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: −6.85 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.[1] The primary pathological injuries are related to the occupied destruction of local brain tissue, [2] whereas the secondary injuries of perihematomal oedema and inflammatory may potentially cause further neurological deterioration. [3] ICH severity is variable due to the differences in hematoma volumes, bleeding sites and related risk factors. [4] Typically, the highest mortality of ICH accounts for 10% to 15% in stroke patients.[5] Notably, the mortality at acute stage remains as high as 30% to 50% in spite of the adopted comprehensive treatment, while the disability is up to 75%.[6] In developed countries, the incidence of ICH has been decreased thanks to the well-controlled blood pressure, [7] but it remains high in developing countries [8] (18%–24% in Japan[9] and Korea,[7] and 8%–15% in USA, UK, and Australia[10,11]). At the acute stage, the continuous expansion of hematoma is a predictor of illness deterioration.[12] Thus, rapid intervention is required to prevent the devastating neurological deficit.

At present, controlling blood pressure and surgical operation are the main interventions for ICH, so as to reduce the intracranial pressure (ICP).[13] Surgery is an important measure at the acute phase; however, many elderly patients cannot tolerate anaesthesia or operation.[14,15] In addition, the long-term application of dehydration drugs is associated with the risk of causing acute kidney injury (AKI). For instance, 2 retrospective studies published in 2014 and 2015 had estimated the incidence of mannitol-related AKI of 10.5 and 6.5%, respectively.[16,17] Notably, traditional Chinese medicine (TCM) has accumulated plenty of clinical experience in treating ICH. For instance, Xingnaojing injection (XNJ) was developed from the Angong Niuhuang Pill, with the main effects of detoxification, cooling blood and resuscitation.[5–8] XNJ has been approved by the China Food and Drug Administration (CFDA) and has achieved efficient therapeutic effect on stroke. [18] Moreover, clinical studies have demonstrated that XNJ exerts the protective effect through alleviating the consciousness disturbance severity, ameliorating neurological deficit symptom, and enhancing the activities of daily living (ADL).[19–22] Additionally, pharmacological study shows that XNJ plays a certain role in the central nervous system (CNS) through reducing blood-brain barrier (BBB) permeability, mitigating brain oedema and ameliorating microcirculation.[23] In addition, XNJ exerts its anti-inflammatory effect through inhibiting the secretion of inflammatory cytokines,[24–27] and plays its anti-autophagy role by repressing p53-DRAM signaling pathway.[28] Naloxone (NX), a competitive antagonist of the mu-opioid receptors, can promote sobriety, relieve respiratory depression and improve the respiratory and circulatory functions.[29] Therefore, the combination of XNJ with NX may be a good adjuvant therapy of ICH for improving the consciousness state, relieving the neurological deficit symptoms and restoring cognitive function.

A number of randomized controlled trials (RCTs) and meta-analyses have reported XNJ-related treatments for ICH; however, the combination of XNJ with NX has not been reported yet. Besides, previous meta-analyses do not conduct the subgroup analysis according to the differences in efficacy evaluation criteria, dosages or treatment duration.[19,20,22] In addition, the evidence from these meta-analyses is insufficient owing to deficiency in methodological quality, small sample size and publication bias. Consequently, it is necessary to systematically evaluate the effectiveness and safety of XNJ combined with NX, so as to provide evidence for clinical applications.

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).[30] 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 OR randomized clinical 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,[31] referred to Chinese guidelines for cerebrovascular disease prevention and treatment,[32] or were diagnosed as acute intracerebral haemorrhage by computerized tomography (CT) or magnetic resonance imaging (MRI), or other recognized diagnostic criteria. The baseline data of patients included age, gender, bleeding volume, and the sites of bleeding were unrestricted;
(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: I/C	Gender (M/F)	Age (years), range, mean (SD)	Cerebral hematoma volume, mean (SD) (ml)	Cerebral hematoma volume, mean (SD) (ml)	Intervention (route of administration, doseage)	Control (route of administration, doseage)	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	I: 33.74 ± 4.12 C: 33.19 ± 4.07	I: 7.65 ± 1.94 C: 7.74 ± 2.09	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	I: 62.3 ± 2.4 C: 62.1 ± 2.0	NS	NS	XNJ 20 ml (intravenous infusion, each time, 2 times a day) NX 4 mg (intravenous infusion, each time, once per 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	I: 26.3 ± 4.2 C: 25.8 ± 5.1	NS	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	NS	I: 7.72 ± 2.03 C: 7.78 ± 2.11	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 C: 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)	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	NS	NS	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	I: 62.34 ± 14.86 C: 61.47 ±15.35	NS	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=the clinical neurological deficit score (NDS), I=activities of daily living (ADL). The average dose of XNJ was 10 to 20 milliliter of intravenously guttae.

Luo XJ 2014 [40]	49/49	I: 29/20 C: 25/24	I: 68.8 ± 4.2 C: 67.2 ± 4.7	I: 19.30 ± 2.98 C: 24.13 ± 4.93	I: 13.55 ± 1.94 C: 9.89 ± 1.44	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+D	NS
Gong TY 2016 [41]	35/35	I: 20/15 C: 19/16	I: 64.28 ± 4.41 C: 65.82 ± 4.78	I: 35.26 ± 2.52 C: 34.16 ± 2.85	I: 8.01 ± 1.75 C: 7.98 ± 1.45	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+D	NS
Zhu L 2015 [42]	30/30	I: 16/14 C: 14/16	I: 62.1 ± 1.2 C: 61.9 ± 1.4	I: 25.19 ± 9.3 C: 26.2 ± 1.8	I: 7.32 ± 1.1 C: 7.29 ± 1.13	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+I	NS
Nie M 2015 [43]	42/42	I: 25/17 C: 24/18	I: 62.47 ± 7.93 C: 62.04 ± 8.16	I: 32.46 ± 4.1 C: 32.61 ± 4.37	I: 7.82 ± 1.95 C: 8.01 ± 2.14	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+D	NS
Zhu JN 2012 [44]	61/60	I: 37/24 C: 33/27	I: 57.8 ± 5.6 C: 58.5 ± 7.0	I: 33.5 ± 5.6 C: 33.7 ± 6.1	I: 7.1 ± 0.9 C: 7.2 ± 1.0	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+D	NS
Wang K 2015 [45]	40/40	Total: 52/28	Range: 55 to 75 (mean: 63.7)	I: 35.9 ± 3.8 C: 34.6 ± 4.7	I: 8.3 ± 2.1 C: 8.1 ± 2.5	XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day)	NX 4 mg (intravenous infusion, each time, once per day)	15	A+B+C+D	NS
Qiang MC 2016 [46]	108/108	I: 62/46 C: 67/41	I: 59.28 ± 5.62 C: 59.33 ± 8.02	I: 35.12 ± 3.87 C: 34.28 ± 3.02	NS	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	B+C+D	NS
Zhu WR 2015 [47]	64/64	I: 36/28 C: 34/30	I: 63.14 ± 4.0 C: 63.14 ± 4.0	I: 34.21 ± 3.18 C: 33.23 ± 4.15	I: 7.93 ± 1.84 C: 7.76 ± 2.12	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+D	NS
Leng XB 2015 [48]	48/48	I: 28/20 C: 29/19	I: 60.6 ± 9.3 C: 60.9 ± 9.5	I: 25.7 ± 4.2 C: 25.5 ± 4.4	NS	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
Li HL 2016 [49]	82/82	I: 42/40 C: 45/37	I: 59.3 ± 4.7 C: 58.8 ± 4.5	NS	NS	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	NS
Ye G 2013 [50]	40/40	I: 21/19 C: 23/17	I: 63.12 ± 4.02 C: 61.21 ± 8.22	I: 34.2 ± 3.19 C: 33.2 ± 4.12	I: 7.92 ± 1.83 C: 7.75 ± 2.1	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+D	NS

