



Original Research

Parenteral nutrition effects of Omega-3 fatty acids on C-reactive protein, high-density lipoprotein, lymphocyte characteristics and the treatment of critically ill patients

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Abstract: To study the effects of omega-3 fatty acid parenteral nutrition on the nutrition, inflammatory responses, immunity and prognoses of critically ill cancer patients. A total of 80 critically ill cancer patients were randomly divided into an observation group and a control group, 40 cases in each group. Both groups of patients received equal-nitrogen and equal-calorie enteral and parenteral nutrition. The observation group, on this basis, was added with omega-3 fatty acid parenteral nutrition. The weekly nutritional status measures, inflammatory response measures, immune function measures and prognosis measures (ICU mortality, ICU stay, infectious complications) of the two groups were observed. The nutrition, inflammatory response and immune measures of the observation group were improved compared with the control group. The ICU stay in the observation group was shorter than the control group. Compared with the control group, the ICU mortality rate and infectious complication rate were lower in the observation group, but the differences were not significant (P mortality = 0.13, P infection rate = 0.165). Omega-3 fatty acid parenteral nutrition could improve patients' nutritional status and immune function, reduce the body's inflammatory responses and shorten the length of hospital stay, but couldn't significantly improve ICU mortality and reduce the incidence of infectious complications.

Key words: Omega-3 fatty acids; Parenteral nutrition; Critical illness; Cancer patients.

Introduction

The invasion of malignant tumours and some invasive treatment procedures such as surgery, radiotherapy and chemotherapy for malignant tumours often result in malnutrition and decreased immunity of patients and various complications. Severe cases may even have respiratory failure, sepsis, acute renal failure, cardiac and respiratory arrest, requiring to be transferred to the ICU for emergency treatment. Studies have indicated that the mortality rate of these critically ill cancer patients transferred to the ICU depends mainly on the severity of organ failure, the physical performance and state, and whether mechanical ventilation is required, rather than cancer-related characteristics (1, 2). In recent years, omega-3 fatty acids in fish oils have attracted much attention. The fatty acids not only can improve patients' nutritional status, achieve immune regulation, reduce inflammation and protect organ function by regulating lipid transmitters, but also can prevent and control osteoporosis and play a potential inhibiting role in certain tumours (3,4). There are few reports simultaneously monitoring the nutritional status, inflammatory responses, immune function and prognoses of critically ill cancer patients treated with omega-3 fatty acid parenteral

nutrition. This study analysed and explored the role of omega-3 fatty acid parenteral nutrition in such patients.

Materials and Methods

Clinical data

A total of 80 critically ill cancer patients transferred to the ICU from January 2017 to December 2018 were included in this study, including respiratory failure 39 cases, heart failure 6 cases, septic shock 15 cases, coma after cardiopulmonary resuscitation (CPR) 14 cases, and acute renal failure 6 cases. Inclusion criteria: (1) Patients who had scores ≥ 4 points with indications for nutritional support according to the Nutrition Risk Screening 2002 (NRS 2002). (2) Hospital stay ≥ 2 weeks. (3) Gastrointestinal function exists; a nasogastric tube and a deep venous catheter can be placed. (4) The patient's family members gave informed consent. Exclusion criteria: (1) Non-neoplastic critically ill patients. (2) patients transferred to the ICU for post-anaesthesia recovery after cancer surgery. (3) Patients who had contraindications for enteral nutrition, such as intestinal obstruction and severe abdominal distension. The patients were randomly divided into two groups, an observation group and a control group, according to the order



when they were transferred to the ICU, 40 cases in each group. The observation group consisted of 25 males and 15 females, aged (52.63±16.74), BMI (21.27±4.25) kg/m² and the APACHE II score (17.3±2.87) points. The control group consisted of 23 males and 17 females, aged (49.65±17.15), BMI (20.9±4.19) kg/m², and the APACHE II score (16.5±3.06) points. The disease composition of the two groups (observation/control): respiratory failure (20/19 cases), heart failure (3/3 cases), septic shock (7/8 cases), coma after CPR (7/7 cases), and acute renal failure (3/3 cases). There were no significant differences in sex composition, age, BMI, APACHE II score, and disease composition between the two groups.

Methods

The two groups of patients were given a nasogastric tube for enteral nutrition within 24 to 48 hours after the transfer to the ICU. Enteral liquid nutrition was provided by the Nutrition Department and was pumped through the nasogastric tube, and then the supply would be gradually increased according to the patient's tolerance. Insufficient calories and protein content were supplemented by parenteral nutrition until the supply reached the basic energy (25 kcal/(kg·d)) and protein (25 kcal/(kg·d)) demand.

