

Does Acupuncture Improve Motor Recovery After Stroke? A Meta-Analysis of Randomized Controlled Trials

Frank Kai-hoi Sze, FRCP; Eric Wong, MA; Kevin K.H. Or, FRCP; Joseph Lau, MD; Jean Woo, FRCP

Background and Purpose—Acupuncture may be a promising treatment for poststroke paralysis. We conducted a meta-analysis, assessing the efficacy of acupuncture with and without stroke rehabilitation.

Methods—We identified randomized trials comparing acupuncture with no acupuncture within 6 months of stroke by searching MEDLINE, CINAHL, EMBASE, Cochrane Library, and Chinese medical literature databases. Two reviewers independently extracted data on study characteristics, patient characteristics, and impairment and disability outcomes. The outcome measures were internationally recognized or nationally approved. The fixed- and random-effects models were used to combine effect size and odds ratio across studies.

Results—Fourteen trials with 1213 patients met all the inclusion criteria. For the comparison of acupuncture with no acupuncture in addition to stroke rehabilitation, the pooled random-effects estimates of the change in motor impairment and disability were 0.06 (95% CI, -0.12 to 0.24) and 0.49 (95% CI, 0.03 to 0.96), respectively, with heterogeneity in disability measures ($P=0.05$, χ^2 test). For the comparison of real with sham acupuncture, the pooled random-effects estimate of the change in disability was 0.07 (95% CI, -0.34 to 0.48). For the comparison of acupuncture with no acupuncture without stroke rehabilitation, the pooled random-effects estimate of the change in motor impairment was 0.46 (95% CI, -0.20 to 1.12), and the pooled random-effects odds ratio for disability was 12.5 (95% CI, 4.3 to 36.2), with no statistically significant heterogeneity ($P=0.97$ and $P=0.12$, respectively, χ^2 test), but the study quality was poor.

Conclusions—This meta-analysis suggests that with stroke rehabilitation, acupuncture has no additional effect on motor recovery but has a small positive effect on disability, which may be due to a true placebo effect and varied study quality. The efficacy of acupuncture without stroke rehabilitation remains uncertain, mainly because of the poor quality of such studies. (*Stroke*. 2002;33:2604-2619.)

Key Words: acupuncture ■ meta-analysis ■ stroke

The modalities of treatment in stroke rehabilitation in Western countries are physiotherapy, occupational therapy, and speech therapy, in addition to skilled medical and nursing care. In this study this mode of care is referred to as conventional stroke rehabilitation. However, the majority of stroke patients in China do not have access to these therapies. They are often provided with acupuncture, together with routine medical and nursing care. In this study this routine medical and nursing care is referred to as conventional care. Rehabilitation workers¹ in the West recognize that more than half of the stroke survivors remain severely disabled despite conventional stroke rehabilitation. This reality drives researchers to search for other modalities of treatment in an attempt to further improve outcome. Acupuncture has become a subject of major interest and one of the most popular complementary therapies in the West in recent years. Researchers started to design randomized controlled trials²⁻⁴ to assess the efficacy of acupuncture in poststroke paralysis in

the early 1990s, and the results were inconsistent. Several review articles⁵⁻¹⁰ have appeared on this subject. Although most of these authors commented that acupuncture might be a promising treatment for poststroke paralysis, none reached conclusions regarding its efficacy. Furthermore, these reviews have important limitations. First, most reviews were based on experts' opinions. One systematic review has been published,¹⁰ but the author did not pool the data, claiming that the outcome measures were too heterogeneous. We believe that heterogeneity could have been improved if inclusion criteria for outcome measures had been set and outcome measures had been classified as impairment and disability measures. Second, all reviews mixed trials that compared acupuncture plus conventional stroke rehabilitation with conventional stroke rehabilitation alone and trials that compared acupuncture plus conventional care with conventional care alone. Mixing conventional stroke rehabilitation and conventional care trials for review is not appropriate because stroke

Received March 6, 2002; final revision received June 10, 2002; accepted June 27, 2002.

From the Department of Medicine and Geriatrics, Shatin Hospital, Hong Kong (F.K.S., K.K.H.O.); Center for Clinical Trials and Epidemiological Research (E.W.) and Department of Medicine and Therapeutics, Prince of Wales Hospital (J.W.), Chinese University of Hong Kong; and Division of Clinical Care Research, Tufts New England Medical Center, Boston, Mass (J.L.).

Correspondence to Dr Frank Kai-hoi Sze, Department of Medicine and Geriatrics, Shatin Hospital, 33 A Kung Kok St, Ma On Shan, N.T. Hong Kong. E-mail fksze@hotmail.com

© 2002 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000035908.74261.C9

TABLE 1. Characteristics of Included Studies Comparing Acupuncture Plus Conventional Stroke Rehabilitation With Conventional Stroke Rehabilitation Alone

| Author | Sample | | | Size Estimate | Consent | Randomization Detail | Intention to Treat | Diagnosis |
|--|---------------|--------------------------------------|---|---------------|-----------|---|--------------------|-----------------------------------|
| | Size | Intervention | Control | | | | | |
| Hu et al (1993) ² | 30 (28M/2F) | 15 (15M/0F) | 15 (13M/2F) | No | Yes | Not reported | No report | CT |
| Johansson et al (1993) ³ | 78 (42M/36F) | 40 | 38 | No | Yes | Not reported | No report | By CT (65.4%), others by clinical |
| Sallstrom et al (1996) ⁴ | 49 | 24 (18M/6F) | 21 (16M/5F) | No | Yes | Block randomization | No report | Clinical and CT |
| Gosman-Hedstrom et al (1998) ³³ | 104 (46M/58F) | 37 (Deep acupuncture) | 34 (superficial acupuncture); 33 (no acupuncture) | Yes | Yes | Computer generated | Yes | CT |
| Wong et al (1999) ³⁴ | 118 (80M/38F) | 59 (38M/21F) | 59 (42M, 17F) | No | No report | Not reported | No report | CT |
| Sze et al (2002) ³⁷ | 106 (56M/50F) | Severe group: 31; moderate group: 22 | Severe group: 31; moderate group: 22 | Yes | Yes | Block randomization and closed envelope | Yes | CT and clinical |

MCA indicates middle cerebral artery; TIA, transient ischemic attack; ADL, activities of daily living; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; PT, physical therapy; OT, occupational therapy; ST, speech therapy; QoL (NHP), Quality of Life (Nottingham Health Profile); LOS, length of stay; TENS, transcutaneous electric nerve stimulation; and FES, functional electric stimulation.

patients who have been given conventional stroke rehabilitation may not gain further motor improvement after acupuncture if conventional stroke rehabilitation has maximized the recovery potential. In contrast, stroke patients on conventional care alone may still benefit from acupuncture for motor recovery. Third, most reviews included only a few trials that were done in China and were published in the English-language literature, leaving a large number of articles in the Chinese literature that were not reviewed. One review¹⁰ did search the Chinese literature, but it was not thorough. At least 7 randomized controlled trials comparing acupuncture with no acupuncture were missed within the search period. Finally, some randomized controlled trials in this area published in recent years were not covered by these reviews.

The objective of this meta-analysis was to determine whether acupuncture improves poststroke motor recovery in addition to stroke rehabilitation and whether acupuncture improves motor recovery without stroke rehabilitation.

Methods

Definitions of Acupuncture

Conventional acupuncture is defined as acupuncture performed at acupoints well documented in historical Chinese medical literature; it is further classified as conventional body acupuncture if acupoints located on the body are used and as conventional cranial acupuncture if acupoints located on the scalp or face are used. Nonconventional acupuncture is defined as acupuncture performed at sites other than these classic acupoints; it is also further classified as nonconventional body acupuncture and nonconventional cranial acupuncture, respectively. Acupuncture can be performed manually (manual acupuncture) or electrically (electric acupuncture).

Literature Search

The literature search was performed with the use of MEDLINE (January 1966 to March 2001), CINAHL (1982 to March 2001), PubMed (to March 2001), Embase (1980 to December 2000), and Cochrane Controlled Trials Register (Issue 1, 2001) in English by 2 reviewers (F.K.S. and J.L.) and with the use of Nanjing Traditional Chinese Medicine University Center for China’s Traditional Chinese

Medicine Database (January 1981 to January 2000) and JiangSu Provincial Science and Technology Information Research Institute Database (January 1989 to December 1999) in Chinese by 2 reviewers (F.K.S. and X.Y.). The key words used for the search were *acupuncture* and *stroke/CVA/cerebrovascular accident/cerebral infarction/intracerebral hemorrhage/cerebral embolism*. The types of publication searched were *clinical trials* and *reviews*. One of the reviewers (F.K.S.) also performed a manual search of *Chinese Acupuncture and Moxibustion* (1981 to December 2000), *Journal of Shanghai Acupuncture and Moxibustion* (1983 to December 2000), references from the retrieved trials and review articles, and acupuncture conference proceedings in China.

Inclusion Criteria

Two reviewers for the English literature (F.K.S. and E.W.) and Chinese literature (F.K.S. and X.Y.) independently reviewed the trials for inclusion. Any disagreements on inclusion were resolved through discussion. The inclusion criteria were the following: (1) randomized controlled trials, comparing acupuncture of any kind with no acupuncture (or sham acupuncture); (2) patients with stroke within 6 months (cerebral infarction, intracerebral hemorrhage, cerebral embolism, or unclassified stroke), diagnosed clinically and/or by CT scan or MRI; and (3) motor impairment and disability measures that are either internationally recognized or nationally approved by an academic body in China. Poststroke motor recovery beyond 6 months is known to be unlikely, and mixing patients with interval to stroke onset of <6 months and >6 months in 1 sample would make the assessment of the efficacy of an intervention methodologically unsound. Therefore, we planned to include in a subgroup trials that met all the other inclusion criteria but used a sample of patients whose interval to stroke onset ranged from <6 months and >6 months or was unreported.

