Advanced Pharmaceutical Bulletin

Adv Pharm Bull, 2014, 4(Suppl 2), 555-561
doi: 10.5681/apb.2014.082
http://apb.tbzmed.ac.ir

TUOMS Publishing Group

Research Article

The Effect of Omega-3 Fatty Acids on ARDS: A Randomized Double-Blind Study

Masoud Parish[1], Farnaz Valiyi[1], Hadi Hamishehkar[2], Sarvin Sanaie[3], Mohammad Asghari Jafarabadi[4], Samad EJ Golzari[5], Ata Mahmoodpoor[1]*

[1] *Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.*
[2] *Applied Drug Research Center, Department of Clinical Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.*
[3] *Tuberculosis & Lung Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*
[4] *Road Traffic Injury Research Center, Faculty of Health, Tabriz University of Medical Sciences, Tabriz, Iran.*
[5] *Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

Article info
Article History:
Received: 9 May 2014
Revised: 11 August 2014
Accepted: 13 August 2014
ePublished: 31 December 2014

Keywords:
· ARDS
· Inflammation
· Omega-3 fatty acids
· ICU

Abstract

Purpose: The aim of this study was to evaluate the effect of an enteral nutrition diet, enriched with omega-3 fatty acids because of its anti-inflammatory effects on treatment of patients with mild to moderate ARDS.

Methods: This randomized clinical trial was performed in two ICUs of Tabriz University of Medical Sciences from Jun 2011 until Sep 2013 in north west of Iran. Fifty-eight patients with mild to moderate ARDS were enroled in this clinical trial. All patients received standard treatment for ARDS based on ARDS network trial. In intervention group, patients received 6 soft-gels of omega-3/day in addition to the standard treatment.

Results: Tidal volume, PEEP, pH, PaO_2/FiO_2 , SaO_2, P platue and $PaCO_2$ on the 7th and 14th days didn't have significant difference between two groups. Indices of lung mechanics (Resistance, Compliance) had significant difference between the groups on the 14th day. Pao_2 had significant difference between two groups on both 7th and 14th days. Trend of PaO_2 changes during the study period in two groups were significant. We showed that adjusted mortality rate did not have significant difference between two groups.

Conclusion: It seems that adding omega-3 fatty acids to enteral diet of patients with ARDS has positive results in term of ventilator free days, oxygenation, lung mechanic indices; however, we need more multi center trials with large sample size and different doses of omega-3 fatty acids for their routine usage as an adjuant for ARDS treatment.

Introduction

ARDS is a clinical syndrome with high mortality rate and incidence of 4.5-7.1% of all patients admitted to intensive care units, and increasing to 12.5% only when patients are treated longer than 24 h in the ICU.[1,2] While low tidal volume ventilation improves survival, there are currently no pharmacologic treatments for ARDS patients. Host inflammatory response is one of the main pathophysiological reasons for tissue injury in critically ill patients with ARDS. This inflammatory response could result in oxidative damage caused by free radicals and protease from neutrophiles and endothelium and by different mediators.[3-5] The lung is one of the main targets for this inflammatory cascade which could result in ARDS.[6] Interest in use of immunonutrition for patients with acute lung injury (ALI) was considered after an article published by Gadek et al which demonstrated that omega-3 fatty acids could reduce patient morbidity.[7]

Studies showed that inflammatory response could be modulated with diets enriched with omega-3 fatty acids and anti oxidants. Omega-3 fatty acids could reduce arachidonic acid (AA) through competition of eicosapentaenoic acid(EPA) with AA for lipoxygenase and cycloxygenase binding sites and reduce synthesis of proinflammatory mediators.[8] In the lung, omega-3 fatty acid could reduce the number of leuckocytes, and permeability of alveolar capillary membrane, and production of proinflammatory cytokines like interleukin 6, 8 and TNFα.[9,10] The ARDSNet trial used an omega 3 and antioxidant supplement added to "usual" feeding. The study stopped for futility and they showed that omega-3 fatty acids did not improve primary end point of ventilator free days or other clinical outcomes in patients with ALI and also omega-3 may be harmful.[11]

