EVIDENCE-BASED INTEGRATIVE MEDICINE

Chinese Herbal Medicine Xingnaojing Injection (醒脑静注射液) for Hypoxic Ischemic Encephalopathy in Newborns: A Systematic Review and Meta-Analysis*

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ABSTRACT **Objectives**: To evaluate the efficacy and safety of Chinese herbal medicine Xingnaojing Injection (醒脑静注射液) for newborns with hypoxic ischemic encephalopathy (HIE). **Methods**: Literatures were identified by searching the PubMed, EMBASE, Cochrane Library, Cochrane Central, and four Chinese literature databases from the establishment of database to October in 2013. Relevant reference lists were also screened. Two reviewers independently evaluated the methodological quality of included studies. We also conducted the meta-analysis. **Results**: Thirteen trials involving 1,169 patients were included. There was no trial reported death or disability at the end of follow-up period. Meta-analysis of 4 trials (n=371) showed that there was no significant difference in the reduction of mortality [risk ratios (RR)=0.48, 95% confidence intervals (CI, 0.21, 1.13), P=0.09] between the Xingnaojing and control groups. Meta-analysis of 5 trials (n=359) showed that there was significant difference in reducing the major neurodevelopmental disability [RR=0.36, 95% CI (0.19, 0.66), P=0.001]. Meta-analysis of 6 trials (n=447) showed that there was significant difference in the author self-defined symptom improvement [RR=1.25, 95% CI (1.14, 1.37), P<0.01]. No fatal side-effects were reported. **Conclusion**: Based on the limited evidence, the routine use of Xingnaojing Injection for treatment of HIE in newborns is not recommended. Further well-conducted trials are justified.

KEYWORDS Chinese herbal medicine, newborns, hypoxic ischemic encephalopathy, systematic review

Hypoxic ischemic encephalopathy (HIE) following perinatal asphyxia is an important cause of neurodevelopmental impairment in infants.[1] The incidence of HIE ranges from 1 to 8 per 1000 live full-term births.[2] It has reported that 10%–60% of affected infants die and at least 25% of survivors have long-term neurodevelopmental sequelae.[3] Although mounting evidence indicate hypothermia as a treatment for term or near term infants with HIE,[4,5] the current treatment for HIE is predominantly supportive. In the absence of any specific intervention to improve the prognosis of infants with HIE, clinical enthusiasms for a novel treatment is understandable.

Chinese herb medicine (CHM) is one of the most important part of Chinese medicine and widely accepted by Chinese people in the treatment of various diseases and conditions.[6] Recently, it has been gaining acceptance in the developed world as a form of complementary and alternative medicine (CAM).[7] Generally speaking, patients may seek CHM for symptomatic relief when conventional medicines are unsuccessful. Some evidence from the Cochrane Collaboration provide preliminary evidence of CHM benefits to certain patient population, such as common cold, side-effects of chemotherapy in breast cancer, irritable bowel syndrome etc.[8]

Xingnaojing Injection (醒脑静注射液) is composed of *Moschus*, *Borneolum syntheticum*, *Radix Curcumae*, *Fructus Gardeniae* and other Chinese medicine and extracted from Angong Niuhuang Pill (安宫牛黄丸). The mechanisms of Xingnaojing Injection include reducing the permeability of blood brain barrier,[9] relieving the inflammatory reactions mediated by cytokines,[10] scavenging radicals and antioxidant activities,[11] and promoting angiogenesis

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and repair glial cells, etc.[12] These mechanisms may produce beneficial effects in newborns with HIE.

Xingnaojing Injection is widely used in China for patients with stroke, acute alcohol intoxication and cerebral infarction.[9,13,14] However, it has not been systematically reviewed for newborns with HIE, therefore we plan to investigate the efficacy and safety of Xingnaojing Injection for newborns with HIE.

METHODS

Design of Studies

We included all randomized controlled trials (RCTs) comparing Xingnaojing Injection with placebo or other drug(s) in the treatment of newborns with HIE.

