Efficacy of high-dose ambroxol for paraquat poisoning: A meta-analysis of randomized controlled trials

Junwu Wang[1], Wensu Yu[2], Na Wu[2], Elaine N Gitonga[1], Haitao Shen[1]

[1]Department of Emergency Medicine, Shengjing Hospital of China Medical University, Shenyang, People's Republic of China, [2]Department of Endocrinology, Shengjing Hospital of China Medical University, Shenyang, People's Republic of China

Background: Paraquat (PQ) poisoning is characterized by rapidly progressive acute poisoning with high mortality and no specific antidote. Although some clinical studies have been conducted to investigate the benefits of high-dose ambroxol as an adjuvant treatment for PQ poisoning, the efficacy is controversial. **Materials and Methods:** After searching for relevant articles in English and Chinese databases from 1978 to 2019 according to the keywords (paraquat poisoning/methy viologen/gramoxone, and ambroxol/mucosolvan/Bromhexine), we found seven articles that met our inclusion and exclusion criteria. A meta-analysis was performed using fixed-effects model and random-effects model according to the I^2 value in Stata software (version 15.0). Four outcome indicators (hospital mortality, partial pressure of oxygen (PaO_2), oxygenation index (PaO_2/FiO_2), and survival time of the deceased patients) were of interest to us. **Results:** The meta-analysis showed that adjuvant treatment with high doses of ambroxol increased PaO_2 (weighted mean difference [WMD] = 13.73 [mmHg], 95% confidence interval [CI]: 8.68–18.79, $Z = 11.80$, $P < 0.001$), PaO_2/FiO_2 (WMD = 38.81 [mmHg], 95% CI: 29.85–47.76, $Z = 8.49$, $P = 0.000$), and survival time of the deceased patients (WMD = 2.58 [d], 95% CI: 0.97–4.18, $Z = 3.15$, $P = 0.002$) compared with usual treatment. Treatment with high doses of ambroxol also appeared to reduce the hospital mortality (relative risk = 0.69, 95% CI: 0.55–0.86, Z = 3.25, $P = 0.001$). **Conclusion:** This study found that high-dose ambroxol is an effective therapy for PQ poisoning and may reduce the in-hospital mortality.

Key words: High-dose ambroxol, meta-analysis, paraquat poisoning

INTRODUCTION

The chemical name and chemical formula of paraquat (PQ), also known as gramoxone, are $C_{12}H_{14}C_{12}N_2$ and 1,1' dimethyl-4,4' dichlorodipyridine, respectively. As an herbicide, its toxicological mechanism is still unclear, and no specific antidote has been developed. The mortality is very high after accidental or intentional ingestion.[1,2] Acute lung injury (ALI) is one of the earliest complications of PQ poisoning. The extent of lung damage and poor prognosis is directly related to the early manifestation of ALI. Early treatment of PQ poisoning by elimination of the oxygen-free radicals, inhibition of the inflammatory reaction, and prevention of pulmonary fibrosis is paramount.[3]

Ambroxol has several therapeutic properties in the respiratory system; it not only acts as a mucolytic agent that aids in the reduction of viscid or excessive secretions in the treatment of chronic bronchitis, but also its antioxidant and anti-inflammatory properties are vital in the treatment of acute respiratory distress syndrome.[4] Furthermore, ambroxol promotes the production of pulmonary surfactant that is essential in increasing pulmonary compliance and overall improving ventilation.[5] As a result, a variety of clinical studies have shown that high-dose ambroxol can

Address for correspondence: Dr. Haitao Shen, Department of Emergency Medicine, Shengjing Hospital of China Medical University, 36 Sanhao Street, Shenyang 110004, People's Republic of China. E-mail: shenht@sj-hospital.org

alleviate the lung damage caused by PQ poisoning and enhance the effect of therapy for PQ poisoning.[6-8] However, some studies disagree.[9-12]

There has been no systematic evaluation of high-dose ambroxol to treat PQ poisoning. It is controversial that high-dose ambroxol could increase the survival rate in paraquat poisoning through improve the respiratory function by antioxidant and anti-inflammatory. Therefore, in order to evaluate the efficacy of high-dose ambroxol in the treatment of PQ poisoning, we conducted a meta-analysis of multiple clinical studies.