Data Extraction

Data were extracted by 2 reviewers (F.K.S. and K.K.H.O.) independently. Once completed, any disagreements on data extraction and evaluation were resolved through discussion. Recorded data included study characteristics, patient characteristics, and outcomes. For motor impairment, measures recognized internationally include the Scandinavian Stroke Scale¹¹ (SSS), Rivermead Mobility Index¹² (RMI), Motor Assessment Scale¹³ (MAS), Brunstrom Stages¹⁴ (BS), and Fugl-Meyer Assessment—motor score¹⁵ (FMAM); measures nationally approved in China include the Chinese Stroke

Downloaded from <http://stroke.ahajournals.org/> by guest on July 21, 2017

TABLE 1. Continued

| Author | Stroke Nature | Stroke Status | Severity on Entry | Interval to Onset | Age, y | Inclusion Criteria | Exclusion Criteria |
|--|---|--------------------------|--------------------|----------------------------|---|--|---|
| Hu et al (1993) ² | Cerebral infarction MCA territory only | 1st stroke | Moderate to severe | <36 h | Acupuncture: mean 63.6, SD 6.7; control: mean 62.8, SD 8; range 46–74 | 1) Infarction in MCA territory 2) With motor deficit | 1) Coma 2) TIA 3) Life-threatening illness 4) Significant systemic disease 5) On anticoagulants 6) No limb weakness |
| Johansson et al (1993) ³ | Cerebral infarction | 1st stroke | Moderate to severe | 4–7 d | Median 76 | 1) Cooperative 2) ADL partially dependent | 1) On pacemakers 2) Previous ADL dependent |
| Sallstrom et al (1996) ⁴ | Cerebral infarction, ICH | 1st stroke | Moderate | Median 40 d; range 15–71 d | Acupuncture: median 57, range 35–69; control: median 58, range 39–72 | 1) Mild to moderate aphasia | 1) SAH 2) Severe comorbidity 3) Severe aphasia |
| Gosman-Hedstrom et al (1998) ³³ | Cerebral infarction | 1st and recurrent stroke | Moderate to severe | <7 d | M: weighted mean 76; F: weighted mean 78.3 | 1) Age \geq 40 y 2) Onset <1 wk 3) Cooperative 4) ADL partially dependent | 1) Severe comorbidity 2) Severe aphasia 3) Unconsciousness 4) On pacemakers 5) Previous ADL dependent |
| Wong et al (1999) ³⁴ | Cerebral infarction, and ICH | 1st stroke | Moderate to severe | 10–14 d | Range 21–80 | 1) Fully conscious 2) Medically uncomplicated 3) With hemiplegia | Not reported |
| Sze et al (2002) ³⁷ | Cerebral infarction, ICH, cerebral embolism | 1st and recurrent stroke | Moderate to severe | 3–15 d | Mean 70.8, SD 8.8 | 1) BI: 3–14 2) Glasgow Coma Scale=15 3) Follow simple command | 1) BI admission <3 or \geq 15 2) History of dementia 3) Hemodynamically unstable 4) Cannot give consent because of impaired cognition/aphasia 5) No motor deficit |

Scale¹⁶ (CSS), Second National Cerebrovascular Diseases Conference 1986¹⁷ Appendix I—the motor impairment score (Second NCDC impairment score), Guidelines on the Use of New Chinese Herbal Medicines in Stroke (UNCHMS guidelines),¹⁸ and Modified Edinburgh-Scandinavian Stroke Scale¹⁹ (MESSS). For disability, measures recognized internationally include the Barthel Index (BI) (2 versions: BI-100²⁰ and BI-20²¹), Functional Independence Measure (FIM),²² and Sunnaas ADL Index (SADLI)²³; measures approved nationally in China include the Second National Cerebrovascular Diseases Conference 1986¹⁷ Appendix IV—disability score (Second NCDC disability score), UNCHMS guidelines,¹⁸ and National Traditional Chinese Medicine Conference on Diagnosis of Stroke and Assessment of Efficacy 1986 (Tai-An Conference 1986).²⁴ If >1 eligible impairment and/or disability measurement score was reported, we extracted data from the internationally or nationally most widely used measure for the sake of data synthesis.

The Jadad scale²⁵ was used to measure the quality of the included studies. This validated scale included the following criteria: method of randomization, double blinding, and reporting of withdrawal and dropouts. Because quality scales have their limitations, we also examined the individual components of study quality for each

included randomized controlled trial, including, in particular, concealment of treatment allocation, assessor blinding, intention-to-treat analysis, dropouts, and sample size.

Data Synthesis

We combined the effect sizes for studies comparing acupuncture plus conventional stroke rehabilitation with conventional stroke rehabilitation alone and studies comparing acupuncture plus conventional care with conventional care alone in motor impairment and disability outcomes, respectively. Then we combined the effect size for studies comparing real acupuncture plus conventional stroke rehabilitation with sham acupuncture plus conventional stroke rehabilitation to estimate the magnitude of placebo effect. We also performed subgroup analysis according to the characteristics of the studies to assess the effect of study quality on the combined effect size. Data from randomized controlled trials whose interval to stroke onset was >6 months or unreported were synthesized separately.

For studies that reported continuous outcomes, the effect size was calculated. The effect size is a dimensionless metric that allows us to combine studies that used different outcome scales, but the interpretation of the result is less intuitive. The effect size is expressed by the

TABLE 1. Continued

| Author | Baseline Matched | Acupuncture Technique | Acupuncture Method | Details of Acupuncture (Acupoints, Frequency, Duration) |
|--|---|---|---|---|
| Hu et al (1993) ² | Yes | Electric acupuncture | Conventional body acupuncture and nonconventional cranial acupuncture | Cranial acupuncture sites described; body acupuncture acupoints GB21, LI11, Ex-UE7, GB34 for upper limb weakness; BL60, GB34, LR3, Ex-UE7 for lower limb weakness; 30–60 min/session; 3 sessions/wk; frequency 9.4 Hz |
| Joansson et al (1993) ³ | Yes | Manual followed by electric acupuncture | Conventional body acupuncture | 10 classic acupoints bilateral; 30 min/session, 2 sessions/wk, for 10 wk; electric frequency 2–5 Hz; exact acupoints not reported |
| Sallstrom et al (1996) ⁴ | Yes | Manual, electric acupuncture, and prn moxibustion | Conventional body acupuncture (manual) and nonconventional cranial acupuncture (electric) | Cranial acupuncture site not described in detail; body acupuncture acupoints are conventional but individualized, no details given; 30 min/session, 3–4 sessions/wk; electric frequency 2–4 Hz |
| Gosman-Hedstrom et al (1998) ³³ | Yes | Manual followed by electric acupuncture | Conventional body and cranial acupuncture | Deep acupuncture group: acupoints of LI4, LI11, ST38, Ex mob bilateral, TE5 on nonparetic side, GV20 on scalp; manual acupuncture on nonparetic side, needling every 5 min; electric acupuncture on paretic side, frequency 2 Hz; 30 min/session, 2 sessions/wk. Superficial acupuncture group: 4 short needles placed just under skin for 30 min without manual/electric stimulation at acupoint LI11 bilateral and Ex mob bilateral; 2 sessions/wk |
| Wong et al (1999) ³⁴ | Yes | Electric acupuncture | Conventional body acupuncture | Acupoints (GB21, TZ14, LI10, LI4, ST32, SP10, GB34, Liv3) on paretic side; electric acupuncture via adhesive surface electrodes; 30 min/session, 5 sessions/wk, for 2 wk; electric frequency 20–25 Hz; magnitude 10–20 mV |
| Sze et al (2002) ³⁷ | Yes (except FMAM in severe control group was lower) | Manual acupuncture | Conventional body acupuncture | 10 main acupoints: LI15, LI11, LI10, LI4, TE5, GB30, GB34, S36, S41; 6 auxiliary acupoints (optional): CV12, CV10, CV6, CV4, S24, S26; allow to add or omit maximum of 3 acupoints; 30 min/session, 5 sessions/wk as inpatient, 3 sessions/wk as day-hospital patient; acupuncture on paretic side |

standardized mean change (g),²⁶ which is defined as the mean difference between pretest and posttest scores divided by the pretest standard deviation. The standardized mean change was first computed for the acupuncture and control groups in each study, and then the unbiased standardized mean change effect size (d) and the corresponding variance were calculated according to the following formulas:^{26,27}

$$d \cong \left(1 - \frac{3}{4n-9}\right)g \text{ and } Var(d) = \frac{2(1-\rho)}{n} \frac{d^2}{2n}$$

where n is the sample size for each group, and ρ is the correlation between the pretest and posttest scores.

When information for the size of the correlations was not directly available in the study, we either calculated it from the prescore, postscore, and gain score standard deviations given,²⁸ or we imputed it by the available correlations. For studies that reported results in graphic forms, the graphic data were transformed into numerical data. For the sake of data synthesis with other similar studies using continuous outcomes, the logarithms of odds ratio were converted to effect size by dividing by 1.81.²⁹ For studies presenting the results in mean gain scores and the associated standard deviations, the effect size was calculated according to the formula reported by Dunlap et al.²⁸ The differences (Δ) in unbiased standardized mean changes ($\Delta = d_{treatment} - d_{control}$) were pooled according to a fixed-effects model and a random-effects model.²⁷

For studies that reported dichotomous outcomes, the odds ratio was calculated and combined with the use of the Der Simonian and Laird random-effects model.³⁰ We also calculated the results using the Mantel-Haenszel fixed-effects model³¹ for comparison.

For both continuous and dichotomous outcomes, the test of homogeneity of effects across studies was performed with a χ^2 statistic, with $P \leq 0.1$ indicating heterogeneity. The test of homogeneity assesses whether the individual study results are likely to reflect a single underlying effect as opposed to a distribution of effects.

Sensitivity analysis was performed to assess the influential studies that might affect the pooled result by deleting each study in turn from the analysis and noting the degree to which the size and significance of the treatment effect change. The robustness of the pooled estimates was also assessed by repeating the meta-analysis on subgroups of the original data set.

We assessed publication bias using the funnel plot regression method³² for studies comparing acupuncture plus conventional care with conventional care alone. If there was no publication bias, the regression slope would have an expected value of zero. A negative regression slope suggests that small negative studies are not published. Data from randomized controlled trials whose interval to stroke onset was >6 months or unreported were included in the plotting if they compared acupuncture plus conventional care with conventional care alone because publication bias is not affected by the interval to stroke onset.

