Systematic review of long-term Xingnao Kaiqiao needling efficacy in ischemic stroke treatment

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Abstract

OBJECTIVE: To systematically evaluate the long-term effect and safety of Xingnao Kaiqiao needling method in ischemic stroke treatment.

DATA RETRIEVAL: We retrieved relevant random and semi-random controlled trials that used the Xingnao Kaiqiao needling method to treat ischemic stroke compared with various control treatments such as conventional drugs or other acupuncture therapies. Searches included China National Knowledge Infrastructure, Weipu Information Resources System, Wanfang Medical Data System, Chinese Biomedical Literature Database, Cochrane Library, and PubMed, from May 2006 to July 2014.

SELECTION CRITERIA: Two authors independently conducted literature screening, quality evaluation, and data extraction. The quality of articles was evaluated according to the Cochrane Reviewers’ Handbook 5.1, and the study was carried out using Cochrane system assessment methods. RevMan 5.2 was used for meta-analysis of the included studies.

MAIN OUTCOME MEASURES: Mortality rate, recurrence rate, and disability rate were observed.

RESULTS: Nine randomized and semi-randomized controlled trials treating 931 cases of ischemic stroke were included in this review. Meta-analysis results showed that there were no significant differences in mortality reduction (risk ratio (RR) = 0.58, 95% confidence interval (CI): 0.17–1.93, Z = 0.89, P = 0.37) or recurrence rate (RR = 0.55, 95% CI: 0.18–1.70, Z = 1.04, P = 0.30) of ischemic stroke patients between the Xingnao Kaiqiao needling and control treatment groups. However, the Xingnao Kaiqiao needling method had a tendency towards higher efficacy in mortality reduction and recurrence rates. The Xingnao Kaiqiao needling method was significantly better than that of the control treatment in reducing disability rate (RR = 0.51, 95% CI: 0.27–0.98, Z = 2.03, P < 0.05).

CONCLUSION: The Xingnao Kaiqiao needling method has a better effect than control treatment in reducing disability rate. The long-term effect of Xingnao Kaiqiao needling against ischemic stroke is better than that of control treatment. However, the limitations of this study limit the strength of the conclusions. Randomized controlled trials with a strict, reasonable design, and multi-center, large-scale samples and follow-up are necessary to draw conclusions about Xingnao Kaiqiao needling.

Key Words: nerve regeneration; Xingnao Kaiqiao needling method; ischemic stroke; randomized controlled trial; systemic reviews; meta-analysis; long-term efficacy; mortality; recurrence; disability; adverse reactions; health economics indicators; neural regeneration

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Inclusion and exclusion criteria

Studies were eligible for inclusion if they met all of the following inclusion criteria. (1) Studies were randomized or semi-randomized controlled trials of patients of any gender and age with ischemic stroke. (2) In the included studies, the diagnosis of ischemic stroke had to meet the diagnostic criteria of the WHO or the National Conference of Cerebral Vascular Disease, and is confirmed by CT/MRI. (3) The treatment groups received Xingnao Kaiqiao needling alone or combined with other treatment methods, while the control groups received traditional acupuncture or combination treatment excluding Xingnao Kaiqiao needling. (4) Mortality, recurrence rate, disability rate, safety, health, and economic indicators at the end of treatment or follow-up (more than 3 months) were evaluated in the studies.

Studies were excluded if both the treatment and control groups used Xingnao Kaiqiao needling.

Data extraction and quality evaluation

According to Cochrane Reviewers’ Handbook 5.1 software (Julian PT Higgins and Sally Green, 2011), the selected articles were evaluated on six criteria including: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues. These criteria are categorized as: “yes,” “no,” and “unclear.” “Yes” indicates a low risk of bias and “no” indicates a high risk of bias. “Unclear” indicates that there is not sufficient information for this criterion. Cochrane systematic review software RevMan 5.2 software (http://handbook.cochrane.org) was used to perform the meta-analysis.

Evaluation of quality was carried out by two reviewers independently using pre-specified selection criteria, and disagreements were resolved by consensus or by a third reviewer.

Main outcome measures

The main outcome measures were mortality rate, recurrence rate, disability rate, adverse reactions, and health economics indicators.

