

Review

Promoting blood circulation for removing blood stasis therapy for acute intracerebral hemorrhage: a systematic review and meta-analysis

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Aim: To conduct a systematic review and meta-analysis to assess the current evidence available regarding the promoting blood circulation and removing blood stasis (PBCRBS) therapy for Chinese patients with acute intracerebral hemorrhage (ICH).

Methods: Six databases were searched from their inception to November 2013. The studies assessed in ≥ 4 domains with 'yes' were selected for detailed assessment and meta-analysis. The herbal compositions for PBCRBS therapy for acute ICH patients were also assessed.

Results: From the 6 databases, 292 studies claimed randomized-controlled clinical trials (RCTs). Nine studies with 798 individuals were assessed in ≥ 4 domains with 'yes' by using the Cochrane RoB tool. Meta-analysis showed that PBCRBS monotherapy and adjuvant therapy for acute ICH could improve the neurological function deficit, reduce the volume of hematoma and perihematomal edema, and lower the mortality rate and dependency. Moreover, there were fewer adverse effects when compared with Western conventional medication controls. Xueshuantong Injection and Fufang Danshen Injection, Buyang Huanwu Decoction and Liangxue Tongyu formula, and three herbs (danshen root, sanqi and leech) were the most commonly used Chinese herbal patent injections, herbal prescriptions and single herbs, respectively.

Conclusion: Despite the apparently positive findings, it is premature to conclude that there is sufficient efficacy and safety of PBCRBS for ICH because of the high clinical heterogeneity of the included studies and small number of trials in the meta-analysis. Further large sample-sizes and rigorously designed RCTs are needed.

Keywords: acute intracerebral hemorrhage; traditional Chinese medicine; promoting blood circulation for removing blood stasis; systematic review; meta-analysis

Acta Pharmacologica Sinica (2015) 36: 659–675; doi: 10.1038/aps.2014.139; published online 11 May 2015

Introduction

Spontaneous intracerebral hemorrhage (ICH) is one of the most detrimental subtypes of stroke. It accounts for 10%–15% of all strokes and is an important public health problem that leads to significant morbidity and mortality^[1]. The epidemiological perspective on ICH remains bleak. ICH affects 24.6 per 100 000 person-years; the median case fatality within 1 month was 40.4%, and the functional dependency after ICH was approximately 75%^[2]. In China, a nation of 1.4 billion, which

accounts for almost one-fifth of the world's total population, stroke is already the leading cause of death^[3]. In addition, a recent systematic review showed that the Chinese have higher overall stroke incidence. ICH accounts for a higher proportion of stroke in Chinese than the white population^[4].

Currently, no specific therapies or treatments improve the outcome after ICH. The updated evidence-based guidelines for the management of ICH from the American Heart Association/American Stroke Association remain multifaceted; most recommendations are symptomatic and supportive^[5]. In the trial in surgery, the results of spontaneous supratentorial lobar intracerebral hematomas (STICH II) confirmed that early surgery did not increase the rate of death or disability at 6 months. This suggested that there is a small survival advantage for patients with ICH who did not have intraventricular

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Received 2014-08-23 Accepted 2014-11-17

hemorrhage^[6]. Acute hemostatic management is not usually recommended to control bleeding in ICH guidelines; the exception is rare cases, such as those including oral anticoagulants, coagulation factor deficiencies, and platelet abnormalities, in which underlying hemostatic abnormalities may contribute to ICH^[7]. Although hemostatic therapy with rFVIIa can limit the extent of hematoma expansion in noncoagulopathic ICH patients, there is an increase in thromboembolic risk with rFVIIa, and the survival or functional outcome after ICH is not increased^[8]. Faced with the limitations of the present available treatments, complementary and/or alternative medicine (CAM) is thus increasingly sought to treat stroke worldwide.

In China, traditional Chinese medicine (TCM), including various forms of herbal medicine, acupuncture, massage (Tuina), exercise (qigong), and dietary therapy, has been used to treat stroke patients for over 2000 years^[9]. In fact, TCM was the major available method of healthcare in the western pacific region of the world before modern Western medicine was introduced. However, stroke was divided into ischemic and hemorrhagic until the end of the Qing Dynasty (1616–1911). A brief history of TCM application in acute ICH has been summarized by Zheng *et al*^[10] as follows: (1) before the 1950s–1960s, the pathogenesis of acute ICH emphasized up-stirring of the liver and adverse-rising of both blood and qi; (2) from the 1970s, the central pathogenesis of acute ICH has been considered as a blocked passage of the middle Jiao, a disorder of qi in ascending and descending and abnormal flow of qi and blood; (3) from the 1980s, it was claimed that the vital pathogenesis of acute ICH was blood stasis; (4) in recent years, theories of endogenous toxins and deficient vital qi have been developed. However, blood stasis syndrome can be found throughout the pathological process of ICH under the TCM theory of ‘abnormal flow of the blood is blood stasis’ in Xuezheng Lun (On Blood Syndromes), written by Tang Rong-chuan during the Qing Dynasty. Thus, the key point of the treatment method for ICH was promoting blood circulation for removing blood stasis (PBCRBS). Blood stasis, known as ‘Oketsu’ in Japanese, ‘Xueyu’ in Chinese and ‘Eohyul’ in Korean, refers to whenever the circulation of blood is not smooth or the blood flow is stagnant and forms stasis^[11]. Although the consensus among the interviewed experts was that the definition of blood stasis is rather complicated and that there is no gold standard marker for detecting blood stasis^[12], blood stasis refers to a group of distinct syndromes. Over the following three decades, there have been a number of clinical trials to evaluate the efficacy and safety of the PBCRBS method for acute ICH. Therefore, the objective of the present systematic review is to assess the current evidence available regarding the PBCRBS method for patients suffering from acute ICH.

Methods

Standard protocol registration

This systematic review was registered in PROSPERO, and the registration identifier of the protocol is CRD42014009003^[13].

Study criteria

Types of studies

Only randomized controlled clinical trials (RCTs), which evaluate the efficacy and safety of the PBCRBS prescription for acute ICH, were included in the qualitative analyses, regardless of blinding, publication status or language. We included the RCTs assessed in ≥ 4 domains with ‘yes’ for the analyses using the Cochrane RoB tool^[14, 15]. Quasi-RCTs, taking those using the admission sequence for treatment allocation as example, were not considered.

Types of participants: patients of any gender, age, or race/ethnicity with ICH within 14 d from the onset were included. The ICH was diagnosed according to the Chinese national criteria in Diagnostic Essentials of Various Cerebrovascular Diseases revised at the Fourth National Conference of the China Society of Medicine on Cerebrovascular Diseases in 1995^[16]. The diagnosis of ICH was confirmed by CT scan or MRI.

Types of interventions

The patients of the control groups were given Western conventional medication (WCM), WCM plus stereotactic microsurgery (SM), or placebo alone. The patients at the treatment groups were given PBCRBS intervention as add-on therapy, which included PBCRBS prescriptions, Chinese patent herbal oral preparations, and Chinese patent herbal injections. PBCRBS therapy was defined as the use of common blood-invigorating and stasis-removing herbal prescriptions, based on the Eight Principles plus differentiation between qi and blood^[11], and any Chinese patent herbal preparation that comes from commonly used blood-invigorating and stasis-removing herbs based on both TCM theory and Western medicine. Studies comparing different forms of TCM were excluded. The clinical trials were included regardless of the dosage or duration of treatment. The mode of delivery was the oral route or injection route.

Types of outcome measurements

The primary outcome measures were mortality and dependency at the end of the treatment course or at the end of follow-up. Dependency was defined as needing assistance in the activity of daily living scale (ADL), using the Barthel Index (BI) and modified Rankin Standard (mRS). The secondary outcome measures were the clinical effective rate, the neurological deficit improvement, volume of hematoma, volume of perihematomal edema and adverse events. The neurological deficit improvement was assessed using the Chinese Clinical Neurological Deficit Scale (CCNDS) and National Institutes of Health Stroke Scale (NIHSS) score after treatment.

Literature search

A comprehensive literature search was conducted in CENTRAL (The Cochrane Library), PubMed, EMBASE, Chinese National Knowledge Infrastructure (CNKI), VIP Journals Database and the Wanfang database from inception to December 2013. The search terms used were ‘(Promoting Blood Cir-

ulation OR Removing Blood Stasis) AND (intracerebral hemorrhage OR hemorrhagic stroke)' in English and (Huoxue OR Huayu) AND (Naochuxue OR Chuxuezhongfeng) in Chinese pinyin in the Chinese databases. The search was restricted to clinical trials or reviews. No limitation was placed on publication date, country or language. The reference lists of all relevant articles were also searched for appropriate studies.

