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ROLE OF OMEGA-3 FATTY ACIDS IN SEVERE SEPSIS CASES

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ABSTRACT

Dietary supplements of omega-3 fatty acids have long been used to influence chronic inflammatory disorders. Omega – 3 fatty acids, derived primarily from fish oils, compete with other fatty acids for incorporation into cell membranes. This study was carried out in 70 patients suffering from severe sepsis admitted in ICU of Pacific Medical College and Hospital, Udaipur to evaluate the impact of omega-3 fatty acids on outcome variables in critically ill severe septic cases. The patients were randomly assigned into two treatment groups: Group I receiving Soya bean based Parenteral nutrition (SO group) and the group II was supplemented Fish oil with the Soy bean based Parenteral Nutrition (FO +SO group) for a period of seven days. The primary endpoints like Gas exchange (Pa02/Fio2), biochemical markers had a significant improvement over the course of nutritional therapy in the FO +SO group as compared to SO group. The duration of stay on Ventilator, no. of days in the ICU and Hospital also reduced significantly in Group II as compared to Group I.

KEYWORDS: Parenteral nutrition, Omega 3 fatty acid, Severe sepsis, ARDS.

INTRODUCTION

Sepsis and septic shock continue to be associated with high mortality rates, despite major advances in critical care medicine. Sepsis thus represents the major cause of death in critical care units worldwide. It is defined as the presence of two or more criteria of systemic inflammation: leukocytosis or leukopenia, tachycardia, tachypnea and fever or hypothermia. With the onset of an organ system failure, sepsis is judged as severe and hypotension or use of vasopressor agents sigsnals the beginning of septic shock.[1] Lipid-derived fatty acids are not only used as energy-providing substrates but possess additional ‘‘pharmacological’’ functions which may beneficially influence healing processes and patient outcome. This consideration appears to be particularly true for the polyunsaturated omega-3 fatty acids like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[2] Fish oils (FOs) are rich sources of ω-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Several clinical trials have shown that FO has immune modulatory effects. The major advantages of EPA- and DHA-acquired metabolites are related to their postulated reductions in proinflammatory effects.[3] Although, several studies have demonstrated the beneficial effects of enteral omega-3 fatty acids on immune competence and patient outcome, controlled clinical trials focusing on the use of parenteral fish oil are scarce.[2] This study was carried out to evaluate the impact of parenteral omega-3 fatty acids (fish oil) on outcome variables in critically ill severe septic cases.

MATERIALS AND METHODS

This study was designed as a prospective, randomized, controlled clinical study in a group of 70 patients from the ICU of Pacific Medical College and Hospital, Udaipur. The subjects were in the age group of 20-70years, with severe sepsis infection and had serum bilirubin > 2mg/dL, serum creatinine ≥ 2mg/dL, platelets ≤ 1000 x 10^3/ µL. Patients were excluded if found to be hypersensitive to egg/soya protein or any other ingredient of PN, cardiogenic shock, diabetes mellitus with known ketoacidosis, severe liver dysfunction or infection by multi-drug resistance. Written Informed Consent was obtained from each patient prior to study enrollment. The screened patients were then randomized to receive either of the following nutritional therapy:

Group I: (SO, Control)

Received a soya bean based fat solution (Lipovenous 20%) delivering a ratio of Omega-6 fatty acid to Omega-3 fatty acid of approximately 7:1.

Group II: (FO + SO Case)

Received a combination of Soya bean based solution and 0.2gm/kg/day fish oil (Omegaven 10%), which altered

the Omega-6 fatty acid to Omega-3 fatty acid ratio to approximately 2:1.

Both groups received isonitrogenous-isocaloric nutritional therapy with a combination of enteral and parenteral nutrition. Preceding therapy the patients were monitored for vital signs like heart rate, temperature and Total Leukocyte Count (TLC). Appropriate antibiotics were given to patients so as to control the source of infection. Primary Endpoints measured were outcomes like number of days on ventilator, length of ICU and Hospital stay; parameters like Gas Exchange (PaO2/ FiO2; Ventilatory variables); Biochemical markers like C-reactive protein, Serum Lactate and Procalcitonin were monitored to assess the difference between the two nutritional therapy groups. These parameters were monitored once prior to Nutrition supplementation and thereafter on the 4^{th} and 7^{th} day of PN. Incidence of new organ failure and mortality percentage was also assessed.

