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Evidence-Based Integrative Medicine

Comparison between Xingnaojing Injection (醒脑静注射液) and Naloxone in Treatment of Acute Alcohol Intoxication: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials*

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ABSTRACT **Objectives:** To investigate the effectiveness and safety of Xingnaojing Injection (XNJ, 醒脑静注射液) compared with naloxone for the treatment of acute alcohol intoxication (AAI), and provide the latest evidence through evidence-based approach. **Methods:** Seven electro-databases including PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Chinese National Knowledge Infrastructure Databases, Chinese Biomedical Literature Database, Chinese Science and Technology Periodical Database (VIP) and Wanfang Database were searched from the inception to January 2018. Randomized controlled trials (RCTs) comparing XNJ with naloxone for patients with AAI and reporting at least one of the below outcomes were included: patients' conscious recovery time, stay length in emergency department, disappearance time of the ataxia symptom, the severity of the symptoms, the blood alcohol content as well as the adverse events. Methodological quality of included trials was assessed using the risk of bias tool which recommended by the Cochrane Collaboration. Meta-analysis was conducted by Review Manager 5.3 software. **Results:** Totally 141 trials with 13,901 patients were included in this review, all of them were assessed as unclear or high risk of bias. Results showed that on the basis of routine therapy, standard dose XNJ (10–20 mL) may have similar results with naloxone on the recovery time of consciousness (MD 12 min, 95% CI 7.2–17.4 min) and disappearance time of symptoms (MD 6 min, 95% CI –13.8–25.8 min) for patients with AAI. Larger dose of XNJ Injection (21–40 mL) may speed up the time (almost 1 h earlier). Combination of XNJ and naloxone seemed superior to the naloxone alone for all the relevant outcomes. The average difference of time in consciousness recovery was 2 h and the number of AAI patients whose consciousness recovery within 1 h was above 50% the combination group than in the control group (RR 1.42, 95% CI 1.29 to 1.56). No severe adverse events or adverse reactions of XNJ were reported in the included trials. **Conclusions:** Low quality of evidence showed XNJ may have equal effect as naloxone and may achieve better effect as add-on intervention with naloxone for patients with AAI. We failed to evaluate the safety of XNJ Injection due to the insufficient evidence in this review. Registration number in PROSPERO (No. CRD42018087804)

KEYWORDS Xingnaojing Injection, naloxone, acute alcohol intoxication, meta-analysis, randomized controlled trial

Alcohol was thought to be implicated in 21% emergency admissions based on a cohort study in UK with 5,497 participants.[1] Acute alcohol intoxication (AAI) is the consequence of excessive alcohol on the central nervous system, and it can inhibit the respiration and heartbeat. The clinical manifestations of AAI include nausea, vomiting, dizziness, delirium, and restlessness. Severe cases can cause coma, incontinence, and respiratory depression. AAI can be diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-Ⅳ-TR) with the recent alcohol consumption exposure and clinically significant behavioral or psychological changes.[2] The severity of AAI in patients was classified into 4 categories considering both severity of the clinical symptoms and blood alcohol level (BAL).[3,4] In China, nearly half of the patients with acute poisoning in emergency department are diagnosed as AAI, and it accounts for 0.5% of the total number of emergency

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patients in the same period. AAI can cause serious injury to the patient in a short time, even lead to death.

Plenty of studies have been published and mainly focused on the epidemiology, pathophysiology and management of alcohol withdrawal seizures,[5-7] but limited evidence can be found on treatment of AAI. According to the European Federation of Neurological Societies (EFNS) guideline on the diagnosis and management of alcohol-related seizure,[8] hyponatremia may develop in alcohol abusers, however, there is no sufficient evidence to recommend routine correction of hypomagnesemia.