TABLE 1. Continued

| Author | Treatment | |
|--|---|--|
| | Control | Intervention |
| Hu et al (1993) ² | Daily standard rehabilitation program | Daily standard rehabilitation program and acupuncture |
| Johansson et al (1993) ³ | Conventional daily PT and OT | Conventional daily PT and OT and acupuncture |
| Sallstrom et al (1996) ⁴ | Individualized rehabilitation program | Individualized rehabilitation program and acupuncture |
| Gosman-Hedstrom et al (1998) ³³ | Group 1: conventional daily PT and OT and superficial acupuncture; group 2: conventional daily PT and OT | Conventional daily PT and OT and deep acupuncture |
| Wong et al (1999) ³⁴ | Conventional daily PT and OT (≥ 2 h/d) | Conventional daily PT and OT (≥ 2 h/d) and acupuncture |
| Sze et al (2002) ³⁷ | Conventional daily PT, OT, ST | Conventional daily PT, OT, ST and acupuncture |

In this meta-analysis, we used Comprehensive Meta Analysis (version 1.0.9; Biostat) for analysis and calculations of dichotomous data, and we calculated the results for continuous data using Microsoft Excel 2000 (Microsoft Corporation).

Results

Qualitative Findings

The English-language literature search identified 105 articles, the abstracts of which were reviewed. Then 35 full articles that were potentially relevant were reviewed further. Of the 35 studies, 13 were randomized controlled trials assessing the effect of acupuncture on poststroke motor recovery. Of the 13 randomized controlled trials, 9^{2-4,16,33-37} met the inclusion criteria. Two^{38,39} were excluded because they were long-term follow-up studies of previously reported samples,^{3,4} and 2^{40,41} were excluded because they did not compare acupuncture with no acupuncture. Among the 9 randomized controlled trials, 6^{2-4,33,34,37} compared acupuncture plus conventional stroke rehabilitation with conventional stroke rehabilitation alone (Table 1), 1¹⁶ compared acupuncture plus conventional care with conventional care alone (Table 2), and 3^{33,35,36} contained arms comparing real acupuncture plus conven-

tional stroke rehabilitation with sham acupuncture plus conventional stroke rehabilitation (Tables 1 and 2).

The Chinese literature search identified 1116 articles, the abstracts of which were reviewed. Then 180 full articles that were potentially relevant were reviewed further. Of the 180 studies, 11 were excluded because of lack of randomization, 82 because of lack of control, and 57 because of comparison of 1 kind of acupuncture with another. Three studies were excluded because of injection of medication at the acupoints, 1 because of lack of statistical analysis, and 1 because of lack of motor assessment. Twelve studies were excluded because the outcome measures were not nationally approved. Eight studies⁴²⁻⁴⁹ used samples whose interval to stroke onset was >6 months or unreported but otherwise met the inclusion criteria, among which 7 randomized controlled trials^{42-44,46-49} compared acupuncture plus conventional care with conventional care alone, and 1 randomized controlled trial⁴⁵ compared acupuncture plus conventional stroke rehabilitation with conventional stroke rehabilitation alone (data were available on request). The remaining 5 studies,^{19,50-53} comparing acupuncture plus conventional care with conventional care alone, met all the inclusion criteria (Table 2).

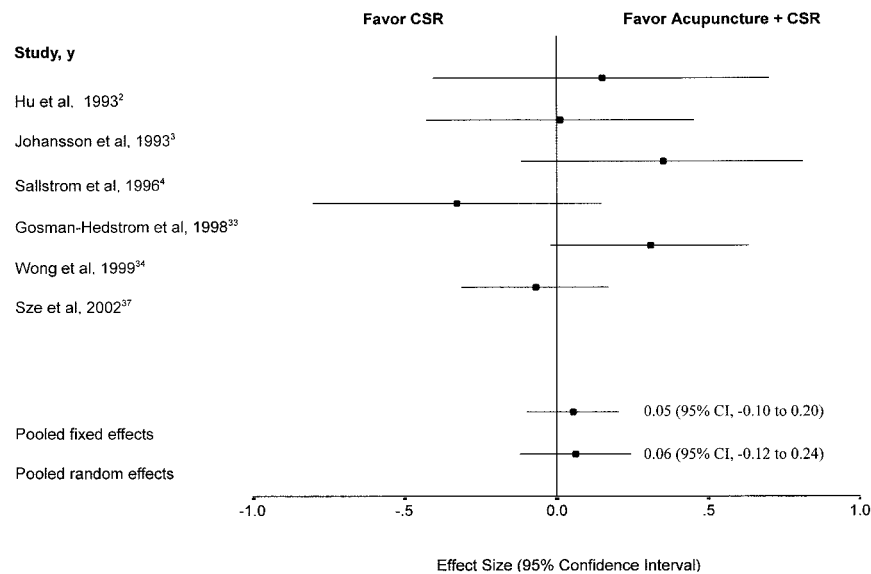


Figure 1. Difference in impairment outcome for the included studies comparing acupuncture plus conventional stroke rehabilitation (CSR) with conventional stroke rehabilitation alone.

Test of homogeneity Q=7.5, d.f.=5, p=0.19

TABLE 1. Continued

| Author | Treat for | Outcome Measure | | Assessor | Assessed at | Results | |
|--|-----------|-----------------|----------------|--------------------------------------|--|--|--|
| | | Impairment | Disability | | | Impairment | Disability |
| Hu et al (1993) ² | 4 wk | SSS | BI -100 | Not blinded, assessed by neurologist | 7, 14, 21, 28, and 90 d | SSS better change at 1 and 3 mo in acupuncture group (subgroup analysis: severe group SSS better at 1 and 3 mo in acupuncture group; mild group SSS no difference at 1 and 3 mo); difference at 4 wk: median 4; difference at 90 d: median 5 | BI: no difference at 1 and 3 mo (acupuncture arm's BI was better at 1 mo only in the severe group) |
| Johansson et al (1993) ³ | 10 wk | Mobility score | BI -100 | Not blinded | 1, 3 mo for mobility score: 1, 3, and 12 mo for BI | Motor: control: pre: 31 (4.7), n=40; 1 mo: 49.8 (6.0), n=39; 3 mo: 62.1 (5.8), n=37; acupuncture: pre: 34.5 (4.7), n=38; 1 mo: 65.2 (5.0), n=35; 3 mo: 73.8 (4.9), n=33 | BI: control: pre: 45.1 (3.0), n=40; 1 mo: 60.6 (3.4), n=39; 3 mo: 72.4 (3.2), n=37; 12 mo: 71.3 (4.0), n=32; acupuncture: pre: 45.1 (2.5), n=38; 1 mo: 69.4 (3.0), n=35; 3 mo: 90.4 (2.2), n=33; 12 mo: 92.0 (2.9), n=28 |
| Sallstrom et al (1996) ⁴ | 6 wk | MAS | SADLI | Blinded for MAS, not for SADLI | 6 wk | MAS (estimated from graph): control: pre: 20 (9.9), n=21; post: 25 (11.0), n=21; acupuncture: pre: 17 (11.0), n=24; post: 26.5 (9.5), n=24 | SADLI (estimated from graph): control: pre: 20 (7.7), n=21; post: 23 (7.7), n=21; acupuncture: pre: 18 (7.1), n=24; post: 24 (7.1), n=24 |
| Gosman-Hedstrom et al (1998) ³³ | 10 wk | SSS | BI -100, SADLI | Assessors (OT) blinded | 3 wk, 3, 12 mo | SSS: deep acupuncture: 3-mo change 9.27 (9.23), n=37; superficial acupuncture: 3-mo change 9.17 (7.37), n=33; no acupuncture: 3-mo change 11.07 (6.88), n=33 | BI: deep acupuncture: 3-mo change 38.18 (24.77), n=37; superficial acupuncture: 3-mo change 32.0 (27.34), n=33; no acupuncture: 3-mo change 40.17 (20.02), n=33 |
| Wong et al (1999) ³⁴ | 2 wk | BS | FIM | Not blinded | Discharge (LOS acupuncture: mean 29.1 d, SD 7.9; control: mean 32.4 d, SD 8.2) | BS: Upper limb: acupuncture: pre: 2.3 (0.8); post: 3.1 (1.1); difference: 0.8 (0.8); control: pre: 2.1 (0.6); post: 2.6 (0.9); difference: 0.4 (0.7); Lower limb: acupuncture: pre: 2.9 (1.1); post: 3.9 (1.3); difference: 1.0 (0.8); control: pre: 2.7 (1.0); post: 3.3 (1.0); difference: 0.5 (0.8) | FIM: acupuncture: pre: 48 (18.6); post: 69.6 (21); difference: 21.4 (12.6); control: pre: 44.9 (15.4); post: 61.8 (16.6); difference: 17.0 (11.4) |
| Sze et al (2002) ³⁷ | 10 wk | FMAM | BI -20, FIM | Blinded | 0, 5, 10 wk | FMAM severe group: acupuncture: pre: 30.5 (20.0); 10 wk: 49.9 (25.8); control: pre: 36.9 (23.3); 10 wk: 52.6 (29.7); moderate group: acupuncture: pre: 74.3 (18.1); 10 wk: 86.3 (12.6); control: pre: 62.6 (18.6); 10 wk: 78.5 (19.3) | BI: severe group: acupuncture: pre: 7.0 (2.5); 10 wk: 14.6 (4.6); control: pre: 6.3 (2.6); 10 wk: 13.2 (5.4); moderate group: acupuncture: pre: 12.2 (1.1); 10 wk: 17.6 (2.9); control: pre: 12.1 (1.1); 10 wk: 18.5 (2.1) |

Therefore, the present meta-analysis included 14 studies^{2-4,16,19,33-37,50-53} of 1213 patients who met all the inclusion criteria and another 8 studies⁴²⁻⁴⁹ in a subgroup of 924 patients whose interval to stroke onset was >6 months or unreported but otherwise met the inclusion criteria. None of the 22 studies reported mixed patient populations, such as stroke with other neurological diseases.

