International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

The Role of Omega-3 Fatty Acid Supplementation on Change in CRP Levels and the Frequency of Illness in Stunting Children Ages 12-36 Months

Lewi Jutomo[1], Bambang Wirjatmadi[2], Rudi Irawan[3]

Post Graduate Program, Program Study of Public Health, Faculty of Public Health, University Airlangga, Surabaya

[1]Student Doctoral, Faculty of Public Health, AirlanggaUniversity, Surabaya

[2]Lecturer Doctoral, Faculty of Public Health, Airlangga University, Surabaya

[3]Lecturer Doctoral Program, Medical Faculty, Airlangga University, Surabaya

Abstract: ***The main cause of children under five is stunting is lack of food and infection, the mutual relationship weakens the immune system. The great burden of infection is its effect carried into adulthood so that it has serious consequences on health, and the formation of the quality of human capital. It is known that omega-3 fatty acids can act as anti-inflammatory. Therefore, supplementation of omega-3 fatty acids is expected to control the synthesis of CRP thereby reducing the frequency of illness.The purpose of this study was to analyze the role of omega-3 fatty acid supplementation in controlling CRP synthesis, thereby reducing the frequency of pain that is often experienced in stunting children aged 12-36 months.This research method is randomized, pre-post test control group design clinical trial. Subjects consisting of 12 children in the control group received placebo, another 12 children in the treatment group were given omega-3 fatty acid supplementation for 2 months. The parameters observed were levels of CRP and frequency of illness. Data were analyzed using t-test.The results of the study, based on observations at the beginning and end of the study, showed that only subjects in the control group CRP levels increased significantly (p <0.05), then subjects in the treatment group frequency of illness were significantly reduced (P <0.05) compared to controls.It was concluded that omega-3 fatty acids play a role in inhibiting CRP synthesis, thereby reducing the frequency of illness in stunting children aged 12-36 months significantly compared to the control group.Need to provide omega-3 fatty acids supplementation in toddlers stunting to improve immune response and reduce the frequency of illness.***

Keywords: omega-3 fatty acids, CRP, frequency of illness, stunting toddlers aged 12-36 months.

1. Introduction

Stunting children are a global public health problem with wide implications, such as malnourished children can increase the risk of death from infection due to disease (Rytter et al, 2014). Calder and Jackson (2000) explain that there is a reciprocal relationship between infection and malnutrition, both of which ultimately weaken the immune system or host defense. Infection causes inflammation which results in increased nutrient requirements. Ironically, the state of infection depresses appetite, consequently exacerbating malnutrition and weakening the immune system. The burden of infection is large, the effects carry over into adulthood. Martorell and Zongrone, (2012) state that failure to encourage linear growth has serious consequences on health both in the short and long term, as well as on the formation of quality human capital. Suliman et al., (2011) found that children in Sudan who are malnourished have higher CRP levels than controls and are higher in children related to respiratory illness and fever. Since 1929, Burr and Burr have confirmed that EPA and DHA omega-3 fatty acids are essential for health, and their deficiencies in the diet can cause illness. Various epidemiological studies have been conducted to prove that omega-3 fatty acids EPA and DHA reduce various diseases (Kohly and Levy, 2009). Its ability in controlling infection, through its derivatives in the form of bioactive compounds namely: resolvin, protectin and maresin. Its action is via specific cells mediated by appropriate receptors (Duvall and Levy, 2015). Hastruck et al. (2007) found that resolvin series E (RvE1) is a derivative of these omega-3 fatty acids, has the ability to encourage inflammation resolution as a target of perfect recovery from local lesions, and reduces systemic inflammatory markers such as CRP and IL-1 in experiments on rabbits. In addition, these omega-3 fatty acids show a protective role in allergic diseases and respiration (Shek et al., 2012).

Therefore, this study wants to prove the role of omega-3 fatty acids in controlling CRP synthesis so that it can reduce the frequency of pain. Thus, in the end it can spur the growth of stunting toddlers aged 12-36 months.