Definition of Participants

The criteria as follows were screened for eligibility: (1) Term newborn infants with at least one of the following evidence of peripartum asphyxia: (a) Apgar score of 5 or less at 10 min, (b) mechanical ventilation or resuscitation at 10 min, and (c) cord pH<7.1, or an arterial pH<7.1 or base deficit of 12 or more within 60 min of birth. (2) Infants that meet criteria peripartum asphyxia should be assessed for whether they meet the evidence of encephalopathy according to Sarnat staging[15] or other validated and reliable criteria: (a) stage 1 (mild): hyperalertness, hyperreflexia, dilated pupils, tachycardia, absence of seizures, (b) stage 2 (moderate): lethargy, hyperreflexia, miosis, bradycardia, seizures, hypotonia with weak suck and Moro, and (c) stage 3 (severe): stupor, flaccidity, small to midposition pupils which react poorly to light, decreased stretch reflexes, hypothermia and absent Moro.

Interventions

All RCTs that examined Xingnaojing Injection used alone or as an add-on to any approved treatments for HIE would be included. Comparisons included: (1) Xingnaojing Injection versus placebo only. (2) Xingnaojing Injection + usual treatment versus placebo + usual treatment. (3) Xingnaojing Injection + usual treatment versus usual treatment only. (4) Xingnaojing Injection+ usual treatment versus approved treatments + usual treatment.

Outcome Measurements

Primary Outcomes

Death or disability at least 12 months. Disability defined as the presence of at least one of the following impairments: (1) cerebral palsy; (2) Bayley Scales of Infant Development [BSID, including mental development index (MDI) and psychomotor development index (PDI)] more than 2 standard deviation SD below mean; (3) intellectual impairment (intelligence quotient more than 2 SD below mean); (4) gross motor function classification system level 3–5 (where the scale is from 1 to 5, with 1 being the mildest impairment); (5) bilateral cortical visual impairment with no useful vision; and (6) sensorineural deafness requiring amplification.

Secondary Outcomes

(1) Death; (2) disability; (3) improved quality of life; (4) authors self-defined symptom improvement of the efficacy; (5) abnormal appearances on electroencephalogram (EEG), cranial ultrasonography, computerized tomography and magnetic resonance imaging (MRI); and (6) adverse events were as reported in the trial.

Search Strategy

The following databases were searched: Cochrane Library (2013, issue 10), PubMed (1966, issue 2013.10), EMBASE (1974–2013, issue 10), Cochrane Controlled Trials databases (CENTRAL 10, 2013), Chinese Biomedical Literature Database (CBM, 1978–2013, issue 10), China National Knowledge Infrastructure (CNKI, 1980–2013, issue 10), Chinese Science and Technique Journals Database (VIP, 1989–2013, issue 10), Wanfang Data (http://www.wanfangdata.com/) (1990–2013, issue 10). The bibliographies of relevant articles were also screened. The 'Xingnaojing', 'newborns', 'neonat*', 'infant' and 'hypoxic ischemic encephalopathy' were used for searching relevant data. The search was restricted to human studies, and the language was restricted to English and Chinese.

Selection of Studies and Data Extraction

Two reviewers independently screened the titles and abstracts of every record. The full articles were obtained when the information given in the title or abstracts conformed to the selection criteria outlined previously. Two reviewers independently performed data extraction. The data extraction form included contents were as follows: (1) general characteristics of studies, (2) the general characteristics of patients, (3) follow-up, (4) sample size, (5) comparisons, (6)

outcome measurements, and (7) adverse events.

Quality Assessment

Two reviewers independently evaluated the methodological quality of the included studies using the 'risk of bias tool' under the domains of six aspects, including (1) sequence generation, (2) allocation concealment, (3) blinding, (4) incomplete outcome data, (5) selective outcome, and (6) other biases. The methodological criteria referred to the Cochrane Handbook for Systematic Reviews of Interventions. version 5.1.0.[16]

Statistical Methods

Results for dichotomous outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CI), and express results for continuous outcomes as mean difference (MD, if the same scale for each trial is available) or standardised mean difference (SMD, if different scales are used). Heterogeneity among included studies was evaluated using I^2 test. A value greater than 50% was considered to indicate substantial heterogeneity. The potential sources of the heterogeneity (clinical heterogeneity and methodological heterogeneity) were sought. Regardless of the size of heterogeneity, random effects model was used for statistical analysis. Meta-analysis was conducted using Cochrane RevMan 5.0 software.

