Int J Clin Exp Med 2017;10(12):15920-15926
www.ijcem.com /ISSN:1940-5901/IJCEM0056992

Review Article

Effect of omega-3 fatty acids on acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis

Ying Chen[1], Zhangqing Zhou[1], Huanhuan Yang[1], Hongguo Lu[2]

[1]*General Internal Medicine, Hangzhou Xixi Hospital, Hangzhou, Zhejiang Province, P.R. China;* [2]*Department of Respiration, No.2 People's Hospital of Yuhang District, Hangzhou, Zhejiang Province, P.R. China*

Received March 26, 2017; Accepted October 7, 2017; Epub December 15, 2017; Published December 30, 2017

Abstract: Background: Omega-3 fatty acids might improve the clinical outcomes of patients undergoing acute lung injury and acute respiratory distress syndrome. However, the results remained controversial. We conducted a systematic review and meta-analysis to explore the effect of omega-3 fatty acids for acute lung injury and acute respiratory distress syndrome. Methods: PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were systematically searched. Randomized controlled trials (RCTs) assessing the effect of omega-3 fatty acids versus placebo on acute lung injury and acute respiratory distress syndrome were included. Two investigators independently searched articles, extracted data, and assessed the quality of included studies. The primary outcome was PaO_2/FiO_2. Meta-analysis was performed using random-effect model. Results: Five RCTs involving 428 patients were included in the meta-analysis. Overall, compared with control intervention in acute lung injury and acute respiratory distress syndrome, omega 3 fatty acids intervention was found to significantly improve PaO_2/FiO_2 (Std. mean difference=32.60; 95% CI=4.13 to 61.08; P=0.02), reduce ICU-free day (Std. mean difference=-0.26; 95% CI=-0.48 to -0.05; P=0.02) and ventilator-free day (Std. mean difference=-0.31; 95% CI=-0.53 to -0.10; P=0.005), but had no influence on mortality (RR=0.95; 95% CI=0.54 to 1.65; P=0.85). Conclusions: Omega-3 fatty acids intervention should be recommended in patients with acute lung injury or acute respiratory distress syndrome.

Keywords: Omega-3 fatty acids, PaO_2/FiO_2, acute lung injury, acute respiratory distress syndrome, meta-analysis

Introduction

Acute lung injury and the acute respiratory distress syndrome were reported to result in a case fatality of 30-40% [1-3]. During acute lung injury, massive of the proinflammatory response were activated and they included the release of inflammatory mediators such as the eiconsanoids which were metabolized from arachidonic acid [4, 5]. Eiconsanoids consisted of 2-series prostaglandins, thromboxanes and 4-series leukotrienes, and they had an important role in fever, vascular permeability, vasodilatation, platelet aggregation, leukocyte adhesion, and cytokine production [6-8]. Acute respiratory distress syndrome was mediated by several vasoactive substances that promoted cell aggregation and modified permeability. And some other factors included histamine, serotonin, the cytokine system, and some lipid mediators (e.g. prostaglandins, leukotrienes and platelet activating factor) etc [9, 10].

Recent studies suggested that omega-3 fatty acids may be able to improve the outcomes of these patients [11, 12]. Omega-3 fatty acids found in fish oil included eicosapentaenoic acid and docosahexanoic acid and could reduce inflammatory eicosanoid production through various anti-inflammatory mechanisms [13, 14]. Previous studies reported that omega-3 fatty acids could improve PaO_2/FiO_2, and reduce ICU-free day and ventilator-free day in patients undergoing acute lung injury and the acute respiratory distress syndrome [15, 16].