Study selection and data collection process

All articles were screened by 2 independent reviewers, who extracted data from the articles according to a standardized data extraction form, including study design, patients' characteristics (age, gender, and onset of ICH), PBCRBS treatment protocol, control intervention, and outcome parameters. The reasons for inclusion and exclusion of studies were recorded at all stages. For eligible studies, 2 authors of this work extracted the data independently. The missing data were obtained by contacting the authors of the original studies. Disagreements were settled through discussion or consultation with corresponding authors.

Risk of bias and grading the quality of evidence

The risk of bias was assessed using the 7 criteria recommended by the Cochrane Handbook^[17]. We included the RCTs assessed in ≥ 4 domains with 'yes' for the analyses; *ie*, we excluded those cases assessed in ≥ 3 domains with 'unclear' or 'no' which were classified as having a high risk of bias^[14, 15]. The level of evidence was assessed by the updated GRADE system^[18]. We classified evidence into 4 grades: high quality, moderate quality, low quality and very low quality. The low and very low quality of evidence showed a serious limitation in the study design, study quality, consistency, directness of the evidence and precision of the results.

Description of the herbal medicine and herbal prescription

The selection criteria of high-frequency herbs and herbal prescriptions in the treatment of ICH were those with cumulative frequencies of over 50%.

Data analysis

All data analyses were performed using Review Manager 5.1.0, compiled by the Cochrane Collaboration. The risk ratio (RR), with a 95% confidence interval (CI), was calculated for dichotomous outcomes, whereas weighted mean differences (WMD) or standardized mean differences (SMD) were used for continuous outcomes. Heterogeneity was examined by the chi-square test at a significance level of 0.05. An I^2 statistic was also calculated to estimate variation among studies as follows: I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high level of heterogeneity, respectively. However, on account of the clinical heterogeneity, all meta-analyses were performed using a random-effect model. Publication bias was detected by funnel plot analyses. Two-tailed P values less than 0.05 were considered statistically significant.

Results

Description of the selection process

We identified 3426 potentially relevant articles from 6 databases. After removal of duplicates, 1330 records remained. After going through the titles and abstracts, we excluded 594 studies for at least one of following reasons: (1) the study was a case report or review, (2) not a clinical trial, or (3) did not include Chinese herbs and formulas for promoting blood circulation and removing blood stasis. By reading the full texts of the remaining 736 articles, we excluded 444 studies for at least one of following reasons: (1) there were no RCTs or no real RCTs, (2) the study did not include the acute phase of intracerebral hemorrhage, or (3) the study compared TCM or acupuncture. The remaining 292 studies examining the efficacy of Chinese herbs and formulas were included for qualitative analysis. Of the 292 studies, 9 studies assessed ≥ 4 domains with 'yes'; these were selected for detailed assessment and meta-analysis. The flow diagram is shown in Figure 1.

Description of the studies

The sample sizes of the 9 studies ranged from 21 to 213, with a total of 830 subjects (Table 1). All studies were carried out in China and published in Chinese language journals from 2000 to 2013. The criteria used in these 9 studies for diagnosis of ICH were the Chinese Cerebrovascular Disease Diagnosis Standard 1995 (CCDDS 1995). Of the 9 studies, 5 studies compared PBCRBS plus WCM with WCM alone, 2 studies^[19, 20] compared PBCRBS plus WCM plus SM with WCM plus SM, one^[21] compared PBCRBS plus WCM plus SM with WCM alone, and only one^[22] used a placebo control. The subjects' durations of ICH reported in the 9 studies were all within 3 d. The course of PBCRBS treatment lasted 10 d to 8 weeks in the 9 studies. Seven of the 9 studies reported follow-up; follow-up was from 30 d to one year after finishing treatment.

Assessment by the Cochrane's risks of bias

Eight of the 9 studies had at least one domain rated as high risk of bias^[19-21, 23-27] (Table 2). In the double-blind study, none of the domains were rated as having high risks of bias. In the 2 single-blind studies, the blinding procedure was not described, and there was a high risk of bias in concealment of allocation. In the 6 open-label studies, there were high risks of bias both in concealment of allocation and blinding; neither the subjects nor the evaluators were blinded.

Description of the PBCRBS herbs and prescriptions

A total of 41 standardized Chinese herbal formulas were examined in 229 (78.4%) of the 292 studies, while the other 63 studies used an individualized approach. The top 8 herbal formulas were used in 142 (48.6%) of the 292 reviewed studies (Table 3). These included Xueshuantong Injection (11.3%), an extract from Sanqi (Radix Notoginseng); Fufang Danshen Injection/Xiangdan Injection (10.3%), composition of Danshen (Radix Salviae miltiorrhizae) and Jiangxiang (Lignum Dalbergiae

Table 1. The characteristics of included studies.

Included trials	Country/ type of case	Eligibility criteria	Study design	Gender (male/female); mean age (years)	Mean hematoma volume (trial/ control) mL (range)	Time of onset	Interventions (n)	Course of treat- ment	Follow- up	Course of treatment outcomes	Intergroup differences	
Wang YQ, 2013	China/inpatient with intracerebral hemorrhage	CCDDS 1995	RCT	Trial 21/8, 63.28±10.19	Control 30/11, 63.37±9.84	<24 h	Trial XZD+ WCM	4 w	1 year	1. Volume of hematoma (1 month) 2. CCNDS score (3 month, 1 year)	1. <i>P</i> <0.05 2. <i>P</i> <0.05	
Zhang SQ, 2012	China/inpatients with intracerebral hemorrhage	CCDDS 1995	RCT	Trial 25/20; 55.70±12.16	Control 26/19; 56.10±11.45	1-3 d	Trial BHHD+ WCM	8 w	90 d	1. Volume of hematoma (7, 14, 28 d) 2. Volume of perihematomal edema (7, 14, 28 d) 3. NIHSS score (14, 28, 60, 90 d) 4. Barthel Index (90 d) 5. Clinical efficacy	1. <i>P</i> <0.05 2. <i>P</i> <0.05 3. <i>P</i> <0.05 4. <i>P</i> <0.05 5. <i>P</i> <0.05	
Wang ZF, 2011	China/inpatient with hypertensive cerebral hemorrhage	CCDDS 1995	RCT	Trial 55/35, 60.78±5.69	Control 53/36, 61.24±5.68	<72 h	Trial THD+ WCM	14 d	90 d	1. Volume of hematoma (14 d) 2. CCNDS score (90 d) 3. Barthel Index (90 d)	1. <i>P</i> <0.05 2. <i>P</i> <0.01 3. <i>P</i> <0.05	
Huang JL, 2010	China/inpatients with severe cerebellopontine hemorrhage	CCDDS 1995	RCT	Trial 8/2; 57	Control 9/2; 56	6-12 h	Trial SM+ XHLP+ WCM	1 m	6 month	1. GOS score 2. Time being awake and awake rate 3. Incidence of complications	1. <i>P</i> <0.01 2. <i>P</i> <0.01 3. <i>P</i> <0.01	
Chen SH, 2010	China/inpatient with intracerebral hemorrhage	CCDDS 1995	RCT	Trial 108>45	Control 105>45	<72 h	Trial ZXOS+ WCM	Placebo+ WCM	30 d	60 d	1. Mortality rate 2. The number of modified rankin score more than 4 3. The number of NIHSS score less than 1 (90 d) 4. GOS score (90 d) 5. The number of modified rankin score less than 2 (90 d) 6. Barthel Index (90 d)	1. <i>P</i> <0.05 2. <i>P</i> <0.05 3. <i>P</i> <0.05 4. <i>P</i> <0.05 5. <i>p</i> <0.05 6. <i>P</i> <0.05