Routine treatments for alcoholism patients include accelerating the alcohol excretion (e.g., furosemidum), maintaining the water, electrolytes and acid-based balance and anti-vomiting (metoclopramide). The Consensus on the Diagnosis and Treatment of Acute Alcoholism recommended to use naloxone to relieve the central inhibition of alcoholism and shorten the time of coma.[9] Naloxone hydrochloride (naloxone), which is for the standard treatment of opioid-induced respiratory depression, has been proved to reduce the plasma β-endorphin level so as to promote the transformation of the alcohol in the body.[10] However, as an opioid antagonist, the most serious adverse effect (AE) of naloxone exposure is respiratory depression which will lead to slow, shallow breathing or complete cessation of voluntary breathing.[11]

Xingnaojing Injection (XNJ, 醒脑静注射液) is a Chinese patent medicine injection commonly used in China in emergency rescue. Its main components include *Moschus*, *Borneolum Syntheticum*, *Fructus Gardeniae* and *Radix Curcumae*, etc. According to Chinese medicine (CM) theory, XNJ has the function of clearing heat and detoxifying, cooling and invigorating the blood circulation, as well as restoring the consciousness. The experimental study found that XNJ could significantly improve the activity of alcohol dehydrogenase in liver and aldehyde dehydrogenase, then promote the metabolism of ethanol.[12] Meanwhile, it could recover the content of glutamate and gamma aminobutyric acid (GABA) in lateral hypothalamus area to promote the awakening of alcoholic coma rats.[13,14]

A systematic review with 27 included trials showed that XNJ plus routine therapy was superior to routine therapy alone, and the curative efficacy of XNJ and naloxone was similar.[15] However, the authors also clarified that the routine therapy had obvious clinical heterogeneity among included trials, and the methodological quality of the included studies were not good enough to confirm the effectiveness and safety of XNJ in treating AAI. Since the previous review was published in 2009, it's worthy to update the evidence with more potential high-quality studies. In this study, we investigated the effectiveness and safety of XNJ compared to naloxone on the patients with AAI, and provided a latest and rigorous evidence through evidence-based approach.

METHODS

This review was registered in PROSPERO (ID. CRD42018087804), and the details are available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018087804.

Included Criteria for Considering Studies

Randomized controlled trials (RCTs) which compared XNJ with naloxone for patients with AAI were included in this review. AAI is diagnosed according to a recognized criterion (e.g., DSM-Ⅳ-TDR),[2] and the patients have symptoms of ataxia or coma, regardless to their age or gender. Routine therapy was used in both groups, including diuretic, rehydration, vitamin supplement, and maintain of electrolyte balance. Combination of XNJ and naloxone compared with naloxone alone was also included to determine the add-on effect of XNJ for AAI.

The primary outcome is the patients' conscious recovery time. The secondary outcomes include length of stay time in emergency department, ataxia symptom disappearance time (defined by the doctor in charge of the case), severity of the symptoms [assessed by recognized scales, e.g., the International Classification of Diseases, 10th Revision, Australian Modification (ICD-10-AM)],[16] BAL and AEs. The included trials report at least one of the abovementioned outcomes. Type of language and publishing status of the literatures were not limited.

Search Strategy for Identification of Studies

PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese National Knowledge Infrastructure Databases (CNKI), Chinese Biomedical Literature Database (SinoMed), Chinese Science and Technology Periodical Database (VIP) and Wanfang Database were searched from the inception to January 2018. "Xing Nao Jing" OR "Xingnaojing" combined with "alcoholism" OR "alcohol intoxication" OR "alcoholic poisoning" OR "ethylalcohol poisoning" were used as the keywords or MeSH during searching, the search strategies were adjusted in different databases.

Two authors (Cheng N and Wang RT) screened the literatures and selected the eligible trials according to the abovementioned criteria. Disagreements were solved by discussion with the third author (Cao HJ).

Data Collection and Quality Evaluation

Two authors (Cheng N and Wang RT) independently extracted the data and assessed the methodological quality of included trials using the risk of bias tool which recommended by the Cochrane Collaboration.[17] Six items were assessed including random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Since the patients were in state of drunken or coma and the outcome indicators were not reported by the patients themselves, the lack of blinding of patients may not influence the outcome assessment. For the primary outcome and majority of the secondary outcome (all except the ataxia symptom disappearance time and severity of the symptoms), blinding of outcome assessors' item was also "in-active" during the quality assessment, since those outcomes were objectively measured.