Different studies showed that dietary lipids could reduce hospital mortality and length of mechanical ventilation support in ARDS patients.[12-15] Previous studies performed in ARDS patients used commercial enteral formula with high fat and low carbohydrate ratio. Considering the fact that this type of diet is not a routine regimen in critically ill patients and because of presence

***Corresponding author:** Ata Mahmoodpoor, Tel: +989141160888, Email: mahmoodpoora@tbzmed.ac.ir

of other nutrients in the formula, independent effects of omega-3 fish oil could not be assessed. Therefore, we evaluated the effect of dietary omega-3 fatty acids on oxygenation parameters, respiratory mechanical indices and morbidity of patients with mild to moderate ARDS in this study.

Materials and Methods

After obtaining ethics committee approval from Tabriz University of Medical Sciences, this clinical trial was performed in ICUs of Shohada and Imam Reza hospitals from Jun 2011 until Sep 2013 (IRCT NO: IRCT2013020612387N1). Informed consent were given from next of kin. Fifty-eight patients with $100<PaO_2/FiO_2<300$, bilateral infiltration, acute onset(< 6 days) and abilty to tolerate enteral nutrition were enrolled in this study. Exclusion criteria were age < 18 y.o, plasma triglycerid more than 400 mg/dl, liver(Child-Pugh) and kidney failure(RIFLE criteria), platelete less than 50000/µl, leuckocyte counte less than 3×10^9/L and previous history of frequent transfusion. Patients were randomized via a centralized Web-based system to one of the study groups.

Sample size calculation

Considering 15% changes in Pao_2/Fio_2 as the primary outcome of the study whose information obtained from Sabatar et al. (2011), the sample size was determined to be 29 per group (total 58) to reach 95% confidence level and a power of 80%. Randomization was performed with a web based software. Flow diagram of the study is showed as Figure 1.

