Omega-3 fatty acids in the treatment of acute lung injury: a systematic review and meta-analysis

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Abstract

Background

Several randomized controlled trials (RCTs) have compared the treatment of acute lung injury (ALI) with or without omega-3 fatty acids, yet the results remained inconsistent. Therefore, we attempted this meta-analysis to analyze the role of T Omega-3 fatty acids in the treatment of ALI patients.

Methods

We searched PubMed et al databases from inception date to Oct 31, 2019 for RCTs that compared the treatment of ALI with or without omega-3 fatty acids. Two authors independently screened the studies and extracted data from the published articles. Summary mean differences (MD) with 95% confidence intervals (CI) were calculated for each outcome by means of fixed- or random-effects model.

Results

Six RCTs with a total of 277 patients were identified, with 142 with omega-3 fatty acids treatment and 135 without omega-3 fatty acids treatment. Omega-3 fatty acids treatments significantly improve the PaO_2 (MD =13.82, 95%CI 8.55– 19.09), $\text{PaO}_2/\text{FiO}_2$ (MD =33.47, 95% CI 24.22– 42.72), total protein (MD =2.02, 95% CI 0.43– 3.62) in ALI patients; furthermore, Omega-3 fatty acids treatments reduced the duration of mechanical ventilation (MD =-1.72, 95% CI -2.84– -0.60) and intensive care unit stay (MD =-1.29, 95% CI -2.14– -0.43) in ALI patients.

Conclusions

Omega-3 fatty acids can effectively improve the respiratory function and promote the recovery of ALI patients. More studies focused on the long-term efficacy and safety of omega-3 fatty acids use for ALI are needed.

Introduction

Acute lung injury (ALI) is a very common type of critically ill disease in the clinic, which is caused by various intrapulmonary and external factors such as severe trauma, shock, acidosis or serious infection et al[1, 2]. if left untreated, it may progress into acute respiratory distress syndrome (ARDS) with high mortality[3]. In the past decade, great progress has been made in the management of patients with ALI and ARDS. However, the mortality of ALI/ARDS is still high with a range of 40–31%[4, 5]. In addition to infection control, low tidal volume protective lung mechanical ventilation, nutritional treatment of ARDS/ALI plays an important role in the treatment strategies[6–8], especially the provision of calories by fat nutrition is a key part[9].

At present, the fat emulsions used in clinical practice are mostly based on soybean oil. Soybean oil-based fat emulsions are rich in long-chain fat emulsions, which can affect granulocyte activity under severe

stress such as trauma and infection, resulting in impaired immune function and increased lipid peroxidation, which in turn increases organ function damage[10, 11]. This tendency to increase the inflammatory response often makes the use of soybean oil-based fat emulsions in a dilemma clinically. In recent years, Omega-3 fatty acids have attracted much attention due to their ability to reduce inflammation and regulate immunity. It's been reported[12, 13] that it produces the effect of inhibiting inflammation and regulating immunity in many diseases. It has achieved good effects in the treatment of severe patients such as sepsis, systemic inflammatory response syndrome et al[14, 15]. Compared to traditional fat emulsions, Omega-3 fatty acids show its superiority in nutritional therapy for critically ill patients[16]. However, the studies on the effects of Omega-3 fatty acids for the treatment of ALI are still lacking.

Based on literature review, we have found that there are several randomized controlled trials (RCTs) focusing on the omega-3 fatty acids in the treatment of ALI, yet the results have remained inconsistent. Furthermore, there aren't related meta-analysis on the role of omega-3 fatty acids in the treatment of ALI, further investigations are needed. Therefore, we have attempted to conduct this meta-analysis to evaluate the efficacy and safety of omega-3 fatty acids in the treatment of ALI, to provide insights into the clinical management of ALI.

Methods

We attempted to conduct and reported this meta-analysis in comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[17]

Literature search

Relevant RCTs on the role omega-3 fatty acids in the treatment of ALI were screened and identified. We searched PUBMED, EMBASE, Cochrane library, China National Knowledge Infrastructure (CNKI) and Wanfang Database, China Biomedical Literature Database (CBM) for relevant trials published in English or Chinese up to Oct 31, 2019. Following search terms were used: "omega-3; fish oil; ω -3; acute lung injury; ALI; acute respiratory distress syndrome; ARDS". We adopted those search terms with combined Boolean operators "AND" or "OR" in every database. Besides, relevant systematic reviews and meta-analyses from these databases were identified, and their bibliographies were scrutinized for further relevant trials, as were those of the RCTs included in the review.