Grading of Recommendations Assessment, Development and Evaluation criteria (GRADE) was conducted to assess the quality of evidence for each primary outcome (with synthesized results). Factors that downgraded the quality include imprecision, inconsistency, indirectness, limitations and bias of the evidence.

Subgroup Analyses

Subgroup analyses were conducted to determine the evidence for the different dosage of drugs (either XNJ or naloxone) or different types of patients (moderate or severe of AAI) if data were available. When there were significant positive results of the outcomes, sensitive analysis was conducted to challenge the robustness of the primary analysis: trials with/without high risk of bias; fixed-effect model (FEM)/ random-effects model (REM).

Statistical Analysis

All statistical analysis was performed using RevMan 5.3 software (The Cochrane Collaboration). Data were summarized using risk ratio (RR) with its 95% confidence interval (CI) for binary outcomes or mean difference (MD) with 95% CI for continuous outcomes. Statistical heterogeneity among included trials was evaluated by I^2 test. Meta-analysis was conducted, if there is no significant clinical and statistical heterogeneity (I^2<75%) among included trials. When I^2 value was less than 25%, FEM was used to pool the data. When I^2 value was between 25%–75%, the source of heterogeneity was estimated. If the statistical heterogeneity was explained successfully by sensitive analysis or subgroup analysis (I^2<25%), FEM are used to pool the data. Otherwise, REM was used. Data was not pooled when there was significant statistical heterogeneity (I^2>75%) which was unable to explain or handle (by subgroup analysis) among trials. Funnel plot was applied to explore the possibility of publication bias, when there were 10 or more trials in a meta-analysis.

RESULTS

Description of the Studies

After searching the pre-defined 7 databases, 1,175 citations were obtained. Finally, 141 trials[18-158] were included in this review, details of the literature screening flow chart are shown in Figure 1.

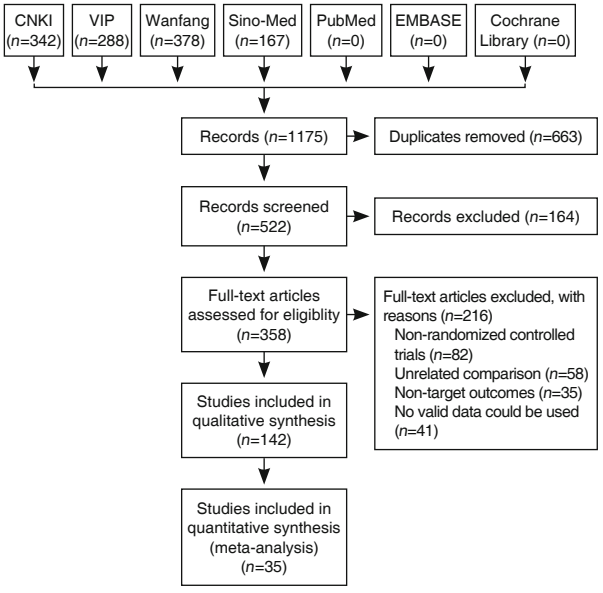

Figure 1. Study Flow Chart of Included Studies

All trials were conducted and published in China. Among the 141 included trials, 14 of them were 3-arms trials,[22,65,66,85,89-91,95,103,119,121,126,138,152] in which both combination of XNJ and naloxone as well as XNJ single application were compared with naloxone, thus, we included the results from 3 arms and the data from naloxone group were used twice in the meta-analysis, separately. Another 9 trials also 3-arms trials,[27,35,44,73,84,86,122,135,137] however, results from only 2 of the 3 groups were included in the meta-analysis since the third group was irrelevant to the topic of this review.

