Review Article

A Systematic Review and Meta-Analysis on the Treatment of Cerebral Hemorrhage with NaoXueShu Oral Liquid

Lijun Wu,1,2 Yanda Li,3,4 Xiaofeng Wang,1 Xiaomeng Ren,1 Haiyan Zhu,1 Yikun Sun,1 Yanwei Xing,4 Lingqun Zhu,1 Yonghong Gao,1 and Hongcai Shang1

1Key Laboratory of Chinese Internal Medicine of Ministry of Education and Beijing, Key Office of Encephalopathy TCM Research, Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, Beijing 100700, China
2Weishi Hospital of Traditional Chinese Medicine, Henan 475500, China
3Beijing University of Chinese Medicine, Beijing 100029, China
4GuangAnMen Hospital, China Academy of Chinese Medical Science, Beijing 100053, China

Correspondence should be addressed to Yonghong Gao; gaoyh7088@hotmail.com and Hongcai Shang; shanghongcai@126.com

Received 13 February 2017; Accepted 16 April 2017; Published 29 May 2017

Academic Editor: Alexander N. Orekhov

Copyright © 2017 Lijun Wu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

NaoXueShu oral liquid invigorates Qi and promotes blood circulation, which is mainly used for treating the acute stage of the meridian of hemorrhagic apoplexy and acute blood stasis syndrome during early convalescence. Its main clinical manifestations include hemiplegia, mouth askew, hemianesthesia, and inarticulateness. It is used mainly in patients with lobar hemorrhage, basal ganglia, and thalamus of the small amount of bleeding without disturbing consciousness of hypertensive cerebral. The purpose of this study was to evaluate the efficacy and adverse effects of NaoXueShu oral liquid on the treatment of cerebral hemorrhage. In this study, literature on randomized controlled trials was collected from seven databases to evaluate the clinical efficiency of the treatment of cerebral hemorrhage alone or combined with Western medicine. The methodologic quality of the included studies was assessed using a standard Cochrane system review and analyzed using RevMan 5.3.0 software. The study included 14 eligible randomized controlled trials. The results showed that the use of NaoXueShu oral liquid alone or combined with other drugs or auxiliary methods can play a significant role in the treatment of cerebral hemorrhage, especially hypertensive intracerebral hemorrhage.

1. Introduction

Intracerebral hemorrhage is a primary nontraumatic hemorrhage, commonly caused by high blood pressure. The mortality rate of patients with cerebral hemorrhage can reach 40% to 50%, and 75% of the survivors cannot live independently after 1 year, which seriously affects quality of life [1]. The main reason for cerebral hemorrhage with high mortality and high disability rates is cerebral edema after brain injury. It affects normal nerve function, increases intracranial pressure, and can form severe cerebral hernia when intracranial pressure increases. Therefore, it is very important to carry out early intervention for patients with cerebral hemorrhage.

NaoXueShu oral liquid’s main ingredients include astragalus root, leech, calamus, Achyranthes, and Rhizoma Chuanxiong; it is intended to replenish Qi and activate blood and remove blood stasis and is mainly used for hemorrhagic stroke in patients with Qi deficiency and blood stasis. It was developed according to the theory that “Qi is the commander of blood; blood is the mother of Qi” [2]. Astragalus is commonly used in Chinese medicine Yiqi, and modern research shows that astragalus can reduce brain damage of neuronal mitochondria after hemorrhage, inhibit neuronal apoptosis, and promote the recovery of neurological function. Moreover, astragalus can also protect the blood-brain barrier permeability, perform antioxidation, and prevent cerebral ischemia [3–5]. Leech has a broken blood and blood stasis eliminating effect; modern research shows that leech has a cerebral protective effect of anticoagulation, inhibiting platelet aggregation, improving blood rheology, and relieving acute brain injury and brain edema, among other benefits [6–8].
In recent years, experiments have shown that NaoXueShu oral liquid on cerebral vascular disease, especially in the treatment of cerebral hemorrhage, has shown advantages: it can regulate the expression of neuroprotective factor-related protein, reduce the release of inflammatory factors, inhibit free radical damage, inhibit apoptosis, thereby reducing the volume of hematoma, and alleviate cerebral edema. Improving cerebral energy metabolism promotes nerve function repair [9–13].

Modern medicine posits that the key to treating cerebral hemorrhage is to control hypertension, and we are currently studying whether calcium channel blockers, statins, endothelin receptor antagonists, magnesium, erythropoietin, and other drugs can prevent or reverse cerebral hemorrhage; however, evidence is still lacking [14, 15]. In recent years, NaoXueShu oral liquid has been widely used in clinics. Studies found that it can obviously promote the absorption of intracranial hematoma in the treatment of cerebral hem- orrhage [16]; promote the recovery of neurological function, especially affecting the treatment of apoplectic aphasia [17–19]; improve blood flow; reduce inflammatory response; effectively reduce brain edema; reduce intracranial pressure; improve the prognosis of patients; reduce the disability rate; and improve the survival rate [20–22].

This study's purpose is to conduct a comprehensive systematic review and evaluate the therapeutic effect of NaoXueShu oral liquid for treating cerebral hemorrhage.