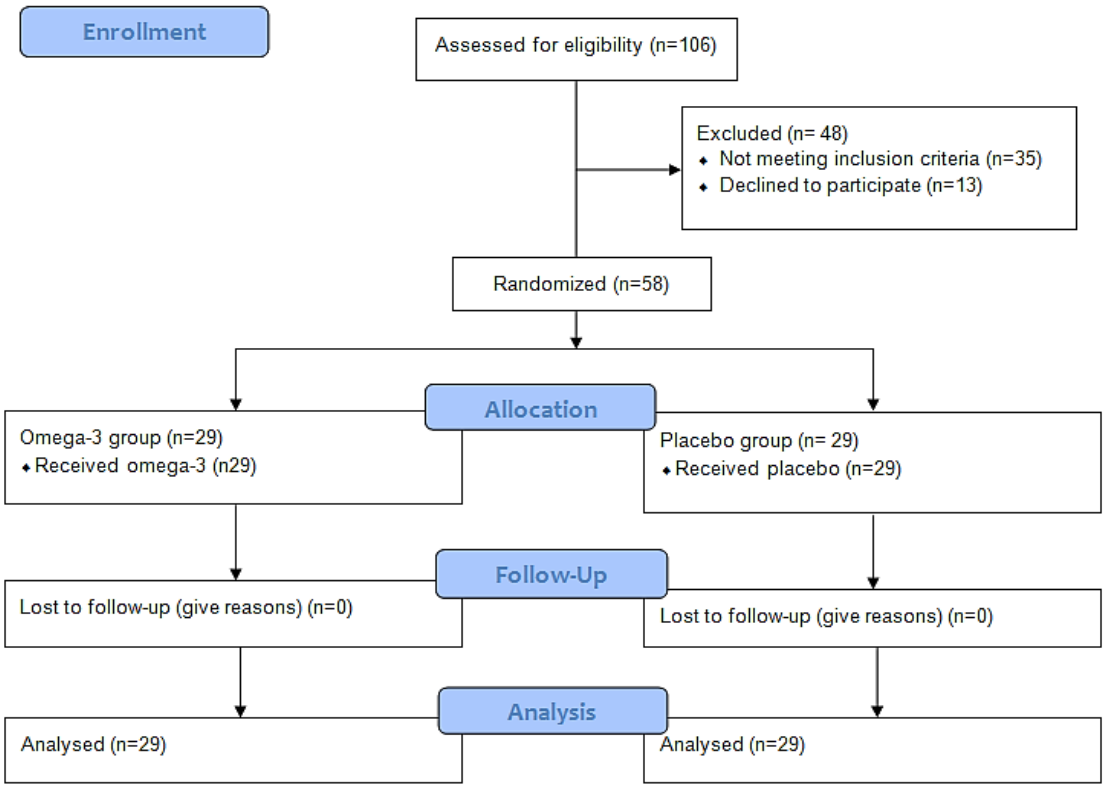

Figure 1. Study overview

Study procedure

All patients were under mechanical ventilation with a volume controlled mode with low tidal volume strategy (tidal volume< 6 cc/kg and P plateau < 30 mmHg) and fluid conservative hemodynamic management protocols.[16] All patients ventilated with the same ventilator. $PEEP/FiO_2$ was set based on ARDS network standards. Patients were kept on semirecumbent position for decreasing pneumonia and better lung performance and keeping PaO_2>55 mmHg. Males were ventilated with tube size 8 and females were ventilated with size 7.5 endotracheal tubes. Insulin therapy was used to target blood glucose ranges of 80-150 mg/dl. All patients received pantoprazol for stress ulcer prophylaxis and heparin for deep vein thrombosis prophylaxis. Patients received 25 kcal/kg enteral formula/day (isocaloric isovolemic carbohydrate rich, 1kcal/cc) via nasogastric tube or PEG (Percutaneous Endoscopic Gastrostomy) feeding tube. In intervention group, patients received 6 omega-3 soft gels per day (2 capsuls/8h) in addition to standard treatment. Every 2 soft gels deliver 720 mg of Omega-3s, including 600 mg of EPA & DHA (360 mg EPA/240 mg DHA). Demographic characteristic of patients, oxygenation and ventilation parameters, pulmonary dynamic indices on the 1st, 7th and 14th days, length of ICU stay and hospital mortality were noted in each group. Primary end point was oxygenation parameters and secondary endpoints were ventilator free day, number of organ failure and 28-day mortality rate.

Statistical analysis

The data were peresented using Mean ± SD for quantitative variables and N(%) for qualitattive variables. The normality of the quantitative variables were assessed and confirmed using Kolmogorov-Smirnov test. The demographic and basline measures of the study varibales were compared using independent samples t-test and Chi -square test respectively for quantitative and qualitative variables. The within group changes were tested by paired t-tests. Additionaly the effect of the intervention were assessed using analysis of covariance (ANCOVA). In this analysis the baseline meausres of the varibels and 4 baseline mortality-predicting covariates were age, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, plateau pressure, number of organ failures. Compliance and resistance were calculated based on ventilators given data. Logistic regression model was used to assess the effect of omega 3 on mortality.[13] In this analysis Odds Ratio (OR) and 95% Confidence Interval (CI) were reported. Analysis was performed with SPSS version 16 and P value<0.05 considered significant.