Totally 13,901 patients were included in this review, with only 19% female. AAI was diagnosed according to the criteria from domestic textbook, 67

trials[18-20,24,26-27,29-33,38,40,42-44,46,48-50,53-55,60-62,64,70,72,75,77-79,81-83,85-89,91,93-95,100,103,105,115,118-119,122,124,127-128,133,135,140,142-144,146-148,152-153,155] included only severe AAI patients, 9 trials[41,51,56,69,99,104,114,149,151] included moderate or severe AAI patients, and the other 65 trials did not report the type of AAI. Twenty-three trials[22,46,54,62,65-66,85,89-91,95,97,98,103,119,121,123,126,134,138,145,149,152] compared XNJ with naloxone on the same routine therapies in both groups, and 131 trials[18-45,47-53,55-61,63-96,99-122,124-129,131-133,135-144,146-148,150-158] compared the combination of XNJ and naloxone with naloxone alone on the basis of routine therapy. Almost all the trials used 0.8 mg naloxone intravenously injection or 0.8–1.2 mg intravenously drip as the control treatment. Another 1 trial[130] compared XNJ with naloxone without any other routine therapy. The routine therapies included accelerating alcohol excretion (e.g., furosemidum), maintenance of water, electrolytes and acid-based balance, emetic (1 h gastric lavage) or anti-vomiting (metoclopramide), details were varied among the trials. According to the instruction, XNJ should be used through intravenous drip with 10–20 mL one time, by diluting with 5%–10% glucose injection or sodium chloride Injection 250–500 mL.[159] However, almost half of the included trials used XNJ 20–40 mL one time. Subgroup analysis was conducted according to the dosage of XNJ to investigate the potential dose-response effect.

The primary outcome was reported in 97 included trials,[19,23-25,27,29-45,47,49-51,54,57-60,63-66,68-69,71,73-76,77-79,81,83-85,87-88,90,94-95,97-99,100,102,105-110,112,114,116-121,123-126,131-132,134-135,137-138,140-142,144-146,148,150-152,154-156,158] 75 trials[19,23-24,29-31,33-42,44-45,47,49-50,54,59,63-66,68-69,71,73-75,77-79,81,83,85,87,90,94-95,97,100,102,105-110,114,116-119,121,124-126,134-135,137-138,140-142,144-146,150,154-155,158] reported the time of disappearance of symptoms, 21 trials[25,27,29,32-33,41,44,47,51,64,66,77,88,90,99,100,112,123,131,150,155] reported the number of patients whose consciousness recovery and symptoms disappear within 1 h, 12 trials[39,43,57-59,71,76,98,120,151-152,156] reported the number of patients whose consciousness recovery and symptoms disappear within 2 h, and 9 trials[50,60,79,84,109,132,148,155,158] reported stay length in emergency department. None of the trials reported severity of the symptoms, BAL and AEs (except the discomfort symptoms post sober up) during and after treatment. Details of the characteristics of included trials are shown in Appendix 1.

Risk of Bias in Included Studies

According to the criteria mentioned above, only 21 (14.79%) of the 141 included trials[34,37,39,40,45,48,50,58,60,74,79,112,115,121,123,136,138,141,143,150,157] were assessed as having low risk of selection bias, since they reported the method for random number generation. Random number table was used in 20 trials to generate the random sequence,[34,37,39,40,45,48,50,58,60,74,79,112,115,121,136,138,141,143,150,157] computer software or draw lots were also mentioned in 1 trial.[123] However, allocation concealment was not reported in any of them.

Except 12 trials,[34,43,52,54,57,70,71,104,105,111,138,148] all the remaining 130 trials reported the outcomes consistent with what they mentioned in the methods section, thus, these 130 trials (91.55%) were evaluated as having low risk of reporting bias. Researchers of 1 of abovementioned 12 trials[105] did not report the primary outcome that they have predefined in the methods section, thus, this study was assessed as having high risk of reporting bias. Other 11 trials[34,43,52,54,57,70,71,104,111,138,148] had unclear risk of reporting bias since they failed to describe the outcomes which were expected to report.

All of the included trials were evaluated as having unclear risk of attribution bias and other bias due to the insufficient information for judgement. Details of the results of risk of bias assessment are also shown in Appendix 1.