Figure 1. Continued.

Study	Sample	Gender	Age			Intervention	Control	Duration	Methodology	Adverse events
Zhang F 2011 [51]	50/50	I: 26/24 C: 28/22	I: 63.12 ± 4.02 C: 61.21 ± 8.22	I: 34.2 ± 3.19 C: 33.2 ± 4.12	I: 7.92 ± 1.83 C: 7.75 ± 2.1	XNJ 20ml 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+D	NS
Guan XD 2015 [52]	40/40	Total: 44/36	I: 63.2 ± 2.2 C: 63.2 ± 2.2	I: 34.4 ± 2.1 C: 33.7 ± 1.3	I: 7.91 ± 1.21 C: 7.98 ± 2.01	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+D	NS
Song GN 2015 [53]	32/31	I: 20/12 C: 15/13	I: 61.2 ± 2.8 C: 62 ± 3	NS	I: 8.0 ± 1.8 C: 7.9 ± 1.8	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
Zhang ZH 2015 [54]	79/79	I: 43/36 C: 44/35	I: 56.3 ± 2.7 C: 57.1 ± 3.4	NS	I: 7.8 ± 2.2 C: 7.9 ± 2.2	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
Hou JX 2014 [55]	32/32	I: 16/16 C: 19/13	I: 61.5 ± 3.2 C: 60.2 ± 2.1	I: 34.5 ± 3.4 C: 33.5 ± 4.3	I: 7.9 ± 1.8 C: 7.7 ± 2.1	XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day)	NX 4 mg (intravenous infusion, each time, once per day)	15	A+B+C+D+E	I: 2 cases C: 5 cases (Not described in detail)
Huang SM 2014 [56]	52/50	Total: 68/34	I: 57.1 ± 6.2 C: 57.1 ± 6.2	Total: 10 to 30 ml (15), 31 to 70 ml (18), over 71 ml (69).	NS	XNJ 20 ml (intravenous infusion, each time, 2 times a day) NX 4 mg (intravenous infusion, each time, once per day)	NX 4 mg (intravenous infusion, each time, once per day)	15	D+F+I	NS
Pan JX 2016 [57]	48/48	I: 27/21 C: 29/19	I: 61.48 ± 5.64 C: 61.57 ± 4.15	I: 34.15 ± 4.65 C: 33.98 ± 4.15	I: 6.64 ± 2.31 C: 6.78 ± 1.65	XNJ 20 ml and NX 2.4 mg (intravenous infusion, each time, 2 times a day)	NX 2.4 mg (intravenous infusion, each time, 2 times a day)	10	A+B+D+E+F	I: chest tightness (2). C: nausea and vomit (3), sleepiness (5), tachycardia (2).
Hen JF 2010 [58]	50/50	I: 26/24 C: 23/27	I: 64.10 ± 10.02 C: 54.65 ± 10.53	NS	I: 9.35 ± 3.01 C: 9.56 ± 2.58	XNJ 20 ml and NX 2 mg (intravenous infusion, each time, once per day)	NX 2 mg (intravenous infusion, each time, once per day)	14	D+F	NS
Huang C 2016 [59]	33/33	I: 18/15 C: 19/14	I: 62.87 ± 7.36 C: 63.14 ± 6.85	NS	NS	XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day)	NX 4 mg (intravenous infusion, each time, once per day)	15	D	NS

Figure 1. Continued.

Yin XQ 2016 [60]	48/48	I: 27/21 C: 23/25	I: 62.5 ± 4.2 C: 63.1 ± 4.6	I: 34.2 ± 3.9 C: 33.8 ± 4.1	I: 7.9 ± 2.3 C: 7.8 ± 1.8	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+D	NS
Zhou HW 2015 [61]	39/39	I: 21/18 C: 22/17	I: 61.3 ± 4.8 C: 61.2 ± 4.7	I: 34.1 ± 4.0 C: 33.9 ± 4.0	I: 7.8 ± 2.1 C: 7.9 ± 1.9	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	A+B+C+D	NS
Wang YJ 2016 [62]	42/41	I: 26/16 C: 27/14	I: 57.34 ± 2.29 C: 56.89 ± 2.13	I: 32.23 ± 3.05 C: 32.37 ± 3.05	I: 5.65 ± 1.36 C: 5.34 ± 1.30	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+D + E+F	NS
Wang LD 2016 [63]	37/37	I: 21/16 C: 22/15	I: 62.58 ± 3.86 C: 63.41 ± 3.94	NS	NS	XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day)	NX 4 mg (intravenous infusion, each time, once per day)	15	B+D	NS
Ye JH 2016 [64]	37/37	I: 24/13 C: 23/14	I: 62.78 ± 3.54 C: 63.12 ± 3.75	I: 33.28 ± 5.21 C: 32.47 ± 5.85	I: 7.91 ± 1.82 C: 7.84 ± 2.64	XNJ 20 ml and NX 4 mg (intravenous infusion, each time, once per day)	NX 4 mg (intravenous infusion, each time, once per day)	15	A+B+D	NS

Figure 1. Continued.

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.