To be continued

Included trials	Country/ type of case	Eligibility criteria	Study design	Gender (male/female); mean age (years)	Mean hematoma volume (trial/ control) mL (range)	Time of onset	Interventions (n) drug/dosage	Course of treat- ment	Follow- up	Course of treatment outcomes	Intergroup differences
Sun JH, 2008	China/inpatient with intracerebral hemorrhage	CCDDS 1995	RCT	Trial 28/17, 58.36±16.54	Control 25/19, 59.62±15.93	7-72 h	Trial SM+ WCM+ SMI	21 d	30 d	1. Volume of perihematomal edema (14, 21 d) 2. NIHSS score (14, 30 d)	1. <i>P</i> <0.05 2. <i>P</i> <0.05
Dai MX, 2002	China/inpatient with hypertensive cerebral hemorrhage	CCDDS 1995	RCT	Trial 26/14, 58.6±10.8	Control 27/13, 58.8±10.5	<24 h	Trial SM+ WCM+ ZXD	10 d	6 month	1. Clinical efficacy 2. CCNDS score 3. The number of hematoma dissipation 4. The number of hospitalization days	1. <i>P</i> <0.05 2. <i>P</i> <0.05 3. <i>P</i> <0.05 4. <i>P</i> <0.05
He D, 2002	China/inpatient with intracerebral hemorrhage	CCDDS 1995	RCT	Trial 7/5, 69.20±14.32	Control 8/4, 67.22±13.83	<48 h	Trial XST+ WCM	14 d	No report	1. Volume of hematoma (10, 21 d) 2. Volume of cerebral edema (4, 10, 21 d) 3. ESS score (4, 10, 21 d)	1. <i>P</i> <0.05 2. <i>P</i> <0.05 3. <i>P</i> <0.05
Fan Y, 2000	China/inpatient with intracerebral hemorrhage	CCDDS 1995	RCT	Trial 19/13, 64.44±12.12	Control 17/15, 61.31±11.91	<2 d	Trial LTOS+ WCM	4 week	No report	1. Total clinical efficacy 2. Barthel Index (28 d) 3. Grade of cerebral edema	1. <i>P</i> <0.05 2. <i>P</i> <0.01 3. <i>P</i> <0.01

Note: CCDDS, Chinese Cerebrovascular Disease Diagnosis Standard 1995; RCT, Randomized Controlled Trial; BHHD, Bushen Huoxue Huatan Decoction; SM, Stereotactic Microsurgery; WCM, Western Conventional Medication; XHLP, Xingnao Huoxue Lishui Prescription; LTOS, Liangxue Tongyu Oral Solution; SMI, Salviae Miltiorrhizae Injection; XZD, Xuefu Zhuyu Decoction; XST, Xue Shuan Tong; ZXOS, Zhongfeng Xingnao Oral Solution; THD, Tongqiao Huoxue Decoction; ZXD, Zhuyu Xiaozhong Decoction; NIHSS, National Institutes of Health Stroke Scale; ADL, Activities of Daily Living; GOS, Glasgow Outcome Score; ESS, European Stroke Scale; CCNDS, Chinese Clinical Neurological Deficit Scale (1995); d, day.

WCM refer to the combination of needed therapies of the following aspects: (1) General supportive care mainly include: (A) airway, ventilatory support and supplemental oxygen, (B) cardiac monitoring and treatment, (C) temperature, (D) blood pressure, (E) blood glucose and (F) nutrition; (2) No Specialized care included; (3) Treatment of acute complications mainly include: (A) brain edema and elevated intracranial pressure, (B) seizures, (C) pneumonia, (D) deep vein thrombosis prophylaxis, (F) stress ulcer. (4) Intensive care units mainly include: (A) surveillance and monitoring of ICP, cerebral perfusion pressure and hemodynamic function; (B) titration and implementation of protocols for management of ICP, BP, mechanical ventilation, fever, and serum glucose; and (C) prevention of complications of immobility through positioning, airway maintenance, and mobilization within physiological tolerance.

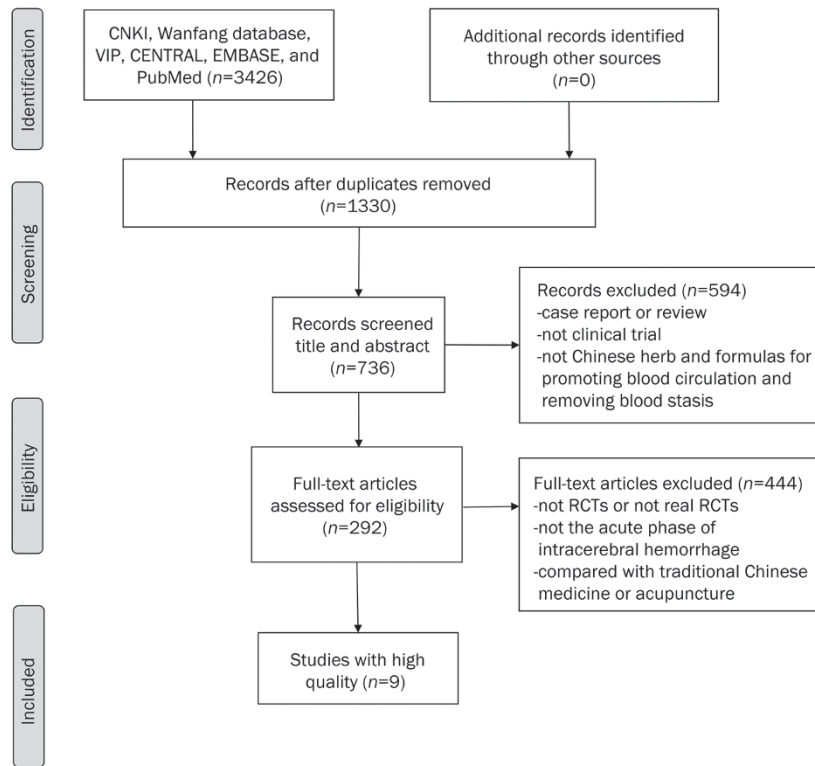


Figure 1. PRISMA 2009 flow diagram.

Table 2. Assessment of study quality and risk of bias.

First author, year	7-item criteria							Total
	A	B	C	D	E	F	G	
Wang YQ, 2013	+	-	-	?	+	+	+	4
Zhang SQ, 2012	+	-	-	?	+	+	+	4
Wang ZF, 2011	+	-	-	?	+	+	+	4
Chen SF, 2010	+	+	+	+	+	+	+	7
Huang JL, 2010	+	-	-	?	+	+	+	4
Sun JH, 2008	+	-	-	?	+	+	+	4
Dai MX, 2002	+	-	-	?	+	+	+	4
He D, 2002	+	-	?	?	+	+	+	4
Fan Y, 2000	+	-	?	?	+	+	+	4

A to G, the 7-Item criteria. A, adequate sequence generation; B, concealment of allocation; C, blinding of participants and personnel; D, blinding of outcome assessment; E, incomplete out-come data; F, selective reporting; G, other bias; +: low risk of bias, -: high risk of bias, ?: uncertain risk of bias.

Odoriferae); Danshen Injection (7.9%), an extract from Danshen root; Shuxuetong Injection (5.5%), composition of Shuizhi (Hirudo) and Dilong (Lumbricus); Shuxuening injection/Yinxingye Preparations (4.1%), an extract from Yinxingye (Folium Ginkgo); Dengzhan Xixin Injection/Dengzhan Huashu Injection (3.8%), an extract from Dengzhan Xixin (Herba Erigerontis); Buyang Huanwu decoction (3.1%), and Liangxue Tongyu Injection/Liangxue Tongyu oral liquid (2.7%). These commonly used prescriptions corresponded to syndromes, including the syndrome of blood stasis (due to bleeding), syndrome

of stagnation of qi and blood stasis, syndrome of blood stasis due to blood deficiency, syndrome of intermingled phlegm and blood stasis, syndrome of blood stasis, syndrome of blood stasis due to coagulated cold, syndrome of blood stasis due to qi deficiency, and syndrome of blood stasis due to heat toxicity, respectively (Table 3). Seven out of the 8 prescriptions are Chinese herbal patent preparations, which are quality controlled for manufacturing methods. In addition, 6 Chinese herbal patent preparations all have injection preparations, which are more convenient during a stroke emergency. The

Table 3. The most commonly used prescription corresponding to syndrome and pharmacological study for acute intracerebral hemorrhage.

