Organophosphate (OP) pesticides are still widely available in developing countries, leading to numerous accidental or suicidal poisonings every year. Lipid emulsion treatments are commonly used in resuscitating OP poisoning patients but few studies regarding their use have been reported. Our meta-analysis aimed to analyze the efficacy and outcomes of lipid resuscitation on OP poisoning patients.

**Methods:** A systematic search for associated studies was conducted in PubMed, EMBASE, MEDLINE, the Cochrane Library and the Chinese National Knowledge Infrastructure. Collected data was pooled using Revman v5.3. Outcomes included prognosis (cured vs. mortality rates), hepatic function (serum ALT, AST, Total Bilirubin (TBIL) level), serum acetylcholinesterase (AchE) level and respiratory function (rate of respiratory muscular paralysis).

**Results:** Seven randomized controlled studies consisting of 630 patients meeting inclusion criteria were identified. Lipid emulsion helped to improve the cure rate [OR = 2.54, 95% CI (1.33, 4.86), p = 0.005] and lower the mortality rate [OR = 0.31, 95% CI (0.13, 0.74), p = 0.009]. Serum ALT, AST and TBIL in patients undergoing lipid resuscitation were lower than those in the control groups [ALT, SMD = −1.52, 95% CI (−2.64, 0.40), p = 0.008; AST, SMD = −1.66, 95% CI (−3.15, 0.16), p = 0.03; TBIL, SMD = −1.26, 95% CI (−2.32, 0.20), p = 0.02]. Serum AchE level were increased in patients treated with lipid emulsion [SMD = 2.15, 95% CI (1.60, 2.71), p < 0.00001]. Rate of respiratory muscular paralysis was lower in patients undergoing lipid resuscitation than those in the control groups [OR = 0.19, 95% CI (0.05, 0.71), p = 0.01].

**Conclusion:** Based on our meta-analysis of included RCT reports, lipid resuscitation seems likely to help improve prognosis and liver function of OP poisoning patients. However, larger multi-center RCTs are still recommended.

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limited especially high quality RCTs or in English-language studies. Also,
there has not yet been a meta-analysis of the available studies exploring
the efficacy of lipid emulsion on OP poisoning patients. Our meta-
analysis aims to review all currently published articles on the efficacy
of lipid emulsions toward OP poisoning and illustrate the efficacy and
outcomes of lipid resuscitation on OP poisoning patients.

2. Methods

2.1. Study selection

Pubmed, EMBASE, Cochrane library, MEDLINE, Chinese National
Knowledge Infrastructure (CNKI), Chinese Biomedical literature (CBM)
and the Chinese Medical Current Contents (CMCC) were all screened
by our search team. English search terms included organophosphorus,
organophosphate poisoning (MeSH term), organophosphorus poison-
ing, OP, OP poisoning, lipid, lipid emulsion, lipid resuscitation and lipid
therapy. Chinese search term included words meaning lipid and poison-
ing, including ‘you ji lin’, ‘zhi fang ru’ and ‘zhong du’. All reference lists
from the main reports were cross-checked by two members of our
team.

2.2. Inclusion and exclusion criteria

Articles were included if they met all of the following criteria:
1) Randomized controlled study (RCT)
2) Study population consisted of accidental or suicidal OP poisoning pa-
tients, regardless of the severity.
3) Study population consisted of patients who potentially received lipid
resuscitation once they presented to the emergency department.
4) One or more of the following were reported: cure rate, mortality
rate, hepatic function and rate of respiratory muscular failure.

Articles were excluded if any of the following were present:
1) Studies not published in Chinese or English
2) Study data unavailable
3) Studies involving primarily special populations (e.g. AIDS or tuber-
culosis patients).

Fig. 1. Flow diagram.
2.3. Quality assessment

Two reviewers (SY and XL) independently conducted the study selection and review of the included studies using the Cochrane Collaboration’s tool [6]. The following seven items were evaluated, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. The results were classified as low risk of bias, high risk of bias and unclear risk of bias.

