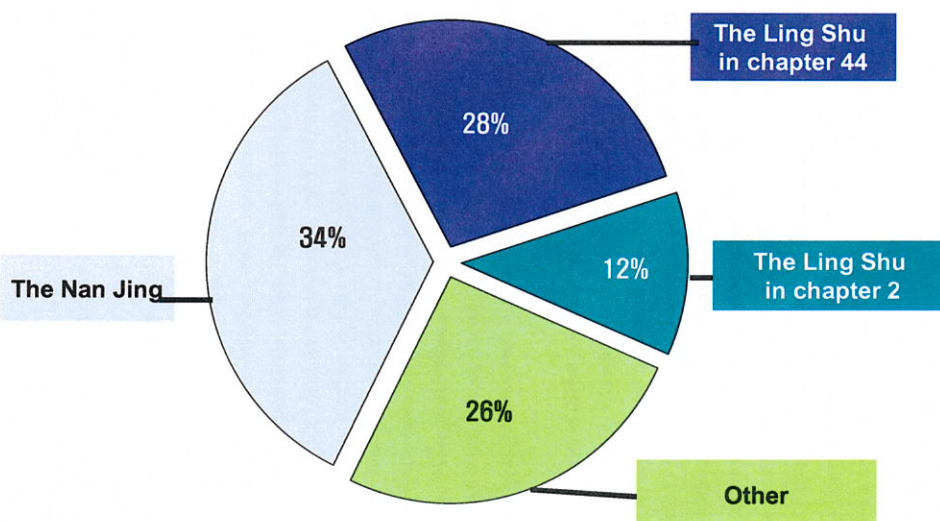
Needle Insertion Points



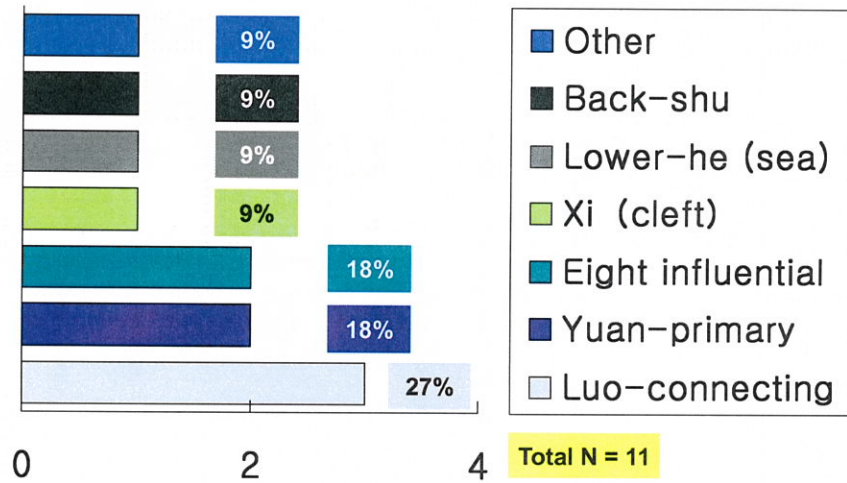
Preference of Five-Shu points



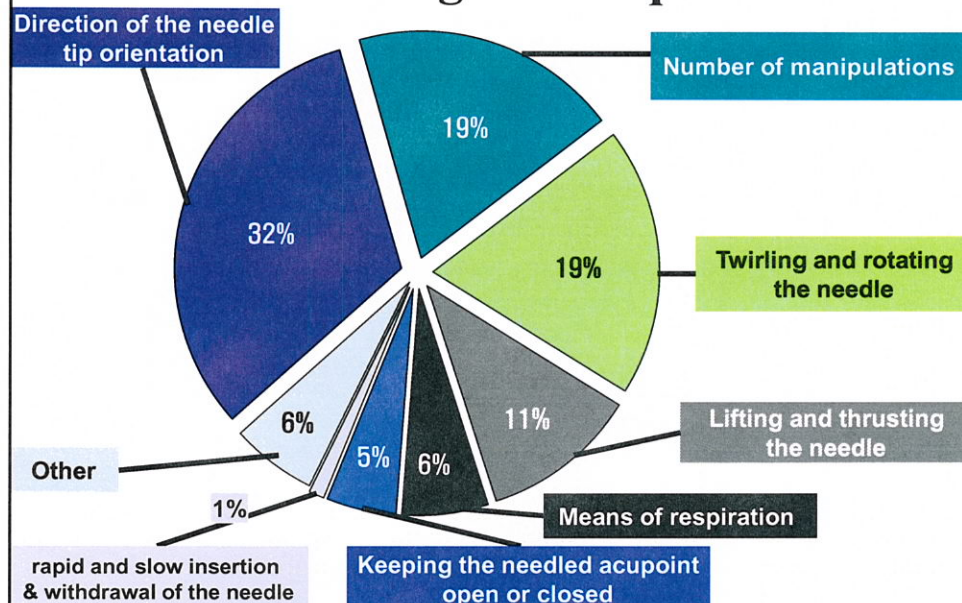
Basic Theory for Five Shu Point Selection



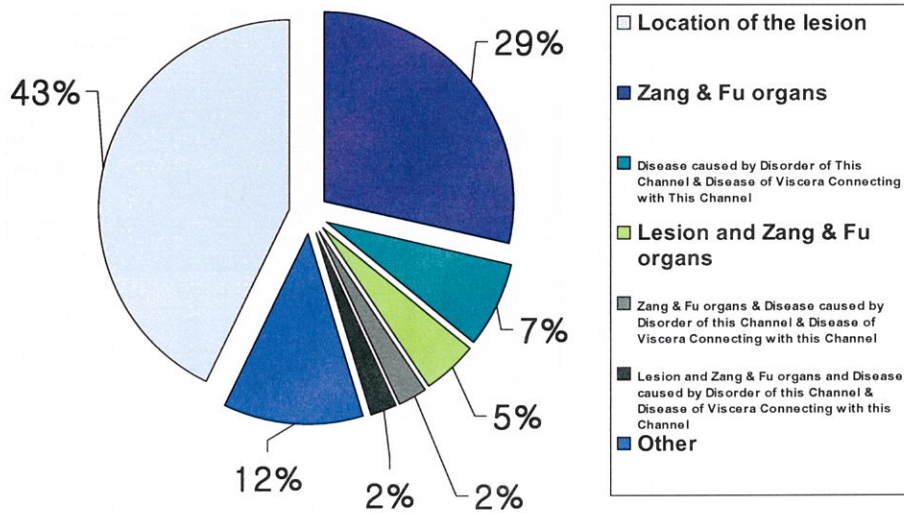
Selection of Acupuncture Points except Five Shu Points



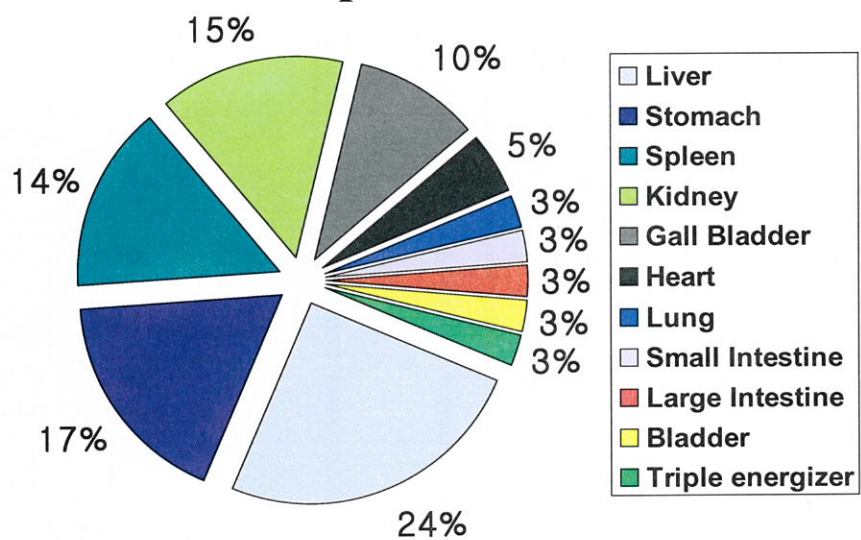
Needling Technique



Method of Selection for Five-Shu point or Sa-am Acupuncture



Main Meridian for Sa-am Acupuncture



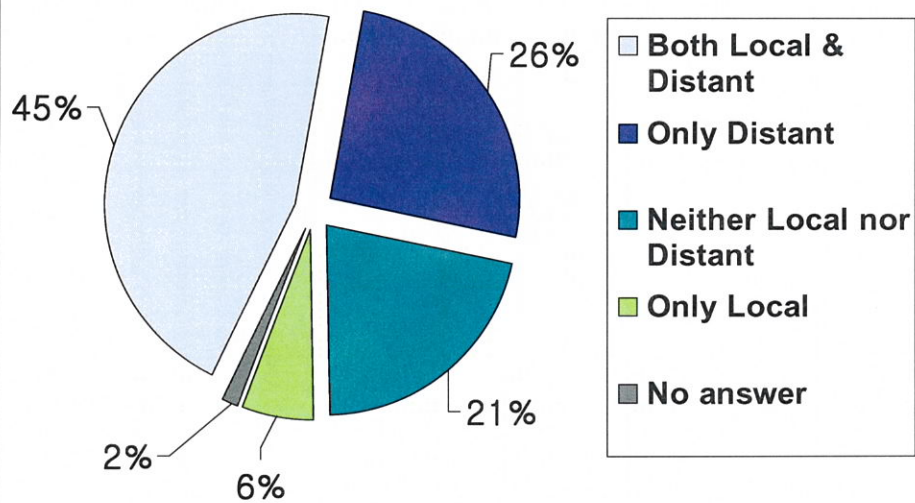
Standard for Choosing in Sa-am Acupuncture Method

Reinforcing Manipulation		Reducing Manipulation	
Chronic or Weak Feature of Symptom & Pulse	7	Acute or Strong Feature of Symptom & Pulse	6
Constitution	2	Constitution	1
Weak Feature of Kidney at Bone	1	Tenderness & Painful Site	1
Dongibogam & Sa-am-chim-gu-jungjun	1	Sa-am-chim-gu-jungjun	1
Tenderness & Painful Site	1	No answer	57
Degree of Disease	1		
Eight principle pattern identification	1		
No answer	52		

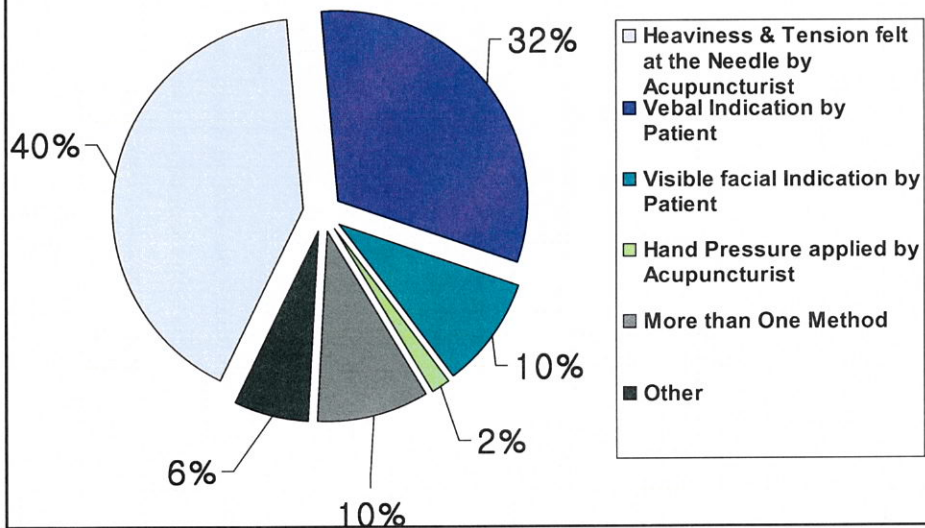
Number of Needle

Local point selection		Distant point selection	
4	6 (9.1%)	4	20 (30.3%)
5	6 (9.1%)	2	10 (15.2%)
8	6 (9.1%)	Other(1~10)	35
Other(1~15)	25	Mean Number	4.1
Mean Number	5.4		

