Review Article

Hemoperfusion in combination with hemofiltration for acute severe organophosphorus pesticide poisoning: A systematic review and meta-analysis

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Background: Acute severe organophosphorus pesticide poisoning (ASOPP) is one of the major diseases that endanger human life and health. However, the effects of conventional therapy including gastric lavages, mechanical ventilation, muscarinic antagonist drugs, and cholinesterase reactivators were uncertain. This meta-analysis aims to investigate the safety and efficacy of hemoperfusion combined with hemofiltration besides routine therapy for ASOPP. **Materials and Methods:** A comprehensive search for candidate publications was performed through PubMed, Medline, Cochrane Library, WanFang, Chinese Biomedical Literature, and China National Knowledge Infrastructure from database inception to May 12, 2020. The retrieved studies were screened by the predefined inclusion and exclusion criteria. The data of important end points were extracted. The risk ratio (RR) and weighted mean difference (WMD) were pooled for categorical variables and continuous variables, respectively. Meta-analyses and publication bias were conducted by using STATA software version 15.1. **Results:** A total of 11 randomized controlled trials with 811 patients were included. Compared to conventional therapy group, patients in the hemoperfusion plus hemofiltration group were significantly superior with regard to mortality (RR 0.38, 95% confidence interval [CI] [0.25, 0.57], $P < 0.001$), total atropine dosing (WMD −147.34 mg, 95% CI [−199.49, −95.18], $P < 0.001$), duration of mechanical ventilation (WMD −2.34 days, 95% CI [−3.77, −0.92], $P < 0.001$), cholinesterase recovery time (WMD −2.49 days, 95% CI [−3.14, −1.83], $P < 0.001$), and length of stay (WMD −4.52 days, 95% CI [−5.31, −3.73], $P < 0.001$). **Conclusion:** Combined hemoperfusion and hemofiltration was a very safe and effective treatment protocol for ASOPP, not only resulting in significantly decreased mortality but also resulting in reduced total atropine dosing, duration of mechanical ventilation, cholinesterase recovery time, and length of stay.

Key words: Hemofiltration, hemoperfusion, meta-analysis, mortality, organophosphorus poisoning

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INTRODUCTION

Organophosphorus pesticide self-poisoning is a major clinical and public health problem all over the world, especially in China, South Asia, and Western Pacific. It is conservatively estimated that the total global burden of pesticide suicide is a plausible range of 9,859,667–17,303,333 deaths from 1960 to 2018.[1] Organophosphorus pesticides inhibit acetyl cholinesterase, resulting in excessive accumulation of acetylcholine at synapses, which causes muscarinic, nicotinic, and central nervous system symptoms, simultaneously with changes in the peripheral nervous system.[2] The conventional therapy mainly includes gastric lavages, wash of skin surface, intubation and mechanical ventilation, muscarinic antagonist drugs, and cholinesterase reactivators.[3] Nevertheless, there is

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currently no high-quality evidence to support the clinical effectiveness of gastric lavages;[4] atropine cannot counter nicotinic symptoms and excessive use will induce atropine poisoning, and oximes are less effective in the management of some organophosphorus insecticides poisoning such as malathion.[5]

It has been extensively recognized that hemoperfusion could effectively adsorb and remove the poisons from extracorporeal circulation since the 1970s.[6] However, hemoperfusion is unable to correct the pathophysiological changes caused by organophosphorus pesticides,[7] and there are some complications related to the procedures such as thrombocytopenia, hypocalcemia, decrease of immunoglobulins, and coagulation factors.[8] Conversely, hemofiltration, the most common modality, is continuous venovenous hemofiltration, not only help eliminate the toxins from the blood and regulate the body fluid balance but also clear the large number of inflammatory mediators and inflammatory factors.[9]

Thus, combined hemoperfusion and hemofiltration may theoretically have compensated for the respective deficiencies.[10] Whether this combined therapy could improve the clinical outcomes of patients with acute severe organophosphorus pesticide poisoning (ASOPP) in practice remains controversial. We aim to perform a meta-analysis evaluating the safety and efficacy among patients with ASOPP receiving hemoperfusion plus hemofiltration versus those not receiving.

MATERIALS AND METHODS

Literature search strategy

A comprehensive search for relevant publications was performed through PubMed, Medline, Cochrane Library, WanFang, Chinese Biomedical Literature, and China National Knowledge Infrastructure from database inception to May 12, 2020. The predefined search terms included hemoperfusion AND hemofiltration AND (organophosphorus OR organophosphate poisoning) AND (random OR "randomized controlled trial" OR RCT). No restrictions in language were implemented. The reference lists of included studies were also manually screened to identify the additional trials.

