Original Article

The Role of Omega-3 on the IL-6 Levels, Malondialdehyde, and Clinical Improvement in Adults with Community-Acquired Pneumonia

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Abstract

Background: Acute lung parenchymal infection, known as pneumonia, can be carried on by multiple microorganisms, including bacteria, viruses, fungi, and parasites. Globally, community-acquired pneumonia is a major factor of morbidity, mortality, and health issues. Malondialdehyde (MDA) is a marker of oxidative stress in pneumonia patients, and interleukin 6 (IL-6) is a marker of inflammatory process. Effect of Omega-3 as an immunomodulator, anti-inflammatory, and antioxidant may be implemented as adjunctive therapy in patient with community-acquired pneumonia.

Methods: Clinical trial research with a true experimental method and pretest-posttest design. The study involved 30 community-acquired pneumonia patients who were admitted at Moewardi Hospital in Surakarta and Dr. Soehadi Prijonegoro Hospital in Sragen from August to September 2022 by consecutive sampling. The control group (n=15) received standard therapy, and the treatment group (n=15) received standard therapy plus Omega-3 at a dose of 1600 mg/day. IL-6 and MDA levels were measured when the subject was admitted to the hospital and there was clinical improvement.

Results: There was a significant difference in reduced IL-6 levels (*P*=0.001), decreased MDA levels (*P*=0.001), and the duration of clinical improvement (*P*=0.042) between the treatment group and the control group. There was a moderate correlation between the decrease in IL-6 (R=0.480) and MDA (R=0.459), while the duration of clinical improvement had a strong correlation (R=0.756) in the treatment group.

Conclusion: Supplementation of Omega-3 was effective in reducing IL-6, MDA levels, and the duration of clinical improvement in community-acquired pneumonia patients.

Keywords: Omega-3, community-acquired pneumonia, IL-6, MDA, Clinical improvement

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INTRODUCTION

Pneumonia is defined as an acute lung parenchymal infection carried on by a variety of pathogens, including bacteria, viruses, fungi, and parasites. Community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP) are types of pneumonia (VAP).[1–3]

Community-acquired pneumonia (CAP) is an acute inflammation of the lung parenchyma that is obtained in the community.[1,2] Despite advancements in its management during the past ten years, CAP remains an important global cause of morbidity, mortality, and healthcare expenses.[4] A fivefold increase in incidence and a twofold increase in mortality with increasing age from 65-69 years. Excessive inflammation can cause exacerbations of lung injury, vascular leakage, and impaired oxygen exchange in the alveoli.[5,6]

The pro-inflammatory cytokines IL-1, IL-6, TNF-α, and IL-8 are released once the antigen interacts with immune system cells, activating the transcription factor NF-κB. Interleukin-8 induces the production of ROS and elastase, which damage tissue by acting as neutrophil chemotactic agents. Through pathogen recognition (PRRs) and NF-B transcription, neutrophils activate innate immunity, which causes the release of proinflammatory cytokines and the expansion of other immune cells to the site of infection.[7,8]

Antioxidants such as glutathione peroxide (GPx), glutathione (GSH), and superoxide dismutase (SOD) are present at low levels and ineffective in pneumonia patients.[9,10] The production of reactive oxygen-species (ROS) exceeds the antioxidant capacity, potentially causing damage, which is known

as oxidative stress. Increased lipid peroxidation due to ROS accumulation and oxidative stress causes elevated malondialdehyde (MDA) levels.[7,8]

An essential nutrient called Omega-3 has anti-inflammatory and antioxidant properties that are important for human health.[6,10] Specifically, peribronchial inflammation and cell death are reduced by Omega-3 in terms of lung pathology.[11,12] Omega-3 supplement is recognized to reduce plasma MDA levels, a marker of oxidative stress, and IL-6 levels, a marker of inflammation, in adult with CAP. Managing inflammation is necessary for avoiding the development of tissue damage and advancing clinical recovery.

The purpose of this experimental study was to analyze the potency of Omega-3 as an adjuvant treatment for pneumonia in reducing IL-6 levels, MDA levels, and clinical improvement duration in patient with community-acquired pneumonia.

METHODS

This is an experimental study with a pretest and post-test group design. The study sample involved 30 CAP patients who were admitted at Moewardi Hospital in Surakarta and dr. Soehadi Prijonegoro Hospital in Sragen from August to September 2022 through consecutive sampling.

The inclusion criteria included age >18 years old with CAP, a PSI score >70 or less than 70 with PDPI criteria, no prior history of consuming fish capsule supplementation containing Omega-3, and giving consent for participating in this study by signing the consent form.