2.5. Assessment of quality of evidence in included studies

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 χ^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
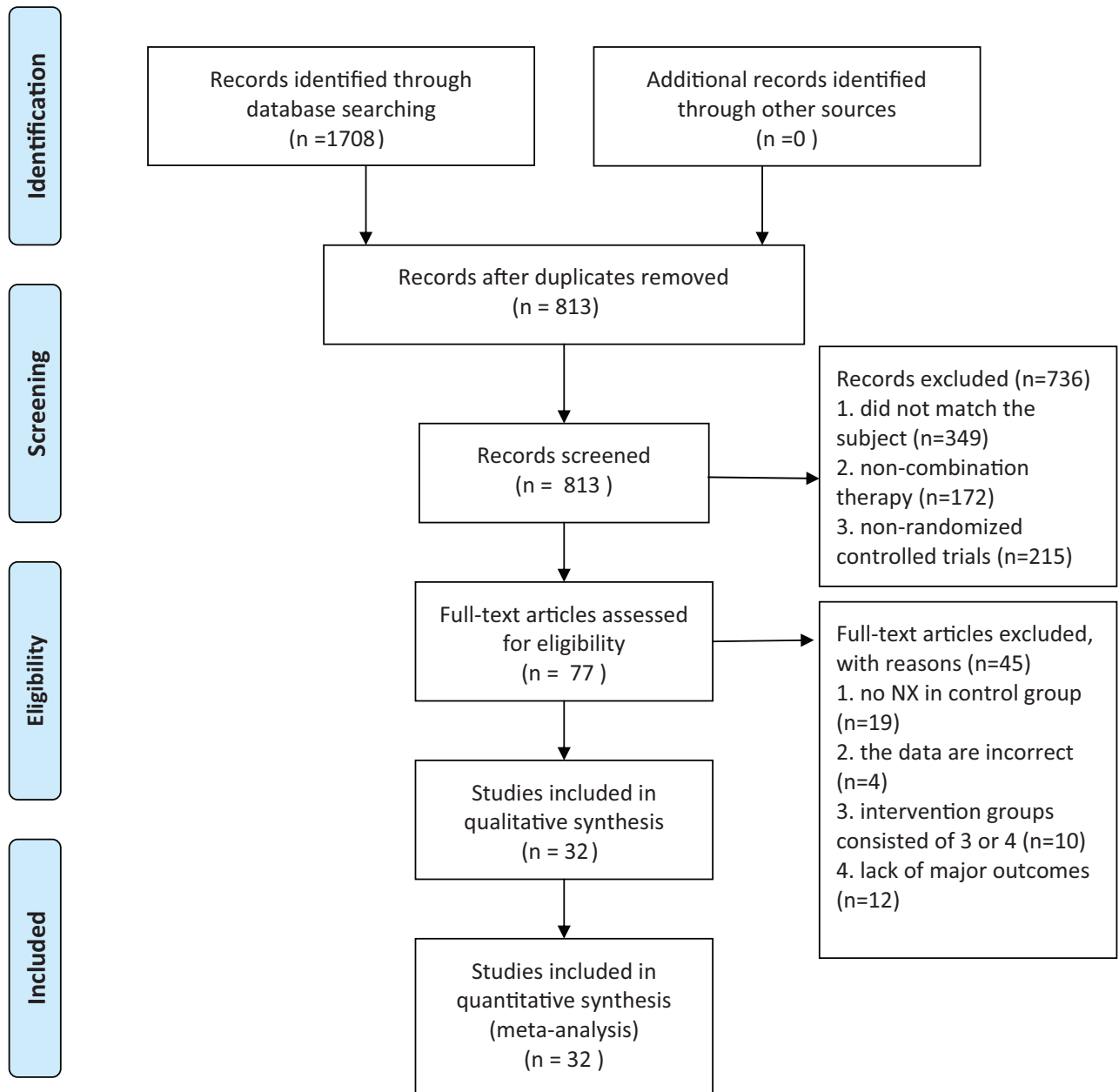
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Figure 2. Flow diagram of literature search of systematic review and meta-analysis. NX, Naloxone.

Figure 3. Risk of bias in the enrolled studies. "+", low risk of bias; "−", high risk of bias; "?", unclear risk of bias.