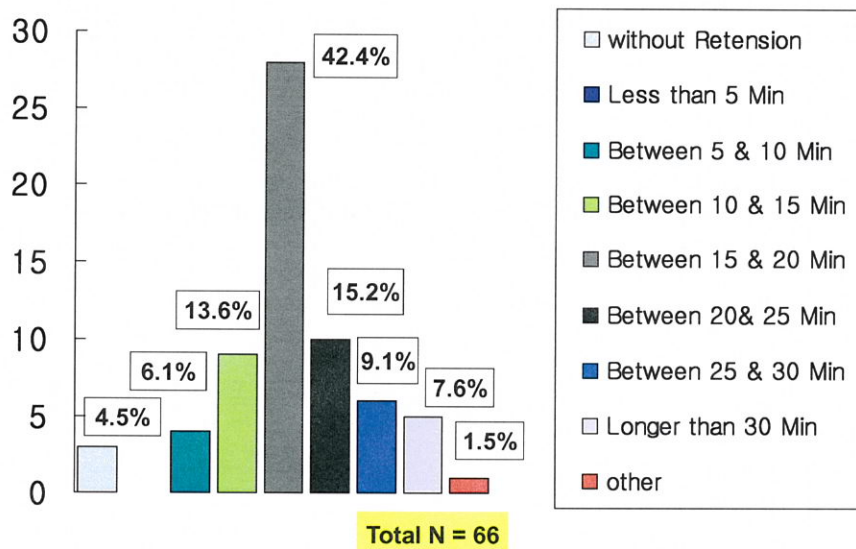
Confirming Arrival of Qi



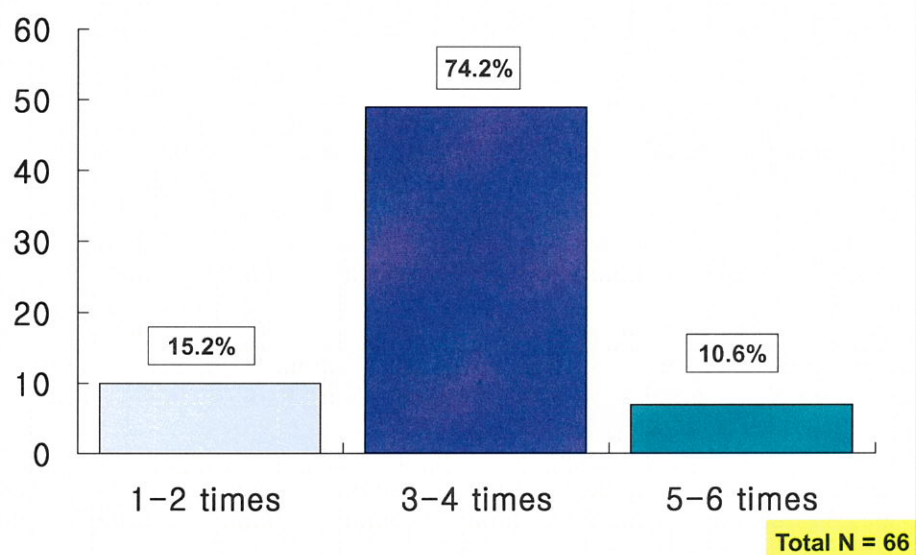
Method of Confirming Arrival of Qi



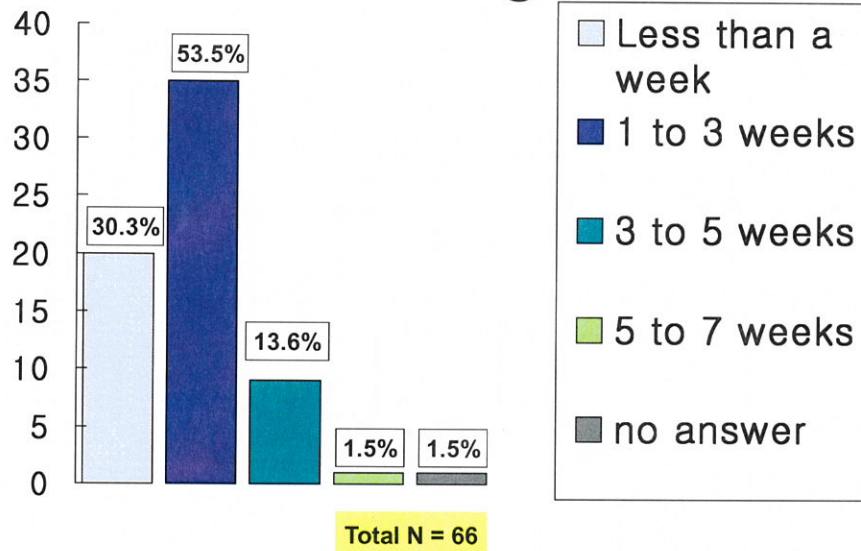
Duration of Needle Retention



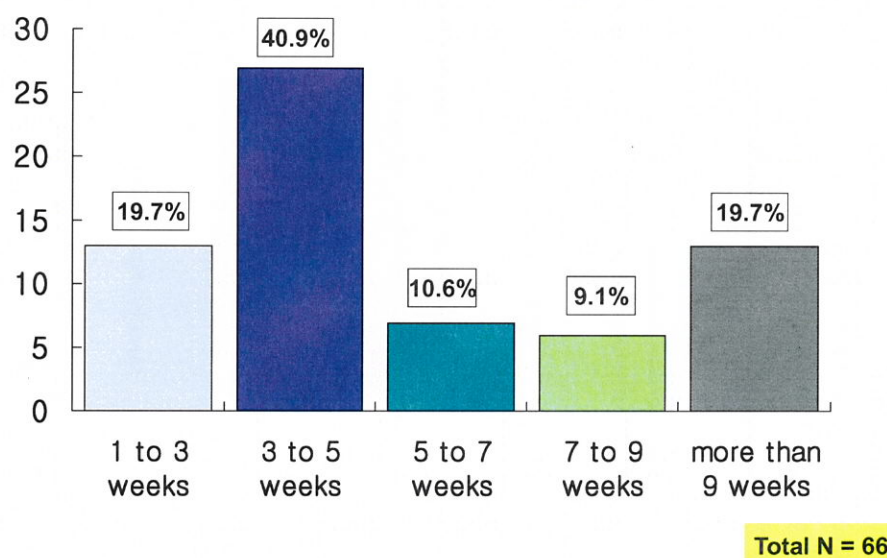
Frequency of Treatment in a Week

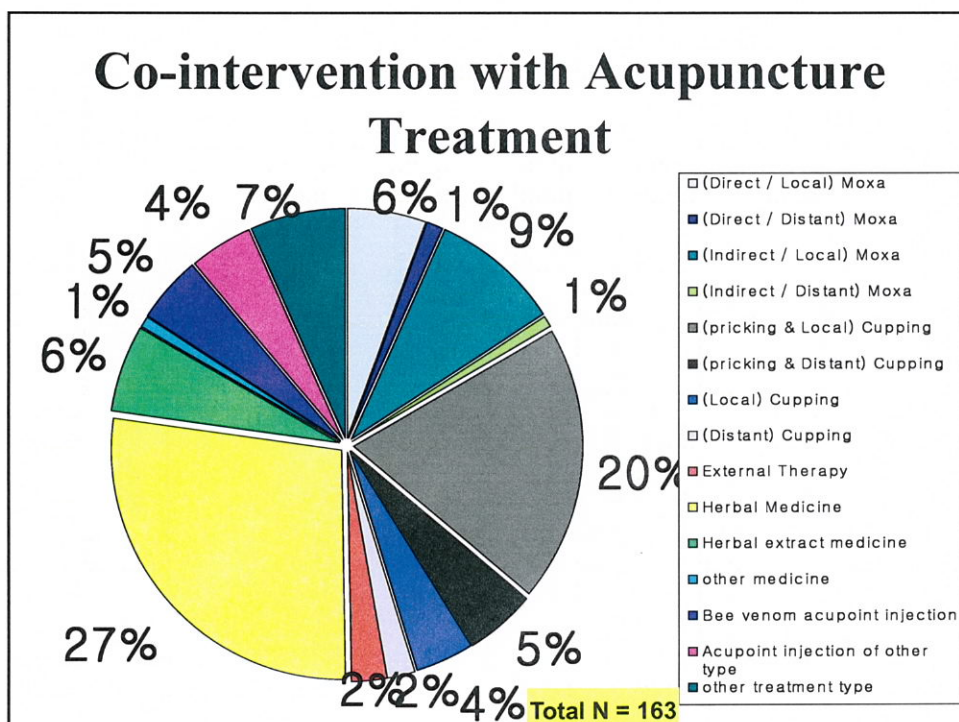
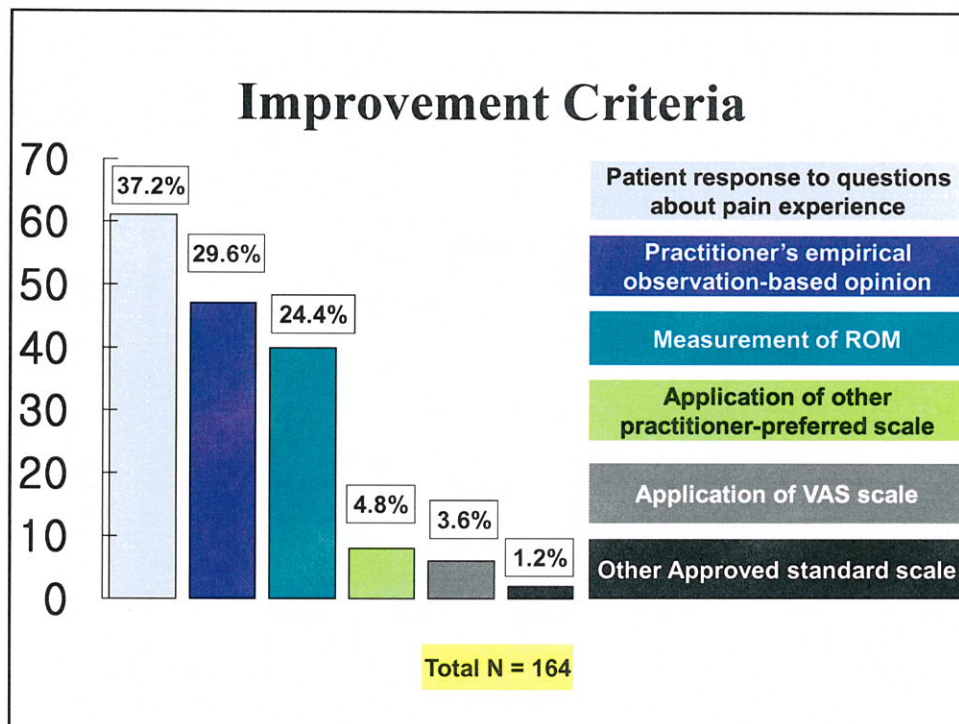