2. Material and Methods

This research method is classified as a clinical trial experiment with randomized, pre-post test control group design. The sample is divided into 2 groups namely; the control group as a placebo and the treatment group were given supplementation of omega-3 fatty acids with each group placed 12 children under five as subjects, so that the total number of subjects participating totaled 24 short children under five. Placement of subjects into the treatment group was done by simple random sampling, using lottery. The 24 children under five who participated in this study were recruited from data available at the Sikumana-Kupang Community Health Center. Criteria for inclusion of subjects in this study were healthy toddlers (physically healthy, mentally, socially and normal activities), ages 12-36 months, short nutritional status (TB / U <2 SD), and parents willing

their children to be involved in this study. The dose of omega-3 fatty acids given to the treatment group was adjusted for the subject's body weight namely; body weight> 10-20 kg were given 500 mg of omega-3 fatty acids and subjects with a weight of ≤ 10 kg were given 350 mg or the range of EPA fatty acids was 60-90 mg and DHA fatty acids was 40-60 mg. The supplementation is carried out every day and carried out for 60 days. Implementation of giving to subjects carried out by health cadres.This trial protocol, has received an ethical review agreement with No. 322-KPK from the Health Research Ethics Commission, Faculty of Public Health, Airlangga University. After the study had been explained orally and writing, both parents of all participating children gave written consent to participate.

Data collection

Before conducting the study as preliminary data or pre-test, blood stunting subjects were taken to determine CRP levels.Blood drawn through the venous arm. A 3 mL blood sample is collected in a heparinized tube. After the blood drawing process, the tube is placed on a shelf in a standing state and allowed to stand for 30 minutes until a clot occurs. Then centrifugation was carried out at a speed of 1500 g for 10 minutes. The resulting serum is then aliquated into the cups that have been provided and sent to the inspection department to be done according to the tool's work instructions. Thus the same process is carried out for the final data collection or post test. The process of collecting blood from subjects and examining CRP levels was carried out at Prodia-Kupang Clinical Laboratory.

Determination of CRP levels

Based on the principle of examination, human CRP agglutinate with latex particles coated with monoclonal anti-CRP antibodies. Precipitates that occur are measured by turbidimetry. CRP examination procedures with particle enhanced immune-turbidimetric techniques. The work step is carried out by calibration first, by dropping a number of calibrator volumes and input into the sample cup. Place it on the calibrator rack on the related device. Work as in the calibration program of the related device. Do the control after the calibration results meet the requirements, by dropping a volume control and put it in the sample cup. Then place it on the relevant tool control rack. After the calibration and controlresults meet the requirements, do the examination for the sample, with a pipette of 100 µL of the serum sample into the cup sample. Place it on the sample in the related tool. Work the sample according to the work instructions of the relevant tool. Reagent performance: (i) linearity: 0.15 - 20.0 mg / L (1.43 - 190 nmol / L; 0.015 - 2.0 mg / dL), (ii) analytic sensitive: 0.3 mg / L ; 0.03 mg / dL).

Frequency of illness

Data collection on the frequency of illness of children under five is obtained from the mother's information reported to the health cadre and recorded through visits every day during the study. Types of illness or reported complaints of pain are subclinical types such as cough heat, colds, fever or a combination that is commonly experienced and then grouped into 2 categories based on their median value: rarely if the number of sick frequencies is smaller or equal to 2 times (≤ 2), and often if the frequency of pain is experienced more than 2 times (> 2) during the study.

Statistics

Data were analyzed with SPSS for Windows, version 23. Test the average difference of the observed parameters observed before and after treatment in each group using paired t-sample tests. While testing the difference in parameter values between groups using the free sample t-test. Before doing statistical tests, all data are tested for the normality of the distribution and homogeneity of the variants. Data normality test uses the Saphiro-Wilk test, and the data homogeneity test uses the Lavene test. If there is an abnormal distribution of data in paired data, further tests will be carried out with the non-parametric Wilcoxon test while the variant data are not homogeneous in the intergroup data then it will be tested with the Mann-Whitney test.