2.4. Statistical analysis

The baseline characteristics and available data of each article were evaluated and extracted separately by two researchers using Microsoft Excel 2013. The main outcomes were cure rate (all symptoms/syndromes disappeared and vital signs returned to normal), mortality rate, hepatic function (serum ALT, AST, TBIL levels) and serum AchE level on the fifth day after OP poisoning and the rate of respiratory muscle failure (progressive dyspnea after cholinergic crisis). The estimated odds ratio (OR), 95% confidence interval (CI) and standardized mean difference (SMD) of the available data were pooled using Review Manager v5.3. A p-value < 0.05 was defined as statistically significant. I² was used to estimate the heterogeneity level of the included studies. I² > 50% was defined as high heterogeneity among studies and a randomized model was conducted to pool the data, while a fixed model was conducted if the I² score was no >50%. Reporting bias was evaluated by using a funnel plot.

3. Results

3.1. Included studies

Our meta-analysis included 1042 potentially eligible articles, including 29 articles from Pubmed, 22 articles from EMBASE, 15 articles from Cochrane library, 19 from MEDLINE, 623 from CNKI, 125 from CBM and 209 from CMCC. Seven articles all from the CNKI database were eventually identified after abstract and full-text screening, which included a total of 630 patients [3,7-12]. The screening process is shown in Fig. 1. All of the included studies were RCTs and all articles were published in Chinese. Details of the included articles are shown in Table 1.

3.2. Baseline characteristics of included articles

Seven RCTs recruited a total of 630 OP patients, all of whom ingested OP. 312 of the patients underwent lipid resuscitation since the first day of OP poisoning, while 318 patients were enrolled as controls. Main characteristics of the patients are shown in Table 2. Baseline characteristics show no significant difference between patients divided into the lipid emulsion group or control group.

3.3. Risk of bias

The methodological quality of selected trials was assessed using the Cochrane Collaboration’s tool. All of the studies included suggested randomization, but only five studies reported the method of random sequence generation while all of the studies failed to report details about allocation concealment. There was a high risk of bias regarding participants, personnel and outcome assessment. The reasons for drop-out between groups were similar in the included studies. The risk of selective reporting bias is low. Six studies had low risk of other bias while one failed to report baseline similarity. Therefore, all studies were
judged to be of a relatively poor methodological quality (Tables 3 and 4).

3.4. Cure rate and mortality rate

Four studies included data on cure rates, consisting of 220 patients. A fixed model was conducted because of low heterogeneity among studies ($I^2 = 0\%$). Pooled statistics demonstrated the cure rate was significantly higher after lipid resuscitation on OP patients compared to patients in the control group [OR = 2.54, 95% CI (1.33, 4.86), $p = 0.005$]. Forest plot is shown in Fig. 2.

Four studies included eligible data on mortality rates, consisting of 301 patients. A fixed model was conducted because of low heterogeneity among studies ($I^2 = 37\%$). Pooled statistics demonstrated mortality rate was significantly lower after lipid resuscitation on OP patients compared to those in the control group [OR = 0.31, 95% CI (0.13, 0.74), $p = 0.009$]. Forest plot is shown in Fig. 3.

3.5. Hepatic function

Hepatic function was evaluated through serum ALT, AST and TBIL levels on the fifth day after OP poisoning.

Three studies included eligible data on serum ALT levels consisting of 255 patients. A randomized model was conducted because of high heterogeneity among studies ($I^2 = 93\%$). Pooled statistics demonstrated serum ALT levels on the fifth day after OP poisoning were significantly lower after lipid resuscitation on OP patients than OP patients in the control group [SMD = −1.52, 95% CI (−2.64, −0.40), $p = 0.008$]. Forest plot is shown in Fig. 4.

Three studies included eligible data on serum AST level, consisting of 255 patients. A randomized model was conducted because of high heterogeneity among studies ($I^2 = 96\%$). Pooled statistics demonstrated serum AST levels on the fifth day after OP poisoning were significantly lower after lipid resuscitation on OP patients than OP patients in the control group [SMD = −1.66, 95% CI (−3.15, −0.16), $p = 0.03$]. Forest plot is shown in Fig. 5.