Patients with underlying diseases (such as HIV, cancer, uncontrolled diabetes, or immunocompromised status) that could develop systemic inflammation and hence affect IL-6 or MDA count were excluded to prevent bias.[13–16] Other exclusion criteria were: patient with community pneumonia who were admitted in intensive care unit; patient with history of intravenous use of antibiotics and corticosteroids in previous 90 days; post-surgery; and pregnancy. Patient who took anti-coagulant drugs in infectious diseases besides CAP, patients with autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and multiple sclerosis were also excluded.

The participants who were qualified and met both inclusion and exclusion criteria were then randomly divided into control and treatment group. The control group (n=15) received standard therapy, and the treatment group (n=15) received standard therapy plus Omega-3 at a dose of 1600mg/day. With the exception of Omega-3 that was administered to the treatment group, both groups were provided with standard therapy.

The independent variable of this study was the administration of Omega-3, while the dependent variables were the IL-6 levels, MDA levels, and clinical improvement of CAP. When stable clinical conditions were met, subjects had their venous blood taken to evaluate serum IL-6 and MDA levels. Clinical improvement is observed based on hospital length of stay.

SPSS was used to analyze the data. Depending on the finding of Shapiro-Wilk normality test, the significance of change in IL-6 and MDA levels between the pretest and posttest was assessed using either paired t-test or Wilcoxon signed rank test. Chi-square test on hospitalization length of stay was applied to assess clinical improvement. The effect of Omega-3 fatty acids on IL-6, MDA, and clinical improvement was then investigated using linear regression.

RESULTS

Participants characteristics in this study included gender, age, PSI score, class of risk, and history of smoking. Participants in both groups were characterized to determine the homogeneity and the viability of clinical trial procedures. The normality test of characteristic distribution in both groups was carried out by using Shapiro-Wilk test.

The categorical characteristic variables included gender, class of risk, and history of smoking. Age and PSI scores were the numerical characteristic variables. The categorical characteristics were presented in frequency (%) while the numerical data

were presented in mean±standard deviation. The homogeneity test for numerical data with normal distribution was performed using independent t test, and if data distribution was abnormal, the Mann-Whitney test was utilized. The homogeneity test revealed value of *P*>0.05 indicating that basic characteristics of both groups of subjects were homogeneous.

Table 1. Participant Characteristics

Characteristics	Group		*P*
	Control (n=15)	Omega 3 (n=15)	
Age[a]	60.33±18.25	56.60±17.31	0.570
Sex[b]			
Male	10 (66.7%)	10 (66.7%)	1.000
Female	5 (33.3%)	5 (33.3%)	
PSI Score[c]	82.73±13.69	78.80±6.95	0,519
Class of risk[c]			
II	1 (3.3%)	0 (0.0%)	
III	10 (66.7%)	14 (93.3%)	0.355
IV	5 (16.7%)	1 (6.7%)	
History of smoking[c]			
Passive	6 (40.0%)	6 (40.0%)	
Mild	2 (13.3%)	1 (6.7%)	0.982
Moderate	6 (40.0%)	8 (53.3%)	
Severe	1 (6.7%)	0 (0.0%)	

Note: [a]*Chi-square*; [b]*Independent t-test*; [c]*Mann-Whitney test*

Based on Table 1, the demographic test result showed *P*>0.05, indicating that the distribution of characteristics of both groups was homogeneous. The average pre-test (before treatment) and post-test (after treatment) of IL-6 levels in the control group were 41.22±43.23 and 43.92±49.95 respectively. It's been reported that there was a slight increase in IL-6 post- treatment group, with an average increase of 2.70±34.18, or 6.6%. In the Omega-3 group, the pre-test IL-6 levels obtained an average of 57.73±58.63 and a post-test average of 18.20±19.62. The difference in post-pre-Omega-3 IL-6 changes was found to have an average decrease of -39.53±44.97, or a decrease of 68.5%.

The paired difference test (pre-post) in the control group revealed *P*=0.140 and the Omega-3 group revealed *P*=0.001, suggesting that the control group did not experience significant changes in IL-6, where the Omega-3 group experienced a significant decrease in IL-6. Thus, the Omega-3 supplementation was effective in reducing IL-6 levels in patients with CAP. The unpaired difference test at the post-pre difference revealed value of *P*=0.003 (Table 2).

Table 2. Difference in IL-6 Levels Between Control and Omega 3 Group

IL-6	Group	
	Control	Omega-3
Pre-test	41.22±43.23	57.73±58.63
Post-test	43.92±49.95	18.20±19.62
P	0.140[a]	0.001*[a]

Note: *Significant (*P*<0.05); [a]*Wilcoxon rank test*

The MDA levels averaged 1303.58±1489.17 in the pre-test control group and 1049.46±1270.12 in the post-test control group. The average difference in MDA changes between post and pretest was found to be reduced by -254.12±455.55 or -19.5%.