Prescription: N/292	Compositions	Function	Syndrome	Pharmacology
Xueshuantong Injection: 33 (11.3%)	Sanqi (Radix Notoginseng)	Promoting blood circulation for hemostasis	Syndrome of blood stasis (due to bleeding)	Ameliorate brain edema by inhibiting the expression of AQP-4 ^[30] and decreasing thrombin generation ^[31] , protect neurons and abate neuronal apoptosis by decreasing the expression of Bax and increasing Bcl-2 ^[32] , protect neurons by regulating excitatory amino acid receptors ^[33] .
Fufang Danshen Injection/Xiangdan Injection: 30 (10.3%)	Danshen (Radix Salviae Miltiorrhizae), Jiangxiang (Lignum Dalbergiae Odoriferae)	Activating qi flowing and promoting blood circulation	Syndrome of stagnation of qi and blood stasis	Ameliorate brain edema by decreasing MDA and increasing SOD activity ^[34] , protect neurons and abate neuronal apoptosis by decreasing caspase-3 ^[35] .
Danshen Injection: 23 (7.9%)	Danshen (Radix Salviae Miltiorrhizae)	Promoting blood circulation and nourishing blood	Syndrome of blood stasis due to blood deficiency	
Shuxuetong Injection: 16 (5.5%)	Shuizhi (Hirudo), Dilong (Lumbricus)	Drastically removing blood stasis and removing obstruction in collaterals	Syndrome of intermingled phlegm and blood stasis	Ameliorate brain edema as a thrombin inhibitor ^[36] , improve the development of hyperlasia of capillary, glial cells and their activities ^[37] .
Shuxuening injection/Yinxingye Preparations: 12 (4.1%)	Yinxingye (Folium Ginkgo)	Promoting blood circulation for removing blood stasis	Syndrome of blood stasis	Abate neuronal apoptosis by decreasing the expression of Bax and caspase-3 and increasing Bcl-2 ^[38] , protect brain against inflammatory injury by the inhibition of IL-8 and ICAM-1 mediated neutrophil infiltration ^[39] .
Dengzhan Xixin Injection/Dengzhan Huashu Injection: 11 (3.8%)	Dengzhan Xixin (Herba Erigerontis)	Dispelling cold and activating blood circulation	Syndrome of blood stasis due to coagulated cold	Protect neurons by decreasing inflammatory factors including TNF- α and IL-8 in brain areas around hemorrhagic focus ^[40] , alleviate secondary nerve damage by repressing the expression of ICAM-1 ^[41] .
Buyang Huanwu Decoction: 9 (3.1%)	Danshen (Radix Salviae Miltiorrhizae), Chishao (Radix Paeoniae Rubra), Danggui (Radix Angelicae Sinensis), Chuanxiong (Rhizoma Ligustici Chuanxiong), Huangqi (Radix Astragali seu Hedysari), Taoren (Semen Persicae), Honghua (Flos Cartham), Niuxi (Radix Achyranthis Bidentatae), Dilong (Lumbricus)	Benefiting qi for activating blood circulation	Syndrome of blood stasis due to qi deficiency	Improve the neurological function deficits and alleviate brain edema through inhibition of AQP4 expression ^[42] , prohibit neuronal apoptosis and promote absorption of the hematoma through decreasing the expression of activated caspase-3 ^[43] , enhance angiogenesis by promoting the expression of VEGF ^[44] .
Liangxue Tongyu Injection/Liangxue Tongyu oral liquid: 8 (2.7%)	Shuniujiao (Cornu Bubali), Dahuang (Radix et Rhizoma Rhei), Shengdi (Radix Rehmanniae Recens), Mudanpi (Cortex Moutan Radicis), Sanqi (Radix Notoginseng), Shichangpu (Rhizoma Acori Tatarinowii), Zhizi (Fructus Gardeniae)	Cooling blood and removing blood stasis, purging fu-viscera, clearing heat-toxicity	Syndrome of blood stasis due to heat-toxicity	Ameliorate brain edema and facilitate hematoma removal through up-regulation of t-PA and tissue inhibitor of metalloproteinase-1, and down-regulation of matrix metalloproteinase-9 ^[45, 46] .

Note: AQP-4, aquaporins-4; MDA, malondialdehyde; SOD, superoxide dismutase; IL-8, interleukin-8; ICAM-1, intercellular adhesion molecule-1; VEGF, vascular endothelial growth factor; t-PA, tissue plasminogen activator; TNF- α , tumor necrosis factor- α .

remaining preparation is a famous Chinese herbal prescription, Buyang Huanwu decoction, which is specifically used to treat stroke, according to the theory of qi deficiency and blood stasis recorded in Yilin Gaicuo (Correction of Errors in Medical Classics), written by Wang Qingren in 1830.

The numbers of Chinese herbs in the formulas varied from 1 to 9. The top 15 single herbs are shown in Table 4. Danshen (Radix Salviae miltiorrhizae) was the most frequently used single herb; it was used in 109 (37.3%) of the 292 studies. This was followed by Sanqi (Radix Panax notoginseng) (36.3%),

Table 4. The most commonly used herbs for acute intracerebral hemorrhage.

Chinese name	English name	Latin name	Family	N/292 (%)
Dan Shen	Danshen root	Radix Salviae Miltiorrhizae	<i>Salvia miltiorrhiza</i> Bge	109 (37.3)
San Qi	Sanqi	Radix Notoginseng	<i>Panax notoginseng</i> (Burk) F H Chen	106 (36.3)
Shui Zhi	Leech	Hirudo	<i>Hirudo nipponica</i> Whitman	88 (30.1)
Chuan xiong	Sichuan lovage rhizome	Rhizoma Ligustici Chuanxiong	<i>Ligusticum chuanxiong</i> Hort	80 (27.4)
Tao Ren	Peach seed	Semen Persicae	<i>Amygdalus persica</i> L	68 (23.3)
Chi Shao	Peony root	Radix Paeoniae Rubra	<i>Paeonia lactiflora</i> Pall	59 (20.2)
Hong Hua	Safflower	Flos Carthami	<i>Carthamus tinctorius</i> L	58 (19.9)
Di Long	Earthworm	Lumbricus	<i>Pheretima aspergillum</i> (E Perrier)	55 (18.8)
Dang Gui	Chinese angelica	Radix Angelicae Sinensis	<i>Angelica sinensis</i> (Oliv) Diels	49 (16.8)
Chuan Niu Xi	Medicinal cyathula root	Radix Cyathulae	<i>Cyathula officinalis</i> Kuan	38 (13.0)
Jiang Xiang	Rosewood	Lignum Dalbergiae Odoriferae	<i>Dallbergia odorifera</i> T Chen	35 (12.0)
Huang qi	Milkvetch root	Radix Astragali seu Hedysari	<i>Astragalus membranaceus</i> (Fisch) Bge var <i>Mongolicus</i> (Bge) Hsiao	20 (6.8)
Yujin	Turmeric root tuber	Radix Curcumae	<i>Curcuma wenyujin</i> YH Chen et C Ling, <i>Curcuma longa</i> L, <i>Curcuma kwangsiensis</i> S G Lee et C F Liang, <i>Curcuma phaeocaulis</i> Val	16 (5.5)
Shexiang	Musk	Moschus	<i>Moschus berezovskii</i> Flerov, <i>Moschus sifanicus</i> Przewalski, <i>Moschus moschiferus</i> Linnaeus	15 (5.1)
Quanxie	Scorpion	Scorpion	<i>Buthus martensii</i> Karsch	13 (4.5)

Shuizhi (*Hirudo*) (30.1%), Chuanxiong (*Rhizoma Ligustici Chuanxiong*) (27.4%), Taoren (*Semen Persicae*) (23.3%), Chishao (*Radix Paeoniae rubra*) (20.2%), Honghua (*Flos Carthami*) (19.9%), Dilong (*Lumbricus*) (18.8%), Danggui (*Radix Angelicae sinensis*) (16.8%), Chuanniuxi (*Radix Cyathulae*) (13.0%), Jiangxiang (*Lignum Dalbergiae Odoriferae*) (12.0%), Huangqi (*Radix Astragali seu Hedysari*) (6.8%), Yujin (turmeric root tuber, *Curcuma longa*) (5.5%), Shexiang (musk) (5.1%), and Quanxie (scorpion) (4.5%).

Efficacy assessment

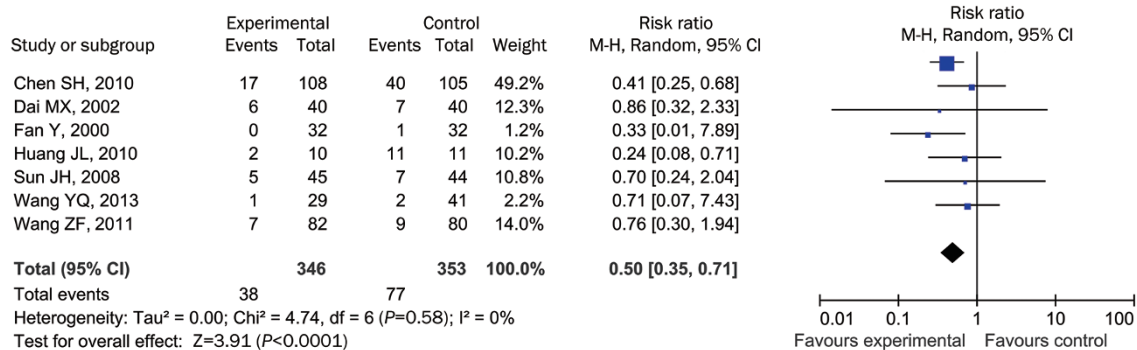
Mortality

The mortality was reported in 7 of the 9 studies. Meta-analysis showed that PBCRBS treatment significantly reduced the mortality rate in the trial group compared with the control group. The risk ratio in the 7 studies varied from 0.24 to 0.86,

with an overall risk ratio of 0.50 (95% CI: 0.35 to 0.71, $P < 0.05$, $I^2 = 0\%$, Figure 2). In the double-blind placebo control study^[22], the risk ratio was 0.41, which was lower than the overall risk ratio.

