JAM
Japanese Acupuncture and Moxibustion

Original research

Re-analysis of acupuncture trials with sham interventions based on data from the Cochrane Review

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Abstract

[Objective] Recent acupuncture trials with sham control groups have failed to show significant beneficial effects of real acupuncture. As a result, the specific effects of acupuncture were discounted and assumed to be placebo and/or expectation effects. However, the sham acupuncture methods used in these studies appeared to be physiologically active. Thus the influence of the different types of sham interventions on the results were re-analysed by subgroup meta-analysis.

[Methods] Clinical acupuncture trials using sham interventions were selected from the Cochrane Database of Systematic Reviews. The outcome measures for the real and sham acupuncture groups from each study were collected. For subgroup analysis, sham interventions were classified into 5 types: Type A, needling to non-acupuncture points; Type B, superficial needling; Type C, non-penetration; Type D, electro-acupuncture to non-acupuncture points; Type E, electro-acupuncture without current. Cochrane Review Manager 5.3 software was used for analysis. Standardized mean difference and risk ratio were used to analyse continuous and dichotomous data, respectively. A random model was applied to all analyses. The heterogeneity of analysed studies was indicated as I^2, and the overall effect of pooled data was shown as Z (P value). Forest and funnel plots were made for each subgroup analysis based on the different types of sham acupuncture and pain or non-pain diseases.

[Results] A total of 116 studies were selected from the Cochrane Database of Systematic Reviews (from 1974 to 2013). The overall effects of real acupuncture were significantly more beneficial than the sham acupuncture groups in both meta-analyses of continuous and dichotomous data sets. The standardized mean difference and 95% confidence intervals were -0.34 [-0.44, -0.23] (Z=6.03, P<0.00001) and for risk ratio were 0.80 [0.73, 0.87] (Z=5.23, P<0.00001). Subgroup analysis based on sham acupuncture (Types A to E) and outcomes (pain or non-pain) demonstrated that half of the data sets were statistically significant although they were not related to the type of sham acupuncture and disease. The heterogeneity of the data sets was relatively high.

[Conclusion] Results from meta-analysis of the pooled data indicated highly significant differences between real and sham acupuncture groups; however, we should interpret these results with caution, as heterogeneity of the trials was relatively high. Despite large variations, effect sizes of non-penetrating sham acupuncture did not generally exceed those of penetrating sham acupuncture. These results suggest that non-penetrating sham acupuncture, similar to Japanese acupuncture procedures, may produce some physiological activity.

Key words: *acupuncture, sham acupuncture, clinical trials, meta-analysis, Cochrane Systematic Reviews*

I. **Introduction**

Numerous basic and clinical studies on acupuncture have been performed; however, several issues remain to be resolved. In 2007, the Society of Acupuncture Research (SAR) held an international symposium for the 10th anniversary of the NIH Consensus Development Conference on Acupuncture, where the gap between basic and clinical studies and the influence of sham acupuncture were important discussion topics[1)]. Regarding the basic mechanisms of acupuncture, several mechanisms of action have been proposed and accepted by the neuroscience field[2,3)]. However, while clinical

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acupuncture trials have been conducted worldwide and various control interventions have been used to compare the efficacy of real acupuncture, the results obtained were usually inconclusive due to the poor quality of research design, small sample size and variation in control interventions including sham acupuncture [1].

Acupuncture involves the insertion of fine needles into specific points to provoke a specific sensation called de-chi[4]. Shallow insertion of fine needles into non-acupuncture points without the "de-chi" sensation was used as sham acupuncture in a series of high quality, large sample size German acupuncture trials named ART[5] and GERAC[6]. These investigations have been conducted independently in patients with migraine, tension-type headache, chronic low back pain, and osteoarthritis of the knee. The sham acupuncture used in these German trials, called minimal acupuncture, was initially assumed to be physiologically inert as the de-chi sensation is essential for producing the therapeutic effects of acupuncture. Summarizing the results of German trials, Cummings clearly demonstrated significantly larger effects with acupuncture compared to those of waiting list controls (ART) and routine care (guideline-based standard therapy) groups (GERAC); however, statistically significant differences between real and sham acupuncture groups (ART, GERAC) were scarcely detected[7]. The misleading conclusions suggested that acupuncture had no specific effects and these were assumed to be strong placebo and/or expectation effects[8], although both real and minimal acupuncture were more effective than standard care[6,7].

Some researchers have argued that sham acupuncture is not a suitable placebo as it is physiologically active[9-11], although an ideal control has yet to be established.

In an attempt to improve acupuncture research, several non-penetrating "placebo" needles have been developed [12,13]. These needles were designed with the aim to mask the patient as the needle looks to be inserted but cannot actually penetrate the skin. A more suitable sham needle for double-masking procedures was developed to also mask the acupuncture practitioner[14]. However, these are still problematic; although the fake needles do not penetrate the skin, it is thought that application exerts enough skin pressure to create a physiological response, and, therefore is not physiologically inert[15].