STATISTICAL ANALYSIS

All results are expressed as mean ± SD. Variables were tested for group differences with the z test or $\chi 2$ test. A p value of < .05 was considered significant.

RESULTS

The total number of subjects enrolled for the study was 70 of which 62.87% were female while 37.14% were males, with the maximum number of patients being in the age group of 40-50 yrs and a weight group of 50- 60 kg. Of the 70 patients enrolled, 31 patients were diagnosed with peritonitis, 16 patients were in septic abortion, 13 patients had post traumatic sepsis and 10 suffered with pneumonia. All cases were associated with Adult Respiratory Distress Syndrome (ARDS). *Table 1.1* and *1.2* shows the baseline vitals and baseline laboratory data of all 70 patients at the time of admission. As depicted, it was found that the difference between the baseline vitals and laboratory parameters were not significantly different in the two groups (p> 0.05).

Table 1.1: Baseline Vitals

Sl. No	Vitals	GroupI (SO) (n=35)	Group II (FO+SO) (n=35)	p
1.	Systolic Blood pressure (mm Hg)	116.46 + 13.06	118.84+ 13.44	>0.1
2.	Heart rate (per minute)	132.48 + 26.43	136.20+ 18.86	>0.1
3.	Temperature (oF)	101.2 + 0.88	100.4+1.26	>0.1
4.	Respiratory rate (per minute)	30 + 3.22	32.00 + 4.28	>0.1

Vitals of all 70 patients at the time of admission.(p > 0.05).

Table – 1.2 Baseline Laboratory Data

Sl. No	Case	SO (n=35)	(FO+SO) (n=35)	p-value
1.	S. albumin (g/dl)	2.6 ± 0.4	2.5±0.4	>0.1
2.	S. Creatinine (mg/dl)	1.2 ± 0.2	1.3±0.4	>0.1
3.	Total bilirubin (mg/dl)	1.3 ± 0.3	1.3±0.4	>0.1
4.	Total leucocyte count (10^9 cells/L)	17.1 ± 0.6	16.8±1.5	>0.1
5.	Platelets ($x10^3$ cells µl	192.1± 24.5	188.6±22.6	>0.1
6.	C-reactive protein (mg/dl)	150.6± 63.4	151.8±79.8	>0.1
7.	Procalcitonin (ng/ml)	15.9 ± .68	16.1+0.82	>0.1
8.	Serum lactate(mmol/l)	9.1± 0.68	9.2±0.76	>0.1

laboratory data of all 70 patients at the time of admission (p > 0.05).

Table 1.3: Baseline Organ System Failure

Sl. No.	Organ system	Group I (SO) (n=35)	Group II (FO+SO) (n=35)	%
1.	Respiratory	35	35	70
2.	Cardiovascular	5	6	11
3.	Renal	3	4	7
4.	Hepatic	3	1	4
5.	Neurologic	4	2	6
Total		**50**	**48**	

$\chi 2 = 1.86$, p = 0.76.

No. of organ system failure present in both groups at the time of admission (p>0.05).

During the course of the study, ventilatory variables for the assessment of Gas exchange, values of biochemical markers were noted on the 4th and the 7th day of administration of PN. The difference of PaO2/ FiO2 ratio at the baseline was not significant but after seven days of therapy, gas exchange improved significantly in Group II in comparison to Group I ($p< 0.05$) *(Table 2.1 and Figure 1)*.

Table: 2.1: Mean Ventilatory Variables.

Sl.No.	Variable	Study day	Group I (SO) (n=35)	Group II (FO+SO) (n=35)	p-value
A	FiO_2	Baseline 4 7	0.53+0.02 0.47 + 0.03 0.48 + 0.02	0.51 ± 0.04 0.41 ± .02 0.40 + .02	
B	PEFP (cm of water)	Baseline 4 7	7.5 + 0.6 6.8 + 0.7 7.6 + 1.2	7.8 ± 0.7 6.1 ± .40 5.7 + .60	
C	PIP (cm of water)	Baseline 4 7	33.50 + 1.4 33.9 + 1.8 34.8+1.4	33.2 ± 1.2 30.3 ± 1.2 31.5 + 1.1	
D	PaO_2 (mm Hg)	Baseline 4 7	84.0 + 3 82 + 2 74 + 4	81 ± 3 92 ± 5 92 + 3	
E	Minute ventilation	Baseline 4 7	8.9 + 0.9 9.1+ .3 9.1 + 1.4	10.6 ± 0.8 9.8 ± .7 8.4 + .9	
F	PaO_2/FiO_2	Baseline 4 7	158.49+66.8 174.46+64.6 154.16+65.4	158.82+78.6 224.39+66.2 230.54+73.4	>0.1 <0.001

