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ORIGINAL ARTICLE

Activating Blood Circulation to Remove Stasis Treatment of Hypertensive Intracerebral Hemorrhage: A Multi-Center Prospective Randomized Open-Label Blinded-Endpoint Trial*

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ABSTRACT **Objective:** To investigate the efficacy and safety of the Chinese herbal therapeutic regimen of activating blood circulation (TRABC) in treatment of hypertensive intracerebral hemorrhage (HICH). **Methods:** This was a multi-center prospective randomized open-label blinded-endpoint (PROBE) trial with HICH admitted to 12 hospitals. Totally 240 participants were randomized to the treatment group treated with TRABC in addition to conventional Western treatment or the control group with conventional Western treatment equally for 3 months. Primary outcome was degree of disability as measured by modified Rankin Scale (mRS). Secondary outcomes were the absorption of hematoma and edema, National Institutes of Health Stroke Scale (NIHSS) scores and patient-reported outcome measures for stroke and Barthel activities of daily living index. Adverse events and mortality were also recorded. **Results:** After 3 months of treatment, the rate of mRS 0-1 and mRS 0-2 in the treatment group was 72.5% and 80.4%, respectively, and in the control group 48.1% and 63.9%, respectively, with a significant difference between groups (P<0.01). Hematoma volume decreased significantly at day 7 of treatment in the treatment group than the control group (P=0.038). Average Barthel scores in the treatment group after treatment was 89.11±19.93, and in the control group 82.18±24.02 (P=0.003). NIHSS scores of the two groups after treatment decreased significantly compared with before treatment (P=0.001). Patient-reported outcomes in the treatment group were lower than the control group at day 21 and 3 months of treatment (P<0.05). There were 4 deaths, 2 in each group, and 11 adverse events, 6 in the treatment group and 5 in the control group. **Conclusion:** The integrative therapy combined TRABC with conventional Western treatment for HICH could promote hematoma absorption thus minimize neurologic impairment, without increasing intracerebral hematoma expansion and re-bleeding.

KEYWORDS hypertensive intracerebral hemorrhage, activating blood circulation to remove stasis, Chinese herbs, prospective randomized open-label blinded-endpoint trial

Intracerebral hemorrhage is nontraumatic bleeding within the brain substance. Worldwide, the incidence is 60 to 80 per 10 million per year, accounting for 20% to 30% of all strokes in Asia.[1] Hypertensive intracerebral hemorrhage (HICH) is the most common type of cerebral hemorrhage, accounting for 40% of all intracerebral hemorrhages, 20%–30% of all strokes, with a fatality rate of 49.4%,[2] and its long-term prognosis is the worst. Brain damage and worsened outcome is primarily from hematoma expansion and perihematoma edema. Therefore, outcome would be improved if hematoma growth was limited and edema eliminated. Current Western medicine treatment of HICH relies on surgical removal of hematoma. However, limitation of indications, complications of surgery, and unfavorable health status of patients render surgery difficult to be widely applied.[3]

Chinese medicine (CM) may have advantages with the theory of activating blood to remove stasis.[4,5] Animal studies have shown that Chinese herbal preparations, such as Xingnaojing Injection (醒脑静注射液) or Naoningkang Granule (脑宁康颗粒) were capable for reducing cerebral edema[6,7] with clinical benefits in lowering mortality compared with non-treated control groups.[8-10] However, low quality of these studies has hampered wider application of

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these CM preparations.

Therefore, we conducted this study to assess the efficacy and safety of the treatment of activating blood circulation (TRABC) for HICH. Preparations used were Xingnaojing Injection, Naoxueshu Oral Liquid (脑血疏口服液), etc., both of which have function of activating blood circulation to remove stasis. The aim was to determine whether TRABC could promote resorption of intracerebral hematoma and improve outcomes in HICH patients.

METHODS

Study Design

This study was a multi-center prospective randomized open-label blinded endpoint (PROBE) trial. It was carried out May 1st, 2011 to March 1st, 2013.

