Meta-analysis of the Efficacy of Hemoperfusion Combined With Hemodialysis in Treating Acute Severe Organophosphorus Pesticide Poisoning

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Abstract

Background

Acute severe organophosphorus pesticide poisoning (ASOPP) is a common severe emergency in developing countries. At present, the incidence of complications and mortality are still very high, and there are some difficulties in treatment. More and more studies have found that hemoperfusion combined with hemodialysis can improve the prognosis of patients based on conventional emergency treatment, but there is a lack of evidence-based medical evidence. Our meta-analysis is mainly to clarify the efficacy of hemoperfusion combined with hemodialysis on ASOPP.

Methods

We searched several databases. After formulating relevant inclusion and exclusion criteria, qualified studies were included and data were extracted. The outcome indicators were cure rate, efficacy, incidence of complications, time for cholinesterase level to return to normal, coma time, time of hospitalization and atropine dosage. Results were analyzed using risk ratios (RR), odds ratios (OR), weighted mean difference (WMD), standard mean difference (SMD), and 95% confidential interval (95% CI). The cochrane collaboration tool was used for the assessment of the risk of bias of every included studies. In terms of statistical methods, we used RevMan software (version 5.3) and Stata (version 14 and 16) for data analysis.

Results

We included 35 RCTs, including 2650 participants. Compared with the emergency conventional treatment group, the use of hemoperfusion combined with hemodialysis to treat ASOPP patients based on conventional emergency treatment significantly increased the cure rate [RR=1.20, 95% CI (1.16, 1.25), $p<0.00001$], improved the efficacy [OR=2.76, 95% CI (2.07, 3.67), $p=0.000$], and reduced the incidence of complications [RR=0.26, 95% CI (0.20, 0.34), $p<0.00001$] and also reduced the patient's time for cholinesterase level to return to normal [WMD=-4.05, 95% CI (-4.40, -3.70), $p<0.00001$], coma time [SMD=-2.62, 95% CI (-3.08, -2.15), $p<0.00001$], time of hospitalization [WMD=-5.80, 95% CI (-6.57, -5.02), $p<0.00001$], and atropine dosage [WMD=-194.81, 95% CI (-223.55, -166.08), $p<0.00001$].

Conclusion

Hemoperfusion combined with hemodialysis can apparently improve the prognosis of patients and has a good effect in the treatment of acute severe organophosphorus pesticide poisoning. In the future, more scientifically designed large-scale, high-quality, multi-center randomized controlled trials are needed to further illustrate the significance of this study.

1. Introduction

The most used pesticides in the world are organophosphorus pesticides. Acute organophosphorus pesticide poisoning (AOPP) is a very common acute and severe disease in the emergency department (ED), according to WHO's estimates, millions of people worldwide suffer from AOPP every year, of which about 200,000 die, most of which occur in developing countries. Early emetic, gastric lavage, catharsis, and early use of conventional emergency treatments such as pralidoxime, atropinization and a series of advanced life support measures have greatly improved the cure rate. However, the mortality rate is still high, especially for patients who are acute severe organophosphorus pesticide poisoning (ASOPP). For ASOPP patients, blood purification is also a common rescue method in emergency departments. However, up to now, blood purification therapy is still controversial in the treatment of ASOPP, and the evidence-based medical evidence for the efficacy of blood purification on ASOPP is insufficient which is not totally recognized by the medical community. Because hemoperfusion, hemodialysis or continuous renal replacement therapy (CRRT), while removing toxins, they also absorb and remove antidotes and therapeutic drugs from the blood to varying degrees, which reduce the efficacy of these drugs, and there is a potential risk of inducing poisoning aggravation¹. Despite this, there are a large number of literature reports that blood purification therapy, especially the current mainstream hemoperfusion combined with hemodialysis to treat ASOPP, is effective, but there is a lack of clinical evidence. According to the clinical guideline for the diagnosis and treatment of acute organophosphorus pesticide poisoning (2016)¹, the expert group recommends that ASOPP patients be given blood purification treatment as soon as possible while giving antidote and conventional emergency treatment. Our meta-analysis aimed to conduct a more comprehensive and in-depth analysis of the efficacy of hemoperfusion combined with hemodialysis on ASOPP patients through several different outcome indicators, providing clinical evidence for ASOPP blood purification therapy.

2. Methods

We reported this meta-analysis based on compliance with the PRISMA guidelines and we have registered on INPLASY with registration number 2021110056 and DOI of 10.37766/inplasy2021.11.0056.