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=437, 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=1537 and control group=1531) 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 [35,37,42,43,46,47,49,53,57] 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-2 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,
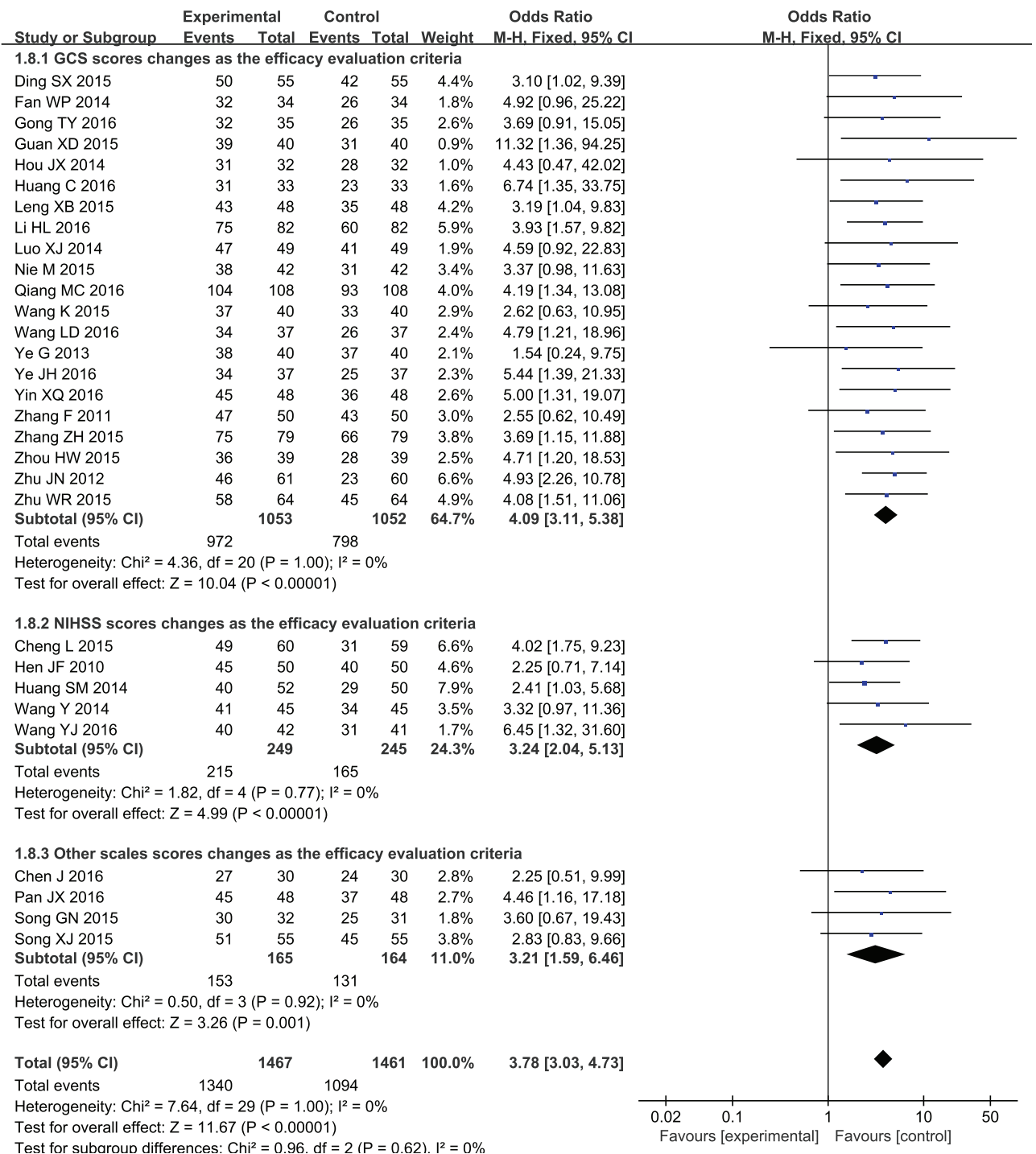
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.8.1 GCS scores changes as the efficacy evaluation criteria							
Ding SX 2015	50	55	42	55	4.4%	3.10 [1.02, 9.39]	
Fan WP 2014	32	34	26	34	1.8%	4.92 [0.96, 25.22]	
Gong TY 2016	32	35	26	35	2.6%	3.69 [0.91, 15.05]	
Guan XD 2015	39	40	31	40	0.9%	11.32 [1.36, 94.25]	
Hou JX 2014	31	32	28	32	1.0%	4.43 [0.47, 42.02]	
Huang C 2016	31	33	23	33	1.6%	6.74 [1.35, 33.75]	
Leng XB 2015	43	48	35	48	4.2%	3.19 [1.04, 9.83]	
Li HL 2016	75	82	60	82	5.9%	3.93 [1.57, 9.82]	
Luo XJ 2014	47	49	41	49	1.9%	4.59 [0.92, 22.83]	
Nie M 2015	38	42	31	42	3.4%	3.37 [0.98, 11.63]	
Qiang MC 2016	104	108	93	108	4.0%	4.19 [1.34, 13.08]	
Wang K 2015	37	40	33	40	2.9%	2.62 [0.63, 10.95]	
Wang LD 2016	34	37	26	37	2.4%	4.79 [1.21, 18.96]	
Ye G 2013	38	40	37	40	2.1%	1.54 [0.24, 9.75]	
Ye JH 2016	34	37	25	37	2.3%	5.44 [1.39, 21.33]	
Yin XQ 2016	45	48	36	48	2.6%	5.00 [1.31, 19.07]	
Zhang F 2011	47	50	43	50	3.0%	2.55 [0.62, 10.49]	
Zhang ZH 2015	75	79	66	79	3.8%	3.69 [1.15, 11.88]	
Zhou HW 2015	36	39	28	39	2.5%	4.71 [1.20, 18.53]	
Zhu JN 2012	46	61	23	60	6.6%	4.93 [2.26, 10.78]	
Zhu WR 2015	58	64	45	64	4.9%	4.08 [1.51, 11.06]	
Subtotal (95% CI)		1053		1052	64.7%	4.09 [3.11, 5.38]	
Total events	972		798				
Heterogeneity: Chi² = 4.36, df = 20 (P = 1.00); I² = 0%							
Test for overall effect: Z = 10.04 (P < 0.00001)							
1.8.2 NIHSS scores changes as the efficacy evaluation criteria							
Cheng L 2015	49	60	31	59	6.6%	4.02 [1.75, 9.23]	
Hen JF 2010	45	50	40	50	4.6%	2.25 [0.71, 7.14]	
Huang SM 2014	40	52	29	50	7.9%	2.41 [1.03, 5.68]	
Wang Y 2014	41	45	34	45	3.5%	3.32 [0.97, 11.36]	
Wang YJ 2016	40	42	31	41	1.7%	6.45 [1.32, 31.60]	
Subtotal (95% CI)		249		245	24.3%	3.24 [2.04, 5.13]	
Total events	215		165				
Heterogeneity: Chi² = 1.82, df = 4 (P = 0.77); I² = 0%							
Test for overall effect: Z = 4.99 (P < 0.00001)							
1.8.3 Other scales scores changes as the efficacy evaluation criteria							
Chen J 2016	27	30	24	30	2.8%	2.25 [0.51, 9.99]	
Pan JX 2016	45	48	37	48	2.7%	4.46 [1.16, 17.18]	
Song GN 2015	30	32	25	31	1.8%	3.60 [0.67, 19.43]	
Song XJ 2015	51	55	45	55	3.8%	2.83 [0.83, 9.66]	
Subtotal (95% CI)		165		164	11.0%	3.21 [1.59, 6.46]	
Total events	153		131				
Heterogeneity: Chi² = 0.50, df = 3 (P = 0.92); I² = 0%							
Test for overall effect: Z = 3.26 (P = 0.001)							
Total (95% CI)		1467		1461	100.0%	3.78 [3.03, 4.73]	
Total events	1340		1094				
Heterogeneity: Chi² = 7.64, df = 29 (P = 1.00); I² = 0%							
Test for overall effect: Z = 11.67 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.96, df = 2 (P = 0.62), I² = 0%							

0.02   0.1   1   10   50
Favours [experimental]   Favours [control]

Figure 4. Forest plot and meta-analysis of the total effective rate. CI = confidence interval, GCS = Glasgow coma scale, NIHSS = National Institute of Health Stroke Scale.