If sham acupuncture is indeed biologically active, it is essential that the results be correctly interpreted. We hypothesizsed that various types of sham acupuncture exert different effects compared to control interventions with some types of sham acupuncture being more active than others. To test thise working hypothesis, we to re-analysed the published data from comparative trials of real versus sham acupuncture assessed in a Cochrane Database of Systematic Reviews (CDSR). A prior analysis by Linde et al[16]. similarly examined the influence of various sham interventions in acupuncture trials and found that sham acupuncture exerted a stronger impact than pharmacological and physical placebos. In a recent international project, MacPherson et al.[17] systematically reviewed acupuncture trials which employed various sham acupuncture methods as control interventions in the treatment of chronic musculoskeletal pain. The findings demonstrated that the effect size of penetrating needle sham was clearly smaller than those of non-penetrating needle sham. Although this study was focused on chronic musculoskeletal pain, the results appear to support our working hypothesis.

It has been well established that diffuse noxious inhibitory controls (DNIC) may play a role, at least in part, in the analgesic action of acupuncture[1,18]. Therefore, it is important to compare the impacts of various sham acupuncture procedures in non-pain diseases since painful diseases may be more strongly affected by sham acupuncture requiring the insertion of needles than non-penetrating sham interventions due to noxious stimulation-induced DNIC mechanisms.

In the present study, we re-analysed clinical trials of acupuncture using different types of sham acupuncture for various diseases and symptoms (pain or non-pain) and to compared the physiological potentials of these sham acupuncture types via subgroup analysis.

Ⅱ. Methods

1. Data extraction from the Cochrane Database of Systematic Reviews

All of the published studies included in the meta-analysis from the CDSR of acupuncture were collected on December 13, 2013. Studies in which real acupuncture groups were compared with any type of sham-intervention groups were then extracted for the present meta-analysis. All studies that used TENS-like acupuncture as a control were excluded. The primary outcomes used in the original study and CDSR were also used as our primary outcomes; however, when there was no sham acupuncture study in the primary outcome, the data from secondary outcomes were also included. We pooled all trials for comparison of the efficacy of true acupuncture against sham acupuncture. Data with both continuous and dichotomous outcomes were collected regardless of the acupuncture conditions.

2. Classification of the types of sham acupuncture

To conduct subgroup analyses, sham acupuncture methods were divided into 5 types. Type A included manual acupuncture (MA) to acupuncture points which were not relevant to the disease or MA to non-acupuncture points; Type B included shallow MA to acupuncture points, acupuncture points which are not relevant to the disease, or non-acupuncture points (known as minimal acupuncture); Type C included MA using a non-penetrating needle to acupuncture points,

non-acupuncture points, pricking sensation to acupuncture points, cocktail stick or guide tube alone; Type D included EA (electro-acupuncture) to acupuncture points which are not relevant to the disease or non-acupuncture points with current; and Type E included EA to non-acupuncture points without current. Subgroup analyses were performed to investigate whether different types of sham acupuncture would significantly impact outcomes. These groups were clustered together according to their presumed stimulus intensity.

3. Procedures of meta-analysis and subgroup analysis

Free software provided by the Cochrane Collaboration, Review Manager (RevMan 5.3), was used for meta-analysis[19]. Standardized mean difference (SMD) and risk ratio (RR) were used for continuous and dichotomous data, respectively. Data were presented with 95% confidence intervals (95% C.I.). For statistical analysis of pooled data heterogeneity, I^2 was used. Forest plots and funnel plots were made for each subgroup analysis. The former plots help to understand the RCT data and overall effect of combined data sets as Z values and P values.

Ⅲ. Results

1. Studies included in the meta-analysis and classification of sham interventions.

Table 1 summarizes the Cochrane systematic reviews used in this study. A total of 32 SRs were included, and 116 RCT studies were selected from them in which sham acupuncture interventions were compared with real acupuncture.

Bibliographic information (first author name, published year and journal name), classified sham

Table 1. List of CDSRs analysed in this study

Author	Year	Issue	Title	ID
Casimiro L	2005	4	Acupuncture and electroacupuncture for the treatment of rheumatoid arthritis	CD003788
Cheong YC	2013	7	Acupuncture and assisted reproductive technology	CD006920
Cheuk DKL	2008	4	Acupuncture for epilepsy	CD005062
Cheuk DKL	2011	9	Acupuncture for autism spectrum disorders (ASD)	CD007849
Deare JC	2013	5	Acupuncture for treating fibromyalgia	CD007070
Dennis CL	2013	7	Interventions (other than pharmacological, psychosocial or psychological) for treating antenatal depression	CD006795
Dodin S	2013	7	Acupuncture for menopausal hot flushes	CD007410
Ezzo J	2006	2	Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting	CD002285
Furlan AD	2005	1	Acupuncture and dry-needling for low back pain	CD001351
Furness S	2013	9	Interventions for the management of dry mouth: non-pharmacological interventions	CD009603
Gates S	2006	1	Auricular acupuncture for cocaine dependence	CD005192
Geeganage C	2012	10	Interventions for dysphagia and nutritional support in acute and subacute stroke	CD000323
Green S	2002	1	Acupuncture for lateral elbow pain	CD003527
Green S	2005	2	Acupuncture for shoulder pain	CD005319
Huang T	2011	12	Complementary and miscellaneous interventions for nocturnal enuresis in children	CD005230
Law SK	2013	5	Acupuncture for glaucoma	CD006030
Lee A	2009	2	Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting	CD003281
Linde K	2009	1	Acupuncture for migraine prophylaxis	CD001218
Linde K	2009	1	Acupuncture for tension-type headache	CD007587
Manheimer E	2010	1	Acupuncture for peripheral joint osteoarthritis	CD001977
Manheimer E	2012	5	Acupuncture for treatment of irritable bowel syndrome	CD005111
Matthews A	2010	9	Interventions for nausea and vomiting in early pregnancy	CD007575
McCarney RW	2003	3	Acupuncture for chronic asthma	CD000008
Paley CA	2011	1	Acupuncture for cancer pain in adults	CD007753
Pennick V	2013	8	Interventions for preventing and treating pelvic and back pain in pregnancy	CD001139
Smith CA	2006	4	Complementary and alternative therapies for pain management in labour	CD003521
Smith CA	2010	1	Acupuncture for depression	CD004046
Smith CA	2011	1	Acupuncture for dysmenorrhoea	CD007854
Smith CA	2011	7	Acupuncture or acupressure for pain management in labour	CD009232
Smith CA	2013	8	Acupuncture for induction of labour	CD002962
Trinh K	2006	3	Acupuncture for neck disorders	CD004870
White AR	2011	1	Acupuncture and related interventions for smoking cessation	CD000009