2.1 Database and search strategies

We searched relevant RCTs in EMbase, Scopus, Cochrane, Web of science, PubMed, Ovid, Chinese Biomedical literature (CBM), Chinese National Knowledge Infrastructure (CNKI), Duxiu, China Science and Technology Journal Database (VIP) and WanFang for English and Chinese studies and Clinical Trials.gov and Chinese clinical trial Registry for registered clinical trials databases from January 1, 2017 until November 11, 2021². We searched the MeSH term organophosphate poisoning and other free words including organophosphate poisonings, organothiophosphonate poisoning, organophosphorus poisoning, organothiophosphate poisoning, organothiophosphate poisonings in English. Similarly, the hemoperfusion (MeSH term), hemoperfusions, hemosorption, hemosorptions, renal dialysis (MeSH term), renal dialyses, extracorporeal dialyses, hemodialysis, hemodialyses, were searched within the restriction limit of randomized controlled trial. Due to the complexity and particularity of Chinese, we had formulated

a more perfect search strategy. Chinese search term included words meaning acute severe organophosphorus pesticide poisoning, hemoperfusion, hemodialysis, and randomized controlled trial. In response to the Chinese term "acute severe organophosphorus pesticide poisoning", we had formulated 10 different search strategies. Similarly, 7 different retrieval strategies had been developed for hemoperfusion combined with hemodialysis in interventions. For study design, our search strategy included RCT, randomized control, random number table, lottery and so on. We had three reviewers to carry out the literature retrieval and screening. When there were differences, the other reviewers would intervene and they would reach a consensus. The search strategy was in the appendix 1.

2.2 Inclusion and exclusion criteria

The inclusion criteria of the studies are as follows:

- 1) Randomized controlled study (RCT)
- 2) All patients in each study were exposed to organophosphorus pesticides by any means, and diagnosed as acute severe organophosphorus pesticide poisoning (ASOPP) and they manifest as pulmonary edema, respiratory failure, coma, cerebral edema or other important organ failures.
- 3) Subjects in each studies may receive hemoperfusion combined with hemodialysis based on conventional emergency treatment.
- 4) Each study must report one or more of the following outcome indicators: cure rate, efficacy, incidence of complications, time for cholinesterase level to return to normal, coma time, time of hospitalization and atropine dosage.
- 5) Studies were from January 1, 2017 to November 11, 2021.

Any research will be excluded if it meets any of the following clauses:

1. The article did not clearly state that the research was RCT.
2. The language used in the research is not English or Chinese
- 3) Unable to obtain data from the study or the data of the study was not rigorous.
- 4) The patients in the study had some special diseases such as blood system disease, mental illness and infectious diseases.
- 5) Repeated literatures
- 6) Sample size was too small.

2.3 Data extraction

After reading all studies, Two reviewers completed data extraction separately and checked by one of them. If there were data conflict, the third evaluator would evaluate it, and finally the three people would

jointly extract consistent data. For all the included studies, we extracted the following information: the first author's name; the year of publication; the magazine where the article was published; the database of studies; the sample size; the gender composition of the sample; the mean age; the time from onset to treatment; the intervention and control measures and the outcome measures.

2.4 Quality assessment

Our two reviewers used the Cochrane collaboration tool to evaluate the 7 indicators in the each included studies. If there was disagreement, the third reviewer would jointly evaluate it, and the last three people would reach a consensus.

2.5 Statistical analysis

Data analysis was performed by RevMan software (version 5.3) and Stata (version 14 and 16). Risk ratios (RR), Odds ratios (OR) and 95% confidential interval (95% CI) were used to count the dichotomous variables and ordinal categorical variables respectively. Weighted mean difference (WMD), standard mean difference (SMD) and 95% CI were used for statistical analysis of continuous variables such as time for cholinesterase level to return to normal, coma time, time of hospitalization, and atropine dosage. We used the Cochrane Intervention System Evaluation Manual (version 5.1) to assess statistical heterogeneity. The degree of heterogeneity was judged by chi-square test and I^2 test³. If there was heterogeneity between the studies ($I^2 > 50\%$, $P < 0.05$), the cause of heterogeneity such as the year of publication, the proportion of male, average age, sample size and unit, and subgroup analysis was searched for³. We will use meta regression to find these factors that may cause heterogeneity. If the final combined result has no or little heterogeneity, we use a fixed-effect model to combine the final effect size. If after meta regression of the above covariates, it is found that they are not the source of heterogeneity, we use a random effects model to combine the final effect size. At the same time, We will conduct sensitivity analysis on each result to judge whether they were stable. For publication bias, we first use funnel diagram to visually check whether they are symmetrical and then we use Begg's test and Egger's test to assess publication bias quantitatively. If there were obvious publication bias, the trim and fill method would be used to correct or eliminate the publication bias and test the impact of the final meta-analysis results on the publication bias.

3. Results

3.1 Study selection

According to the search strategy we developed, a total of 159 studies were queried, and after deleting duplicate studies, there were 69 studies. One meta-analysis, five nursing studies, and 19 studies whose experimental design does not conform to this research were eliminated. There were 7 studies with incorrect or inaccurate data. Although we actively contacted the authors and the publishers, we did not contact them or received a satisfactory answer, so all these 7 studies were rejected. Finally, after reading the full text, we found that one article was not an RCT, and the outcome index of another article was not

what we wanted. The remaining 35 studies⁴⁻³⁸ all contain all or part of the outcome indicators we need, so they are included in this study. The review process was outlined in Figure 1.