Effects of Intervention

XNJ plus Routine Therapy *vs.* Naloxone plus Routine Therapy

Seventeen trials[22,54,62,65,66,89-91,97,103,121,123,126,134,138,145,149] reported the time of recovery of consciousness. Subgroup analysis showed patients in the XNJ group (10–20 mL intravenous drip one time) was shorter in conscious recovery time compared with the naloxone group (MD 12 min, 95%CI 7.2–17.4 min, I^2=4%, P<0.01, 11 trials, 888 patients).[22,54,62,66,89-91,97,121,126,145] Large dose of XNJ (21–40 mL one time) may speed up the recovery time of consciousness and the effect was even superior to naloxone (MD –47.4 min, 95%CI –88.2 min to –6.6 min, P<0.01, 6 trials, 534 patients).[65,103,123,134,138,149] However, the reliability of the result is affected by serious statistical heterogeneity (I^2=99%). Results from each of these 17 trials are shown in Figure 2.

Fourteen trials[46,54,65,66,85,90,95,97,119,121,126,134,138,145] reported the time of disappearance of symptoms. Subgroup analysis showed no significant difference between XNJ (10–20 mL) and naloxone group (MD 6 min, 95%CI –13.8 to 25.8, I^2=70%, P=0.55, 10 trials, 680 patients),[54,66,85,90,95,97,119,121,126,145] large dose of XNJ (21–40 mL) may accelerate the disappearance of symptoms (MD –65.4 min, 95%CI –123.6 to

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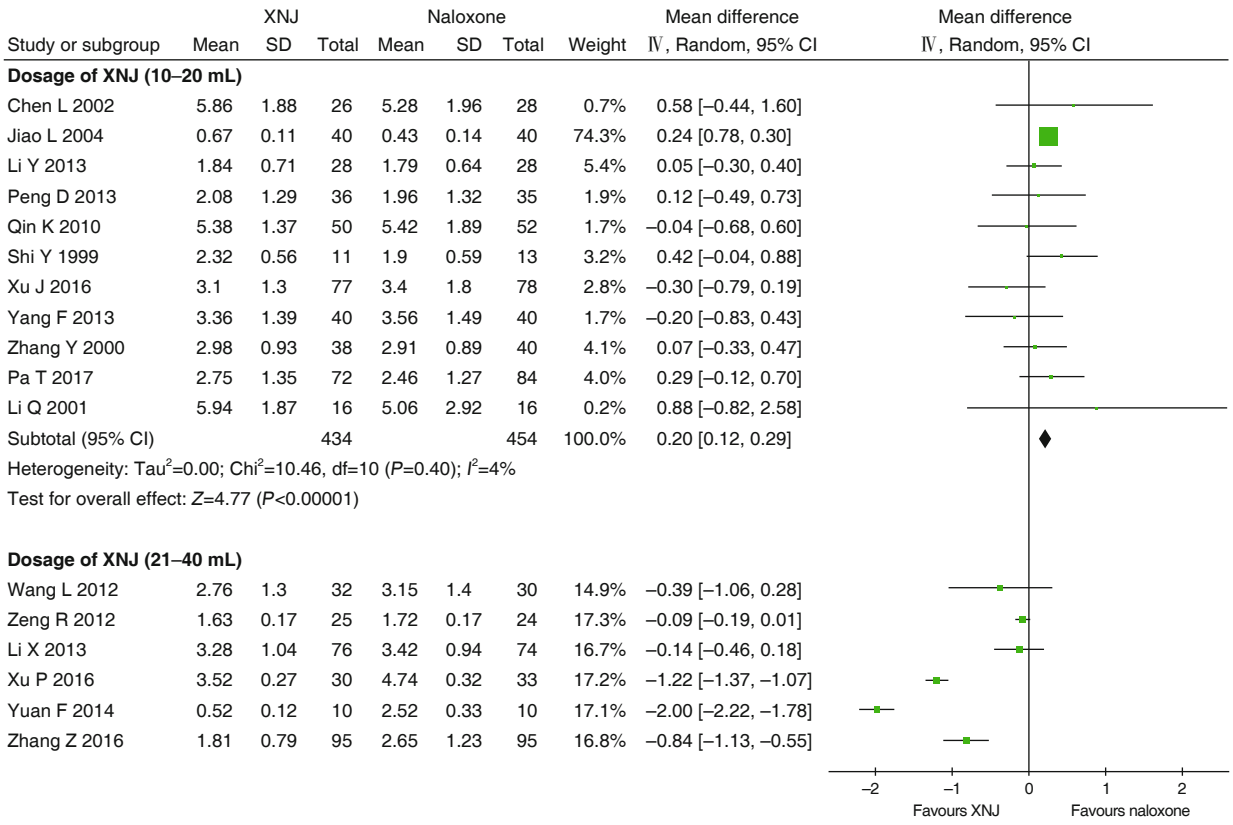