Duration expected for observable Change in OA

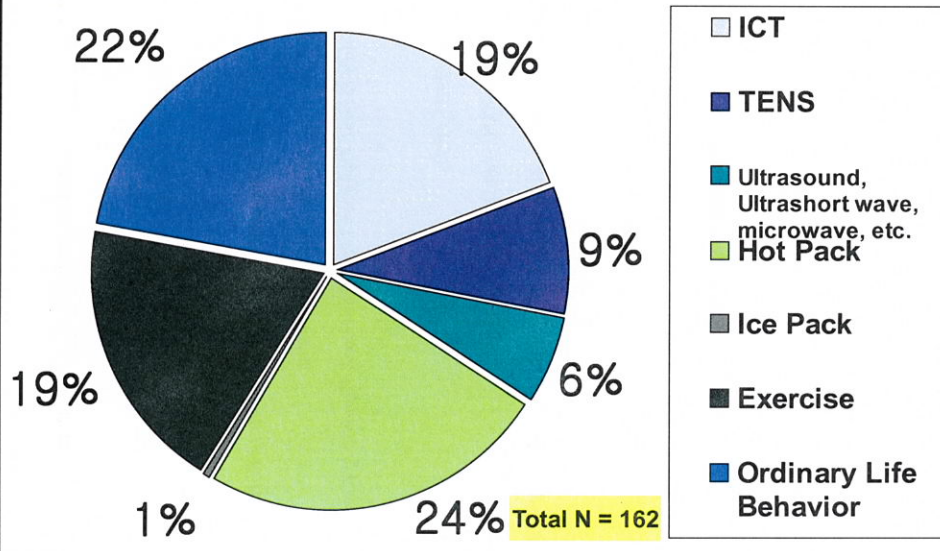


Duration expected for Cure of OA

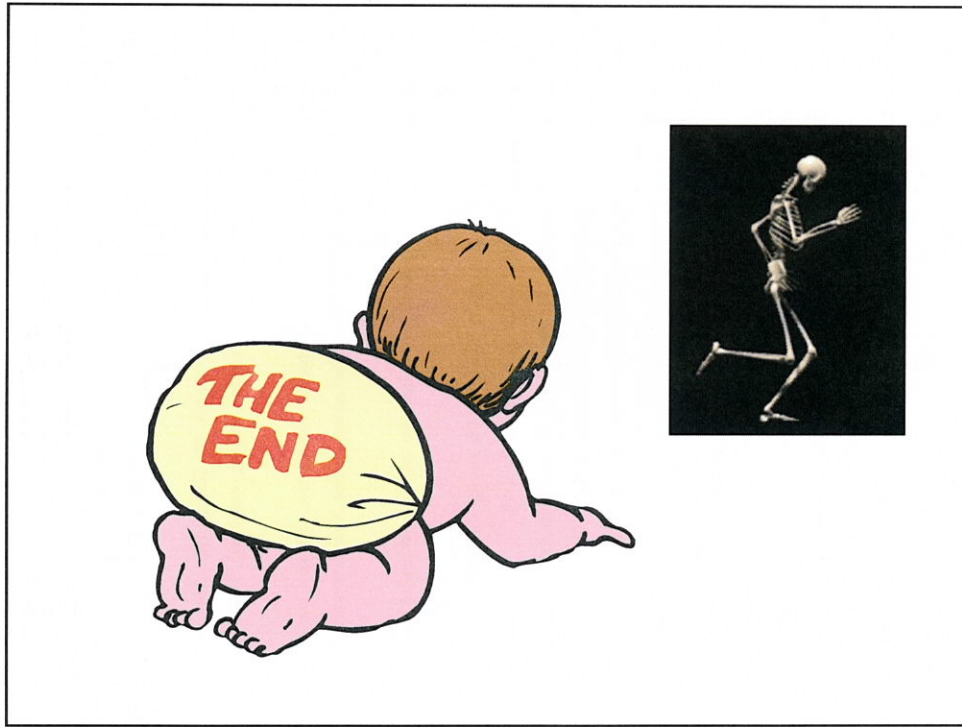




Co-intervention with Acupuncture Treatment



- Korean medical doctors preferred to use five transport points, especially 'spring point' or 'stream point', on the contra-lateral side of lesion and that the main affected viscera was liver.
- Five transport points theory was mainly based on 'Nanjing' and 'Hwangdi Neijing'.
- De-qi sensation was identified by doctor and patient's feeling.
- This study showed that Korean medical doctors prefer to follow the Korean traditional acupuncture methods respecting the old classic principles.
- And these results can guide us to develop advanced clinical trial protocols more close to acupuncture practice; individualized acupuncture treatment protocol.



**Multi-center, A Randomized, Single-Blind, Two arm,
Parallel-Group Study to Compare the Effectiveness of
'Individualized acupuncture' with one of 'standardized
minimal acupuncture' in Korean and Japanese patients with
Knee Osteoarthritis (Phase IV)**

Objectives

Primary Objective:

To determine whether individualized acupuncture provides greater pain relief compared with standardized minimal acupuncture in patients with osteoarthritis of the knee.

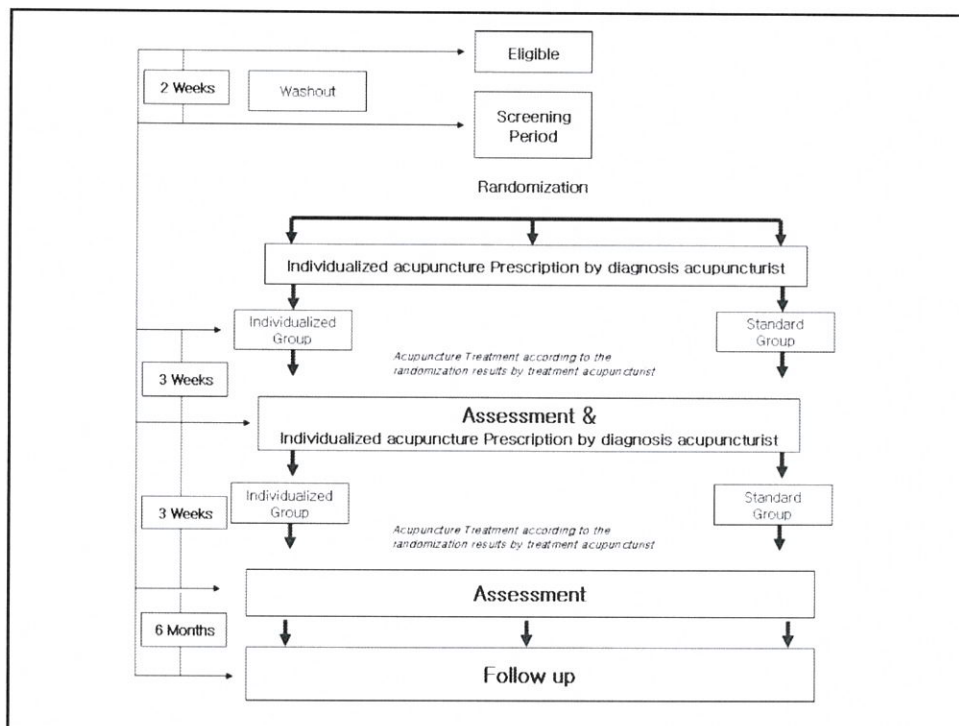
Secondary Objective:

To determine if individualized acupuncture has more change in pain, stiffness, physical function of knee (WOMAC), compared to standardized minimal acupuncture at 6 weeks and 6 months.

To determine if individualized acupuncture increases average Quality of Life (SF-36) compared to standardized minimal acupuncture at 6 weeks and 6 months.

To determine if individualized acupuncture increases average joint function (LFI score) compared to standardized minimal acupuncture at 6 weeks and 6 months.

To determine if individualized acupuncture increases average physical function (HAQ) compared to standardized minimal acupuncture at 6 weeks and 6 months.



① **Orthopedist**

Vital Signs
Medical History
VAS
Physical Examination
X-ray
Laboratory test
Inclusion and Exclusion

② **Evaluation: Korean Medical Doctors or Japanese acupunctuists**

Vital Signs
VAS
WOMAC
SF-36
LFI
HAQ

③ **Diagnosis: Korean Medical Doctors or Japanese acupunctuists**

Diagnosis will be based on traditional Korean and Japanese medicine
Selection of acupoints and manipulations

④ **Intervention: Korean Medical Doctor or Japanese acupunctuist**

Intervention according to the diagnosis in the randomized group

Criteria

- **Inclusion Criteria**
- **Exclusion Criteria**
- **Withdrawal Criteria**

Randomization and Stratification ?

Intervention	Item	Description
Acupuncture rationale	1	<p>Style of acupuncture Individualized acupuncture</p> <p>Rationale for treatment and individualization if used Traditional Korean Medicine meridian theory to treat knee joint pain, known as the "Bi" syndrome</p> <p>Literature sources to justify rationale Yang Jizhou. <i>Zhenju Dacheng</i>(1601) : Heilongjiang Sheng ziguao yiyao yanjiusuo Jiaoshi, Zhenju dacheng Jiaoshi Beijing, 1991</p>
	2	<p>Points used Selection 5 local points among 13 local acupoints pool acupoints pools: Xiyangguan (GB33), Yanglingquan (GB34), Yuzhen (SP6), Xiguan (LV7), Quxian (LV8), Xuehai (SP10), Lingqian (ST34), Dabi (ST35), Zusanli (ST36), Weizhong (BL40), Heding (EX-LE1), Xiyao (EX-LE5), and Ashi point in collateral ligament areas on meridians that traverse the area of pain If both knees were affected, 5 needles were inserted in each leg.</p> <p>Selection 4 distal points among 8 distal acupoints pools: Ganshu (BL13), Shenshu (BL23), Kunlun (BL60), Xuanzhong (GB39), Sanyinjiao (SP6), Xinguan (LV2), Jem (SA1) and Tenu (KI3)</p> <p>If both knees were affected, 4 needles were inserted in the lesser-affected side.</p> <p>All patients have to be treated with a selection of proximal local and distal points, which must be selected according to the principles of traditional Korean and Japanese medicine by experienced KMD or acupuncturists.</p>

Intervention	Item	Description
Needling details (Continued)	2	<p>Needle type Pre-packed, sterile, disposable 50s×0.35mm needles</p> <p>Depth of insertion Intervention KMD or Japan acupuncturist accomplish acupuncture according to the acupuncture description by diagnosis KMD or Japan acupuncturist.</p> <p>Response elicited All participants in the treatment group achieved the "De-Qi" sensation, a local sensation of heaviness, numbness, soreness, or pruritus that accompanies the insertion and manipulation of needles during acupuncture at acupoints.</p> <p>Needle stimulation Diagnosis KMD or Japan acupuncturist orders a needling technique on the basis of "On Governing the Needles," in "Yellow Emperor's Canon Internal Medicine."</p> <p>Intervention KMD or Japan acupuncturist accomplish the needling technique according to the acupuncture description by diagnosis KMD or Japan acupuncturist.</p> <p>Electro acupuncture The needles in local points are stimulated according to method, Min frequency, Low 1, High 30, and over-range 1 by PG-306 pulse generator (Guzuki Iyoki, Japan).</p> <p>Needle retention time 20 minutes</p>
	3	<p>Number of treatment session 12 sessions</p> <p>Frequency of treatment Twice a week, Tuesday = 1 day, Thursday = 1 day</p>
Co-interventions	4	<p>Other interventions Nothing is done.</p>
Practitioner background	5	<p>Duration of relevant training More than 3 years in Korean medical hospital</p> <p>Length of clinical experience More than 3 years in Korean medical hospital</p> <p>Expertise in specific condition Completion of the first-year residents' course in acupuncture and manipulation or 3 years' experience of acupuncture for knee osteoarthritis in clinic</p>

Intervention	Item	Description
Control intervention(s)	6	<p>Intended effect of control intervention and its appropriateness to research question and, if appropriate, blinding of participants:</p> <p>It seems that standardized minimal acupuncture as control intervention also may have positive outcomes although less than does individualized acupuncture</p> <p>standardized minimal acupuncture is active minimally penetrating</p> <p>Single blind is intended</p> <p>Explanation: given to patients of treatment and control interventions:</p> <p>Patients are informed in the study as follows: 'In this study, different types of acupuncture will be compared. All types are the acupuncture treatments used in knee OA. Each type has been associated with positive outcome in clinical studies.'</p> <p>Details of control intervention</p> <p>- Points used</p> <p>5 local points:</p> <p>Yanglingquan [GB34], Yinlingquan [SP9], Zhusanku [ST36], Dabai [ST35], Xuyan [EX-LE5]</p> <p>If both knees were affected, 5 needles were inserted in each leg</p> <p>4 distal points:</p> <p>Kunlun [BL60], Xunzhong [GB39], Sanyinjiao [SP6], and Taixi [KI3]</p> <p>The same points are treated for each affected leg</p> <p>If both knees were affected, 4 needles were inserted in the lesser-affected side</p>

Intervention	Item	Description
Control intervention(s) (Continued)	6	<p>- Needle type</p> <p>Pre-packed, sterile, disposable 40mm-0.35mm needles</p> <p>- Depth of insertion</p> <p>Intervention KMD or Japan acupuncturist inserts needles into the subcutaneous layer with the Acugun</p> <p>The needles should be placed subcutaneously</p> <p>- Responses elicited</p> <p>De qi' and manual stimulation of the needles should be avoided. All acupuncturists were trained to apply minimal acupuncture and received a videotape and a brochure showing detailed information on minimal acupuncture</p> <p>- Needle stimulation</p> <p>Nothing is done.</p> <p>- Needle retention time</p> <p>20 minutes</p> <p>Sources that justify choice of control</p> <p>Berman has identified the effectiveness of standardized minimal acupuncture for knee OA with the same acupoints in 'Effectiveness of Acupuncture as Adjunctive Therapy in Osteoarthritis of the Knee: A Randomized, Controlled Trial', <i>Annals of Internal Medicine</i>, 2004; 141: 901-10.</p>

6.1.1. Primary outcome measure

The primary outcome measure is participant pain rating based on a 100 mm VAS.