3. Result

CRP levels

The results of measurements of CRP levels can be seen in Table 1. From the table it appears that the average CRP level of the control group at the initial observation of the study was 0.90 mg / dL with a variation of 0.63 mg / dL, then at final observations of the study average CRP levels, an increase of 1.66 mg / dL to an average of 2.56 with a variation of 1.93. Statistical test results showed that there were significant differences (p <0.05) in average CRP levels in the control group between the initial observations and the end of the study.

In the treatment group, ie subjects given omega-3 fatty acid supplementation, there was a smaller change in mean CRP levels between the initial observations and the end of the study. At the beginning of the observation, the average CRP level was 0.99 mg / dL with a variation of 0.45 mg / dL. At the end of the observation, the average CRP level was 1.73 mg / dL with a variation of 1.14 mg / dL or there was a change in the increase in CRP levels, which was 0.74 mg / dL. Statistical test results (t-test) showed no significant difference (p> 0.05) in average CRP levels of subjects between the initial observations and the end of the study in this treatment group.

In addition, the results of statistical tests on average CRP levels between the control group and the treatment group at the initial and final observations of the study showed no significant difference (p> 0.05), as well as the results of the statistical tests on the final observation of the study between the control group and the treatment group average CRP levels showed no significant differences (p> 0.05) in the two groups. This can be said that there were no significant changes in CRP levels in the same observations between the two groups.

Table 1: Mean CRP levels initial dan final observation and its difference

Group	CRP Level (mg/dL)				P-value
	n	Initial	Final	Difference (Δ)	
Control	12	0,90 ± 0,63	2,56 ± 1,93	1,49 ± 1,58	0,033*
Treatment	12	0,99 ± 0,45	1,73 ± 1,14	0,74 ± 0.99	0,096ns
P-Value		0,765^{ns}	0,334^{ns}	0,296^{ns}	

Information:* = significant (P<0,05)
ns = non significant (P>0,05)

Frequency of Pain

The results of monitoring the frequency of pain experienced by subjects during the study in the control group and the treatment group can be seen in Table 2.From the table it appears that in the control group the distribution of pain frequency in the category of rare and often sick as much as 50% each. Different from the treatment group, the frequency of pain with a category is rarely more, which is 75%, while the frequency of pain with a category often relatively small is only 25%. Thus it can be said that, subjects in the treatment group that were given omega-3 fatty acid supplementation were less exposed to illness, compared to the control group. In addition, based on the average results of monitoring the frequency of pain based on the incidence of pain experienced for 2 months from subjects in the control group and the treatment group can be seen in Table 3

Table 2: Frequency distribution of pain

Pain frequency category (times/2 months)	Control group		Treatment group	
	n	%	n	%
Rare ≤ 2	6	50	9	75%
Often> 2	6	50	3	25%
Total	12	100	12	100

From the table it appears that the average frequency of pain experienced in the control group was more, 3.08 times the pain during 2 months of the study with a variation of 1.78 times compared to the control group, which the average frequency of pain experienced a little, only 1.75 times or the incidence of illness for 2 months with a variation of 1.22 times. Statistical test results (t-test) showed that there was a significant difference (p <0.05) on average frequency of pain in these two groups. Thus it can be said that supplementing omega-3 fatty acids imposed in the treatment group can significantly reduce the average frequency of pain experienced by the subjects in the group compared to the control group.

Table 3: Average frequency of pain

Group	n	Average (Times/2 months)	P-value
Control	12	3,08 ± 1,78	0,044*
Tretment	12	1,75 ± 1,22	

Information:* = significant (P <0,05)
ns = non significant (P >0,05)

4. Discussion

The results of this study illustrate that omega-3 fatty acid supplementation plays a role in inhibiting CRP production, so that CRP levels do not increase significantly. Then Wall et al. (2010) explained the total concentration of omega-3 fatty acids was associated with low levels of pro-inflammatory markers (IL-6, TNF-α, C-reactive protein) and high concentrations of anti-inflammatory markers (IL-10, TGF -β). It was concluded that omega-3 fatty acids were beneficial in patients affected by diseases with active inflammatory characteristics.