Inclusion and exclusion criteria

The following inclusion criteria were considered in this meta-analysis. (1) Randomized controlled trials (RCTs) investigating the benefits of hemoperfusion in combination with hemofiltration for patients. (2) All patients were certainly diagnosed as ASOPP by the exposure history of known organophosphorus pesticides and decreased cholinesterase activity (less than 30%). (3) Patients who received conventional therapy were included into control group, whereas those received hemoperfusion plus hemofiltration besides were included into trial group. (4) Mortality is the primary outcome, and the secondary outcomes include at least one or more as follows: atropine dosing, duration of mechanical ventilation, restoration time of cholinesterase, and length of stay. Articles were excluded if any of the following were present: (1) with other adjuvant treatments, (2) study data unavailable, (3) duplicate publications of the same study population, and (4) case reports, review articles, and letters to editor.

Data extraction and quality assessment

Two researchers independently screened titles and abstracts of all trial reports we identified above. Discrepancies were resolved through discussion with a third reviewer, as required. Then, another two authors independently extracted the following information from the included trials: first author's name, publication year, sample size, mean age of patients, intervention, and main outcome measures.

Two reviewers independently assessed the risk of bias of the included studies using the tool described in the Cochrane Handbook.[11] When the assessors disagreed, the final rating was decided through discussion or with the involvement of another member of the review group, if necessary. Quality assessment was assessed by the Review Manager software (version 5.4, the Cochrane's collaboration, Oxford, UK).

Statistical analysis

The outcomes were described as risk ratio (RR) with 95% confidence interval (CI) for dichotomous data (mortality) and the weighted mean difference (WMD) with 95% CI for continuous data (atropine, ventilation, cholinesterase, and length of stay). Heterogeneity among the studies was quantified by using the Cochrane test (Q) and I-square (I^2) test.[12] The fixed-effect model (Mantel–Haenszel method) would be selected when there were no heterogeneity ($P > 0.10$ and $I^2 < 50\%$), whereas the random-effect model (DerSimonian–Laird method) was used when there were obvious heterogeneity ($P \leq 0.10$ and $I^2 \geq 50\%$).[13] To evaluate the influence of an individual study on the pooled estimate, we performed sensitivity analysis by excluding studies one by one. To determine the potential publication bias, both the Begg's and Egger's test, and the funnel plots were performed.[14] Statistical significance for all analyses was set at $P < 0.05$. All the statistical analyses were performed by using the STATA software (version 15.1, Stata Corporation, College Station, TX, USA).

RESULTS

Characteristics of eligible studies

An initial search identified 342 articles from searching databases including 54 from PubMed, 27 from Medline,

Table 1: Main characteristics of included articles

First author	Year	Trial group				Control group				Outcomes
		Therapy	*n*	Male/female	Age	Therapy	*n*	Male/female	Age	
Han[15]	2017	HP+HF+Con	11	6/5	38.7±4.3	HP+Con	13	7/6	38.1±4.2	①②③④⑤
Jiao[16]	2016	HP+HF+Con	37	14/23	41.9±5.1	HP+Con	37	17/20	42.1±5.2	①④⑤
Liu[17]	2016	HP+HF+Con	17	9/8	43.1±8.0	HP+Con	17	10/7	42.9±8.3	①②③④⑤
Wang[18]	2016	HP+HF+Con	60	21/39	68.5±5.3	HP+Con	60	21/39	68.5±5.3	①③④
Xia[19]	2013	HP+HF+Con	34	12/22	45.5±9.1	Con	32	12/20	46.5±8.2	①②⑤
Xie[20]	2019	HP+HF+Con	55	30/25	44.4±4.7	HP+Con	55	32/23	44.5±4.8	①②④⑤
Xu[21]	2014	HP+HF+Con	34	12/22	36.2±2.3	Con	32	11/21	35.6±7.4	①③④⑤
Xue[22]	2019	HP+HF+Con	31	10/21	66.7±6.2	HF+Con	31	12/19	67.5±5.3	①④⑤
Yang[23]	2014	HP+HF+Con	41	19/22	38.5±6.2	HP+Con	40	17/23	37.8±3.6	①④
Yang[24]	2016	HP+HF+Con	32	24/8	40.5±3.2	Con	30	25/5	40.4±3.3	①④⑤
Yue[25]	2015	HP+HF+Con	56	24/32	43.2±8.4	Con	56	28/28	44.3±8.2	③④⑤

Outcomes: ①=mortality; ②=atropine dosing; ③=duration of mechanical ventilation; ④=restoration time of cholinesterase; ⑤=length of stay. HP=Hemoperfusion; HF=Hemofiltration; Con=Conventional