Sample size planning based on large cohort studies allowed us to estimate that in our patient population at least 70% would have poor outcomes (Rankin scores[11] 4–6). Our aim was to reduce these poor outcomes to 50%. A two group χ^2 test with a 0.05 two-sided significance level would result in 80% power to detect the difference between the control group proportion of 0.70 and the treatment group proportion of 0.50 (odds ratio of 0.429), arriving at a sample size in each group of 95 (190 patients total). After considering a certain number of dropouts, each group was determined to be 120 with total 240 patients.

Participants were randomly assigned to herbal intervention or conventional care. Randomization was achieved using SAS software (SAS Institute, North Carolina, USA), generating serial numbers from 1–240 in blocks of 4. A third-party individual uninvolved in the research oversaw the randomization process, inserting corresponding group numbers into envelopes based on a randomization code list, then sealing and numbering the envelopes. Each center was assigned 24 envelopes. Investigators unsealed envelopes sequentially during enrollment and assigned participants into intervention and control groups by coding. A physician at each center who was masked to treatment allocation scored the assessment scales of each participant at baseline of the trial, and on days 7, 14, and 21, and 3 months after baseline. Head CT scans were obtained within 72 h of the hemorrhagic episode and 7 days after entering the trial. At each center, the scans were evaluated blindly by a radiologist who was uninvolved in the study.

The Ethics Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine approved this study. Twelve hospitals in Beijing area participated in the trial from May 2011 to March 2013. All patients provided written informed consents.

Study Eligibility

Inclusion criteria were: 18–80 years of age; non-traumatic intracerebral hemorrhage confirmed by head CT scan; treatment initiated within 72 h of onset of the first signs; National Institutes of Health Stroke Scale (NIHSS) scale[12] score of 5–22; pre-stroke modified Rankin Scale (mRS) score of 0 or 1.

Exclusion criteria were: hematoma caused by subarachnoid hemorrhage, arteriovenous malformation or cerebral amyloidosis; cerebral hemorrhage caused by cerebral tumor, cerebral trauma, or blood disorder; osteoarthropathy, psychosis, or serious dementia; current active ulcer or blood disorder; current participation in another experimental treatment.

Interventions

The control group received conventional treatment according to the Chinese Society of Neurology 2005 guidelines,[13] which included blood pressure regulation, blood glucose management, intracranial hypertension reduction, hydrocephalus treatment, and infection resolution.

The treatment group, in addition to conventional treatment, received TRABC. Diagnosis of CM syndrome patterns of HICH were made if patients' scores were ⩽7 according to standards for syndrome differentiation and diagnosis of stroke.[14] Composition of the herbal formula administered was based on one of three CM syndrome presentations detailed below.

Blood stasis accompanied by stagnation of heat toxin was treated with a formula aimed at promoting blood flow and relieving heat toxin. The formula was composed of *Panax notoginseng* (Burkill) F.H. Chen 10 g, raw *Typha angustifolia* L. 9 g, raw *Rheum palmatum* L. 9 g, *Scutel lariabaicalensis* Georgi 20 g, *Curcuma zedoaria* (Christm.) *Roscoe* 10 g, *Poria cocos* (Schw.) Wolf 20 g, *Gardenia jasminoides Ellis* 10 g, *Trichosanthes kirilowii Maxim* 20 g.

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Blood stasis accompanied by internal stirring of Gan (Liver) wind was treated with a formula aiming at promoting blood flow and extinguishing wind. The formula was made of *Panax notoginseng* (Burk.) F.H. Chen 10 g, raw *Typha angustifolia* L. 9 g, *Haliotis asinina* Linnaeus 15 g, *Paeonia lactiflora* Pall. 12 g, *Curcuma zedoaria* (Christm.) *Roscoe* 10 g, *Poria cocos* (Schw.) Wolf 20 g, *Uncaria rhynchophylla* (Miq.) Havil. 30 g, *Gastrodiaelata Blume* 12 g.