Hastruck et al, (2007) in their study found resolvin series E1 (RvE1) is a derivative of omega-3 fatty acids, has the ability to encourage inflammation resolution as a therapeutic target resulting in complete recovery from local lesions, and reduces systemic inflammatory markers such as CRP and IL -1 in his experiments on rabbits.Seki et al. (2010) explain that inflammation is the first response of the immune system to infection or injury, but excessive or inappropriate inflammatory response contributes to various acute and chronic diseases. Clinical assessment of EPA and DHA omega-3 fatty acid supplementation shows that they have an impactbeneficial for disease. In this decade, it has been revealed that EPA and DHA are enzymatically converted into bioactive metabolites in certain acute inflammation and resolution. This metabolite can regulate immune cell function and show anti-inflammatory ability both in vitro and in vivo.

Furthermore, it is mentioned that the anti-inflammatory mechanism of omega-3 fatty acids is; 1) reduce the production of eicosanoid mediators from arachidonic acid, most of which have a proinflammatory role, 2) increase the production of eicosanoids that can weaken inflammation or anti-inflammatory from EPA, 3) increase anti-inflammatory production and encourage inflammation resolution by decreasing resolvin lipid mediators originating from EPA and DHA, 4) reduce the chemotactic response of leukocytes, 5) reduce the expression of adhesion molecules in leukocytes and in endothelial cells and reduce inter-cell adhesion interactions, 6) reduce the production of proinflammatory cytokines and other inflammatory proteins induced via the NFκB system (Seki et al, 2010; Calder, 2010).

The results of this study also illustrate that in the group that received omega-3 fatty acid supplements, proven, rarely exposed to illness. Thus, the role of omega-3 fatty acids can endogenously reduce exposure to pain, and speed recovery. Reducing the frequency of illness or exposure to illness can provide a better opportunity for subjects to grow. Then fever is one indicator of immune system activity that can suppress appetite and relocate nutrients away from growth (Dewey and Mayers, 2011). This is in line with research conducted by Theinprasert et al, (2009) who provided fish oil supplements containing EPA and DHA in school children aged 9-12 years and consume them every five days per week for 6 months in Thailand. The group treated with fish oil had fewer episodes of illness and shortened the duration of illness, especially respiratory infections compared with placebo.

Meanwhile, Calder, (2010) explained that omega-3 fatty acids are known to have anti-inflammatory action so that they got the initial idea that this supplementation in the diet in patients with inflammatory disease could be clinically beneficial.Shek et al, (2012) reported that omega-3 fatty acids showed a protective potential against respiratory and allergic diseases during pregnancy and early childhood. The action of these fatty acids via several mechanisms of immune function. These fatty acids, further modify cellular membranes, replace eicosanoid metabolism, and alter gene expression.

Then Barnig and Levy (2015) describe omega-3 fatty acid supplements as beneficial in the treatment of asthma and inflammatory diseases associated with respiratory tract. In addition, Chiang et al. (2012) reported that omega-3 fatty acids, especially DHA, reduce their metabolism and their

action on macrophages and neutrophils stimulate phagocytosis of E. coli and limit their infection, and reduce the regulation of pro-inflammatory genes including NFκB and TNF -α thereby reducing the need for antibiotics.Imai (2015) in his research found the role of the D1 protective mediator derived from omega-3 fatty acids, in influenza infection, shown to suppress the replication of influenza viruses through its mechanism of blocking viral mRNA, thereby inhibiting the nucleus releasing viral mRNA which thus regulates inflammatory resolution. It was concluded, the protective lipid mediator derived from omega-3 fatty acids could become a new innate immune, suppressing the replication of influenza viruses that could future investigations into a potential antiviral and biomarker drug for some severe viral infections.

5. Conclusions

1) Supplementing omega-3 fatty acids can regulate CRP levels in stunting toddlers. While in the control group CRP levels increased significantly.
2) Supplementation omega-3 fatty acid in stunting children can significantly reduce exposure to the frequency of illness compared to the control group

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