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
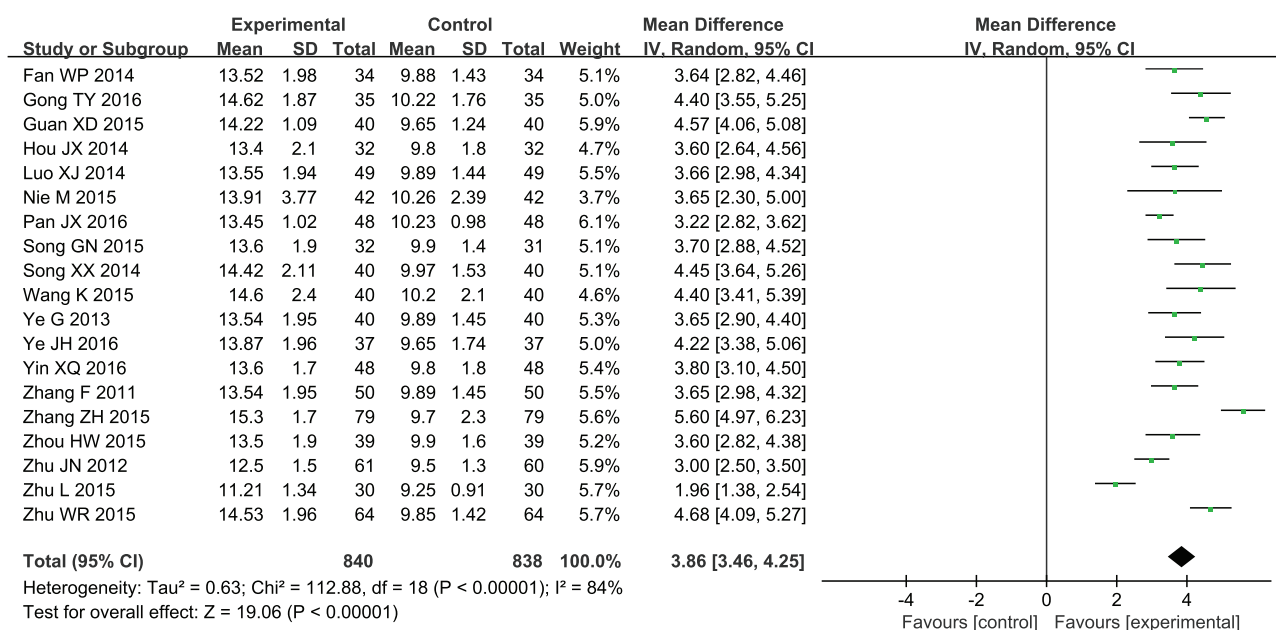
Figure 5. Forest plot and meta-analysis of the Glasgow Coma Scale. CI = confidence interval, SD = standard deviation.
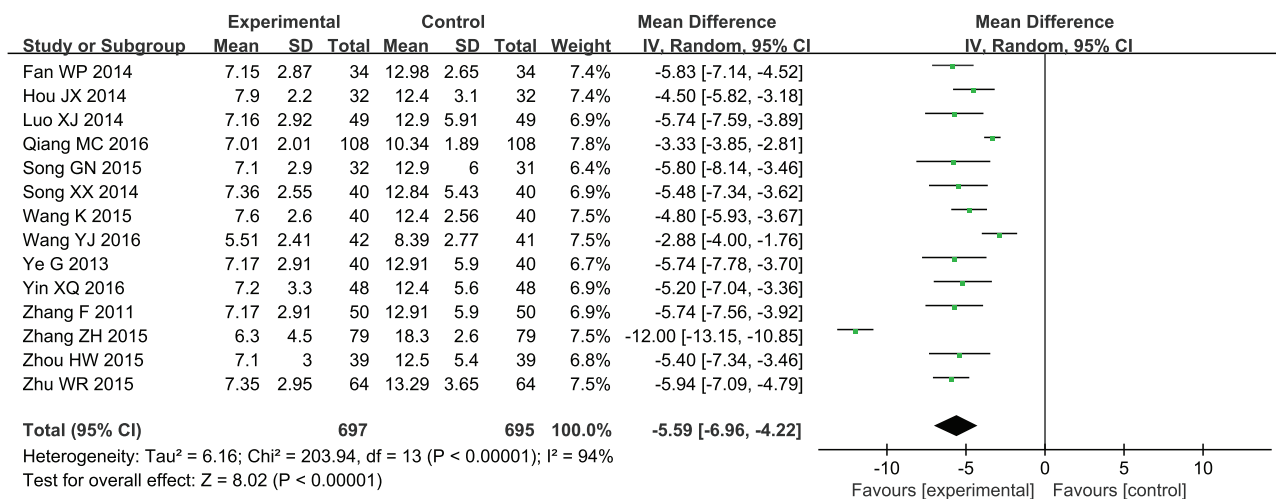

Figure 6. Forest plot and meta-analysis of the coma duration. CI = confidence interval, SD = standard deviation.

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[33,36,40–45,47,50–55,57,60–62,64], XNJ combined with NX would lead to remarkably improved arousal status (MD 3.86, 95% CI: 3.46–4.25; $P < .00001$) compared with NX application alone (Fig. 5). In addition, one study [62] did not carry out amalgamation of effect sizes due to the lack of specific GCS values.

3.3.3. Assessment of coma duration.
As presented in Figure 6 [33,36,40,45–47,50,51,53–55,60–62], 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,[35,38,39,48,56–58,62] and the NIHSS score was evidently reduced compared with that 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.[35,39,48] As demonstrated
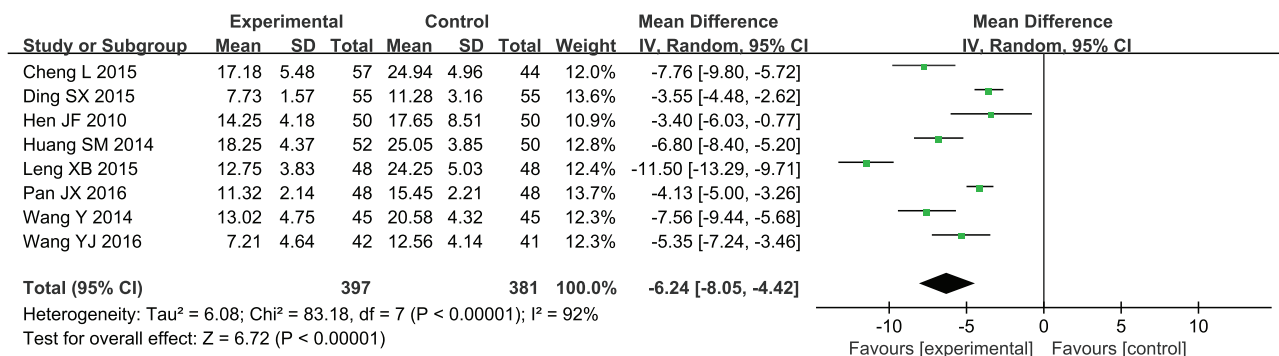
Study or Subgroup	Experimental			Control			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Cheng L 2015	17.18	5.48	57	24.94	4.96	44	12.0%	-7.76 [-9.80, -5.72]
Ding SX 2015	7.73	1.57	55	11.28	3.16	55	13.6%	-3.55 [-4.48, -2.62]
Hen JF 2010	14.25	4.18	50	17.65	8.51	50	10.9%	-3.40 [-6.03, -0.77]
Huang SM 2014	18.25	4.37	52	25.05	3.85	50	12.8%	-6.80 [-8.40, -5.20]
Leng XB 2015	12.75	3.83	48	24.25	5.03	48	12.4%	-11.50 [-13.29, -9.71]
Pan JX 2016	11.32	2.14	48	15.45	2.21	48	13.7%	-4.13 [-5.00, -3.26]
Wang Y 2014	13.02	4.75	45	20.58	4.32	45	12.3%	-7.56 [-9.44, -5.68]
Wang YJ 2016	7.21	4.64	42	12.56	4.14	41	12.3%	-5.35 [-7.24, -3.46]
Total (95% CI)			397			381	100.0%	-6.24 [-8.05, -4.42]