Three studies include eligible data on serum TBIL levels, consisting of 255 patients. A randomized model was conducted because of high heterogeneity among studies ($I^2 = 93\%$). Pooled statistics demonstrated serum TBIL levels on the fifth day after OP poisoning were significantly lower after lipid resuscitation on OP patients than OP patients in the control group [SMD = −1.26, 95% CI (−2.32, −0.20), $p = 0.02$]. Forest plot is shown in Fig. 6.

3.6. Cholinesterase function

Only two studies included eligible data on activated cholinesterase levels, consisting of 82 patients. A fixed model was conducted because of low heterogeneity among studies ($I^2 = 0\%$). Pooled statistics demonstrated activated cholinesterase level on the fifth day after OP poisoning was significantly higher after lipid resuscitation on OP patients than OP patients in the control group [SMD = 2.15, 95% CI (1.60, 2.71), $p < 0.0001$]. Forest plot is shown in Fig. 7.

3.7. Respiratory muscle function

Only two studies included eligible data on the rate of respiratory muscle failure, consisting of 305 patients. A fixed model was conducted because of low heterogeneity among studies ($I^2 = 0\%$). Pooled statistics demonstrated the rate of respiratory muscle failure in OP poisoning patients was significantly lower after lipid resuscitation on OP patients than OP patients in the control group [OR = 0.19, 95% CI (0.05, 0.71), $p = 0.01$]. Forest plot is shown in Fig. 8.
4. Discussion

OP poisoning is still a leading cause of death among accidental or suicidal poisonings worldwide. China has reported a majority of OP patients worldwide [9,13]. In recent years, lipid emulsion therapy has been actively applied to OP poisoning cases in China. However, except for a handful of case reports, retrospective analyses and a few low-quality RCTs, higher level evidence for the use of lipid emulsion therapy for resuscitating OP poisoning patients is rather limited. Our meta-analysis, which is the first one in this area, combined seven studies with a combined total of 630 OP poisoning patients. The results of this meta-analysis demonstrate that starting lipid emulsion therapy when an OP patient presents to the emergency department is likely to improve the overall prognosis and certain organ performance (e.g. liver and respiratory muscle function).

Current treatment targeting OP poisoning is made up of two aspects. The first is to administer symptom relieving agents such as atropine and the second is to reactivate the function of cholinesterase (AchE) [14]. However, the dose of atropine administration is case-dependent, and can lead to over/underdosing of atropine [15].

Currently, OP challenged rats have demonstrated the positive effect of lipid emulsion therapy on resuscitating respiratory and pancreatic function. Dunn carried out research on 18 OP poisoning (parathion) rats undergoing tracheostomy, recording their air flow, respiratory rate, tidal volume, mean arterial pressure, and pulse rate [16]. They found that lipid resuscitation was able to prolong the time to apnea. Tuzcu carried out a research on 50 OP poisoning (malathion) rat models [17]. They recorded serum levels of glucose, insulin and oxidants as an observational index for the pancreas and concluded that lipid resuscitation helped to prevent pancreatic beta cell injury, oxidative stress and hyperglycemia. A meta-analysis on animal models also supported use of lipid resuscitation on liposoluble drug intoxication [18].

In a case study, an OP patient presenting with muscarinic symptoms and hemodynamic collapse insensitive to vasoactive agents was administered lipid emulsion starting on the first day of poisoning [19]. With a combined treatment with atropine and lipid emulsion, the AchE level and liver function returned to normal by the 12th day after poisoning. The effect of lipid emulsion therapy has also reported in adolescents. Yesilbas also reported a child suffering from OP poisoning, who was treated with atropine and lipid emulsion therapy and subsequently recovered [20].

Similarly, our included 7 articles all reported positive outcomes towards LR therapy in OP poisoning patients, who underwent standard atropine combined with pyridine aldoxime methiodide (PAM) therapy. But the baseline hemodynamic state of the recruited patients was not strictly restrained to those presenting hemodynamic collapse and insensitivity to vasoactive agents, which may expand the use of LR therapy beyond its previous ACMT indications.