RESULTS

Results of the Search

Fifty-six potentially relevant articles were identified, of which all articles were Chinese; and 13 RCTs were included by removing duplicate articles, reviewing the titles or abstracts and full-text. Flow chart of literature screening and selection process was shown in Figure 1.

Characteristics of Included Studies

Thirteen studies were included involving 1,169 Participants. Individual study sample size ranged from 52 to 160 cases. All studies were conducted in mainland China. Ten studies (10/13, 84.6%) were open control, which was defined as having 2 groups with the same usual treatment with intervention in the treatment group (i.e., usual treatment + test drug versus usual treatment). Three studies (3/13, 15.4%) were positive drug control, which was defined as the control group having an active control (i.e., test drug versus control drug, or usual treatment + test drug versus usual treatment + control drug). Two studies

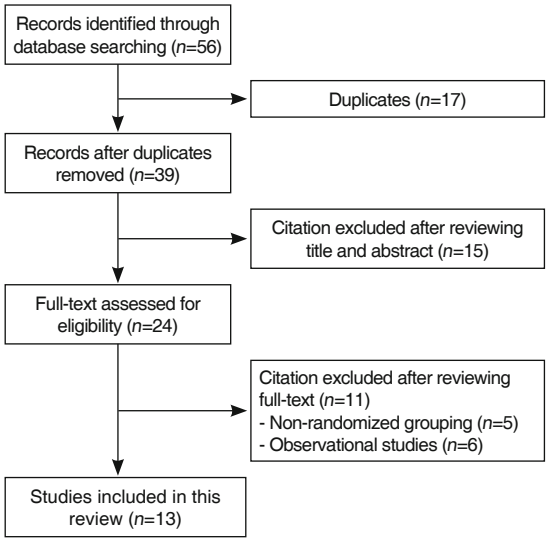

Figure 1. Flow Chart of Literature Screening and Selection Process

used cytoplasmic as control and one used Danshen Injection as control. The duration of treatment ranged from 2–30 days. The period of follow-up was 6 to 24 months. There was no trial reported death or disability at the end of follow-up period (Table 1).

Quality Assessment

All studies only mentioned 'random allocation' without specific description. All studies did not report whether the allocation concealment and blinding had been implemented. Four studies (4/13, 30.8%) reported loss to follow-up, of which none study used intention to treat analysis (ITT) for incomplete outcome data. None of the studies had a registration of protocol, so it was unclear whether there was possibility of selective reporting. There were no significant differences in the comparability of baseline data except one trial was unclear (Table 2).

Primary Outcome: Death or Disability

There was no trial reported death or disability at the end of follow-up period.

Secondary Outcome: Incidence of Death

Meta-analysis of 4 trials (n=371) showed that there was no significant difference in the reduction of mortality [RR=0.48, 95% CI (0.21, 1.13), P=0.09, I^2=0%] between the Xingnaojing Injection and open control groups at the end of treatment period (Figure 2).