The pre-test MDA levels in the Omega-3 group averaged 1559.27±1511.38 and the post-MDA levels in this group averaged 315.28±397.90. It was reported that the difference in post-pre MDA changes in the Omega-3 group had an average decrease of -1243.98±1325.02 or -79.8%.

Table 3. Difference in MDA Levels Between Control and Omega 3 Group

MDA	Group	
	Control	Omega-3
Pre-test	1303.58±1489.17	1559.27±1511.38
Post-test	1049.46±1270.12	315.28±397.90
P	0.012[a]	0.001*[a]

Note=*Significant (*P*<0.05); [a]*Wilcoxon rank test*

Both the Omega-3 group and control group showed a significant decrease in MDA based on the result of paired difference test (*P*=0.012 and *P*=0.001). Omega-3 patients had a lower MDA level than the control group. The Omega-3 therapy treatment was observed to be more effective in lowering MDA levels, according to the unpaired difference test at the post-pre difference value of *P*=0.049 (Table 3).

The control and Omega-3 group showed a significant decrease in MDA based on the result of paired difference test (*P*=0.012 and *P*=0.001). Omega-3 patients had significantly lower MDA than the control group. The unpaired difference test at the post-pre difference revealed value of *P*=0.049 indicating that Omega-3 therapy was more effective in lowering MDA levels (Table 4).

Table 4. Difference in Length of Stay Between Control and Omega 3 Group

Clinical Improvement	Group		*P*
	Control	Omega-3	
≤7 days	10 (66.7%)	15 (100.0%)	0.042[a]*
>7 days	5 (33.3%)	0 (0.0%)	

Note: *Significant (*P*<0.05); [a]*Chi square test*

R value of Omega-3 effect on reduction of IL-6 level was 0.480, indicating a moderately significant correlation between Omega-3 administration and reduction in IL-6 level (r=0.400–0.599). Despite an Omega-3 supplement, it showed a significant relationship between lower IL-6 levels and the value of *P*=0.007.

The effect of Omega-3 on reducing MDA levels showed R value of 0.459, implying that close relationship between Omega-3 administration and lower IL-6 levels was in the moderate category (r=0.400–0.599). The value of *P*=0.011 suggests that there was a significant effect of taking Omega-3 on reducing MDA levels (Table 5).

The effect of Omega-3 on clinical improvement reported R-value of 0.756, which indicated that close relationship between Omega-3 administration and lower IL-6 level was in a strong category (r = 0.600–0.799). Value of *P*<0.001 implies that there was a significant effect of administering Omega-3 on accelerating clinical improvement.

Table 5. Effect of Omega-3 on IL-6 levels, MDA levels and clinical improvement.

Effect of Omega	R	RC	95% CI	*P*
IL-6 Levels	0.480	-42.24	-72.12 to -12.36	0.007[a]*
MDA Levels	0.459	-989.86	-1730.92 to -248.80	0.011[a]*
Clinical Improvement	0.756	-2.27	-3.03 to -1.51	<0.001[a]*

Note; *Significant (*P*<0.05); *Chi square test*; RC=Regretion Coefficient

DISCUSSION

The mean age of patients in the control group was 60.33±18.25 years, and in the Omega-3 group it was 56.60±17.31 years. The risk of CAP increases with age. The annual incidence of hospitalization for community pneumonia in adults aged 65 years is approximately 2000 per 100,000 population in the United States. Two percent of the older adult population is at risk for hospitalization for community pneumonia.[17]

PSI scores obtained from the control group averaged 82.73±13.69 while in the Omega-3 group the average was 78.80±6.95. The PSI score is used to identify patient at risk of death and plan the patient's care for outpatient or inpatient care. The PSI score criteria include respiration rate >30 times/minute, PaO_2/FiO_2 >250 mmHg, multilobed infiltrates on chest X-ray, systolic blood pressure <90 mmHg, and diastolic blood pressure <60 mmHg.[18,19]

This study observed that participants in control and Omega-3 group had smoking history of similar proportion. Patients with a history of moderate smoking had the highest proportion with 6 patients (40.0%) in the control group and 8 patients (53.3%) in the Omega-3 group. A systematic review with a meta-analysis by Baskaran et al reveals that exposure to cigarette smoke is significantly related to the development of community pneumonia.[20]

Adults aged >65 years who are passive smokers also have a high risk of developing community pneumonia. Piatti et al. found that smoking modifies the epithelial surface, leading to increased compliance of pneumococci compared to never-smokers. Greater bacterial attachment may lead to greater oropharyngeal colonization and, therefore, a greater risk of developing community pneumonia.[21]