We assessed the clinical heterogeneity of the 14 randomized controlled trials^{2-4,16,19,33-37,50-53} that met all the inclu-

sion criteria. In terms of patient selection, 853 patients (11 studies) had first stroke, and 360 patients (3 studies comparing acupuncture plus conventional stroke rehabilitation with conventional stroke rehabilitation alone) had first or recurrent stroke. A total of 789 patients (11 studies) had moderate to severe stroke; for 424 patients (3 studies comparing acupuncture plus conventional care with conventional care alone), severity was not reported. In terms of intervention, 787 patients (10 studies) received acupuncture within 2 weeks,

Downloaded from <http://stroke.ahajournals.org/> by guest on July 21, 2017

TABLE 1. Continued

| Author | Dropout | Statistical Method | Note |
|--|---|---|---|
| Hu et al (1993) ² | No dropout | Wilcoxon rank sum test | 1) No details of standard rehab program, assuming PT, OT included. 2) With charts only; Jadad score: 2; SSS positive; BI negative |
| Johansson et al (1993) ³ | At 3 mo: 3 dropouts in control arm; 5 dropouts in acupuncture arm | Mann-Whitney; Friedman's; Kruskal-Wallis | 1) Comparison between 2 groups at each time point using Mann-Whitney was improper 2) Reported QoL (NHP) results; Jadad score: 2; Motor negative; BI positive |
| Sallstrom et al (1996) ⁴ | 4 dropouts | ANCOVA | 1) No rehabilitation detail, assuming PT, OT included 2) Also QoL (NHP) results; Jadad score: 3; MAS positive; SADLI positive |
| Gosman-Hedstrom et al (1998) ³³ | Deep acupuncture: 4 deaths, 2 dropouts; superficial: 10 deaths, 2 dropouts; control group: 5 deaths | Fisher's permutation test? | 1) Also QoL (NHP) and use of healthcare and social services; Jadad score: 5; SSS negative; BI negative |
| Wong et al (1999) ³⁴ | Not reported | <i>t</i> test, Mann-Whitney | Jadad score: 1; BS positive; FIM positive |
| Sze et al (2002) ³⁷ | 14 dropouts (6 in acupuncture arm, 8 in control arm), no deaths | χ^2 test, <i>t</i> test, Mann-Whitney test | 8 patients on TENS; 5 patients on FES; post hoc analysis: same negative results by excluding 13 patients; Jadad score: 3; FMAM negative; BI negative |

and 426 patients (4 studies) received acupuncture within 90 days of acute stroke. A total of 543 patients (6 studies) received electric plus manual acupuncture, 164 patients (3 studies) received electric acupuncture, and 506 patients (5 studies) received manual acupuncture. Among the 506 patients, 400 were from studies comparing acupuncture plus conventional care with conventional care alone. All 14 studies described the acupoints in detail, but the selected acupoints varied significantly except acupoints LI4, LI10, LI11, and GB34, which were repeatedly selected. The acupuncture method also varied significantly, with conventional body acupuncture being the most common method, used in 464 patients (5 studies). The duration of acupuncture was 10 weeks in 4 studies comparing acupuncture plus conventional stroke rehabilitation with conventional stroke rehabilitation alone (438 patients), was 4 to 6 weeks in 7 studies (530 patients), was 2 weeks in 2 studies (181 patients), and was not

reported in 1 study (64 patients). In terms of methodology, 33,36,37 (360 patients) of the 8 studies comparing acupuncture plus conventional stroke rehabilitation with conventional stroke rehabilitation alone reported concealment of treatment allocation and intention-to-treat analysis, whereas none of the 6 studies comparing acupuncture plus conventional care with conventional care alone did so. The 3 studies^{33,36,37} that reported intention-to-treat analysis also reported dropouts and death, which were included in the effect calculation. Of the 11 studies that did not report intention-to-treat analysis, 3,4,51 reported dropouts or death, but we could not be certain whether their scores were counted in the analysis.^{33,35-37,54} We found that 425 patients of the 8 studies comparing acupuncture plus conventional stroke rehabilitation with conventional stroke rehabilitation alone were assessor blinded, whereas none of the 6 studies comparing acupuncture plus conventional care with conventional care alone were assessor

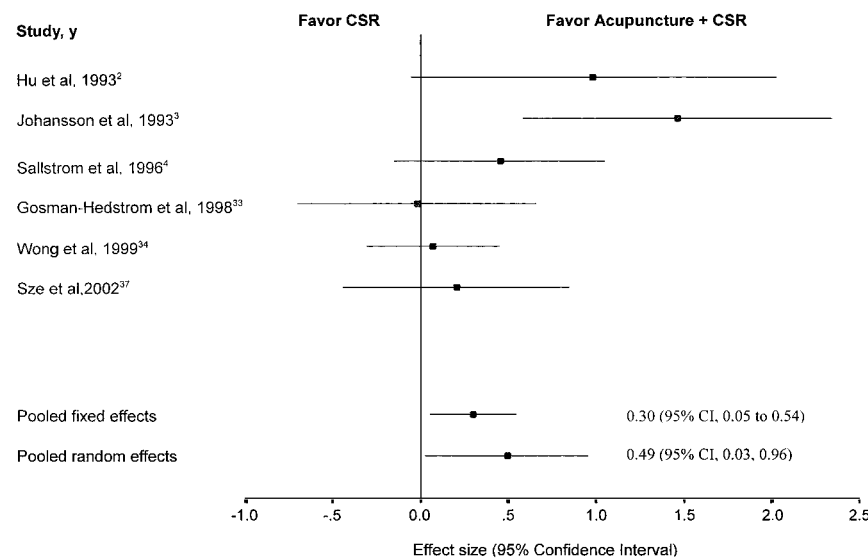


Figure 2. Difference in disability outcome for the included studies comparing acupuncture plus conventional stroke rehabilitation (CSR) with conventional stroke rehabilitation alone.

Test of homogeneity $Q=11$, $d.f.=5$, $p=0.05$

TABLE 2. Characteristics of Included Studies Comparing Acupuncture Plus Conventional Care With Conventional Care Alone (Naeser et al 1992³⁵ and Johansson et al 2001³⁶ Comparing Real Acupuncture Plus Conventional Stroke Rehabilitation With Sham Acupuncture Plus Conventional Stroke Rehabilitation)

| Author | Sample | | | Size Estimate | Consent | Randomization Detail | Intention to Treat | Diagnosis |
|--------------------------------------|----------------|--------------------------|--------------|---------------|-----------|---|--------------------|-----------------|
| | Size | Intervention | Control | | | | | |
| Tang et al (1996) ⁵⁰ | 63 (43M/22F) | 30 | 33 | No | No report | Not reported | Not reported | CT |
| Si et al (1998) ¹⁶ | 42 (33M/9F) | 20 (15M/5F) | 22 (18M/4F) | No | No report | Not reported | Not reported | CT |
| Jin et al (1999) ⁵¹ | 120 (74M/46F) | 60 | 60 | No | No report | Not reported | Not reported | CT |
| Li et al (1999) ⁵² | 64 (36M/28F) | 30 (17M/13F) | 34 (19M/15F) | No | No report | Quasirandomization | Not reported | CT |
| Zhang et al (1999) ⁵³ | 241 (179M/62F) | 145 (108M/37F) | 96 (71M/25F) | No | No report | Not reported | Not reported | No report |
| Chou et al (2000) ¹⁹ | 32 | 16 | 16 | No | No report | Quasirandomization (by admission order) | Not reported | CT |
| Naeser et al (1992) ³⁵ | 16 | 10 | 6 | No | Yes | Not reported | Not reported | CT |
| Johansson et al (2001) ³⁶ | 150 (14M/136F) | Group 1: 48; group 2: 51 | 51 | Yes | Yes | Computer generated, closed envelope | Yes | CT and clinical |

BMIT indicates Boston Motor Inventory Test. Other abbreviations are as defined in Table 1.

blinded. In summary, between randomized controlled trials comparing acupuncture plus conventional stroke rehabilitation with conventional stroke rehabilitation alone and randomized controlled trials comparing acupuncture plus conventional care with conventional care alone, there were significant differences in patient selection, intervention, and methodology. On the whole, the methodological quality was reasonably good for studies comparing acupuncture plus conventional stroke rehabilitation with conventional stroke rehabilitation alone but was poor for studies comparing acupuncture plus conventional care with conventional care alone.

We also assessed the clinical heterogeneity of the 8 randomized controlled trials⁴²⁻⁴⁹ whose interval to stroke

onset was >6 months or unreported. Between these 8 randomized controlled trials and the 14 randomized controlled trials that met all the inclusion criteria, there was significant difference in patient selection, intervention, and, in particular, methodology. None of the 8 randomized controlled trials reported how the randomization was performed except 1 study,⁴⁶ which used quasi randomization and did not report concealment of treatment allocation. None of the 8 randomized controlled trials reported assessor blinding, intention-to-treat analysis, and dropouts and death. Thus, the quality of the 8 randomized controlled trials whose interval to stroke onset was >6 months or unreported was very poor.

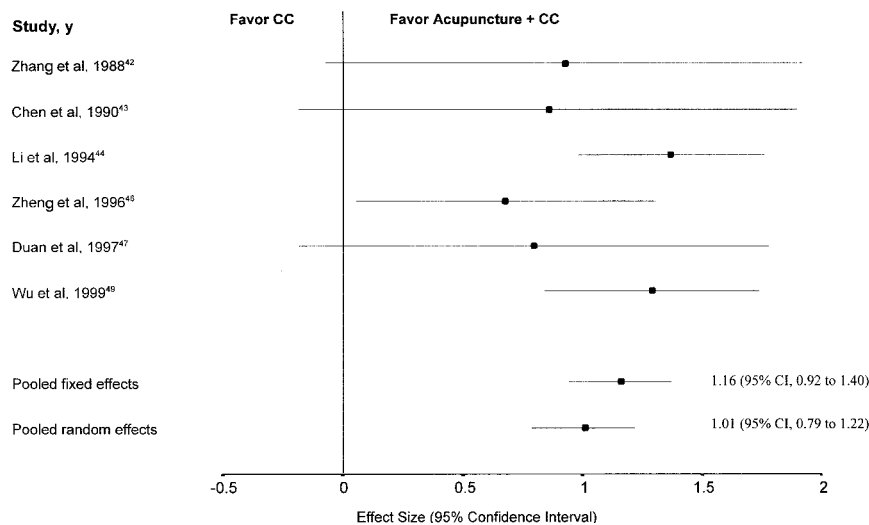


Figure 3. Difference in impairment outcome for studies comparing acupuncture plus conventional care (CC) with conventional care alone whose interval to stroke onset was >6 months or unreported.