3.2 General content of included studies

The studies we retrieved are from CNKI, Wanfang, VIP, CBM, and Duxiu. A total of 2650 ASOPP patients were recruited from the 35 studies⁴⁻³⁸ we selected. All 35 studies⁴⁻³⁸ were clear RCTs. All patients meet the diagnostic criteria of ASOPP and have clinical manifestations of coma. There were 1325 subjects in the experimental group and the control group. In general data such as gender, age, time from onset to treatment, and sample size, there was no statistical difference between the studies ($P>0.05$). The treatment methods of all control groups were conventional emergency treatment, such as oxygen inhalation, early emesis, gastric lavage, catharsis, and early use of pralidoxime and atropine. For patients who cannot breathe spontaneously, tracheal intubation and ventilator-assisted ventilation were required. Give mannitol to lower intracranial pressure in patients with cerebral edema and diuretics were given to patients with pulmonary edema. The treatment method of the experimental group, that is, intervention measures, was to apply hemoperfusion combined with hemodialysis on the basis of the above conventional emergency treatment. All experimental groups underwent hemoperfusion and then hemodialysis. The general characteristics of the included studies were shown in Table 1. The specific intervention measures of each study were shown in Table 1 in the appendix 2.

3.3 Quality Assessment

Our two reviewers had reached a highly consistent conclusion on the quality evaluation of these 35 documents⁴⁻³⁸. Among them, 10 studies^{4,6,9,10,17,18,24,28,29,31} did not explain the random method used. All 35 studies⁴⁻³⁸ did not specify whether to use the allocation concealment method. With regard to the blinding of participants and personnel, because of the particularity of ASOPP patients in treatment, we believed that the measurement of results was almost unaffected by the absence of blinding. The blinding of outcome assessment, due to various subjective and objective reasons, except for one article that clearly stated that the blinding method was used, the remaining 34 studies⁵⁻³⁸ were judged to be unclear. All of 35 studies⁴⁻³⁸ were assessed as having a low risk of attrition and reporting bias. As for other sources of bias, we carefully compared the specific interventions of 35 studies⁴⁻³⁸ and found that 14^{4,6,9,10,16,18,21,24,29,31,34-37} studies were highly consistent or similar. The other 21 studies^{5,7,8,11-15,17,19,20,22,23,25-28,30,32,33,38} did not specify specific interventions or implemented interventions based on the specific conditions of the patients, so this Twenty-one studies were rated at risk of possible other sources of bias. The specific evaluation results are shown in Figure 2.

3.4 Outcomes

3.4.1 Cure Rate

3.4.1.1 Statistical results

The cure rate was the main outcome indicator of our analysis. A total of 23 studies^{4-9, 11,16,17, 20-25,27,29,30, 32-34,36,38} out of 35 studies⁴⁻³⁸ counted the cure rate. The specific cure rate was shown in Table 2 in the appendix 2. Forest plot was shown in Figure 3(a). Because there was small heterogeneity between the studies ($P=0.13$ for Q test, $I^2=26\%$), we used the fixed effect model. The combined effect size was [RR=1.20, 95%CI (1.16, 1.25), $p<0.00001$], which was statistically significant.

3.4.1.2 Publication bias

We Drew a funnel plot to investigate whether there was publication bias in this study and we found that the funnel plot was asymmetric. Funnel plot was shown in Figure 3(b).

The Begg's test yielded $P=0.000<0.05$, and the Egger's test yielded $P=0.000<0.05$. It was found that this study had obvious publication bias. So we used the trim and fill method to correct for publication bias. The plot of trim and fill was shown in Figure 3(c). According to the calculation results and the figure, we need to find 10 studies in the future to correct the publication bias. After the inclusion of 10 new studies, the RR value was 1.116, 95%CI was (1.083, 1.051), which was not much different from the previous RR 1.20, 95%CI (1.16, 1.25), and it was statistically significant ($p=0.000<0.05$), which could be considered that the outcome indicators were relatively robust. Although the publication bias was large, it had little effect on the outcome indicators. See the figure 1 of appendix 2 for the results of the trim and fill method.

3.4.2 Efficacy

3.4.2.1 Statistical results

The efficacy in these studies was an ordinal categorical variable, divided into 3 levels. The first, total effective, referred to the disappearance of clinical symptoms and the complete recovery of vital signs; the second, effective, referred to the relief of clinical symptoms and the basic stability of vital signs; the last one, ineffective, referred to the failure of the above standards after treatment. A total of 12^{4-6,8,17,20,22-24,32,34,38} studies counted the outcome indicator of efficacy. However, the P value of the effective index of two studies^{5,24} was >0.05 , which was not statistically significant. Therefore, a total of 10^{4,6,8,17,20,22,23,32,34,38} studies were included for the combined effect size. The specific efficacy was shown in the Table 3 of appendix 2. Forest plot was shown in Figure 4(a). There was almost no heterogeneity between the studies ($P=0.984$ for Q test, $I^2=0\%$), so we used the fixed effect model. The final combined effect size [OR=2.76, 95%CI (2.07, 3.67), $p=0.000$], which was statistically significant.