Results

Demographic characteristic of patients didn't have any statistical difference between two groups (Table 1). Daily calorie intake in both groups did not have significant difference during the study. Patients in both groups didn't have significant difference in number and type of multi organ failure. Patients in control group received almost 83% of their daily requirements and patients in omega-3 group received almost 85% of daily need. Enteral feeding complications such as diarrhea, constipation, intolerance and gastric residue didn't have statistically significant difference between two groups. APACHE, ventilator free days and length of ICU stay didn't have significant difference between two groups (Table 1). Baseline variables between two groups didn't have statistical difference. Compliance at first day in omega-3 group was significantly lower compared to control group (p=0.019) and P plateau at first day was significantly higher in omega-3 than control group (p=0.004). Tidal volume, PEEP, pH, PaO_2/FiO_2 , SaO_2, P plateau and $Paco_2$ on the 7^{th} and 14^{th} days didn't have significant difference between two groups. Indices of lung mechanics (resistance, compliance) had significant difference between the groups on the 14^{th} day. PaO_2 had significant difference between two groups on both 7^{th} and 14^{th} days. Trend of PaO_2 changes during the study period in two groups were significant. Data on oxygenation parameters, lung mechanic indices and ventilation parameters are shown in Table 2. Trend of compliance, tidal volume, resistance, tidal volume during the study are shown in Figures 2-5. We showed that adjusted mortality rate did not have significant difference between two groups (Table 1).

Table 1. Demographic characteristics and mortality rate in two groups

Variable	Omega-3 group	Placebo group	*P* value
Age[α]	64.4± 10.2	62.7± 13.7	0.401
M/F[β]	16/11 (59.3% / 40.7%)	15/13 (53/6%/ 46/4%)	0.671
APACHE[α]	26.1± 4.5	24.5± 4.8	0.313
Vent Free Days[α]	6.6± 2	6± 2.5	0.304
Length of ICU stay[α]	15.0± 3.5	15.6± 4.3	0.524
Mortality, n%[β]	7(25.9)	9(32.1)	0.612

α: Data presented as mean±SD, Analysis with t-test
β: Analysis with chi square test
Results of mortality adjusted comparisons between intervention and control groups: 87% (OR: 0.13. 95% CI= (0.01 To 1.97), P =0.14

Table 2. Oxygenation, ventilation parameters and respiratory mechanical indices of patients

Variable [a]	Day	Omega-3 group	Placebo group	*P* value
PaO_2 (cm H_2O)	0 [b]	56.2± 5.6	55.0± 3.8	0.360
	7 [c]	64.0± 9.6	64.6± 8.8	0.732
	14 [c]	81.2± 10.9	67.3± 13.8	0.004
$PaCO_2$	0 [b]	39.8± 5.3	37.4± 4.9	0.091
	7 [c]	42.0± 7.2	42.4± 5.9	0.789
	14 [c]	44.3± 5.5	46.7± 8.0	0.274
SaO_2	0 [b]	90.1± 1.1	89.9± 1.1	0.466
	7 [c]	92.9± 1.8	92.4± 1.8	0.066
	14 [c]	95.5± 2.6	93.2± 3.9	0.087
pH	0 [b]	7.36± 0.06	7.35± 0.05	0.753
	7 [c]	7.35± 0.07	7.35± 0.07	0.934
	14 [c]	7.38± 0.08	7.35± 0.1	0.408
Compliance	0 [b]	46.6± 6.7	50.6± 5.6	0.029
	7 [c]	51.7±13.9	58.4± 11.1	0.176
	14 [c]	71.6± 16.8	58.9± 19.6	0.005
Resistance	0 [b]	10.5± 1.6	10.5± 1.4	0.967
	7 [c]	8.9± 2.4	9.2± 3.3	0.596
	14 [c]	6.5± 2.4	9.2± 3.3	0.001
P/F ratio [μ]	0 [b]	149.1± 27.5	145.5± 30.2	0.638
	7 [c]	176.4± 49.2	172.4± 52.6	0.560
	14 [c]	221.1± 56.3	179.3± 71.6	0.218
P plateau	0 [b]	30.2± 1.7	28.5± 2.4	0.004
	7 [c]	27.1± 4.0	25.8± 3.7	0.980
	14 [c]	22.7± 4.8	25.2± 6.1	0.116
V_T [γ]	0 [b]	11.3± 1.3	11.7± 0.8	0.313
	7 [c]	9.7± 2.7	9.9± 2.3	0.869
	14 [c]	6.8± 3.6	9.4± 3.8	0.070

a: Data presented as mean±standard deviation
b: Analysis with students t-test
c: Analysis of covariance (ANCOVA)
μ: PaO_2/FiO_2
γ: Tidal Volume