2. Methods

This systematic review was conducted in accordance with the guidelines for systematic review and meta-analysis of the preferred reporting items. This systematic study does not require an ethical review.

2.1. Databases and Retrieval Strategies. In this study, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Scientific Journal Database, the Chinese Biomedical Literature (CBMdisc), Wanfang database, EMBase, PubMed, and the Cochrane database were searched for original studies and search was conducted in January 2017. The other related research studies were manually retrieved. The following key words were used alone or in combination: “NaoXueShu”; “NaoXueShu injection”; “nxst”; “cerebral hemorrhage”; “hemorrhagic stroke”; “hemorrhagic apoplexy.”

More studies were also searched for in the selected references. In addition, we used a flow chart to make the search process more rigorous and detailed (Figure 1).

2.2. Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria. The literature had no special requirements on the language, demographic characteristics, and types of publications. The included patients were not more than 80 years old, and the amount of bleeding was less than 50 mL; moreover, the patients had the basic clinical symptoms of cerebral hemorrhage and, after CT imaging examination, adhered to the clinical diagnostic criteria of cerebral hemorrhage. Oral administration of NaoXueShu oral liquid was 10 mL, oral or nasal feeding, 3 times a day, 1 month as a course of treatment. In the included randomized controlled trials (RCTs), the patients were treated with NaoXueShu alone or in combination with other drugs for treating cerebral hemorrhage. The literature included National Institutes of Health Stroke Scale (NIHSS) score combined with neurologic deficit or corresponding disease diagnostic criteria. The results of the first, second, and third were the efficacy evaluation, NIHSS score at 2 weeks and 4 weeks (in the literature there are descriptive differences of 30 days, 4 weeks, and 1 month; for the convenience of statistics, all of them were unified for 4 weeks), hematoma volume, BI, and GCS.

2.2.2. Exclusion Criteria. We excluded repeat publications in the same group of patients.

2.3. Data Screening and Quality Evaluation. We searched 513 published articles about NaoXueShu treatment of cerebral hemorrhage in 7 databases and excluded the literature that was not consistent and repeated. The remaining 24 articles were screened according to the following criteria: (1) whether the literature focused on patients with cerebral hemorrhage; (2) whether the included samples were randomized controlled studies; (3) whether the final study index of the literature met the requirements; (4) whether the grouping of the literature was scientific; (5) the author's experience of the literature; (6) the published year of the literature. Finally, we got 14 papers. Two authors (Lijun Wu and Xiaofeng Wang) independently performed the literature search, selection, and the data exaction. Any disagreements were discussed, and if the discussion did not yield a final decision, the 3rd author (Xiaomeng Ren) was invited to make a decision. The information included the following: title, author, publication time, literature sources, research scale, number of cases, diagnostic criteria, research methods, and treatment process. We also considered the control group, the results, and adverse reactions. To ensure the quality of the included literature, we used RevMan 5.3.0 software to evaluate the studies systematically and comprehensively. Eventually we obtained the “risk of bias graph” and “risk of bias summary” (Figures 2 and 3). The reliability of the results was further verified by using the forest map to evaluate the efficacy and the funnel plot to evaluate the publication bias.

2.4. Statistical Analysis. The RevMan 5.3.0 software provided by the Cochrane Collaboration was used for data analysis, and, through the study of the content and research indicators for classification, the final packet data entry was carried on. Dichotomous data were expressed as relative risk (RR); continuous outcomes were presented as weighted mean difference (WMD); and the 95% confidence intervals (CIs) were calculated for both. The meta-analysis was performed if the intervention and control groups, as well as the outcomes, were the same or similar. For the significant efficiency, we used Barthel index (BI), the odds ratio (OR) value, hematoma volume, NIHSS score, and Glasgow coma score (GCS), score mean difference (MD) value. According to the results of $I^2$,
we analyzed the data using random ($I^2 > 50\%$, heterogeneity) or fixed effects model ($I^2 < 50\%$).

### 3. Result

A total of 14 studies were incorporated into the information integration (Table 1) [16–18, 20, 21, 23–31].

#### 3.1. Characteristics of Included Studies

Initially, we retrieved 513 articles from 7 common databases. At present, NaoXueShu is mainly used in China clinical practice. We collected most of the articles from the Wanfang database and CNKI. In all the articles collected, we excluded duplicate, non-conforming, incomplete data. In addition, according to our requirements, 14 papers were included in the study. All the articles focused on treating cerebral hemorrhage in patients with NaoXueShu.

#### 3.2. Methodologic Quality of Included Studies

The selected articles were all screened and belonged to RCT literatures. By choosing 14 articles, we were able to consider a sample size greater than 30 cases. In the 14 articles, 10 were randomized by more scientific methods, including the use of blind method for 3 articles. In the literature, patients in the observation group and the control group had clear inclusion criteria or the patients’ data were initially analyzed statistically, if not statistically significant, to be included in the control group. We also objectively analyzed the offset risk, and we evaluated the offset of each article according to the relevant criteria of the offset table. In this process, we tried be objective and fair, especially in the “other biases” column. We were particularly
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other biases

0% 25% 50% 75% 100%
Low risk of bias
Unclear risk of bias
High risk of bias

Figure 2: Risk of bias graph. Each item was evaluated as a percentage of the literature, and the quality of the selected literature was evaluated according to the Cochrane criteria.