In contrast to this promising finding, however, some relevant RCTs showed that omega-3 fatty acids had no influence on PaO_2/FiO_2, ICU-free day, ventilator-free day and mortality for acute lung injury and the acute respiratory distress syndrome [17, 18]. Considering these inconsistent effects, we therefore conducted a systematic review and meta-analysis of RCTs to evaluate the effectiveness of omega-3 fatty acids

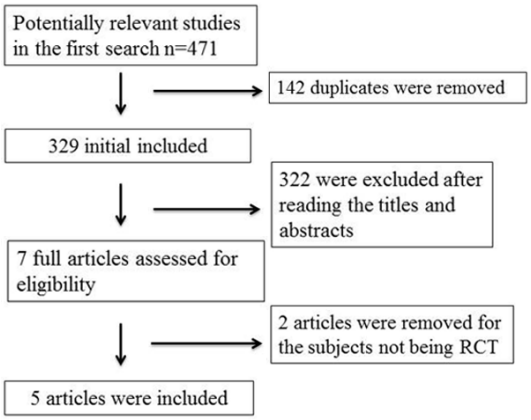

Figure 1. Flow diagram of study searching and selection process.

intervention on the treatment of acute lung injury and the acute respiratory distress syndrome.

Materials and methods

This systematic review and meta-analysis were conducted according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [19] and the *Cochrane Handbook for Systematic Reviews of Interventions* [20]. All analyses were based on previous published studies, thus no ethical approval and patient consent were required.

Literature search and selection criteria

PubMed, EMbase, Web of science, EBSCO, and the Cochrane library were systematically searched from inception to April 2017, with the following keywords: omega-3 fatty acids, and acute lung injury or ALI or acute respiratory distress syndrome or ARDS. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews were also handsearched and the process above was performed repeatedly until no further article was identified. Conference abstracts meeting the inclusion criteria were also included.

The inclusion criteria were as follows: patients with acute lung injury or acute respiratory distress syndrome required enteral nutrition, and the intervention was between omega-3 fatty acids intervention and placebo. The study design was RCT.

The exclusion criteria included pregnancy, liver failure, HIV+, leukopenia and renal failure.

Data extraction and outcome measures

The following information was extracted for the included RCTs: first author, publication year, sample size, baseline characteristics of patients, omega-3 fatty acids, control, study design, PaO_2/FiO_2, ICU-free day, ventilator-free day, mortality. The author would be contacted to acquire the data when necessary.

The primary outcome was PaO_2/FiO_2. Secondary outcomes included ICU-free day, ventilator-free day and mortality.

Quality assessment in individual studies

The Jadad Scale was used to evaluate the methodological quality of each RCT included in this meta-analysis [21]. This scale consisted of three evaluation elements: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). One point would be allocated to each element if they have been mentioned in article, and another one point would be given if the methods of randomization and/or blinding had been detailedly and appropriately described. If methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals had not been recorded, then one point was deducted. The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score ≤ 2 was considered to be of low quality. If the Jadad score ≥ 3, the study was thought to be of high quality [22].

Statistical analysis

Standard Mean differences (Std. MDs) with 95% confidence intervals (CIs) for continuous outcomes (PaO_2/FiO_2, ICU-free day, ventilator-free day), and risk ratios (RRs) with 95% CIs for dichotomous outcomes (mortality) were used to estimate the pooled effects. All meta-analyses were performed using random-effects models with DerSimonian and Laird weights. Heterogeneity was tested using the Cochran Q statistic ($p<0.1$) and quantified with the I^2 statistic, which described the variation of effect size that was attributable to heterogeneity across studies. An I^2 value greater than 50% indicated significant heterogeneity. Sensitivity analysis was performed to detect the influence

of a single study on the overall estimate via omitting one study in turn when necessary. Owing to the limited number (<10) of included studies, publication bias was not assessed. P<0.05 in two-tailed tests was considered statistically significant. All statistical analyses were performed with Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

The flow chart for the selection process and detailed identification was presented in **Figure 1**. 471 publications were identified through the initial search of databases. Ultimately, five RCTs were included in the meta-analysis [9, 15-18].

The baseline characteristics of the five eligible RCTs in the meta-analysis were summarized in **Table 1**. The eleven studies were published between 2008 and 2011, and sample sizes ranged from 16 to 272 with a total of 428. There were two RCTs reporting the same clinical study but with difcal outcomes [9, 18]. There was no significant difference of age, PaO_2/FiO_2, and APACHE II score between omega 3 fatty acids group and control group at baseline. The methods and doses of taking omega 3 fatty acids were different, detail in the **Table 1**.

