Adjuvant Treatment with Fish Oil-based Lipid Emulsion for Patients with Septic Shock in Intensive Care Unit: A Clinical Safety Evaluation

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Purpose: The aim of this study was to evaluate the clinical safety of critically ill patients with septic shock who received fish oil-based lipid emulsion (FOBLE) as adjuvant therapy.

Materials and Methods: A prospectively study was performed on the patients with septic shock who received a 5-days course of parenteral FOBLE as adjuvant treatment in the ICU. Analyzed variables, including consciousness, pulmonary, liver, renal functions, platelet counts, coagulations, blood sugar and lipid levels, were compared before FOBLE and on days 3, 7, and 14 after FOBLE infusion.

Results: Ten patients fulfilled the criteria and were enrolled for analysis. Comparison results disclosed no statistically adverse impact on consciousness, pulmonary, liver, renal functions, coagulations, and blood sugar and lipid levels following on the days 3, 7 and 14. Significant statistically low platelet counts occurred on day 3 (p = 0.022), but there were no significant differences on the days 7 and 14. All patients survived in the following 28 days.

Conclusions: A 5-day course of parenteral FOBLE as an adjuvant treatment in critically ill patients with septic shock is clinically safe. Our findings provide a valuable safety experiment on additional study with FOBLE in critically septic patients in the future.

Key words: fish oil-based lipid emulsion, septic shock, clinical safety evaluations

Introduction

Severe sepsis and septic shock are the major causes of death in intensive care medicine worldwide, with a high mortality rate of up to 60%1,2. Proinflammatory cytokines cascades and complex autotoxic mediators followed by microbe infection with sepsis causing life-threatening organs sequelae and death have been implicated3. The high mortality rate has prompted gathering of intensive worldwide debate and the assembling of superior researches into the constructive development of new therapeutic guidelines; the work is still progressing without slack4.

A fish oil-based lipid emulsion (FOBLE), enriched with ω-3 fatty acids which belong to a long-chain of polyunsaturated fatty acids including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Several large studies on various patient subgroups have demonstrated that administration

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of ω-3 fatty acids increased beneficial outcomes, including cardiovascular diseases, autoimmune diseases, Alzheimer disease, atopic dermatitis, HIV infection, and respiratory distress\(^5\text{-}^\text{10}\), as well as in abdominal surgery\(^11\text{-}^13\). Nevertheless, relevant sepsis studies on ω-3 fatty acids have been explored over the past decade, and these substrates would be considered as immunomodulator rather than energy sources\(^4\). It was disclosed that possess an anti-inflammatory processes and cytokine-shifting effects due to diminishing arachidonic acid derivatives production\(^5\text{-}^7\). The effects were deemed beneficial enough to potentially influence the clinical outcome on septic patients.

However, in the process of exploring FOBLE in varied clinical aspects, safety considerations and avoid iatrogenic adverse effects for patient is important, especially when the patient is critical. The safety issue had once been reported in relatively stabilized abdominal surgery patients by Wichmann et al.\(^8\), but the data is lacking in critical septic patients. There is rational, but still some doubt as to whether intravenous administration of FOBLE as a pharmacologic intervention to septic patients with life-threatening shock could worsen clinical conditions. We therefore undertook this hospital-based study with the objective to assess the clinical safety evaluations of critical patients who received parenteral FOBLE as adjuvant therapy for septic shock.

**Materials and Methods**

The prospective study was performed in the 42-bed general intensive care unit (ICU) of Landseed hospital, a 580-bed of primary and referral teaching hospital in northern Taiwan. The study was approved by the hospital’s institutional review board and written informed consent was obtained from all participants or their authorized representatives. From April to September 2008, admitted patients who fulfilled the criteria of septic shock and received parenteral FOBLE as adjuvant treatment were enrolled for analysis. The FOBLE used was of 10% Omegaven (Fresenius-Kabi, Bad Homburg, Germany), and was prescribed 100 ml daily for 5 days, via a central venous catheter within 24 hours of ICU admission. Each infusion was started at 12 am or pm and lasted for 6 hours. The patients were followed for 28 days after the start of the infusion or until death.