3.4.2.2 Publication bias

The funnel plot was shown in Figure 4(b). It could be roughly seen from the figure that the funnel plot was symmetrical.

The Begg's test yielded $P=0.210>0.05$, and the Egger's test yielded $P=0.376>0.05$. It was found that this study had no publication bias.

3.4.3 Incidence of complications

3.4.3.1 Statistical results

A total of 24 studies^{4,6,8-11,14,15,17,18,20-24,27,31-38} out of 35 studies⁴⁻³⁸ counted the incidence of complications, but there was an article with a P value of <0.05 for the incidence of complications. So, the effect size of 23 studies^{4,6,8-11,14,15,17,18,20-22,24,27,31-38} was finally merged. The complications counted in these studies were respiratory muscle paralysis, intermediate syndrome, rebound phenomenon, delayed polyneuropathy, toxic liver injury, toxic myocarditis, chest distress, thrombocytopenia, fever, urinary retention, atropine poisoning and multiple organ failure. The specific data was shown in Table 4 in the appendix 2. Since these studies did not perform chi-square test on individual complications, we only combined the effect size of the total complication rate calculated in each study. There was almost no heterogeneity between the studies ($P=0.98$ for Q test, $I^2=0\%$), so we used the fixed effect model. The final combined effect size was $[RR=0.26, 95\%CI (0.20, 0.34), p<0.00001]$, which was statistically significant. The forest plot was shown in Figure 5(a).

3.4.3.2 Publication bias

The funnel plot was shown in Figure 5(b). We found that the funnel plot was basically symmetrical.

The Begg's test yielded $P=0.107>0.05$, but the Egger's test yielded $P=0.003<0.05$, so there was likely to be serious publication bias. We used the trim and fill method to try to correct for publication bias. The plot of trim and fill was shown in Figure 5(c). We found that there were no studies that need to be added. The RR after the calculation of trim and fill method was 0.279, 95% CI was (0.214, 0.363), which was not much different from the previous $[RR=0.26, 95\%CI (0.20, 0.34)]$ and it was statistically significant ($P=0.000<0.05$), indicating that the results were relatively robust. Publication bias had little effect on the statistical results. See the figure 2 of appendix 2 for the results of the trim and fill method.

3.4.4 Time for cholinesterase level to return to normal (days)

3.4.4.1 Statistical results

A total of 24 studies^{5-7,9-11,13,15,17-20,22-26,29,31,33-36,38} counted the results of the time for the cholinesterase level return to normal. The specific data was shown in Table 5 in the appendix 2. There was high heterogeneity between the studies ($P<0.00001$ for Q test, $I^2=74\%$), so we used the random effect model. The final combined effect size was $[WMD=-4.05, 95\%CI (-4.40, -3.70), p<0.00001]$, which was statistically significant. The forest plot was shown in Figure 6(a).

3.4.4.2 Meta-regression analysis

According to the data we extracted from the corresponding studies, it was considered that the heterogeneity may be related to the year of publication, the proportion of male, sample size and average age. After meta-regression of the above covariates, it was found that the average age was the reasons for the heterogeneity, whose P values was $0.001<0.05$, which was statistically significant. The τ^2 of

estimate of between-study variance was 0.6278. After introducing the average age into the meta regression model, the τ^2 of estimate of between-study variance was 0.5408, so 13.86% of the source of heterogeneity could be explained by average age. Meta-regression analysis showed that the time for cholinesterase level to return to normal was not affected by the year of publication, the proportion of male and the sample size, and might be affected by the average age. The specific values were shown in Figure 6(b). Because the heterogeneity was still large after considering the age factor, the effect quantity was finally combined by the random effect model.

3.4.4.3 Publication bias

The funnel plot was shown in Figure 6(c), which was basically symmetrical. The Begg's test yielded $P=0.472>0.05$, and the Egger's test yielded $P=0.405>0.05$. It could be considered that there was no publication bias in this outcome indicator.

3.4.5 Coma time (days and hours)

3.4.5.1 Statistical results

As shown in the forest plot in Figure 7(a), 28 studies^{5,6,9-20,22-31,33-35,38} had counted the coma time. The specific data was shown in Table 6 in the appendix 2. There was great heterogeneity between them. ($P<0.00001$ for Q test, $I^2=94\%$), so we used the random effects model to combine them. Because the unit of coma time of 5 studies^{6,16,20,28,34} were days, and the other 23 studies^{5,9-15,17-19,22-27,29-31,33,35,38} were all hours, so we use SMD as the final result. The final combined effect size was [SMD=-2.62, 95%CI (-3.08,-2.15), $p<0.00001$], which was large, and it was statistically significant.

3.4.5.2 Meta-regression analysis

After doing meta regression on year, the proportion of male, sample size, average age and the unit of coma time, We found that the source of heterogeneity was not the above factors. Meta-regression analysis showed that the coma time was not affected by the above 5 factors. Therefore, in the end, the random effects model was also used to merge this effect size. The specific values were shown in Figure 7(b).