category and sum of subject numbers (experimental and control groups) were listed. The references were sorted by sham type. Among the 116 studies, the numbers of classified sham types were: Type A=39, Type B=23, Type C=17, Type D=8, and Type E=4. Regarding outcome measures, 56 studies used continuous data and 60 used dichotomous data.

2. Diseases and symptoms from the acupuncture trials included in this study

To examine the different influences of sham interventions on pain diseases and non-pain diseases, subgroup analyses were conducted. Thirty-one symptoms and diseases were included; 54 were pain and 62 were non-pain. Table 3 summarizes the diseases and symptoms of the studies analysed. Chronic pain diseases such as migraine, low back pain, and tension-type headache were common target diseases among the acupuncture studies. In the pain table, cancer pain, shoulder pain, and pelvic pain were included in the "others" box. For non-pain diseases, smoking cessation, hot flashes and depression were the top three symptoms; others included dysmenorrhoea, dysphagia, enuresis, epilepsy, birth and vomiting.

3. Results of meta-analysis and examples of forest and funnel plots

Table 2. List of references of the studies analysed in this study

ID	Author	Year	Journal name	Type	n
1	Alimi	2003	*J. Clin. Oncol.*	A	57
2	Allen	1998	*Psychol Sci.*	A	17
3	Allen	2006	*J Clin Psychiatry*	A	74
4	Avants	1995	*J Subst Abuse Treat.*	A	40
5	Avants	2000	*Arch Intern Med*	A	55
6	Baust	1978	*Med Welt*	A	44
7	Bokmand	2013	*Breast J*	A	60
8	Cho	2008	*J Altern Complement Med.*	A	12
9	Clavel	1992a	*Rev Epidemiol Sante Publique.*	A	515
10	Clavel	1992b	*Rev Epidemiol Sante Publique.*	A	481
11	Dieterle	2006	*Fertil Steril.*	A	225
12	Dundee	1986	*BMJ*	A	50
13	Edelist	1976	*Canad Anaesth Soc J*	A	30
14	Fan	2005	*Chin J Clin Rehabil*	A	39
15	Forbes	2005	*World J Gastroenterol.*	A	51
16	Gilliams	1984	*Practitioner*	A	55
17	Harris	2005	*J Altern Complement Med*	A	56
18	Henry	1985	*Updating in Headache*	A	30
19	Kim	2011	*Acupunct Med.*	A	54
20	Lacroix	1977	*Ann Med Interne*	A	117
21	Lagrue	1980	*Nouv Presse Med.*	A	154
22	Manber	2004	*J Affect Disord.*	A	35
23	Manber	2010	*Obstet Gynecol*	A	86
24	Margolin	2002	*JAMA*	A	425
25	Martin	1981a	*New Zeal Med J*	A	126
26	Medici	2002	*J Altern Complement Med*	A	45
27	Parker	1977a	*Am J Acupunct.*	A	18
28	Romer	2000	*Geburtshilfe Frauenheilkd.*	A	553
29	Shenkman	1999	*Anesthesiology*	A	100
30	Smith	2002	*Birth*	A	296
31	Smith	2010	*eCAM*	A	92
32	Steiner	1982	*Am J Chin Med.*	A	32
33	Tavola	1992	*Pain*	A	30
34	Vandevenne	1985	*J North Am Menopause Soc*	A	200
35	Vincent	2007	*Menopause*	A	88
36	von Mencke	1988	*Akupunktur*	A	65
37	White	2000	*Anesthesia Analgesic*	A	46
38	Wu	2007	*J Chin Med Assoc.*	A	131
39	Ziaei	2006	*Int J Gynecol Obstet*	A	90
40	Alecrim	2005	*Cephalalgia*	B	64
41	Alecrim	2006	*Cephalalgia*	B	31
42	Alecrim	2008	*Clin J Pain*	B	37
43	Anastasi	2009	*Gastrointest. Nurs.*	B	27
44	Andrzejowski	1996	*Acupunct Med.*	B	36
45	Asher	2009	*J Matern Fetal Neonatal Med*	B	44
46	Avis	2008	*Menopause*	B	38
47	Bai	2007a	*Zhongguo Zhenjiu*	B	56
48	Birch	1998	*Clin. J. Pain*	B	31
49	Blom	1992	*Oral Surg Oral Med Oral Pathol*	B	21
50	Blom	1996	*Oral Oncol.*	B	38
51	Ceccherelli	2001	*Acupunct Electrother Res.*	B	44
52	Ceccherelli	2002	*Clin J Pain*	B	42
53	Diener	2006	*Lancet Neurol*	B	37
54	Eich	2000	*Fortsch Neurol Psychiatrie*	B	49
55	Endres	2007	*J Headache Pain*	B	409
56	Haker	1990a	*Clin. J. Pain*	B	82
57	Hantoushzadeh	2007	*Aust N Z J Obstet Gynaecol*	B	150
58	Hervik	2009	*Breast Cancer Res Treat*	B	59