DATA AND METHODS

Search strategy
We searched China National Knowledge Infrastructure (CNKI), Wanfang Database, VIP Database, PubMed Database, and Web of Science. The timeline was between 1978 and 2019, and the language was Chinese or English. Potentially relevant papers were identified by Medical Subject Headings including combinations of the following keywords: Paraquat poisoning/Methy viologen/gramoxone, ambroxol/mucosolvan/Bromhexine, and Metabolite VIII. Afterward, any papers that may be missed by the citation lists in the identified literature were manually searched [Figure 1].

Inclusion criteria
The inclusion criteria were as follows: (1) studies that were on the treatment of PQ poisoning with high-dose intravenous ambroxol (more than 500 mg by intravenous infusion per day);[13] (2) patients who had PQ poisoning; (3) interventions: high-dose ambroxol was used in the treatment group on the basis of the dose used in the control group,

while conventional supportive treatment was used in the control group; (4) study outcome indicators include at least one of the following: hospital mortality, partial pressure of oxygen (PaO_2), oxygenation index (PaO_2/FiO_2), and survival time of the deceased patients; (5) the study was designed as a randomized controlled trial.

Exclusion criteria
The exclusion criteria were as follows: (1) both the treatment and control groups were treated with ambroxol; (2) patients had other serious diseases; and (3) the study was not randomized or controlled.

Quality assessment
We used the Cochrane Collaboration's tool for assessing risk of bias to evaluate the quality of the literature. This table contains six parts ([1] sequence generation;[2] allocation concealment;[3] blinding;[4] incomplete outcome data;[5] no selective outcome reporting; and[6] other sources of bias), and the low risk of each part will get 1 point. The higher points mean better quality.[14] If a study was no more than 3 points, the trial was considered to have high risk of bias, and if a study got more than 3 points, the trial was considered to have low risk of bias.

Statistical methods
Data collection was carried out for studies that met the inclusion criteria, and meta-analysis was performed using Stata SE15.0 (StataCorp LLC, College Station, TX, USA). The death outcome in hospital, PaO_2, PaO_2/FiO_2, MODS incidence, and survival time of the deceased patients were taken as the observation indicators. The relative risk (RR), weighted mean difference (WMD) calculated by the inverse variance method, and their confidence intervals (CIs) were calculated accordingly. Heterogeneity was evaluated using the Cochran Chi-square test and the Cochrane-I^2 statistics (test level: $\alpha = 0.05$). The I^2 value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. If $I^2 < 50\%$, the fixed-effect model was used for analysis, and if $I^2 > 50\%$, the random effects model was used.[15]

Publication bias was assessed by visual inspection of funnel plots, and statistical assessment of asymmetry was done with Egger's regression asymmetry test and Begg's adjusted rank correlation test. The sources of publication bias were also evaluated using sensitivity analysis, in which each individual study was removed from the analyses.

RESULTS

Quality assessment and basic information of the included studies
According to the search strategy, a total of 111 articles were initially included. Among these, 87 were in Chinese and 24
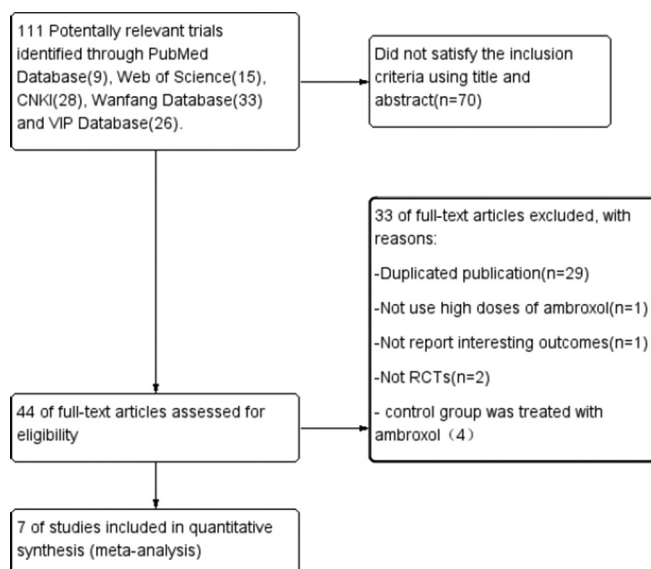

Figure 1: Flow diagram of the study search and selection process

Text within figure:
111 Potentially relevant trials identified through PubMed Database(9), Web of Science(15), CNKI(28), Wanfang Database(33) and VIP Database(26).

