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Research Article

Influence of Intravenous Fish Oil-Enriched Lipid Emulsion on the Inflammatory Response in Children Post Gastrointestinal Surgery

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Abstract

Background and Objective: Surgery can increase morbidity and mortality due to the production of proinflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α. Intravenous fish oil-enriched lipid emulsion (FOLE) contains ω-3, which can reduce the release of proinflammatory cytokines. The influence of FOLE compared to that of the standard medium chain triglyceride (MCT)/long chain triglyceride (LCT) emulsion on the inflammatory response in children post gastrointestinal surgery has never been studied. The current study was designed to explain the influence of FOLE on the inflammatory response in children post gastrointestinal surgery. **Materials and Methods:** A randomized controlled trial was conducted in August 2018-January 2019 at Dr. Soetomo Hospital in children post gastrointestinal surgery due to esophageal and intestinal atresia that requires parenteral nutrition for at least 3 days. The samples were divided randomly into MCT/LCT and FOLE groups. Laboratory and cytokine parameters were examined before and at 3 days after surgery. **Results:** Among all patients, 7/14 were male and 7/14 received FOLE. There were no significant differences in Hb, leukocyte, CRP, albumin, SGOT and SGPT levels in either group. The difference in IL-6 levels was significant between the two groups before surgery ($p = 0.048$), at 3 days after surgery ($p = 0.013$) and in changes within 3 days ($p = 0.003$). TNF-α levels were not significantly different compared to MCT/LCT at day 3 post surgery ($p = 0.482$). **Conclusion:** FOLE, compared to standard emulsions, can decrease IL-6 in postoperative children.

Key words: Esophageal atresia, fish oil, intestinal atresia, lipid emulsion, parenteral nutrition

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Surgery in children impairs the systemic inflammation response and increases the risk of complications due to the excessive production of inflammation biomarker cytokines, such as IL-6 and tumor necrosis factor (TNF)-α, ischemia reperfusion injury and organ damage[1,2].

Parenteral nutrition (PN) plays an important role in children undergoing gastrointestinal surgery[1]. Fat emulsion, conventionally used in PN, contains only soybean oil, which is rich in linoleic acid, ω-6 fatty acids, or a 50:50 mix from vegetable oil rich in medium chain triglyceride (MCT)/long chain triglyceride (LCT). The current standard is the MCT / LCT fat emulsion mix[2].

Several studies have shown that ω-6 is associated with a decrease in cell-mediated[3]immunity, an increase in inflammatory biomarkers and the severity of the inflammatory response[4-6].

Li *et al.*[7] stated that fish oil containing long chain ω-3 fatty acids has been added to several fat emulsions. Fish oil is a source of long chain ω-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA). Several studies have shown that the PN regimen enriched with fish oil could help to reduce inflammation after surgery[8,9]. The new generation of IVLE (SMOFlipid 20%, Fresenius Kabi, Bad Homburg, Germany) is made of 30% soybean oil, 30% MCT, 25% olive oil and 15% fish oil. Due to its ω-3 fatty acid content, the ω-6:ω-3 ratio is 2.5:1, which is within the optimal range suggested by the current literature[5]. Compared to LCT, SMO Flipid is better in modulating the inflammatory response and is also useful in improving immunity and reducing hospitalization duration after surgery[3,10]. This study aimed to explain the influence of FOLE on the modulation of the inflammatory response in children post gastrointestinal surgery.

MATERIALS AND METHODS

Experimental site: This study was an experimental study that used a randomized controlled group pretest-posttest design, aiming to explain the effect of fish oil-enriched fat emulsion administration as parenteral nutrition on the inflammatory response in children after surgery. Sampling was performed using the total sampling method from children who underwent gastrointestinal surgery in RSUD Dr. Soetomo Surabaya from August 2018-January 2019 with inclusion criteria of 0-18 years of age at the start of the study, undergoing gastrointestinal surgery due to duodenal/jejunal/esophageal atresia, needing parenteral nutrition for at least 3 days and agreeing to participate in the study, with the consent of the parent/guardian. Exclusion criteria were chronic diseases and allergy history of fish/egg/soy/bean protein. The dropout criteria were resignment during the study, death before parenteral nutrition administration for 3 days, missing from observation and allergic reaction.

Research procedure

Data collection: Data on body weight were collected through anthropometric measurements, which were measured using digital scales.

Experimental design: The fish oil-enriched intravenous fat emulsion SMOFlipid® and the standard intravenous fat emulsion Lipofundin 20%®, containing 50% LCT and 50% MCT, was given for 3 consecutive days at 1-4 g kg^{-1} day^{-1}.

Parameters measured: Serum IL-6 and TNF-a measurements with an ELISA technique (pg mL^{-1}) were obtained before surgery and at 72 h after surgery. Fig. 1 shows the study flowchart.

Statistical analysis: The data were analyzed using descriptive analysis and a paired t test.