The difference between post- and pretest levels of IL-6 in the Omega-3 group decreased by 68.5%. The relationship between Omega-3 administration and lower IL-6 level in this study was classified as moderate category, indicating that Omega-3 treatment was able to reduce IL-6 levels more than those without Omega-3 supplementary therapy. The addition of Omega-3 therapy has an effect on reducing IL-6 levels compared to standard therapy in patients with CAP. The study by Zhou et al. revealed that IL-6 level were normal at level <10 pg/ml. Another study by Liu et al, 2020 stated that level of IL-6 >32.1 pg/ml had higher risk for severe complications. Several healthy individuals were observed to have IL-6 levels of 43.5 pg/ml. In this study, IL-6 levels following Omega-3 administration was observed to be significantly decreased but yet to reach normal level as healthy people in general,

however, it could reduce IL-6 levels to <32.1 so that the risk for severe complications could be prevented.[21,22]

Interleukin-6 is a pleiotropic cytokine that plays an important role in transmitting defense signals from invading pathogens or against tissue damage to stimulate acute-phase reactions, immune responses, hematopoiesis, and various internal organs as host defense. IL-6 is a protein secreted by 26-kD, a soluble protein produced by T cells that activates B cell differentiation to produce antibodies.[23,24]

The pathophysiology of CAP in the early stages is associated with proinflammatory cytokines produced by alveolar macrophages, particularly IL-6 and tumor necrosis factor-α, where IL-6 levels are significantly elevated in conditions of pulmonary consolidation, hypoxia, and shock. Several studies have suggested that IL-6 can be used as an independent predictor of CAP mortality. This is based on findings showing a positive correlation between serum IL-6 concentrations and recent mortality in community pneumonia.[23–25]

Omega-3 plays an important role as an anti-inflammatory resulting from PPAR-γ activation and reduces cytokine production. As previously noted by Gutiérrez et al, Omega-3 fatty acids can reduce inflammation and have a positive effect on inflammation-related illnesses. According to Doaei et al's research, the treatment of Omega-3 dramatically lowered IL-6 levels in critically ill individuals with COVID-19, all of whom had pneumonia.[26–28]

The treatment group's administration of Omega-3 supplements decreased MDA level significantly. In this group, the difference in MDA levels between the pretest and posttest was 79.8%. The administration of Omega-3 was able to lower MDA levels compared with patients without receiving Omega-3 therapy because of the strong links between the treatment of Omega-3 and the lowering of IL-6, which was in the moderate range.

Malondialdehyde could be utilized as a biomarker of oxidative stress, though it is a stable end product of the process that leads to a rise in lipid peroxidation during oxidative stress. Based on recent research in 2021 by Koyuncu et al, patients with CAP showed higher levels of MDA in their pleural fluid than individuals who had cancer and heart failure.[29–31]

Research by Buonocore et al revealed a significant correlation between Omega-3 supplementation and a reduction in MDA levels.[32] According to Heshmati et al's systematic review and meta-analysis, Omega-3 n-3 PUFA supplementation could reduce plasma MDA levels in both young and old people.[33] By enhancing the host's nonspecific and specific immune responses, Omega-3 treatment has a positive impact on acute pneumonia, according to experimental studies on the subject conducted by Sharma et al in 2013 using experimental animals.[34,35]

Normal value of MDA is currently yet to be established. Age and the activity of enzymes like glutathione peroxidase, catalase, and superoxide dismutase can, as antioxidants, have an impact on MDA levels. MDA levels could also be affected by environmental factors like pollution and disease-related antioxidant medicines. MDA levels are a specific indicator of oxidative stress in each disease. Suhartika et al's research indicates that MDA levels in healthy individuals were about 3.01 nmol/mL, whereas Mas-Bargues et al's study found that the MDA reference values were 0.62–1.22 for young individuals, 0.36-2.80 for adults, and 2.19-3.63 for old individuals.[36–38] In this study, an ELISA kit with ng/ml units and a detection range of 31.25–2000 ng/ml was employed. No study classifies typical MDA concentrations into ng/ml categories.

Clinical improvements were seen in all patients within 7 days after receiving Omega-3 supplement. This reveals that providing additional Omega-3 therapy decreases the time they need to take medication for CAP. Clinical improvements may develop earlier with Omega-3 therapy than without it.

According to Hinojosa et al's research, supplementation with Omega-3 fatty acids for two months boosted animal stability, reduced bacteremia, and reduced lung pathology, particularly peribronchial inflammation and cell death. It is believed that Omega-3 fatty acids have anti-inflammatory activity in pneumococcal pneumonia. Oral supplementation with Omega-3 fatty acids showed a protective impact due to its being linked to

fewer immune cell infiltrates and pneumonia consolidation based on pulmonary histopathology.[12]

CONCLUSION

Omega-3 supplementation as adjuvant therapy at a dose of 1600 mg/day can reduce IL-6 and MDA levels associated with the duration of clinical improvement in community-acquired pneumonia.

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