Did not satisfy the inclusion criteria using title and abstract(n=70)

33 of full-text articles excluded, with reasons:
-Duplicated publication(n=29)
-Not use high doses of ambroxol(n=1)
-Not report interesting outcomes(n=1)
-Not RCTs(n=2)
- control group was treated with ambroxol（4）

44 of full-text articles assessed for eligibility

7 of studies included in quantitative synthesis (meta-analysis)

were in English. According to the inclusion and exclusion criteria, seven articles were finally included after manual screening and evaluation. All the included studies were randomized controlled trials, including 326 patients in total. In general, although all of the included studies mentioned the randomized allocation of participants, none of the trials described the methods of sequence generation, allocation concealment, and blinding. As a result, the quality of the seven studies was of low quality (the score ranged from 2 to 3). The quality of the literature is shown in Table 1, and the basic information about the studies is shown in Table 2.

Heterogeneity test and combined effects
Partial pressure of oxygen index
Of the seven clinical studies, four measured the PaO_2 index after using high-dose ambroxol to treat PQ patients. A total of 204 patients were included, and the heterogeneity test (I^2 = 91.4%, P = 0.000) indicated that there was heterogeneity between the four studies. The results of the analysis using a random effects model (WMD = 13.73 [mmHg], 95% CI: 8.68–18.79, Z = 11.80, P = 0.000) showed a statistically significant difference, indicating that high-dose ambroxol can improve PaO_2 in patients with PQ poisoning [Figure 2].

Oxygenation index
Of the seven clinical studies, three reported the PaO_2/FiO_2 after using high-dose ambroxol to treat PQ patients. A total of 127 patients were included. The heterogeneity test (I^2 = 0.0%, P = 0.446) indicated no heterogeneity between the three studies. The results were then analyzed using a fixed-effect model (WMD = 38.81 [mmHg], 95% CI: 29.85 –47.76, Z = 8.49, P = 0.00). The difference was statistically significant, indicating that high-dose ambroxol can improve the PaO_2/FiO_2 of patients with PQ poisoning [Figure 3].

Survival time of the deceased patients
Of the seven clinical studies, five measured survival time of dead cases in the experimental group and the control group. A total of 116 patients were included, and

the heterogeneity test (I^2 = 73.7%, P = 0.004) indicated heterogeneity between the five studies. The results were analyzed using a random effects model (WMD = 2.58 [*d*], 95% CI: 0.97–4.18, Z = 3.15, P = 0.002). The difference was statistically significant, which indicated that high-dose ambroxol can increase the survival time of the deceased patients with PQ poisoning [Figure 4].
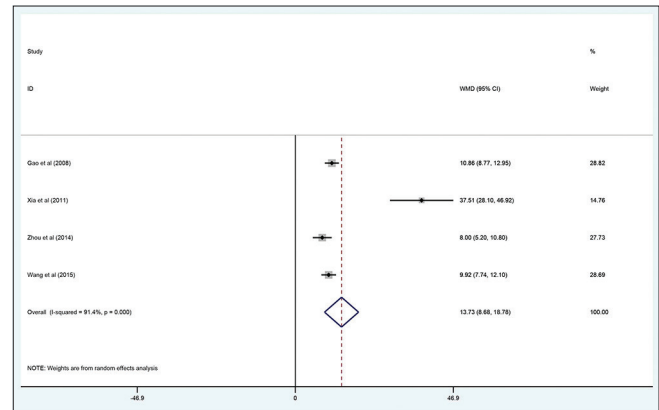

Figure 2: Random effects analysis of the six randomized controlled trials of the use of the PaO_2 index after using high-dose ambroxol to treat paraquat poisoning patients
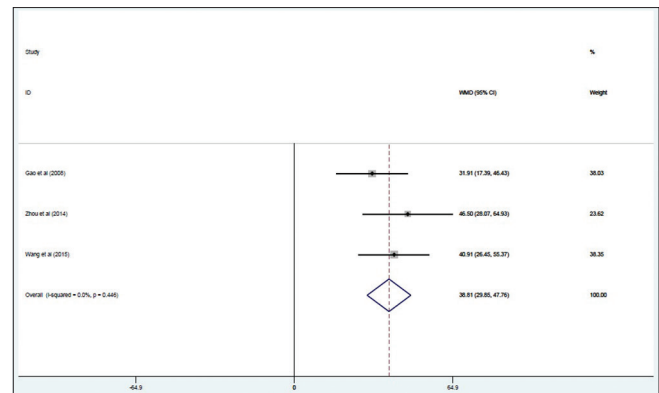