Among the five RCTs, two studies reported the PaO_2/FiO_2 [15, 17, 18], two studies reported the ICU-free day and ventilator-free day [16, 17], and three studies reported the mortality [15-17]. Jadad scores of the five included studies varied from 3 to 5, all five studies were considered to be high-quality ones according to quality assessment.

Primary outcome: PaO_2/FiO_2

This outcome data was analyzed with a random-effects model, the pooled estimate of the three included RCTs suggested that compared to control group, omega 3 fatty acids intervention was associated with a significantly improve PaO_2/FiO_2 (Std. mean difference=32.60; 95% CI=4.13 to 61.08; P=0.02), with no heterogeneity among the studies (I^2=0%, heterogeneity P=0.38) (**Figure 2**).

Sensitivity analysis

No heterogeneity was observed among the included studies for the PaO_2/FiO_2. Thus, we did not perform sensitivity analysis by omitting one study in each turn or performed subgroup analysis to detect the source of heterogeneity.

Secondary outcomes

Compared with control intervention for acute lung injury and acute respiratory distress syndrome, omega 3 fatty acids intervention showed significantly reduced ICU-free day (Std. mean difference=-0.26; 95% CI=-0.48 to -0.05; P=0.02; **Figure 3**), ventilator-free day (Std. mean difference=-0.31; 95% CI=-0.53 to -0.10; P=0.005; **Figure 4**), but had no influence on mortality (RR=0.95; 95% CI=0.54 to 1.65; P= 0.85; **Figure 5**).

Discussion

Acute lung injury and acute respiratory distress syndrome were life-threatening disorders that was mainly caused by predisposing disorders such as pneumonia, aspiration, shock, and severe sepsis [23-25]. During their pathophysiology, neutrophils infiltrated into the alveolar space and pulmonary mesenchyme, and pro-inflammatory cytokines were released to eventually result in leakage of edema fluid and mismatch of ventilation and perfusion [23, 26, 27].

And there were still lack of effective treatment for these two diseases [28]. The current treatments were supportive care and they mainly included maintaining oxygenation and avoiding complications [29]. Previous studies reported that omega-3 fatty acids was able to modulate inflammatory processes such as reducing leukotriene production [30], scavenge free radicals [31], decrease the synthesis of prostaglandin E_2 [32] and the permeability of the alveolar-capillary membrane for acute lung injury and acute respiratory distress syndrome [32].

One recent meta-analysis concluded that the enteral immunomodulatory diet consisting of omega-3 fatty acid, γ-linolenic acid and antioxidant supplementation showed no decrease in the mortality, 28-day ventilator-free days or 28-day ICU-free days in patients with acute lung injury and acute respiratory distress syndrome. But these patients with high mortality might benefit from enteral immunomodulatory

Table 1. Characteristics of included studies

NO.	Author	Omega 3 fatty acids group						Control group						Jada scores
		Number	Age (years)	Male (n)	PaO_2/FiO_2	APACHE II score	Methods	Number	Age (years)	Male (n)	PaO_2/FiO_2	APACHE II score	Methods	
1	Stapleton 2011	40	49.0±16.5	24	154.7±46.5	22.8±7.3	7.5 cc every 6 hours equalling 9.75 g EPA and 6.75 g DHA daily	49	50.7±16.5	33	172.5±65.3	21.1±5.9	0.9% saline	4
2	Sabater 2011	8	56±15	8	141±37	17.4±2.1	A dose of 0.12 g/kg/h for 12 h, emulsion Lipoplus® 20%, B. Braun Medical (50% medium-chain fatty acids, 40% long-chain fatty acids, 10% fish oil)	8	59±12	6	158±43	17.4±2.1	A dose of 0.12 g/kg/h for 12 h, emulsion Intralipid® Fresenius Kabi (100% long-chain fatty acids)	3
3	Rice 2011	143	55.5±17.0	20	159.9±75.6	93.8±24.9	Twice-daily enteral supplementation of omega 3 fatty acids, omega 6γ-linolenic acid, and antioxidants	129	52.9±16.5	15	172.5±84.6	91.8±29.3	An isocaloric-isovolemic carbohydrate-rich control	4
4	Gupta 2011	31	51.16±15.58	19	145±100	64.06±21.55	Standard diet + parenteral omega 3 fatty acids, Omegaven® (Fresenius Kabi), an emulsion of 10% fish oil	30	46.63±16.44	18	199±124	68.47±21.43	Standard diet	5
5	Sabater 2008	8	56±15	8	141±37	17.4±2.1	A dose of 0.12 g/kg/h for 12 h, emulsion Lipoplus® 20%, B. Braun Medical (50% medium-chain fatty acids, 40% long-chain fatty acids, 10% fish oil)	8	59±12	6	158±43	17.4±2.1	A dose of 0.12 g/kg/h for 12 h, emulsion Intralipid® Fresenius Kabi (100% long-chain fatty acids)	3