However, the mechanism of lipid emulsion therapy on OP poisoning is not completely understood and is still a matter under investigation.
OP pesticide damages body tissue due to its toxic characteristics and lipid emulsion may help sequester these fat-soluble OP molecules and slow down their absorption into organs [21]. Besides the direct toxic effect of OP on end-organs, immune system reaction is another cause of tissue damage in OP patients. The release of inflammatory factors such as IL-1 and TNF-alpha, as well as the activation of the overall immune system, may also contribute to worse end-organ damage [22,23]. A lipid emulsion may help to take away OP molecules and reduce the inflammatory factors released after OP poisoning, thus improving hepatic and respiratory function [11]. Also, the initial injection of lipid emulsion may reduce the amount of atropine needed, helping to avoid severe adverse effect of anti-muscarinic receptor effects [12]. However, the exact mechanism of lipid emulsion on OP patients still needs further elucidation.

Our meta-analysis had some limitations. First, all the identified RCTs included were carried out in a single country (China), mainly due to OP being one of the most common means for suicide in the country. The methodological quality of these included studies was relatively low, especially considering the procedures of allocation concealment and blinding. Four out of the seven included studies carried out their research only on severe OP poisoning patients, but baseline characteristics such as circulatory and respiratory function were not restricted to those patients insensitive to basic therapy [22,23]. A lipid emulsion may help to take away OP molecules and reduce the inflammatory factors released after OP poisoning, thus improving hepatic and respiratory function [11]. Also, the initial injection of lipid emulsion may reduce the amount of atropine needed, helping to avoid severe adverse effect of anti-muscarinic receptor effects [12]. However, the exact mechanism of lipid emulsion on OP patients still needs further elucidation.

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Despite of these limits, our research synthesis of the most current studies of lipid resuscitation on OP patients is still helpful giving an overall state of lipid resuscitation for OP poisoning patients. Our research suggests that the initial administration of lipid resuscitation improves overall survival and leads to better liver and neuromuscular function. Nevertheless, our current results are based on relatively low quality evidence and future multi-center studies utilizing larger sample sizes are still needed to figure out the best procedures for lipid resuscitation administration and a better understanding of potential complications for OP poisoning patients.

5. Conclusion

Lipid emulsion may help improve the overall prognosis for OP poisoning patients, including improved liver function, acetylcholinesterase levels and respiratory muscle function. However, the best protocols for lipid emulsion administration as well as a better understanding of potential complications resulting from lipid resuscitation are not yet fully understood. Larger high quality multi-center RCTs are needed in the future to better elucidate these issues.

**Abbreviations**

- OP: organophosphate
- ALT: alanine aminotransferase
- AST: aspartate aminotransferase
- TBIL: total bilirubin
- AchE: acetylcholinesterase
- OR: odd ratio
- RCT: randomized controlled trial
- CNKI: Chinese National Knowledge Infrastructure
- CBM: Chinese Biomedical literature
- CMCC: Chinese Medical Current Contents
- CI: convinced interval
- SMD: standard mean difference
- LR: lipid resuscitation

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**Fig. 6.** The 5th day TBIL level between LR and control group on OP patients.

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**Fig. 7.** The 5th day AchE level between LR and control group on OP patients.

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**Fig. 8.** Rate of respiratory muscular paralysis between LR and control group on OP patients.
Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and supporting materials section

Data sharing not applicable to this article as no new datasets were generated or analyzed during the current study.

Competing interest

On behalf of all authors, the corresponding author states that there are no conflicts of interest for this study.

Authors’ contributions

Shiyuan Yu, Shanshan Yu, Lili Zhang, Xin Lu, Yanxia Gao and Yong Ma identified the included articles and performed the statistical analysis. Shiyuan Yu was a major contributor in writing the manuscript. Yi Li, Yanxia Gao, Huadong Zhu, Joseph Walline and Xuezhong Yu read and modified the manuscript. All authors approved the final manuscript.

Acknowledgements

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References