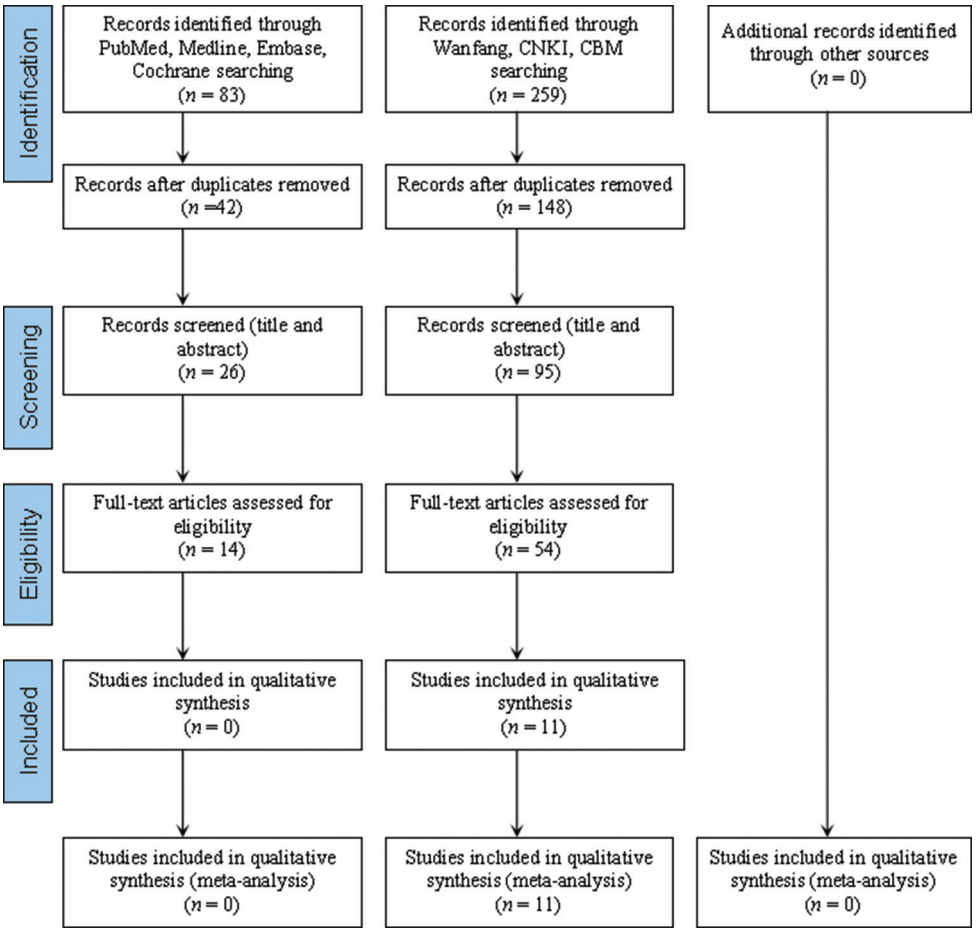

Figure 1: Flowchart for the procedure of the literature search

2 from Cochrane Library, 158 from WanFang, 30 from CNKI, and 71 from CBM. The flow diagram that detailed the process is shown in Figure 1. A total of 11 studies (including 811 patients) were eventually identified after abstract and full-text screening, which were all carried out in China.[15-25] Main characteristics of the patients enrolled as trial group and control group are shown in Table 1.

All of the included studies suggested randomization, but only six studies reported the method of random sequence generation, while all of the studies failed to report details about allocation concealment, only one article applied blinding. There were low risk of incomplete outcome data, selective reporting bias, and other bias. Therefore, all studies were judged to be of a relatively poor methodological quality [Figures 2 and 3].

Meta-analysis

Mortality

Ten studies with a total of 699 patients included eligible data on mortality. About 352 patients were in the trial group, of which 28 died (7.95%), while 347 cases were in the control group, of which 84 died (24.21%). A fixed-effect model was conducted because of low heterogeneity among studies (I^2 = 0.00%, P = 0.99). Pooled statistics demonstrated that patients in the trial group was associated with a lower mortality than the control group (RR = 0.38, 95% CI [0.25, 0.57], P < 0.001). Forest plot is shown in Figure 4.

Atropine dosing

Four studies with a total of 234 patients included eligible data on atropine. A random-effect model was conducted because of high heterogeneity among studies (I^2 = 95.0%, P = 0.00). Pooled statistics demonstrated that patients in the trial group was significantly associated with less atropine dosing than control group (WMD = −147.34 mg, 95% CI [−199.49, −95.18], P < 0.001). Forest plot is shown in Figure 5.