Heterogeneity: Tau² = 6.08; Chi² = 83.18, df = 7 (P < 0.00001); I² = 92%
Test for overall effect: Z = 6.72 (P < 0.00001)

Figure 7. Forest plot and meta-analysis of the NIHSS score. CI = confidence interval, NIHSS = National Institute of Health Stroke Scale, SD = standard deviation.

Study or Subgroup	Experimental			Control			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Cheng L 2015	75.62	8.43	57	61.57	8.75	44	32.6%	14.05 [10.66, 17.44]
Ding SX 2015	82.41	6.85	55	62.34	6.43	55	33.7%	20.07 [17.59, 22.55]
Leng XB 2015	72.25	6.98	48	64.01	5.17	48	33.7%	8.24 [5.78, 10.70]
Total (95% CI)			160			147	100.0%	14.12 [6.70, 21.54]

Heterogeneity: Tau² = 40.98; Chi² = 44.05, df = 2 (P < 0.00001); I² = 95%
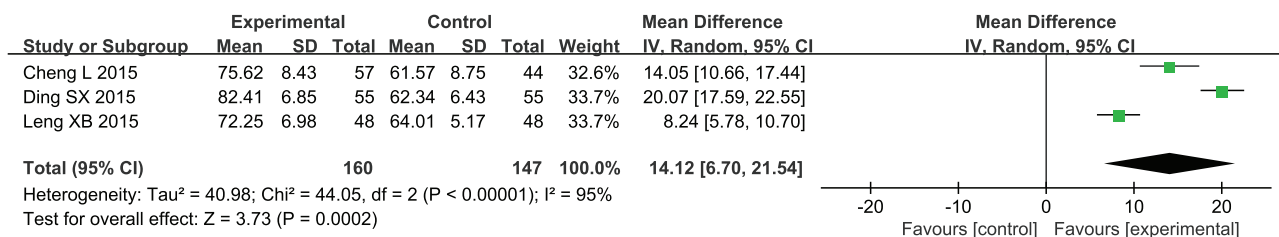Test for overall effect: Z = 3.73 (P = 0.0002)

Figure 8. Forest plot and meta-analysis of the Barthel Index score. CI = confidence interval, SD = standard deviation.

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; $P < .00001$).

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
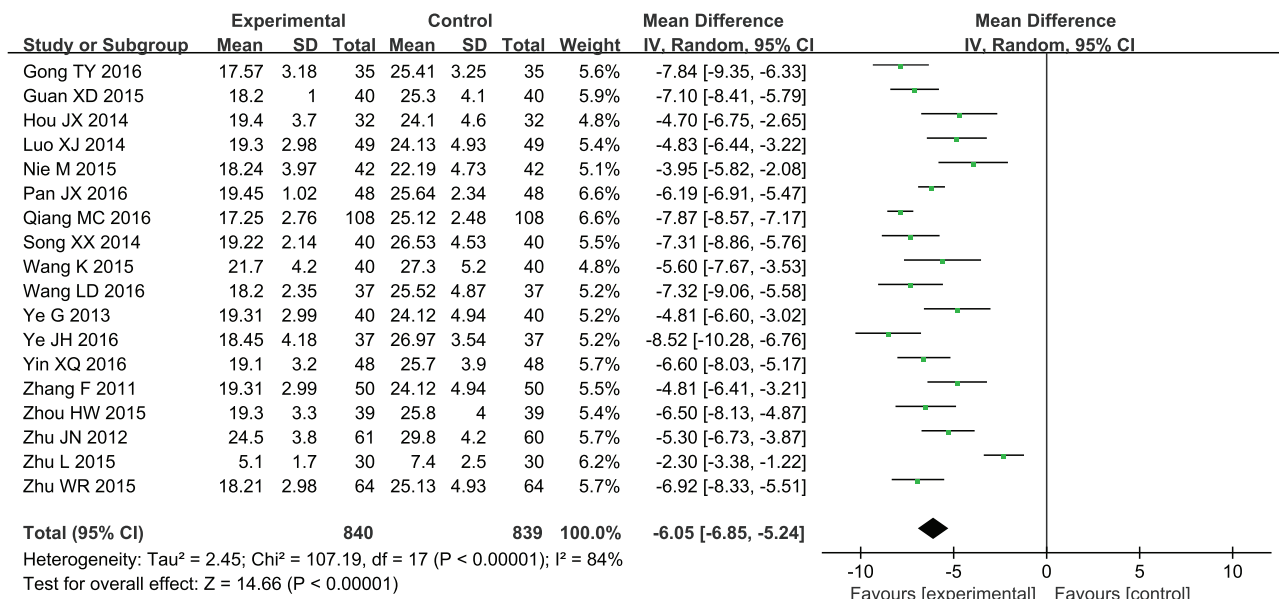
Study or Subgroup	Experimental			Control			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Gong TY 2016	17.57	3.18	35	25.41	3.25	35	5.6%	-7.84 [-9.35, -6.33]
Guan XD 2015	18.2	1	40	25.3	4.1	40	5.9%	-7.10 [-8.41, -5.79]
Hou JX 2014	19.4	3.7	32	24.1	4.6	32	4.8%	-4.70 [-6.75, -2.65]
Luo XJ 2014	19.3	2.98	49	24.13	4.93	49	5.4%	-4.83 [-6.44, -3.22]
Nie M 2015	18.24	3.97	42	22.19	4.73	42	5.1%	-3.95 [-5.82, -2.08]
Pan JX 2016	19.45	1.02	48	25.64	2.34	48	6.6%	-6.19 [-6.91, -5.47]
Qiang MC 2016	17.25	2.76	108	25.12	2.48	108	6.6%	-7.87 [-8.57, -7.17]
Song XX 2014	19.22	2.14	40	26.53	4.53	40	5.5%	-7.31 [-8.86, -5.76]
Wang K 2015	21.7	4.2	40	27.3	5.2	40	4.8%	-5.60 [-7.67, -3.53]
Wang LD 2016	18.2	2.35	37	25.52	4.87	37	5.2%	-7.32 [-9.06, -5.58]
Ye G 2013	19.31	2.99	40	24.12	4.94	40	5.2%	-4.81 [-6.60, -3.02]
Ye JH 2016	18.45	4.18	37	26.97	3.54	37	5.2%	-8.52 [-10.28, -6.76]
Yin XQ 2016	19.1	3.2	48	25.7	3.9	48	5.7%	-6.60 [-8.03, -5.17]
Zhang F 2011	19.31	2.99	50	24.12	4.94	50	5.5%	-4.81 [-6.41, -3.21]
Zhou HW 2015	19.3	3.3	39	25.8	4	39	5.4%	-6.50 [-8.13, -4.87]
Zhu JN 2012	24.5	3.8	61	29.8	4.2	60	5.7%	-5.30 [-6.73, -3.87]
Zhu L 2015	5.1	1.7	30	7.4	2.5	30	6.2%	-2.30 [-3.38, -1.22]
Zhu WR 2015	18.21	2.98	64	25.13	4.93	64	5.7%	-6.92 [-8.33, -5.51]
Total (95% CI)			840			839	100.0%	-6.05 [-6.85, -5.24]