Discussion

Our results showed that enteral supplementation of omega-3 fatty acids improved oxygenation and lung mechanic parameters in patients with mild to moderate ARDS compared to control group who received isocaloric energy. Attempts have been made to modulate the inflammatory response in ARDS using different strategies. Different studies showed that enteral nutrition enriched with EPA/GLA(Gamma Linoleic Acid) diets in critically ill patients who were under mechanical ventilation resulted in reduction of ICU and hospital length of stay.[6,12-14] Based on

previous studies, omega-3 fatty acids were able to reduce pulmonary hypertension, pulmonary edema and improve oxygenation and bacterial killing,[17-20] which some of them are in accordance to our results. We used bolus enteral nutrition like some previous studies[6,12,14] but unlike the study of Rice T.W *et al.*[11] who had results opposed to ours. Another major difference between our study and previous ones is that our enteral formula was standard isovolemic isocaloric compared to high-fat formulation containing predominantly omega-6 and omega-9 fatty acids used in previous studies. Previously, there were concerns about carbohydrate usage for ARDS patients because of possible hypercapnia, but now we know that it is not a correct idea and we could use carbohydrate for ARDS patiens.[11] Our formula consists of normal ratio carbohydrate, otherwise we controled blood sugar in our study between 80-150 mg/dl. As omega-6 and 9 are proinflammatory, the difference in outcome of groups can be possible. In addition, we controlled fluid intake as conservative strategy and ventilation parameters as lung protective strategy, which are important in improving outcome in patients with ARDS.[21-24] The positive effects of omega-3 fatty acids on treatment of patients with ARDS might be due to a shifted production of proinflammatory mediators to some less inflammatory mediators and formation of resolvins. Also there are two trials that used enteral omega-3 as bolus form in ARDS patients and did not reach any positive results which might be due to administration rout of omega-3.[11,25] The study stopped for futility (no realistic chance that the intervention could be proven to be beneficial with the size trial). However it would not be appropriate to make any conclusions about any other feeding product based upon this study, as it would also be inappropriate to conclude that their treatment was "harmful". Stapleton et al showed that enteral fish oil did not lead to a clear decrease in any broncho-alveolar fluid or plasma inflammatory biomarker IL-8. In this study, LTB4 increased in the fish oil group and decreased in the placebo group and the reasons for these LTB4 changes are not clear, and we must consider that these results should be interpreted with caution because they did not adjust for multiple comparisons. In addition, organ failure, ventilator-free days, ICU-free days, or mortality did not have significant difference between the groups in this study.[25] Stapleton used only omega-3 as bolus doses, which could describe the results as other nutrients like EPA/GLA may have some additional or synergistic effects with omega-3, but our placebo didn't have any nutrient properties that interfere with results of the study. Other reason for positive results of our study may be due to the fact that high proportion of patients had trauma as their risk factor for ARDS because patients with trauma related ARDS have less severe endothelial and alveolar epithelial lung injury.[26]

