Role of Xingnaojing combined with naloxone in treating intracerebral haemorrhage

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Xingnaojing injection (XNJ) sharpen the mind and induce consciousness and are widely used in acute phases of intracerebral hemorrhage (ICH). Naloxone hydrochloride injection (NX) performs equally well and replace the effects of morphine-like substances to promote conscious awareness. The applications of XNJ combined with NX for ICH show some advantages compared with NX applied individually. The aim of this systematic review is to evaluate the effectiveness and safety of XNJ combined with NX for ICH.

Methods: Comprehensive searches were conducted in 8 medical databases (PubMed, Cochrane Library, Web of Science, Embase, CNKI, VIP, CBM and Wanfang database) from inceptions to October 2017 for randomized controlled trials (RCTs) that compared the applications of XNJ and NX with NX applied individually in ICH. Literature screening, assessing risk of bias and data extraction were conducted by 2 reviewers independently. According to the Cochrane Collaboration’s RevMan5.3 software to perform the data analysis.

Results: 32 RCTs (3068 cases) were selected and the quality of studies were low. All trials compared XNJ and NX with NX applied individually. The overall meta-analysis results showed that XNJ combined with NX have significant effect on clinical efficacy (OR 3.78, 95% CI: 3.03–4.73; P < .00001), GCS score (MD 3.86, 95% CI: 3.46–4.25; P < .00001), coma duration (MD −5.59, 95% CI: −6.96 to −4.22; P < .00001), NIHSS score (MD −6.24, 95% CI: −8.05 to −4.42; P < .00001), Barthel Index score (MD 14.12, 95% CI: 6.7–21.54; P < .0002), cerebral hematoma volume (MD −6.05, 95% CI: −8.65 to −5.24; P < .00001) than NX applied individually. Adverse events reported in 4 studies and included mild discomfort symptoms.

Conclusion: The effectiveness and safety of XNJ combined with NX for ICH cannot be determined due to the low quality of literature, publication bias and heterogeneity. More rigorous RCTs are necessary to verify the role of XNJ combined with NX in the treatment of ICH.

Abbreviations: ADL = activities of daily living, AKI = acute kidney injury, CI = confidence intervals, CNS = central nervous system, GCS = Glasgow coma scale, GOS = Glasgow outcome scale, ICH = intracerebral hemorrhage, NDS = Neurological Dysfunction Score, NIHSS = National Institute of Health Stroke Scale, OR = odds ratio, RCTs = randomized controlled trials, TCM = traditional Chinese medicine, TER = total effective rates, TNF-α = tumor necrosis factor-alpha, XNJ = xingnaojing injection.

Keywords: Intracerebral haemorrhage, naloxone, systematic review, xingnaojing.
1. Introduction

Intracerebral haemorrhage (ICH) is characterized by brain parenchymal hemorrhage, with lesions locating in small intracerebral arteries and arterioles. ICH can be induced by hypertension, cerebral amyloid angiopathy, and other risk factors. The primary pathological injuries are related to the occupied destruction of local brain tissue, whereas the secondary injuries of perihematomal oedema and inflammatory may potentially cause further neurological deterioration. ICH severity is variable due to the differences in hematoma volumes, bleeding sites and related risk factors. Typically, the highest mortality of ICH accounts for 10% to 15% in stroke patients. Notably, many elderly patients cannot tolerate anaesthesia or operation. In addition, the long-term application of dehydration drugs is associated with the risk of causing acute kidney injury (AKI). For instance, retrospective studies published in 2014 and 2015 had estimated the risk of causing acute kidney injury (AKI) as high as 30% to 50% in spite of the adopted comprehensive treatment, while the disability is up to 75%.[6]

2. Methods

2.1. Database and search strategy

To conduct literature searches and gather results, we strictly followed the guidelines recommended in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (i.e., PRISMS statement). We retrieved the databases using the combination of keywords and free-words (PubMed, Cochrane Library, Web of Science, Embase, CNKI, VIP, CBM, and Wanfang database). The search period was from inception to October 2017, which of the languages are Chinese and English.

PubMed search strategy:
(1) cerebral haemorrhage OR intracerebral haemorrhage OR hemorrhagic stroke OR hypertensive intracerebral haemorrhage OR hemorrhagic apoplexy OR cerebral brain haemorrhage (in full text);
(2) xingnaojing OR xingnaojing injection (in full text);
(3) naloxone OR naloxone hydrobromide OR naloxon curamed OR naloxone hydrochloride dihydride OR naloxone hydrochloride (in full text);
(4) clinical trial OR controlled clinical trial OR randomized controlled trial (in full text);
(5) #1 AND #2 AND #3 AND #4.