In a bottle of 10% Omegaven emulsion contains 10.0 g refined fish oil, the fatty acids contents are as follows: eicosapentaenoic acid, 12.5-28.2 g/L; docosahexaenoic acid, 14.4-30.9 g/L; myristic acid, 1.0-6.0 g/L; palmitic acid, 2.5-10.0 g/L; palmitoleic acid, 30.0-90.0 g/L; stearic acid, 0.5-2.0 g/L; oleic acid, 6.0-13.0 g/L; linoleic acid, 1.0-7.0 g/L; linolenic acid, ≤ 2.0 g/L; octadecatetraenoic, 0.5-4.0 g/L; eicosanoic acid, 0.5-3.0 g/L; arachidonic acid, 1.0-4.0 g/L; docosanoic acid, 1.5 g/L; docosapentaenoic acid, 1.5-4.5 g/L; other fatty acid, 10.51 g/L.

In brief, clinical diagnosis of sepsis was defined as systemic inflammatory response syndrome (SIRS) with a documented infection. SIRS is manifested by 2 or more of the following variables: (1) hyperthermia > 38.3°C or hypothermia < 36°C; (2) tachycardia (rate > 90 beats/min); (3) tachypnea (rate ≥ 20 breath/min) or hypoxia (oxygen saturation < 90% or need for oxygen supplementation of 0.4 FiO\(_2\) or higher to maintain adequate saturation); (4) leukocytosis (white blood cell [WBC] count > 12.0 × 10\(^9\)/L), leucopenia (WBC < 4 × 10\(^9\)/L), or immature or band forms > 10%. Severe sepsis was defined as sepsis with the additional complication of acute organ dysfunction, hypotension, or hypoperfusion, which may cause abrupt change in mental status, lactic acidosis, or acute oliguria (urine < 0.5 ml/kg/hr). Septic shock was defined as persistent arterial hypotension despite adequate volume resuscitation (20-40 ml/kg)\(^19\text{-}^20\). Exclusion criteria...
included patients’ age younger than 18 years old, pregnancy, treated with immunosuppressive drugs or the equivalent of hydrocortisone more than 300 mg daily during the admission, infection with human immunodeficiency virus, a plasma triglyceride concentration of more than 400 mg/dl, cirrhotic liver and/or acute hepatitis (elevation of serum glutamic-oxalacetic transaminase [GOT] or glutamic-pyruvic-transaminase [GPT] > 350 IU/L), chronic renal failure (creatinine > 3.5 mg/dl) or end stage of renal diseases, acute myocardial infarction, recent stroke, the presence of irreversible underlying disease anticipated to be rapidly fatal, and allergic reactions against fish or egg proteins.

Blood was collected from either brachial or radial arterial catheters before the first lipid preparation was infused, as a baseline, and on days 3, 7 and 14 after a 2-hour interval of lipid infused. Laboratory tests, including PaO\textsubscript{2}/FiO\textsubscript{2} ratios, GOT, GPT, bilirubin, blood urea nitrogen (BUN) and creatinine, were used to determine the function of pulmonary, liver and renal functions. Platelet counts, prothrombin time (PT) and partial thromboplastin time (APTT) were obtained to assess the probability of bleeding tendency. Thrombocytopenia was defined as platelet counts less than \(150 \times 10^9/L\). Blood sugar, cholesterol and triglyceride also obtained to analysis before and after FOBLE infusion. In addition, serial clinical consciousness evaluation, adapted from the neurologic measurement of APACHE (Acute Physiology, Age, Chronic Health Evaluation) III\textsuperscript{(2)}, from the best 0, to the worst 48, was performed before FOBLE infusion, and on days 3, 7 and 14.

Statistical analysis was carried out with the program SPSS (version 14.0; Chicago, IL, USA). Data is presented as arithmetic mean ± standard deviation (SD). Paired variable comparison within group of baseline versus days 3, 7 and 14 was performed by using Wilcoxon signed-ranks test; \(p \leq 0.05\) is considered statistically significant.

Results

During the study period, a total of 10 patients (9 men and 1 woman) were eligible for analysis (Fig. 1). The mean of age was 64.5 ± 20.3 years (range, 32-88 years), with a body mass index (BMI) of 20.0 ± 3.8 (range, 16.0-27.1), and received daily dosages of fish oil was 0.19 g/kg (range, 0.13-0.26 g/kg). All patients tolerated a 5-days course of FOBLE infusion well. Clinical diagnosis of the patients was pneumonia in 5, lung abscess in 1, pyelonephritis in 1, anal abscess in 1, endocarditis in 1, and infectious diarrhea in 1. Among them, 7 patients needed vasopressor infusion and required mechanical ventilator supplement, respectively. The mean of APACHE III scores was 83.2 ± 37.4 (range, 31-162). All participants survived in the

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Assessed for eligibility (n=86)

Excluded (n=76)
Not meeting criteria (n=74)
Refused to participate (n=2)

Allocated to study (n=10)

Discontinued intervention (0)

Completed followed up for 28 days (n=10)

Analyzed (n=10)

Fig. 1 Flow of participants through each stage.
following 28 days. The demographic and clinical data is shown in Table 1.

