IJCNP Indonesian Journal of Clinical Nutrition Physician
p-ISSN: 2597-4297
e-ISSN: 2775-5215
Volume 5 No. 1, Februari 2022

EFFICACY OF IMMUNONUTRITION CONTAINING OMEGA-3 FATTY ACIDS TO REDUCE MORTALITY IN ACUTE RESPIRATORY DISTRESS SYNDROME: AN EVIDENCED-BASED CASE REPORT

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Abstract

Background: Acute respiratory distress syndrome (ARDS) remains one among the most reasons for ICU admission. It is related to high rates of mortality despite many recent advances in overall support. A relative increase in oxidative stress in patients with ARDS results in increased alveolar injury. Immunonutrion containing omega 3 fatty acids is one among the strategies that currently receiving attention within the management of ARDS since they are known to have anti-inflammatory effects, but the results are still inconsistent.
Objective: This study aimed to find out the efficacy of immunonutrition containing omega 3 fatty acids in reducing mortality in patients with ARDS.
Methodology: Electronic literature researches were performed in PubMed, Cochrane, and Scopus. MeSH term and title/abstracts were screened based on inclusion and exclusion criteria before relevant journals were reviewed.
Results: Two articles were selected based on the eligibility criteria and relevance to the clinical questions. The study of Langlois P. et al. found significantly reduced mortality in patients receiving continuous enteral infusion route of immunonutrition containing omega 3 fatty acids. While Dushianthan A. et al. found little or no mortality benefit with the administration of immunonutrition containing omega 3 fatty acids.
Conclusions: There is little or no mortality reduction within the administration of immunonutrition containing omega 3 fatty acids.

Keywords : acute respiratory distress syndrome, ARDS, immunonutrition, omega 3 fatty acids, mortality.

Introduction

Acute respiratory distress syndrome (ARDS) is life-threatening condition due to severe hypoxic respiratory failure with the systemic inflammatory process and multiple organ dysfunction. The incidence of this syndrome varies between 16 – 78 per 100.000 population with hospital mortality reaching 27 – 45%.[1] This syndrome is characterized by several criteria using the Berlin definition in 2012 including timing that begins within 1 week of a known clinical origin or new or worsening respiratory symptoms, chest imaging showing bilateral pulmonary infiltrate, hypoxemia that not fully due to cardiac failure or fluid overload, and oxygenation with the ratio of partial pressure of arterial

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e-ISSN: 2775-5215
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oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) of 200 – ≤300 mmHg (categorized as mild ARDS), 100 – ≤200 mmHg (categorized as moderate ARDS), and ≤100 mmHg (categorized as severe ARDS).[2] ARDS accounting for 10% of intensive care unit (ICU) admissions and 24% of patients receiving mechanical ventilation in the ICU. The higher mortality in ARDS was related to greater lung injury severity degrees at onset.[3] The alveolar injury in ARDS is marked by significant recruitment of neutrophils, release of pro-inflammatory cytokines and chemokines, and activation of procoagulant cascades and prostaglandin pathways results in a relative increase in oxidative stress.[4]

Therapies for patients with ARDS are still an ongoing challenge and no specific therapy regimens are known to moderate the disease process yet.[1] Omega 3 fatty acids are essential fatty acids that consist of eicosapentaenoic acids (EPA), alpha-linoleic acid (ALA), and docosahexaenoic acids (DHA). Omega 3 fatty acids are one among the immunonutrition that are well known for their anti-inflammatory effects that have been proposed to ameliorate the syndrome. Omega 3 fatty acids can regulate the synthesis of lipid mediators, release anti-inflammatory lipids such as resolvins and protectin, reduce reactive oxygen species and pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8, reduce chemotaxis and adhesion molecule expression, thereby regulating the body's excessive inflammatory response to reduce the lung inflammation.[5]

The American Society For Parenteral and Enteral Nutrition (ASPEN) in 2016 did not make a recommendation about the use of inflammation-modulating diets such as omega 3 fatty acids in ARDS.[6] Later in 2019, The European Society For Parenteral and Enteral Nutrition (ESPEN) have supported the use of omega 3 fatty acids in critically ill patients, but still no specific recommendation for ARDS.[7] Moreover, omega 3 fatty acids supplementation in ARDS patients are remains controversial. For that reason, this evidence-based case report (EBCR) is to critically analyze the efficacy of immunonutrition containing omega-3 fatty acids in patients with ARDS to reduce mortality.