Test of homogeneity Q=4.76, d.f.=5, p=0.45

Downloaded from <http://stroke.ahajournals.org/> by guest on July 21, 2017

TABLE 2. Continued

| Author | Stroke Nature | Stroke Status | Severity on Entry | Interval to Onset | Age, y | Inclusion Criteria | Exclusion Criteria |
|--------------------------------------|--|----------------------|--------------------|-------------------|---|--|--|
| Tang et al (1996) ⁵⁰ | Cerebral infarction | 1st stroke | No report | <7 d | 51–70 | Not specified | 1) Impaired consciousness 2) Significant comorbidity |
| Si et al (1998) ¹⁶ | Cerebral infarction | 1st stroke | Moderate | <7 d | Acupuncture: mean 68 (SD 10); control: mean 67 (SD 8) | Hemiplegia with limb power grading 3/6 | Coma |
| Jin et al (1999) ⁵¹ | Cerebral infarction | 1st stroke | No report | <30 d | 50–85 | Not specified | Not reported |
| Li et al (1999) ⁵² | ICH | 1st stroke | Moderate | ≤2 d | 52–75 | Not specified | 1) Impaired consciousness 2) Significant comorbidity 3) Epilepsy 4) Acupuncture-induced dizziness 5) Extensive ICH |
| Zhang et al (1999) ⁵³ | ICH; cerebral infarction; SAH (n=4) | 1st stroke | No report | <43 d | 35–85 | Not specified | Not reported |
| Chou et al (2000) ¹⁹ | Cerebral infarction and hemorrhagic transformation | 1st stroke | Moderate | 2 d | Not reported | Not specified | Not reported |
| Naeser et al (1992) ³⁵ | Cerebral infarction | 1st stroke | Moderate | 1–3 mo | 44–74 | Significant right hemiplegia | Not reported |
| Johansson et al (2001) ³⁶ | Cerebral infarction | 1st/recurrent stroke | Moderate to severe | 5–10 d | Weighted mean 76.3 | BI ≤70; 9 hole peg >60 s; walk 10 min with support | 1) Previous neurological/psychiatric/other disorders 2) Unable to comprehend 3) Concurrently in another trial |

Quantitative Findings

The first main finding is that with stroke rehabilitation, acupuncture had no additional effect on motor recovery (pooled random-effects estimate of change, 0.06; 95% CI, -0.12 to 0.24) (Figure 1) but had a positive effect on disability (pooled random-effects estimate of change, 0.49; 95% CI, 0.03 to 0.96) (Figure 2). Heterogeneity was found among the included studies^{2–4,33,34,37} for disability outcome and was mainly due to differences in intervention and methodological quality among these studies, as shown above. Because the pooled estimated change of 0.49 is less intuitive,

we converted it to the changes in BI²⁰ in 1 of the included studies,³ assuming that all the other conditions were unchanged. To have an estimated change of 0.49, the BI score at 3 months in the acupuncture group would be 75 instead of 90.4, and the BI change at 3 months in the acupuncture group would be 29.9 instead of 45.3. Because the BI change at 3 months in the control group was 27.3, the difference in BI changes between the 2 groups would be 2.6 points, which is clinically a small effect.

The second main finding is that without stroke rehabilitation, acupuncture had a positive effect on motor recovery on

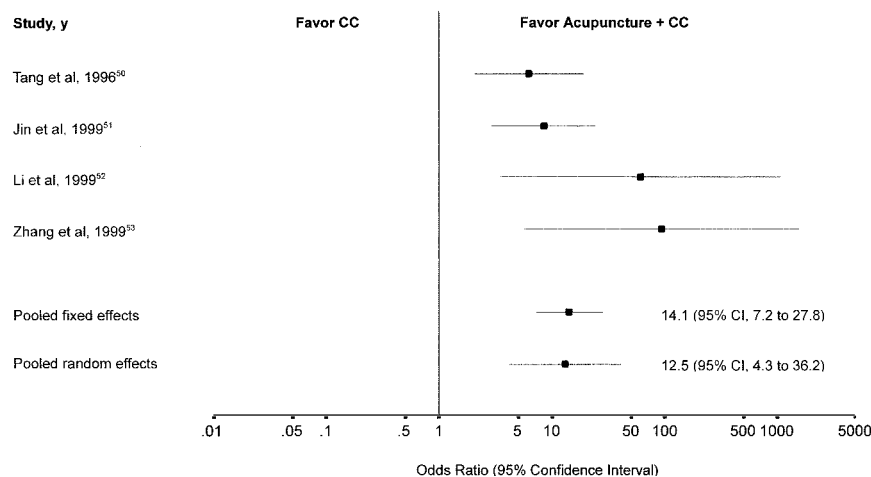


Figure 4. Difference in disability outcome for the included studies comparing acupuncture plus conventional care (CC) with conventional care alone.

Test of homogeneity Q=5.78, d.f.=3, p=0.12

Downloaded from <http://stroke.ahajournals.org/> by guest on July 21, 2017

TABLE 2. Continued

| Author | Baseline Matched | Acupuncture Technique | Acupuncture Method | Details of Acupuncture (Acupoints, Frequency, Duration) |
|--------------------------------------|------------------|-----------------------------|---|--|
| Tang et al (1996) ⁵⁰ | No report | Manual | Nonconventional cranial acupuncture | From Baihui (GV20) through Qubin (G7); needling 200 times/min for 5 min, then rest for 5 min; repeat 3 cycles |
| Si et al (1998) ¹⁶ | Yes | Manual followed by electric | Conventional body acupuncture | Acupoints (DU20, DU24, LI4, P6, SP6, LV3) on paretic side; 30 min/session, 5 sessions/wk, from admission to discharge (mean 36 d); electric frequency 5/45 Hz, 3.0 mA |
| Jin et al (1999) ⁵¹ | Yes | Manual followed by electric | Conventional body acupuncture | Main acupoints: Renzhong (GV26), Shangxing (GV23), Baihui (GV20); subsidiary acupoints: Jianjing (G21), Jianyu (LI15), Beilu (LI14), Quchi (LI11), Waiguan (TE5), Huantiao (G30), Chengfu (B36), Yinmen (B37), Yanglingquan (G34), Xuanzhong (G39), Taichong (Liv3); 50 min/session, 5 sessions/wk; electric frequency 1/s; electric intensity 7.5 mA |
| Li et al (1999) ⁵² | Yes | Manual | Nonconventional cranial acupuncture | Nonclassic acupoints: points along a line between Baihui (GV20) and Qubin (G7); 30 min/session daily |
| Zhang et al (1999) ⁵³ | No report | Manual | Nonconventional body acupuncture | Nonclassic acupoints on head and body of hemiplegic side; site of acupoints described; 40 min/session daily |
| Chou et al (2002) ¹⁹ | Yes | Manual | Conventional cranial acupuncture | Acupoints: GV20 through Tai Yang; needling for 3 min followed by 5 min rest for 2 cycles; 1 session daily for 20 d |
| Naeser et al (1992) ³⁵ | No report | Electric | Conventional body and nonconventional cranial acupuncture | Acupoints: 1) area of specific decreased electric resistance on skin of body +2) conventional body acupoints (LI3, 4, 11, 15; TW5, 9; ST31, 36; GB34, 39; Shenmen) +3) along motor cortex line on scalp (no details); 20 min/session; 5 sessions/wk for 4 wk; electric frequency 1–2 Hz |
| Johansson et al (2001) ³⁶ | Yes | Manual followed by electric | Conventional body and cranial acupuncture | Group 1: treatment A and B on alternate days; treatment A acupoints: LI4, ST36 on nonparetic side, +LI11, 4, EX28:2, ST36, 40, EX36:1, mobility point on paretic side +LI11, 4, EX28:2, GB34, ST40, EX36:1 on paretic side+GV20 (scalp); electric frequency 2 Hz; 30 min/session; 2 session/wk; group 2: TENS, corresponding to LI4, 11, ST36, 40, GB34 electric frequency 2 Hz, 30 min/session, 2 sessions/wk |

the basis of studies^{42–44,46,47,49} whose interval to stroke onset was >6 months or unreported (pooled random-effects estimate of change, 1.01; 95% CI, 0.79 to 1.22) (Figure 3) but not on studies^{16,19} that met all the inclusion criteria (pooled random-effects estimate of change, 0.46; 95% CI, –0.20 to 1.12). Without stroke rehabilitation, acupuncture also showed a positive effect on disability, either on the basis of studies^{50–53} that met all the inclusion criteria (pooled random-effects odds ratio, 12.5; 95% CI, 4.3 to 36.2) (Figure 4) or studies^{44,46,48} whose interval to stroke onset was >6 months or unreported (pooled random-effects odds ratio, 8.9; 95% CI, 3.5 to 22.3).

The third main finding is that there was no statistical difference between the real acupuncture plus conventional stroke rehabilitation group and the sham acupuncture plus conventional stroke rehabilitation group in either motor recovery^{33,35,36} (pooled random-effects estimate of change, –0.06; 95% CI, –1.24 to 1.12) or disability improvement^{33,36} (pooled random-effects estimate of change, 0.07; 95% CI, –0.34 to 0.48) (Figure 5).

Sensitivity and Subgroup Analyses

Sensitivity analyses for the 3 subgroups of randomized controlled trials that met all the inclusion criteria are shown in Table 3. For the 6 studies^{2–4,33,34,37} that compared acupuncture plus conventional stroke rehabilitation with conventional stroke rehabilitation alone in disability, when the study by Johansson et al³ or the study by Sallstrom et al⁴ was excluded, the pooled estimated change became statistically insignificant. After careful comparison, we were still uncertain of which patient or study characteristics in the 2 studies had influenced the pooled estimates.

We then performed subgroup analysis on these 6 studies^{2–4,33,34,37} according to the study quality (sample size ≥ 50 or < 50 , details of randomization, and assessor blinding). The pooled effects in motor impairment change and disability change are shown in Table 4. The significant differences in disability improvement between the acupuncture plus conventional stroke rehabilitation group and the conventional stroke rehabilitation alone group were

TABLE 2. Continued

| Author | Treatment | |
|--------------------------------------|---|--|
| | Control | Intervention |
| Tang et al (1996) ⁵⁰ | Conventional care | Conventional care+acupuncture |
| Si et al (1998) ¹⁶ | Conventional care (heparin, low-molecular dextran, and nimodipine) | Conventional care (heparin, low-molecular dextran, nimodipine)+acupuncture |
| Jin et al (1999) ⁵¹ | Conventional care+Chinese herbs | Conventional care+Chinese herbs+acupuncture |
| Li et al (1999) ⁵² | Conventional care | Conventional care+acupuncture |
| Zhang et al (1999) ⁵³ | Conventional care | Conventional care+acupuncture |
| Chou et al (2000) ¹⁹ | Conventional care | Conventional care+acupuncture |
| Naeser et al (1992) ³⁵ | Daily physiotherapy+sham acupuncture | Daily physiotherapy+real acupuncture |
| Johansson et al (2001) ³⁶ | Conventional daily PT, OT, ST+low-intensity, high-frequency TENS (electric frequency 80 Hz, amplitude 0.4 mA) | Conventional daily PT, OT, ST+acupuncture (group 1) or TENS (group 2) |

now seen only in studies^{2,3,34} with inadequate randomization and studies^{2-4,34} without assessor blinding.