The control group received routine nutrition care. The observation group, on this basis, was also given the Omega-3 Fish Oil Fat Emulsion Injection (Approval No. J20150040, specification 10 g/100 ml), 100 ml, IV drip, once a day, the IV flow rate not exceeding 0.5 ml/kg, continuously treated for 2 weeks.

Observation measures

Blood specimen collection was performed on d1, d7 and d14 after the patients' transfer to the ICU and the specimens were sent to the Clinical Laboratory of our hospital for testing. (1) Nutritional status measures: albumin (ALB), prealbumin (PA), cholesterol (CHO), triglyceride (TG), high-density lipoprotein (HDL-C), and low-density lipoprotein (LDL-C). (2) Inflammatory response measures: C-reactive protein (CRP) and high-sensitivity C-reactive protein (hs-CRP). (3) Immune function measures: peripheral blood total lymphocyte count (TLC), T lymphocyte subsets (CD3, CD4 and the CD4/CD8 ratio). (4) Prognostic measures: ICU mortal-

ity, ICU stay, and whether new infectious complications occur.

Statistical analysis

SPSS 21.0 statistical software was used for data analysis. Measurement data were expressed by $\bar{x} \pm s$. Repeated measurement data ANOVA was used for repeated measurement data comparison. The group's t-test was used for comparison between groups at the same time point. Count data were expressed by (n, %) and compared by the χ^2 test. $P < 0.05$ was considered statistically significant.

Results

Nutritional status measures

There were statistically significant differences in the average values of ALB, PA, CHO, TG and HDL-C between the two groups at different time points after nutrition support (average $P_{\text{time}} < 0.01$). There was an interaction between the observation group and time points (average $P_{\text{interaction}} < 0.05$). As the treatment time prolonged, the levels of ALB, PA, CHO, TG and HDL-C showed an upward trend. On d14, the levels of ALB, PA and HDL-C of the observation group were higher than the control group, and the levels of CHO and TG were lower than the control group (average $P < 0.05$). There was no significant change in LDL-C between the two groups over time, and the difference was not statistically significant ($P = 0.82$) (Table 1).

Inflammatory response measures

There were statistically significant differences in the average values of CRP and hs-CRP between the two groups at different time points after nutrition support (average $P_{\text{time}} < 0.01$). There was an interaction between the observation group and time points (average $P_{\text{interaction}} < 0.05$). As the treatment time prolonged, the levels of CRP and hs-CRP showed a downward trend. On d14, the levels of CRP and hs-CRP of the observation group were both lower than the control group (Table 2).

Immune function measures

There were statistically significant differences in the average values of TLC, CD4 and CD4/CD8 between

Table 1. Comparison of nutritional measures between the two groups.

Item	Group	d1	d7	d14	F _{time}	F _{between-group}	F _{interaction}
ALB (g/L)	Observation	25.37±2.25	30.65±1.98	35.41±2.32 [▲]	189.37 [#]	18.99 [*]	7.68 [#]
	Control	25.47±2.34	28.11±1.34	30.68±1.57			
PA (mg/L)	Observation	106.5±20.6	160.7±10.6	222.8±16.5 [▲]	102.28 [#]	15.90 [#]	6.84 [#]
	Control	105.6±21.4	126.7±13.7	174.7±15.2			
CHO (mmol/L)	Observation	1.96±0.24	2.68±0.23	3.54±0.22 [▲]	184.22 [#]	10.77 [*]	5.99 [*]
	Control	1.94±0.34	3.18±0.24	4.19±0.39			
TG (mmol/L)	Observation	1.02±0.23	1.61±0.16	1.79±0.16 [▲]	566.26 [#]	5.37 [*]	32.58 [#]
	Control	0.99±0.25	2.04±0.25	2.27±0.27			
HDL-C (mmol/L)	Observation	0.69±0.21	1.13±0.16	1.25±0.19 [▲]	113.45 [#]	7.25 [*]	13.48 [#]
	Control	0.89±0.18	0.91±0.13	0.98±0.18			
LDL-C (mmol/L)	Observation	1.89±0.18	1.92±0.19	1.93±0.19	2.29	0.06	0.51
	Control	1.89±0.22	1.97±0.24	1.91±0.21			

Note: * $P < 0.05$; [#] $P < 0.01$; compared with the control group, [▲] $P < 0.05$.

Table 2. Comparison of inflammatory response measures between the two groups before and after treatment.