Clinical Question

A 42-year-old man came to the emergency department with a chief complaint of difficulty to breath since three days before admission that getting worse within 12 hours before admission. The difficulty of breath did not get heavier with activity or changing position. He also had a

cough for one week with sputum containing blood, fever, headache, and pain in all his body. The patient also experienced night sweats, weight loss, and decreased appetite one month before admission. The patient had already gone to the clinic but there was no change. The blood pressure was 90/60 mmHg, heart rate was 121x per minute, respiratory rate was 32x per minute, body temperature was 38,3°C, and pulse oxymetry was 76% with nonrebreathing mask 12 liter per minute. The patient then fell unconscious. Physical examination showed anemic conjunctiva, chest and abdominal retraction, crackles in both lungs, no pretibial edema found, and capillary refill time longer than 2 seconds. There was no history of hypertension, diabetes mellitus, malignancy, and pulmonary medication before. The patient had a smoking habit since 13 years old as much as 10 – 15 cigarettes per day. The patient then got intubated and admitted to the ICU. The laboratory results were hemoglobin 7,4 g/dL, leucocyte 4600/µL, platelet 158.000/µL, erythrocyte sedimentation rate 71 mm/hour, blood glucose 102 mg/dL, C-reactive protein 154 mg/L, ureum 21 mg/dL, creatinine 0.65 mg/dL, blood gas analysis showed respiratory acidosis. The chest X-ray showed diffuse pulmonary infiltrates in both lungs. The patient's last body weight was 45 kg when in the clinic, with a height of 165 cm, and a body mass index of 16,53 kg/m^2. According to his family, the patient has lost weight because his face and body looked thinner than before. After the patient's vital signs are stable, the doctor in charge then consults the patient to a clinical nutrition specialist for further nutritional management. This case raises a question: does an immunonutrition containing omega 3 fatty acids can reduce mortality in patients with ARDS?

P : Adult patients with ARDS
I : Immunonutrion containing omega 3 fatty acids
C : Standard nutrition
O : Mortality

Methods

Literature search was conducted on July 2nd, 2020 on 3 journal databases including PubMed, Cochrane, and Scopus using the keyword 'acute respiratory distress syndrome' AND 'omega 3 fatty acids' AND 'mortality'. MeSH Term was used in PubMed database search. The title and abstract are screened based on the inclusion and exclusion criteria and filtered for duplicates and availability for full text. The inclusion criteria used for this study were: 1) adult patients diagnosed with acute respiratory distress syndrome; 2) the study design was a systematic review or meta-

analysis Randomized Controlled Trial; 3) study's outcome measure was mortality; 4) publication within the last 5 years. The exclusion criteria were: 1) no available research full text and 2) non-English journals. The search flow shows in Figure 1. Critical appraisal of the study was conducted using the guidance published by the University of Oxford Centre for Evidence-Base-Medicine (CEBM) which includes validity, importance, and applicability with the standardized critical appraisal for therapy study.

Results

There were 4 journals from PubMed, 8 journals from Cochrane, and 71 journals from Scopus were identified based on the keywords used (Tabel 1). From all the literature obtained, 2 literatures met the eligibility criteria.

Discussion

The two systematic reviews and meta-analysis of RCTs in this review were obtained from advanced searching from three main databases: PubMed, Cochrane Library, and Scopus that is accordance with clinical questions and has been critically appraised for systematic review and meta-analysis of RCTs from The Center of Evidence-Based Medicine (www.cebm.net). The study characteristics, validity criteria and relevance criteria can be seen in tabel 2, 3, and 4 respectively.

In the first study by Langlois P. et al, 12 articles were included in the analysis with a total of 1280 patients. This study conducted a literature search through Medline, CINAHL, EMBASE, and Cochrane databases for RCTs published until December 2017 with no language restrictions. Other individual files and significant articles references were also reviewed to optimize study identification. Five trials were multicenter, and seven other trials were single-center. Three trials recruited sepsis-induced ARDS, one recruited trauma patients, and the remaining recruited a heterogenous ICU patient population with ARDS. All the trials administered oral, enteral, or parenteral omega 3 fatty acids with or without antioxidants for the intervention group and either placebo or a non-fish oil standard nutrition for the control group. The duration of administration varied across different trials. The PaO2/FiO2 ratio was the primary outcome; 30-day or hospital mortality, ICU LOS, hospital LOS, duration of ventilation, and incidence of infectious complications were the secondary outcomes.