6.1.2. Secondary outcome measures

Secondary endpoint: Western Ontario MacMaster Questionnaire (WOMAC) Scale

Other outcomes that will be assessed are:

1. Quality of Life (SF-36)
2. Lequesne Functional Index (LFI) score
3. Physical function was evaluated by the Health Assessment Questionnaire (HAQ)

Sample size and Power?

Statistical analysis ?

Period	Screening Wash-out	Active Treatment											
Week	- 2	1	2	3	4	5	6 End	7	8	9	10 FU	11	12
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13
Telephone screening	X												
Informed Consent	X												
Patient Education		X _____											
Post History	X												
Injection or Drug History	X												
Physical Exam.	X				X						X		
X-ray	X												
Laboratory test ^(*)	X										X	X	
NSAIDs Hold Order	X												
NSAIDs Hold Check		X _____											
Inclusion Exclusion	X	X											
Randomization		X											
Traditional Korean and Japan syndrome diagnosis		X				X							
Vital Signs	X	_____											

Period	Screening Wash-out	Active Treatment											
Week	- 2	1	2	3	4	5	6 End	7	8	9	10 FU	11	12
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13
100mg VAS	X	_____											
WOMAC pain	X	_____											
WOMAC index		X				X					X	X	
HQ		X				X					X	X	
LEF1		X				X					X	X	
SF-36		X				X					X	X	
adverse events Documentation ^(†)		X _____											
Moskang ^(‡)		X _____											
Acupuncture belief ^(§)		X _____											

Event		Yes	No	Comment
Administration problems	Needle lost or forgotten			
	Patient forgotten in treatment room			
	Broken needle			
Application site problems	Skin infection			
	Blister following moribundation			
	Needle allergy			
	Needle-site pain			
	Hematoma			
Cardiovascular problems	Fainting			
	Dizziness			
Gastrointestinal problems	Nausea			
	Vomiting			
Neurological and Psychiatric problems	Anxiety and panic			
	Rage			
	Released emotional state (ephoric)			
	Depressed emotional state, neurovegetative dystonia			
	Headache for 3 days			
	Hyperaesthesia with numbness for 3 days			
General problems	Seizure shortly after insertion of needles			
	Drowsiness			
	Disorientation			
	Lethargy			
	Sleep disturbance			
	Patient fell asleep during treatment			
	Aggravation of existing ailments			

Others

- **Blinding**
- **Acupuncture beliefs**
- **Data Management/CRF**
- **Statistics**
- **Monitoring**
- **Informed Consent**
- **Insurance**
- **Remuneration**

The 55th Congress of the Japan Society of Acupuncture and Moxibustion in KANAZAWA Jun.16.2006.
The 3rd Japan-Korea Workshop on Acupuncture and EBM

Proposal of clinical trial design N-of-1 trials for the individualized therapy on the knee pain

Meiji University of Oriental Medicine
TAKAHASHI, Norihito.

The 55th Congress of the Japan Society of Acupuncture and Moxibustion in KANAZAWA Jun.16.2006.
The 3rd Japan-Korea Workshop on Acupuncture and EBM

Proposal

We propose to use the n-of-1 design
for the Japan-Korea cooperated clinical
trial for acupuncture and moxibustion
treatment of knee pain.

The 55th Congress of the Japan Society of Acupuncture and Moxibustion in KANAZAWA Jun.16.2006.
The 3rd Japan-Korea Workshop on Acupuncture and EBM

Reasons

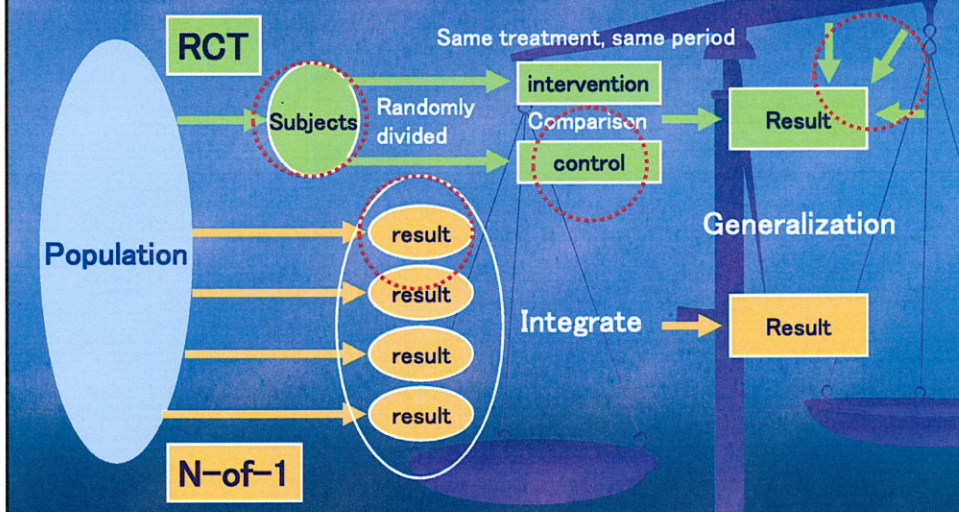
RCT is ...

Difficult to recruit many subjects
in the same time.

Difficult to manage many subjects
with many institutions.

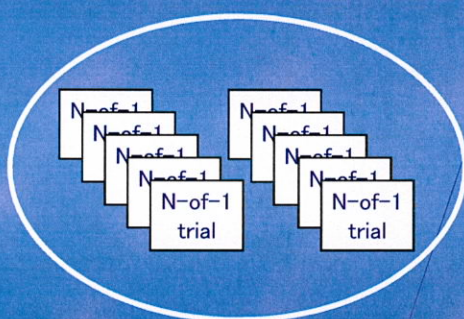
The 55th Congress of the Japan Society of Acupuncture and Moxibustion in KANAZAWA Jun.16.2006.
The 3rd Japan-Korea Workshop on Acupuncture and EBM

RCT and integrate N-of-1



The 55th Congress of the Japan Society of Acupuncture and Moxibustion in KANAZAWA Jun.16.2006.
The 3rd Japan-Korea Workshop on Acupuncture and EBM

Is it possible?



Various N-of-1 trials
(same disease such as knee pain)
Various patients
Various treatments
Various trial periods
Various the trial season
.
.
.
etc...

Meta-analysis?

Generalization?

The 55th Congress of the Japan Society of Acupuncture and Moxibustion in KANAZAWA Jun.16.2006.
The 3rd Japan-Korea Workshop on Acupuncture and EBM

Problems

It may incline toward the patient
who is likely to be effective.
(selection bias)



We have to recruit a patient so that there may be no deviation.
(It's at random ?)

The 55th Congress of the Japan Society of Acupuncture and Moxibustion in KANAZAWA Jun.16.2006.
The 3rd Japan-Korea Workshop on Acupuncture and EBM

Problems

Methods to integrating the result of the trials
for an individual and to generalization.



Can the statistics technique for a group divert as it is?

The 55th Congress of the Japan Society of Acupuncture and Moxibustion in KANAZAWA Jun.16.2006.
The 3rd Japan-Korea Workshop on Acupuncture and EBM

If problems were solved ...

It may be released from the difficulty
which manages many patients simultaneously.

Furthermore, more clearly curative effect of
acupuncture and moxibustion may be able to be
discovered.

膝OAに対する鍼RCT

—そのデザインの方法の要点—

日韓共同研究アドバイザー

七堂 利幸

Randomized Clinical Trials of Acupuncture in Patients with Osteoarthritis of the Knee

—Its Designing and planning order—

Korea/Japan Joint Research

Adviser: Toshiyuki SHICHIDO

デザインの順序

- 1. 評価表の検討
 - 信頼性・妥当性試験
- 2. 対照の置き方
 - ①プラセボ鍼、②Sham処置(微鍼、..)、③その他(標準治療、無処置など)
 - 信頼性(信憑性)・妥当性試験
- 3. 実施可能性
 - ①そんな治療出来るの？
 - ②集まるの？; サンプルサイズの設計
- 4. その他(経験的から得た注意; 割付の遮蔽など)

Procedure

1. Designing Questionnaires and Scales
Pretest: Validity (Face Validity), Reliability (reproducibility)
2. Control: ①placebo acupuncture; 「acting cause always placebo effect」,
②sham control (minimal acupuncture., except acupuncture points,..),
③others (Standard Treatment, no treatment...).
- Reliability/Validity Test
3. Feasibility (number of subject, technical expertise,..)
4. Warning against points (allocation concealment..)

1. 評価表の検討

- ①信頼性・妥当性試験
- ②尺度の理解(比、間隔、順序、分類)と処理
尺度の非科学的変換はデータねつ造になり、試験そのものが無駄になる。
- ③海外の評価表なら、翻訳してその国の文化の適合するものかどうか必ず確かめてから使用する。

1.Examination in Questionnaires

- Reliability (reproducibility), Validity Test
- Scale (ratio, interval, ordinal, nominal): accurate choosing & using.
- Example ;percentage change from baseline should not be used in statistical analysis. Very risky variable!
- Translated Oversea Questionnaire ; need the reliability/validity test.

1-1 実際の手順(評価表)

- 先行RCTでの使用頻度と信頼性・妥当性試験が済んでいるかの確認。
- 膝評価表の調査結果; ①WOMAC(痛み;これだけでは?・機能尺度;「鍼をすると楽になる」の評価。以上2尺度)、それとの併用では②VAS、・・③SF-36、・・
- 例)膝JOA(日本整形外科学会判定基準)は腰JOA同様、信頼性・妥当性試験なしで使えない。JOAはWOMAC日本語版の著作権が高価なため獲得断念、SF-36も参考にして独自の評価表JKOMを作成中。

1-1.Examination in Questionnaires

- If foregoing papers, must confirm its frequency and reliability /validity test.
- Selection; WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index; only pain/function scale), VAS, ..SF-36
- Example; Gonarthrosis by Japan Orthopedic Association (JOA) score; no reliability /validity test. JOA give up copyright of WOMAC Japan Edition, new score JKOM making out.

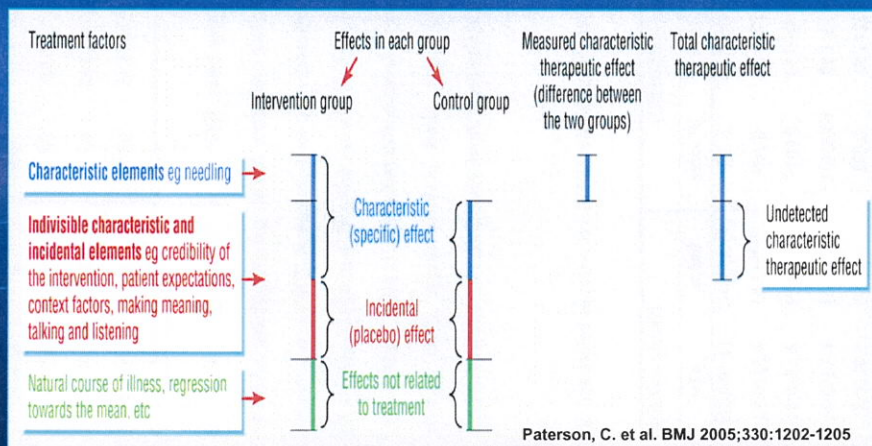
2. 対照の置き方

- ①. プラセボ鍼; Streitberger鍼、Park鍼？
信頼性(信憑性)・妥当性試験必要。reliability(再現性)
≠credibility(信憑性)
Credibility: 試験のつど、「鍼や何か(介入)をどう感じますか？本物の鍼と意思しますか？」＝被験者・術者間信頼性。
- ②. Sham処置(微鍼、..)；微鍼は生理学的活性作用があるのでプラセボ鍼ではない。後の実例で説明するが、RCTは鍼効果が偽陰性に出やすい設定なので、効果は対照との比較で相対的なので差の大きい対照を選ぶ。
 - プラセボの条件：心理的に試験群と同じインパクト＋生理学的非活性。非刺入は刺入のコントロールになるか？プラセボ鍼を使った場合、一般の鍼治療と異なる試験群(Non-pragmatic)となる。
 - 鍼治療行為自体、プラセボ効果を生む？
- ③. その他(偽TENS、標準治療、無処置、..)；試験群の鍼と心理的に異なる対照(unfair control)の是非：目的に応じて使い分け！
 - ◎：鍼群は対照群との相対効果で有効率は一定でない。

2.Plannig Control Group

1. Streitberger needle、Park needle、..
Park; credibility & Validity. reliability≠ credibility=inter- rater reliability.
Necessary condition; reliability← validity.
2. Sham Control; minimal acupuncture, missing acupuncture points, waiting list control,..
3. Placebo: psychological impact to the experimental treatment+ physiologic inactivity. ①Non-Insert control? ②Acting causes placebo. ③Non-pragmatic experimental group.