Disability: Major Neurodevelopmental Disability

Meta-analysis of 5 trials (n=359) showed that

Table 1. General Characteristics of Included Studies

References	Characteristics of participants		Interventions		Duration of treatment (Day)	Outcome measures indicators	Follow-up (Month)
	Sample (male)	Comparability of baseline	Treatment group	Control group			
Chen LG (2001)[17]	88 (45)	Comparable	Xingnaojing Injection (5–10 mL, once a day)+ usual therapy	Usual therapy	10	1. Death; 2. The improvement of clinical symptoms	Unclear
Yu XY (2007)[18]	90 (55)	Comparable	Xingnaojing Injection (0.5 mL/kg daily)+ usual therapy	Usual therapy+Danshen Injection	30	1. Disability; 2. NBNA scales; 3. Bayley of infant development (MDI and PDI)	12
Xu DJ (2002)[19]	52 (34)	Comparable	Xingnaojing Injection (2–4 mL) + usual therapy	Usual therapy	7–21	1. Disability; 2. Head CT examination; 3. Author self-defined symptom improvement of the efficacy	6–12
Yang FY (2001)[20]	59 (28)	Comparable	Xingnaojing Injection (10 mg, once a day)+ usual therapy	Usual treatment+ cytoplasmic (0.125 g)	Unclear	1. Physiological reflex; 2. Head CT examination	Unclear
Cui N (2001)[21]	60 (48)	Comparable	Xingnaojing Injection (0.4–0.6 mL/kg daily)+ usual therapy	Usual therapy	5–10	1. Disability; 2. Author self-defined symptom improvement of the efficacy	18–24
Li GL (2008)[22]	91	Comparable	Xingnaojing Injection (2 mL, once a day)+ usual therapy	Usual treatment	10–28	1. NBNA scales	12–24
Mei H (2008)[23]	58 (36)	Comparable	Xingnaojing Injection (0.5 mL/kg, once a day)+ usual therapy	Usual therapy	10	1. Author self-defined symptom improvement of the efficacy	Unclear
Xu HQ (2001)[24]	88 (45)	Unclear	Xingnaojing Injection (5–10 mL, once a day)+ usual therapy	Usual therapy	7	1. Death; 2. The mortality rate; 3. The improvement of clinical symptoms	Unclear
Jia ML (2002)[25]	77	Comparable	Xingnaojing Injection (3 mL, twice daily)+ usual therapy	Usual therapy	10	1. Death; 2. Disability; 3. Author self-defined symptom improvement of the efficacy; 4. Head CT examination and hearing, visual inspection	Unclear
Wang XH (2003)[26]	118 (73)	Comparable	Xingnaojing Injection (2 mL, once a day)+ usual therapy	Usual therapy	7–10	1. Death; 2. Author self-defined symptom improvement of the efficacy	18
Li XL (2007)[27]	148 (78)	Comparable	Xingnaojing Injection (0.5–1.0 mL/kg daily)+ usual therapy	Usual therapy	20	1.The improvement of clinical symptoms; 2. NBNA scale	13.8–14.1
Liu YZ (2003)[28]	160 (101)	Comparable	Xingnaojing Injection (0.4–0.6 mL/kg daily)+ usual therapy	Usual therapy	2–4	1. The improvement of clinical symptoms	Unclear
Wen YX (2007)[29]	80 (48)	Comparable	Xingnaojing Injection (2 mL, once a day)+ usual therapy	Usual therapy+ cytoplasmic (100 mg/kg daily)	10	1. Disability; 2. NBNA scales; 3. Author self-defined symptom improvement of the efficacy	13.4–14.2

Notes: NBNA: neonatal behavioral neurological assessment; CT: computed tomography; overall, the usual treatment are similar in each study, including oxygen inhalation, sedation, decreasing intracranial pressure and elimination of brainstem symptoms etc.

Table 2. Bias Risk Assessment of Included RCTs

References	Quality assessment					
	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Bias from other resources
Chen LG (2001)[17]	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk
Yu XY (2007)[18]	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk
Xu DJ (2002)[19]	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk
Yang FY (2001)[20]	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk
Cui N (2001)[21]	Unclear	Unclear	Unclear	High risk	Unclear	Low risk
Li GL (2008)[22]	Unclear	Unclear	Unclear	High risk	Unclear	Low risk
Mei H (2008)[23]	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk
Xu HQ (2001)[24]	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Jia ML (2002)[25]	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk
Wang XH (2003)[26]	Unclear	Unclear	Unclear	High risk	Unclear	Low risk
Li XL (2007)[27]	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk
Liu YZ (2003)[28]	Unclear	Unclear	Unclear	High risk	Unclear	Low risk
Wen YX (2007)[29]	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk

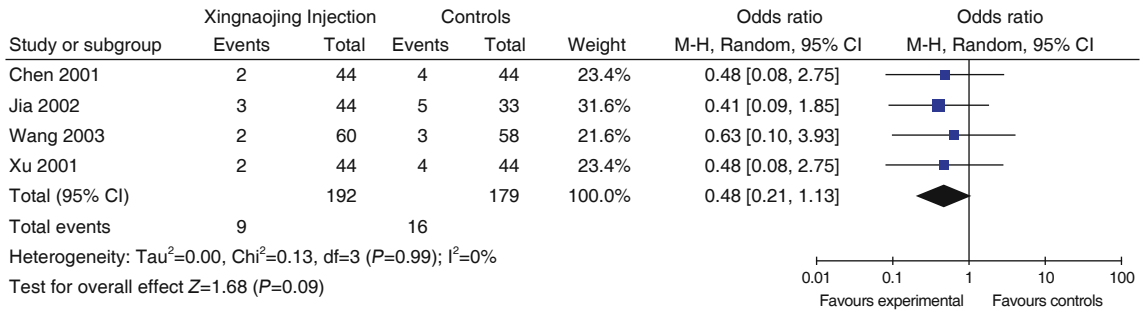

Figure 2. Meta-Analysis of the Incidence of Death

there was significant difference in the reducing of major neurodevelopmental disability [RR=0.36, 95% CI (0.19, 0.66), *P*=0.001, I^2=0%] between the Xingnaojing Injection and control groups at the end of follow-up period. Of them, 3 studies (*n*=189) comparing Xingnaojing Injection with open control showed there was significant difference in reducing the major neurodevelopmental disability [RR=0.28, 95% CI (0.12, 0.64), *P*=0.003]. One study (*n*=80) comparing Xingnaojing Injection with cytoplasmic showed there was no significant difference in reducing the major neurodevelopmental disability [RR=0.71, 95% CI (0.25, 2.06), *P*=0.53]. One study (*n*=90) comparing Xingnaojing Injection with Danshen Injection showed there was significant difference in reducing the major neurodevelopmental disability [RR=0.12, 95% CI (0.02, 0.92), *P*=0.04] (Figure 3).

Cerebral Palsy

Meta-analysis of 3 trials (*n*=216) showed that there was no significant difference in the reduction of cerebral palsy [RR=0.33, 95% CI (0.08, 1.36), *P*=0.13, I^2=0%] (Figure 4).

Neuromotor Development (BSID, MDI and PDI) Assessed in Survivors

One study comprising 90 survivors reported the effect of Xingnaojing Injection on neuromotor development in survivors assessed using the BSID MDI and BSID PDI. There was significant difference in mean MDI [mean difference (MD)=9.00, 95% CI (5.27, 12.73)] and in mean PDI [MD=9.00, 95% CI (5.75, 12.25)] in the Xingnaojing Injection group at the end of 6 months follow-up. There was also significant difference in mean MDI [MD=15.00, 95% CI (10.04, 19.96)] and PDI [MD=16.00, 95% CI (12.85, 19.15)] at the end of 12 months follow-up.

Efficacy Evaluation by Authors Self-defined

Meta-analysis of 6 trials (*n*=447) showed that there was significant difference in the authors self-defined symptom improvement of the efficacy at the end of the treatment period [RR=1.25, 95% CI

(1.14, 1.37), P<0.001, I^2=0%] between the Xingnaojing Injection and control groups. Of them, 5 studies (n=308) comparing Xingnaojing Injection with open control showed there was significant difference in efficacy [RR=1.27, 95% CI (1.15, 1.39), P<0.001]. One study comparing Xingnaojing Injection with cytoplasmic