3.4.5.3 Publication bias

The funnel plot was shown in Figure 7(c), which was obviously asymmetric. The Begg's test yielded $P=0.000<0.05$, and the Egger's test yielded $P=0.000<0.05$. There was a big publication bias. we used the trim and fill method to try to correct for publication bias. After trim and fill method, 8 studies were added. The result of the calculation was SMD=-3.352, 95%CI (-3.980, -2.723), $p=0.000<0.05$, which was statistically significant. There was a certain difference from the previous SMD=-2.62, 95%CI (-3.08, -2.15), indicating that the existence of publication bias had affected the combined effect size. The plot of trim and fill was shown in Figure 7(d). We considered that the existence of publication bias was related to the search languages only Chinese and English, and the studies included are all Chinese. In addition, the studies included in this research are all published studies, and gray literature was not included, such as

the special meeting minutes, unpublished materials, etc., which might miss negative results and cause publication bias. In the future, we would include similar studies with the above 8 studies to correct Publication bias. Despite the publication bias, SMD was still consistent with the previous direction, and the effect size was huge.

3.4.6 Time of hospitalization (days)

3.4.6.1 Statistical results

26 studies^{5-7,9-16,18,19,23-31,33,34,36,38} had counted this outcome indicator. The specific data was shown in Table 7 in the appendix 2. There was also great heterogeneity between them ($P < 0.00001$ for Q test, $I^2 = 96\%$). We used the random effects model to combine them. The final combined effect size was [WMD = -5.80, 95%CI (-6.57, -5.02), $p < 0.00001$], and it was statistically significant. The forest plot was shown in Figure 8(a).

3.4.6.2 Meta-regression analysis

We also did a meta-regression on year, the proportion of male, sample size, and average age, and we found that the heterogeneity were from the average age, whose P was $0.004 < 0.05$, which was statistically significant. The τ^2 of estimate of between-study variance was 2.945. After introducing the average age into the meta regression model, the τ^2 of estimate of between-study variance was 2.882, so 2.14% of the source of heterogeneity could be explained by average age. The specific values were shown in Figure 8(b). Here, almost none of the above factors was a source of heterogeneity, so we used the random effects model to combine the effect size.

3.4.6.3 Publication bias

We could see funnel plot in Figure 8(c), which was obviously symmetric. The Begg's test yielded $P = 0.758 > 0.05$, and the Egger's test yielded $P = 0.347 > 0.05$. There was no publication bias.

3.4.7 Atropine dosage (mg)

3.4.7.1 Statistical results

There were 12 studies^{6,7,9,10,12,13,15,19,23,36,38} that included the indicator of atropine dosage. The specific data was shown in Table 8 in the appendix 2. There was also great heterogeneity between them ($P < 0.00001$ for Q test, $I^2 = 100\%$). We used the random effects model to combine them. The final combined effect size was [WMD = -194.81, 95%CI (-223.55, -166.08), $p < 0.00001$], which was statistically significant. Because Revman's forest plot was not very clear, we also added the forest plot made by Stata, which were shown in Figure 9(a) and 9(b).

3.4.7.2 Meta-regression analysis

After doing meta regression on year, the proportion of male, sample size, average age and the unit of coma time, we found that none of the above factors were the source of heterogeneity, so we used the

random effects model to combine the effect size. The specific values were shown in Figure 9(c).

3.4.7.3 Publication bias

The funnel plot was shown in Figure 9(d), which might be asymmetric. The Begg's test yielded $P=0.193>0.05$, and the Egger's test yielded $P=0.652>0.05$. There was no publication bias.

3.5 Sensitivity analysis

We determined the sensitivity of meta-analysis by deleting a study for each combined effect quantity and then checking whether its corresponding value was within the first 95% CI. The results showed that all 7 outcome indicators were within 95% CI after deleting any study, indicating that our meta-analysis results were stable.

3.6 subgroup analysis

Since the unit of coma time, namely days or hours, and other covariates were not statistically significant after meta-regression analysis, and the average age had little effect on the heterogeneity of other outcome indicators, so we would not do subgroup analysis here.

4. Discussion

4.1 Explanation of main findings

We performed a meta-analysis of 2,650 subjects in 35⁴⁻³⁸ studies from 11 databases to evaluate the efficacy of hemoperfusion combined with hemodialysis in ASOPP in this meta-analysis. The results showed that hemoperfusion combined with hemodialysis based on conventional emergency treatment can improve the cure rate of patients, and could also increase the number of patients who were total effective and effective in the ordinal categorical variable efficacy, reduce the number of patients who were ineffective, and at the same time, it could also greatly reduce The incidence of various complications in ASOPP treatment. They could also reduce the time for cholinesterase level to return to normal, coma time, time of hospitalization and atropine dosage during treatment. All outcome indicators were statistically significant.