Figure 3: Fixed effects analysis of the three studies related to the oxygenation index (PaO_2/FiO_2) after using high-dose ambroxol to treat paraquat poisoning patients
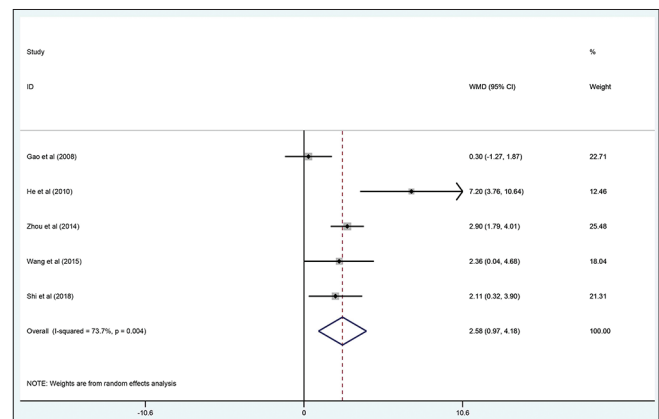

Figure 4: Random effects analysis of the seven studies related to survival time in the experimental group and the control group

Table 1: The methodological quality of included randomized controlled trials

Study	A	B	C	D	E	F	Total
Yufeng *et al.*, 2008[9]				✓	✓	✓	3
Yufeng *et al.*, 2010[10]				✓	✓	✓	3
Dejian *et al.*, 2010[6]				✓	✓		2
Min *et al.*, 2011[7]				✓	✓		2
Juan *et al.*, 2014[8]				✓	✓		2
Wang *et al.*, 2015[11]				✓	✓	✓	3
Weiliang, 2018[12]				✓	✓	✓	3

A=Sequence generation, B=Allocation concealment, C=Blinding, D=Incomplete outcome data, E=No selective outcome reporting, F=Other sources of bias, ✓=Low risk

Table 2: Basic information of the studies included

Study	Type of study	Numbers (T/C)	Oral dose of paraquat	Age (years)	Intervention		Main outcomes (follow time)
					Text group	Control group	
Yufeng *et al.*, 2008[9]	RCT	21/20	20-150 ml	35.6±9.2	Ambroxol 20 mg/kg/day×3 – 5 days + usual treatment (HP, HD, methylprednisolone, antioxidation, hepatic protector, fluid infusion)	Usual treatment (HP, HD, methylprednisolone, antioxidation, hepatic protector, fluid infusion)	①②③④ (NM)
Yufeng *et al.*, 2010[10]	RCT	16/15	2-30 g	Median age, 33	Ambroxol 20 mg/kg/day×3 days + usual treatment (HP, HD, glucocorticoid, antioxidation, hepatic protector, fluid infusion)	Usual treatment (HP, HD, glucocorticoid, antioxidation, hepatic protector, fluid infusion)	① (NM)
Dejian *et al.*, 2010[6]	RCT	13/14	NT	T: 31.3±10.6 C: 30.5±9.5	Ambroxol 15 mg/kg/day×5 – 7 days + usual treatment (gastric lavage, mannitol, diuresis, magnesium sulfate, vitamin, propranolol, reduced glutathione, methylprednisolone, cyclophosphamide)	Usual treatment (gastric lavage, mannitol, diuresis, magnesium sulfate, vitamin, propranolol, reduced glutathione, methylprednisolone, cyclophosphamide)	①④ (NM)
Min *et al.*, 2011[7]	RCT	38/39	10-200 ml	T: 13-75 C: 15-78	Ambroxol 1.0 g/day× 14 days + usual treatment (HD, gastric lavage, activated carbon, vitamin, magnesium sulfate, mannitol, compound danshen, anisodamine, hepatic protector, fluid infusion)	Usual treatment (HD, gastric lavage, activated carbon, vitamin, magnesium sulfate, mannitol, compound danshen, anisodamine, hepatic protector, fluid infusion)	①② (2 m)
Juan *et al.*, 2014[8]	RCT	23/23	5-100 ml	T: 41.9±17.5 C: 36.2±11.8	Ambroxol 20 mg/kg/day×3 days + usual treatment (HP, gastric lavage, vitamin, diuresis, reduced glutathione, methylprednisolone, cyclophosphamide, omeprazole)	Usual treatment (HP, gastric lavage, vitamin, diuresis, reduced glutathione, methylprednisolone, cyclophosphamide, omeprazole)	①②③④ (NM)
Wang *et al.*, 2015[11]	RCT	20/20	20-150 ml	T: 29.6±8.2 C: 30.3±9.1	Ambroxol 20 mg/kg/day×5 days + usual treatment (HP, gastric lavage, activated carbon, Mannitol, glucocorticoid, diuresis, activated carbon, mannitol, fluid infusion)	Usual treatment (HP, gastric lavage, activated carbon, mannitol, glucocorticoid, diuresis, activated carbon, mannitol, fluid infusion)	①②③④ (NM)
Weiliang, 2018[12]	RCT	32/32	T: 44.38±23.58 ml C: 45.92±29.34ml	T: 31.94±10.89 C: 31.48±10.36	Ambroxol 20 mg/kg/day×5 days + usual treatment (gastric lavage, diuresis, glucocorticoid, hepatic protector, fluid infusion)	Usual treatment (gastric lavage, diuresis, glucocorticoid, hepatic protector, fluid infusion)	①④ (NM)