Heterogeneity: Tau² = 2.45; Chi² = 107.19, df = 17 (P < 0.00001); I² = 84%
Test for overall effect: Z = 14.66 (P < 0.00001)

Figure 9. Forest plot and meta-analysis of the cerebral hematoma volume. CI = confidence interval, SD = standard deviation.

(6.7%). Moreover, Cheng[39] 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[55] reported that 5 cases in the control group (15.6%) and 2 in the treatment group had developed adverse events (6.3%). Pan[57] had reported 2 cases of chest distress in the treatment group (4.17%), together with 3 of nausea and vomit, 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. [34–41,43–64] 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 [5–8], which has the anti-inflammatory pharmacological effects. [65] On the 1 hand, the formed hematoma has multiple effects, including hemiplegia, aphasia, and other neurological deficits.[66] Neurological dysfunction is also caused by the secondary inflammatory injury of cerebral haemorrhage.[67] Moreover, the severity and prognosis of ICH are closely related to the concentrations of these inflammatory factors.[68] 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.[69,70] XNJ can inhibit the inflammatory response and reduce the serum levels of inflammatory factors, so as to protect the nerve cells. [70] It is also found that XNJ has an adjunctive effect [71,72] 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]),[73] increasing the content of superoxide
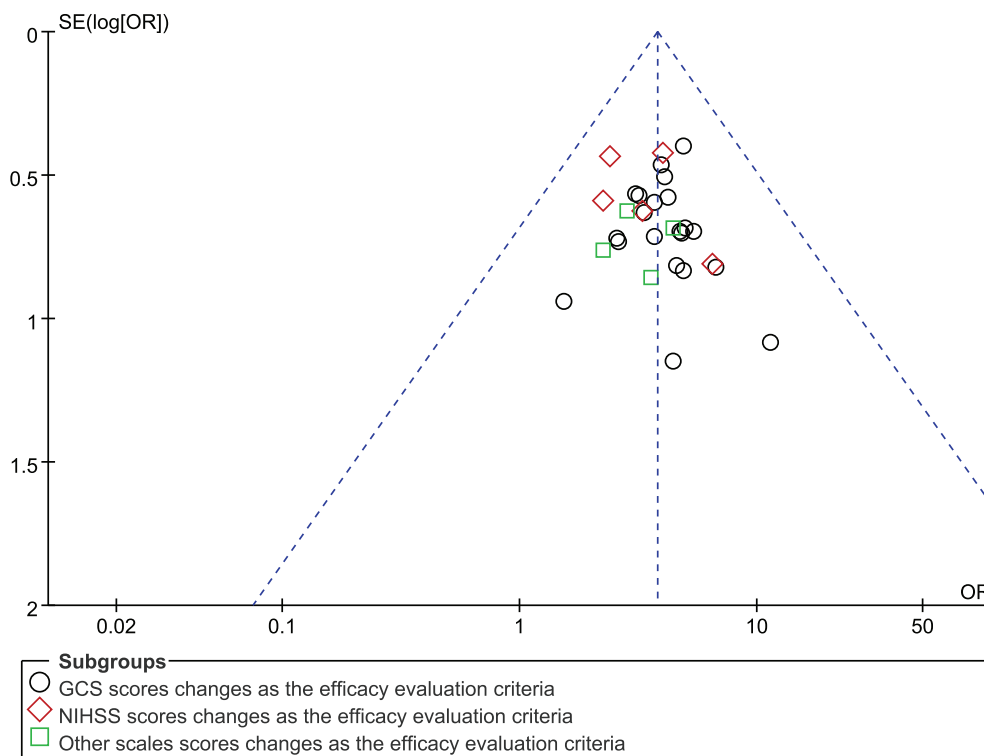

Figure 10. Funnel plot. OR=odds ratio, GCS=Glasgow Coma Scale, NIHSS=National Institute of Health Stroke Scale.
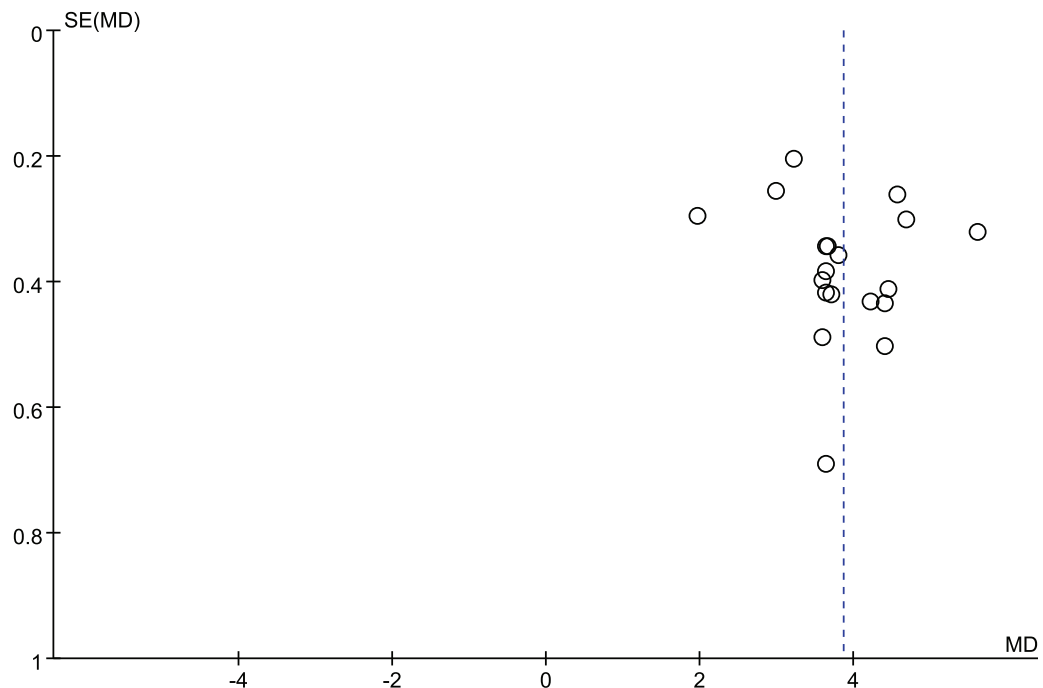
Figure 11. Funnel plot of Glasgow Coma Scale (GCS). MD=mean difference.