Table shows that the difference of PaO_2 / FiO_2 ratio (measure of gas exchange) at the base line between both groups was not significant ($p >0.05$) but after 7 days of therapy, gas exchange was improved significantly in group II.

Also, as seen in Figure 2.1, 2.2 and 2.3, the difference in baseline values of biochemical markers used was not significant, but after 7 days of therapy there was marked reduction in values of all the markers which is statistically significant *(Table 2.2)*.

Figure 2.1: Biochemical Markers
C-Reactive Protein

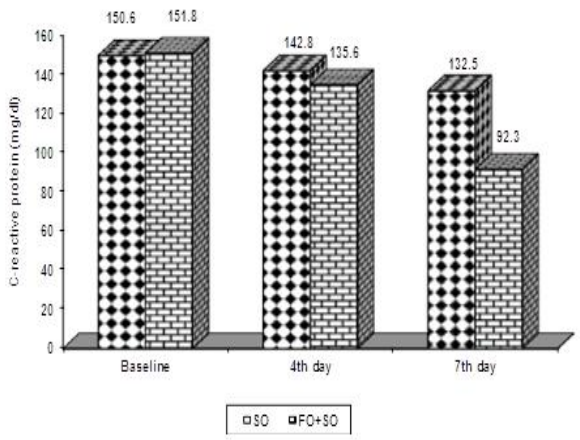


Figure 2.2: Biochemical Markers
Serum Lactate

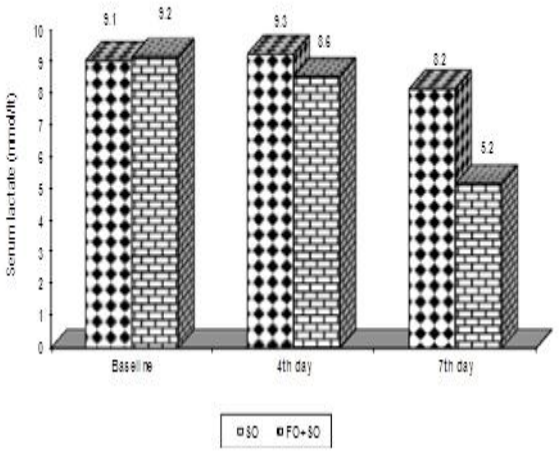


Figure 2.3: Biochemical Markers
Procalcitonin

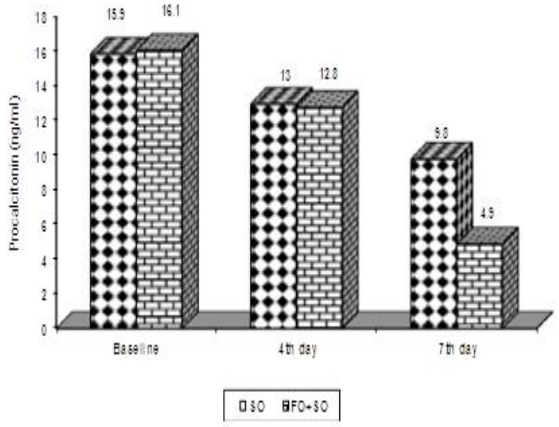


Table 2.2: Biochemical Markers

Sl.No.	Marker	Study day	Group I (SO) (n=35)	Group II (FO+SO) (n=35)	p
1.	C-reactive protein (mg/dl)	Baseline 4 7	150.6 + 63.4 142.8 + 88.1 132.5 + 65.3	151.8 + 79.8 135.6 + 88.2 92.3 + 73.6	>0.1 <0.02
2.	Procalcitonin (ng/ml)	Baseline 4 7	15.9 + .68 13.0 + .36 9.8 + .35	16.1 + 8.2 12.8 + .24 4.9 + .52	>0.1 <0.001
3.	Serum lactate (mmol/l)	Baseline 4 7	9.1+0.68 9.3+ 0.24 8.2 + 0.32	9.2 + 0.76 8.6 + 0.11 5.2 + 0.50	>0.1 <0.001

Table shows that the difference in baseline values of biochemical markers used was not significant but after 7 days of therapy there was marked reduction in values of all the markers which is statistically significant. (p <0.05).