ID	Author	year	Journal name	Type	n
59	Kloster	1999	*Seizure*	B	34
60	Leibing	2002	*Pain*	B	75
61	Linde M	2005	*JAMA*	B	652
62	Lund	2006	*Acta Obstet. Gynecol. Scan*	B	47
63	Mackenzie	2011	*BJOG*	B	53
64	Melchart	2005	*BMJ*	B	195
65	Molsberger	2002	*Pain*	B	116
66	Roschke	2000	*J Affect Disord*	B	46
67	Scharf	2006	*Ann. Intern. Med.*	B	673
68	Skilnand	2002	*Acta Obstet Gynecol Scan*	B	208
69	Smith	2008	*Obstet Gynecol*	B	360
70	Vincent	1989	*Clin J Pain*	B	32
71	Weinschutz	1993	*Verh Dtsch Ges neurol*	B	226
72	Weinschutz	1994	*DZA*	B	41
73	Whiting	2008	*Complement Ther Med.*	B	17
74	Witt	2005	*Lancet*	B	218
75	Araki	2001	*JSAM*	C	40
76	Assefi	2005	*Ann Intern Med.*	C	37
77	Ceccherelli	1992	*XV Congresso Nazionale A.I.S.D. S. Margherita Ligure:*	C	30
78	David	1999	*Rheumatology*	C	55
79	Deng	2007	*J Clin Oncol*	C	67
80	Foster	2007	*BMJ*	C	228
81	Harris	2009	*NeuroImage*	C	20
82	Harris	2008	*Arthritis Rheumatol*	C	10
83	Inoue	2000	*JSAM*	C	27
84	Inoue	2001	*JSAM*	C	21
85	Karst	2001	*Cephalalgia*	C	69
86	Kim	2004	*Am J Chin Med.*	C	30
87	Lembo	2009	*Am J Gastroenterol.*	C	153
88	Linde M	2005	*Cephalalgia*	C	31
89	Mao	1998	*J Tradit Chin Med.*	C	111
90	Modlock	2010	*BJOG*	C	125
91	Molsberger	1994	*Br J Rheumatol.*	C	48
92	Nir	2007	*Maturitas*	C	29
93	Painovich	2012	*Menopause*	C	24
94	Paulus	2003	*Hum Reprod.*	C	200
95	Schneider	2006	*Gut*	C	41
96	Streitberger	2003	*Clin Cancer Res*	C	80
97	Streitberger	2004	*Anaesthesia*	C	212
98	Takeda	1994	*Arthritis Care Res*	C	40
99	Tremeau	1992		C	56
100	Vas	2004	*BMJ*	C	97
101	Venzke	2010	*Complement Ther Med.*	C	51
102	White	2000	*Cephalalgia*	C	50
103	Wong a	2010	*J Altern Complement Med.*	C	50
104	Yeung	2009a	*Sleep*	C	57
105	Deluze	1992	*BMJ*	D	55
106	Gaudet	2008	*J Obstet Gynaecol Can.*	D	16
107	Man	1974	*J Rheumatol.*	D	20
108	Parker	1977b	*Am J Acupunct.*	D	23
109	Rusy	2002	*Anesthesiology*	D	120
110	Waite	1998	*Br J Gen Pract*	D	78
111	Wong b	2010	*Altern Med Review*	D	55
112	Wyon	2004	*Climacteric*	D	28
113	Berman	2004	*Ann Intern Med*	E	331
114	Christensen	1984	*Allergy*	E	17
115	Martin	2006	*Mayo Clin Proc.*	E	49
116	White	1998	*Arch Intern Med*	E	76

Type A: penetrating needle sham; Type B: superficial penetrating sham; Type C: non-penetrating sham;
Type D: penetrating needle sham with electrical current; and Type E: electro-acupuncture without current.

Table 3. List of diseases or symptoms in the studies analysed in this study

rank	diseases or symptoms			
	pain	n	non pain	n
1	migraine	12	smoking cessation	13
2	labour	8	hot flush	10
3	low back pain	8	depression	8
4	osteoarthritis	6	nausea	5
5	fibromyalgia	6	irritable bowel syndrome	4
6	tension-type headache	5	dry mouth	3
7	elbow pain	2	cocaine addiction	3
8	neck pain	2	asthma	2
9	rheumatoid arthritis	2	autism	2
10	others	3	others	12
	total	54	total	62

Among the 116 studies, the data were classified as continuous or dichotomous, and each data type was analysed separately by forest plots and funnel plots using the Review Manager software. Fifty-six studies reported continuous data and included a total of 4,206 subjects (2,142 in the acupuncture groups and 2,164 in the sham groups). Sixty studies reported dichotomous data for a total of 7,613 subjects (3,700 in the acupuncture groups and 3,913 in the sham groups).