4.2 Possible physiological mechanism

High frequency of multiple organ failure and various complications are the causes of high mortality of ASOPP. The direct effects of organophosphorus pesticides and the indirect effects of causing secondary damage may be the cause of organ failure in ASOPP patients. ASOPP patients suffer from respiratory failure due to respiratory muscle paralysis, followed by cerebral edema, hypoxia, and the body will produce a series of inflammatory reactions, and various inflammatory mediators will cause serious damage to the body. Early hemoperfusion combined with hemodialysis can absorb and remove inflammatory mediators, resist the body's systemic inflammatory response, and restore cholinesterase activity. Hemoperfusion can remove fat-soluble organophosphorus pesticides, but cannot remove excess

water from the body, and cannot correct water-electrolyte disorders and acid-base imbalances. However, due to the accumulation of acetylcholine, ASOPP patients often have pulmonary edema, and due to the direct effect of organophosphorus pesticides, heart and kidney damage are also common. The effect of hemoperfusion alone is often unsatisfactory³⁹. Diffusion is the basic principle of hemodialysis. In this process, solutes in the blood pass from the side of the semipermeable membrane with high concentration to the other side with low concentration. Hemodialysis can remove small molecules in the body's circulation, thereby reducing the body's blood volume, promoting stable blood circulation, and further correcting water electrolyte and acid-base disorders. In addition, some reports pointed out that hemodialysis treatment can also reduce the load on the kidneys and heart, and avoid organ dysfunction.⁴⁰. Therefore, many qualified hospitals will use hemoperfusion combined with hemodialysis treatment on the basis of emergency conventional treatment once they receive ASOPP patients. In the treatment of ASOPP patients, hemoperfusion combined with hemodialysis can not only remove the most direct organophosphorus pesticides, but also remove all kinds of harmful chemicals produced by the body stimulated by them. They also maintained a stable internal environment, reduced the incidence of various complications and organ failure, and greatly improved the prognosis of patients.

4.3 Strengths and weaknesses of the review

The research we included in this meta-analysis was the latest in the past 5 years, and the technology of conventional emergency treatment of ASOPP tends to be comprehensive, that is, the control group was more stable and reliable. Our inclusion criteria were very strict this time. For example, in the initial selection of studies, all studies with any contradictions or missing data will be excluded. All production steps, from literature search, literature screening, quality assessment, data extraction to the final statistical analysis, were done by two people together, which was more rigorous. In terms of statistical methods, we had additionally applied the trim and fill method in this study to explore the impact of publication bias on the study. Five years ago, a similar meta-analysis was published, but their study only searched 4 databases, and the inclusion and exclusion criteria were not as strict as ours. Finally, 5 studies were included, and the outcome indicator was only the cure rate, which could not fully explain the effect of hemoperfusion combined with hemodialysis on ASOPP patients, and their statistical methods were not as comprehensive as ours.

Of course, there were many deficiencies in this study. This study only included Chinese literature, which may cause language bias. All the studies were conducted in Chinese mainland. These studies did not evaluate different countries and races, which may cause the result being unable to be generalized. In terms of the quality of the studies, about 1/3 of the studies did not specify the random method used. All the included 35 studies⁴⁻³⁸ did not indicate whether the allocation concealment was used, and more than half of the studies may have other sources of bias. The quality of the included literature needs to be improved. In addition, the outcome indicators recorded in the included literature were not the same. We believed that the most important cure rate, efficacy, and the incidence of complications were not recorded in many studies.

Although the heterogeneity of cure rate was relatively small, and the heterogeneity of efficacy and the incidence of complications are almost non-existent, the heterogeneity of the other 4 continuous data was relatively large. We conducted a meta regression analysis on each heterogeneous outcome index, including the year of publication, the proportion of male, the sample size and the average age. It was found that only the average age was the source of heterogeneity in the time for cholinesterase level to return to normal and time of hospitalization, accounting for 13.86% and 2.14% respectively. Heterogeneity did not mainly come from them. Therefore, we did not do subgroup analysis either. After comprehensive analysis, we considered that the heterogeneous sources may include: the type of organophosphorus pesticide, the toxicity intensity, and factors such as the dosage, the difference in the part where the poison enters the human body, which may affect the final absorption and cause different clinical outcomes. The time from the patient's exposure to the poison to the medical treatment was also an important source of heterogeneity. Of course, the types and doses of drugs used in conventional emergency treatment were also sources of heterogeneity. Pralidoxime can be divided into phosphos-iodide, phosphos-chloride, and obidoxime chloride. Ordinary atropine or penehyclidine hydrochloride can also be used. Whether the hemoperfusion machine uses resin or activated carbon, the manufacturer and model of hemoperfusion machine and dialysis machine, as well as the number, time and frequency of treatment with them, were the sources of heterogeneity. However, because some of the included studies did not specify the above information in detail, we could not make an assessment one by one, that is, whether they were the source of heterogeneity, we could not analyze them through meta-regression. In this case, we could only take the second place in the merger of the final effect quantity - using the random effect model.

After the rough evaluation of the funnel plot and the quantitative evaluation of Begg's test and Egger's test, there were publication bias in 3 outcome indicators, including cure rate, the incidence of complications and coma time. Although we found that publication bias had little effect on the cure rate and the incidence of complications after revision by trim and fill method, it still significantly affected the coma time. The source of publication bias may be related to the fact that we only searched Chinese and English databases, and all the literature we included are Chinese literature. The studies included in this study were published studies, excluding grey literature, such as special meeting minutes and unpublished materials, which may fail to report negative results. In the future, we will include more literature to correct publication bias.