Figure 2. Forest Plot of Comparison between XNJ plus Routine Therapy and Naloxone plus Routine Therapy on Time of Consciousness Recovery

Notes：XNJ：Xingnaojing Injection; SD: Standard deviation; CI: Confidence interval

–7.2 min, *P*=0.03, 4 trials, 311 patients),[46,65,134,138] however, results of the meta-analysis were also doubted due to the serious statistical heterogeneity (I^2=100%, Figure 3).

Three trials[66,90,123] reported the number of patients whose conscious recovered and symptoms disappeared within 1 h (RR 1.26, 95%CI 0.85 to 1.87, I^2=9%, *P*=0.26, 3 trials, 190 patients), and other 2 trials[98,152] reported the number of patients whose consciousness recovered and symptoms disappeared within 2 h (RR 1.00, 95% CI 0.79 to 1.26, I^2=0%, *P*=0.99, 2 trials, 166 patients). All of them showed no difference between XNJ and naloxone on these two outcomes.

Combination of XNJ and Naloxone plus Routine Therapy *vs.* Naloxone plus Routine Therapy

Totally 107 trials[18-31,33-37,39-42,44,45,47-49,52,53,55,56,60,61,63-75,77,78,80,82-84,86-93,96,100-107,110,111,113,115-118,120-122,124-129,132,133,136-144,146-148,150,151,153-155,157,158] reported the time of recovery of consciousness. Meta-analysis was not conducted due to the serious statistical heterogeneity (I^2=100%), results from each single study showed that the combined therapy may accelerate the consciousness recovery compared with the naloxone group. Similar results were showed for the time of disappearance of symptoms with 71 included trials,[19,23,24,29-31,33-42,44,45,47,49,50,59,63-66,68,69,71,73-75,77-79,81,83,85,87,90,94,95,100,102,105-110,114,116-119,121,124-126,135,137,138,140-142,144,146,150,154,155,158] details of the results from each study are listed in Appendixes 2 and 3. The statistical heterogeneity could not be explained by the different dosage of XNJ or type of AAI, which may be caused by the difference of the time reported in each trial (from 23.4 to 454.2 min), intervention details (such as the details of the routine therapy) and the variety of the patients' characteristics.

Twenty trials[25,27,29,32,33,41,44,47,51,64,66,77,88,90,99,100,112,131,150,155] reported the number of patients whose consciousness recovered and symptoms disappeared within 1 h (RR 1.42, 95% CI 1.29 to 1.56, I^2=0%, *P*<0.01, 20 trials, 1,875 patients), and other 11 trials[39,43,57-59,71,76,120,151,152,156] reported the number of patients whose consciousness recovered and symptoms disappeared within 2 h (RR 1.45, 95% CI 1.31 to 1.59, I^2=1%, *P*<0.01, 11 trials, 1,272 patients).