Eicosapentaenoic acid (EPA), docosahexanoic acid (DHA).

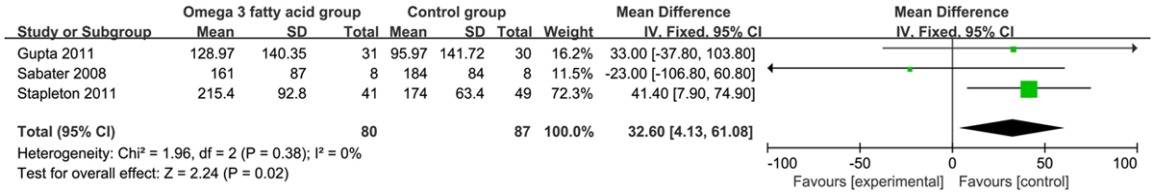

Figure 2. Forest plot for the meta-analysis of PaO_2/FiO_2.

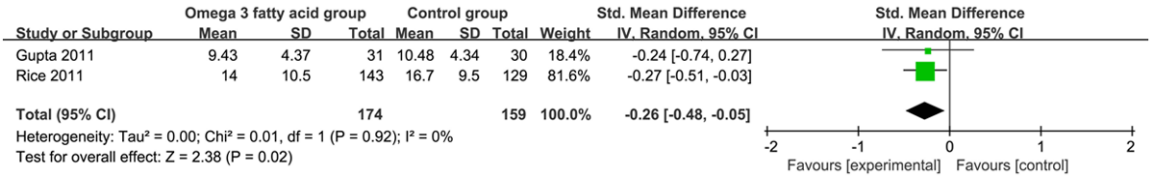

Figure 3. Forest plot for the meta-analysis of ICU-free day.

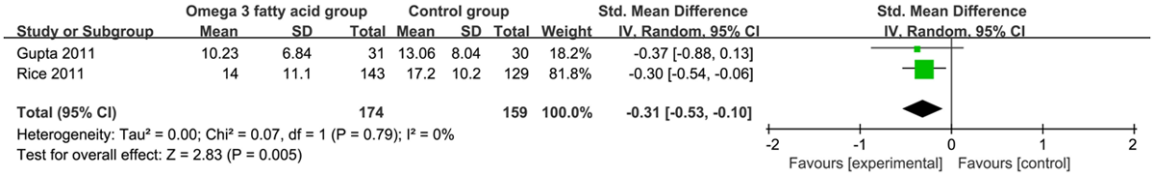

Figure 4. Forest plot for the meta-analysis of ventilator-free day.

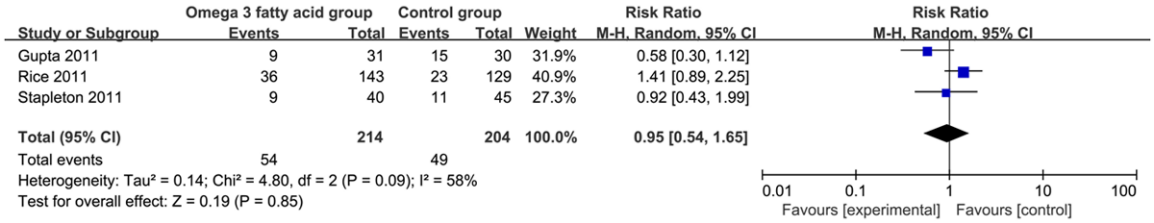

Figure 5. Forest plot for the meta-analysis of mortality.

diet [29]. And our meta-analysis only focused on the RCTs regarding the influence of omega-3 fatty acids on acute lung injury and acute respiratory distress syndrome, and more RCTs were included [9, 15, 17]. The results concluded that omega-3 fatty acids intervention was associated with a significantly improved PaO_2/FiO_2, as well as reduced ICU-free day and ventilator-free day, but had no positive influence on the mortality for acute lung injury and acute respiratory distress syndrome.