4.4 Challenges for the field of this research, implications for clinicians, and future directions

For ASOPP, our research results indicated that the efficacy was accurate, which could significantly improve the cure rate and reduce the incidence of complications. Although there were some heterogeneity in the four secondary outcome indicators of the study, the heterogeneity of the primary outcome indicators was very small or no heterogeneity, and the combination of the secondary outcome indicators through the random effect model also showed that hemoperfusion combined with hemodialysis was effective in the treatment of ASOPP, which is a promising field worthy of research.

However, in general, our meta-analysis may have various inevitable heterogeneities discussed previously. Since hemoperfusion technology is now used less in developed countries in Europe and the United States, and there are few relevant reports and randomized controlled studies, the probability of future research is to continue to collect randomized controlled studies in developing countries. In this way, the quality of research may not be greatly improved, because their allocation concealment method and blind method may not well implemented, and there may be other sources of bias. Moreover, their collection of outcome indicators is also different. Apart from the cure rate, the incidence of complications in acute organophosphorus pesticide poisoning is also extremely important, especially the complications such as intermediate syndrome and delayed polyneuropathy, which seriously affect the prognosis of patients and the quality of life after treatment. However, some doctors or researchers do not pay attention to the most critical cure rate and the incidence of complications. They didn't record these data in the research, which makes it difficult for our research to make better progress.

Although this study has limitations, because there are too many patients with ASOPP in developing countries and the mortality is very high, we sincerely hope that clinicians can further carry out high-quality RCTs if conditions permit, so as to facilitate our follow-up further research, so that hemoperfusion combined with hemodialysis can form corresponding evidence-based medical evidence for the treatment of ASOPP and further benefit patients.

5. Conclusion

Our research showed that hemoperfusion combined with hemodialysis can significantly improve the cure rate, efficacy and reduce the overall incidence of complications in acute severe organophosphorus pesticide poisoning patients based on conventional emergency treatment, and can reduce time for cholinesterase level to return to normal, coma time, time of hospitalization, and atropine dosage. In the future, more scientifically designed large-scale, high-quality, multi-center randomized controlled trials are needed to further illustrate the significance of this study.

Abbreviations

AOPP, Acute organophosphorus pesticide poisoning

ASOPP, Acute severe organophosphorus pesticide poisoning

RCT, randomized controlled trials

CBM, Chinese Biomedical literature

CNKI, Chinese National Knowledge Infrastructure

VIP, China Science and Technology Journal Database

RR, Risk ratios

OR, Odds ratios

WMD, Weighted mean difference

SMD, Standard mean difference

CI, confidential interval

RevMan, Review Manager

ED, Emergency department

CRRT, Continuous renal replacement therapy

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

DOI, digital object identifier

MeSH, Medical Subject Headings

Declarations

Acknowledgments

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Authors' contributions

The first author Siyao Zeng devoted himself to the entire process of meta-analysis, including literature search and screening, data extraction, quality assessment, statistical analysis and wrote and this article. Lei Ma contributed to statistical methods and the revision of this article. Xiaodong Hu contributed to the quality evaluation of the studies. Cheng Wang contributed to literature screening. Yi Gou contributed to data extraction and verification. Yi Li contributed to the search of the literature. All authors agreed to the publication of this article.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Literature retrieval process.