The mean duration of days on ventilator in Group I was 16.9 days whereas in Group II it was 12.4, the difference was statistically significant (*Figure3.1*). The duration of intensive care unit stay in Group I was 21.2 days vs. 15.3 days in Group II which is a statistically significant difference (*Figure3.2*). There was a significant difference in the mean duration of hospital stay in both the groups: Group I with 36.3 days and Group II- 29.2 days. The mortality though lesser in Group II (17.14%) as compared to Group I (25.71%) was not statistically significant. The incidence of new organ failure was also lesser in Group II as compared to Group I *(Figure3.3)* and the difference was statistically significant (p= 0.02).

Figure 3.1: Time on Ventilator(Days)

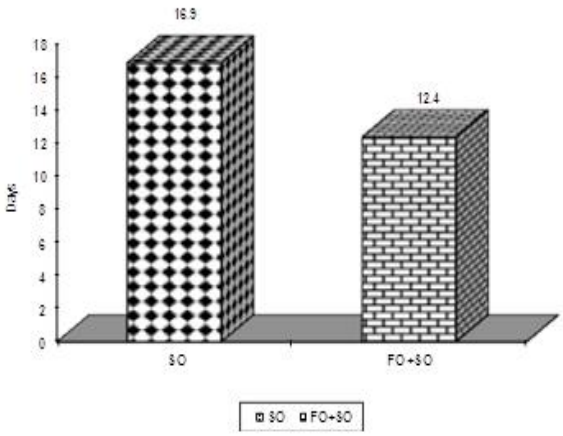


Figure 3.2: Intensive care Unit Stay (Days)

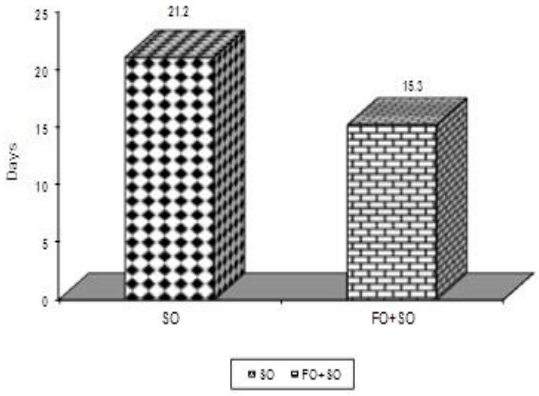
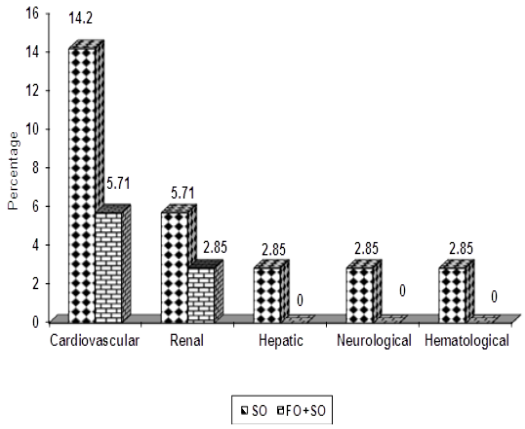


Figure 3.3: Organ system Failure



DISCUSSION

Dietary supplements of omega-3 fatty acids have long been used to influence chronic inflammatory disorders. Recent studies with an immune-enhancing diet partly based on omega-3 fatty acids report beneficial effects in patients with acute hyper-inflammatory diseases, such as the sepsis syndrome or adult respiratory distress syndrome (ARDS). The possible suppression of exaggerated leucocyte activity, the improvement of microcirculatory events, as well as the opportunity to administer intravenous lipids enriched in omega-3 fatty acids signal the possibility of a combination of parenteral caloric support and pharmacological intervention. Using parenteral administration of fish oil-based lipids, a new rapid and highly effective anti-inflammatory agent may allow the option to alter the immune status in hyper-inflammatory diseases such as sepsis and ARDS.