Figure 1 shows an example of a forest plot for meta-analysis of the 56 studies using continuous data as outcome measures. The results of each study were summarized as SMD with 95% C.I. and are shown as short horizontal lines in the right column. The length of the bar indicates the upper and lower 95% CI. The overall effect is shown as a diamond mark at the bottom. When the overall effect is significantly different ($P<0.05$), the mark does not cover the vertical zero line.

In this meta-analysis, the SMD and 95% C.I. of the pooled studies was -0.34 (-0.44, -0.23). The overall effects were shown as $Z=6.09$ ($P<0.00001$). The results indicate that the acupuncture group was significantly more effective than the sham acupuncture group. Heterogeneity of the pooled studies was also calculated, and high heterogeneity among the analysed studies was shown by Tau^2, chi square and P and I^2 values. The relatively high heterogeneity among the studies was shown to be 60% of I^2, thus results of the meta-analysis should be interpreted with caution.

Figure 2 shows a funnel plot in which the distribution of each study is indicated as a circle based on its SMD and SE. This plot is used for analysing the publication bias of pooled studies. On visual inspection of the figure, in which data are distributed equally from the central vertical line (SMD of pooled data), this plot suggests a relatively small publication bias among these data sets.

Figure 3 summarizes the results of subgroup analyses based on the type of sham acupuncture and outcome of disease or symptom (pain or non-pain). To compare the results of SMD (continuous) and RR (dichotomous) data, Z values were used. High Z values indicate larger differences between acupuncture and sham control groups. Two columns show Z values of SMD and RR. The detailed results of subgroup analyses are summarized in Table 4.

As shown in Table 4, highly significant overall effects were detected in almost every sham type from A to D, although their heterogeneities calculated as I^2 were relatively high. Only Type E showed no significant difference between real and sham acupuncture groups although the study number was small. In subgroup analysis based on disease, several sets of data showed no statistical difference between the real and sham groups. In the pain subgroup, sham A SMD, sham C SMD and sham D RR showed no statistical significance, although the P values of the former two sets were P=0.06 and 0.07. In the non-pain subgroup, sham A SMD, sham B SMD, sham D SMD and sham E SMD, RR was not significantly different.

Table 5 shows the results of subgroup analysis using studies of chronic musculoskeletal pain syndromes. In the continuous data set, 6 low back pain (LBP) and 6 osteoarthritis (OA) studies were included. In the dichotomous data, 2 LBP, 12 migraine and 5 tension-type headache (TTH) studies were included. In the RR data, Z values gradually increased and P values decreased; in other words, sham A had a stronger effect when compared with sham C, although actual SMD did not.