Eligibility criteria

Two investigators independently reviewed the identified articles. The inclusion criteria for RCTs were as follows: (1) RCT design; (2) comparative analysis of ALI treatment with or without omega-3 fatty acids; (3) the details of omega-3 fatty acids treatment and related outcomes were reported. The exclusion criteria were as follows: (1) case reports, reviews, editorial comments, meeting abstracts and articles without applicable data; (2) studies with insufficient data, such as missing the standard deviation (SD); (3) Considerable overlaps between the authors, research centers among the published literature.

Study selection

The search results were imported into the software of Endnote X7 for literature management. Two authors independently reviewed the title, abstract or descriptors of the identified studies and excluded studies that clearly did not meet the inclusion criteria. After excluding duplicate and apparently irrelevant studies, the full text of the remaining studies was reviewed to assess eligibility for inclusion. Any disagreements were resolved by discussion or by asking an independent third opinion.

Data collection

Two authors independently extracted the data from each study with a standardized data extraction checklist, which included the study characteristics (e.g., first author's name, publication year, journal, country where the study was conducted), characteristics of included study subjects (e.g., number of participants, age, gender distribution et al), details of omega-3 fatty acids treatment intervention, outcome variables (e.g., follow-up period) and study conclusion. Outcomes were extracted preferentially by intention to treat (ITT) at the end of follow-up. Quantitative data were extracted to calculate effect sizes. Data on effect size that could not be obtained directly were recalculated when possible or contacted the original authors for data. Any discrepancy was resolved by further consensus.

Risk of bias assessment

Two authors independently assessed the methodological quality of the included studies for major potential sources of bias using the Cochrane Collaboration's risk of bias tool, which includes the method of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. We evaluated the methodological quality of every included RCT by rating each criterion as low, high or unclear risk of bias. Any disagreements were resolved through further discussion whenever necessary.

Statistical analysis

Review Manager Version 5.3 software were used for data-analysis. All the data syntheses and interpretations were also performed by two authors independently to ensure the accuracy of the results. Binary outcomes were presented as Mantel–Haenszel-style odds ratios (OR) with 95% confidence intervals (CIs). Continuous outcomes were reported as mean differences (MDs). A fixed-effect model was adopted in cases of homogeneity (P-value of χ^2 test > 0.10 and $I^2 < 50\%$), whereas a random-effect model was used in cases of obvious heterogeneity (P-value of χ^2 test > 0.10 and $I^2 \geq 50\%$). Publication bias was evaluated by using funnel plots, and asymmetry was assessed by conducting Egger regression test. The statistical significance level was 0.05 in this present study.

Results

Study selection

Figure 1 shows a flow diagram of study selection. The electronic searches identified 111 literatures, and 80 reports were clearly not relevant after the first screening. The full text of 21 studies was retrieved for further in-depth consideration, and 15 studies were excluded for the several reasons. Finally, 6 RCTs[18-23] were included in this meta-analysis. References cited in published original and review papers were examined, and no further studies were found.

Characteristics of included RCTs

The characteristics of RCTs included in this present meta-analysis are presented in Table 1. Of these included studies, one were performed in India[23], the resting five in China[18-22]. The combined sample size across the 6 included studies was 277 participants, with 142 ALI patients with omega-3 fatty acids treatment and 135 patients without omega-3 fatty acids treatment. The patient samples in the included studies were variable with a range of 34 to 61. For study results, one study didn't support the use of omega-3 fatty acids in ARDS patients, whereas the other studies all favored the the use of omega-3 fatty acids for the treatment of ALI.

Methodological quality of the included studies

Figure 2 and 3 show the quality assessment of the studies in this present meta-analysis. All 6 included studies were randomized, but only two RCTs[21, 23] specified the method of randomization. All the RCTs did not reference whether any allocation concealment process was used. 4 RCTs[20-23] reported the design on blinding patients, personnel and outcome assessors. No other significant biases amongst the included RCTs were found. Intention to treat (ITT) was performed for all patients.

Outcomes

The changes of PaO₂ Three RCTs[19, 20, 22] reported the changes of PaO₂ for ALI patients with or without omega-3 fatty acids treatment, the pooled data from the three RCTs revealed that the omega-3 fatty acids treatments significantly improve the PaO₂ in ALI patients (MD =13.82, 95% CI 8.55– 19.09, P < 0.001, I² = 0%; Figure 4).