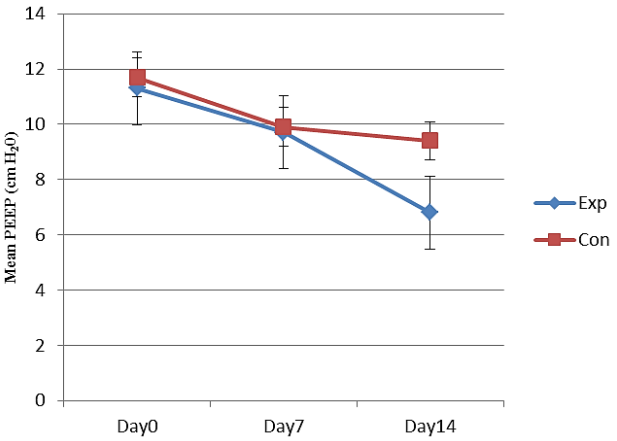

Figure 2. Mean PEEP during study in two groups

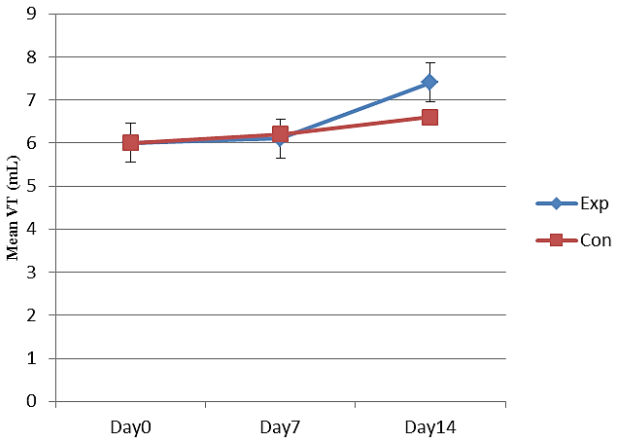

Figure 3. Mean Tidal Volume during study in two groups

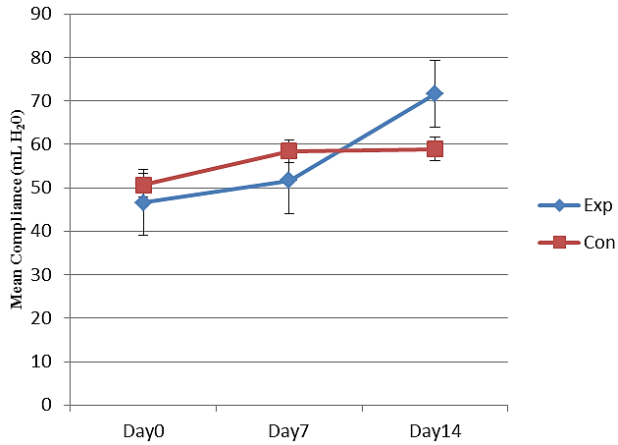

Figure 4. Mean Compliance during study in two groups

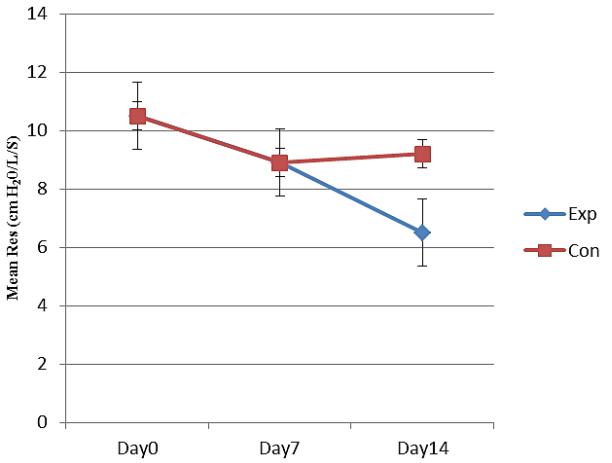

Figure 5. Mean Resistance during study in two groups

Gadek et al showed that enteral nutrition supplemented with EPA and gamma linoleic acid in ARDS patients could lead to 39% increase in ventilator free days, 45% decrease in length of stay, important decrease in BAL leuckocyte count and PaO_2/FiO_2 ratio.[3] In a single centered study, Singer et al showed that in patients with ALI, enteral nutrition enriched with EPA/GLA for 14 days resulted in better oxygenation, lung mechanic indices and reduced mortality in intervention group[11] which is similar to our results. However, Grau-Carmona T. et al showed that a diet enriched with EPA, GLA and anti-oxidants does not improve gas exchange or decrease the incidence of novel organ failures in critically ill septic patients with acute lung injury or ARDS. Patients treated with the EPA-GLA diet stayed in the ICU for less time, but we did not find any differences in infectious complications[27] which are in contrast to our results and may be because of less heterogeneity in our patients which could be showed with the difference between excluded patients in two study. Another reason may be due to the fact that our patients had PaO_2/FiO_2 <300 but in mentioned study, the inclusion criteria was PaO_2/FiO_2 <200. Other reason is that the mentioned study is not blinded so it might have bias. A recently performed study showed that diets with key pharmaconutrients decrease the appearance of new organ failure.[28] The different results in studies also could be explained by different genetic polymorphism, dose, way and duration of administration of nutrient.[29,30]