2.2. Inclusion criteria

We used the following criteria to filter the retrieved results at the initial stage of the study searches:
(1) The included studies were RCTs published in English or Chinese Journals;
(2) Clinical symptoms and signs of patients were in line with diagnostic criteria, referred to Chinese guidelines for cerebrovascular disease prevention and treatment, or were diagnosed as acute intracerebral haemorrhage by computed tomography (CT) or magnetic resonance imaging (MRI), or other recognized diagnostic criteria.
(3) The control groups were treated with NX (2–4 mg, 1–2 times a day) on the basis of conventional therapy to decrease intracranial pressure, prevent infection or symptomatic treatment. The treatment group was given XNJ (20 mg, 1–2 times a day) on the foundation of the control group. Treatment periods were at least 10 days in duration.
(4) The primary outcome measurement was the total effective rates (TER) evaluated by differences in means of change-from-baseline in the Glasgow Coma Scale (GCS), which the
| Included studies       | Randomized sample size | Gender (M/F) | Age (years), range, mean (SD) | Cerebral hematoma volume, mean (SD) (ml) | Cerebral hematoma volume, mean (SD) (ml) | Intervention (route of administration, dosage) | Control (route of administration, dosage) | Treatment duration (days) | Outcomes | Adverse events (number of events) |
|------------------------|------------------------|--------------|-------------------------------|------------------------------------------|------------------------------------------|-----------------------------------------------|------------------------------------------|----------------------------|------------|-------------------------------|
| Song XX 2014 [33]     | 40/40                  | I: 24/16     | C: 25/15                      | I: 60.36 ± 6.72                          | C: 61.27 ± 6.63                          | XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day) | NX 4 mg (intravenous infusion, each time, once per day) | 14            | A+B+C                         | NS                       |
| Chen J 2016 [34]      | 30/30                  | Total: 32/28 | NS                            | I: 62.3 ± 2.4                             | C: 62.1 ± 2.0                            | XNJ 20 ml (intravenous infusion, each time, 2 times a day) | NX 4 mg (intravenous infusion, each time, once per day) | 15            | D+E                            | I: 2 cases C: 5 cases (Not described in detail) |
| Ding SX 2015 [35]     | 55/55                  | I: 31/24     | C: 33/22                      | I: 59.8 ± 6.3                             | C: 60.5 ± 6.9                            | XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day) | NX 4 mg (intravenous infusion, each time, once per day) | 14            | D+F+G                         | NS                       |
| Fan WP 2014 [36]      | 34/34                  | I: 24/10     | C: 25/9                       | I: 55.53 ± 1.47                          | C: 54.57 ± 1.08                          | XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day) | NX 4 mg (intravenous infusion, each time, once per day) | 14            | A+C+D                         | NS                       |
| Song XJ 2015 [37]     | 55/55                  | Total: 67/43 | I: 56.4 ± 4.7                 | Total: 10 to 30 ml (19), 31 to 70 ml (26), over 71 ml (65) | NS                                       | XNJ 20 ml (intravenous infusion, each time, 2 times a day) | NX 4 mg (intravenous infusion, each time, once per day) | 15            | D+H                            | NS                       |
| Wang Y 2014 [38]      | 45/45                  | I: 23/22     | C: 29/16                      | I: 55 ± 13.6                              | C: 57 ± 16.1                             | XNJ 20 ml and NX 2 mg (intravenous infusion, each time, once per day) | NX 2 mg (intravenous infusion, each time, once per day) | 15            | D+F+I                         | NS                       |
| Cheng L 2015 [39]     | 60/59                  | I: 37/23     | C: 36/24                      | I: 58.92 ± 7.48                          | C: 60.05 ± 8.36                          | XNJ 20 ml and NX 2 mg (intravenous infusion, each time, administered every 12 hours) | NX 2 mg (intravenous infusion, each time, administered every 12 hours) | 14            | D+E+F+G                       | I: nausea and vomit (3), skin itch (2), dizziness (2), tachycardia (1), C: nausea and vomit (4), arrhythmia (1), irritability (2) |