Consciousness evaluation: Eight of 10 patients had varying degrees of consciousness disturbance upon ICU admission, but all of them subsequently improved on the following days. On day 14, six of 8 patients completely recovered consciousness, and 2 obviously improved. When using the neurologic measurement of APACHE III score, a comparison of conscious levels at initial (scores’ range, 0-48) versus days 3 (0-13), 7 (0-3) and 14 (0-3) were \( p = 0.018, 0.011 \) and 0.011; respectively (Fig. 2A).

Pulmonary oxygenation indexes: Seven patients were complicated with acute respiratory failure requiring ventilator support. Of them, 2 patients were weaned-off ventilator by day 7, 4 by day 14 and 1 on day 19. The mean of baseline \( \text{PaO}_2/\text{FiO}_2 \) ratio was 169.9 ± 74.2 (range, 62-304), and the following day 3 (n=7) and 7 (n=5), with a statistical comparison of baseline data, were 225.8 ± 68.6 (range, 170-360; \( p = 0.463 \)) and 259.6 ± 23.4 (range, 242-289; \( p = 0.138 \)), respectively (Fig. 2B).

Liver and renal functions, platelet counts, coagulations, blood lipids and sugar: The laboratory findings, including GOT, GPT, bilirubin, BUN, creatinine, platelet, APTT, PT, cholesterol, triglyceride and blood sugar values, at baseline, days 3, 7, and 14, are shown in Table 2. When compared with baseline, there were statistical differences of bilirubin (\( p = 0.041 \)), creatinine (\( p =

### Table 1 Demographic and clinical data of the 10 patients with septic shock

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/Age</th>
<th>BMI</th>
<th>Fish oil</th>
<th>Major Diagnosis</th>
<th>Underlying disease</th>
<th>Pathogens</th>
<th>APACHE III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/ 88</td>
<td>18.2</td>
<td>0.21</td>
<td>Pneumonia, respiratory failure</td>
<td>Dementia</td>
<td>Providencia sp.</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>M/ 32</td>
<td>20.8</td>
<td>0.14</td>
<td>Pneumonia, respiratory failure</td>
<td>Nil</td>
<td>Klebsiella pneumoniae</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>M/ 74</td>
<td>22.4</td>
<td>0.17</td>
<td>Infectious colitis</td>
<td>HTN, Af</td>
<td>#Salmonella sp.</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>M/ 78</td>
<td>25.0</td>
<td>0.15</td>
<td>Pneumonia, respiratory failure</td>
<td>DM</td>
<td>#Staph aureus, enterococcus</td>
<td>109</td>
</tr>
<tr>
<td>5</td>
<td>M/ 81</td>
<td>17.1</td>
<td>0.26</td>
<td>Lung abscess, respiratory failure</td>
<td>Asthma</td>
<td>Klebsiella pneumoniae</td>
<td>162</td>
</tr>
<tr>
<td>6</td>
<td>M/ 74</td>
<td>16.0</td>
<td>0.25</td>
<td>Anal abscess</td>
<td>DM, stroke</td>
<td>Klebsiella pneumoniae, Streptococci</td>
<td>105</td>
</tr>
<tr>
<td>7</td>
<td>M/ 80</td>
<td>19.9</td>
<td>0.17</td>
<td>Pneumonia, respiratory failure</td>
<td>HTN, stroke</td>
<td>Acinetobacter sp.</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>M/ 51</td>
<td>16.6</td>
<td>0.20</td>
<td>Pneumonia, respiratory failure</td>
<td>DM</td>
<td>None identified</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>F/ 52</td>
<td>17.2</td>
<td>0.23</td>
<td>Pyelonephritis, respiratory failure</td>
<td>DM</td>
<td>#Klebsiella pneumoniae</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>M/ 35</td>
<td>27.1</td>
<td>0.13</td>
<td>Infective endocarditis</td>
<td>Nil</td>
<td>#Staphylococcus aureus</td>
<td>39</td>
</tr>
</tbody>
</table>

\(^1\)Gram per kg of daily dosage.