Application of randomised controlled design to trial of non-pharmaceutical intervention such as acupuncture



Copyright ©2005 BMJ Publishing Group Ltd.

bmj.com

Streitberger 鍼 (1998)

Lancet, Vol352, 364-5

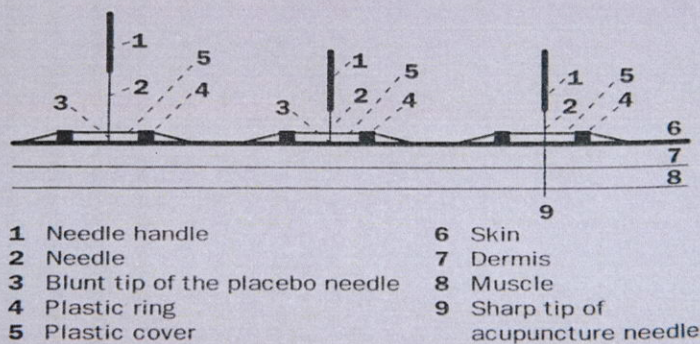


Figure 1: Placebo needle

Streitberger needle

- Subjects: None had acupuncture experience, volunteers. :External Validity?
- Streitberger needle causes a pricking sensation.:not inert?
- Nearly 40% were able to detect a difference in treatment type between needles.(Pain,109,2004)
- Underpowered study (Pain, Valid study ;White et al.2003)
- Inter-practitioner reliability is needed.

Streitberger の鍼

- 研究対象は鍼経験の無いボランティア :一般化?
- Streitbergerの鍼はちくりと刺す感覚を起こす。これは非活性でない。
- 40%近くの人が鍼間の治療タイプの違いを検出可能。(Pain,109,2004)
- Underpower(Valid study; White et al.2003)
- Inter-practitioner reliability is needed.

Park鍼(2002)

Acupuncture Med 20(4)、168-74

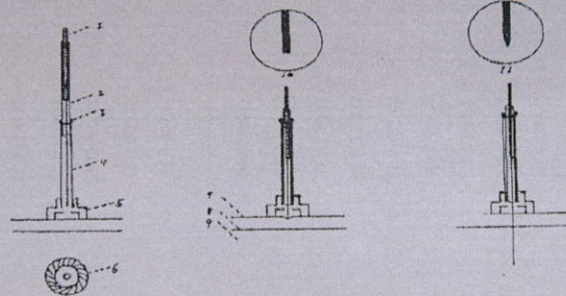


Figure 1a Park Sham Device with sham needle and real needle. 1. Needle handle, 2. Guide tube, 3. Guide O-Ring, 4. Park tube, 5. Flange, 6. Double sided tape, 7. Skin, 8. Dermis, 9. Muscle, 10. Dull tip of sham needle, 11. Sharp tip of real needle

Park needle(2002)

- Jongbae Park
- Telescopic device
- Validating device by inter-rater reliability.
- Indistinguishable Real acupuncture and inactive, for use in Sham-controlled trials.
- Acupuncture Med 20(4)、168-74

円皮鍼(セイリン製)

- 適応症委員会による施術者間・被験者間信頼性試験の結果、鍼体長0.6mm以下の円皮鍼では偽円皮鍼との区別がつかない。
- そこでこの偽円皮鍼をRCTのプラセボ鍼として使える。



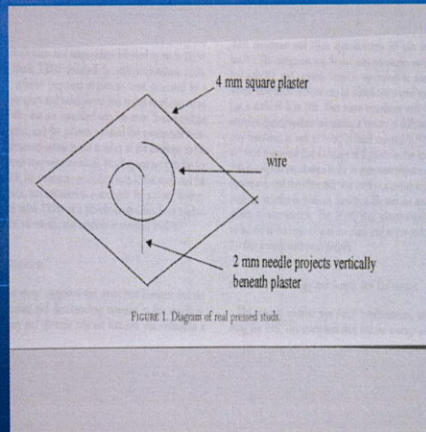
Round skin needle

- a needle stuck to the skin, made in Japan (Seirin Company).
- By Our Inter-rater reliability test, 0.6mm round skin needle can use placebo needle.



Real pressed studs(鋌鍼)

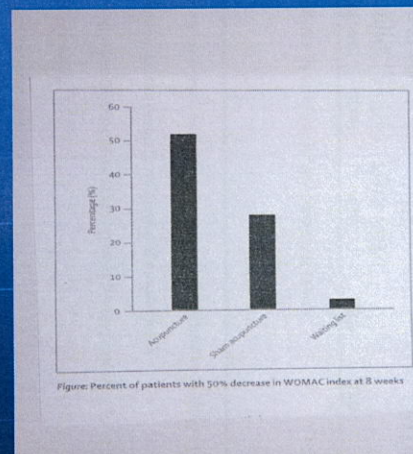
- Lewith and colleagues(2004),
- Chest/125/5/1783-90.
- For Disabling breathlessness



Witt and Colleagues(2005)

Lancet, 366, 136-43

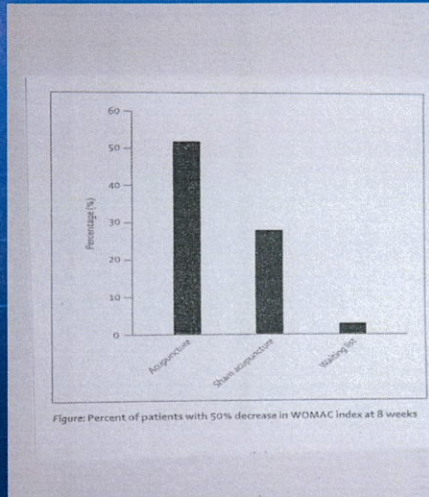
- NNT (Number-needed-to-treat)
- Waiting List vs. Acupuncture = 2 [95%CI;1.7-2.5].
- Waiting List vs. Sham acupuncture = 4 [95%CI;2.8-7.0]
- Sham acupuncture vs. Acupuncture = 4.2 [95%CI2.7-9.3]



Witt and Colleagues(2005)

Lancet, 366, 136–43

- NNT(Number-needed-to-treat)
- 鍼:無処置コントロールでは鍼のNNTは2
- 鍼:Shamコントロール(微鍼)を使うと、鍼のNNTは4.2
- コントロール次第で試験群の効果が変わる！



適応症委員会での対照群？

- 我々の研究:「円皮鍼は有効か？」
- 「鍼」 vs. 「円皮鍼」の比較では、心理的影響が異なる可能性
- 例えば週2回の1回を円皮鍼、あるいは週2回とも円皮鍼を加える治療。
- 偽円皮鍼は0.6mm以下なら被験者も術者も見破れない。
- (鍼+円皮鍼):試験群
- (鍼+偽円皮鍼):対照群

Our Group RCT's Control

- Research Question: round skin needle effectiveness?
- Acupuncture versus round skin needle: psychological difference? And so ..
- Experiment group: acupuncture + real round skin needle
- Control group: acupuncture + sham round skin needle

治療頻度・期間

- 膝OAの鍼RCT調査結果；
- 治療間隔は2回／週。
- 治療期間は8週間。
- フォローアップ；六ヶ月以上。鍼とSham鍼の効果が同じになる期間（Wittら、2005）。
- 試験終了後、鍼＋大腿四頭筋の強化運動を指導。「鍼効果は8W以後長持ちしない」；対策。

サンプルサイズ

- 膝OAに対する円皮鍼の試験データ(文献)なし。
- そこで、Pilot試験を実施して探索。
- サンプルサイズは解析法で決まる。
- 一元配置・繰り返し測定ANOVA: $\alpha=0.05$, $\beta=4\alpha$ とすると、 $\text{power}=0.8$ 、系列相関 $=0.4$ で(測定点数 $=16$)、3群、仮定ES: 0.5 とすると約40名/群。脱落3割として約50例。ちなみに仮定ES: 0.30 とすると、 $n=130$ /群。
- 考察)最近の良質当該論文の症例数は、 <70 例と多い、同条件なら仮定ES <0.5 とみている。

Sample size

- No literature of acupuncture efficacy for OA of the knee.
- Pilot study for exploratory.
- One-way Repeated measurement ANOVA : $\alpha=0.05$, $\beta=4\alpha$; $\text{power}=0.8$, correlation among the repeated observations $=0.4$ (number of repeated points per person $=16$)、3 Groups, hypothesis effect size $=0.5$; about 40/Group, dropout rate 30% $\Rightarrow 50/G(2 \text{ arm})$
- Recently high quality (RCT) Acupuncture literatures: Hypothesis Effect size ≤ 0.5

3. 実施可能性(Feasibility)

①. その方法は現実に来るの？

器具・日程・費用・その他のプランなど。

Pragmaticな試験; 日常診療に類似した試験デザインで、単なる実用的試験ではない。

②. そんなに集まるの? ; サンプルサイズの設計後、取り込み基準を広く、不要な除外基準を除き、デザインを考慮。

③. 必要とされる専門性: 測定方法、データ処理の専門性。

Feasibility

- Adequate number of subjects
- Adequate technical expertise

The investigation must have the skills ,..., measuring the variables, and managing analyzing the data.

- Affordable in time and money
- Manageable in scope

Problem often arise!

4. 解析方法

- WOMAC (VAS, SF-36) で経時的測定。「痛み」と「身体機能」の2項目必須選択。
- 線型混合モデル: 多施設共同研究であるから、施設(患者)および施設×試験治療の交互作用を変量効果として扱う(臨床試験のための統計的原則より)。
- 試験治療効果の不均一性の探索(施設不均一の経験)。
- 欠測値が多い時でも解析可能。多施設数には適切。
- 回帰モデルGEE (Generalized Estimating Equations): 二値、順序データ向き。

4. Data analysis Methods

- Score for WOMAC (VAS, SF-36): longitudinal analysis.
- Multi-centre trials: centre/patients: random-effect (model).
- Mixed effect model suitable for unbalanced data, number of multi-centre trials, exploratory imbalance of center.
- GEE (Generalized Estimating Equations): suitable for binary & ordinal data.

4-1. その他; Randomization

- 「自らランダム割付をした」: それは信用できる? 背景因子などの確認の手段は?
- 背景因子の検定をして有意差なしで群間差なしと結論しても、この帰無仮説は「真」で有意差検定無意味。
- 比較可能性: ランダム割付していない2群は比較は可、でも検定は?

4-1. others; Randomization

- Do you believe the entry 'do randomized' without background factor analysing?
- Do you mean significance test in Background factor?
- Even before test, null hypothesis is true. Insignificant!
- Comparable Possibility?—baseline analysis -- failure in randomization?—significance test meaningless?

4-2. その他; Allocation Concealment

- 不十分な試験は平均的に介入の効果を約40%過大評価する(Schulz, 1995)。
- 我々の経験から: 学生対象の、鍼: 無処置の試験では、各群に割り当てられた学生たちが被験者どうしで意見交換をし、割付隠蔽の不十分さがHawthorne 効果(期待効果)を生み、結果を歪める。(確認バイアスという)
- これは病院の患者どうしでも起こり得る。
- 対照がプラセボ鍼でないかぎり起こりうる。

4-2. Others; Allocation Concealment

- Trials with inadequate allocation concealment can exaggerate the effects of interventions by as much as 40% on average (Schulz et al. JAMA, 1995).
- We experience the failure of Hawthorne effect (acupuncture versus no treatment). : Ascertainment bias
- Expectation effect necessarily happen except using perfect placebo needle.