**Figure 1.** Characteristics of the included studies in the meta-analysis. I: intervention group, C: control group, M/F: male/female, SD: standard deviation, NS: not stated, GCS: Glasgow coma scale, XNJ: xingnaojing, NX: naloxone, A = Glasgow coma scale (GCS), B = cerebral hematoma volume, C = awake time, D = total effective rate (TER), E = adverse events, F = National Institute of Health Stroke Scale (NIHSS), G = The Barthel index, H = clinical neurological deficit score (NDS), I = activities of daily living (ADL). The average dose of XNJ was 10 to 20 milliliters of intravenously guttae.
**Table 1.**

| Study  | Year | Treatment | Initial Blood Pressure | Final Blood Pressure | Follow-up Time | Treatment Duration | Blood Pressure Change |
|--------|------|-----------|------------------------|----------------------|-----------------|--------------------|----------------------|
| Luo XJ | 2014 [40] | XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day) | 68.8 ± 4.2 | 93.2 ± 4.7 | 1.5 | 14 | A+B+C+D NS |
| Dong TY | 2016 [41] | NX 4 mg (intravenous infusion, each time, once per day) | 64.28 ± 4.41 | 75.26 ± 4.41 | 1.5 | 14 | A+B+D NS |
| Zhu L | 2015 [42] | NX 4 mg (intravenous infusion, each time, once per day) | 62.1 ± 1.2 | 70.2 ± 1.8 | 1.5 | 14 | A+B+I NS |
| Nie M | 2015 [43] | NX 4 mg (intravenous infusion, each time, once per day) | 62.47 ± 7.93 | 73.62 ± 8.16 | 1.5 | 14 | A+B+D NS |
| Zhu JN | 2012 [44] | NX 4 mg (intravenous infusion, each time, once per day) | 57.8 ± 5.6 | 66.6 ± 7.0 | 1.5 | 14 | A+B+D NS |
| Wang K | 2015 [45] | NX 4 mg (intravenous infusion, each time, once per day) | 35.9 ± 3.8 | 43.6 ± 4.7 | 1.5 | 14 | A+B+C+D NS |
| Qiang MC | 2016 [46] | NX 4 mg (intravenous infusion, each time, once per day) | 59.28 ± 5.62 | 67.28 ± 8.02 | 1.5 | 14 | B+C+D NS |
| Zhu WR | 2015 [47] | NX 4 mg (intravenous infusion, each time, once per day) | 63.14 ± 4.0 | 71.38 ± 4.0 | 1.5 | 14 | A+B+C+D NS |
| Long XB | 2015 [48] | NX 4 mg (intravenous infusion, each time, once per day) | 60.6 ± 9.3 | 69.2 ± 9.5 | 1.5 | 14 | D+F+G NS |
| Li HL | 2016 [49] | NX 4 mg (intravenous infusion, each time, once per day) | 59.3 ± 4.7 | 68.8 ± 4.5 | 1.5 | 14 | D NS |
| Ye G | 2013 [50] | NX 4 mg (intravenous infusion, each time, once per day) | 63.12 ± 4.02 | 71.23 ± 4.12 | 1.5 | 14 | A+B+C+D NS |

**Figure 1.** Continued.
| Author    | Year  | Group | Detailed Description                                                                                                                                 |
|-----------|-------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zhang F   | 2011  | 50/50 | I: 63.12 ± 4.02 C: 61.21 ± 8.22 XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day)                                                                 |
| Guan XD   | 2015  | 40/40 | I: 34.2 ± 3.19 C: 33.2 ± 4.12 XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day)                                                                 |
| Song GN   | 2015  | 32/31 | Total: 44/36 I: 34.4 ± 2.1 C: 33.7 ± 1.3 XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day)                                                                 |
| Zhang ZH  | 2015  | 79/79 | NS I: 63.2 ± 2.2 C: 63.2 ± 2.2 XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day)                                                                 |
| Hou JX    | 2014  | 32/32 | Total: 68/34 I: 34.5 ± 3.4 C: 33.5 ± 4.3 XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day)                                                                 |
| Huang SM  | 2014  | 52/50 | Total: 10 to 30 ml (15), 31 to 70 ml (18), over 71 ml (69) XNJ 20 ml (intravenous infusion, each time, 2 times a day)                                                                 |
| Pan JX    | 2016  | 48/48 | I: 61.48 ± 5.64 C: 61.57 ± 4.15 XNJ 20 ml and NX 2.4 mg (intravenous infusion, each time, 2 times a day)                                                                 |
| Hen JF    | 2010  | 50/50 | I: 64.10 ± 10.02 C: 54.65 ± 10.53 XNJ 20 ml and NX 2 mg (intravenous infusion, each time, once per day)                                                                 |
| Huang C   | 2016  | 33/33 | NS NS XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day)                                                                                                                      |
TER was defined as GCS score reached 3 points at least, awaken consciousness, patients of ICH cannot fully take care of themselves and need care assistance. The therapeutic evaluation criteria assess as follows:

(1) Clinical cure as GCS score reached 5 points, the nervous system functions recovery well and self-reliant completely;

(2) Markedly effective as GCS score reached 4 points, part of the intellectual and neurological damage and could take care of themselves basically;

(3) Effective as GCS score reached 3 points, awaken consciousness, patients of ICH cannot take care of themselves completely and need care assistance;

(4) Ineffective as GCS score reached 2 points, and patient of ICH is in a vegetative state, and

(5) Death as GCS score was 1 point. The total number of "cure, markedly effective, effective" were used to calculate total effective rate.

The second outcome included score changes on GCS, awake time, National Institute of Health Stroke Scale (NIHSS), Barthel Index (BI), Neurological Dysfunction Score (NDS), ADL, hematoma volume, adverse events, or other measurement indicators.

### 2.3. Exclusion criteria

The following situations were excluded:

(1) Repeatedly published studies, case reports or reviews;

(2) Intervention measures in the control group where TCM preparations;

(3) Patients with cerebral haemorrhage were in a recovery period.

### 2.4. Study selection and management

The data extraction table was formulated and extracted by 2 researchers (Y-MX and X-CW). Extract content includes the title, author, date of publication, literature sources, sample sizes, baseline data of subjects (age, gender, hematoma volume and state of consciousness), diagnostic criteria, interventions, treatment period, outcomes and the adverse events. In the case of disagreements on data extraction after cross-checking, researchers (Y-MX and X-CW) discussed and reached a consensus with the senior author (W-XL). One researcher (Y-MX) contacted the corresponding author via e-mail or telephone to confirm and request information when literature data and outcomes were uncertain.

The RCTs included in this meta-analysis were evaluated on methodological quality according to the Cochrane Handbook for Systematic Reviews of Intervention, which mainly include 7 components: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Quality assessments were carried out.
independently by the researchers (Y-MX, X-CW), and the resolution was sought from the senior author (W-XL) when the discrepancy occurred.

2.6. Data analysis

Statistical analyses were performed using Review Manager [Computer program] Version 5.3, (RevMan5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The model of random-effects or fixed-effects was applied to gather the effect estimates. The odds ratio (OR) was used to analyze the dichotomous data, and the mean difference (MD) was used for the analysis of continuous data, both comprising 95% confidence intervals (CI). The heterogeneity between the studies was examined by the $\chi^2$ test. The random-effects model was applied to the meta-analysis with significant heterogeneity ($P<.1$ and $I^2>50\%$). Simultaneously, the application of subgroup analysis and sensitivity analysis to explore the sources of heterogeneity. Homogeneity studies were performed using a fixed-effects model for meta-analysis. When the number of studies was more than 10, a funnel analysis was used to determine whether there was publication bias. In addition, Egger’s test detected the publication bias when the study numbers were less than 10 or fewer cases in each study. If the data provided by the

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**Figure 2.** Flow diagram of literature search of systematic review and meta-analysis. NX, Naloxone.
clinical trial was not sufficient for meta-analysis, descriptive analysis was performed only.