Mortality rate in this study was 25.9 % which is similar to previous omega-3 trials in ALI patients. Although the relation was not significant however a clinical important effect was observed so that intervention decreased the mortality by 87% (OR=0.13, 95%CI). We used 3 doses per day, as the previous study by Rice T.W and colleagues showed that despite using 2 doses of omega-3 per day and rise of omega-3 levels in blood, level of inflammatory biomarkers did not significantly decrease. One other reason for positive results of our study might be due to the long duration (14 days) of treatment with omega-3 which help the immunonutrition to show its effect.[31,32]

Limitation of study

We did not assay omega-3 blood levels and level of inflammatory biomarkers in plasma and also pharmacokinetics. And we did not perform bronchoalveolar lavage, although we had significant improvement in oxygenation and lung mechanic parameters. Other limitation of our study was small sample size due to our decision to include ARDS patients with low-moderate severity.

Conclusion

From the obtained results, it may be conclude that omega-3 fatty acids in enteral diet of patients with ARDS has positive results in term of ventilator free days, oxygenation, lung mechanic indices. However, more multi center trials with large sample size and different doses of omega-3 is required for its routine usage as an adjuant for ARDS treatment.

Acknowledgments

Special thanks to research center of Tabriz University of Medical Sciences, Mr.Shahrokh Teshnedel, Mr.Qorbanali Tarinezhad and ICU staff of shohada and Imam reza hospitals.

Conflict of Interest

There is no conflict of interest to be reported.

References

1. Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. *Intensive Care Med* 2004;30(1):51-61.
2. Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002;287(3):345-55.
3. Najafi A, Mojtahedzadeh M, Mahmoodpoor A, Aghamohammadi M, Ahmadi A, Nahreini SH, et al. Effect of N-acetylcysteine on microalbuminuria in patients with acute respiratory distress syndrome. *Arch Med Sci* 2009;5:408-14.
4. Tabeefar H, Beigmohammadi MT, Javadi MR, Abdollahi M, Mahmoodpoor A, Ahmadi A, et al. Effects of Pantoprazole on Systemic and Gastric Pro- and Anti-inflammatory Cytokines in Critically Ill Patients. *Iran J Pharm Res* 2012;11(4):1051-8.
5. Eslami K, Mahmoodpoor A, Ahmadi A, Abdollahi M, Kamali K, Mousavi S, et al. Positive effect of septimeb on mortality rate in severe sepsis: a novel non antibiotic strategy. *Daru* 2012;20(1):40.
6. Martin GS, Bernard GR, International Sepsis Forum. Airway and lung in sepsis. *Intensive Care Med* 2001;27 Suppl 1:S63-79.