Blood stasis accompanied by phlegm blocking channels and collaterals was treated with a formula composed of *Panax notoginseng* (Burk.) F.H. Chen 10 g, raw *Typha angustifolia* L. 9 g, *Pinellia ternata* (Thunb.) Makino 10 g, *Trichosanthes kirilowii* Maxim 20 g, *Curcuma zedoaria* (Christm.) *Roscoe* 10 g, *Poria cocos* (Schw.) Wolf 20 g, and raw *Rheum palmatum* L. 3 g.

Additionally, two patent injections were administered: Xingnaojing (Wuxi Jimin Kexin Shanhe Pharmaceutical, batch number 110305), 20 mL in 250 mL 0.9% sodium chloride injected intravenously once daily for 14 days; and oral solution of Naoxueshu (Shandong Wohua Pharmaceutical, batch number 101205) after 21 days' hospitalization, 10 mL, thrice daily for 60 days.

Outcome Measure

Primary endpoints were degree of disability at 3 months after entering the trial as scored by Rankin score. Secondary end points included: amount of hematoma and edema resorption based on CT imaging and Coniglobus formula[15] calculation within 72 h of the episode and on day 7 of the trial; disability degree as scored by Barthel index[16] after 3 months; neurologic deficit as indicated by NIHSS scores at trial entry, days 7, 14, 21, and 3 months after trial entry. Other indicators that were considered were therapy adherence; patient-reported outcomes for stroke assessed at trial entry, days 7, 14, 21, and 3 months after trial entry. Safety outcomes included routine laboratory parameters such as complete blood count, liver and kidney functions, blood coagulation, and electrocardiography (ECG), which were assessed at trial entry and on day 21. Adverse events and mortality rate were also recorded.

Adverse Events

Adverse events were recorded when deterioration of disease or abnormal laboratory results existed. Laboratory exams included routine blood and urine, stool exam, kidney and liver functions, blood coagulation, ECG and head CT. Adverse events were categorized as mild, moderate, and severe. Mild events consisted of slight changes in laboratory parameters that did not affect treatment and could be reversed after symptomatic treatment. Severe adverse events were those that were life-threatening, extended hospitalization, or that lead to severe disability or death, or caused ⩾30% hematoma expansion. Moderate adverse events were between the extent of the light and severe.

Statistical Analysis

Data was expressed as mean ± standard deviation ($\bar{x} \pm s$) and evaluated with SAS software by the Clinical Evaluation Center, Institute of Basic Clinical Medicine, China Academy of Chinese Medical Sciences. All statistical tests were two-sided, with 95% confidence intervals. Age, height, weight, hypertension, and the time before treatment at baseline were analyzed with *t*-test. Sex, history of smoking, alcohol use, and treatment in the two groups were analyzed with Wilcoxon signed rank test or Mann-Whitney rank sum test. Hematoma was classified to three categories: large, medium, and small by different bleeding sites and volume (Table 1), and was analyzed by Chi-square test. The mRS scores and Barthel index of two groups at day 21 and 3 months after trial entry were assessed using Mann-Whitney rank sum test. NIHSS and patient-reported outcomes for stroke were analyzed with Wilcoxon signed rank test for each time points. Chi-square test was used to evaluate adverse events and mortality. $P<0.05$ was regarded as statistical significance.

RESULTS

Comparison of Baseline Characteristics between the Two Groups

A total of 228 cases were enrolled in this trial (Figure 1). There were no significant differences in the baseline

Table 1. Criteria Used to Determine Hematoma Size (mL)

Hematoma volume	Basal nuclei	Cranial lobe	Cerebellum	Encephalocoele	Brain stem
Large	>50	>30	>15	>30	>5
Medium	30–50	15–30	10–15	15–30	3–5
Small	<30	<15	<10	<15	<3