Nine trials[50,60,79,84,109,132,148,155,158] reported the length of stay in the emergency department and found the combined therapy may shorten the treatment time

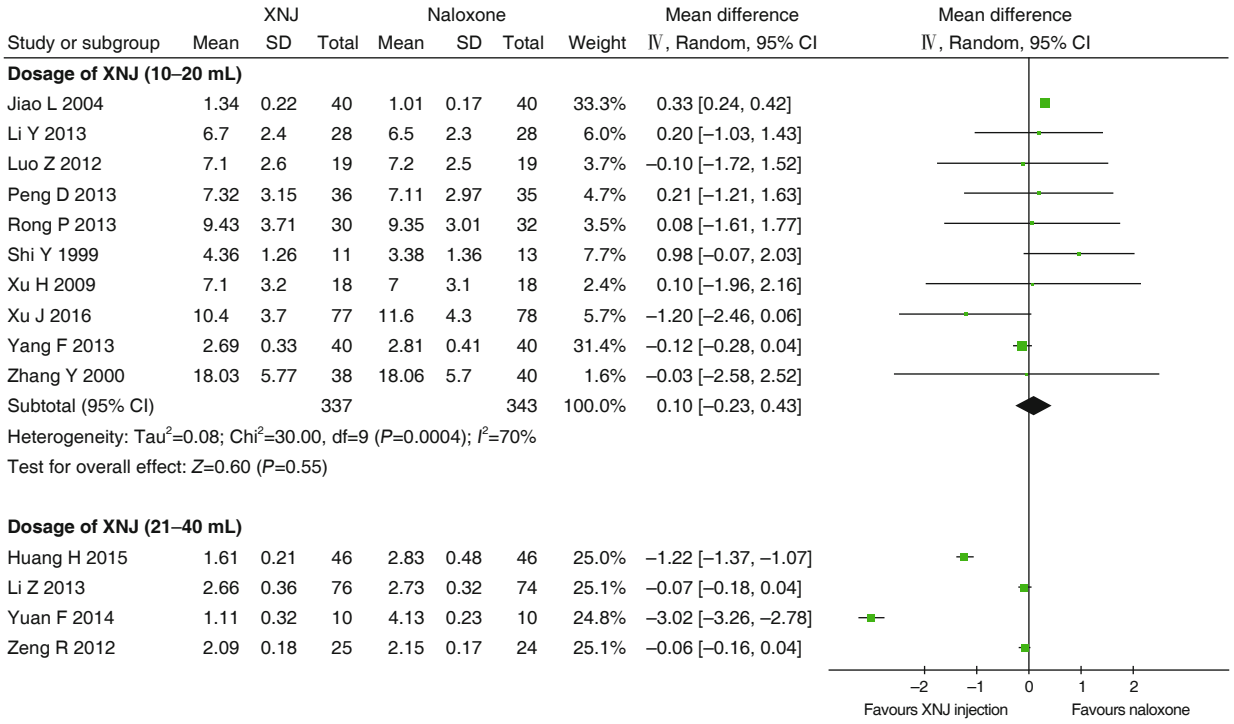

Figure 3. Forest Plot of Comparison between XNJ Injection plus Routine Therapy and Naloxone plus Routine Therapy on Time of Symptoms Disappear

Notes：XNJ: Xingnaojing Injection; SD: Standard deviation; CI: Confidence interval

in emergency department (MD –338.4 min, 95% CI –471.6 min to -258.6 min, *P*<0.01, 9 trials, 870 patients). However, the time of stay was reported from 3 h to 43 h among trials, which resulted in serious statistical heterogeneity (I^2=95%), thus, meta-analysis was not conducted.

XNJ *vs.* Naloxone

One trial[130] compared XNJ and naloxone without any other routine therapy, time of recovery of consciousness was reported and showed XNJ was superior to naloxone on this outcome (MD –264.6 min, 95% CI –293.4 min to –235.8 min).

Funnel Plot

Totally 6 meta-analysis were conducted in this review, funnel plot of all these 6-analysis showed potential asymmetry which may cause by the publication bias. Since all the included trials were assessed as having unclear risk of bias, sensitive analysis which was planned in the protocol did not conduct in the review.