\(^2\)Indicate that pathogens isolated from bloods. HTN: hypertension; Af: atrial fibrillation; DM: diabetes mellitus.
0.005), platelet counts ($p = 0.022$), PT ($p = 0.005$) and cholesterol ($p = 0.038$) on day 3, of creatinine ($p = 0.011$) and triglyceride ($p = 0.05$) on day 7, and of creatinine ($p = 0.018$) and blood sugar ($p = 0.028$) on day 14, respectively. (Table 2)

**Discussions**

In order to improve the outcome of critical septic patients, a lot of relevant research has being explored, ω-3 fatty acids as part of them\(^{(22)}\). This
study’s purpose was safety evaluations in the clinical approaches under an adequate dosage of FOBLE infusion for the critical patients with septic shock. In the study, all patients were treated according to general surviving sepsis campaign’s guideline adjuvant with FOBLE continuously infused for 5 days. As previously reported, a dose dependence of FOBLE with about > 0.1 g/kg per day would obtain clinical beneficial effects\(^{(22)}\); therefore, the prescribed dosage for our patients ranging from 0.13 to 0.26 g/kg per day was optimal and sufficient to carry out a pharmacologic intervention.

Acute organ dysfunction caused by sepsis carries a higher morbidity and mortality rate in the ICU\(^{(23)}\). Consciousness alteration is a common manifestation of severe sepsis, particularly in elderly patients, and it may be associated with a poor prognosis\(^{(24,25)}\). Liver is an innate immunity of defenses in clearing bacteria-derived and enteric-derived endotoxin products, and as a major site of infection-associated metabolic adaptations\(^{(26)}\). Cholestatic jaundice could concurrently occur in septic patients with or without pre-existing liver disease\(^{(27)}\). Acute renal dysfunction attributed to tubular necrosis, vasoconstriction, and proinflammatory mediators in the meanwhile\(^{(26)}\). Therefore, it is reasonable that sequential assessments and iatrogenic avoidance of failing organs provides determination of the patients’ diagnoses and the effectiveness of treatment. As a result, consciousness, pulmonary oxygenation indexes, liver and renal functions had no negative impact resulting from infusing FOBLE in clinical. On the contrary, these organs improved and were followed by recovery from sepsis. Whether the beneficial effects, as theorized by Mayer et al. reported\(^{(16,17)}\), were gained from FOBLE could not be postulated here however.

Lung injury is often seen in septic patients due to injured microvascular endothelial and disturbed alveolo-capillary causing membrane ventilation-perfusion mismatch and arterial hypoxemia\(^{(26)}\). In the Gadek, and Pontes-Arruda A et al studied\(^{(11,28)}\), they reported that enteral feeding with \(\omega-3\) fatty acids immune formula could significant improve pulmonary functions. In the ventilated patients, even though their oxygenation indexes were improved on the following days of treatment; there

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Laboratory data at baseline, days 3, 7, and 14, of the 10 patients with septic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>mean ± SD</td>
</tr>
<tr>
<td>GOT(^{†})</td>
<td>42.1 ± 44.5</td>
</tr>
<tr>
<td>GPT(^{†})</td>
<td>35.9 ± 33.2</td>
</tr>
<tr>
<td>Bilirubin(^{‡})</td>
<td>0.7 ± 0.5</td>
</tr>
<tr>
<td>BUN(^{‡})</td>
<td>39.8 ± 27.4</td>
</tr>
<tr>
<td>Creatinine(^{‡})</td>
<td>1.8 ± 0.8</td>
</tr>
<tr>
<td>Platelet(^{‡})</td>
<td>215.5 ± 100.7</td>
</tr>
<tr>
<td>APTT(^{‡})</td>
<td>35.0 ± 3.8</td>
</tr>
<tr>
<td>PT(^{‡})</td>
<td>12.0 ± 1.2</td>
</tr>
<tr>
<td>Cholesterol(^{‡})</td>
<td>110.5 ± 31.0</td>
</tr>
<tr>
<td>Triglyceride(^{‡})</td>
<td>131.2 ± 48.7</td>
</tr>
<tr>
<td>Blood sugar(^{‡})</td>
<td>291.3 ± 210.2</td>
</tr>
</tbody>
</table>

\(^{†}\)International units per liter (IU/L). \(^{‡}\)Milligrams per deciliter (mg/dl). \(^{‡}\)1 x 10^9/L cell counts. \(^{‡}\)second of time.
was no statistically significant difference when compared to the baseline. Parenteral FOBLE for the ventilated patients showed no harm here, but the clinical benefits should be further studied with a controlled group.