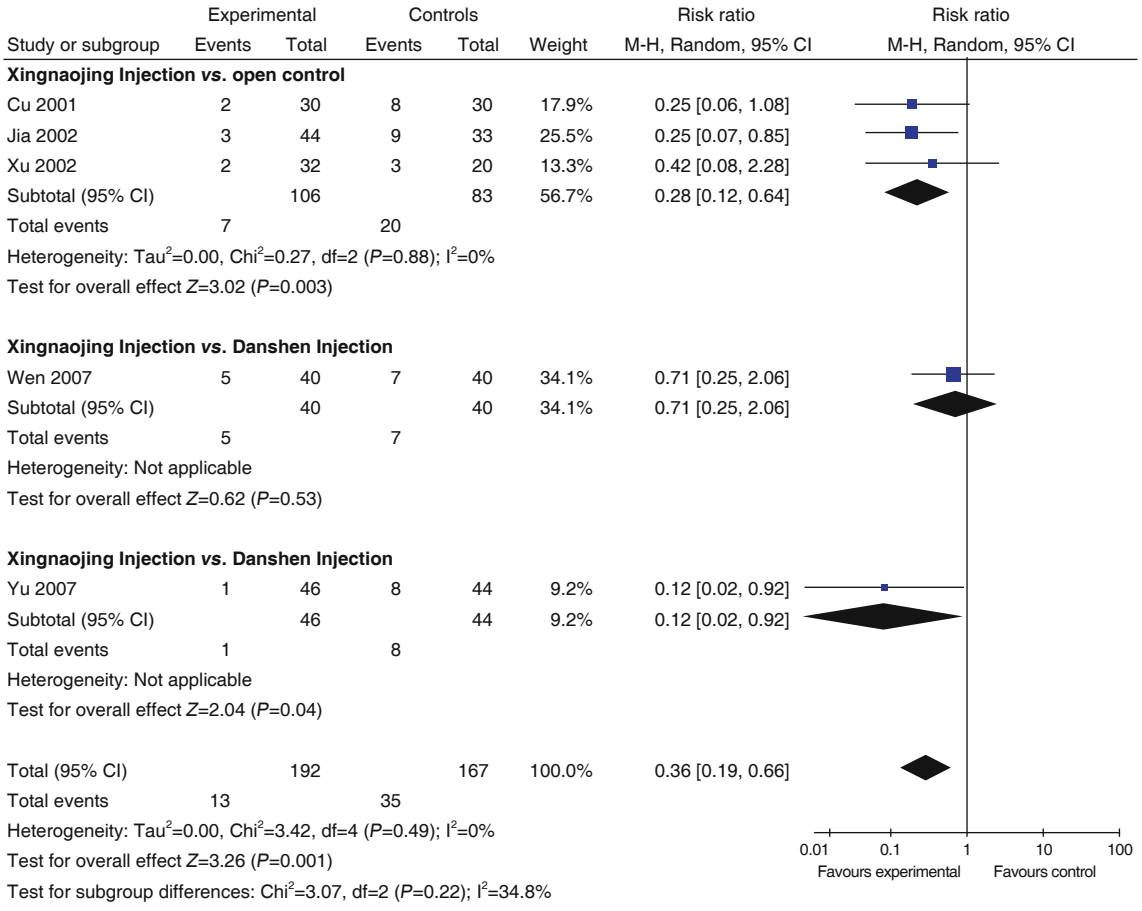

Figure 3. Meta-Analysis of the Major Neurodevelopmental Disability in Survivors Assessed