Treatment Term & Frequency

- By Acupuncture RCT on OA of the knee,
- Treatment term: 8 Weeks
- Treatment frequency: 2 times/week
- Follow-up: 6 months \geq . When the acupuncture has a similar efficacy to sham acupuncture.
- Practical & clinically methods, On acupuncture add in exercise.

適格基準

- American College of RA.の診断基準: 50歳以上、30分以上の朝のこわばり、コツコツという動き。
- 論文: Streitberger et al. (2004), BMC, study protocol.
- 取り込み基準; 研究テーマにふさわしい母集団
- 除外基準; 研究対象にふさわしくない者除外
- 実施可能性を考慮。

Eligibility Criteria

- The criteria of diagnosis of OA of the knee (Age>50, Morning stiffness<30 min., Crepitus on motion).; Definition from American College of RA.
- Reference: Streitberger et al.(2004),BMC,study protocol.
- ①Inclusion criteria
 - <40 years, Signed IC,
- ②Exclusion criteria
 - Bone tumor, Acute infection, Acupuncture treatment of gonarthrosis,..

Point selection in the references of Knee OA research

*Department of Clinical Acupuncture¹,
Physiology²*

Meiji University of Oriental Medicine,

Hiyoshi, Funai, Kyoto, 629-0392, JAPAN

***ITO H K¹, Hirota S¹, Kitakoji H¹,
Okada K², Kawakita K²***

Background

In the evaluation of the efficacy of acupuncture, important parameters are the stimulation site, intensity and the modality of stimulation of the needle. For the assessment of the stimulation site, one can indicate certain variable, numbers of stimulation sites, and the location of the stimulation site.

On the other hand, in most previous studies, the location of the stimulation site in knee osteoarthritis patients is a traditional acupuncture point around the knee .

Aim of Investigation

Our main aim in this study was to examine the widely-used and effective stimulation sites on osteoarthritis of the knee.

Methods 1

1. Database search

Medline (from 1966 to 2005)

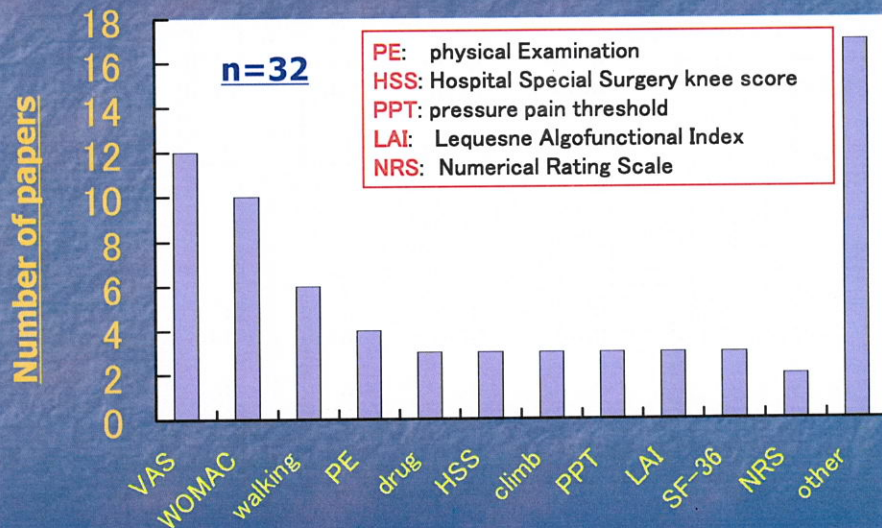
2. Search terms (① and ②)

- ① 'acupuncture' or 'moxibustion'
- ② 'osteoarthritis of knee', 'knee osteoarthritis', or 'knee pain'

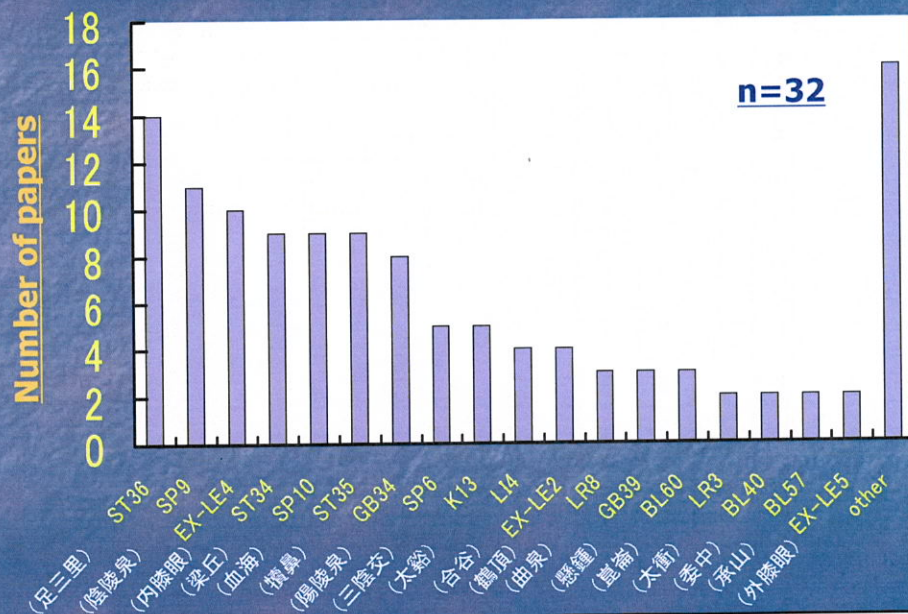
The search was also limited to 'humans' and 'English'.

* On the other hand, we also searched the references of each papers. These papers with knee osteoarthritis were included in this review.

Frequency of use on outcome measure



Frequency of use on treatment point



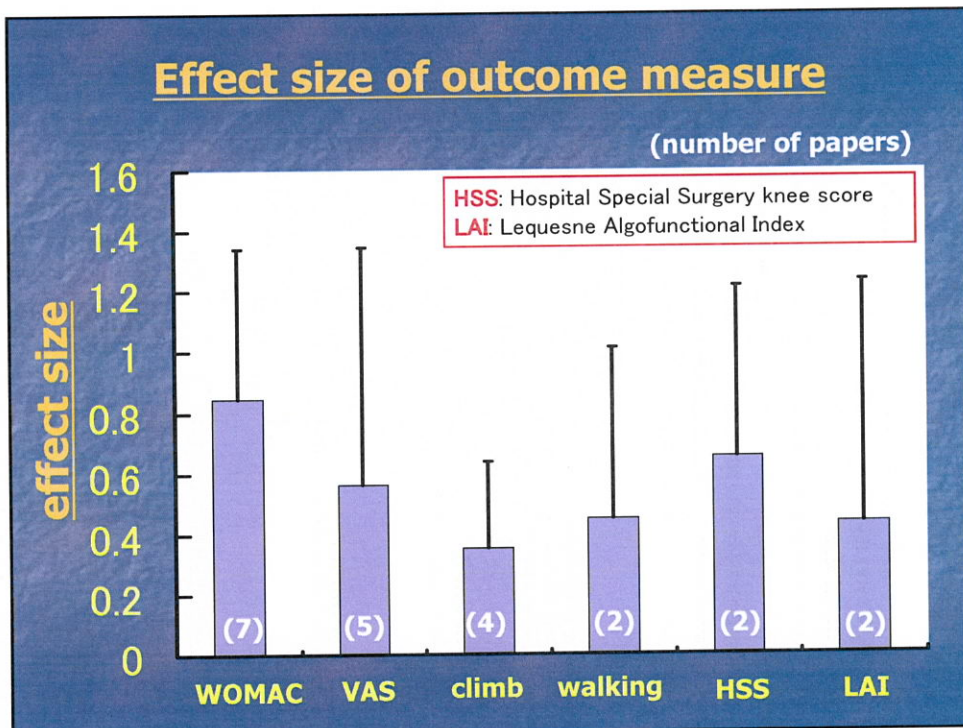
Methods 2

3. Effect size

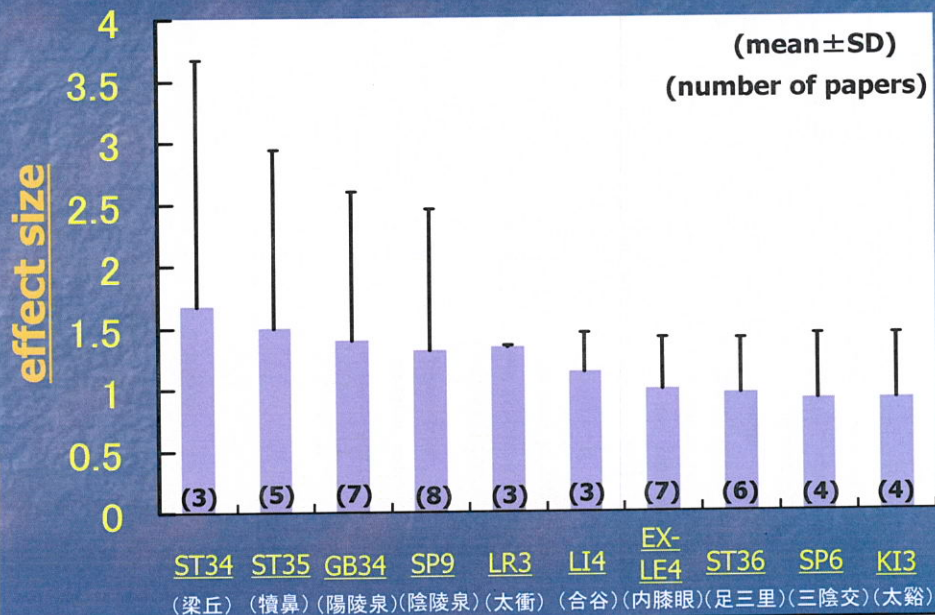
- Effect size is change in endpoint divided by standard deviation (SD).

$$\text{Effect size} = \left(\frac{\text{Mean}_{\text{acupuncture}} - \text{Mean}_{\text{control}}}{\text{SD}} \right)$$

* However, it was not possible to calculate formal effect size because too few authors reported standard deviation. Therefore, we analyzed only the written papers of standard deviation.



Effect size of treatment points



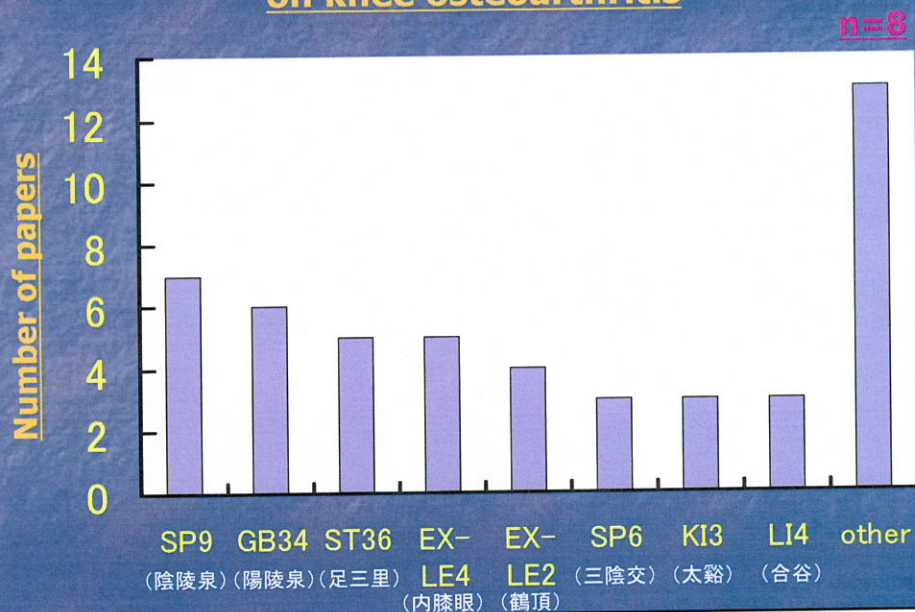
effect size: more than 1.0

	n	controls	outcome measure	effect size
Yurtkuran M et al Am J Acupunct; 1999	100	placebo (EA)	walking times (50 m)	3.96
Tukmachi E et al Acupunct Med; 2004	30	non-treatment	WOMAC	1.55
			VAS	1.46
Berman BM et al Rheumatology; 1999	73	non-treatment	WOMAC	1.36
Vas J et al BMJ; 2004	97	sham	VAS	1.36
			WOMAC	1.08
Sangdee C et al BMC Complement Altern Med; 2002	193	placebo (EA)	VAS	1.18

effect size: more than 0.5

	n	controls	outcome measure	effect size
Takeda W et al Arthritis Care Res; 1994	40	sham	McGill WOMAC	0.83 0.51
Berman BM et al Ann Intern Med; 2004	570	non-treatment	WOMAC	0.68
Tillu A et al Acupunct Med; 2001	75	non-treatment	walking time(50mm) Climb 20 step	0.54 0.53

Distribution of effective points on knee osteoarthritis



Conclusion

The SP9·GB34·EX-LE4·ST35·ST36 is more useful and effective than the other points on osteoarthritis of the knee.

effective points

SP9(陰陵泉), GB34(陽陵泉), EX-LE4(內膝眼)
ST35(犢鼻), ST36(足三里)

Supplement explanation

How large is that effect of VAS?