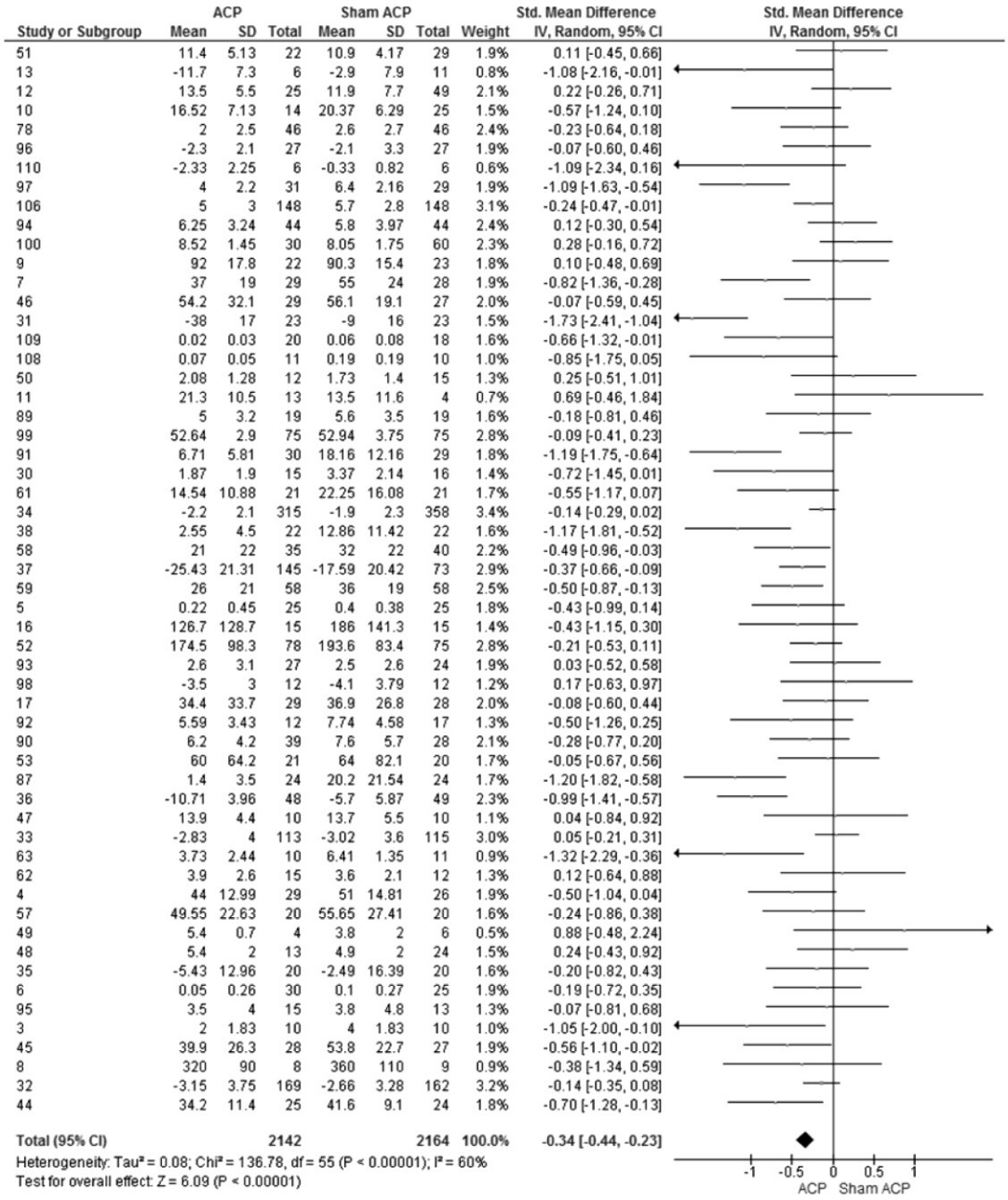

Figure 1. An example of a forest plot of continuous data

For details of the parameters used in the forest plot, please refer to the text and the Cochrane Handbook of Systematic Review[19].

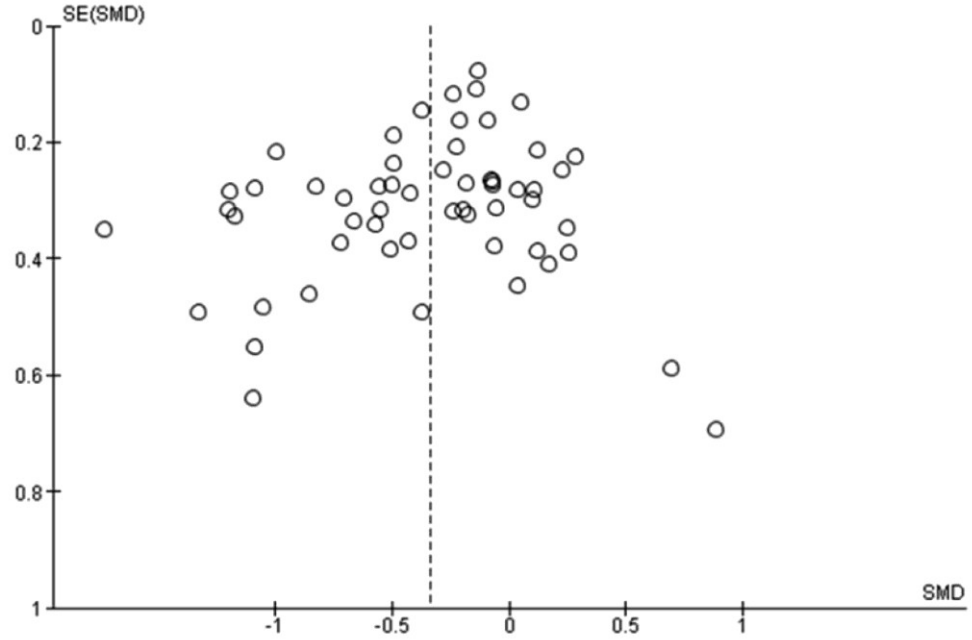

Figure 2. **An example of a funnel plot of contineous data.The same data set in Figure1 was used. （n=56）**

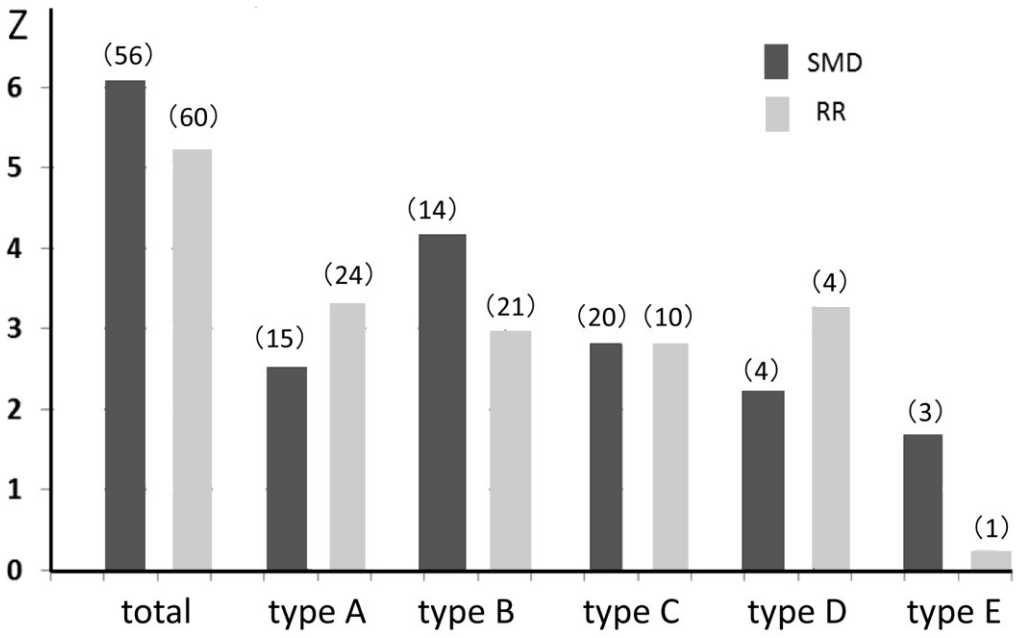

Figure 3. **Summary of Z values from subgroup analysis. Numbers on each column indicate studies included for analysis.**

