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: Literature was 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 a 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 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 Niuwuhuang 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.
and repair glial cells, etc. 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. 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 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)