Langlois P. et al conducted analysis in ten studies including 1165 patients for overall effect on mortality. The result of the

meta-analysis showed no effect on mortality (RR= 0.84; 95% CI 0.57 – 1.24; P=0.38) with no statistical heterogeneity found. In the subgroup analysis, there are significant effect on mortality in trials conducted before 2011 (RR= 0.49, 95% CI 0.32 – 0.76, P=0.001; I^2=0%); and there is a significant reduction in mortality when conducted analysis in 6 trials administering fish oils by continuous enteral route (RR= 0.64, 95% CI 0.45 – 0.92, P=0.02; I^2=3%). The strength of this systematic review and meta-analysis was the comprehensive literature search with no language restriction with specific criteria for research, and thorough analysis that focuses on the effects of immunonutrition on important clinical outcomes in patients with ARDS. Another strength is the databases were searched and screened by two independent reviewers. The limitations for this study were the variety and difference of immunonutrition supplementation given that might have led to heterogeneity and included various ARDS definitions. This author also did not register the study protocol previously.

In the second systematic review and meta-analysis of RCTs, Dushianthan A, et al conducted a meta-analysis of RCTs studies with literature search through Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, scanned World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov for ongoing and unpublished trials until April 2018. Reference lists and citations of included trials and relevant systematic reviews were also scanned for further references, and relevant citations from published studies, previous systematic reviews, and conference proceedings from major intensive care and nutrition societies were manually searched. All-cause mortality was the primary outcome in this systematic review and meta-analysis. The secondary outcomes were 28-day mortality, intensive care unit (ICU) length of stay (LOS) and ICU-free days at day 28, ventilator days and ventilator-free days at day 28, hospital LOS, indices of oxygenation, another organ failures, nosocomial infection, and adverse events. Ten studies were included in the analysis with 1015 participants. All studies involving mechanically ventilated adult participants (aged 18 years or older) with ARDS as defined by Berlin definition of ARDS, and for older studies as defined by American-European Consensus Criteria for both ARDS and Acute lung injury (ALI). All studies compared an enteral or parenteral immunonutrient using omega 3 fatty acids (EPA, DHA), GLA with or without antioxidants that additionally supplemented

or as part of the nutritional formula with placebo or standard nutrition that usually given to patients with ARDS. The duration of intervention was varied between 7 or fewer days to 28 days.

Dushianthan A. et al analyzed all studies for overall effect on mortality. The results of this second study showed no difference in all-cause mortality at the longest period reported with the use of immunonutrition containing omega 3 fatty acids (RR= 0.79, 95% CI 0.59 – 1.07, P=0.13; I^2=42%), even though the pooled control group mortality rate was 28% and the intervention group was 23.5%, with overall mortality rate varied between 6% to 43%. The strength of evidence for the mortality in ARDS patients receiving immunonutrition containing omega 3 fatty acids were low in this study. Dushianthan A. dently conducted by 2 review authors, and 1 more review author to resolve a disagreement. This study also assessed the risk of bias of included literature using criteria presented in the Cochrane Handbook for Systematic Reviews of Interventions. This study used six domains to assess the risk of bias in the included literature including selection bias, performance bias, detection bias, attrition bias, reporting bias, and any other potential biases. The limitations of this study are clinical et al also analyze the 28-day mortality in six studies with 466 participants (RR=0.64, CI 0.49-0.84, P=0; I^2 = 0%), but the quality of evidence was very low due to the limited total participants included in the analysis. In the subgroup analysis, there is a significant statistical reduction in mortality in groups receiving immunonutrients containing omega 3 fatty acids and/or antioxidant versus a lipid-rich control group in two studies with 178 participants (RR 0.57, 95% CI 0.42 – 0.78, P=0; I^2 = 0%), but the evidence is very low due to the lipid-rich diet given to the control group was contained high linoleic acid and the effects may be harmful.

The strength of the second study was no language restrictions or publication status was applied in selecting literature. Another strength is the data extraction was indepen heterogeneity concerning to type, mode, and duration of intervention provided, as well as the type of enteral nutrition formulation received by the control group. Another limitation is lack of standardized statistical data from the included studies may lead to additional bias.

Conclusion

The results of two meta-analyses found no mortality benefit with the administration of immunonutrient containing omega 3 fatty acids in patients

p-ISSN: 2597-4297
e-ISSN: 2775-5215
Volume 5 No. 1, Februari 2022

with ARDS. There is a positive benefit to reduce mortality from subgroup analysis when the continuous enteral infusion is given. Continuous supplementation with omega 3 fatty acids within a balanced formula seems to be a promising area for future research.

Competing Interest

The authors declare that there are no competing interests related to this study.