The present study was designed to evaluate the impact of Omega-3 fatty on days on ventilator, length of ICU stay, length of stay in hospital, mortality percentage and incidence of new organ dysfunction in severe sepsis cases in a prospective, randomized, controlled manner.

One of the most important clinical findings in this study was the significant improvement in gas exchange and result and reduction in ventilatory support in patients on omega-3 fatty acids. There was a marked improvement in the PaO_2 / FiO_2 ratio from baseline to study day 7. In contrast, patients on soyabean based parenteral nutrition did not show an improvement in oxygen status, as the PaO_2 / FiO_2 ratio remained to baseline values through study day 7. In addition, patients on omega -3 fatty acids were able to significantly increase their PaO_2 compared with contrast by study day 7. The increase in PaO_2 was accompanied by a decrease in FiO_2, PEEP and minute ventilation in this group. In contrast, patients receiving the soyabean based nutrition were found to have their PaO_2 decrease despite maintenance of FiO_2 and a slight increase in PEEP and minute ventilation, reflecting persistent pulmonary inflammation. These findings in ARDS patients parallel those observations in a pig model of sepsis induced ARDS.[4] Gadek et al.[5] also reported improved oxygenation in patients with ARDS on omega-3 fatty acid therapy.

In our study, no significant differences were noticed in starting CRP levels (151.8 ± 79.8 mg/dl in FO + SO group vs 150.6 ± 63.4 in SO group), Procalcitonin levels (16.1 ± 0.82 ng/ml in FO + SO group vs 15.9 ± 0.68 ng/ml in SO group) and serum lactate levels (9.2 ± 0.76 mmol/L in FO + SO group vs 9.1 ± 0.68 mmol/L in SO group).

After 7 days of therapy there was marked reduction in levels of all these biochemical markers in FO + SO group in comparison to SO group. Results are comparable to study conducted by Grecu et al.[6] (2003) who demonstrated that infusion of a mixture of SO and FO (66%: 33% by vol.) over 5 days significantly decreased serum C-reactive protein concentrations in patients with abdominal sepsis; parenteral. So alone did not significantly alter the CRP concentration. In a study by Mayer et al.[7] (2003), septic patients who were intolerant of enteral nutrition received an SO based emulsion or an emulsion containing FO for 5 or 10 days. Serum CRP levels tended to be lower in patients who received FO.

This study showed significant reduction in days on ventilator, intensive care unit stays and length of stay in hospital in FO + SO group vs SO group. Gadek et al.[5] reported reduced days on ventilator, length of stay in intensive care unit in patients of ARDS on omega-3 fatty acid therapy. Grecu et al.[6] (2003) reported significantly lower intensive care unit stays and hospital stays in patients who received FO (as a 66% SO and 33% FO mix) than in those who received SO. Heller[2] et al.[8] included 268 patients with abdominal sepsis in their study of parenteral omega-3 PUFA infusion. They found a significantly lower lengths of intensive care unit and hospital stay in those patients receiving >0.05 of FO/kg per day than in those receiving less than this.

In our study mortality was 17.14% FO + SO group vs 25.75% in SO group and the difference is not significant. Grecu et al.[6] (2003) also reported that there was no difference in mortality between the 2 groups.

It must be noted that the persistence of inflammation in ARDS results in additional nonpulmonary organ dysfunction that contributes to excess mortality rates. Although respiratory failure usually precedes other organ failures, ARDS and multiple organ failure are closely linked. Primed neutrophils and the unregulated release of inflammatory mediators circulate throughout the body, activating a systemic inflammatory response syndrome. Each organ can be affected by these mediators, resulting in local or generalized tissue injury. An important finding in this trial was that patients infused with omega-3 FA developed significantly fewer instances of new organ failures while in the study compared with those given the control diet. This further supports the concept that the anti-inflammatory effects of omega-3 FA may modulate the systemic inflammatory response as well as neutrophil mediated lung injury.

In conclusion, our prospective evaluation provides evidence that supplementation of fish oil provides evidence that derived ω-3 fatty acids improves gas exchange, arterial oxygenation, reduces oxygen requirement, hence reducing the requirement of ventilation, ICU and hospital stay as compared to lipids supplementation with soybean oil alone.

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