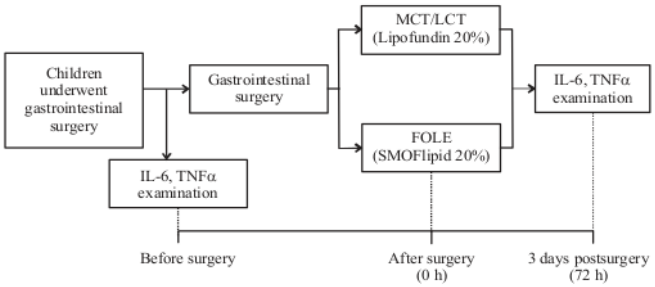

Fig. 1: Study flowchart

RESULTS

From the total consecutive samples, we obtained 14 subjects. The subjects were then classified into two groups: One group received intravenous MCT/LCT fat emulsion and the other received fish oil-enriched intravenous fat emulsion.

No significant difference was found between the two groups based on age, gender, body weight on admission, surgery type, PN duration and hospitalization duration ($p>0.05$).

IL-6 measurement results: There were significant differences in IL-6 levels before surgery ($p = 0.048$), at 3 days after surgery ($p = 0.013$) and in the changes in IL-6 levels at 3 days after surgery ($p = 0.007$).

TNF-α measurement results: The TNF-α level did not differ significantly between the two groups both before surgery ($p = 0.798$) and at 3 days after surgery ($p = 0.796$). The 3-day change in TNF-α level also did not differ significantly ($p = 0.995$).

DISCUSSION

Nutritional support is crucial for the recovery, growth and development of a child after gastrointestinal surgery. Studies have shown that fish oil-enriched intravenous fat emulsions are safe to use, well tolerated and cause positive changes in fatty acid profiles compared to soya-based intravenous fat emulsions[3,10].

This study is the first in Indonesia to assess the effect of fish oil-enriched intravenous fat emulsion on the inflammatory response compared to that of MCT/LCT intravenous fat emulsion on children after gastrointestinal surgery.

Subject characteristics: The subjects in this study were pediatric patients undergoing gastrointestinal surgery due to intestinal or esophageal atresia. Nusinovich *et al.*[11] stated that intestinal atresia is the most common cause of gastrointestinal obstruction, with an incidence ranging from 0.4 to 3.1/10,000 live births. Pediatric patients with intestinal atresia have a high risk of long-term complications and death. Based on a previous study by Soemitro *et al.* at RS Dr. Soetomo Surabaya, the incidence of intestinal atresia was 38 cases in 2 years (2016-2017) (Unpublished Data).

Sfeir *et al.*[12] reported the incidence of esophageal atresia at 1.8/10,000 live births. According to Ghorbani *et al.*[13], babies with esophageal atresia are at risk of malnutrition and other post surgical complications.

In this study, IL-6 and TNF-α levels were measured before surgery and at 72 h after surgery. According to Lin[14], the response to systemic inflammation that occurs after surgery will stimulate both pro- and anti-inflammatory cytokines. Among all cytokines, TNF-α is the first to appear, followed by IL-6, which has the highest level. TNF-α and IL-6 levels peaked during the first 1-2 h. We measured the levels of both pro-inflammatory cytokines on the third day because during wound healing, both TNF-α and IL-6 are very important in early phase inflammation, which occurs 0-3 days after surgery.

In this study, as shown in Table 1, no significant difference was found between the MCT/LCT intravenous fat emulsion group and the fish oil-enriched intravenous fat emulsion group based on age, gender, body weight on admission, surgery type, PN duration and hospitalization duration ($p>0.05$). This finding is in line with previous studies[15-26].

IL-6 levels: As shown in Table 2, this study shows a significant difference in the IL-6 level between the MCT/LCT intravenous fat emulsion group and the fish oil-enriched intravenous fat

Table 1: Subject characteristics

Characteristic	MCT/LCT fat emulsion	Fish oil-enriched fat emulsion	p-value
Age (days)	14.0±12.11	14.1±17.10	0.749*
Gender			
Boy	6 (42.8%)	5 (35.7%)	1.000**
Girl	1 (7.2%)	2 (14.3%)	
Body weight on admission	2271.4±603.25	2608.5±911.78	0.430***
Surgery type			
Esophageal atresia	1 (7.1%)	1 (7.14%)	1.000
Duodenal atresia	3 (21.4%)	3 (21.4%)	
Jejunoileal atresia	1 (7.1%)	1 (7.1%)	
Ileal atresia	2 (14.3%)	2 (14.3%)	
PN duration (days)	30.0±20.34	18.2±15.67	0.201*
Hospitalization duration (days)	32.2±23.11	31.5±38.69	0.406*

*Mann-whitney test, **Fisher's exact test, ***T-test, ****Chi-squared test

Table 2: IL-6 level

IL-6 level	MCT/LCT fat emulsion	Fish oil-enriched fat emulsion	p-value
Before surgery (ng mL^{-1})	212.26±425.03	510.36±532.77	0.048*
3 days after surgery (ng mL^{-1})	569.72±526.82	51.21±85.64	0.013*
3 day change (ng mL^{-1})	357.37±465.40	-459.15±478.1	0.007**

*Mann-whitney test, **T-test

Table 3: TNF-α levels

TNF-α level	MCT/LCT fat emulsion	Fish oil-enriched fat emulsion	p-value
Before surgery (ng mL^{-1})	20.21±3.21	20.96±6.73	0.798*
3 days after surgery (ng mL^{-1})	21.77±5.61	22.44±3.84	0.796**
3 day change (ng mL^{-1})	1.56±3.38	1.48±3.61	0.995**

*Mann-whitney test, **T-test

emulsion group before surgery (p = 0.048), at 3 days after surgery (p = 0.013) and in the 3-day change after surgery (p = 0.003). This finding supports previous findings by other studies[1,9,15].