Publication Bias

Only 7 studies^{44,46,48,50-53} had dichotomous disability data suitable for funnel plotting, which is shown in Figure 6. With the use of the funnel plot regression method, the slope of the regression was positive, with a predicted value of 0.01 ($P=0.10$).

Discussion

The study population well represented the general stroke population in terms of age and stroke nature. Most of the patients were within 15 days of stroke (64.8%) and had strokes that were moderate to severe (65.1%). Because motor recovery was most readily detectable in such patients, evaluation of the efficacy of acupuncture in them was appropriate, and the conclusion was likely to be applicable to the majority of stroke patients undergoing rehabilitation.

In the previous systematic review,¹⁰ the author failed to pool the data mainly because of the heterogeneity of outcome measures used in the studies. We took 2 measures to improve the homogeneity. First, we included only randomized controlled trials that used outcome measures that were internationally recognized or nationally approved. In China, the

Ministry of Health delegates specialists to develop an outcome measure first, which is then discussed by a panel of experts and finally approved at a national academic congress after amendments. Therefore, outcome measures created by the author of a clinical trial without details of validation and reliability testing were excluded from this meta-analysis. Second, we classified outcome measures into impairment and disability measures, which are categorically different and whose data should not be pooled together. Impairment measures the degree of intrinsic recovery of a neurological deficit, whereas disability measures the degree of adaptation of a patient to the environment. Impairment is therefore much less likely to be affected than disability by nonspecific effects, also called true placebo effects, such as expectation, suggestion, and therapeutic relationship.

In addition to improving the homogeneity of outcome measures, we took 2 more measures to improve the overall homogeneity. One was to divide trials into those with and without stroke rehabilitation according to the background intervention. Conventional stroke rehabilitation is a mode of intervention with proven value, and therefore it is inappropriate to pool trials with and without conventional stroke rehabilitation together. Our meta-analysis confirmed clinical heterogeneity between randomized controlled trials comparing acupuncture plus conventional

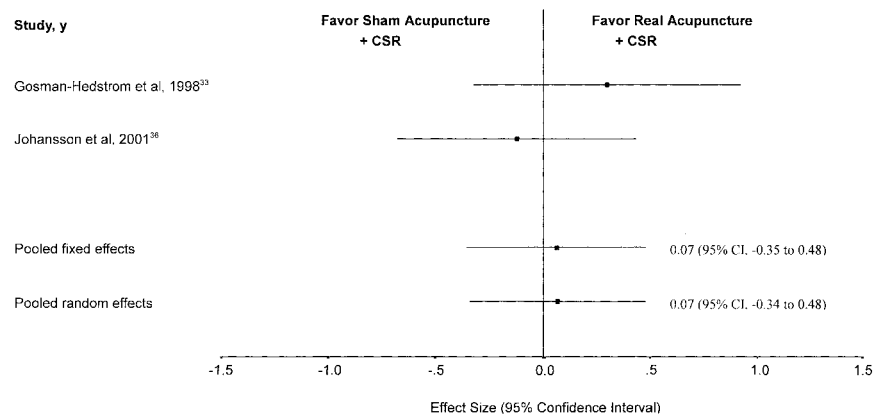


Figure 5. Difference in disability outcome for the included studies comparing real acupuncture plus conventional rehabilitation (CSR) with sham acupuncture plus conventional stroke rehabilitation.

TABLE 2. Continued

| Author | Treat for | Outcome Measure | | | |
|--------------------------------------|------------------------------------|---------------------------|---------------------------|------------------|--|
| | | Impairment | Disability | Assessor | Assessed at |
| Tang et al (1996) ⁵⁰ | 15 d | Muscle power | 2nd NCDC disability score | Not blinded | 2, 15 d |
| Si et al (1998) ¹⁶ | Admission to discharge (mean 36 d) | CSS (range 0–43) | NA | Not blinded | Discharge (LOS acupuncture: mean 37 d, SD 12; control: mean 36 d, SD 13) |
| Jin et al (1999) ⁵¹ | 40 d | 2nd NCDC impairment score | 2nd NCDC disability score | Not blinded | 40 d |
| Li et al (1999) ⁵² | Not reported | 2nd NCDC impairment score | 2nd NCDC disability score | Not blinded | Not reported |
| Zhang et al (1999) ⁵³ | 20–30 sessions | UNCHMS guidelines | UNCHMS guidelines | Not blinded | Not reported |
| Chou et al (2000) ¹⁹ | 20 d | MESSS | NA | Not blinded | Not reported |
| Naeser et al (1992) ³⁵ | 4 wk | BMIT | NA | Assessor blinded | Within 5 d of completing treatment |
| Johansson et al (2001) ³⁶ | 10 wk | RMI | BI –100 | Assessor blinded | 0, 3, 12 mo |

stroke rehabilitation with conventional stroke rehabilitation alone and randomized controlled trials comparing acupuncture plus conventional care with conventional care alone. The second measure was to place trials whose interval to stroke onset was >6 months or unreported in a separate group for data synthesis. Our meta-analysis also confirmed significant clinical heterogeneity between this group of studies and studies that met all the inclusion criteria.

In this meta-analysis, we showed that with stroke rehabilitation, acupuncture had no additional effect on motor recovery but had a small positive effect on disability. We then further assessed this positive effect on disability by 2 means. The first means was to analyze the pooled effect size of studies comparing real acupuncture plus conventional stroke rehabilitation with sham acupuncture plus conventional stroke rehabilitation to see whether this effect could be a true placebo effect. In this analysis we found no difference in disability improvement between the real and sham acupuncture groups, suggesting that the positive effect on disability found in the previous analysis could be a true placebo effect. One study⁵⁴ comments that procedures intimately involving

the patient and those that are invasive, such as acupuncture, are associated with more powerful true placebo effects than oral drug treatment. Another review⁵⁵ comments that various aspects of the physician-patient relationship may influence the effect of an intervention and that the quality of the communication between physician and patient may influence the patient’s adherence to treatment. Therefore, it is possible that stroke patients who have received acupuncture become more motivated and better adapted to the disability and therefore have a more favorable disability score, although the motor impairment may remain the same. The second means was to perform a subgroup analysis to see whether this effect was due to inclusion of studies with poor quality. In this analysis we found no difference in disability between the acupuncture plus conventional stroke rehabilitation and the conventional stroke rehabilitation alone groups, except in subgroups without adequate information regarding randomization or without assessor blinding. This suggests that the positive effect on disability found in the previous analysis could also be the result of inclusion of studies with poor quality.

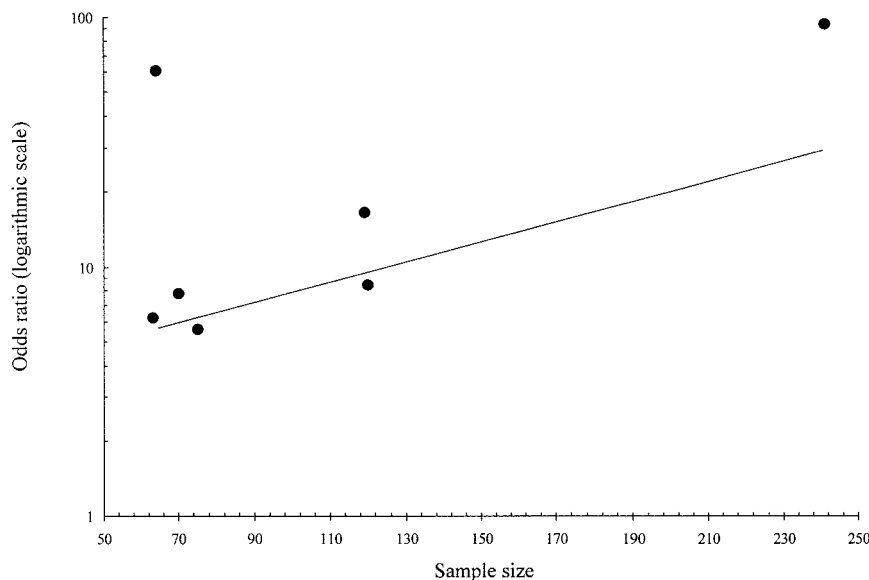


Figure 6. Funnel plot of studies comparing acupuncture plus conventional care with conventional care alone in disability (by the funnel plot regression method³²). A regression of the treatment effect as the dependent variable (y axis) on sample size as the independent variable (x axis), weighted by the inverse of the pooled variance of each study, is shown. When there is no publication bias, the regression slope has a predicted value of zero, forming a horizontal regression line. A non-zero slope would suggest an association between the treatment effect and sample size. A negative slope would suggest that small studies with large effects are preferentially published and small studies with negative results remain hidden, possibly as a result of publication bias. In this study the slope of the regression line was positive, with a predicted value of 0.01, but was statistically not significant ($P=0.10$), suggesting no evidence of publication bias.