3.3. Effects of Interventions

3.3.1. Comparison of Hematoma Volume Change. The following 5 RCTs showed that NaoXueShu can effectively reduce cerebral hemorrhage and had statistical significance \( (n = 509; \text{MD}, -3.82; 95\% \text{CI}, -7.32\text{--}0.31; I^2 = 97\%; P = 0.03; \text{Figure 4}) \).

3.3.2. GCS Comparison. The following 2 RCTs showed that NaoXueShu had a certain effect in treating cerebral hematoma, had obvious function of arousal, and had statistical significance \( (n = 198; \text{OR}, 1.49; 95\% \text{CI}, 1.06\text{--}1.92; I^2 = 3\%; P < 0.00001; \text{Figure 5}) \).

3.3.3. NIHSS Score Comparison. The following 7 RCTs showed NaoXueShu oral liquid's effect on cerebral hemorrhage after 2 weeks and 4 weeks of nerve function protection. The results showed that, 2 weeks after treatment of cerebral hemorrhage, the difference was not statistically significant \( (P > 0.05) \), indicating that NaoXueShu did not show a significant effect in 2 weeks. But, after 4 weeks of treatment, NaoXueShu can improve nerve function to a certain extent and had statistical significance \( (n = 318; \text{MD}, -0.62 95\% \text{CI}, -1.25\text{--}0.02; I^2 = 0\%; P = 0.06; \text{Figure 6}) \) \( (n = 574; \text{MD}, -2.68; 95\% \text{CI}, -4.77\text{--}0.59; I^2 = 94\%; P = 0.01; \text{Figure 7}) \). In a comparison of 2 and 4 weeks of treatment, after cerebral hemorrhage, \( P \) value gets smaller and smaller, which showed that the difference between the treatment group and the control group increases.

3.3.4. BI Comparison. The following 2 RCTs showed that NaoXueShu had a certain effect in treating cerebral hematoma, and it can obviously improve the patient's quality of life and had statistical significance \( (n = 237; \text{OR}, 2.47; 95\% \text{CI}, 1.46\text{--}4.18; I^2 = 0\%; P = 0.0007; \text{Figure 8}) \).

3.3.5. Efficacy Comparison. The following 6 RCTs showed a good effect in treating cerebral hemorrhage compared with the control group and had statistical significance \( (n = 814; \text{OR}, 3.16; 95\% \text{CI}, 2.09\text{--}4.76; I^2 = 0\%; P < 0.00001; \text{Figure 9}) \).

3.3.6. Adverse Reactions. Included in the 14 articles, 2 RCTs were related to adverse reactions, neither of which mentioned the adverse effects of NaoXueShu, which meant this drug had no obvious side effects so far. Therefore, the authenticity and scientific nature of the literature, as well as the integrity of the information provided, have some credibility.

3.3.7. Publication Bias. We used Stata software to evaluate the articles’ publication bias. Because the indicators of GCS and the BI had only two included RCTs, did not meet the standard of the funnel map, and were without special significance, we conducted the migration analysis to the other 4 indexes and used the Egger method to conduct the diagnosis analysis. The results were shown as in Figure 10 and Table 2.

We used Stata software to conduct migration analysis on the included articles. The results showed that the hematoma volume, NIHSS score at 2 weeks, and efficiency comparison were not offset \( (P > 0.05) \), while the NIHSS score at 4 weeks shows a slight deviation \( (P < 0.05) \). Based on this, an NIHSS score at 4 weeks of the literature was removed one by one. We eventually found that when deleting the study by Wang and...
| Study                      | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other biases |
|---------------------------|--------------------------------------------|-----------------------------------------|----------------------------------------------------------|-----------------------------------------------|----------------------------------------|-------------------------------------|-------------|
| Chen et al. 2016          | +                                          | +                                       | +                                                        | +                                             | +                                      | +                                   | +           |
| Gu and Ma 2010            | ?                                          | ?                                       | +                                                        | +                                             | +                                      | ?                                   | ?           |
| Li et al. 2014            | ?                                          | -                                       | ?                                                        | +                                             | +                                      | +                                   | ?           |
| Lu et al. 2004            | ?                                          | -                                       | ?                                                        | +                                             | +                                      | ?                                   | ?           |
| Miao and Yan 2014         | ?                                          | -                                       | ?                                                        | +                                             | +                                      | +                                   | ?           |
| Wang et al. 2014          | ?                                          | -                                       | ?                                                        | +                                             | +                                      | +                                   | ?           |
| Wang and Ding 2014 (2)    | +                                          | +                                       | ?                                                        | +                                             | +                                      | +                                   | ?           |
| Wang and Zhao 2015        | -                                          | -                                       | ?                                                        | +                                             | +                                      | +                                   | ?           |
| Wang et al. 2015 (2)      | +                                          | +                                       | +                                                        | +                                             | +                                      | ?                                   | ?           |
| Wang et al. 2016          | +                                          | +                                       | ?                                                        | +                                             | +                                      | ?                                   | ?           |
| Xie et al. 2007           | -                                          | +                                       | +                                                        | +                                             | +                                      | ?                                   | ?           |
| Yang and Xue 2015         | ?                                          | -                                       | ?                                                        | +                                             | +                                      | +                                   | ?           |
| Y. Yuan and D. Yuan 2012  | -                                          | -                                       | ?                                                        | +                                             | +                                      | ?                                   | ?           |
| Zhou et al. 2015          | ?                                          | -                                       | ?                                                        | +                                             | +                                      | ?                                   | ?           |