3. Results

3.1. Characteristics of the included studies

A total of 1708 articles were retrieved from the electronic databases (including CNKI = 397, Wan Fang database = 442, VIP = 442, and CBM = 432), among which, 32 [33–64] were included through scanning the titles, abstracts and full texts. The basic characteristics of all studies (n = 3,068; including experimental group = 1,537 and control group = 1,531) were generalized in Figure 1. The flow diagrams of systematic review and meta-analysis were shown in Figure 2. At the same time, foreign studies, conference papers and other databases were excluded. In addition, 32 RCTs [33–64] were conducted in parallel design, with the test sites locating in China. As could be observed, the studies were published in Chinese journals from 2010 to 2016, and the age of patients [33–64] ranged from 54 [58] to 68 [40] years. Besides, the volume of cerebral hematoma ranged from 10 [37,56] to 71 [37,56] millilitres, and the GCS score was stated to range from 5.34 [62] to 13.55 [40]. Moreover, NX (2–4 mg, for 1~2 times a day) and routine pharmacotherapy were utilized in both the treatment and control groups, while XNJ (20 mg, for 1~2 times a day) was used in the treatment groups individually, with the course of treatment spanning from 10 to 15 days. 20 trials had evaluated the GCS score, [33,36,40–45,47,50–55,57,60–62,64] 19 had assessed the cerebral hematoma volume [33,40–47,50–52,55,57,60–64] 13 had examined the awake time, [33,36,40,45–47,50,51,53,55,60–62] 30 had investigated the total effective rate (TER), [34–41,43–64] 8 had studied the NIHSS score, [35,38,39,48,56–58,62] 3 had evaluated the Barthel Index (BI), [38,42,56] 1 had evaluated the clinical neurological deficit score (NDS) [37] and 3 had studied the ADL. [38,42,56] Additionally, adverse events were reported in 4 trials [34,39,55,57], with the common discomfort symptoms of nausea, vomiting, skin itching, dizziness, palpitations and irritability. No studies had carried out follow-up observations after the trials.

3.2. Risk of bias in the enrolled studies

The risks of bias in the enrolled studies were generalized in Figure 3. Specifically, 10 studies had described the specific methods of random sequence generation, including random number tables [33,37,42,43,46,47,49,53,57] or sealed envelopes [62], while the remaining studies had mentioned “random” without providing detailed methods. All trials failed to mention the allocation concealment and were assessed as unclear risk. Besides, one study [60] applied the double-blind method in participants and personnel, but the details on the blinding of outcome assessments were not provided. Additionally, one study [62] lacked a specific value of the GCS score and was assessed as high risk regarding the incomplete outcome data; meanwhile, the other sources of bias in this study were evaluated as unclear risk. In addition, the remaining trials describing the efficacy indicators and specific values were assessed as low risk. Thirty-two studies had reported the expected outcomes, and the quality evaluations were rated as low risk. The baseline data of all the enrolled trials were comparable,
and the results were evaluated as low risk due to the absence of other sources of bias.

3.3. Effect of interventions

3.3.1. Assessment of TER. The TER of XNJ combined with NX on ICH was reported in 30 studies, involving 1467 subjects in experiment groups and 1461 in control groups.\[34–41,43–64\] As presented in Figure 4, the overall meta-analysis showed that the TER was superior in intervention groups superior to NX application alone (OR 3.78, 95% CI: 3.03–4.73; \(P < .00001\)). There was no heterogeneity between trials, and a fixed-effects model was thereby utilized for statistical analysis (\(\chi^2 = 7.64, \ P = 1.00, \ I^2 = 0\%\)). Meanwhile, subgroup analysis between studies was coordinated utilizing different evaluation criteria of GCS, NIHSS and other scores, due to the inconsistent evaluation criteria of TER. Specifically, the subgroup meta-analysis (Fig. 3) suggested that XNJ combined with NX was more effective than NX.
application alone under the efficacy evaluation criteria of changes in GCS scores (OR 4.09, 95% CI: 3.11–5.38; \( P < .00001 \)), NIHSS scores (OR 3.24, 95% CI: 2.04–5.13; \( P < .00001 \)) and the other scales scores (OR 3.21, 95% CI: 1.59–6.46; \( P = .001 \)).

### 3.3.2. Assessment of GCS

As shown by the GCS score in 19 studies\[33,36,40,45,47,50,53–55,60–62\] of NXJ combined with NX would lead to remarkably improved arousal status (MD -5.59, 95% CI: -6.96 to -4.22, \( P < .00001 \)) compared with NX application alone (MD -5.74, 95% CI: -7.56 to -3.90). Note that the meta-analysis of the GCS scores in 19 studies\[33,36,40,45,47,50,53–55,60–62\] showed that the arousal status in the NXJ group was significantly higher than that in the NX group (MD 3.86, 95% CI: 3.46–4.25; \( P < .00001 \)).

### 3.3.3. Assessment of coma duration

As presented in Figure 6\[33,36,40,45,47,50,53–55,60–62\], coma duration was markedly decreased after cerebral hemorrhage in 14 studies (MD -5.59, 95% CI: -6.96 to -4.22, \( P < .00001 \)).