The changes of PaO₂/FiO₂ Five RCTs[18-22] reported the changes of PaO₂/FiO₂ for ALI patients with or without omega-3 fatty acids treatment, the pooled data from the five RCTs revealed that the omega-3 fatty acids treatments significantly improve the PaO₂/FiO₂ in ALI patients (MD =33.47, 95% CI 24.22– 42.72, P < 0.001, I² = 0%; Figure 5).

The changes of total protein (TP) Three RCTs[18, 21, 22] reported the changes of TP for ALI patients with or without omega-3 fatty acids treatment, the pooled data from the three RCTs revealed that the omega-3 fatty acids treatments significantly increase the TP in ALI patients (MD =2.02, 95% CI 0.43– 3.62, P=0.01, I² = 30%; Figure 6).

The duration of mechanical ventilation (MV) Three RCTs[21-23] reported the duration of MV for ALI patients with or without omega-3 fatty acids treatment, the pooled data from the three RCTs revealed that the omega-3 fatty acids treatments significantly reduced the duration of MV in ALI patients (MD =-1.72, 95% CI -2.84– -0.60, P=0.003, $I^2 = 0\%$; Figure 7).

The length of ICU stay Three RCTs[21-23] reported the length of ICU stay for ALI patients with or without omega-3 fatty acids treatment, the pooled data from the three RCTs revealed that the omega-3 fatty acids treatments significantly reduced the length of ICU stay in ALI patients (MD =-1.29, 95% CI -2.14– -0.43, P=0.003, $I^2 = 59\%$; Figure 8).

Subgroup and sensitivity analyses

No subgroup analyses were performed in our study because the heterogeneity among included RCTs in the synthesized results remained small. We attempted to evaluate publication bias by using a funnel plot if 10 or more RCTs[24]. However, the number of included RCTs were only six, we could not evaluate publication bias by using a funnel plot. Sensitivity analyses, which investigate the influence of one study on the overall risk estimate by removing one study in each turn, suggested that the overall risk estimates were not substantially changed by any single study.

Discussion

Patients with ALI are in a state of high metabolism, and it's necessary to provide nutritional support[25]. Besides, the nutritional support of critically ill patients should fully consider the tolerance of the damaged organ, critically ill patients should start EN as soon as the conditions permit[25]. It's been reported that early EN support improves immune function and protein levels in ARDS patients, which may reduce mortality and shorten the duration of MV and ICU stay[26]. With six RCTs included, the results of this present meta-analysis have indicated that omega-3 fatty acids significantly improve the PaO_2 , PaO_2/FiO_2 increase the TP level, and reduce the length of MV and ICU stay for ALI patients. Therefore, the use of omega-3 fatty acids is a promising and effective treatment strategy for ALI.

The potential mechanism of omega-3 fatty acids for ALI treatment should be considered. A number of studies[27-29] have found that omega-3 fatty acids can regulate the synthesis of lipid mediators, release cytokines, activate white blood cells and endothelial cells, thereby regulating the body's excessive inflammatory response to reduce the lung inflammation. Moreover, it's possible that omega-3 fatty acids increase the patient's PaO_2 and PaO_2/FiO_2 to improve the patient's respiratory function. Furthermore, omega-3 fatty acids can reduce the concentration of IL-8, leukotriene and neutrophils in the bronchial lavage fluid of patients, and reduce alveolar permeability, thereby improving patients' gas exchange[30, 31]. Meanwhile, it not only provides energy as a nutrient-supporting substance, maintains nitrogen balance, but also can reduce insulin resistance and hyperlipidemia[32]. However, the potential risks of omega-3 fatty acids use should also be concerned. Two included RCTs[21, 22] reported the adverse events after the use of omega-3 fatty acids, mainly diarrhea, bloating, gastric contents reflux. It be related

to that after long-term or unreasonable use of antibiotics, the intestinal flora is dysfunctional, it's easy to diarrhea[33]. And it's possible that the nutrient solution temperature is too low, or with improper preparation ratio[34]. The occurrence of diarrhea is negatively correlated with serum protein levels[35]. Attention should be paid to the speed of infusion, the temperature of the nutrient solution is kept constant.

The pathological feature of ALI is pulmonary edema caused by increased pulmonary capillary permeability, the pathological basis of which is neutrophil-mediated local inflammatory response in the lung[36]. Pathophysiological changes were mainly due to increased Qs/Qt and imbalance of ventilation/blood flow ratio[37]. The application of omega-3 fatty acids not only can quickly reduce the inflammatory reaction of lung tissue, but also transform LTB₄, which aggravates inflammatory reaction, into LTB₅ series, which is less active, thereby significantly reducing pulmonary edema, improving the pulmonary vascular permeability[38-40]. Besides, as specific immunonutrients, omega-3 fatty acids can regulate the activity of lipid mediators, cytokines and endothelial cell, thereby regulating the excessive inflammatory response of the body under infection and trauma[41]. Given all this together, the use of omega-3 fatty acids may be a useful adjuvant therapy for ALI patients.