Several limitations should be taken into account. Firstly, our analysis was based on five RCTs but four of them have a relatively small sample size (n<100). Overestimation of the treatment effect was more likely in smaller trials compared with larger samples. More clinical trials with large sample were needed to explore this issue. The doses and methods of omega-3 fatty acids in the included studies were different and it probably affected the pooled results. Next, the inflammation biomarkers such as interleukin-8 levels was not analyzed because of the limited data in the included RCTs. Finally, some unpublished and missing data might lead bias to the pooled effect.

Conclusion

Omega-3 fatty acids showed an important ability to improve PaO_2/FiO_2, as well as decrease ICU-free day and ventilator-free day in patients undergoing acute lung injury and acute respira-

tory distress syndrome. Omega-3 fatty acids was recommended to be administrated for acute lung injury and acute respiratory distress syndrome.

Disclosure of conflict of interest

None.

Address correspondence to: Hongguo Lu, Department of Respiration, No.80 Anle Road, Yuhang Town, Yuhang District, Hangzhou, Zhejiang Province, P.R. China. E-mail: 108800139@qq.com

References

[1] Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ and Hudson LD. Incidence and outcomes of acute lung injury. N Engl J Med 2005; 353: 1685-1693.

[2] Stapleton RD, Wang BM, Hudson LD, Rubenfeld GD, Caldwell ES and Steinberg KP. Causes and timing of death in patients with ARDS. Chest 2005; 128: 525-532.

[3] Standiford TJ and Ward PA. Therapeutic targeting of acute lung injury and acute respiratory distress syndrome. Transl Res 2016; 167: 183-191.

[4] Bastarache JA, Fremont RD, Kropski JA, Bossert FR and Ware LB. Procoagulant alveolar microparticles in the lungs of patients with acute respiratory distress syndrome. Am J Physiol Lung Cell Mol Physiol 2009; 297: L1035-1041.

[5] Muller-Redetzky H. Targeting neutrophil extracellular traps in acute lung injury: a novel therapeutic approach in acute respiratory distress syndrome? Anesthesiology 2015; 122: 725-727.

[6] Tilley SL, Coffman TM and Koller BH. Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. J Clin Invest 2001; 108: 15-23.

[7] Bulger EM and Maier RV. Lipid mediators in the pathophysiology of critical illness. Crit Care Med 2000; 28: N27-36.

[8] Yaqoob P, Pala HS, Cortina-Borja M, Newsholme EA and Calder PC. Encapsulated fish oil enriched in alpha-tocopherol alters plasma phospholipid and mononuclear cell fatty acid compositions but not mononuclear cell functions. Eur J Clin Invest 2000; 30: 260-274.

[9] Sabater J, Masclans JR, Sacanell J, Chacon P, Sabin P and Planas M. Effects of an omega-3 fatty acid-enriched lipid emulsion on eicosanoid synthesis in acute respiratory distress syndrome (ARDS): a prospective, randomized, double-blind, parallel group study. Nutr Metab (Lond) 2011; 8: 22.

[10] Dinglas VD, Aronson Friedman L, Colantuoni E, Mendez-Tellez PA, Shanholtz CB, Ciesla ND, Pronovost PJ and Needham DM. Muscle weakness and 5-year survival in acute respiratory distress syndrome survivors. Crit Care Med 2017; 45: 446-453.

[11] Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E and Cohen J. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. Crit Care Med 2006; 34: 1033-1038.

[12] Pontes-Arruda A, Aragao AM and Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. Crit Care Med 2006; 34: 2325-2333.

[13] Calder PC and Grimble RF. Polyunsaturated fatty acids, inflammation and immunity. Eur J Clin Nutr 2002; 56 Suppl 3: S14-19.