VAS: 0.71 ± 0.72 (effect size)

- v.s. Control (non-treatment): 2 papers

effect size: 1.12 ± 0.49 (0.77~1.4)

ST36, SP9, SP10

- v.s sham: 3 papers

effect size: 0.66 ± 1.03 (0.5~1.3)

ST36, EX-LE4

- v.s. other treatment: 1 paper (drug)

effect size: 0.68

ST36, EX-LE4, LR8

How large is that effect of WOMAC?

WOMAC: 0.64 ± 0.65 (effect size)

- v.s. Control (non-treatment): 3 papers

effect size: 1.19 ± 0.45 (0.68~1.5)

ST36, GB33, GB34, EX-LE4

- v.s. sham: 3 papers

effect size: 0.33 ± 0.72 (0.35~1.1)

ST36, GB33, GB34

- v.s. other acupuncture: 2 papers

effect size: 0.28 ± 0.01 (0.27~0.28)

ST36, GB33, GB34, EX-LE2, EL-LT4

Conclusion 2

The standard acupuncture treatment (GB34,SP6, ST36, ST35, EX-LE5) is not more effective than the other acupuncture treatment on knee osteoarthritis.

**The problems in carrying out the
questionnaire in Japan, that had
carried out in Korea**

Meiji University of Oriental Medicine

SUMIYA Eiji

- **The questionnaire survey on the osteoarthritis of knee that had already carried out in Korea would be carried out even in Japan.**
- **The content of this questionnaire is almost same as that carried out in Korea, but it is changed in order to be suitable for present acupuncture treatment style of Japan.**
- **In this presentation, I will discuss about the problems in carrying out this questionnaire in Japan.**

- 1. In present Japan, there are 4 main acupuncture and moxibustion treatment styles.**
 - 1) based on Western Medicine**
 - 2) based on Traditional Chinese Medicine**
 - 3) meridian treatment style**
 - 4) eclectic style**
- 2. Japanese acupuncturists can infer but not determine osteoarthritis of knee.**

- 3. Not a few acupuncturist who don't know about the theory of meridian and collateral or the theory of Yin and Yang organs well.**
- 4. Many acupuncturist who treat using the style based on Western Medicine don't understand reinforcing and reducing manipulations.**

- 5. Many acupuncturist who treat using the style based on Western Medicine don't understand arrival of qi well.**
- 6. The treatment effect on osteoarthritis is influenced by the degree of seriousness of symptoms.**
- 7. And now In Japan, all acupuncturists can't treat using Pricking and cupping therapy for the purpose of hemorrhage on the law.**

- The problems in carrying out the questionnaire in Japan is the above.**
- It will send to and received answers from 1,000 members chosen randomly from 6,000 registration members of The Japan Acupuncture and Moxibustion Association by computer.**
- It is thought that the result of this questionnaire survey will be report in next opportunity.**
- Thank you very much for your attention.**

Effect of press tack needle(PTN) treatment on shoulder stiffness

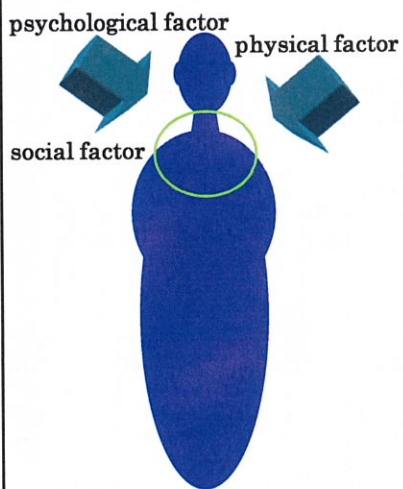
Tokyo Therapeutic Institute

Eiji Furuya ph.D

Out line

1. What is shoulder stiffness?
2. Characteristic of PTN
3. Examination design
4. Effect on shoulder stiffness by PTN

Shoulder stiffness



the cause of shoulder stiffness

Shoulder Stiffness is frequently treated with acupuncture moxibustion treatment.

It is caused by a psychological factor, a physical factor and a social factor.

We also think that shoulder stiffness occurs by a reduce of pain threshold and is concerned with autonomous nerve.

A definition of shoulder stiffness.

- Unpleasantness and a strain of trapezius
- These symptoms is improved by a rub or a slight pressure.

In additional, there are patients with "a stiffness feeling" without strain.

Medical examination

I do a physical examination to investigate a cause of shoulder stiffness.
for example ;

- | | | |
|-----------------------------|---|----------------------|
| herniated nucleous pulposus | → | radiculopathy |
| | | Jackson test |
| | | Spurling test |
| | | biceps reflex |
| | | brachioradial reflex |
| | | triceps reflex |
| thoracic outlet syndrom | → | Adson test |
| | | Morley test |
| | | Allen test |
| | | Right test |
| | | Eden test, etc. |

When I can find a cause, we must give priority to a decision of diagnosis of modern western medicine before acupuncture and moxibustion treatment.

PTN treatment

PTN is used for the purpose of a pain reduce or a to prolong the effect of regular acupuncture moxibustion treatment.

For example, PTN is used for relaxation of shoulder stiffness in chronic symptoms.

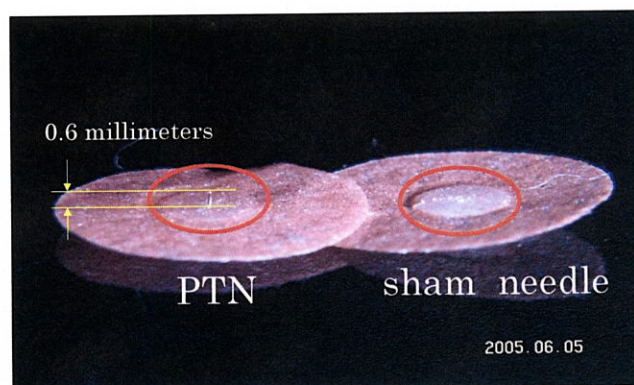
However, there are few reports that inspected the effectiveness of PTN itself.

Therefore this study was planned to inspect curative effect of PTN.

A change of subjective symptoms after treatment was compared with PTN or sham needle for a shoulder stiffness volunteer.

This study investigated a clinical significance of PTN treatment by a randomised control trial (RCT).

PTN and sham needle



The length of PTN is 0.6 millimeters. The needle is fixed to plastic. And these are attached to an adhesive plaster. We can treat to putting an adhesive plaster with PTN on skin.

The sham needle removed a part of needle from PTN.

This photograph was offered by Dr. Ito of an indication committee.

Method

Subject; volunteers for awareness of shoulder stiffness.

56 men and women totals

the staff and a student of Tokyo Therapeutic Institute.

Screening of shoulder stiffness; a subjective symptoms of fatigue test
(Japanese Society of Occupational Health
fatigue meeting)

Investigation period; from October 10th to November 27th, 2000.

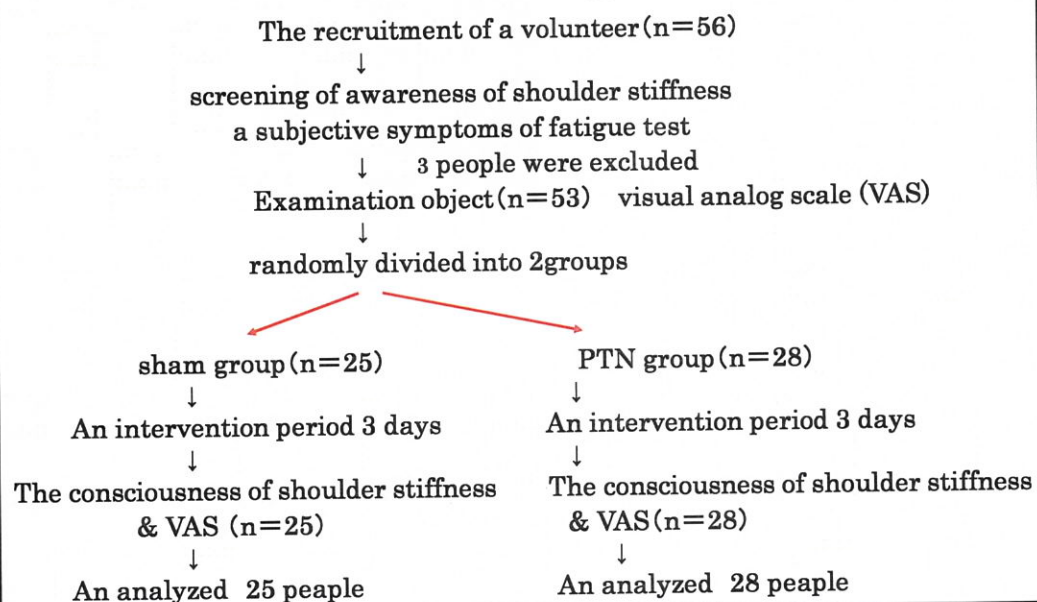
Stimulation method; maximum of 4 tender points

leave PTN or sham for three days

PTN (pyonex) ; Length is 0.6mm.

PTN and sham ; made by Seirin Co., Ltd.

Flow diagram



Results

A subject	Sham group	PTN groupe
male	7	8
female	18	20
age (years old)	31.8±9.0	35.1±11.9
height(cm)	161.0±6.9	162.0± 9.5
body weight(kg)	57.1±10.4	57.4±11.3
duration of		
shoulder stiffness (year)	7.7±5.3	9.7±7.8

Physical examination

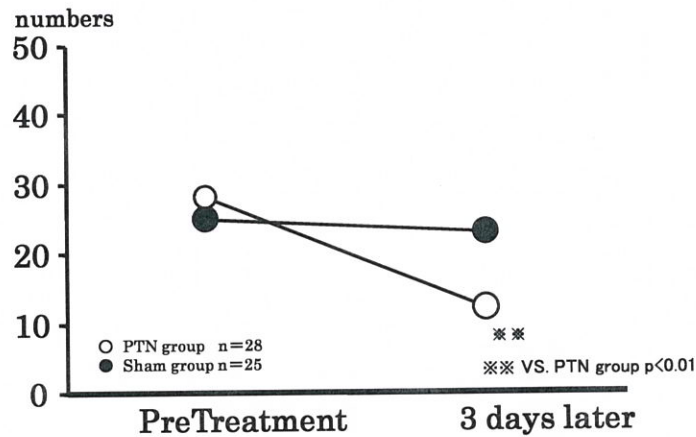
positive sign

	sham group 6 out of 25 people	PTN group 9 out of 28 people
Morley test	4	5
Right test	3	5
Allen test	3	2
Eden test	1	3
Biceps reflex	0	1(reduce)
Triceps reflex	0	1(reduce)

diagnosis

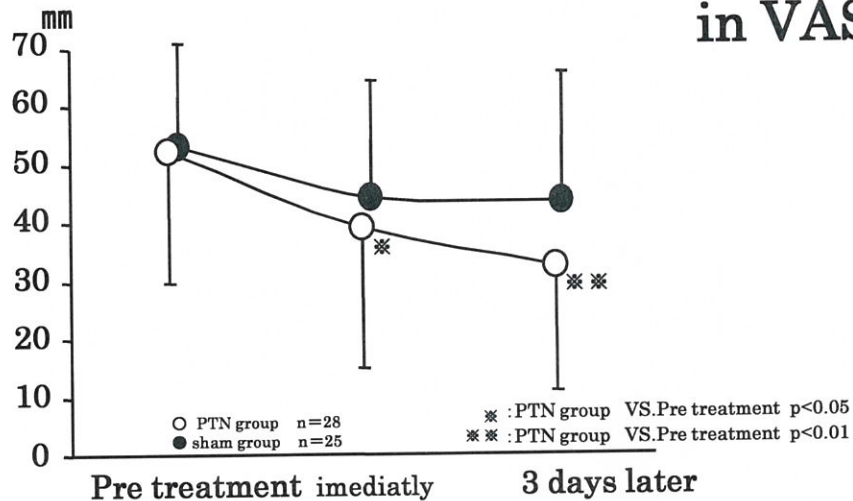
thoracic outlet syndrom	1	0
cervical spondylosis	1	1
shoulder stiffness	0	1
muscle pain	0	1