dismutase (SOD), decreasing the concentration of model-driven architecture (MDA),[74] up-regulating the level of matrix metalloprotein-9 (MMP-9) and Complement 3,[75] and inhibiting the expression of aquaporin-4 (AQP-4).[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).[77]
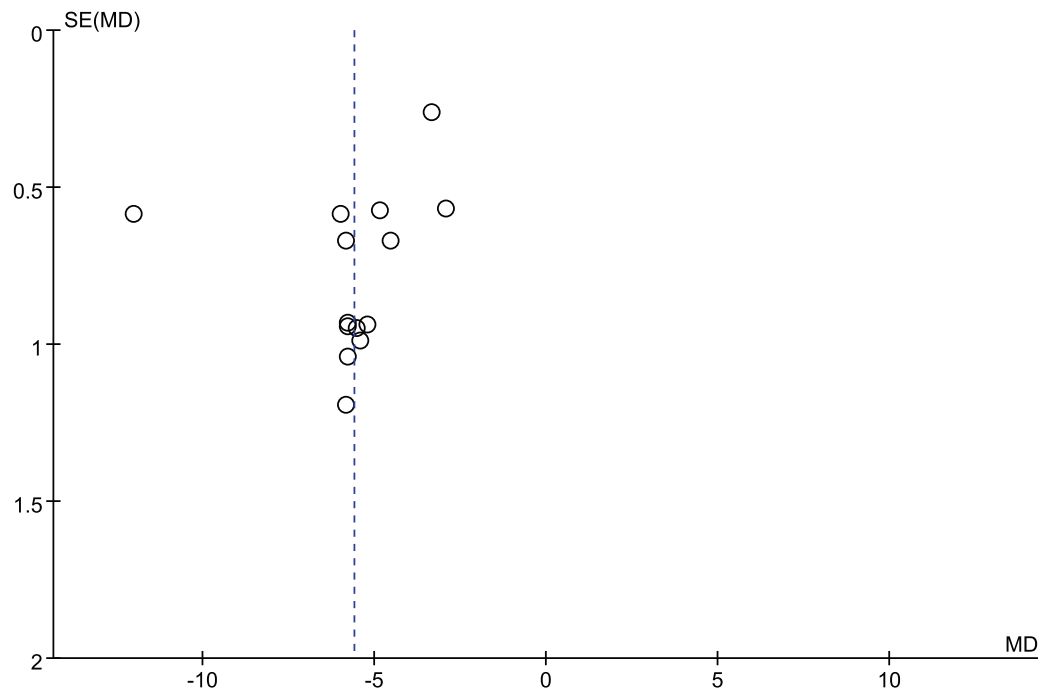
Figure 12. Funnel plot of coma duration. MD=mean difference.
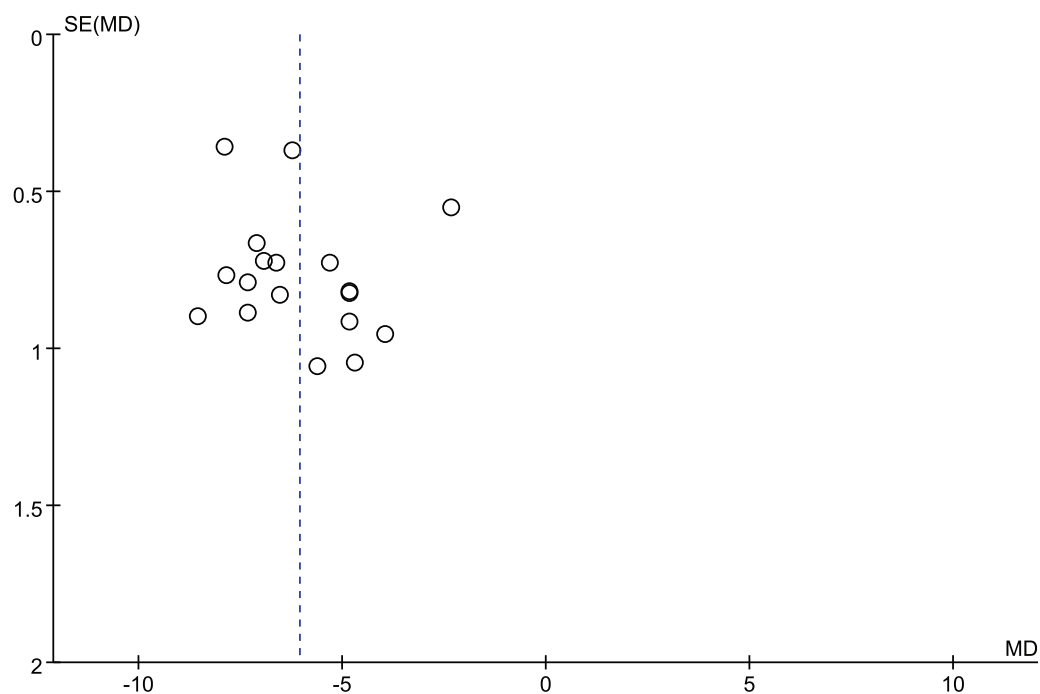
Figure 13. Funnel plot of cerebral hematoma volume. MD=mean difference.

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),[40,43,46,50,51,59,60,61,63,64] the GCS score[33,35,42,42,44,45,47,48,52,53,54,55,57] or the NIHSS score [38,39,56,58] to assess the clinical efficacy, while the other studies have adopted the hospital questionnaire,[34] NDS[37] and the ADL.[56] 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[34,39,55,57] 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[78,79] 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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