TABLE 2. Continued

| Author | Results | | | | |
|--------------------------------------|--|--|---|------------------------|--|
| | Impairment | Disability | Dropout | Statistical Method | Note |
| Tang et al (1996) ⁵⁰ | Not recognized impairment scale | Acupuncture 20/30; control: 8/33 | Not reported | Not reported | Impairment data not suitable for meta-analysis; Jadad score: 1; disability result positive |
| Si et al (1998) ¹⁶ | CSS control: pre: 25 (8.3), n=22; post: 19.9 (9.1), n=22; difference: 5.1 (3.4); acupuncture: pre: 24 (7.4), n=20; post: 15.8 (6.4), n=20; difference: 8.2 (3.4) | NA | Not reported | <i>t</i> test | 1) No disability score; Jadad score: 1; impairment result positive |
| Jin et al (1999) ⁵¹ | Not reported | Improved: 55/60 (acupuncture) (1 dead); improved: 34/60 (control) (2 dead) | Reported 3 deaths | <i>t</i> test | Impairment score not reported; Jadad score: 2; disability result positive |
| Li et al (1999) ⁵² | Not reported | Improved: 30/30 (acupuncture); improved: 17/34 (control) | Not reported | Not reported | Impairment score not reported; duration of treatment not reported; Jadad score: 0; disability result positive |
| Zhang et al (1999) ⁵³ | Not reported | Improved: 145/145 (acupuncture); improved: 73/96 (control) | Not reported | χ^2 | UNCHMS not referenced in detail; impairment score not reported; Jadad score: 1; disability result positive |
| Chou et al (2000) ¹⁹ | MESSS acupuncture: pre: 21.74 (5.3); post: 11.17 (4.53); control: pre: 21.4 (3.72); post: 15.74 (3.61) | NA | Not reported | <i>t</i> test | Disability score not reported; Jadad score: 0; impairment result positive |
| Naeser et al (1992) ³⁵ | BMIT: real acupuncture: 4/10 had good response >10% change in >2/7 of BMIT; sham acupuncture: 0/6 had good response | NA | Not reported | Fisher's exact test | Significant difference between 2 groups shown when patients stratified according to infarct size; Jadad score: 2; impairment result negative |
| Johansson et al (2001) ³⁶ | RMI: mean score (SD): acupuncture: pre: 2.96 (2.84); 3 mo: 7.25 (4.80); TENS: pre: 2.96 (2.47); 3 mo: 7.47 (4.49) | BI-100: mean score (SD): acupuncture: pre: 31.8 (18.4); 3 mo: 64.4 (31.2); TENS: pre: 35.4 (19.1); 3 mo: 65.9 (28.9) | Group 1: 2 died 2 dropouts; Group 2: 1 died | Wilcoxon rank sum test | Mean values obtained from author; Jadad score: 5; impairment and disability results negative |

BMIT indicates Boston Motor Inventory Test. Other abbreviations are as defined in Table 1.

For studies comparing acupuncture plus conventional care with conventional care alone, the results for the impairment outcome were inconclusive. Acupuncture was shown to be more effective only in studies whose interval to stroke onset was >6 months or unreported. Because the quality of these studies was very poor, no conclusion could be drawn safely. As for disability outcome, acupuncture was shown to be much more effective than no acupuncture in all studies comparing acupuncture plus conventional care with conventional care alone. However, we must consider 3 issues before we draw any conclusions. The first issue is publication bias. Because the funnel plot that did not show significant publication bias in this meta-analysis was based on only 7 randomized controlled trials and had many limitations,⁵⁶ we did a post hoc analysis using the fail-safe method. Given the overall disability improvement rate of approximately 23% in the control group of studies comparing acupuncture plus conventional care with conventional care alone, it will require a single negative

study of approximately 16 000 subjects with an odds ratio of 1.0 to nullify the positive result in this meta-analysis. This is a very unlikely scenario, and therefore the significant effect shown by the acupuncture group is unlikely to be due to publication bias. The second issue is the conversion of various disability measures into a dichotomous measure. The disability measures used in studies comparing acupuncture plus conventional care with conventional care alone were expressed in such categories as deterioration, no change, improvement, significant improvement, and almost recovered or the categories of no effect, with effect, significant effect, and almost recovered. For data synthesis, we adopted a dichotomous measure by combining the categories of deterioration, no change, and no effect as "no improvement" and the categories of improvement, significant improvement, with effect, significant effect, and almost recovered as "with improvement." In so doing, the sensitivity of these measures might be compromised, but this was unlikely to have changed the

TABLE 3. Sensitivity Analyses of 3 Subgroups of Randomized Controlled Trials That Met All Inclusion Criteria

| Mode of Treatment | Excluded Study | Overall Fixed Effects (95% CI) | |
|---|---|--------------------------------|--------------------------|
| | | Impairment | Disability |
| Acupuncture+ CSR vs CSR alone | Hu et al, 1993 ² | 0.046 (−0.111 to 0.203) | 0.257 (0.006 to 0.508) |
| | Johansson et al, 1993 ³ | 0.059 (−0.101 to 0.220) | 0.201 (−0.053 to 0.455) |
| | Sallstrom et al, 1996 ⁴ | 0.018 (−0.141 to 0.178) | 0.267 (−0.0002 to 0.534) |
| | Gosman-Hedstrom et al, 1998 ³³ | 0.097 (−0.063 to 0.256) | 0.345 (0.083 to 0.606) |
| | Wong et al, 1999 ³⁴ | −0.015 (−0.185 to 0.155) | 0.467 (0.145 to 0.790) |
| | Sze et al, 2002 ³⁷ | 0.132 (−0.06 to 0.325) | 0.313 (0.049 to 0.577) |
| Real acupuncture+ CSR vs sham acupuncture+ CSR* | Naeser et al, 1992 ³⁵ | −0.466 (−0.817 to −0.115) | |
| | Gosman-Hedstrom et al, 1998 ³³ | −0.567 (−1.153 to 0.019) | |
| | Johansson et al, 2001 ³⁶ | −0.223 (−0.635 to 0.190) | |
| Acupuncture+ CC vs CC alone† | Tang et al, 1996 ⁵⁰ | | 20.04 (8.28 to 48.51) |
| | Jin et al, 1999 ⁵¹ | | 19.37 (7.90 to 47.50) |
| | Li et al, 1999 ⁵² | | 11.96 (5.92 to 24.14) |
| | Zhang et al, 1999 ⁵³ | | 9.91 (4.86 to 20.20) |

CSR indicates conventional stroke rehabilitation; CC, conventional care.

*Sensitivity analysis was not performed for disability effect sizes of the 2 trials Gosman-Hedstrom et al³³ and Johansson et al,³⁶ which were 0.30 (95% CI, −0.32 to 0.92) and −0.12 (95% CI, −0.67 to 0.43), respectively.

†Sensitivity analysis was not performed for impairment effect sizes of the 2 trials Si et al¹⁶ and Chou et al,¹⁹ which were 0.47 (95% CI, 0.03 to 0.91) and 0.45 (95% CI, −0.43 to 1.33), respectively.

direction of the overall effects. Therefore, we think that the significant effect shown by the acupuncture group is not due to conversion of these outcome measures. The third issue is the quality of these studies. Studies comparing

acupuncture plus conventional care with conventional care alone, particularly studies whose interval to stroke onset was >6 months or unreported, had poor methodological quality and small sample size. We believe that the overall

TABLE 4. Subgroup Analyses of Effects of Acupuncture Based on Study Quality

| Criteria | Study | Impairment | | Disability | |
|---------------|---|-------------------------------|-------------------------|------------------------------|-------------------------|
| | | Fixed Effects (95% CI) | Random Effects (95% CI) | Fixed Effects (95% CI) | Random Effects (95% CI) |
| Sample size | ≥50 | | | | |
| | Johansson et al, 1993 ³ | 0.05 (−0.12 to 0.23) Q=3.33 | 0.10 (−0.13 to 0.32) | 0.26 (−0.04 to 0.57) Q=8.16* | 0.56 (−0.31 to 1.43) |
| | Wong et al, 1999 ³⁴ | | | | |
| | <50 | | | | |
| | Hu et al, 1993 ² | 0.05 (−0.23 to 0.34) Q=4.17 | 0.002 (−0.38 to 0.38) | 0.36 (−0.05 to 0.77) Q=2.69 | 0.41 (−0.15 to 0.97) |
| | Sallstrom et al, 1996 ⁴ | | | | |
| | Gosman-Hedstrom et al, 1998 ³³ | | | | |
| Randomization | Adequate information | | | | |
| | Sallstrom et al, 1996 ⁴ | −0.04 (−0.24 to 0.16) Q=4.20 | −0.05 (−0.43 to 0.33) | 0.23 (−0.14 to 0.60) Q=1.06 | 0.18 (−0.07 to 0.42) |
| | Gosman-Hedstrom et al, 1998 ³³ | | | | |
| | Inadequate information | | | | |
| | Hu et al, 1993 ² | −0.09 (−0.33 to 0.15) Q=5.70* | 0.01 (−0.36 to 0.38) | 0.35 (0.03 to 0.68) Q=9.70* | 0.81 (0.02 to 1.61) |
| | Johansson et al, 1993 ³ | | | | |
| | Wong et al, 1999 ³⁴ | | | | |
| Blinding | Assessor blinded | | | | |
| | Sallstrom et al, 1996 ⁴ | −0.04 (−0.24 to 0.16) Q=4.20 | −0.05 (−0.43 to 0.33) | 0.10 (−0.37 to 0.56) Q=0.23 | 0.13 (−0.06 to 0.33) |
| | Gosman-Hedstrom et al, 1998 ³³ | | | | |
| | Assessor not blinded | | | | |
| | Hu et al, 1993 ² | 0.01 (−0.21 to 0.22) Q=8.39* | 0.13 (−0.17 to 0.43) | 0.37 (0.09 to 0.66) Q=9.77* | 0.72 (0.12 to 1.31) |
| | Johansson et al, 1993 ³ | | | | |
| | Wong et al, 1999 ³⁴ | | | | |
| | Sallstrom et al, 1996 ⁴ | | | | |

*Test of homogeneity was significant at 10% level.

effect can be greatly affected by the quality and size of the included studies and that the possibility that this significant effect shown by the acupuncture group was due to methodological bias cannot be excluded. Therefore, we conclude that we are still uncertain about the efficacy of acupuncture when stroke rehabilitation is not available, and we recommend more properly designed randomized controlled trials comparing acupuncture with no acupuncture in settings in which stroke rehabilitation is not available.

Compared with the previous systemic review¹⁰ that concludes that there is no compelling evidence to show that acupuncture is effective in stroke rehabilitation, our meta-analysis has taken an additional step to conclude that there is reasonably good evidence to show that, with stroke rehabilitation, acupuncture has no additional effect on motor recovery but has a small positive effect on disability, which may be due to a true placebo effect and varied study quality. However, without stroke rehabilitation the efficacy of acupuncture remains uncertain, mainly because of the poor quality of such studies.

Acknowledgments

This study was supported by the Hong Kong Association for Health Care Ltd. We are particularly indebted to Xiang Yi, MD, for her participation in searching and reviewing the Chinese literature. We also wish to thank Kjell Asplund, MD, for provision of the raw data of their publication.