Shoulder stiffness



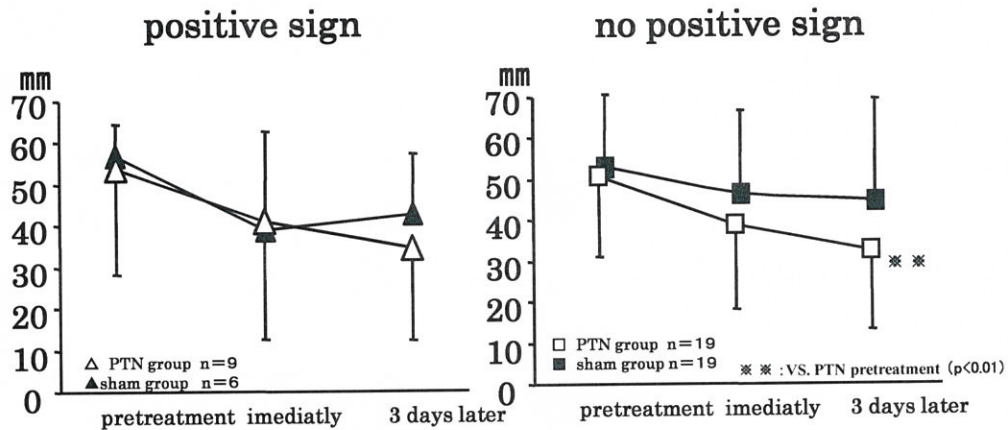
The number of the voluntree reporting awareness of shoulder stiffness after 3 days decreased from 28 to 12 people in the PTN group, and from 25 to 23 in the sham group. There was a significant difference between the 2 groups ($p<0.01$).

The degree of shoulder stiffness in VAS



The VAS value decreased in the PTN group from 52.5 ± 20.7 mm to 40.5 ± 22.4 mm, and to 34.2 ± 19.7 mm. While in the Sham group from 55.2 ± 17.5 mm to 46.5 ± 19.7 mm to 45.9 ± 21.7 mm. PTN group were significant difference between pretreatment and treatment imediately ($p<0.05$), and between pretreatment and 3 days later ($p<0.01$).

A classification by physical examination



The right slide did not have positive sign. The degree of shoulder stiffness decreased by PTN in 3 days later.

Adverse event

An incidence of advers event; 16.9% (3.8% by PTN group)

PTN group ... Feel of sticking 1 person, An itch 4 people

Sham group ... Sense of incongruity 1 person, an itch 3 people

* Feel of sticking disappeared by removing PTN.

A cause of itch; Affixed an adhesive plaster for 3 days.

→ If only for one day, it will not occur.

Conclusion


1. "Shoulder stiffness" was decreased with PTN ($p < 0.01$).
2. VAS value of shoulder stiffness decreased PTN treatment immediately ($p < 0.05$), and 3 days later ($p < 0.01$), too.

PTN stimulated skin area which was controlled by the nervous system as same as muscle tissue of shoulder stiffness.

I thought that this stimulation changed the pain threshold and adjusted autonomous nerve system.

It was suggested that PTN treatment on the tender points improved shoulder stiffness.

Safety of Acupuncture for Knee OA

YAMASHITA, Hitoshi
Committee for Safe Acupuncture
 JSAM



Published Case Reports on Acupuncture Adverse Events in Treating Knee OA

- Woo PC, et al. **Acupuncture mycobacteriosis**. N Engl J Med 2001; 345(11): 842-843.
- Kao CL, et al. **Pseudoaneurysm of the popliteal artery**. Tex Heart Inst J 2002; 29(2): 126-129.
- Saw A, et al. **Necrotising fasciitis**: a life-threatening complication of acupuncture in a patient with diabetes mellitus. Singapore Med J 2004; 45(4): 180-182.
- Oda T, et al. Experience of treatment for **candida arthritis of the knee**. Kansai Kansetsu-kyo Hiza Kenkyu Kai Shi 1997; 8(1): 28-29.

How often? Causal relationship established?

Problems in Safety Assessment of Acupuncture

- 1a. Systematic Review of RCTs
- 1b. Randomized Controlled Trial
- 2b. Cohort Study (Prospective)
- 3b. Case-Control Study (Retrospective)
4. Case Series Study
5. Experts' Opinion, Case Report

Hierarchy of Clinical Evidence
(Level of Evidence)

A Review of Safety Information from Acupuncture RCTs on Knee OA

- Data Source
 - PubMed
 - Igaku Chuo Zasshi (Japan Central Review of Medicine)
- Keywords
 - acupuncture, electroacupuncture, osteoarthritis, knee, gonalgia, gonarthrosis
- “Limits” (PubMed)
 - randomized controlled trial

Located RCT Papers

- 11 papers (1992-2005)
 - 1) Christensen BV, et al. Acta Anaesthesiol Scand 1992; 36: 519-525.
 - 2) Takeda W, et al. Arthritis Care Res 1994; 7(3): 118-122.
 - 3) Yurtkuran M, et al. Am J Acupunct 1999; 27(3-4): 133-140.
 - 4) Berman BM, et al. Rheumatology 1999; 38(4): 346-354.
 - 5) Sangdee C, et al. BMC Complement Altern Med 2002; Mar 21; 2: 3.
 - 6) 小澤庸宏, et al. 鍼灸OSAKA 2002; 18(4): 393-396.
 - 7) Ng MM, et al. J Altern Complement Med 2003; 9(5): 641-649.
 - 8) Tukmachi E, et al. Acupunct Med 2004; 22(1): 14-22. 1)
 - 9) Vas J, et al. BMJ 2004; 329: 1216-1219 (BMJ, doi: 10.1136/bmj.38238.601447.3A).
 - 10) Berman BM, et al. Ann Intern Med 2004; 141: 901-910.
 - 11) Witt C, et al. Lancet 2005; 366: 136-143.

Reported AEs in acupuncture RCTs

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" (no specific description) (of 190 patients treated)	(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)

Reported AEs in acupuncture RCTs

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

Papers Which Reported AEs

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 sequelae). 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" (no specific description) (of 190 patients treated)	(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)

Recommendations for Establishing Safety Information on Adverse Events in Acupuncture RCTs

1. Calculate each event's incidence (frequency)
 - Number of each adverse reaction
÷ the number of patients/treatment sessions
2. Classify the events caused by acupuncture
 - Avoidability (Inherent reaction or human error?)
 - Fainting, bruise etc...true "side effects"
 - Pneumothorax, infection...therapist's negligence
 - Severity (NCI CTC?)





Center for Integrative Medicine, Tsukuba University of Technology

Ethical Consideration on Conducting and Publishing Randomized Controlled Trial

Hiroshi TSUKAYAMA

Center for Integrative Medicine,
Faculty of Health Science,
Tsukuba University of Technology

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

Ethical standards in biomedical field

- The Nuremberg Code (1947)
 - Nuremberg Trials (1945-46)
- Helsinki declaration (1964)
 - World Medical Association Declaration of Helsinki
- The Belmont Report (U.S.A)
 - National Research Act (1974)
 - Ethical Principles and Guidelines for the Protection of Human Subjects of Research
 - National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (April 18, 1979)
 - Standards for Institutional Review Board.

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

International Guideline for Ethics in biomedical field

- Good Clinical Practice Guidelines (ICH-GCP) (1996)
 - International Committee on Harmonization (ICH)
- International Ethical Guidelines for Biomedical Research Involving Human Subjects
 - Council for International Organizations of Medical Sciences (CIOMS)
- Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (Updated February 2006)
 - International Committee of Medical Journal Editors

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

Principle of Micro-Ethics

1. Respect for the Autonomy of Persons
2. Non-maleficence
3. Beneficence
4. Justice

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

Potential Conflict between Micro-Ethics and Macro-Ethics

- Macro-Ethics
 - Maximized benefit for the people
 - Permit limitation on benefit for persons.
- Micro-Ethics
 - Maximized benefit for each person
- e.g.
 - Use placebo in clinical trial

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

ICH/GCP

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.

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

ICH/GCP

3. INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

- 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 fulfil its responsibilities.

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

ICH/GCP

3. INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

- The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:
 - approval/favourable opinion;
 - modifications required prior to its approval/favourable opinion;
 - disapproval / negative opinion; and
 - termination/suspension of any prior approval/favourable opinion.

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

ICH/GCP

3. INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

- 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.

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

ICH/GCP

4.4 Communication with IRB/IEC

- 4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.
- 4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.
- 4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

ICH/GCP

4.8 Informed Consent of Trial Subjects

4.8.1

- In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

ICH/GCP

4.8 Informed Consent of Trial Subjects


4.8.2

- The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/ favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3

- Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006




Center for Integrative Medicine, Tsukuba University of Technology

I C M J E

Ethical Considerations in the Conduct and Reporting of Research

- **II.A Authorship and Contributorship**
 - **II.A.1. Byline Authors**
- [Byline Authors](#)
 - Contributors Listed in Acknowledgements
- [Editorship](#)
 - The Role of the Editor
 - Editorial Freedom
- [Peer Review](#)
- [Conflicts of Interest](#)
 - Potential Conflicts of Interest Related to Individual Authors' Commitments
 - Potential Conflicts of Interest Related to Project Support
 - Potential Conflicts of Interest Related to Commitments of Editors, Journal Staff, or Reviewers
- [Privacy and Confidentiality](#)
 - Patients and Study Participants
 - Authors and Reviewers
- [Protection](#) of Human Subjects and Animals in Research

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

Everybody should agree important role of IRB/IEC on conducting clinical study.....But!

- **Members of IRB/IEC**
 - Management of IRB/IEC require special discipline.
 - A few person were trained on Bio-medical ethics.
 - Central IRB can regard as a solution?
- **Role of IRB/IEC not finish by acceptance of protocol and other forms.**
 - In reality, IRB/IEC can support continuously until end of study?

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

Conflicts of Interest

- Potential Conflicts of Interest Related to Individual Authors' Commitments
- Potential Conflicts of Interest Related to Project Support
- Potential Conflicts of Interest Related to Commitments of Editors, Journal Staff, or Reviewers
- Acupuncturist research acupuncture, it regard Conflicts of Interest, or not?

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006



Center for Integrative Medicine, Tsukuba University of Technology

Problem on insurance

- Insurance companies in Japan do not cover clinical trial initiated by researchers.
 - It is probable that IRB in University are regarded as lack of ability!
- Korean insurance companies will cover clinical trial initiated by researchers?

The 55th Congress of the JSAM, Kanazawa, 16-18 Jun. 2006

1. Why primary and secondary outcome?

- WOMAC include in the pain scale and physical function scale. Why VAS?
- HAQ include in physical function items, Why overlap with both in secondary outcome?
- LFI score (joint function), Why need it?
- How many measurements, its frequency? Masked evaluator?
- How about consideration of subject writing load, spending time?

2. Where Randomization?

- When randomization by Individual clinic ; Selection Bias?
- Central register system on site by trials operation unrelated staff.
- Coordinating center on site.

3. Analysis and sample size

- Baseline analysis; qualitative data → χ^2 test, quantitative data → t test. But VAS data is non-normal distribution?
- Main data is serial correlation data, so necessarily Analysis of longitudinal or repeated measurement, but not univariate, also multiple-endpoints = multivariate. → mixed model?; General Linear mixed model?
- What is 'a multiple imputation analysis' (page 33)?
- Sample size calculation; Why does it estimate by another race? Asian mean weight (confounding factor?) are different from westerner.

4. Others

- Which 'Intention-to-treat' or 'per protocol analysis'?
- Methods of follow-up?
- Cost-effectiveness analysis conduct?
- Specify the computer software used. [The International Committee of Medical Journal Editors (ICMJE)]