ADL score

The Barthel Index was used in 2 studies^[22, 27] and evaluated at 90 d after PBCRBS treatment. There were significant differences between the PBCRBS group and the control group (1.86, 95% CI: 1.39 to 2.49, $P < 0.05$, $I^2 = 0\%$, Figure 3). In addition, the mRS was used in Chen's study^[22]. At the last time point investigated, there were 60 patients (55.5%) who achieved a good outcome (mRS 0, 1, 2) in the PBCRBS group and 30 patients (28.5%) in the control group; there were significant differences among these studies, according to the Cochran-Mantel-Hansel (CMH) test ($P = 0.048$). For the subjects who began treatment

**Figure 2.** The forest plot: mortality rate.

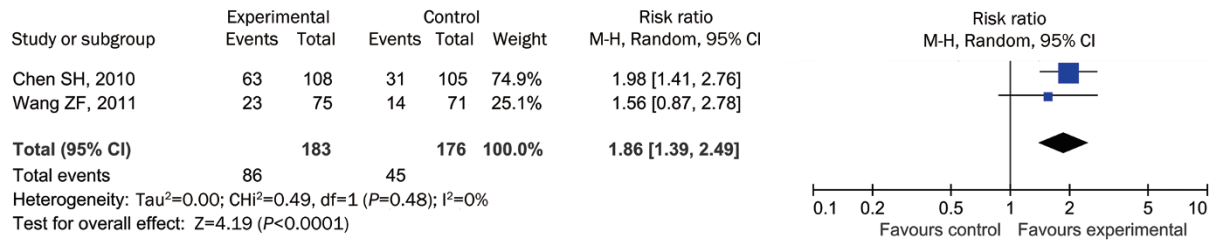


Figure 3. The forest plot: the barthel index.

within 24 h after an attack, there were 5 patients (4.6%) who had severe disability (mRS 4, 5, 6) in the PBCRBS group and 9 patients (8.6%) in the control group; there were no significant differences between these groups, according to the CMH test ($P=0.741$). For the subjects who began treatment between 24 and 48 h after the attack, there were 5 patients (5.1%) who had severe disability (mRS 4, 5, 6) in the PBCRBS group and 15 patients (16.7%) in the control group; there was a significant difference between these two groups, according to the CMH test ($P=0.048$). For the subjects who began treatment between 48 and 72 h after an attack, there were 7 patients (7.5%) who had severe disability (mRS 4, 5, 6) in the PBCRBS group and 19 patients (21.2%) in the control group; there were significant differences between these groups, according to the CMH test ($P=0.031$).

Clinical effective rate

The clinical efficacy was reported in 3 of the 9 studies. The definition of effective rate was not standardized. It was defined according to CCNDS 1995 in 2 studies^[20, 26] and according to the clinical guidelines for new drugs for TCM^[28] in the remaining 1 study^[24]. The risk ratio of clinical efficacy in the 3 studies varied from 1.35 to 1.59, with an overall risk ratio of 1.44 (95% CI: 1.16 to 1.78, $P<0.05$, $I^2=0\%$, Figure 4); for the SM group^[20], the risk ratio was 1.35; for the non-SM groups^[24, 26], the risk ratios were 1.47 and 1.59, respectively.

Volume of hematoma

The volume of hematoma was used as an outcome measure in 3 of the 9 studies; the volume was evaluated at 14 and 28 d after PBCRBS treatment. Meta-analysis showed that PBCRBS treatment significantly reduced the volume of hematoma in the trial group when compared with the control group (-2.72,

95% CI: -4.12 to -1.32, $P<0.05$, $I^2=77\%$). The volume of hematoma in the trial group was more significantly reduced than that in the control group at 28 d (-2.05, 95% CI: -2.89 to -1.22, $P<0.05$, $I^2=0\%$) after PBCRBS treatment, but not at 14 d (-3.21, 95% CI: -6.34 to -0.09, $P=0.04$, $I^2=91\%$, Figure 5).

Volume of perihematoma edema

The volume of perihematoma edema was used as an outcome measure in 3 of the 9 studies and evaluated at 7, 14, and 21 d after PBCRBS treatment. Meta-analysis showed that PBCRBS treatment significantly reduced the volume of perihematoma edema in the trial group compared with the control group (-5.84, 95% CI: -8.62 to -3.06, $P<0.05$, $I^2=95\%$). After PBCRBS treatment, significant differences between the trial group and control group were detected at 21 d (-7.27, 95% CI: -7.91 to -6.64, $P<0.05$, $I^2=0\%$), but not at 7 d (-3.08, 95% CI: -7.23 to 1.07, $P=0.15$, $I^2=54\%$) or 14 d (-7.39, 95% CI: -15.06 to 0.28, $P=0.06$, $I^2=88\%$, Figure 6).

NIHSS score

Two^[19, 26] of the 9 studies used NIHSS scores to determine the effect of PBCRBS on the neurological function of the patients. The NIHSS score was assessed at 14 and 28 d after PBCRBS treatment. The overall results indicate that the PBCRBS group had a measurably better recovery of neurological functions than the control group (-5.34, 95% CI: -7.14 to -3.53, $P<0.05$, $I^2=92\%$). Furthermore, the NIHSS score in the PBCRBS group was significantly lower when compared with the control group at 14 d (-4.75, 95% CI: -5.57 to -3.93, $P<0.05$, $I^2=0\%$) and 28 d (-5.68, 95% CI: -8.87 to -2.49, $P<0.05$, $I^2=94\%$, Figure 7).

CCNDS score

The CCNDS score was used in 2 studies^[25, 27] and assessed at

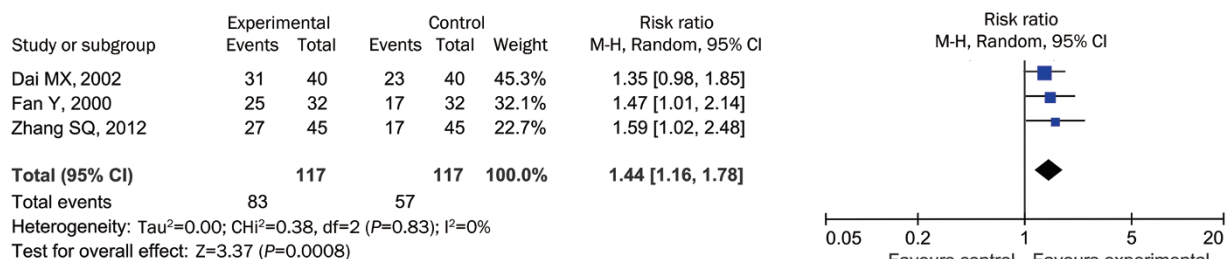


Figure 4. The forest plot: Clinical effective rate.

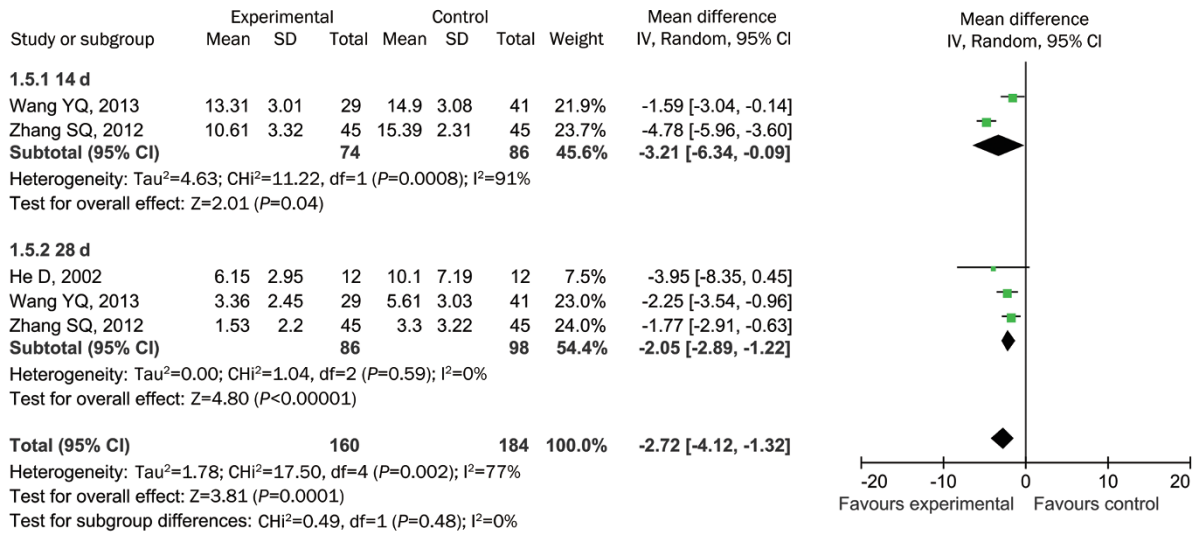


Figure 5. The forest plot: volume of hematoma.