RCT=Randomized controlled trial, T/C=Text group/control group, ①=Death outcome in hospital, ②=PaO₂, ③=PaO₂/FiO₂, ④=Survival time of the deceased patients, HP=Hemoperfusion, HD=Hemodialysis, NM=Not mention

Mortality

Of the seven clinical studies, all studies indicated the mortality of PQ patients treated with high-dose ambroxol. A total of 326 patients were included. The heterogeneity test ($I^2 = 0\%$, $P = 0.698$) indicated no heterogeneity between studies. The results were then analyzed using a fixed effects model (RR = 0.69, 95% CI: 0.55–0.86, Z = 3.25, $P = 0.001$). The difference was statistically significant, which indicated that high-dose ambroxol can increase the survival of patients with PQ poisoning [Figure 5].

Publication bias and sensitivity analysis

To reduce the impact of publication bias on the credibility of the results, the bias of the included studies was analyzed using Begg rank correlation analysis and Egger linear regression analysis [Table 3]. If $P > 0.05$, there is publication bias between the included studies, and if $P < 0.05$, there is no publication bias between the included studies. By the way, the funnel plots were carried out [Figure 6]. Furthermore, sensitivity analyses' results showed no significant change in the estimated overall incidence as well as its values in subgroup analyses in this meta-analysis after excluding each individual study.

DISCUSSION

The major findings of our meta-analysis indicated that treatment with high doses of ambroxol could improve

arterial PaO_2 and PaO_2/FiO_2. Our meta-analysis results also showed that mortality in hospitals with PQ poisoning was reduced and survival time of the deceased patients was prolonged.

Table 3: The results of publication bias

| | Begg test | | Egger test |
	Z	P	P
PO_2	1.7	0.089	0.111
PaO_2/FiO_2	0.00	1.000	0.483
Survival time of the deceased patients	0.73	0.462	0.554
Hospital mortality	0.90	0.368	0.337

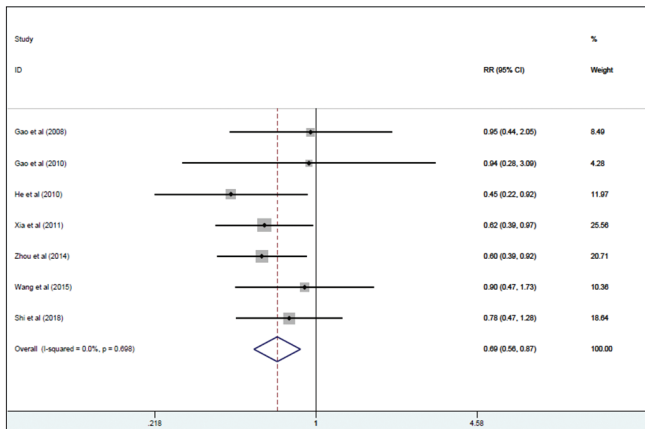*P*>0.05, there is no statistical significance

Figure 5: Fixed effects analysis of the ten studies of mortality in paraquat poisoning patients treated with high-dose ambroxol

Because there is no specific antidote and no definite diagnostic guide or method, the mortality related to PQ poisoning is currently very high (50%–70%).[3] Studies have shown that high-dose ambroxol has a therapeutic effect on ALI and acute respiratory distress.[16,17] On that basis, some experimental studies have shown that high-dose ambroxol may also have a certain therapeutic effect on PQ poisoning.[18] However, there has been no confirmed consensus or guidance.[3,19,20] In this study, a significant difference was found between the test group and the control group after using the treatment with high-dose ambroxol. The in-hospital mortality (RR = 0.69, 95% CI: 0.55–0.86) was reduced significantly. At the same time, the difference of survival time for death patients (WMD = 2.58 [*d*], 95% CI: 0.97–4.18) showed indirectly that high-dose ambroxol slowed down the progress of the poisoning.