**Figure 3:** Risk of bias summary: review authors’ judgments about each risk of bias item for each included study.
| Study                  | Sample size (treatment/control) | Diagnosis | Intervention Treatment | Treatment Control | Treatment course | Clinical standards                                                                 | Outcome measure                                                                 |
|-----------------------|---------------------------------|-----------|------------------------|-------------------|------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Y. Yuan and D. Yuan 2012 [23] | 60 (36; 24)                     | CH        | NaoXueShu + routine    | Naoxuekang + Conventional treatment | 30 days          | The standard of TCM and Western medicine                                             | Curative effect; hematoma absorption rate; integral value of neurological deficit; clinical symptom integral value of TCM |
| Wang et al. 2014 [24]                | 122 (64; 58)                    | HICH      | NaoXueShu + routine    | Conventional treatment | 4 weeks          | CH + standards (95)                                                                | GCS score; BI score; hematoma volume                                               |
| Xie et al. 2007 [25]                | 440 (310; 130)                  | HS        | NaoXueShu               | Naoxuekang         | 30 days          | TCM diagnostic code (96)                                                            | Stroke score; hematoma uptake; therapeutic effect                                   |
| Miao and Yan 2014 [26]               | 69 (35:34)                      | HICH      | NaoXueShu + routine    | Conventional treatment | 4 weeks          | CH standards (95) + CT                                                              | NIHSS score and curative effect                                                     |
| Lu et al. 2004 [27]                  | 140 (70; 70)                    | HICH      | NaoXueShu               | Naoxuekang         | 1 month          | WHO diagnostics; CT; diagnostic criteria of stroke in Chinese Medicine             | Hematoma uptake; stroke diagnosis score, NIHSS; 3-month mRS                        |
| Wang and Zhao 2015 [16]              | 30 (15; 15)                     | ACH       | NaoXueShu + routine    | Conventional treatment | 1 month          | CH standards (95)                                                                  | Neurological deficit score; clinical efficacy                                      |
| Gu and Ma 2010 [28]                  | 62 (32; 30)                     | CH        | NaoXueShu + routine    | Conventional treatment | 1 month          | CT                                                                                   | Curative effect; hematoma volume change (10, 20, 25)                              |
| Chen et al. 2016 [17]                | 67 (35; 32)                     | HICH      | NaoXueShu + routine    | Conventional treatment | 90 days          | Relevant standards of the Ministry of Health and criteria for diagnosis and treatment of stroke | Curative effect; hematoma volume change                                             |
| Wang and Ding 2014 (2) [29]          | 86 (43; 43)                     | CH        | NaoXueShu + routine    | Naoxuekang + Conventional treatment | 1 month          | Guidelines for prevention and treatment of cerebrovascular diseases in China (2005) | NIHSS score; BI score                                                                 |
| Wang et al. 2016 [30]                | 96 (48; 48)                     | HICH      | NaoXueShu + acupuncture + routine | Conventional treatment | 1 month          | WAB score; mRS score; NIHSS score; hemorheological indicators; (blood viscosity, fibrin, red blood cell index) | WAB score; mRS score; NIHSS score; hemorheological indicators; (blood viscosity, fibrin, red blood cell index) |
| Wang et al. 2015 (2) [18]            | 102 (51; 51)                    | Mixed stroke | NaoXueShu + routine    | Conventional treatment | 4 weeks          | CT and/or MRI                                                                         |                                                                                   |
| Zhou et al. 2015 [20]                | 170 (87; 83)                    | CH        | NaoXueShu + routine    | Conventional treatment | 90 days          | CT                                                                                   | ESS; Neurological deficit score; BI score                                          |
| Li et al. 2014 [31]                  | 76 (39; 37)                     | HICH      | NaoXueShu + routine    | Conventional treatment | 2 weeks          | CT                                                                                   | GCS score; Neurological deficit score                                              |
| Yang and Xue 2015 [21]               | 86 (43; 43)                     | HICH      | NaoXueShu + routine    | Conventional treatment | 4 weeks          | CH standards (95)                                                                    | NIHSS score; curative effect; hematoma                                             |
| Study or subgroup | Naoxueshu Mean | Control Mean | Weight | Mean Difference IV, random, 95% CI | Year |
|------------------|----------------|--------------|--------|----------------------------------|------|
| Lu et al. 2004   | 6.58 ± 5.15    | 70           | 8.77 5.2  | 20.6% -2.19 [−3.90, -0.48]      | 2004 |
| Xie et al. 2007  | 6.58 ± 5.15    | 310          | 7.77 5.2  | 21.2% -1.19 [−2.25, -0.13]      | 2007 |
| Wang et al. 2014 | 5 ± 1.25       | 64           | 2.53 58  | 21.4% -2.00 [−2.72, -1.28]      | 2014 |
| Wang and Zhao 2015 | 11.6 ± 8.5    | 30           | 9.4 30   | 15.9% -2.90 [−7.43, 1.63]       | 2015 |
| Chen et al. 2016 | 4.69 ± 1.38    | 35           | 15.31 36.4 34  | 21.0% -10.62 [−11.96, -9.28] | 2016 |
| Total (95%) CI | 5.15 ± 5.2     | 58           | 310 7.77 | 21.2% -3.82 [−7.32, -0.31]      |      |