Statistical analysis

Clinical and methodological heterogeneity analysis was performed for the included studies, and then subgroup analysis (RevMan 5.2 software, http://handbook.cochrane.org) was performed. The chi-square test was used for statistical analysis of heterogeneity, and a probability value of less than 0.10 was considered statistically significant. $P < 0.10$ indicates that heterogeneity exists between the results of the studies. Meanwhile, $I^2$ was used for quantitative assessment. Heterogeneity is not obvious when $I^2 < 25$, moderate heterogeneity exists when $I^2$ ranges from 25% to 50%, and excessive heterogeneity exists when $I^2 > 50$. Heterogeneous test results were expressed with the random effect model and homogenous test results were expressed with the fixed effect model. Efficacy effect size was evaluated using interval estimation and hypothesis test. Risk ratio ($RR$) was used for enumeration data, and weighted mean difference ($WMD$)
Figure 2 Meta-analysis of the mortality of ischemic stroke treated with Xingnao Kaiqiao needling.
95% CI: 95% Confidence interval.

Figure 3 Meta-analysis of the recurrence rate of ischemic stroke treated with Xingnao Kaiqiao needling.
95% CI: 95% Confidence interval.

Figure 4 Meta-analysis of the disability rate of ischemic stroke treated with Xingnao Kaiqiao needling.
95% CI: 95% Confidence interval.
was used for continuous variables. Interval estimation was performed using 95% confidence interval (CI). The $U$ test was used for hypothesis testing, and results are represented by $Z$ and $P$ values. The difference between the curative effect was statistically significant when $P < 0.05$. Hypothesis test results are listed in a forest plot. Sensitivity analysis was performed for low-quality studies in subgroups.

### Results

#### Data retrieval

A total of 568 articles were retrieved, and 129 articles including “random” in the title and abstract were selected. Among the 129 selected articles, 85 were excluded because of repetition and 35 were excluded because the intervention and observed subjects did not meet the inclusion criteria. Nine articles (Liu et al., 2006, 2012; Meng et al., 2006; Rao et al., 2006; Yang et al., 2008a, b; Shi, 2010; Liu and Chen, 2012; Tang, 2013) were included in the analysis, all of which were published in Chinese (Figure 1).

### General characteristics of the included studies

The number of enrolled subjects was 20 to 118 for each study, with 931 subjects in total. All studies focused on the *Xingnao Kaiqiao* needling method, and some were accompanied by conventional therapy. In the included studies, comparisons were performed between the *Xingnao Kaiqiao* needling method and traditional acupuncture, or conventional therapy. Three studies (Liu et al., 2006; Rao et al., 2006; Yang et al., 2008a) described mortality, four studies (Liu et al., 2006, 2012; Yang et al., 2008b; Shi, 2010; Liu and Chen, 2012) described recurrence rate, two studies (Liu et al., 2006; Rao et al., 2006) described disability rate, and seven studies (Liu et al., 2006, 2012; Meng et al., 2006; Rao et al., 2006; Yang et al., 2008b; Liu and Chen, 2012; Tang, 2013) described safety. Outcome data in one study (Liu et al., 2006) were incomplete, while other studies were integrated. The risk of bias for selective
outcome reporting was low in all studies. Other sources of bias were unclear. Details and features of the included studies are shown in Table 1.

Quality of included studies
Four studies (Liu et al., 2006; Rao et al., 2006; Yang et al., 2008a, b) reported detailed randomization methods. Among these four studies, three (Rao et al., 2006; Yang et al., 2008a, b) used computerized randomization methods, while one (Liu et al., 2006) used randomized digital tables. Allocation concealment was adequately described in three studies (Rao et al., 2006; Yang et al., 2008a, b), whereas the other studies did not report allocation concealment. In addition, assessor blinding was carried out in two studies, but blinding was not described in any other studies (Table 2). Subject drop-outs were reported in one study, whereas other studies were integrated. All studies did not have selective reporting outcomes, and it cannot be determined whether other sources of bias were present.

Meta-analysis

Mortality at the end of treatment or final follow-up (≥ 3 months)
Mortality at the end of treatment of 6 months was reported in two studies (Liu et al., 2006; Yang et al., 2008a), and mortality at the end of treatment of 3 and 6 months was reported in one study (Rao et al., 2006). Heterogeneous test was performed for four sets of data (P = 0.66, I² = 0%), which demonstrated that the included studies are not of clinical or statistical heterogeneity, and can be analyzed using the fixed effect model in meta-analysis. The combined effect size (RR = 0.58, 95%CI: 0.17–1.93, Z = 0.89, P = 0.37) indicated no statistical significance. However, the Xingnao Kaiqiao needling method trended towards reducing the mortality rate of ischemic stroke (Figure 2).