SMD: standardized mean difference; RR: risk ratio.

Table 4. Summary of results of subgroup meta-analysis on sham types and pain or non-pain.

Sham	Data Type	Z	SMD or RR (95% C.I.)	P	n	I^2 (%)
All sham	SMD	6.09	−0.34 (−0.44, −0.23)	0.00001	56	60
	RR	5.23	0.80 (0.73, 0.87)	0.00001	60	50
A	SMD	2.49	−0.33 (−0.58, −0.07)	0.01	15	73
	RR	3.26	0.80 (0.70, 0.91)	0.001	24	58
B	SMD	4.13	−0.43 (−0.64, −0.23)	0.0001	14	62
	RR	2.97	0.81 (0.70,0.93)	0.003	21	43
C	SMD	2.80	'−0.27 (−0.46, −0.08)	0.005	20	54
	RR	2.80	0.75 (0.61, 0.92)	0.005	10	17
D	SMD	2.22	−0.40 (−0.74, −0.05)	0.03	4	14
	RR	3.26	0.66 (0.52, 0.85)	0.001	4	0
E	SMD	1.68	−0.32 (−0.70, 0.05)	0.09	3	40
	RR	0.23	1.07 (0.62, 1.83)	0.82	1	n.a.
All sham	SMD	5.36	−0.47 (−0.65, −0.30)	0.00001	25	70
(pain)	RR	3.46	0.80 (0.70, 0.91)	0.0005	29	38
type A	SMD	1.86	−0.85 (−1.75, 0.05)	0.06	3	86
(pain)	RR	2.13	0.73 (0.54, 0.97)	0.03	6	30
type B	SMD	3.87	−0.47 (−0.70, −0.23)	0.0001	7	61
pain	RR	2.14	0.84 (0.72, 0.99)	0.02	16	47
type C	SMD	1.82	−1.65 (−3.43, 0.13)	0.07	11	83
(pain)	RR	2.36	0.65 (0.45, 0.93)	0.02	6	11
type D	SMD	2.83	−0.68 (−1.15, −0.21)	0.005	2	0
(pain)	RR	0.29	0.78 (0.14, 4.23)	0.77	1	n.a.
type E	SMD	1.29	−0.36 (−0.89, 0.18)	0.2	2	69
(pain)	RR	n.a.	n.a.	n.a.	0	n.a.
All sham	SMD	3.21	−0.22 (−0.35, −00.08)	0.001	31	43
(non-pain)	RR	3.91	0.80 (0.71, 0.89)	0.001	31	55
type A	SMD	1.59	−0.19 (−0.42, −0.01)	0.11	12	60
(non-pain)	RR	2.54	0.81 (0.69, 0.95)	0.01	18	68
type B	SMD	1.55	−0.34 (−0.78, 0.09)	0.12	7	69
(non-pain)	RR	1.66	0.70 (0.46, 1.07)	0.1	5	44
type C	SMD	2.2	−0.20 (−0.37, −0.02)	0.03	9	0
(non-pain)	RR	2	0.82 (0.67, 1.00)	0.05	4	3
type D	SMD	0.66	−0.15 (−0.58, 0.29)	0.51	2	0
(non-pain)	RR	3.26	0.66 (0.51, 0.85)	0.001	3	0
type E	SMD	0.76	−0.38 (−1.34, 0.59)	0.45	1	n.a.
(non-pain)	RR	0.23	1.07 (0.62, 1.83)	0.82	1	n.a.

SMD: standardized mean difference, RR; risk ratio

Table 5. Summary of results of subgroup meta-analysis on the chronic musculos keletal pain diseases.

Sham	Data Type	Z	SMD or RR (95% C.I.)	P	n	I^2 (%)
A, B, C	RR	3.13	0.77 (0.65, 0.91)	0.002	19	44
A	RR	1.58	0.75 (0.53, 1.07)	0.11	5	41
B	RR	1.7	0.85 (0.70, 1.03)	0.09	10	45
C	RR	2.65	0.57 (0.38, 0.86)	0.008	4	10
B, C, E	SMD	3.63	−0.33 (−0.51, −0.15)	0.003	12	63
B	SMD	3.49	−0.33(−0.51, −0.14)	0.0005	5	39
C	SMD	1.64	−0.39 (−0.86, 0.08)	0.1	6	78
E	SMD	1.26	−0.14 (−0.36, 0.08)	0.21	1	n.a.

n.a.=not applicable

Ⅳ. Discussion

Meta-analysis based on RCT has been ranked at the top of the list of evidence in evidence based medicine (EBM), and it is expected that accumulation of high quality RCTs could yield clear conclusions in the field of acupuncture trials. The present re-analysis of clinical acupuncture trials using data from the CDSR clearly despite considerable heterogeneity. In contrast, subgroup analyses based on 5 types of sham acupuncture did not demonstrate obvious differences among the sham types compared, that is, high Z values and lower P values were detected in subgroups from Type A (penetrating), Type B (superficial), and Type C (non-penetrating needling) although the results were not stable and much variation existed.