References

- Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Acute stroke: prognosis and a prediction of the effect of medical treatment on outcome and health care utilization: the Copenhagen Stroke Study. *Neurology*. 1997;49:1335-1342.
- Hu HH, Chung C, Liu TJ, Chen RC, Chen CH, Chou P, Huang WS, Lin JC, Tsuei JJ. A randomized controlled trial on the treatment for acute partial ischemic stroke with acupuncture. *Neuroepidemiology*. 1993;12:106-113.
- Johansson K, Lindgren I, Widner H, Wiklund I, Johansson BB. Can sensory stimulation improve the functional outcome in stroke patients? *Neurology*. 1993;43:2189-2192.
- Sallstrom S, Kjendahl A, Osten PE, Stanghelle JH, Borchgrevink CF. Acupuncture in the treatment of stroke patients in the subacute stage: a randomized, controlled study. *Complement Ther Med*. 1996;4:193-197.
- Vincent CA, Richardson PH. The evaluation of therapeutic acupuncture: concepts and methods. *Pain*. 1986;24:1-13.
- Ernst E, White AR. Acupuncture as an adjuvant therapy in stroke rehabilitation? *Wien Med Wochenschr*. 1996;146:556-558.
- NIN Consensus Development Panel on Acupuncture. Acupuncture. *JAMA*. 1998;280:1518-1524.
- Tang JL, Zhan SY, Ernst E. Review of randomised controlled trials of traditional Chinese medicine. *BMJ*. 1999;319:160-161.
- Mayer DJ. Acupuncture: an evidence-based review of the clinical literature. *Annu Rev Med*. 2000;51:49-63.
- Park J, Hopwood V, White AR, Ernst E. Effectiveness of acupuncture for stroke: a systematic review. *J Neurol*. 2001;248:558-563.
- Scandinavian Stroke Study Group. Multicenter trial of hemodilution in ischemic stroke: background and study protocol. *Stroke*. 1985;16:885-890.
- Collen FM, Wade DT, Robb GF, Bradshaw CM. The Rivermead Mobility Index: a further development of the Rivermead Motor Assessment. *Int Disabil Stud*. 1991;13:50-54.
- Carr J, Shepherd R, Nordholm L, Lynne D. Investigation of a new motor assessment scale for stroke patients. *Phys Ther*. 1985;65:175-180.
- Brunnstrom S. *Movement Therapy in Hemiplegia*. New York, NY: Harper & Row; 1970.
- Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient, I: a method for evaluation of physical performance. *Scand J Rehabil Med*. 1975;7:13-31.
- Si QM, Wu GC, Cao XD. Effects of electroacupuncture on acute cerebral infarction. *Acupunct Electrother Res Int J*. 1998;23:117-124.
- The Second National Cerebrovascular Diseases Conference. Recommendations on clinical research in stroke [in Chinese]. *Chin J Neurol Psychiatry*. 1988;21:57-60.
- Ministry of Health of People's Republic of China. *Guidelines on the Use of New Chinese Herbal Medicines in Stroke* [in Chinese]. Beijing, Republic of China: Ministry of Health; 1993.
- Chou TH, Yeung Y, Sun MY, Yu CK. 32 cases with ischemic stroke and haemorrhagic transformation treated with acupuncture [in Chinese]. *Acupunct Clin J*. 2000;16:6-7.
- Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J*. 1965;14:61-65.
- Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? *Int Disabil Stud*. 1988;10:64-67.
- Hamilton BB, Granger CV, Sherwin FS, Sielezny M, Tasman JS. A uniform national data system for medical rehabilitation. In: Fuhrer MJ, ed: *Rehabilitation Outcomes: Analysis and Measurement*. Baltimore, Md: Brookes; 1987:137-147.
- Vardeberg K, Kolsrud M, Laberg T. The Sunnaas Index of ADL. *World Fed Occup Ther Bull*. 1991;24:30-35.
- National Traditional Chinese Medicine Conference on Diagnosis of Stroke and Assessment of Efficacy 1986 (Tai-An Conference 1986). Diagnosis of stroke and assessment of efficacy [in Chinese]. *Acta Med Sinica*. 1986;1:56-57.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12.
- Becker BJ. Synthesizing standardized mean-change measures. *Br J Math Stat Psychol*. 1988;41:257-278.
- Hedges LV, Olkin I. *Statistical Methods for Meta-analysis*. San Diego, Calif: Academic Press; 1985.
- Dunlap WP, Cortina JM, Vaslow JB, Burke MJ. Meta-analysis of experiments with matched groups or repeated measures designs. *Psychol Meth*. 1996;1:170-177.
- Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. *Stat Med*. 2000;19:3127-3131.
- Der Simonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
- Robbins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large strata limiting models. *Biometrics*. 1986;42:311-323.
- Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stat Med*. 2001;20:641-654.
- Gosman-Hedstrom G, Claesson L, Klingenstierna U, Carlsson J, Olausson B, Frizell M, Fagerberg B, Blomstrand C. Effects of acupuncture treatment on daily life activities and quality of life: a controlled, prospective, and randomized study of acute stroke patients. *Stroke*. 1998;29:2100-2108.
- Wong AMK, Su TY, Tang FT, Cheng PT, Liaw MY. Clinical trial of electrical acupuncture on hemiplegic stroke patients. *Am J Phys Med Rehabil*. 1999;78:117-122.
- Naeser MA, Alexander MP, Eder DS, Galler V, Hobbs J, Bachman D. Real versus sham acupuncture in the treatment of paralysis in acute stroke patients: a CT scan lesion site study. *J Neurol Rehabil*. 1992;6:163-173.
- Johansson BB, Haker E, von Arbin M, Britton M, Langstrom G, Terent A, Ursing D, Asplund K. Acupuncture and transcutaneous nerve stimulation in stroke rehabilitation: a randomized, controlled trial. *Stroke*. 2001;32:707-713.
- Sze FKH, Wong E, Xiang Y, Woo J. Value of acupuncture to standard post-stroke motor rehabilitation: a randomized controlled trial. *Stroke*. 2002;33:186-194.
- Magnusson M, Johansson K, Johansson BB. Sensory stimulation promotes normalization of postural control after stroke. *Stroke*. 1994;25:1176-1180.
- Kjendahl A, Sallstrom S, Osten PE, Stanghelle JK, Borchgrevink CF. A one year follow-up study on the effects of acupuncture in the treatment of stroke patients in the subacute stage: a randomized, controlled study. *Clin Rehabil*. 1997;11:192-200.
- Sun ST, Li SR, Zhu YZ, Chen SL, Wan GZ, Sun YZ, Hou GW, Yu ZH. Clinical study on 500 cases of cerebro-vascular hemiplegia treated by acupuncture through Baihui to Qubin. *J Trad Chin Med*. 1985;5:167-170.

41. Qi LY, Zhang ZH, Liu YP, Lin BQ, Zhao GL, Huang SX, Wei S. Acupuncture treatment of cerebrovascular occlusion and changes in hemorrheological indices during treatment: a clinical analysis of 100 cases. *J Trad Chin Med*. 1986;6:105–110.
42. Zhang ZJ. Clinical report on acupuncture therapy for 330 hemiplegic cases [in Chinese]. *Chin Acupunct Moxibustion*. 1988;1:8–9.
43. Chen DZ, Liu V, Chao FY, Wu ZC, Fung ZQ. Evaluation of the clinical efficacy of conventional body acupuncture on ischemic stroke [in Chinese]. *J Chin West Med Integrat*. 1990;10:526–528.
44. Li YQ, Chang X, Wong S, Qin Y, Ma L. Efficacy of treatment using cranial acupuncture and medication for 59 cases with cerebrovascular accident [in Chinese]. *Chin Acupunct Moxibustion*. 1994;5:13–14.
45. Li WL, Sun L, Chiu GM, Chao R. Efficacy of acupuncture with rehabilitation on hemiplegia [in Chinese]. *Chin Acupunct Moxibustion*. 1996;10:3.
46. Zheng JG. Clinical effectiveness of acupuncture using “Xian-Nau-Kai-Xiau” technique for acute cerebral haemorrhage [in Chinese]. *Tianjing Trad Chin Med Coll Bull*. 1996;4:21–23.
47. Duan GJ, Tong X, Chang CY, Yang Y, Chang B, Sun ST. Sites of cerebral infarction and their responses to acupuncture therapy [in Chinese]. *Chin Acupunct Moxibustion*. 1997;10:591–593.
48. Liu MA, Kou WY, Wai M, Xe ZH. Clinical report of 38 patients with cerebral infarction treated with acupuncture and medications [in Chinese]. *Chin Acupunct Moxibustion*. 1998;8:457–458.
49. Wu P, Leung YL. Clinical report of 47 patients with cerebrovascular accident treated with acupuncture and medications [in Chinese]. *J Shanghai Acupunct Moxibustion*. 1999;10:13–14.
50. Tang QS, Sun ST. Clinical, electrophysiological and biochemical changes following cranial acupuncture therapy to acute cerebral infarction [in Chinese]. *Beijing Trad Chin Med Univ Bull*. 1996;19:37–39.
51. Jin ZQ, Ku FL, Chan SX, Chen GX. Effect of acupuncture using acupoints of the Du Meridian on acute cerebral infarction [in Chinese]. *Acupunct Res*. 1999;1:5–7.
52. Li Q, Xiao GY, Tung KY. Clinical study of the effect of cranial acupuncture on acute cerebral haemorrhage [in Chinese]. *J Chin West Med Integrat*. 1999;19:203–205.
53. Zhang QC, Lo LB, Yu L, Chang LT, Chang YM. The effectiveness of acupuncture using “six acupoints for hemiplegia” method in the treatment of 145 acute stroke patients with Middle-Meridians abnormality [in Chinese]. *Clin Acupunct J*. 1999;15:46–48.
54. Ernst E, Resch KL. Concept of true and perceived placebo effects. *BMJ*. 1995;311:551–553.
55. Hrobjartsson A, Gotzsche PC. Placebo intervention compared with no treatment (Cochrane review). In: *The Cochrane Library*, issue 1, 2001. Oxford, UK: Update Software.
56. Tang JL, Liu JL. Misleading funnel plot for detection of bias in meta-analysis. *J Clin Epidemiol*. 2000;53:477–484.

Does Acupuncture Improve Motor Recovery After Stroke?: A Meta-Analysis of Randomized Controlled Trials

Frank Kai-hoi Sze, Eric Wong, Kevin K.H. Or, Joseph Lau and Jean Woo

Stroke. 2002;33:2604-2619

doi: 10.1161/01.STR.0000035908.74261.C9

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2002 American Heart Association, Inc. All rights reserved.

Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/33/11/2604>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>