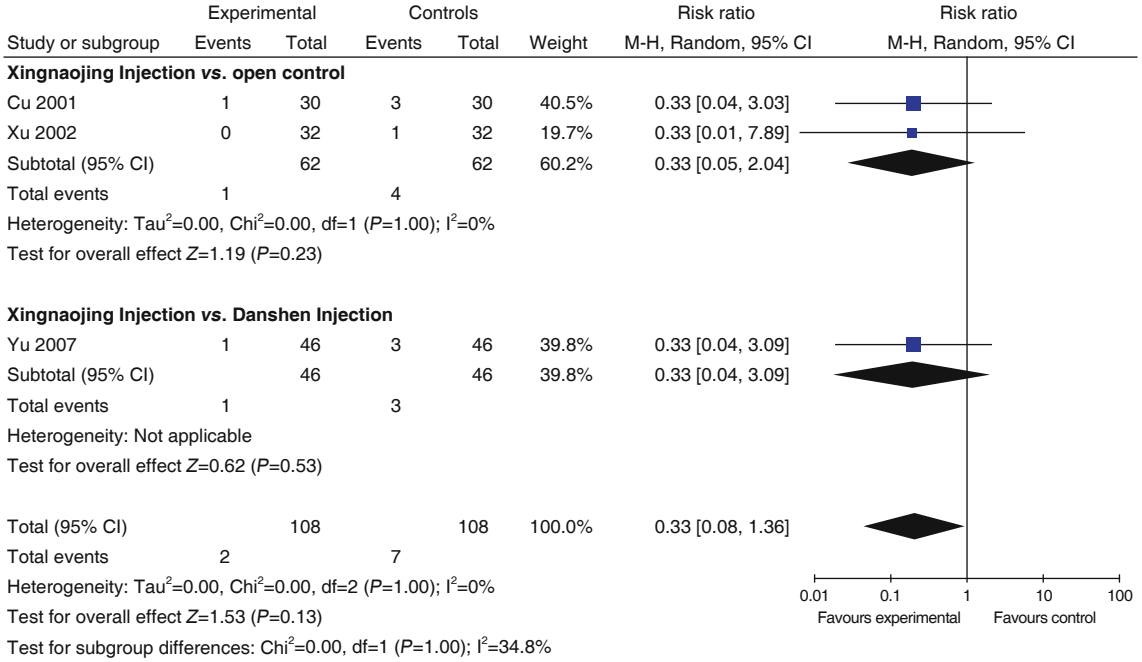

Figure 4. Meta-Analysis of Cerebral Palsy in Survivors Assessed

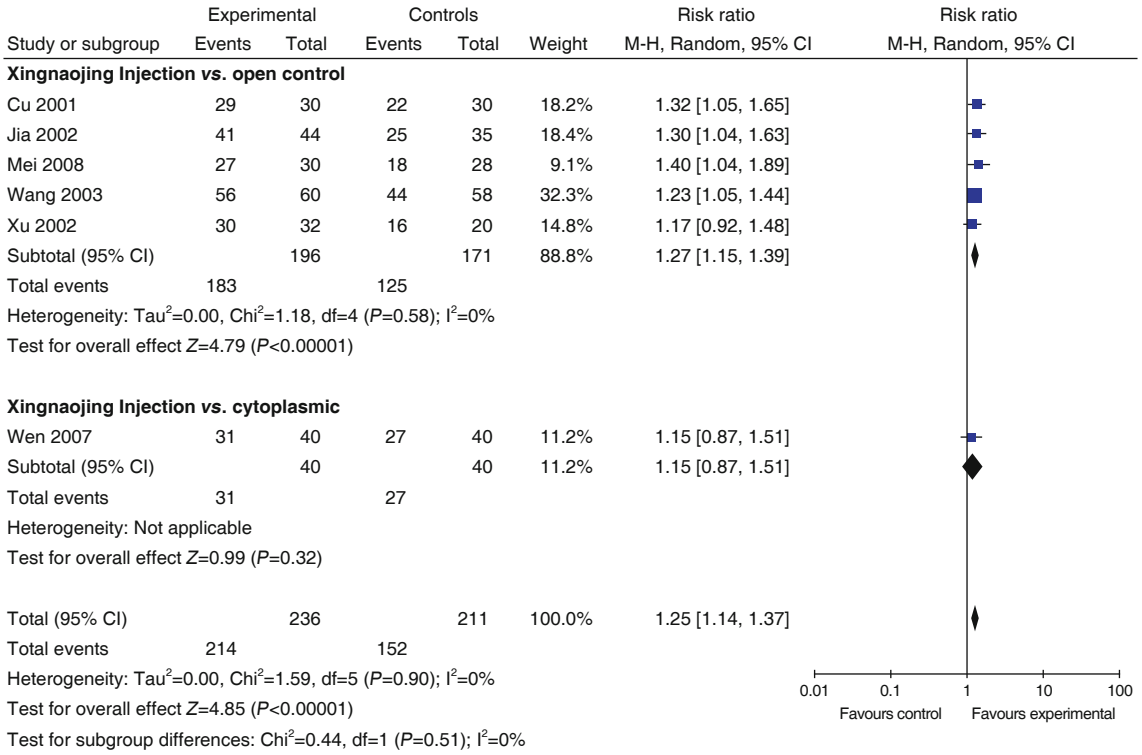

Figure 5. Meta-Analysis of Efficacy Evaluation by Authors Self-defined

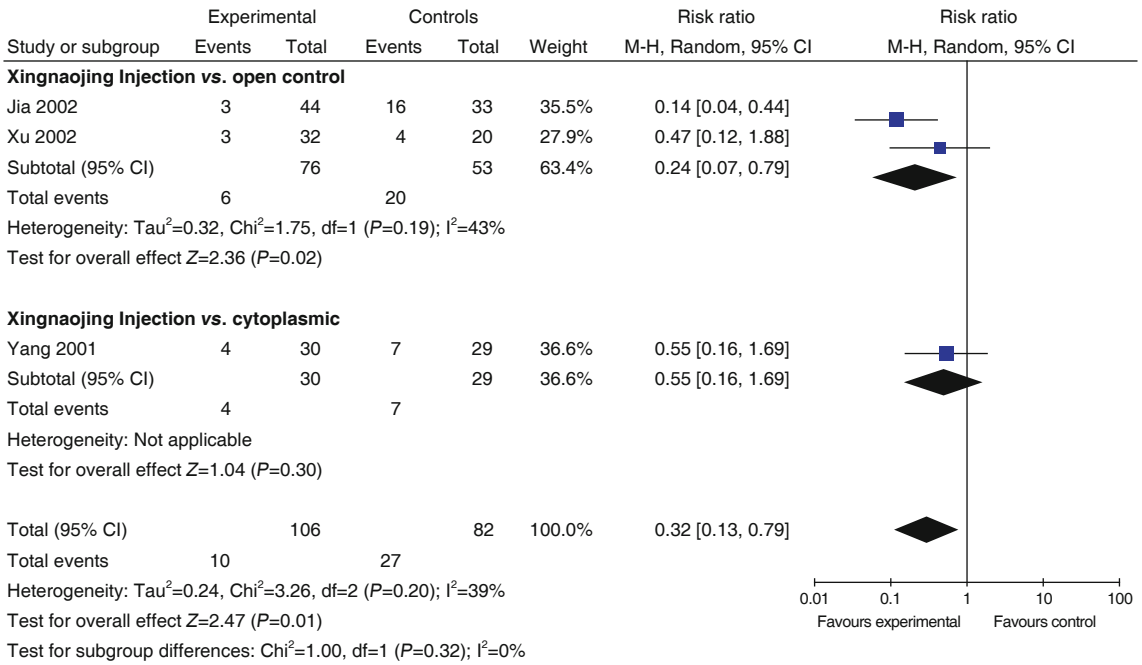

Figure 6. Meta-Analysis of the Incidence of Abnormal CT Examination

showed there was no significant difference in efficacy [RR=1.15 , 95% CI (0.87, 1.51), *P*=0.32] (Figure 5).

The Rate of Abnormal CT Examination

Meta-analysis of 3 trials (*n*=188) showed that there was significant difference in reducing the rate of abnormal head CT examination [RR=0.32, 95% CI (0.13, 0.79), *P*=0.01, I^2=39%] between the Xingnaojing Injection and control groups (Figure 6).

Adverse Events

In our study, 53.8% (7/13) of included studies reported adverse events, of which 85.7% (6/7) reported no adverse events were found. No fatal

side-effect was reported.

DISCUSSION

Our study showed that Xingnaojing Injection did not significantly reduce the incidence of death, cerebral palsy in survivors, but can reduce the major neurodevelopmental disability in survivors, neuromotor development (BSID MDI and PDI), authors self-defined and abnormal CT examination for newborns with HIE. No fatal side-effect was reported.

In general, the quality of included RCTs was poor. All trials only reported 'randomly allocating' participants but the method of randomisation was not described. The success of adequately concealed the randomisation sequence was not reported. No trials used placebo as control group, and the success of blinding was not recorded. None of included trials stated an intention to treat analysis had been performed.