Ambroxol has antioxidant and anti-inflammatory effects so that it is theoretically an alternative dose for treating ALI caused by PQ poisoning. The combined results showed high-dose ambroxol could increase arterial PaO_2 (WMD = 13.73 [mmHg], 95% CI: 8.68–18.79) and PaO_2/FiO_2 (WMD = 38.81 [mmHg], 95% CI: 29.85–47.76). The findings indicated that ambroxol was able to improve respiratory function.

However, there are still limitations to this study. First, no large-scale randomized controlled trials have been conducted. Second, although the seven studies included
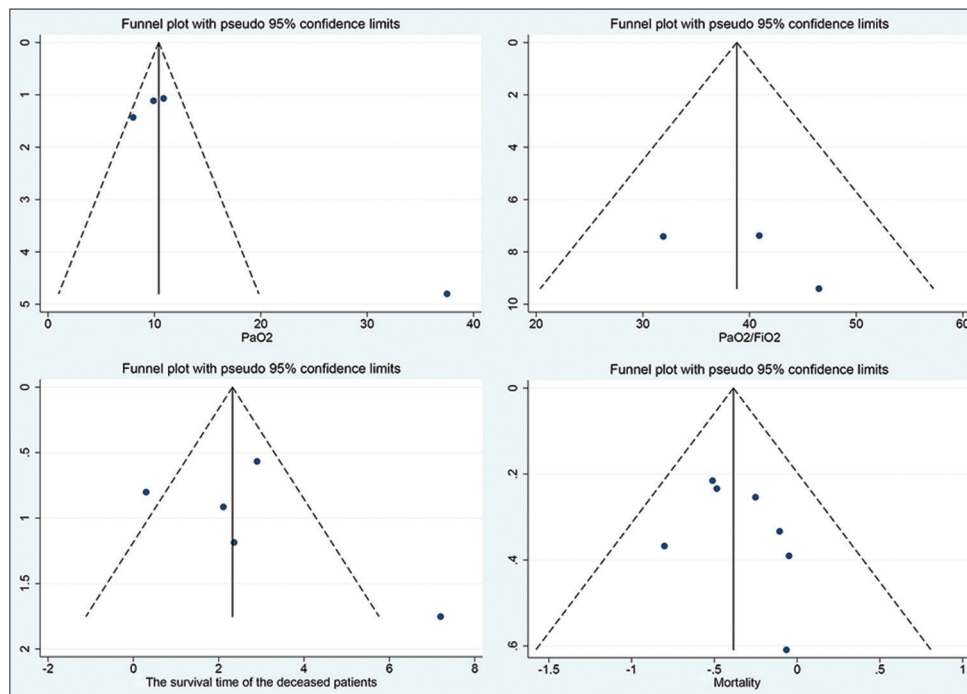

Figure 6: ① Funnel plot of high-dose ambroxol and conventional therapy versus conventional therapy in paraquat poisoning PaO2; ② funnel plot of high-dose ambroxol and conventional therapy versus conventional therapy in paraquat poisoning PaO2/FiO2; ③ funnel plot of high-dose ambroxol and conventional therapy versus conventional therapy in survival time of the deceased patients; ④ funnel plot of high-dose ambroxol and conventional therapy versus conventional therapy in hospital mortality

in the present study are randomized controlled trials, randomness cannot be assured because not all studies explained how the sequence was generated, how patients were allocated, whether researchers were blinded. For these reasons, the randomness and bias of those studies is uncertain, and the conclusion should be evaluated carefully. In addition, there were no high-quality studies in English. Next, there was significant heterogeneity in the analysis of PaO_2 (4 studies, 204 patients) and survival time (5 studies, 116 patients) in the experimental group and the control group, and these conclusions should be treated cautiously. In addition, ambroxol may have side effects such as hypersensitivity reactions when used.[21] However, all the studies made no mention of side effects or adverse reactions. Hence, specific studies should be conducted later to clarify this point.

CONCLUSION

The results of this meta-analysis indicate that high-dose ambroxol appears to increase PaO_2, PaO_2/FiO_2, and survival time of the deceased patients and reduce the mortality of patients with PQ poisoning. These benefits of ambroxol might be related to its antioxidant and anti-inflammatory effects. Therefore, it is necessary to conduct rigorously designed randomized controlled trials to further confirm the role of high-dose ambroxol in the treatment of PQ poisoning.

Conflicts of interest
There are no conflicts of interest.

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