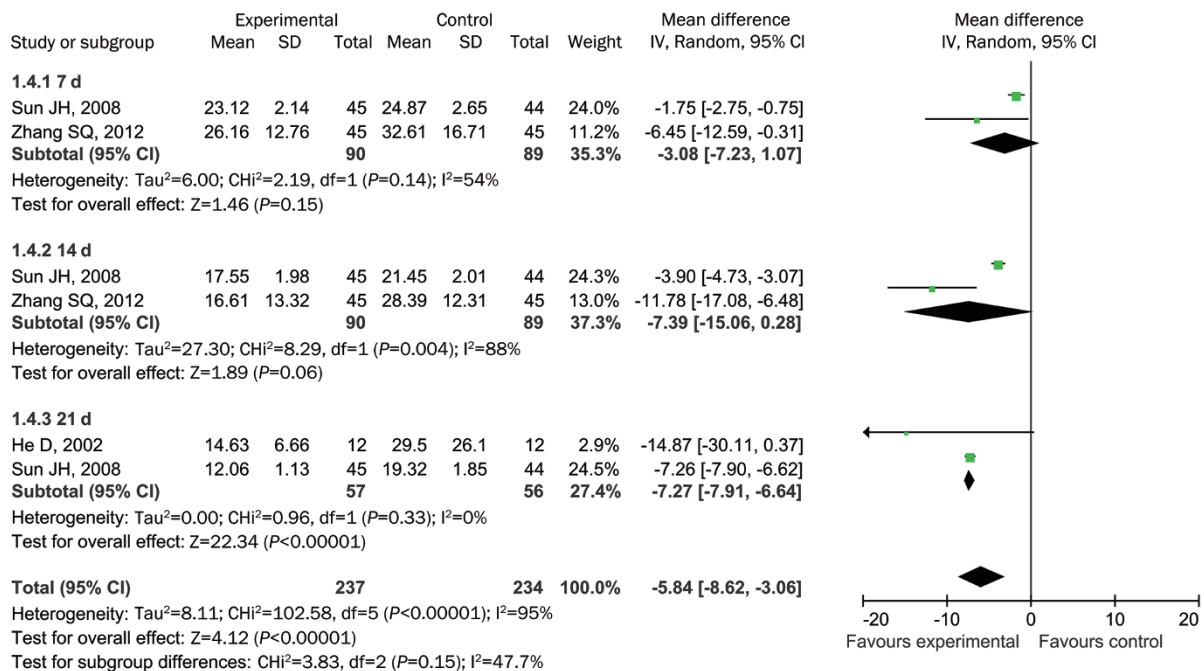


Figure 6. The forest plot: volume of perihematoma edema.

14, 30 and 90 d following PBCRBS treatment. Meta-analysis showed that PBCRBS treatment significantly reduced the CCNDS score in the trial group compared with the control group (-4.50, 95% CI: -6.44 to -2.57, $P<0.05$, $I^2=83\%$). After PBCRBS treatment, significant differences between the trial group and control group were detected at 30 d (-5.38, 95% CI: -7.73 to -3.03, $P<0.05$, $I^2=52\%$) and 90 d (-2.96, 95% CI: -3.99 to -1.92, $P<0.05$, $I^2=83\%$), but not at 14 d (-4.74, 95% CI: -10.49 to 1.01, $P=0.11$, $I^2=90\%$, Figure 8).

Adverse event reporting

Adverse events were reported in 2 of the 9 studies and not mentioned in the remaining 7 studies. Chen *et al*^[22] reported that there were 24 cases of adverse events related to drugs and 2 cases of serious adverse events in the trial group, but there were 41 cases of adverse events and 6 cases of serious adverse events in the control group. The frequency of adverse events in this study was 26/108 in the trial group and 47/105 in the control group. Fan *et al*^[24] reported 7 types of adverse events,

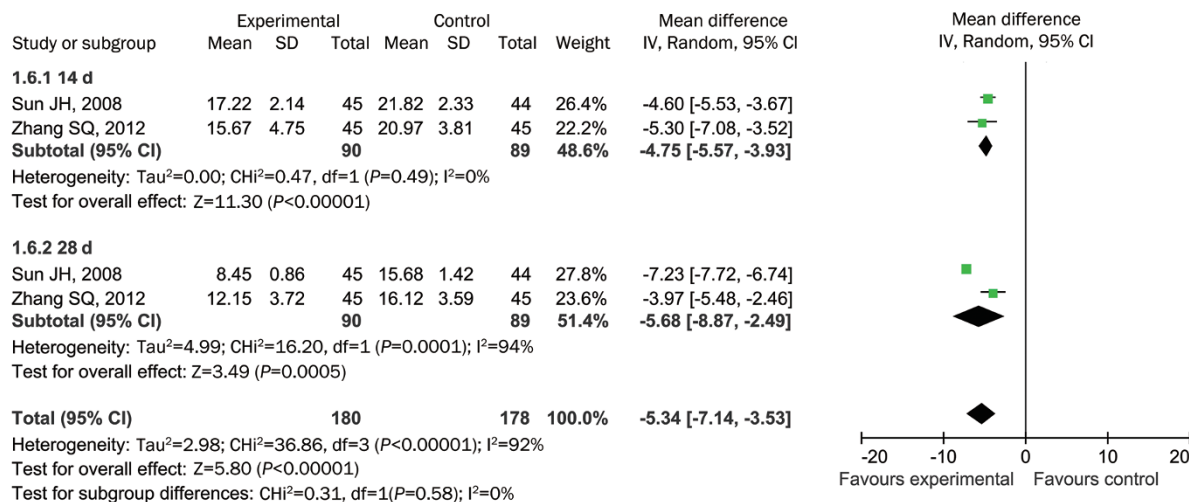


Figure 7. The forest plot: national institute of health stroke scale (NIHSS) score.

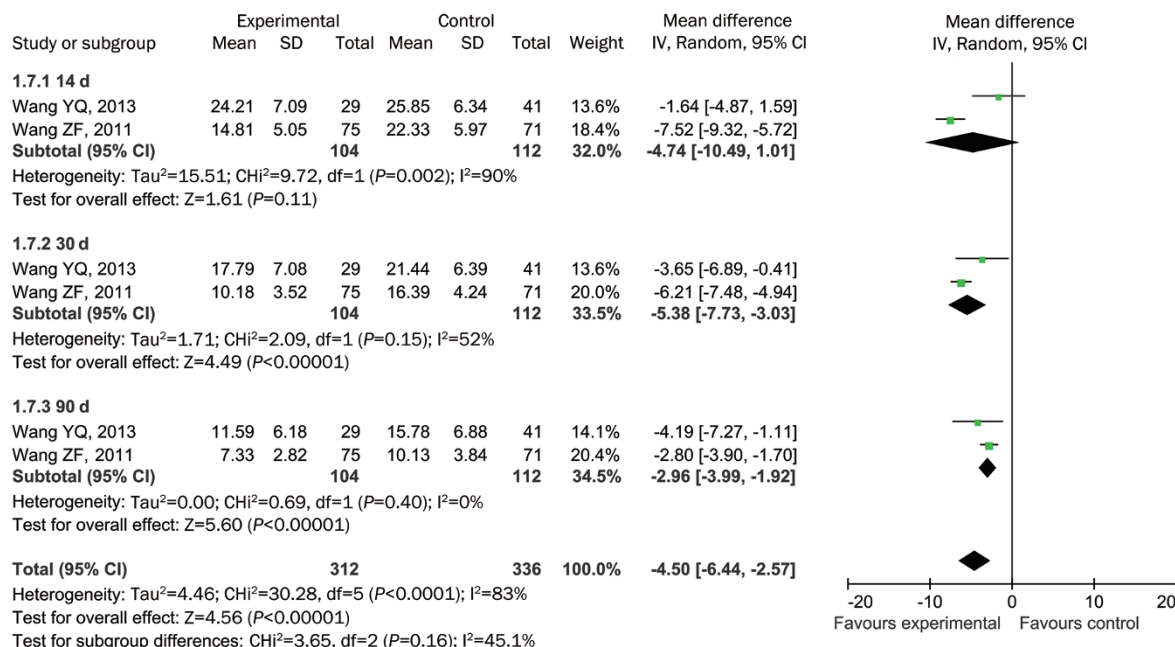


Figure 8. The forest plot: Chinese clinical neurological deficit scale (CCNDS) score.

including 2 cases of mild diarrhea, 3 cases of mild epigastric discomfort, 3 cases of transient renal damage, 5 cases of electrolyte imbalances, and 1 case of melena in the trial group; there were 8 cases of transient renal damage, 17 cases of electrolyte imbalances, 3 cases of transient liver damage, 6 cases of melena and 1 case of hematemesis in the control group.