### 3.3.4. Assessment of NIHSS scoring scale

As revealed in Figure 7, there were significant differences among studies\[33,36,40,45,47,50,53–55,60–62\] and the NIHSS score was evidently reduced compared with NX application alone (MD -6.24, 95% CI: -8.05 to -4.42, \( P < .00001 \)).

### 3.3.5. Assessment of Bscoring scale

Three studies had reported the BI scores in the meta-analysis\[33,36,40,45,47,50,53–55,60–62\]. As demonstrated...
in Figure 8, the BI scores in the intervention groups were dramatically improved after 2 weeks (MD 14.12, 95% CI: 6.7–21.54; P < .0002).

3.3.6. Assessment of the cerebral hematoma volume. As shown in Figure 9, 18 studies had reported that XNJ combined with NX could promote the absorption of cerebral hematoma and reduce the inflammation in the surrounding tissues, and the difference between the intervention and control groups was significant (MD –6.05, 95% CI: –6.85 to –5.24; P < .0001).

3.3.7. Adverse events. Adverse events were reported in 4 trials, with the common discomfort symptoms of nausea, vomiting, skin itching, dizziness, palpitations, and irritability. Chen [34] had reported that 5 patients from the control group (16.7%) and 2 from the treatment group had presented adverse reactions.
Moreover, Cheng had reported 3 cases of nausea and vomiting, 2 of skin itching, 2 of dizziness and 1 of tachycardia in the treatment group (13.11%); whereas 4 of nausea and vomiting, 1 of arrhythmia, and 2 of irritability in the control group (11.86%). There was no significant difference between the 2 groups in the incidence of adverse events. Hou reported that 5 cases in the control group (15.6%) and 2 in the treatment group had developed adverse events (6.3%). Pan had reported 2 cases of chest distress in the treatment group (4.17%), together with 3 of nausea and vomiting, 5 of sleepiness and 2 of tachycardia in the control group (20.83%).

3.3.8. Publication bias. The potential publication bias was evaluated using funnel plot. The funnel plot (Fig. 10) indicated that all points had exhibited mild asymmetry, demonstrating potential publication bias in all trials. In addition, the funnel plot of other outcomes (GCS, coma duration, cerebral hematoma volume) illustrated the existence of publication bias in this study. (Figs. 11–13).

4. Discussion

4.1. Summary of main results

In this study, findings from overall meta-analysis and subgroup meta-analysis indicate that XNJ combined with NX is superior to NX alone for ICH. In this meta-analysis, 32 trials involving 3068 patients have been systemically reviewed, and an intervention therapy of XNJ combined with NX is employed to observe its effectiveness and safety in ICH. The outcomes confirm that XNJ combined with NX shows significant therapeutic effects on clinical effective rates, GCS scores, coma duration, NIHSS score, BI and cerebral haemorrhage volume. Noteworthily, adverse events associated with XNJ combined with NX are not reported in a majority of studies, except for some individual trials. Specifically, the comprehensive outcome indicators make the meta-analysis results more trustworthy in guiding clinical application. Nevertheless, the effects of XNJ combined with NX on ICH can not be recognized yet, due to deficiency in methodological quality, disability to collect the unpublished literature, and the lack of information on other bias evaluation. Therefore, more well-designed research with high quality is demanded in future study.

4.2. Advantages and further elaboration of study

Currently, XNJ combined with NX has been widely used in ICH patients, which has achieved significant effect. Concretely, XNJ is mainly comprised of musk, synthetic borneol, gardenia, and turmeric, which has the anti-inflammatory pharmacological effects. On the 1 hand, the formed hematoma has multiple effects, including hemiplegia, aphasia, and other neurological deficits. Neurological dysfunction is also caused by the secondary inflammatory injury of cerebral haemorrhage. Moreover, the severity and prognosis of ICH are closely related to the concentrations of these inflammatory factors. Typically, high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-alpha (TNF-α) are the non-specific markers, which serve as the important indicators of inflammatory response. XNJ can inhibit the inflammatory response and reduce the serum levels of inflammatory factors, so as to protect the nerve cells. It is also found that XNJ has an adjucctive effect mainly reflected by improving the consciousness state, ameliorating the clinical symptoms and reducing brain edema at the acute phase. In experimental research, XNJ plays a role in reducing the release of toll-like receptors-4 (TLR4), TNF-α, and Interleukin-1 beta (interleukin [IL-1β]), increasing the content of superoxide...
dismutase (SOD), decreasing the concentration of model-driven architecture (MDA)\textsuperscript{[74]} up-regulating the level of matrix metalloprotein-9 (MMP-9) and Complement 3\textsuperscript{[75]} and inhibiting the expression of aquaporin-4 (AQP-4).\textsuperscript{[76]} On the other hand, NX can reduce the concentration of β-endorphins, decrease the inhibitory effect of endogenous opioid peptides on CNS, improve the state of cerebral ischemia and hypoxia, and unleash the anti-apoptotic effect through down-regulating the expression of Fas-associated with death domain protein (FADD).\textsuperscript{[77]}