Heterogeneity: $\tau^2 = 14.80$; $\chi^2 = 143.21$, df = 4 ($P < 0.00001$); $I^2 = 97$
Test for overall effect: $Z = 2.13$ ($P = 0.03$)

Figure 4: Comparison of hematoma volume.

| Study or subgroup | Naoxueshu Mean | Control Mean | Weight | Mean difference IV, fixed, 95% CI | Year |
|------------------|----------------|--------------|--------|----------------------------------|------|
| Li et al. 2014   | 14.08 ± 0.84   | 39           | 12.49 1.21 | 82.9% 1.59 [1.12, 2.06]      | 2014 |
| Wang et al. 2014 | 12 ± 3.25      | 64           | 1.25 58  | 17.1% 1.00 [−0.04, 2.04]      | 2014 |
| Total (95%) CI | 103 ± 95       | 100.0%       | 1.49 [1.06, 1.92] |                  |      |

Heterogeneity: $\chi^2 = 1.03$, df = 1 ($P = 0.31$); $I^2 = 3$
Test for overall effect: $Z = 6.81$ ($P < 0.00001$)

Figure 5: GCS comparison at 2 weeks.

| Study or subgroup | Naoxueshu Mean | Control Mean | Weight | Mean difference IV, random, 95% CI | Year |
|------------------|----------------|--------------|--------|----------------------------------|------|
| Miao and Yan 2014 | 16.12 ± 1.81   | 35           | 16.73 1.95 | 51.3% -0.61 [−1.50, 0.28]      | 2014 |
| Wang and Zhao 2015 | 12.7 ± 4.5    | 30           | 13.2 5.1  | 6.8% -0.50 [−2.93, 1.93]      | 2015 |
| Wang et al. 2015 (2) | 8.72 ± 7.09  | 48           | 10.57 4.81 | 6.8% -1.85 [−4.30, 0.60]      | 2015 |
| Wang et al. 2016 | 3.56 ± 2.49    | 48           | 3.97 2.87 | 35.1% -0.41 [−1.48, 0.66]      | 2016 |
| Total (95%) CI | 161 ± 157      | 100.0%       | -0.62 [−1.25, 0.02] |                  |      |

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.13$, df = 3 ($P = 0.77$); $I^2 = 0$
Test for overall effect: $Z = 1.90$ ($P = 0.06$)

Figure 6: NIHSS score comparison at 2 weeks.

| Study or subgroup | Naoxueshu Mean | Control Mean | Weight | Mean difference IV, random, 95% CI | Year |
|------------------|----------------|--------------|--------|----------------------------------|------|
| Lu et al. 2004   | 8.56 ± 5.45    | 70           | 10.67 5.38 | 16.6% -2.11 [−3.76, -0.46]      | 2004 |
| Miao and Yan 2014 | 6.61 ± 2.19   | 35           | 7.85 2.63 | 17.5% -1.24 [−2.38, -0.10]      | 2014 |
| Wang et al. 2015 (2) | 5.89 ± 5.74  | 48           | 9.69 7.31 | 14.2% -3.80 [−6.48, -1.12]      | 2015 |
| Wang et al. 2016 | 1.97 ± 1.02    | 48           | 3.01 2.01 | 18.2% -1.94 [−1.68, -0.40]      | 2016 |
| Yang and Xue 2015 | 9.37 ± 2.32   | 43           | 15.87 2.53 | 17.7% -6.50 [−7.53, -5.47]      | 2015 |
| Y. Yuan and D. Yuan 2012 | 5.73 ± 4.88 | 60           | 7.22 4.23 | 15.9% -1.49 [−3.34, 0.46]      | 2012 |
| Total (95%) CI | 304 ± 270      | 100.0%       | -2.68 [−4.77, −0.59] |                  |      |

Heterogeneity: $\tau^2 = 6.14$; $\chi^2 = 84.58$, df = 5 ($P < 0.00001$); $I^2 = 94$
Test for overall effect: $Z = 2.52$ ($P = 0.01$)

Figure 7: NIHSS score comparison at 4 weeks.
Zhao [16], the heterogeneity was significantly reduced (from 94% to 19%) and $P$ value was increased, indicating that the literature shows an offset in the efficiency comparison.

4. Discussion

Cerebral hemorrhage is a common cerebrovascular disease, commonly caused by hypertension. Primitive hematoma first appears after intracerebral hemorrhage, and the hematoma’s location and size are closely related to the prognosis, then perihematoma accompanied the emergence of edema. Decreased cerebral blood flow from the perihematoma or peripheral lesion may result in decreased oxygen extraction fraction and tissue ischemic injury, which may be related to the inflammatory process induced by the hematoma [32, 33]. Cerebral hemorrhage and cerebral ischemia belong to the category of “stroke” in the field of Chinese medicine. Chinese medicine’s definition of stroke is based on the deficiency of Qi and blood loss because of internal root, emotional disorders, eating Feiganhouwei, or excessive alcohol and tobacco use, causing the imbalance of yin and Yang and reversal of Qi and blood, blood stasis, or blood overflow pulse; therefore, Qi deficiency and blood stasis are the main mechanisms of acute stage and early recovery. NaoXueShu oral liquid’s main ingredients include astragalus root, leech, calamus, Achyranthes, and Rhizoma Chuanxiong, with the effect of tonifying Qi, activating blood, and removing blood stasis. It is suitable for treating cerebral hemorrhage.