According to Li *et al.*[7], the ω-3 content in fish oil functions as an immunomodulator with anti-inflammatory effects, unlike the ω-6 content in MCT/LCT intravenous fat emulsion. The fish oil-enriched intravenous fat emulsion consists of EPA and DHA, which reduce inflammation by modulating the synthesis of eicosanoid, activating nuclear receptors and nuclear transcription factors and producing resolvin. Wichman *et al.*[27] stated that the beneficial effect of fish oil added to intravenous fat emulsion could contribute to the immune function in patients after gastrointestinal surgery. The content of fish oil, especially EPA and DHA, acts as an alternative fat precursor in cyclooxygenase and lipoxygenase pathways by forming trienoic prostanoids (as a replacement for series 2 prostanoid derivatives from Arachidonic Acid(AA) and series 5 leukotrienes (as a replacement for series 4 leukotriene derivatives from AA). AA metabolism activates inflammation and weakens cell-mediated immune function. This effect could be decreased by increasing the EPA content of the membrane phospholipids because ω-3 competes with ω-6 in metabolism and EPA is the preferred substrate in the lipoxygenase pathway. Similarly, Weiss *et al.*[16] explained that PUFA plays an important role in cellular membrane synthesis as a precursor of biochemical process modulators. The fat mediator system is very important for mediating the inflammatory response. Fat mediators include the products of AA oxidation, such as thromboxane, prostaglandin and leukotrienes. AA metabolites could cause vasoconstriction, bronchoconstriction, thrombocyte activation, increased vascular permeability, inflammation activation and the suppression of cell-mediated immunity function. ω-3 competes with ω-6, producing an EPA derivative that is less inflammatory than the AA derivative. Han *et al.*[9] showed that unlike ω-6, immunomodulation by ω-3 is able to modify leukocyte activity, change the generation of fat mediators and modulate cytokines. Fish oil could promptly add ω-3 to leukocyte cell membrane phospholipids, causing a decrease in the production of pro-inflammatory cytokines due to a higher ω-3:ω-6 ratio. Leukotrienes have several effects on inflammation and immune function, such as leukocyte-endothelial interactions, lymphocyte proliferation and the induction of cytokine gene expression (such as IL-6 and TNF-α).

In contrast to our study, Ma *et al.*[23] and Ma *et al.*[28] found no significant difference in IL-6 levels before and at 6 days after surgery. There are several possible explanations for the discrepant results between Ma *et al.* and our study. In the previous two studies, surgery was performed using a minimally invasive technique that could affect the level of inflammatory cytokines, so the immunomodulatory effect of fish oil-enriched intravenous fat emulsion was not evident. Several studies have shown significantly lower levels of IL-6 in laparoscopy surgery compared to those in more invasive surgery[29,30].

TNF-α levels: As shown in table 3, this study supports previous studies that also did not find significant differences in TNF-α levels at 3 days after surgery[1,10,16,28].

Han *et al.*[9] studied 38 adult patients after gastrointestinal surgery and found no significant difference in TNF-α levels on day 4 (p>0.05). However, there was a significant difference on day 7 (p = 0.003). Wachtler *et al.*[15] studied 40 adult patients after gastrointestinal surgery who received either MCT/LCT intravenous fat emulsion or fish oil-enriched intravenous fat emulsion for 5 days. In the fish oil-enriched intravenous fat emulsion group, there was a significant decrease in the TNF-α level on day 6 (p = 0.03). Wang *et al.*[1] found a significant decrease in TNF-α levels at 6 days after surgery (p = 0.002) compared to the those in the MCT/LCT intravenous fat emulsion group.

Oliver *et al.*[31] showed that TNF-α reaches its peak plasma concentration after 2 h, followed by a rapid decrease (half time 18.2 min), while IL-6 reaches its peak concentration in a biphasic manner at 6 and 74 h after endotoxin exposure. In this study, the TNF-α level was measured at 3 days after surgery, so the TNF-α concentration might have decreased, causing the treatment group to show similar results.

SIGNIFICANCE STATEMENT

This study shows the influence of fish oil-enriched lipid emulsion on the inflammatory response, which could be beneficial for children post gastrointestinal surgery. This study will help clinicians choose the right lipid emulsion in parenteral nutrition for better inflammatory response modulation in children post gastrointestinal surgery. Thus, a new theory on the influence of fish oil-enriched lipid emulsion may be developed.

CONCLUSION

Based on this study, the administration of fish oil-enriched fat emulsion compared to standard fat emulsion in parenteral nutrition plays a significant role in decreasing the IL-6 inflammation response in children after gastrointestinal surgery. This study did not find a significant impact towards the TNF-α inflammation response.

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