Duration of mechanical ventilation

Five studies with a total of 234 patients included eligible data on ventilation. A random-effect model was conducted because of high heterogeneity among studies (I^2 = 95.4%, P = 0.00). Pooled statistics demonstrated that patients in the trial group was significantly associated with shorter duration of mechanical ventilation than control group (WMD = −2.34 days, 95% CI [−3.77, −0.92], P < 0.001). Forest plot is shown in Figure 6.

Restoration time of cholinesterase

Ten studies with a total of 745 patients included eligible data on cholinesterase. A random-effect model was conducted because of high heterogeneity among studies (I^2 = 90.0%,

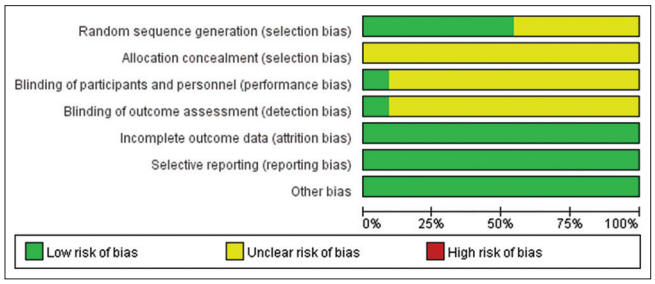

Figure 2: Risk of bias graph

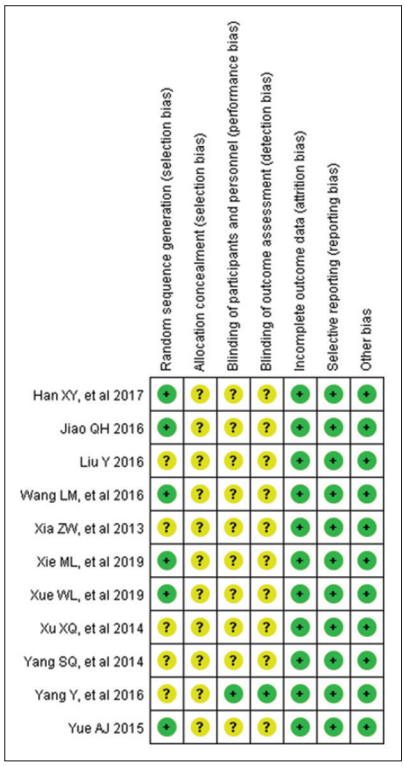

Figure 3: Risk of bias summary

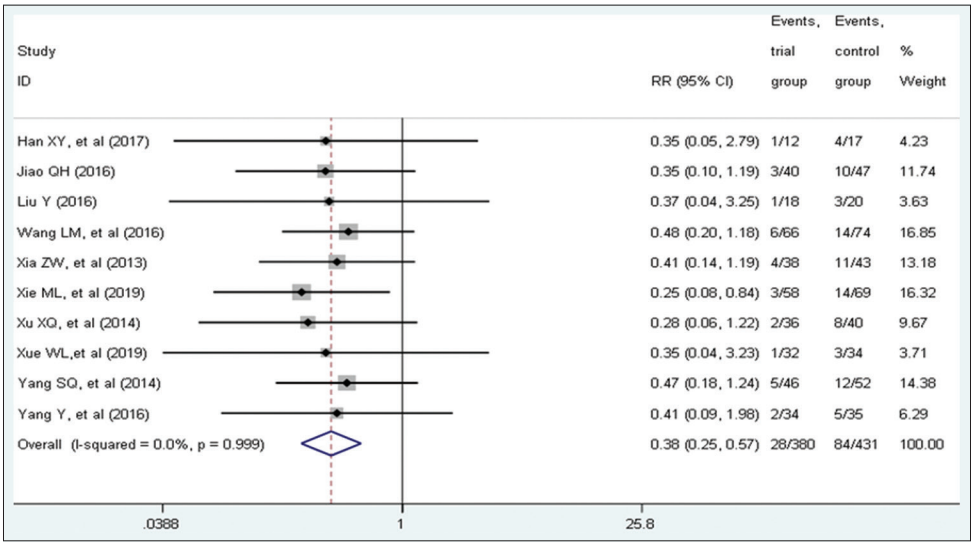

Figure 4: Forest plot of mortality

P = 0.00). Pooled statistics demonstrated that patients in the trial group was significantly associated with shorter cholinesterase than control group (WMD = −2.49 days, 95% CI [−3.14, −1.83], P < 0.001). Forest plot is shown in Figure 7.

Length of stay

Nine studies with a total of 610 patients included eligible data on length of stay. A randomized-effect model was conducted because of high heterogeneity among studies (I^2 = 87.1%, P = 0.00). Pooled statistics demonstrated that patients in the trial group was significantly associated with shorter length of stay than control group (WMD = −4.52 days, 95% CI [−5.31, −3.73], P < 0.001). Forest plot is shown in Figure 8.