As sepsis proceeds, cytokine mediators influence lipid metabolism, and a substantial fluctuation in cholesterol levels has been reported as a risk factor for multiple organ failure and mortality (29,30). In the study, the cholesterol and triglyceride levels were significantly lower on days 3 and 7, respectively, but both on day 14 had no significant difference compared to initiation. The lipid mediator, arachidonic acid, which caused inflammatory processes, would be inhibited by EPA or DHA along with fish oil infusion and to modulate inflammatory responses (16-18). As the data shows, FOBLE infusion in the critical septic patients did not markedly elevate blood cholesterol and triglyceride levels, which might have caused unfavorable macro- and/or microvascular events. As well, the result was also similar to the patient’s blood sugar levels. Acute metabolic responses with gluconeogenesis and glycogenolysis to infection, steadies the blood sugar. Additional parenteral nutrition for critical septic patient may cause insulin resistance and supplant adaptive mechanisms resulting fluctuation of blood sugar. Four of the patients had diabetes mellitus with a high blood sugar levels at admission, however their blood sugar levels were well controlled with insulin infusion suggesting that parenteral FOBLE infusion would not lead uncontrolled hyperglycemia in the critically septic patients. On comparison with initiation, there was statistically significant improvement of blood sugar level on day 14, but the result was contributed to septic control.

Inflammation and coagulation are importantly linked (31,32). Haemostatic abnormalities due to activation of coagulation with deplete platelets and coagulation factors preceding sepsis cause a bleeding tendency (33). Three of the patients had a thrombocytopenia upon ICU admission, two patients increased in platelet counts on day 3. However, 5 other patients had normal platelet counts at initiation but developed thrombocytopenia, resulting in a lower mean of platelet counts with a statistically significant difference on day 3; three of them recovered on day 7. All patients had a normal platelet counts on day 14. Several studies had reported that a lower platelet count would occur as sepsis proceeds, especially on the first 4 days (32,34). This fact indicated that a transient thrombocytopenia might be induced by parenteral FOBLE, but more probably contributed to by sepsis progression. As part of coagulations of PT and APTT, there was no adverse influence, but a significant improvement in PT on day 3. Here also no postulations can be made about the effect of FOBLE.

Finally, in view of the distribution of APACHE III scores of the patients in the study ranged 31 to 162 with a mean of 83.2 score. A percentile at 25% and 75% was 62.2 and 106, which was subject to predicted risks of hospital death accounted for 20-70% (21). However, all patients survived on day 28, suggesting that parenteral FOBLE might not increase the risk of hospital death. In contrast, there were some values which reached a statistical difference in positive effects in Figure 2, but it is inadequate to draw conclusions on clinical effectiveness of FOBLE in the study.

In conclusion, a 5-days course of parenteral FOBLE as an adjuvant treatment in patients with septic shock is safe. It has no adverse impact on consciousness, pulmonary, liver, renal functions, coagulations, and blood sugar and lipid levels, but may possibly carry out a transient thrombocytopenia. This study provides a safety experiment to those who will perform additional study on clinical relations on FOBLE and septic patients in the future.
Acknowledgement

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References


以深海魚油脂肪乳劑輔助治療敗血性休克重症病患之臨床安全性評估

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吳銘斌¹ 丁 熹¹ 廖浩欽¹ 廖詠禎¹

目的：本研究旨在以靜脈輸注深海魚油脂肪乳劑來輔助治療敗血性休克重症病患，探討其臨床安全性。

材料與方法：本研究為前瞻性之臨床研究設計，符合設定條件之敗血性休克病患於入院加護病房24小時內，經由中央靜脈導管輸注深海魚油脂肪乳劑；並記錄病患於治療前與治療後第3、7及14天的意識狀態、肺功能、肝功能、腎功能、凝血功能、血糖值和血脂值之變化。

結果：研究期間，一共有10位病患納入研究分析。病患之意識狀態、肺、肝、腎功能、血糖和血脂值於第3、7及14天時，未有負面影響的統計意義；血小板於第3天時有顯著性的統計意義降低，但於第7和14天時則沒有差異。

結論：本研究結果顯示，靜脈輸注深海魚油脂肪乳剤輔助治療敗血性休克病患的臨床安全性，以提供未來發展深海魚油脂肪乳剤與敗血症之研究者做為參考。

關鍵詞：深海魚油脂肪乳剤，敗血性休克，臨床安全性評估