7. Gadek JE, Demichele SJ, Karlstad MD, Pacht ER, Donahoe M, Albertson TE, et al. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Enteral Nutrition in ARDS Study Group. *Crit Care Med* 1999;27(8):1409-20.
8. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr* 2006;83(6 Suppl):1505S-19S.
9. Pacht ER, Demichele SJ, Nelson JL, Hart J, Wennberg AK, Gadek JE. Enteral nutrition with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants reduces alveolar inflammatory mediators and protein influx in patients with acute respiratory distress syndrome. *Crit Care Med* 2003;31(2):491-500.
10. Preiser JC, Van Gossum A, Berre J, Vincent JL, Carpentier Y. Enteral feeding with a solution enriched with antioxidant vitamins A, C, and E enhances the resistance to oxidative stress. *Crit Care Med* 2000;28(12):3828-32.
11. Rice TW, Wheeler AP, Thompson BT, Deboisblanc BP, Steingrub J, Rock P, et al. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA* 2011;306(14):1574-81.
12. Pontes-Arruda A, Aragao AM, 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(9):2325-33.
13. Pontes-Arruda A, Demichele S, Seth A, Singer P. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. *JPEN J Parenter Enteral Nutr* 2008;32(6):596-605.
14. Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E, 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(4):1033-8.
15. Heller AR, Rossler S, Litz RJ, Stehr SN, Heller SC, Koch R, et al. Omega-3 fatty acids improve the diagnosis-related clinical outcome. *Crit Care Med* 2006;34(4):972-9.
16. Asghari Jafarabadi M, Soltani A, Mohammadi SM. Statistical Series: Tests for Comparing of Means. *Iranian Journal of Diabetes and Lipid Disorders* 2013;12(4):265-91.
17. Grimminger F, Wahn H, Kramer HJ, Stevens J, Mayer K, Walmrath D, et al. Differential influence of arachidonic vs. eicosapentaenoic acid on experimental pulmonary hypertension. *Am J Physiol* 1995;268(6 Pt 2):H2252-9.
18. Grimminger F, Wahn H, Mayer K, Kiss L, Walmrath D, Seeger W. Impact of arachidonic versus eicosapentaenoic acid on exotonin-induced lung vascular leakage: relation to 4-series versus 5-series leukotriene generation. *Am J Respir Crit Care Med* 1997;155(2):513-9.
19. Grimminger F, Mayer K, Kramer HJ, Stevens J, Walmrath D, Seeger W. Differential vasoconstrictor potencies of free fatty acids in the lung vasculature: 2-versus 3-series prostanoid generation. *J Pharmacol Exp Ther* 1993;267(1):259-65.
20. Kelbel I, Koch T, Prechtl A, Heller A, Schlotzer E, Schiefer HG, et al. Effects of Parenteral Application of Fish Oil versus Soy Oil Emulsions on Bacterial Clearance Functions. *Infusionsther Transfusionsmed* 1999;26(4):226-32.
21. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354(24):2564-75.
22. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012;38(10):1573-82.
23. Roch A, Guervilly C, Papazian L. Fluid management in acute lung injury and ards. *Ann Intensive Care* 2011;1(1):16.
24. Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med* 2005;33(1):1-6; discussion 230-2.
25. Stapleton RD, Martin TR, Weiss NS, Crowley JJ, Gundel SJ, Nathens AB, et al. A phase II randomized placebo-controlled trial of omega-3 fatty acids for the treatment of acute lung injury. *Crit Care Med* 2011;39(7):1655-62.
26. Calfee CS, Eisner MD, Ware LB, Thompson BT, Parsons PE, Wheeler AP, et al. Trauma-associated lung injury differs clinically and biologically from acute lung injury due to other clinical disorders. *Crit Care Med* 2007;35(10):2243-50.
27. Grau-Carmona T, Moran-Garcia V, Garcia-De-Lorenzo A, Heras-De-La-Calle G, Quesada-Bellver B, Lopez-Martinez J, et al. Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. *Clin Nutr* 2011;30(5):578-84.
28. Beale RJ, Sherry T, Lei K, Campbell-Stephen L, Mccook J, Smith J, et al. Early enteral supplementation with key pharmaconutrients improves Sequential Organ Failure Assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial. *Crit Care Med* 2008;36(1):131-44.
29. Lin MT, Albertson TE. Genomic polymorphism in sepsis. *Crit Care Med* 2004;32:569-79.

30. Tilley SL, Coffman TM, Koller BH. Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. *J Clin Invest* 2001;108(1):15-23.
31. Barbosa VM, Miles EA, Calhau C, Lafuente E, Calder PC. Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: a randomized, controlled clinical trial. *Crit Care* 2010;14(1):R5.
32. Friesecke S, Lotze C, Kohler J, Heinrich A, Felix SB, Abel P. Fish oil supplementation in the parenteral nutrition of critically ill medical patients: a randomised controlled trial. *Intensive Care Med* 2008;34(8):1411-20.