NaoXueShu oral liquid is relatively extensive in clinical application. Relevant literature can be found about NaoXueShu, among which the clinical research literature was far greater than experimental studies. This document’s purpose is to understand the NaoXueShu’s effect of the treatment of cerebral hemorrhage. We divided the literature into five categories: volume of hematoma, GCS, BI, NIHSS score of the patients in each stage (for a period of 2 weeks and 4 weeks), and the curative effect.

There are some advantages and disadvantages of the meta-analysis and the system evaluation: we had a detailed record of the process of selecting the documents. Most included literature was published in Chinese journals. In addition to a small part of the poor quality of literature, most literature was published in more well-known publications with recent publication years. Besides Xie et al. [25] and Lu et al. [27], which were published before 2010, other literatures were published after 2010. In addition, the evaluation system still has many deficiencies: the quality of literature was low, the content was not comprehensive enough (e.g., most of the included RCTs were without follow-up and adverse reactions), and assessment of the neurological function score may be influenced by the subjective factors in the process; therefore, the consistency of the data may differ between documents. $I^2$ is a measure of heterogeneity. The greater $I^2$, the greater the heterogeneity [34]. According to the statistical results, the heterogeneity of hematoma volume (Figure 4) and NIHSS
score at 4 weeks (Figure 7) was 97% and 94%, respectively. The reasons for the high heterogeneity may be related to the number of samples, the quality of the literature, the subject of study, and the duration of treatment. In addition, compared with the two classification variables, high heterogeneity is more common in continuous variables [35], and the volume of hematoma and NIHSS score at 4 weeks were continuous variables, and the possibility of heterogeneity was relatively large. Other GCS of 2 weeks (Figure 5), NIHSS score of 2 weeks (Figure 6), BI of 90 days (Figure 8), and evaluation of the effect (Figure 9) were 3%, 0%, 0%, and 0%, respectively; since they were less than 50%, or even close to 0%, these outcomes cannot have obvious heterogeneity and the results were reliable and relatively stable. However, although there
are two indicators of heterogeneity, $P$ value of each index is less than 0.05, indicating that the study of NaoXueShu oral liquid in the above indicators is statistically significant.

5. Conclusion

NaoXueShu oral liquid is made of BuYangHuanWu decoction from The Errors in Medicine Corrected and Rhubarb Magic Pill from the Golden Chamber. It is mainly used for removing blood stasis, supplementing tonifying Qi, and activating blood circulation. According to the pathogenesis, “where the bleeding must leave the meridians, blood stasis is left meridian” and the guidelines that state, “Qi is the commander of blood, blood is the mother of Qi, blood gas runs, qi stagnation and blood stasis.” NaoXueShu mainly treated stroke with Qi deficiency and blood stasis. In recent years, it has often been used to treat cerebrovascular disease, and the experimental results show that NaoXueShu oral liquid can obviously improve cerebral microcirculation, inhibit apoptosis, and inhibit oxygen free radicals and protect brain cells function. Clinical study also showed that NaoXueShu oral liquid can reduce the volume of hematoma, improve the recovery of nerve function, reduce brain edema, relieve inflammatory reaction, and promote the prognosis of patients with cerebral hemorrhage.

In conclusion, according to preliminary statistics and evaluation of 14 included studies, we concluded the following: NaoXueShu oral liquid in the treatment of acute cerebral hemorrhage had more obvious effects than conventional medical treatment ($P < 0.01$). To a certain extent, it can promote the absorption of hematoma in the brain and then rapidly reduce the brain hematoma volume ($P < 0.05$); however, Wang and Zhao [16] suggested that the absorption of intracranial hematoma did not represent an improvement in clinical outcome. Compared with the control group, there was no obvious advantage in the treatment of cerebral hemorrhage from 2 weeks with NIHSS ($P > 0.05$). However, compared with the NIHSS ($P < 0.05$) of 4 weeks and BI ($P < 0.01$) after 90 days, we found that NaoXueShu oral liquid can reduce the neurological damage and improve the prognosis. With NaoXueShu, drug taking time prolonged and the differences between the two groups increased gradually, which showed that long-term use can improve the neurological dysfunction of patients and their quality of life and living ability.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| ACH          | Acute cerebral hemorrhage |
| BI           | Barthel Index |
| CNKI         | Chinese National Knowledge Infrastructure |
| CBMdisc      | Chinese Biomedical Literature Database |
| CT           | Computer Tomography |
| CI           | Confidence interval |
| CH           | Cerebral hemorrhage |
| Coef.        | Coefficient |
| GCS          | Glasgow coma scores |
| HICH         | Hypertensive intracerebral hematoma |
| HS           | Hemorrhagic stroke |
| MD           | Mean difference |
| mRS          | Modified Rankin scale |
| NIHSS        | National Institutes of Health Stroke Scale |
| OR           | Odds ratio |
| RCTs         | Randomized controlled trials |
| RR           | Relative risk |
| Std. Ef.:     | Standard Effect |
| Std. Err.:    | Standard Error |
| TCM          | Traditional Chinese Medicine |
| VIP          | The Chinese Scientific Journal Database |
| WMD          | Weighted mean difference |
| WHO          | World Health Organization |
| WAB          | Western aphasia battery |
| ESS          | European Stroke Scale |

Conflicts of Interest

The authors declared that there are no conflicts of interest.