AEs

Eighty-three of 141 included trials did not mention the safety information during the treatment. Thirty-two trials[20,22,23,25,47-49,53,58,63,65,68,71,72,83,87,88,91,93,97,100,107,113,115,116,121,125,127,128,136,141,143] found no AE in both groups. The remaining 26 trials[32,39,40,46,55-57,64,69,75,89,92,101,105,106,112,117,126,129-131,135,139,146,150,153] reported the numbers of AEs in XNJ or control group. However, AEs were defined as symptoms after awakening such as acid reflux, headache, vomit, nausea, fatigue, etc. And, most of them found no difference in incidence rate of AEs between groups. No severe AEs or adverse reactions of XNJ was reported.

DISCUSSION

Compared to the previous review,[15] this study included more than 115 studies and investigate the dose-response effect of XNJ for patients with AAI. Due to the unclear risk of bias of all the included trials, the obvious statistical heterogeneity among trials and the potential publication bias, level of the evidence for effect of XNJ single use or combined with naloxone *vs.* naloxone alone on basis of routine therapy for increasing number of patients whose consciousness recovery and symptoms disappear within 30 min were all assessed as 'very low' or 'low' according to the GRADE assessment criteria (Appendix 4). This limited the power to confirm the effectiveness of XNJ for patients with AAI, future high quality RCTs are still needed to improve the quality of the evidence.

We found that combination of XNJ and naloxone may

have better effect than naloxone used alone on shortening the consciousness time recovery and disappearance of symptoms, the average difference time between these two groups is 120 min (either for conscious recovery or symptoms disappearance), and the dose of XNJ seems not affect the effect of the combination therapy. But we should aware that the specific time of the reduction is uncertain due to the heterogeneity among the trials. When XNJ was used alone on the basis of routine therapy, larger dose (21–40 mL) may cause better effect compared to naloxone. However, according to the instruction, the standard dose of XNJ is 10–20 mL intravenous drip one time, none of the relevant studies explained the rationale for the overdose of XNJ. Though the instruction also points out that the dose of the XNJ could be determined following the doctor's advice, and the safety of the XNJ for patients with AAI is still unclear according to our study, thus, we suggest that clinicians should follow the regular dose as far as possible for prescribing XNJ.

Since the advantages regarding effectiveness of XNJ are not certain for AAI compared with naloxone, the cost-effectiveness assessment between XNJ and naloxone should be done in the future, as well as the studies to determine whether the advantages of combination therapy were still existing in consideration of the economic outcomes.

Besides the effectiveness, safety issue is also concerned for herbal medicine injection. However, few of the published articles mentioned the safety outcomes of this kind of intervention. In this review, none of the included trial reported AE during treatment, thus, no conclusion could be drawn for the safety of XNJ. The previous published systematic review[160] concerned XNJ Injection also found insufficient data regarding to safety issue, even though no severe adverse event was ever recorded according to the relevant trials. We suggest that future researches should report safety outcomes relevant to the treatment of XNJ.

Furthermore, the low methodological quality of the included RCTs limited the level of the evidence, future studies should also aware of the potential bias during the research and try to improve the quality of the trials. For example, participants should be randomly assigned to the different groups to avoid the selection bias, appropriate methods of allocation concealment should be used as well. Pre-designed protocol was necessary before trial application to avoid the potential bias (such as selective report bias).

With 13,901 participants from 141 included trials, this review found low quality evidence on XNJ, that it may have equal effect as naloxone when single application and get better effect as add-on intervention with naloxone on shorten the conscious recovery and symptoms disappearance's time for patients with AAI. Future studies may work on the dose-response effect of XNJ or the cost-effective analysis to further discuss its clinical application value. Safety of the XNJ is also suggested to be reported in the future researches.

Conflict of Interest

All authors declare no competing financial interest.

Author Contributions

Wu JR and Cao HJ conceived the research topic and formulated the plan of the study. Cheng N, Wang RT, and Huang XY screened the literatures and selected the eligible trials according to the above criteria. Disagreements were solved by discussion with Cao HJ. Cao HJ performed the statistical analysis and drafted the manuscript. Wu JR helped to draft the protocol and the final manuscript. All authors read and approved the final manuscript.

Electronic Supplementary Material: Supplementary material (Appendixes) are available in the online version of this article at http://dx.doi.org/10.1007/s11655-019-3037-3.

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