Linde et al.[16] analysed continuous data from 19 studies included in one CDSR[20] and demonstrated a significant difference between the real and sham acupuncture groups. However, no differences were detected between penetrating versus non-penetrating needle sham acupuncture procedures. Conversely, MacPherson et al. conducted a project of re-analysis of acupuncture trials focusing on their control interventions[17]. This study posed a research question similar to that presented in our protocol. They analysed patients of chronic pain diseases and classified sham acupuncture into penetrating (deep, superficial) and non-penetrating, and their results clearly indicated differences among the types of sham acupuncture used. The effect size of the penetrating groups (superficial=8, deep=1) and non-penetrating sham group (n=7) were 0.17 (0.11, 0.23) and 0.76 (0.31, 1.21), respectively.

MacPherson's data clearly demonstrated that penetrating needle sham had a small effect size compared to non-penetrating sham in chronic musculoskeletal pain diseases. On the contrary, our subgroup analysis focused on the chronic musculoskeletal pain diseases (table 5), a portion of the results demonstrated larger Z values with small I^2 values; however, there was much variation in general. One of the possible reasons for the discrepancy in results might be related to the different data sets used for analysis. We only used data sets included in the CDSR. Some of the reviews were not up-to-date, so several newly published high quality RCTs were not included in the present analysis. Further collection of high quality studies with adequate sham controls and further re-analysis of pooled data should be conducted in pain or non-pain diseases.

Heterogeneity of pooled data represents an important issue in meta-analysis. The Cochrane handbook of Systematic Review[19] recommends the use of a random-effects model and standardized mean difference (SMD) as a means for reducing heterogeneity. Therefore, we employed random-effects model and the SMD in the present study. The guideline for interpreting the heterogeneity of I^2 is as follows: 0-40%: might not be important, 30-60%: may represent moderate heterogeneity, 50-90%: may represent substantial heterogeneity, 75-100%: considerable heterogeneity[19].

In the present study, the I^2 of the overall pooled SMD and RR were 60% and 50%, respectively. The I^2 indices in the subgroup analysis of sham acupuncture for pain versus non-pain diseases also indicated relatively high heterogeneity, but the small study numbers tended to generate a lower I^2 value (Table 4). While subgroup analyses may be generally conducted to explore heterogeneity, our primary subgroup analyses clearly did not show a reduction in heterogeneity. One of possible reasons is that the outcome measures varied widely across the studies selected in the analysis. Further subgroup analysis employing more restrictive study inclusion criteria may be useful in minimizing heterogeneity.

In the electrophysiological study on human skin, superficial needle insertion and non-penetrating stimulation with a blunt needle tip as well as needle penetration in the skin could activate the sensory afferents referred to as C mechano-heat (CMH) units[15]. The CMH units are thought to be polymodal receptor units and are considered possible candidates for the common sensory receptor for acupuncture and moxibustion[18]. Regarding cutaneous CMH units, insertion of deep, superficial needling and blunt needle stimulation elicited similar rates of discharge[15]. Thus the lack of difference among sham types (penetrating, superficial and non-penetrating acupuncture) could be explained from the view point of the sensory afferents of the skin, although the afferents from deep structures might only be evoked by the penetration type of sham acupuncture. Another important finding was that press tack needle (PTN), a fine short needle (0.6 mm in length, 200 μm in diameter) attached to a plastic basement, when applied to the receptive field of a CMH unit, could elicit phasic discharges but its sham device (with the needle tip removed) did not evoke any response. Given that sham PTN is physiologically inert and readily available, PTN and its sham might be useful devices for future clinical acupuncture trials.

Whereas the present study focussed on the types of sham acupuncture, the detailed subgroup analyses focussed on the real acupuncture interventions, selection of acupuncture points, and their manipulating procedures have not been performed. From the perspective of evidence- based acupuncture, establishing suitable acupuncture procedure for each specific disease is important, and further subgroup analyses with the addition of newly published, well-designed clinical trials in acupuncture trials are required.

Ⅴ. Conclusions

The results from meta-analyses of the pooled data indicate highly significant differences between real and sham acupuncture groups; however, we should interpret this data with caution as heterogeneity of the trials was relatively high. Effect sizes of non-penetrating sham acupuncture did not generally exceed those of penetrating sham acupuncture despite large variations. These findings indicated that our working hypothesis that "penetrating needling sham exerts a stronger impact than non-penetrating sham" may be false and suggest that non-penetrating sham acupuncture, similar to those Japanese acupuncture procedures, may produce some physiological activity.

Acknowledgements

The authors thank Dr. Kaoru Okada for her help in data collection and analysis, and Dr. Masayoshi Hosaka for his valuable technical support on meta-analysis using the Review Manager.

Conflict of interest

There is no conflict of interest.

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