The limitations exist in this study must be considered. Firstly, the number of RCTs included in this study is too small, and five out of six RCTs were from China, and the representativeness is poor. Secondly, the potential risk of bias in the allocation concealment process, blinding of researchers, blinding of outcome assessments must be considered since the information on those issues remains unclear, further studies with strict design are needed. Thirdly, no relevant economic indicators were reported among included RCTs, thus we could not perform analysis on this issue. Future clinical trials should focus on collecting and reporting relevant economic data to evaluate the cost of omega-3 fatty acids treatment. Future studies on the ALI treatment with omega-3 fatty acids should pay attention to study design. And the selected indicators should reflect the purpose of the study as much as possible with longer follow-up period.

In conclusion, as a new type of nutritional preparation, omega-3 fatty acids can improve the respiratory function and respiratory status of ALI patients by increase PaO₂ and PaO₂/FiO₂. Meanwhile, it can increase the TP level, and reduce the length of MV and ICU stay for ALI patients. Therefore, omega-3 fatty acids may be a potential effective and safe strategy for the ALI treatment. Future larger-scale RCTs are needed to further explore the timing and dosage of omega-3 fatty acids application in the ALI treatment.

Abbreviations

RCTs: randomized controlled trials

ALI: acute lung injury

OR: odds ratios

MD: mean differences

CI: confidence intervals

ARDS: acute respiratory distress syndrome

CNKI: China National Knowledge Infrastructure

CBM: China Biomedical Literature Database

ITT: intention to treat

TP: total protein

MV: mechanical ventilation

PUFA: polyunsaturated fatty acids

Declarations

Ethics approval and consent to participate

None

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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None.

Author contributions

C H, J Z and Y H designed research; C H, J Z, W H, M Y, L H, R J, X H, H F and H C conducted research; C H, J Z, H Y, W S and X H analyzed data; C H wrote the first draft of manuscript; C H, J Z and Y H had primary responsibility for final content. All authors read and approved the final manuscript.

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Table

Table 1 The characteristics of included RCTs

Studies	Countries	Group	Participants	Age(years)	Length of diet	Conclusions
Dai 2009	China	Omega 3 fatty acids	17	39.5±5.8	1W	Omega 3 fatty acids are beneficial to the recovery of respiratory function in patients with ARDS
Gupta 2010	India	Control Omega 3 fatty acids	17 31	51.16±15.58	1W	In ventilated patients with ARDS , intravenous Omega 3 fatty acids alone do not improve ventilation, length of ICU stay or survival
Shen 2010	China	Control Omega 3 fatty acids	30 20	46.63±16.44 66.1±15	1W	Omega-3 polyunsaturated fatty acid improves respiratory function and prognosis in patients with ALI.
Shen 2011	China	Control Omega 3 fatty acids	19 22	61.9±18.9 64.0±9.0	1W	The use of omega-3 polyunsaturated fatty acids helps to improve inflammatory factor levels in ALI patients.
Wang 2011	China	Control Omega 3 fatty acids	21 26	68.0±10.0 75.2±8.9	1W	Omega-3 fatty acids are beneficial to the recovery of respiratory function in ALI patients, and it shorten the time of mechanical ventilation and length of ICU stay.
Zhao 2010	China	Control Omega 3 fatty acids	22 26	40.2±6.1	1W	The Omega 3 polyunsaturated fatty acids enriched enteral nutrition solution can facilitate the recovery of respiratory function.

Notes: W, week; ARDS, acute respiratory distress syndrome; ALI, acute lung injury

Figures

Figure 1

The flow chart of study selection

Figure 2

Risk of bias graph

	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
Dai 2009	+	?	?	?	+	+	+
Gupta 2010	+	?	+	?	+	+	+
Shen 2010	+	?	?	?	+	+	+
Shen 2011	+	?	+	?	+	+	+
Wang 2011	+	?	+	?	+	+	+
Zhao 2010	+	?	+	?	+	+	+

Figure 3

Risk of bias summary

Figure 4

Forest plot for the changes of PaO2

Figure 5

Forest plot for the changes of PaO2/FiO2

Figure 6

Forest plot for the changes of TP

Figure 7

Forest plot for the duration of MV

Figure 8

Forest plot for the length of ICU stay