Authors’ Contributions

Lijun Wu, Yanda Li, Xiaofeng Wang, Xiaomeng Ren, and Haiyan Zhu contributed equally to this work.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (no. 81673899) and the outstanding project of Beijing University of Chinese Medicine (2015-JYB-XJQ001).

References

[1] D. Klebe, D. McBride, J. J. Flores, J. H. Zhang, and J. Tang, “Modulating the immune response towards a neuroregenerative peri-injury milieu after cerebral hemorrhage,” Journal of Neuroimmune Pharmacology, vol. 10, no. 4, pp. 576–586, 2015.

[2] C. Chen, L. X. Yuan, and G. M. Zhang, “Clinical application and experimental research progress of nao-xue-shu oral liquid in cerebrovascular disease,” Chinese Journal of Integrated Traditional Chinese and Western Medicine, vol. 12, no. 8, pp. 1005–1006, 2014.

[3] D. K. Wang, H. Y. Zhang, H. Y. Liu et al., “Analyses on stereology of mitochondrion of neurons that surround intracerebral hemorrhage in rats and the neuroprotective effect of astragalus injection for intracerebral hemorrhage,” Chinese Journal of Clinical Anatomy, vol. 31, no. 6, pp. 692–695, 2013.

[4] H. Y. Liu, Z. Sun, D. K. Wang et al., “The inhibition of astragalus and salvaike miltiirohiae injection on the neuronal apoptosis of the penumbra around the intracerebral hemorrhage in rats,” Lishizhen Medicine and Materia Medica Research, vol. 23, no. 8, pp. 1892–1895, 2012.

[5] J. Cai, R. Pan, X. Jia et al., “The combination of astragalus membranaceus and ligustrine ameliorates micro-haemorrhage by maintaining blood-brain barrier integrity in cerebrally ischaemic rats,” Journal of Ethnopharmacology, no. 158, pp. 301–309, 2014.

[6] K. M. Li, G. Zhang, and J. B. Wu, “Overview of pharmacological research of leech,” Traditional Chinese Medicine Research, vol. 20, no. 2, pp. 62–64, 2007.
[7] Y. Zhang, J. C. Feng, J. Wu et al., "Protective effects of hirudin on acute experimental intracerebral hemorrhage," *China Journal of Chinese Materia Medica*, vol. 31, no. 1, pp. 69–72, 2006.

[8] H. Dong, J. X. Ren, J. J. Wang et al., "Chinese medicinal leech: ethnomedical pharmacology, phytochemistry, and pharmacological activities," *Evidence-Based Complementary and Alternative Medicine*, vol. 2016, Article ID 7895315, 11 pages, 2016.

[9] X. Ai and C. Liu, "Effect of nao-xue-shu oral liquid on the volume of hematoma in rats with cerebral hemorrhage and the protective effect of nerve function," *Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease*, vol. 12, no. 7, pp. 859–861, 2014.

[10] L. Sun, Y. B. Liu, L. Wang et al., "Effect of Astragalus Injection on expression of BDNF in cerebral ischemia reperfusion injury in rats," *World Chinese Medicine*, vol. 11, no. 4, pp. 686–689, 2016.

[11] B. Chen, X. Y. Miao, and W. Shi, "Effect of Naoxueshu on the expression of esophageal cancer related gene 4 in choroid plexus epithelial cells in intracerebral hemorrhage rats," *China Medicine*, vol. 11, no. 2, pp. 1713–1717, 2016.

[12] Y. Hu, Y. H. Zhang, and C. X. Liu, "Effects of Nao-Xue-Shu oral liquid on cerebral function and apoptosis of peripheral penumbra after intracerebral hemorrhage in rats," *Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease*, vol. 14, no. 15, pp. 1735–1737, 2016.

[13] X. Ai and C. Liu, "Neuroprotective effects of Nao-Xue-Shu oral liquid on acute cerebral infarction in rats," *Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease*, vol. 13, no. 11, pp. 1278–1280, 2015.

[14] P. Adamczyk, S. He, A. P. Amar, and W. J. Mack, "Medical management of cerebral vasospasm following aneurysmal subarachnoid hemorrhage: a review of current and emerging therapeutic interventions," *Neurology Research International*, vol. 2013, Article ID 462491, 10 pages, 2013.

[15] G. Grasso, C. Alafaci, R. L. Macdonald et al., "Management of aneurysmal subarachnoid hemorrhage: state of the art and future perspectives," *Surgical Neurol Internation*, no. 8, p. 11, 2017.