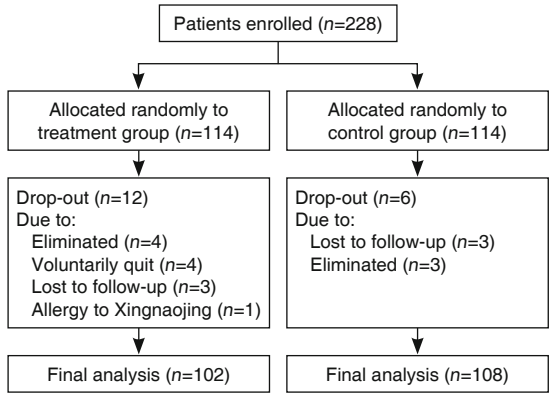

Figure 1. Flow Diagram of Chinese Herbal Treatment of HICH

Table2. Baseline Characteristics of Participants ($\bar{x} \pm s$)

Characteristics	Treatment (*n*=102)	Control (*n*=108)
Age (Yr)	59.2 ± 12.1	62.1 ± 10.8
Female/Male (Case)	71/31	67/41
Weight (kg)	67.3 ± 10.4	69.5 ± 11.4
Height (cm)	166.1 ± 8.2	167.4 ± 7.8
Blood pressure (mm Hg)		
Systolic	163.8 ± 25.1	159.9 ± 23.7
Diastolic	93.4 ± 14.2	92.9 ± 13.0
History of disease [Case (%)]		
Hypertension	85 (83.3)	80 (74.1)
Unknown	14 (13.7)	24 (22.2)
No history	3 (2.9)	4 (3.7)
Diabetes	10 (9.8)	12 (11.1)
Hyperlipidemia	5 (4.9)	6 (5.5)
Smoking history [Case (%)]	45 (44.1)	47 (43.5)
Alcohol use [Case (%)]	46 (45)	43 (39.8)
CM treatment history [Case (%)]	6 (5.8)	3 (2.7)
Western medicine treatment history [Case (%)]	28 (27.4)	16 (14.8)
Time from HICH to treatment (h)	10.9 ± 16.1	11.2 ± 15.0

characteristics between the two groups (Table 2).

Differences in hematoma size and site between the two groups were not statistically significant (*P*=0.983). The treatment group had 82 cases with hematoma in basal nuclei of brain (80 were small and 2 were medium), 10 in cranial lobe (8 small and 2 medium), 3 in encephalocoele (1 small and 2 medium), 4 small in cerebellum, and 3 small in brain stem. The control group had 83 cases with hematoma in basal nuclei of brain (79 were small, 3 were medium and 1 was large), 13 in cranial lobe (12 small and 1 medium), 4 in encephalocoele (2 small, 1 medium and 1 large), 5 small in cerebellum, and 3 small in brain stem.

Primary Outcomes

The rate of mRS 0-1 and mRS 0-2 at days 21 of treatment in the two groups showed no significant differences, while at 3 months of treatment the disability degree decreased remarkably in the treatment group (*P*<0.01, Table 3).

Table 3. Comparison of mRS Scores between Groups [Case (%)]

Group	Case	mRS 0-1		mRS 0-2	
		Day 21	3 months	Day 21	3 months
Treatment	102	49 (48)	74 (72.5)	65 (63.7)	82 (80.4)
Control	108	42 (38.9)	52 (48.1)	57 (52.8)	69 (63.9)
P-value		0.115	<0.0001	0.07	0.006

Secondary Outcomes

Average Barthel scores in the treatment group after 3 months of intervention were 89.11 ± 19.93, and in the control group 82.18 ± 24.02 (*P*=0.003). NIHSS scores of the treatment group at days 7, 21, and 3 months of treatment were decreased significantly compared with the control group (*P*<0.05; Table 4).

Table 4. Comparison of NIHSS Scores between Groups ($\bar{x} \pm s$)

Group	Time	Case	NIHSS score	*P*-value
Treatment	Baseline	102	8.19 ± 4.69	
	7 d	102	5.25 ± 3.93*	–2.94 ± 2.69△
	14 d	102	4.19 ± 3.87*	–4.00 ± 3.03
	21 d	102	3.42 ± 3.67*	–4.76 ± 2.94△
	3 months	102	1.90 ± 2.87*△	–6.28 ± 3.68△
Control	Baseline	108	7.88 ± 4.07	
	7 d	108	5.91 ± 4.61*	–1.97 ± 2.61
	14 d	108	4.72 ± 4.28*	–3.16 ± 2.71
	21 d	108	4.19 ± 4.37*	–3.69 ± 3.12
	3 months	108	3.07 ± 4.11*	–4.81 ± 3.33

Notes: *P<0.05, compared with baseline in the same group; △P<0.05, compared with the control group at the same time point

Areas of edema in the two groups were not significantly different (*P*>0.05). Hematoma volumes in the treatment group were markedly decreased than those in the control group (*P*<0.05; Table 5).