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e-ISSN: 2775-5215
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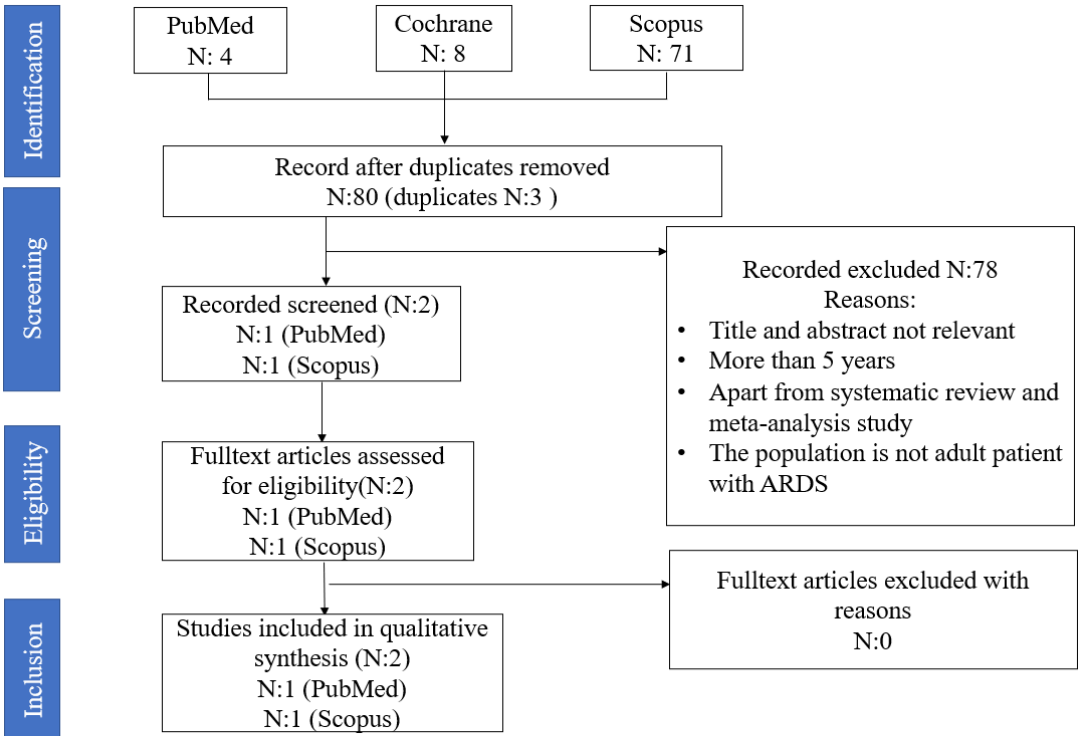

Figure 1. Prisma's Flow Chart of Literature Searching

Tabel 1. Resources and search strategy

Database	Search strategy	Hits
Pubmed	(((acute respiratory distress syndrome[MeSH Terms]) AND (omega 3 fatty acids[MeSH Terms])) AND (mortality[MeSH Terms])	4
Cochrane Library	#1 "acute respiratory distress syndrome" N:3110 #2 "omega 3 fatty acids' N:5029 #3 "mortality" N:101052 #4 #1 AND #2 AND #3 N:8	8
Scopus	(TITLE-ABS-KEY (acute AND respiratory AND distress AND syndrome) AND TITLE-ABS-KEY (omega 3 fatty AND acids) AND TITLE-ABS-KEY (mortality))	71

Tabel 2. Study characteristics

Characteristics	Langlois P, et al[8]	Dushianthan A, et al[4]
Prediction	Omega 3 PUFA administration by enteral or parenteral route could reduce mortality	Immunonutriton containing omega 3 fatty acids with or without antioxidants can improve long-term survival
Patient	Patients ≥18 years of age hospitalized in any kind of ICU and presenting an ARDS	Patients aged ≥18 years with ARDS
Determinant (intervention/comparative/outcome)	Intervention: oral, enteral, or parenteral omega 3 PUFA for at least three consecutive days Comparative: placebo or a non-fish oil nutritional therapy administered in the context of standard nutrition	Intervention: enteral or parenteral nutrition supplemented with omega 3 fatty acids with or without antioxidants Comparative: placebo or standard nutrition
Study type	Therapy	Therapy
Study design	Systematic review and meta-analysis	Systematic review and meta-

Outcome	of RCT Mortality was significantly reduced in the continuous enteral infusion route	analysis of RCT Little or no difference in all-cause mortality

Table 3. Validity Criteria

Articles	Relevance							Level of evidence
	Clear clinical questions	Good study selection	Appro-priate	Sufficient validity	Similari-ty of the results	Clinically impor-tant	applica bility	
Langlois P, et al (2019)[8]	+	+	+	+	+	+	+	1
Dushianthan A, et al (2020)[4]	+	+	+	+	+	+	+	1

Tabel 4. Relevance Criteria

	Similarity Population	Similarity Determinant	Similarity Outcome
Langlois P, et al (2019)[8]	+	+	+
Dushianthan A, et al (2020)[4]	+	+	+