![Funnel plot of coma duration. MD = mean difference.](image1)

![Funnel plot of Glasgow Coma Scale (GCS). MD = mean difference.](image2)
4.3. Quality of evidence

Most trials are associated with the drawback of methodological quality deficiencies, which can be attributed to the incapability to collect unpublished literature and the lack of information on other bias evaluation. Simultaneously, the quality of the enrolled trials has restricted us from drawing definite conclusions, due to the existence of the random sequence generation, allocation concealment, as well as blinding of participants, personnel and outcome assessments, incomplete outcome data, and selective reporting bias. Firstly, literature quality is evaluated using the Cochrane risk of bias to avoid the biases of selection, performance, detection and reporting. Secondly, up-to-date literature is searched up to October 2017, and the published time of studies ranges from 2010 to 2016, which has ensured the timeliness and novelty. Thirdly, a comprehensive list of efficacy measurements as outcome indicators can provide more information for clinical practice in this meta-analysis.

4.4. Limitations

There are several limitations in this review, as shown below. First, the differences in bleeding site, hematoma volume and consciousness state between studies may represent sources of heterogeneity. Second, the criteria for efficacy evaluation are varied in the trials. Most studies have referred to the standardized Glasgow outcome scale (GOS), the GCS score or the NIHSS score to assess the clinical efficacy, while the other studies have adopted the hospital questionnaire, NDS and the ADL. Thus, subgroup analysis is performed to avoid potential heterogeneity. Thirdly, methodological heterogeneity or risks of bias exists in the included trials. Most studies do not elaborate the specific methods of random sequence generation, allocation concealment and blinding. Thus, potential risks of selective bias, performance bias and detection bias may exist. Moreover, none of the enrolled studies has reported the follow-up period. In addition, only 4 trials had reported the adverse events, which can not comprehensively reflect the safety of XNJ combined with NX for ICH. Fourthly, all the research sites are in China, and the subjects are domestic patients, which will lead to obvious publication bias. Additionally, all the included studies are derived from the Chinese databases, which is associated with a risk of incomplete retrieval.

4.5. Implications

More prospective and well-designed studies are necessary to assess the efficacy and safety of XNJ combined with NX for ICH. In RCT design, the CONSORT 2010 statement serves as a standard used to guide implementation. Typically, the methodology trial design has stressed the importance of randomization, allocation concealment, masking, baseline characteristics, follow-up, intention-to-treat analysis, and other measures. At the same time, strict and unified criteria of inclusion, exclusion, diagnostic and efficacy evaluation should be formulated. Besides, the severity of ICH, disease stage, syndrome, specific treatment, follow-up period, and incidence of adverse events should also be noted. In future studies, rigorous research should be designed to improve the quality of RCTs and evidence, which may result in a higher degree of confidence of systematic reviews.

In conclusions, the effectiveness and safety of XNJ combined with NX for ICH cannot be determined yet, which can be ascribed to the low quality of literature, publication bias and heterogeneity. Consequently, more rigorous RCTs are necessary to verify the role of XNJ combined with NX in treating ICH.
Author contributions
Wei-Xiong Liang, Qi Wang, Yun-Zhi Ma and Ze-Huai Wen select and design scheme in the meta-analysis. The document search, literature screening, formulation of inclusion and exclusion criteria, quality assessment, data extraction were carried out by Yu-Min Xu, Xin-Chen Wang, Shi-Jie Zhang, Ting-Ting Xu, Hong-Ying Li and Shang-Yan Hei were responsible for the data of statistics and analysis. All authors of this article have approved the final version of the manuscript.

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