Patient-Reported Outcomes for Stroke Scores

Total scores for patient-reported outcomes in the treatment group at days 21 and 3 months of treatment was lower than the control group (*P*<0.05; Table 6).

Table 5. Hematoma Volume and Edema Area between Groups ($\bar{x} \pm s$)

Group	Case	Hematoma volume (cm^3)			Edema area (cm^2)		
		Baseline	7 d	D-value	Baseline	7 d	D-value
Treatment	102	12.86 ± 11.44	9.18 ± 10.65	3.68 ± 6.64	6.38 ± 4.50	8.75 ± 6.41	–2.37 ± 4.86
Control	108	13.02 ± 11.31	11.41 ± 13.13	1.61 ± 9.63	6.46 ± 5.45	9.05 ± 6.20	–2.59 ± 6.01
P-value		0.808	0.093	0.044	0.68	0.73	0.58

Table 6. Patient-Reported Outcomes for Stroke Scores ($\bar{x} \pm s$)

Group	Time	Total scores	Physical function	Mental status	Social condition	Satisfaction
Treatment	Baseline	38.72 ± 20.87	23.60 ± 13.23	8.83 ± 5.42	4.51 ± 3.35	3.64 ± 2.40
	7 d	35.34 ± 19.04	20.20 ± 12.35	7.25 ± 4.86	4.10 ± 2.95	3.07 ± 2.11
	14 d	29.27 ± 19.34	16.50 ± 12.41	5.75 ± 4.58	3.48 ± 2.72	2.67 ± 2.20*
	21 d	24.94 ± 19.26*	13.70 ± 11.92*	5.12 ± 4.87*	2.85 ± 2.68	2.59 ± 2.18*
	3 months	17.66 ± 18.21**	8.99 ± 10.64**	3.98 ± 4.77	1.85 ± 2.43*	2.21 ± 2.40**
Control	Baseline	38.78 ± 20.14	22.83 ± 12.58	8.54 ± 5.63	4.56 ± 3.27	4.05 ± 2.11
	7 d	37.91 ± 19.99	21.60 ± 13.14	7.51 ± 4.64	4.50 ± 2.93	3.64 ± 2.28
	14 d	31.51 ± 19.24	17.55 ± 12.32	6.50 ± 4.58	3.59 ± 2.52	3.31 ± 2.35
	21 d	29.60 ± 19.28	16.94 ± 12.19	6.29 ± 4.19	3.30 ± 2.64	3.32 ± 2.42
	3 months	25.04 ± 18.22	14.33 ± 11.20	4.38 ± 3.99	2.63 ± 2.62	3.17 ± 2.48

Notes: *P<0.05, **P<0.01, compared with the control group; D means difference.

Table 7. The Details of Adverse Events in In Two Groups

Group	Symptom	Degree	Case	Time of occurrence (treatment initiation)	Handling process/Continuation of study (yes or not)	Endpoint
Treatment	Pressure ulcer	Light	1	At Baseline	Symptomatic treatment/yes	Recovered
	Diarrhea	Light	1	Within 7 d	Symptomatic treatment/yes	Recovered
	Deep venous thrombosis	Light	1	Within 7 d	Transferred to another department/not	Recovered
	Allergic to Xingnaojing	Light	1	At Baseline	Stop using Xingnaojing / not	Recovered
	Femoral fracture	Medium	1	After 3 months	Symptomatic treatment / not	Recovered
	Kidney function decline	Severe	1	Within 21 d	Symptomatic treatment / yes	Death
	Hematoma enlargement	Severe	1	Within 7 d	Symptomatic treatment / yes	Death
Control	Stomach pain	Light	1	Within 14 d	Symptomatic treatment / yes	Recovered
	Hematoma enlargement	Medium	2	Within 7 d	Symptomatic treatment /yes	Improved
	Deterioration of disease and bleeding	Severe	1	Within 7 d	Symptomatic treatment /yes	Recovered
	Kidney function decline	Severe	1	Within 21 d	Symptomatic treatment /yes	Recovered
	Hematoma enlargement	Severe	2	Within 7 d	Symptomatic treatment /yes	Death