For the included participants, although the majority of RCTs have used accepted diagnostic criteria in worldwide, the details of inclusion and exclusion criteria were not described. In our study, none of the included RCTs reported the outcome of death or disability at least 12 months. Only 4 RCTs reported the mortality, but the death was observed in the period of treatment and the long-term outcomes were not reported. Due to most studies only evaluate the short-term efficacy, these results could not be extrapolated for the long-term efficacy.

Of note, the Xingnaojing Injection for newborns is off-label use due to a lack of pediatric RCTs. However, difficulties in obtaining a guardian's consent, obtaining research funding, and ethical concerns often limit the conduction of RCTs in children. Using of drugs in pediatric settings are often forced to extrapolate from the results of clinical trials in adults, which is inappropriate because there are many differences in physiological function, pharmacokinetics, and pharmacodynamics between children and adults. More attention should be paid to the quality of research in clinical trials evaluating drugs in children in future.

There are several limitations in our study: (1) All included studies were conducted in single-centre in China with small sample (52–160 cases), the efficacy of Xingnaojing Injection need to be tested in other ethics; (2) All included studies used open control or positive drug as control, lacking of reasonable placebo-controlled; (3) No study completed clinical trial registration, which make it difficult to monitor the quality of the conduction and whether there is a selective reporting of results of studies.

In conclusion, based on the limited evidence, the routine use of Xingnaojing Injection for treatment of HIE in newborns is not recommended. Further well-conducted trials are justified.

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