[16] X. G. Wang and X. Q. Zhao, "Paired study on the treatment of acute cerebral hemorrhage with nao-xue-shu oral liquid," *Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease*, vol. 13, no. 7, pp. 937–938, 2015.

[17] S. J. Chen, H. Y. Wang, Y. Zuo et al., "Clinical observation on the treatment of secondary brain damage after intracerebral hemorrhage by Nao-Xue-Shu oral liquid," *Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease*, vol. 14, no. 2, pp. 199–202, 2016.

[18] M. Z. Wang, L. Zhang, W. F. Jiang et al., "Clinical observation of nourishing qi, resolving stagnation, cooling blood and eliminating phlegm method in treating aphasia of mixed stroke," *Journal of Shanghai University of Traditional Chinese Medicine*, vol. 29, no. 3, pp. 23–26, 2015.

[19] Y. Yan, M. Wang, L. Zhang et al., "Nao-Xue-Shu oral liquid improves aphasia of mixed stroke," *Evidence-Based Complementary and Alternative Medicine*, vol. 2015, Article ID 709568, 6 pages, 2015.

[20] X. W. Zhou, Y. Zuo, S. J. Chen et al., "Observation of clinical effect of nao-xue-shu oral liquid on patients with basal ganglia hemorrhage," *Shanghai Medical Journal*, vol. 44, no. 7, pp. 866–867, 2015.

[21] Y. Q. Yang and T. Xue, "Clinical study on naoxueshu oral liquid combined with nimodipine in treatment of hypertensive cerebral hemorrhage," *Drugs & Clinic*, vol. 30, no. 11, pp. 1341–1344, 2015.

[22] H. Jiang, Y. Qin, T. Liu et al., "Nao-xue-shu oral liquid protects and improves secondary brain insults of hypertensive cerebral hemorrhage," *Evidence-Based Complementary and Alternative Medicine*, vol. 2016, Article ID 9121843, 6 pages, 2016.

[23] Y. Yuan and D. Yuan, "HuoxyueYiqi huatan qingre treatment of hemorrhagic stroke clinical research," *Chinese Journal of Aesthetic Medicine*, vol. 21, no. 9, pp. 189–190, 2012.

[24] S. X. Wang, R. X. Song, Z. Wang et al., "Evaluation of clinical effect of naoxueshu oral liquid on hematoma absorption," *Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease*, vol. 12, no. 4, pp. 452–453, 2014.

[25] D. Z. Xie, B. Y. Xu, Y. Sun et al., "Naoxueshu Liquid for Hemorrhagic Stroke," *Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease Journal*, vol. 5, no. 8, pp. 690–691, 2007.

[26] W. C. Miao and R. Yan, "Clinical observation on the treatment of hypertensive cerebral hemorrhage with naoxueshu oral liquid," *Chinese Journal of Practical Nervous Diseases*, vol. 17, no. 14, pp. 102–103, 2014.

[27] M. Lu, R. P. Xie, and Y. Fu, "Effect of naoxueshu oral liquid on cerebral hemorrhage caused by hypertension," *Chinese Journal of Rehabilitation Theory and Practice*, vol. 10, no. 5, pp. 304–305, 2004.

[28] Y. Y. Gu and Y. Ma, "Naoxueshu oral liquid for the treatment of cerebral hemorrhage in 32 cases," *Henan Traditional Chinese Medicine*, vol. 30, no. 10, pp. 982–983, 2010.

[29] Z. Y. Wang and Z. C. Ding, "Application of huoxyue yiqi huatan tongluo treatment of cerebral hemorrhage in patients with clinical observation," *Contemporary Medicine Forum*, vol. 12, p. 8, 2014.

[30] H. Wang, X. Z. Niu, and T. S. Su, "Clinical observation on the treatment of cerebral hemorrhage in convalescent stage with acupuncture combined with naoxueshu oral liquid," *World Latest Medicine Information*, vol. 16, no. 3, pp. 110–111, 2016.

[31] S. H. Li, X. H. Han, G. Y. Jiang et al., "Clinical observation on the treatment of hypertensive cerebral hemorrhage with minimally invasive surgery of intracranial hematoma combined with naoxueshu oral liquid," *Chinese Journal of Practical Nervous Diseases*, vol. 17, no. 17, pp. 82–83, 2014.

[32] C. Herweh, E. Jüttler, P. D. Schellinger et al., "Evidence against a perihemorrhagic penumbra provided by perfusion computed tomography," *Stroke*, vol. 38, no. 11, pp. 2941–2947, 2007.

[33] H. B. Brouwers and J. N. Goldstein, "Therapeutic strategies in acute intracerebral hemorrhage," *Neurotherapeutics*, vol. 9, no. 1, pp. 87–98, 2012.

[34] D. Wang, J. X. Zhai, Z. Y. Mou et al., "Discussing on the research of heterogeneity in meta-analysis," *Chinese Journal of Evidence-Based Medicine*, vol. 9, no. 10, pp. 1115–1118, 2009.

[35] A. C. Alba, P. E. Alexander, J. Chang, J. Macisaa, S. Defry, and G. H. Guyatt, "High statistical heterogeneity is more frequent in meta-analysis of continuous than binary outcomes," *Journal of Clinical Epidemiology*, vol. 70, pp. 129–135, 2016.