Sensitivity analysis

The heterogeneity among the included studies was tested by using the sensitivity analysis. The pooled RR for mortality was not changed when any individual study was omitted [Figure 9]. The pooled WMDs for

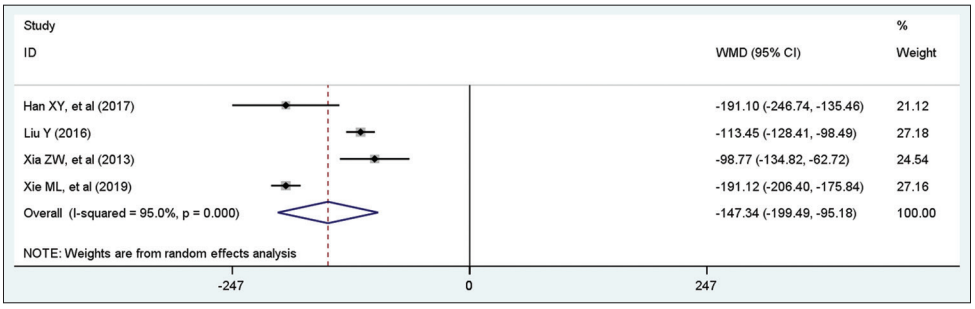

Figure 5: Forest plot of atropine dosing

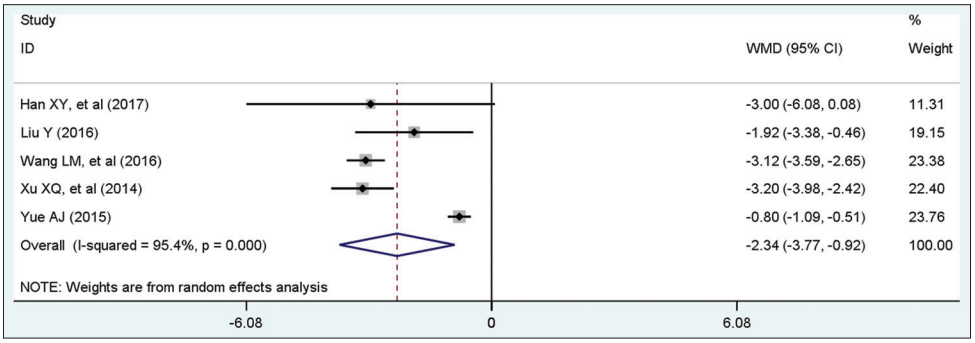

Figure 6: Forest plot of duration of mechanical ventilation

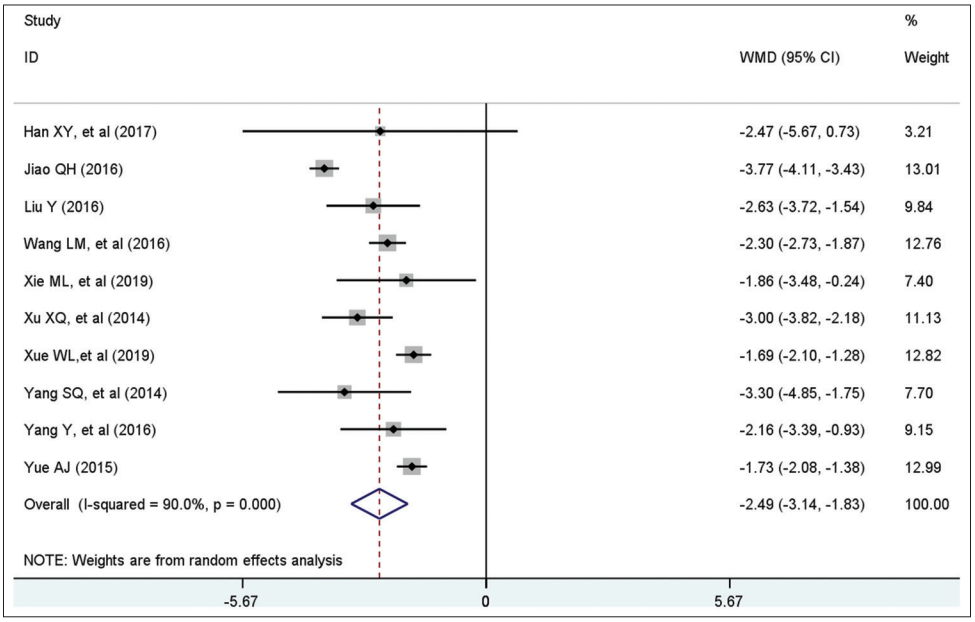

Figure 7: Forest plot of restoration time of cholinesterase

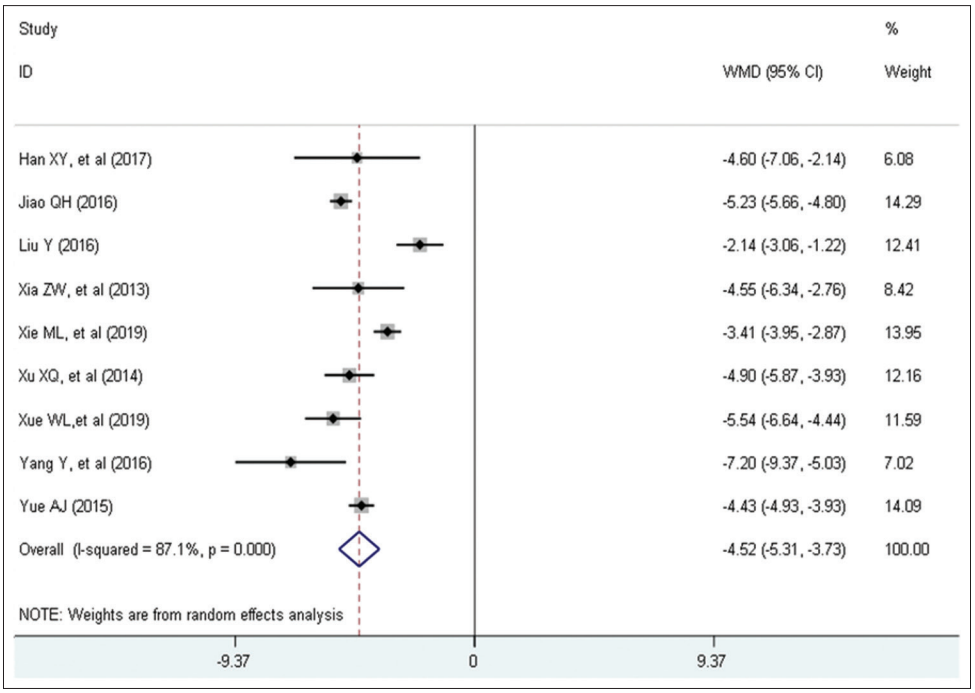

Figure 8: Forest plot of length of stay

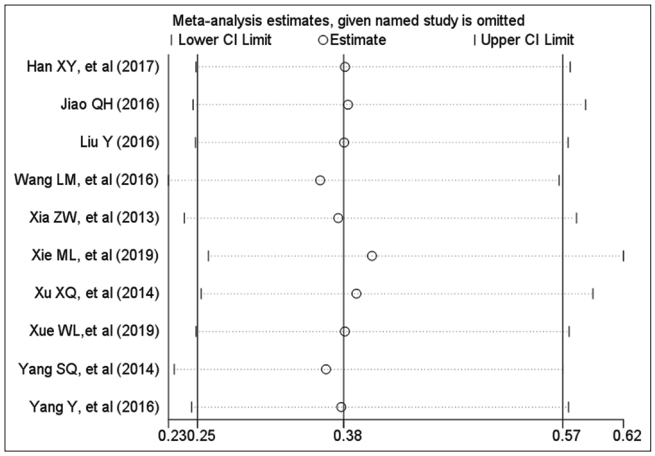

Figure 9: Influence plot. The graph demonstrates the sensitivity analysis for mortality

atropine, ventilation, cholinesterase, and length of stay were not changed when any individual study was omitted [Figure 10].

Publication bias

The publication bias was explored via funnel plot with the Begg's and Egger's tests. The funnel plots showed no obviously asymmetry among studies [Figures 11 and 12]. No evidence of publication bias was found for mortality (Begg's test: $P = 0.283$, Egger's test: $P = 0.205$). In addition, there was no publication bias for atropine (Begg's test: $P = 0.734$, Egger's test: $P = 0.945$), ventilation (Begg's test: $P = 1.00$, Egger's test: $P = 0.379$), cholinesterase (Begg's test: $P = 0.721$, Egger's test: $P = 0.988$), and length of stay (Begg's test: $P = 0.754$, Egger's test: $P = 0.906$).

DISCUSSION

It is the first meta-analysis to systematically evaluate the beneficial effects in patients who had undergone hemoperfusion in combination with hemofiltration besides conventional therapy. Our meta-analysis demonstrated that mortality was significantly lower in patients of the trail group compared with the control group. On the other hand, combined hemoperfusion and hemofiltration could more effectively decrease the length of stay, total atropine dosing, duration of mechanical ventilation, and restoration time of cholinesterase than those received classic treatments alone.