Safety Evaluation

There were 15 adverse events, 8 occurred in the treatment group and 7 in the control group (Tables 7). There were 4 deaths in the adverse events and 2 in each group respectively. The deaths were all resulted from cerebral hemorrhage within 21 days.

DISCUSSION

Therapeutic regimen of TRABC has proven to be effective in treating acute cerebral hemorrhage in both CM and Western medicine. In CM, cerebral hemorrhage is known as congestion outside meridians. In the acute stage, stasis outside of the vessels damages mental activity and generates phlegm and fluids by blocking transport and transformation of body fluids. Stasis, phlegm, and fluids combine and transform into a new pathogenic factor—toxic pathogen, which can destroy the brain violently and rapidly.[17] In the recovery phase, qi deficiency and blood stasis become the main pathogenic factors. Thus, if stasis can be removed through treatment in a timely manner, damage can be reduced. Based on these pathologic stages, our study used herbs such as *Panax notoginseng*, *Curcuma*

zedoaria (Christm.) *Roscoe*, and *Paeonia lactiflora* Pall to promote blood circulation to remove blood stasis. In addition, the patent medicine Xingnaojing was used to clear heat, resolve toxicity, and awaken the spirit (brain).[18] During the recovery stage, qi deficiency and blood stasis were addressed using a second patent medicine Naoxueshu whose actions are to enrich qi and activate blood circulation.

Hematoma enlargement and recurrence of bleeding are closely associated with intracranial pressure. Treatment based on activating blood circulation has been shown to be effective for re-bleeding. In particular, herbs with activate blood circulation action may inhibit platelet aggregation, relieve vasospasm, and improve the microcirculation around the hemorrhage to promote the resorption of hematoma and edema.[6]

Hematoma from cerebral hemorrhage produces secondary damage, such as perihematomal edema, cerebral hernia caused by high intracranial pressure, thrombin neurotoxin effects, nerve cell necrosis, and local inflammatory response.[19] Applying herbs with activate blood circulation action can decrease this secondary damage by reducing cerebral edema, decreasing cranial pressure, improving cerebral metabolism and local microcirculation, increasing nerve cell tolerance to hypoxia, and adjusting blood coagulation and fibrinolytic processes.[20,21]

Wider application of TRABC for the treatment of HICH is lacking due to concern for recurrence of bleeding. However, Zhu, et al[22] supported the immediate treatment of intracerebral hemorrhage with activating blood circulation herbs. In our clinical practice we found that when intracranial pressure and blood pressure is under control appropriately, application of TRABC treatment does not cause re-bleeding.

In this study, adverse events were not significantly different in the treatment and control groups, indicating that TRABC treatment for HICH is safe. We also found that TRABC treatment for HICH significantly reduced the area of hematoma, thus lessened post-hemorrhage neurologic deficits.

Limitations of our study include possible bias due to the center effect from variation in investigator capability and hospital care standards. In addition, patients with serious illness were not included, thus it is unknown whether TRABC treatment is safe for such patients. To resolve these issues, more studies are needed.

Conflict of Interests

None of authors received funding or research grants from the relevant drug manufacturers in this research. The authors declare that they have no conflict of interests.

Author Contributions

Gao Y, Zhang GM and Zhou L were involved in study design. Li QB, Li JY, Yuan LX, and Chen C contributed to study performance and data analysis. Li JY and Yuan LX wrote the manuscript. All authors read and approved the final manuscript.

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