(a) Risk of bias graph

(b) risk of bias summary

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen shihua 2019	Low	Unclear	Low	Unclear	Low	Low	Unclear
Guo lin 2020	Low	Unclear	Low	Unclear	Low	Low	Low
Hei yaozong 2018	Low	Unclear	Low	Unclear	Low	Low	Low
Hou jingxing 2021	Low	Unclear	Low	Unclear	Low	Low	Low
Hou juan 2019	Low	Unclear	Low	Unclear	Low	Low	Low
Jiang yongkun 2017	Low	Unclear	Low	Unclear	Low	Low	Unclear
Liao zhaopeng 2017	Unclear	Unclear	Low	Unclear	Low	Low	Low
Li bo 2020	Low	Unclear	Low	Unclear	Low	Low	Unclear
Liu jinxing 2021	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Li youyi 2020	Unclear	Unclear	Low	Unclear	Low	Low	Low
Li zifei 2019	Low	Unclear	Low	Unclear	Low	Low	Unclear
Ma xiaomei 2020	Low	Unclear	Low	Unclear	Low	Low	Unclear
Peng xinggan 2020	Low	Unclear	Low	Unclear	Low	Low	Unclear
Ping liying 2017	Low	Unclear	Low	Unclear	Low	Low	Unclear
Qiu yongsheng 2020	Unclear	Unclear	Low	Unclear	Low	Low	Low
Shen man 2021	Low	Unclear	Low	Unclear	Low	Low	Unclear
Shi wenxue 2019	Low	Unclear	Low	Unclear	Low	Low	Unclear
Song junshuai 2019	Low	Unclear	Low	Unclear	Low	Low	Low
Wang guijie 2017	Low	Unclear	Low	Unclear	Low	Low	Unclear
Wang guotao 2019	Low	Unclear	Low	Unclear	Low	Low	Unclear
Wang xiuli 2018	Unclear	Unclear	Low	Unclear	Low	Low	Low
Wang yalin 2021	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Wu jianfeng 2020	Low	Unclear	Low	Unclear	Low	Low	Low
Wu qihua 2018	Low	Unclear	Low	Unclear	Low	Low	Unclear
Wu xiaofang 2018	Low	Unclear	Low	Unclear	Low	Low	Unclear
Xiong yuqin 2020	Low	Unclear	Low	Unclear	Low	Low	Unclear
Xu youdui 2019	Low	Unclear	Low	Unclear	Low	Low	Unclear
Yue shuxia 2019	Low	Unclear	Low	Unclear	Low	Low	Unclear
Zhang kun 2018	Unclear	Unclear	Low	Unclear	Low	Low	Low
Zhang mingming 2018	Unclear	Unclear	Low	Unclear	Low	Low	Low
Zhang xiaolan 2020	Low	Unclear	Low	Unclear	Low	Low	Unclear
Zhang xiaoxia 2019	Low	Unclear	Low	Unclear	Low	Low	Unclear
Zhang ye 2019	Low	Unclear	Low	Unclear	Low	Low	Unclear
Zhang yingxi 2017	Unclear	Unclear	Low	Unclear	Low	Low	Low
Zhang yuting 2021	Unclear	Unclear	Low	Unclear	Low	Low	Low

Figure 2

Methodological quality evaluation of included studies. (a) Risk of bias graph; (b) risk of bias summary.

(a) Forest plot

(b) Funnel plot

(c) Plot of trim and fill

Figure 3

Cure rate. (a) Forest plot; (b) Funnel plot; (c) Plot of trim and fill

(a) Forest plot

(b) Funnel plot

Figure 4

Efficacy (a) Forest plot; (b) Funnel plot.

(a) Forest plot

(b) Funnel plot

(c) Plot of trim and fill

Figure 5

Incidence of complications. (a) Forest plot; (b) Funnel plot; (c) Plot of trim and fill.

(a) Forest plot

(b) Meta-regression

	Item	Coef	Std. Err.	t	tau ²	P
Covariates	None	-4.0522	0.0035	-20.40	0.6278	0.000
	year	0.0088	0.1593	0.06	0.6693	0.946
	the propotion of male	-0.3315	3.229	-0.10	0.6643	0.053
	sample size	0.0028	0.0090	0.31	0.6623	0.000
	average age	0.0642	0.0397	1.62	0.5408	0.001

(c) Funnel plot

Figure 6

Time for cholinesterase level to return to normal (**a**) Forest plot; (**b**) Meta-regression; (**c**) Funnel plot.

(a) Forest plot

(b) Meta-regression

	Item	Coef	Std. Err.	t	tau ²	P
Covariates	None	-2.7362	0.4029	-6.79	4.076	0.000
	year	0.0235	0.3162	0.07	4.267	0.938
	the propotion of male	-5.8923	5.8174	-1.01	4.105	0.843
	sample size	-0.01479	0.01827	-0.81	4.148	0.257
	average age	0.0282	0.0821	0.34	4.247	0.266
	unit	-1.3173	1.0331	-1.28	3.975	0.861

(c) Funnel plot

(d) Plot of trim and fill

Figure 7

Coma time (a) Forest plot; (b) Meta-regression; (c) Funnel plot; (d) Plot of trim and fill.

(a) Forest plot

(b) Meta-regression

Item	Coef	Std. Err.	t	tau ²	P
None	-5.7990	0.3615	-16.04	2.945	0.000
Year	0.2684	0.2872	0.93	2.968	0.354
Covariates the proportion of male	-1.5046	5.1918	-0.29	3.062	0.111
Sample size	-0.0021	0.01518	-0.14	3.071	0.000
Average age	0.0832	0.0700	1.19	2.882	0.004

(c) Funnel plot

Figure 8

time of hospitalization (a) Forest plot; (b) Meta-regression; (c) Funnel plot.

(a) Forest plot by RevMan

(c) Meta-regression

	Item	Coef	Std. Err.	t	tau ²	P
	None	-194.94	29.9416	-6.51	10722	0.000
	year	7.1342	27.9982	0.801	11721	0.801
Covariates	the propotion of male	-73.719	438.482	-0.17	11766	0.556
	sample size	-1.7343	1.06252	-1.63	9306	0.692
	average age	-2.5939	6.2820	-0.41	11599	0.732

(b) Forest plot by Stata

(d) Funnel plot

Figure 9

Atropine dosage (a) Forest plot by RevMan; (b) Forest plot by Stata; (c) Meta-regression; (d) Funnel plot.

Supplementary Files

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- Appendix1.doc
- Appendix2.docx
- Table1.docx