GRADE profile evidence

Quality assessment of the evidence is shown in Table 5. The quality of evidence in the outcomes of the clinical effectiveness rate, Barthel Index (90 d), volume of perihematomal edema (21 d), volume of hematoma (28 d), and neurological deficit scores (NIHSS score and CCNDS score) were high; the quality

of evidence in the outcomes of mortality rate, volume of perihematomal edema (7 d and 14 d), and volume of hematoma (14 d) were moderate.

Discussion

Summary of evidence

This study is an updated systematic review and meta-analysis of the efficacy and safety of PBCRBS for ICH. Two hundred and 29 studies claimed RCTs. Nine better quality studies with 798 individuals assessed in ≥ 4 domains with 'yes' were identified based on the Cochrane RoB tool. The main findings were that PBCRBS monotherapy and adjuvant therapy for acute ICH could improve neurological function deficits, reduce

Table 5. The updated GRADE profile.

		Quality assessment				Summary of findings			
No of studies (design)	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	No. of patients		Relative risk (95% CI)	Quality
						Experimental	Control		
The clinical effective rate									
3 (RCT)	Concealment and blinding not clear in most studies ¹	No serious inconsistency	No serious indirectness	No serious imprecision	Funnel plot asymmetrical ²	83/117	57/117	RR 1.46 (1.17 to 1.81)	⊕⊕⊕⊕ High ³
Mortality rate									
7 (RCT)	Concealment and blinding not clear in most studies ⁴	No serious inconsistency	No serious indirectness	Serious imprecision ⁵	Funnel plot asymmetrical ²	38/346	77/353	RR 0.5 (0.35 to 0.7)	⊕⊕⊕⊕ Moderate due to imprecision ⁶
Barthel Index 90 d									
2 (RCT)	Lack of concealment and blinding ⁷	No serious inconsistency	No serious indirectness	No serious imprecision	Funnel plot asymmetrical ²	84/183	45/176	RR 1.4 (1.22 to 1.55)	⊕⊕⊕⊕ High ³
Volume of perihematoma edema ⁸ - 7 d									
2 (RCT)	Lack of concealment and blinding ⁷	No serious inconsistency	No serious indirectness	Serious imprecision ⁵	Funnel plot asymmetrical ²	90	89	-8	⊕⊕⊕⊕ Moderate due to imprecision ⁶
Volume of perihematoma edema ⁸ - 14 d									
2 (RCT)	Lack of concealment and blinding ⁷	CI show no overlap and P-value on test for heterogeneity <0.0001, I ² =88% ⁹	No serious indirectness	No serious imprecision	Funnel plot asymmetrical ²	90	89	-8	⊕⊕⊕⊕ Moderate due to inconsistency ¹⁰
Volume of perihematoma edema ⁸ - 21 d									
2 (RCT)	Concealment and blinding not clear in most studies ¹	No serious inconsistency	No serious indirectness	No serious imprecision	Funnel plot asymmetrical ²	57	56	-8	⊕⊕⊕⊕ High ³
Volume of hematoma ⁸ - 14 d									
2 (RCT)	Lack of concealment and blinding ⁷	CI show no overlap and P-value on test for heterogeneity <0.0008, I ² =91% ⁹	No serious indirectness	No serious imprecision	undetected	74	86	-8	⊕⊕⊕⊕ Moderate due to inconsistency ¹⁰
To be continued									

		Quality assessment							Summary of findings		
									No. of patients		
No. of studies (design)	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Experimental	Control	Relative risk (95% CI)	Quality		
3 (RCT)	Volume of hematoma ⁸ - 28 d Concealment and blinding not clear in most studies ¹	No serious inconsistency	No serious indirectness	No serious imprecision	Funnel plot asymmetrical ²	86	98	-8	⊕⊕⊕⊕ High ³		
2 (RCT)	Neurological deficit scores ⁸ - NIHSS score Lack of concealment and blinding ⁷	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	90	89	-8	⊕⊕⊕⊕ High ¹¹		
3 (RCT)	Neurological deficit scores ⁸ - CCNDS score Lack of concealment and blinding ⁷	P-value on test for heterogeneity <0.008, I ² =79% ⁹	No serious indirectness	No serious imprecision	Funnel plot asymmetrical ²	138	145	-8	⊕⊕⊕⊕ High ¹²		

RCT, random clinical trial; CI, confidence interval; MD, mean difference.

- ¹Unclear allocation concealment in all studies, participants and personnel blinded in only one study, outcome assessors not blinded in any study. Final decision was not to rate down for risk of bias.
- ²Funnel plot was asymmetrical, while number of included trials were limited and further research may change the estimate. Final decision was not to rate down for risk of bias.
- ³Although there also was concern about a risk of bias and publication bias, we did not further rate down the quality of evidence because not every criterion appeared to justify rating down by one level.
- ⁴Allocation concealment in only one study, participants and personnel blinded in two studies, outcome assessors blinded in only one study. Final decision was not to rate down for risk of bias.
- ⁵The confidence interval (CI) included no effect.
- ⁶We rated down for imprecision. Although there also was concern about a risk of bias and publication bias, we did not further rate down the quality of evidence because not every criterion appeared to justify rating down by one level.
- ⁷Unclear allocation concealment and blinding in all studies. Final decision was not to rate down for risk of bias.
- ⁸Continuous outcome, therefore no relative effect is given.
- ⁹CI show no overlap and the statistical test for heterogeneity shows a low P-value and the I² is large. Final decision was rate down for inconsistency.
- ¹⁰We rated down for inconsistency. Although there also was concern about a risk of bias and publication bias, we did not further rate down the quality of evidence because not every criterion appeared to justify rating down by one level.
- ¹¹Although there also was concern about a risk of bias, we did not further rate down the quality of evidence because not every criterion appeared to justify rating down by one level.
- ¹²Although there also was concern about a risk of bias, inconsistency and publication bias, we did not further rate down the quality of evidence because not every criterion appeared to justify rating down by one level.

the volume of hematoma and perihematomal edema, and lower the mortality rate and dependency; there were fewer adverse effects in comparison with WCM controls. The quality of the evidence was mostly moderate to high, according to the quality assessment, using the GRADE methodology and profiler. Despite the apparently positive findings, it is premature to conclude that there is increased efficacy and safety of PBCRBS for ICH because of the high clinical heterogeneity of the included studies and small number of trials in the meta-analysis.

Limitations

There are several limitations to this review. First, none of the included studies in this review had been formally registered. Thus, protocols were not available to confirm free of selective reporting^[29]. Second, although the strength of this systematic review and meta-analysis was that all the RCTs included were of better quality and assessed in ≥ 4 domains with 'yes', we did acknowledge some methodological weaknesses in the primary studies, such as allocation concealment and blindness. Research outcomes could possibly be influenced by either the selection bias or the observer bias. Third, among the 9 included studies, only one^[22] used a formal placebo control. Because of the lack of placebo controls, the interpretation of the positive findings of treatment with Chinese herbal medicine (CHM) should be made with caution. Fourth, most of the included studies were of relatively small sample size and did not include a formal sample size estimation. Trials with inadequate sample sizes often run the risk of overestimating intervention benefits^[30]. Fifth, the clinical heterogeneity compromised the validity of the included studies. There were large variations in the formulation, dosage, administration, and duration of treatments of the CHM in the included studies.