Organophosphorus pesticides are mostly lipophilic and low-molecular-weight poisons (e.g., chlorpyrifos 350 Da, malathion 330 Da, dichlorvos 221 Da), which are rapidly absorbed to the blood and distributed to target tissues and organs after ingestion, and then display a high degree of protein binding.[26] The toxicial mechanism mainly involves the combination with cholinesterase to form a stable phosphorylated cholinesterase which could hardly be broken down by acetyl cholinesterase and results in accumulation of large amounts of acetylcholine in synapses of the autonomic nervous system, central nervous system, and neuromuscular junction.[27]

Blood purification has been recommended as a therapeutic modality by extracorporeal circulation to remove organophosphorus pesticide from blood in recent decades. With the improved efficacy of hemodialysis, hemoperfusion is now less frequently performed in

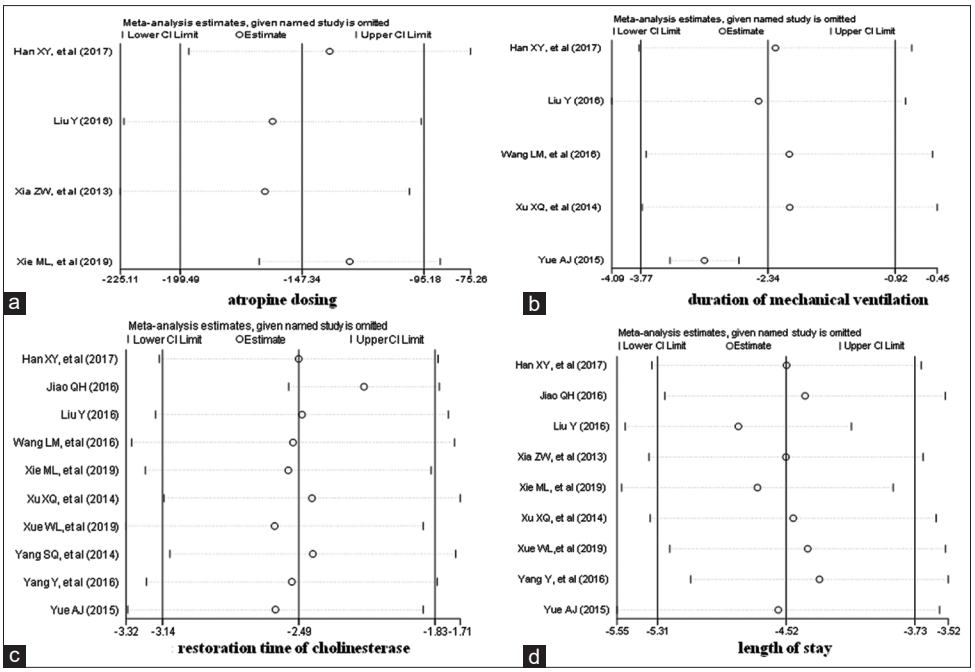

Figure 10: Influence plot. The graph demonstrates the sensitivity analysis for atropine, ventilation, cholinesterase, and length of stay

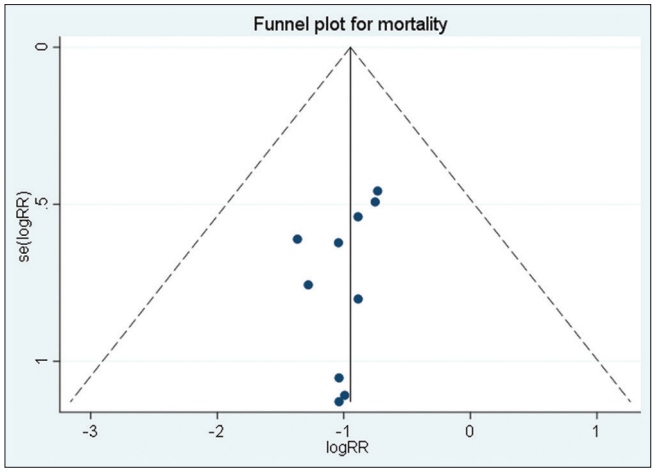

Figure 11: Funnel plot to show publication bias (mortality)

the United States but still remains popular in China.[28] Hemoperfusion is favored to eliminate poisons with middle-molecular-weight (less than 5000 Da), low volume of distribution, and high protein binding.[8] Previous studies have reported hemoperfusion could effectively decrease poisoning severity by removing significant amounts of organophosphate pesticides and increasing serum cholinesterase level.[29] Compared to activated charcoal column, the synthetic resin column is exhibit enhanced adsorption and clearance of organophosphorus pesticide and has less of a tendency to serious complications including thrombocytopenia, leukocytopenia, and decrease in platelet count.[30] However, we could not compare the effects and complications between these two columns due to the absence of information. In addition, although there is currently insufficient evidence to support the routine use of polymyxin B-immobilized hemoperfusion to treat patients with sepsis, this specific technique has been clinically used in many countries.[31]