[14] Calder PC. Polyunsaturated fatty acids, inflammation, and immunity. Lipids 2001; 36: 1007-1024.

[15] Stapleton RD, Martin TR, Weiss NS, Crowley JJ, Gundel SJ, Nathens AB, Akhtar SR, Ruzinski JT, Caldwell E, Curtis JR, Heyland DK, Watkins TR, Parsons PE, Martin JM, Wurfel MM, Hallstrand TS, Sims KA and Neff MJ. A phase II randomized placebo-controlled trial of omega-3 fatty acids for the treatment of acute lung injury. Crit Care Med 2011; 39: 1655-1662.

[16] Rice TW, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P, Investigators NNARDSNo and Network NACT. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. JAMA 2011; 306: 1574-1581.

[17] Gupta A, Govil D, Bhatnagar S, Gupta S, Goyal J, Patel S and Baweja H. Efficacy and safety of parenteral omega 3 fatty acids in ventilated patients with acute lung injury. Indian J Crit Care Med 2011; 15: 108-113.

[18] Sabater J, Masclans JR, Sacanell J, Chacon P, Sabin P and Planas M. Effects on hemodynamics and gas exchange of omega-3 fatty acid-enriched lipid emulsion in acute respiratory distress syndrome (ARDS): a prospective, randomized, double-blind, parallel group study. Lipids Health Dis 2008; 7: 39.

[19] Moher D, Liberati A, Tetzlaff J, Altman DG and Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535.

[20] Higgins JPT GS. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane collaboration 2011. Available from www.cochrane-handbook.org.

[21] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ and McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996; 17: 1-12.

[22] Kjaergard LL, Villumsen J and Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Annals of Internal Medicine 2001; 135: 982-989.

[23] Pierrakos C, Karanikolas M, Scolletta S, Karamouzos V and Velissaris D. Acute respiratory distress syndrome: pathophysiology and therapeutic options. J Clin Med Res 2012; 4: 7-16.

[24] Kurahashi K. Therapeutic strategy for acute respiratory distress syndrome: recent understanding of the pathophysiology of the disease. J Anesth 2011; 25: 155-156.

[25] Berngard SC, Beitler JR and Malhotra A. Personalizing mechanical ventilation for acute respiratory distress syndrome. J Thorac Dis 2016; 8: E172-174.

[26] Muller-Redetzky HC, Felten M, Hellwig K, Wienhold SM, Naujoks J, Opitz B, Kershaw O, Gruber AD, Suttorp N and Witzenrath M. Increasing the inspiratory time and I:E ratio during mechanical ventilation aggravates ventilator-induced lung injury in mice. Crit Care 2015; 19: 23.

[27] Herridge MS, Moss M, Hough CL, Hopkins RO, Rice TW, Bienvenu OJ and Azoulay E. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. Intensive Care Med 2016; 42: 725-738.

[28] Adhikari N, Burns KE and Meade MO. Pharmacologic treatments for acute respiratory distress syndrome and acute lung injury: systematic review and meta-analysis. Treat Respir Med 2004; 3: 307-328.

[29] Li C, Bo L, Liu W, Lu X and Jin F. Enteral immunomodulatory diet (omega-3 fatty acid, gamma-linolenic acid and antioxidant supplementation) for acute lung injury and acute respiratory distress syndrome: an updated systematic review and meta-analysis. Nutrients 2015; 7: 5572-5585.

[30] El Kebir D, Gjorstrup P and Filep JG. Resolvin E1 promotes phagocytosis-induced neutrophil apoptosis and accelerates resolution of pulmonary inflammation. Proc Natl Acad Sci U S A 2012; 109: 14983-14988.

[31] Zhao W, Zhou S, Yao W, Gan X, Su G, Yuan D and Hei Z. Propofol prevents lung injury after intestinal ischemia-reperfusion by inhibiting the interaction between mast cell activation and oxidative stress. Life Sci 2014; 108: 80-87.

[32] Wang B, Gong X, Wan JY, Zhang L, Zhang Z, Li HZ and Min S. Resolvin D1 protects mice from LPS-induced acute lung injury. Pulm Pharmacol Ther 2011; 24: 434-441.