Implications for practice

Based on a brief overview of TCM application history of acute ICH^[10], the main methods for ICH were the following: (1) subduing the liver yang, calming down the internal wind and clearing heat; (2) purging the Fu organ and the harmony of qi and blood; (3) PBCRBS; and (4) anti-toxin or benefiting vital qi. However, PBCRBS is the essence of the TCM treatment method for ICH because blood stasis syndrome can be found throughout the pathological process of ICH. On a practical level, this systematic review provides premature evidence for the efficacy and safety of PBCRBS therapy after acute ICH; the evidence remains limited because of the high clinical heterogeneity and small number of trials included. However, it should be remembered that a lack of scientific evidence does not necessarily mean that the treatment is ineffective^[31].

Modern pharmacological studies further supported the potential use of PBCRBS therapy for acute ICH as follows

(1) Sanqi (Radix Notoginseng) could ameliorate brain edema by inhibiting the expression of AQP-4^[32] and decreasing thrombin generation^[33], protect neurons and abate neuronal

apoptosis by decreasing the expression of Bax and increasing Bcl-2^[34], and protect neurons by regulating excitatory amino acid receptors^[35]; (2) Danshen (Radix Salviae miltiorrhizae) could ameliorate brain edema by decreasing malondialdehyde (MDA) and increasing superoxide dismutase (SOD) activity^[36], and protect neurons and abate neuronal apoptosis by decreasing caspase-3^[37]; (3) Shuizhi (Hirudo) could ameliorate brain edema as a thrombin inhibitor^[38], improve the development of hyperplasia of the capillaries, glial cells and their respective activities^[39]; (4) an extract from Yinxingye (Folium Ginkgo biloba) could abate neuronal apoptosis by decreasing the expression of Bax and caspase-3 and increasing Bcl-2^[40], protect the brain against inflammatory injury by the inhibition of interleukin (IL)-8 and intercellular adhesion molecule (ICAM)-1 mediated neutrophil infiltration^[41]; (5) an extract from Dengzhan Xixin (Herba Erigerontis) could protect neurons by decreasing inflammatory factors, including TNF- α and IL-8 in the brain areas around the hemorrhagic focus^[42], alleviate secondary nerve damage by repressing the expression of ICAM-1^[43]; (6) Buyang Huanwu decoction could improve the neurological function deficits and alleviate brain edema through inhibition of AQP-4 expression^[44], prohibit neuronal apoptosis and promote absorption of the hematoma through decreasing the expression of activated caspase-3^[45], enhance angiogenesis by promoting the expression of VEGF^[46]; and (7) Liangxue Tongyu preparations could ameliorate brain edema and facilitate hematoma removal through up-regulation of t-PA and tissue inhibitor of metalloproteinase-1, and down-regulation of matrix metalloproteinase-9^[47, 48]. These herbal preparations may clinically contribute to further combating ICH.

It is worth noting that PBCRBS for acute ICH may raise a concern regarding the enlargement of the hematoma because doctors are afraid of potentially increasing bleeding. In actuality, hematoma size and hematoma expansion is an independent predictor of mortality and functional outcomes^[49]. It has been well established that initial hemorrhage volume in approximately one-third of spontaneous ICH patients is not static but frequently progresses, usually within the early 6 h after the ictus^[50]. Thus, the selection of patients at high risk for hematoma enlargement is crucial for PBCRBS treatment. Although most studies reporting PBCRBS therapy did not increase or reduce hemorrhage volume and mortality rate, an issue of hematoma expansion may still warrant consideration. In addition, Nie *et al*^[51] reported that Panax Notoginseng saponins were used in treating ICH patients with large amounts of hematoma at super-early stages, which may worsen brain edema and increase the nerve defect score, although it could promote the absorption of the hematoma. Thus, we suggest several aspects for safety considerations as follows: (1) the contrast extravasation on CT angiography (CTA) is a well-established imaging predictor for subsequent hematoma expansion that may be used as a useful imaging marker to guide therapies; (2) a number of risk factors have been associated with hematoma progression, such as an irregularly shaped hematoma, coagulation abnormalities, hyperglycemia,

hypertension, and anticoagulation. These risk factors should be controlled when the levels are compatible; (3) PBCRBS therapy is best to use 24 h, or at least 6 h, after ICH onset; (4) the most common herbs and prescriptions, especially their method of treatment, that are identified in the present study may be used prior to the clinic visit; (5) intensive monitoring of adverse reactions related to PBCRBS use in ICH patients should be performed.

Implications for further research

This work identifies some key areas for further research. Firstly, PBCRBS is widely used in the treatment of ICH. The most common herbal preparation is a promising candidate for further mechanism study and clinical trial of ICH. For example, thrombin plays dual roles both in brain injury and in brain protection after ICH; its deleterious effects come either from resident neural cells or from prothrombin in the blood^[52]. Hirudin, a thrombin inhibitor, is a naturally occurring peptide in the salivary glands of medicinal leeches (such as *Hirudo medicinalis*) that has a blood anticoagulant property. An upcoming random double-blind controlled clinical trial will investigate the safety and efficacy of acute ICH treated with *Hirudo* and *Tabanus* PBCRBS therapy. The question whether the traditional methods can influence brain hematoma enlargement must be verified. This study is currently recruiting participants^[53]. Secondly, disease-syndrome combination mainly refers to the idea and theory of disease differentiation in Western medicine as well as syndrome differentiation in TCM. The syndrome is not only the core of TCM basic theory and syndrome differentiation but also the bridge to associate disease and prescription, *ie*, prescription corresponding to syndrome^[54]. Based on each individual syndrome, a precisely tailored Chinese herbal prescription for individuals can help to improve the efficacy of the selected TCM herbal prescription (Fufang) intervention^[55]. One high-quality study published in *JAMA*^[56] indicated that using individualized CHM for the treatment of irritable bowel syndrome is more effective than prescribing a common hypnotic prescription. The research on blood stasis syndrome and corresponding PBCRBS therapy is one of the most active areas regarding syndrome identification in China^[57]. In recent years, the essence of blood stasis syndrome was mostly investigated in the form of disease-syndrome combination. Interesting, all patients suffering from ICH may be considered as having a blood stasis syndrome according to the TCM theory of 'the blood flow outside the vessels is the blood stasis'; this also takes advantage of the utility of a CT scan or MRI in the diagnosis of ICH. Thus, all ICH patients can be treated with PBCRBS therapy. However, the syndrome summarizes the nature, location, and syndrome of diseases, which is traditionally identified from a comprehensive analysis of clinical information from four main diagnostic TCM methods: observation, listening, questioning, and pulse analyses^[58]. Whether modern blood stasis is different from traditional blood stasis and whether their correlation with prescriptions corresponds to the syndrome requires further clarification; this may contribute to not only the essence of

the blood stasis syndrome but also evidence-based syndrome identification in ICH. Thirdly, although the PBCRBS evaluated in this review was well tolerated by ICH patients, the safety of PBCRBS could not be confirmed because only 2 studies reported the safety of interventions or investigated adverse events. Investigators of these studies might have underestimated possible adverse events. In addition, the safety of herbal patent injection itself has become a major concern to both national health authorities and the general public^[59]. A standard reporting format for adverse drug reactions (ADR) has been developed^[60], and we suggest that improvement of the reporting of adverse events and ADRs of PBCRBS should be closely followed. Fourthly, improvement in the methodological quality of primary RCTs is still crucial for future clinical studies. We recommend that specific guidelines, such as the CONSORT 2010 statement^[61], guidelines for RCTs investigating CHM^[62] and CONSORT for TCM^[63], should be used as a combined guideline when designing and reporting RCTs for CHM.

Conclusion

Despite the apparently positive findings, it is premature to conclude that there is increased efficacy and safety of PBCRBS for ICH because of the high clinical heterogeneity in the included studies and small number of trials in the meta-analysis. However, this work identifies some key areas for further research. Further large sample size and rigorously designed RCTs are still needed.

Acknowledgements

This project was supported by the National Natural Science Foundation of China (81173395/H2902); the young and middle-aged university discipline leaders of Zhejiang province, China (2013277); the Project of Wenzhou Municipal Science and Technology Bureau in Zhejiang province (Y20110031); and the Administration of Traditional Chinese Medicine of Zhejiang Province (2011ZB094).

Author contribution

Ji-ping FAN, Guo-qing ZHENG, Hui-qin LI, and Jing-jing WEI designed the research; Hui-qin LI, Jing-jing WEI, Wan XIA, Ji-huang LI, Ai-ju LIU, Su-bing YIN, Chen WANG, Liang SONG, and Yan WANG performed the research; Hui-qin LI, Jing-jing WEI, Wan XIA, Ji-huang LI, Ai-ju LIU, Su-bing YIN, Chen WANG, Liang SONG, and Yan WANG analyzed the data; Hui-qin LI, Jing-jing WEI, Guo-qing ZHENG, and Ji-ping FAN wrote the paper.

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