Hemofiltration not only helps maintain stable hemodynamics, resulting in improved cardiovascular tolerability, but also protect a favorable balance of water and salt metabolism, resulting in better homeostasis.[32] It is reported that the poison and solvent of organophosphorus pesticide are simultaneously removed by convection and replaced by a physiological solution during hemofiltration.[33] On the other hand, hemofiltration can effectively decrease in serum interleukin 1 (IL-1), IL-6, IL-8, and tumor necrosis factor alpha, increase in serum IL-10 levels, reduce the chain reaction initiated by inflammatory cytokines, and limit damage resulting from ASOPP, which may be beneficial for critical patients with multiple organ dysfunction syndrome.[34]

In the present study, the whole descriptions of organophosphorus pesticides in all included articles were not available, which may contribute a lot to the heterogeneity among trials. There is substantial variability in clinical course, response to oximes, and mortality with different organophosphorus insecticides in human self-poisoning.[35] Acikalin *et al*. reported that long hospital stay, low initial serum cholinesterase level, respiratory depression necessitating intubation, and mechanical ventilation are independently associated with poor prognostic factors for ASOPP.[36] However, the usefulness of the serum cholinesterase level remains controversial,[37]

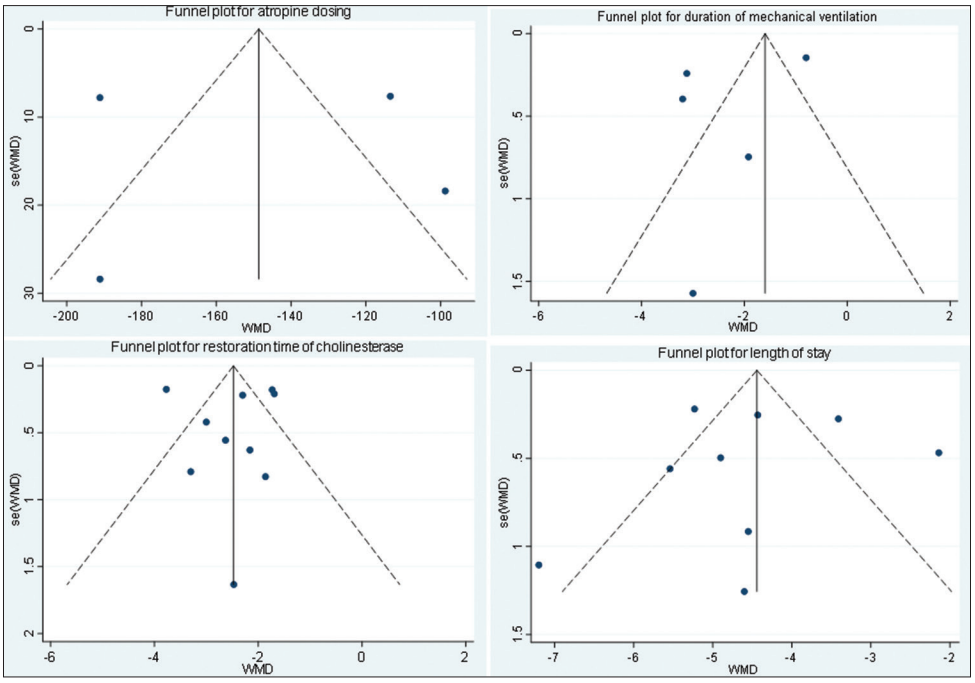

Figure 12: Funnel plot to show publication bias (atropine, ventilation, cholinesterase, and length of stay)

and some organophosphate pesticides inhibit butyryl cholinesterase more effectively than they inhibit acetyl cholinesterase. Although chlorpyrifos inhibits acetyl cholinesterase and initial serum cholinesterase level is generally low, it is least mortality in patients of acute chlorpyrifos poisoning.[38]

Limitations

There are still some limitations as follows. First of all, the identified articles included were all carried out in China and published in Chinese. Furthermore, the methodological quality of these included studies was generally low, especially none considered the procedures of allocation concealment. Only six studies carefully descripted the random sequence generation method, and only one used blinding methods during their implementations. Last but not least, we were unable to obtain the unpublished data based on current conditions. Those may have some effects on the pooled results.

CONCLUSION

ASOPP still has a high incidence and mortality despite the banning of rang poison and improved therapy. This systematic review indicated that combined hemoperfusion and hemofiltration may be beneficial adjuncts to patients with ASOPP. However, this evidence is inadequate to recommend their use in clinical practice. Larger high-quality multicenter RCTs are required to establish effectiveness.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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