Recurrence rate at the end of treatment or final follow-up (≥ 3 months)
The recurrence rate was reported in four studies (Liu et al., 2006, 2012; Yang et al., 2008b; Shi, 2010). Heterogeneity tests were performed on the included studies and the results (P < 0.01, I² = 75%) indicate that they are of statistical heterogeneity. Therefore, the random effects model was used in the meta-analysis. Analysis of combined effect size (RR = 0.55, 95%CI: 0.18–1.70, Z = 1.04, P = 0.30) indicated that there was not statistical significance in recurrence rate. Analysis of subgroups was performed according to different follow-up periods. The heterogeneity tests of follow-up for 3 months (P = 0.08, I² = 0%) showed that included studies were not of clinical and statistical heterogeneity, so the fixed effect model was used in their meta-analysis. Analysis of combined effect size (RR = 0.81, 95%CI: 0.43–1.52, Z = 0.65, P = 0.52) indicated that there was not statistical significance in recurrence rate. The heterogeneity test of follow-up for 6 months (P = 0.02, I² = 82%) indicated that the included studies are of statistical heterogeneity, so the random effects model was used in their meta-analysis. Combined effect size (RR = 0.43, 95%CI: 0.04–4.28, Z = 0.72, P = 0.47) indicated that there was no statistical significance in recurrence rate. Although no significant difference was found, the Xingnao Kaiqiao needling had a trend towards reduction in recurrence rate of ischemic stroke (Figure 3).

Disability rate at the end of treatment or final follow-up (≥ 3 months)
Disability rate 6 months after treatment was reported in one study (Liu et al., 2006), and disability rate 3 and 6 months after treatment reported in one study (Rao et al., 2006). Heterogeneity tests of these data (P = 0.67, I² = 0%) showed that the included studies were not of clinical and statistical heterogeneity, so the fixed effect model was used for their meta-analysis. The combined effect size (RR = 0.51, 95%CI: 0.27–0.98, Z = 2.03, P < 0.05) showed that there was statistical significance in disability rate. Therefore, Xingnao Kaiqiao needling was better at reducing disability rate after ischemic stroke than other treatments in the control group (Figure 4).

Adverse reactions
One study (Liu et al., 2006) reported that one patient in the treatment group had syncpe. In another study (Liu and Chen, 2012), bleeding at the acupuncture site was reported in three patients, and syncpe in one patient in the observation group. The same study reported bleeding at the acupuncture site in two patients, and syncpe in two patients in the control group. No adverse reactions were reported in other studies.
Health economics indicators
None of the included studies reported the costs or other information of health economics indicators.

Discussion
Safety analysis
Xingnao Kaiaqiao needling method is a relatively safe treatment. Fainting during acupuncture treatment was the most common adverse event. Fainting during acupuncture treatment, hematoma, and pain during treatment are related to personal physical differences and acupuncture manipulation.

Limitations of meta-analysis in this study
The nine studies included in this evaluation mostly failed to describe the randomization methods, allocation concealment, and blinding. Therefore, it is highly likely that there is performance bias, selection bias, and measurement bias. Clinical trials should be strictly randomized, controlled, include allocation concealment, and use blinding to evaluate any experimental results. The use of an international standardization such as CONSORT should be implemented in all clinical trials (David Moher et al., 2006). The blinding methods used in clinical trials are an effective means to reducing bias and improving study quality (Zhang and Liu, 2007). Evaluation criteria should include determination of quality of life, well-defined endpoints, and adverse reactions. In stroke clinical trials, mortality and disability rates are regarded as the most useful endpoints. Because mortality rate is closely related to the follow-up period, conclusions based on this meta-analysis are not strong because only four studies included a 6-month follow-up, and the remaining studies did not describe the follow-up period. In the included clinical trials, analysis was performed based on whether patients were disabled or not, which was based on dichotomous data (Yang and Shi, 2007).

Directions for future research
Future clinical trials should pay attention to follow-up, and possibly include categorical variables (such as death and disability) to evaluate the curative effect. Furthermore, patients need more time to achieve functional recovery after stroke, so efficacy evaluation should be followed-up for at least 3 to 6 months (Yang and Shi, 2007). In the future, randomized controlled trials that are reasonably designed, strictly implemented, and include multiple centers with large sample sizes and adequate follow-up are necessary. Then, updated systematic reviews may provide more useful information.

Author contributions: ZXY and JHXX participated in the study concept, design and wrote the manuscript. YPL, GXM, YHW, SMW, and YL were responsible for data integration and analysis. All authors approved the final version of the manuscript.

Conflicts of interest: None declared.

References

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