Item	Group	d1	d7	d14	F _{time}	F _{between-group}	F _{interaction}
CRP	Observation	103.61±38.38	31.91±13.96	10.95±4.33 [▲]	81.50 [#]	5.39*	5.29*
	Control	109.47±40.32	64.81±23.98	35.61±18.65			
hs-CRP	Observation	15.07±5.73	7.43±1.23	3.89±1.77 [▲]	172.52 [#]	9.95*	10.09*
	Control	15.14±4.90	10.29±1.70	8.24±1.15			

Note: *P < 0.05; [#]P < 0.01; compared with the control group, [▲]P < 0.05.

Table 3. Comparison of immune function measures between the two groups before and after treatment.

Item	Group	d1	d7	d14	F _{time}	F _{between-group}	F _{interaction}
TLC (×10 ⁹ /L)	Observation	0.88±0.29	1.34±0.29	1.85±0.33 [▲]	268.38 [#]	5.56*	9.55 [#]
	Control	0.89±0.29	1.12±0.19	1.56±0.32			
CD4 (%)	Observation	29.71±3.25	36.19±6.29	39.48±7.09 [▲]	109.35 [#]	5.51*	10.01 [#]
	Control	29.57±4.05	32.09±5.75	35.26±6.75			
CD8 (%)	Observation	18.59±4.81	24.04±7.63	22.03±7.99	2.57	0.16	1.15
	Control	18.38±4.59	19.78±11.53	23.23±3.47			
CD4/CD8	Observation	1.39±0.39	1.98±0.33	2.68±0.54 [▲]	292.98 [#]	6.05*	18.51 [#]
	Control	1.43±0.29	1.63±0.37	2.19±0.49			

Note: *P < 0.05; [#]P < 0.01; compared with the control group, [▲]P < 0.05.

Table 4. Comparison of prognostic measures between the two groups.

Group	Mortality (case (%))	ICU stay (d)	Infectious complication rate (case (%))
Observation	17(37.78)	16	11(24.44)
Control	21(46.67)	21	18(40.00)
t/x ² value	0.616	-5.643	1.925
P-value	0.431	0.000	0.164

the two groups at different time points after nutrition support (average P_{time} < 0.01). There was an interaction between the observation group and time points (average P_{interaction} < 0.01). As the treatment time prolonged, the levels of TLC, CD4 and CD4/CD8 showed an upward trend. On d14, the levels of TLC, CD4 and CD4/CD8 of the observation group were higher than the control group. There was no significant change in CD8 between the two groups over time, and the difference was not statistically significant (P = 0.82) (Table 3).

Comparison of prognostic measures

The ICU mortality and infectious complication rates in the observation group were lower than the control group, but the differences were not statistically significant (P > 0.05). The ICU stay of the observation group was shorter than the control group, and the difference was statistically significant (P < 0.05) (Table 4).

Discussion

Due to the consumption and invasion of tumour diseases and the injuries brought by various treatment procedures, cancer patients often have a process of fat and muscle consumption and weight loss, resulting in malnutrition, low immunity, poor tolerance to treatment and high mortality.^(5,6) Clinical studies have preliminarily shown that omega-3 fatty acids can improve the prognosis of critically ill patients (7,8). In addition, the fatty acids can also improve the inflammatory responses and nutritional status of malignant tumour patients, enhance their immune function and the sensitivity and tolerance to tumour radiotherapy and chemotherapy, and inhibit tumour growth. This study compared the clinical data

of critically ill cancer patients with and without omega-3 fatty acid treatment, and analysed their measures in nutritional status, immune function, inflammatory responses and prognoses.

In terms of nutrition, critically ill cancer patients are often in a state of high catabolism. Providing omega-3 fatty acids may inhibit the production and release of inflammatory factors, shortening the time of high catabolism and reducing nutritional consumption (9,10). The results of this study found that as the treatment time prolonged, the levels of ALB, PA, CHO, TG and HDL-C increased in both groups. In the later stage, the levels of ALB, PA and HDL-C of the observation group were all significantly higher than the control group, but the levels of CHO, TG and LDL-C were lower than the control group, indicating that these patients' nutritional status was improved after nutritional support. The observation group using omega-3 fatty acids showed more significant improvement than the control group in the later stage, and the treatment didn't cause an excessive elevation of blood cholesterol, triglyceride, and low-density lipoprotein, indicating that omega-3 fatty acids had a better performance in the nutrition improvement of critically ill cancer patients.

In terms of inflammatory responses, critically ill cancer patients, due to infection and various complications, often face the release of tumour necrosis factors, interleukin-1, leukotrienes and thromboxanes, resulting in systemic inflammatory response syndrome (SIRS). CRP and hs-CRP are elevated when infection and inflammatory responses are aggravated, and dynamic observation can reflect patients' inflammatory response status. Berger *et al.* (11) found that omega-3 fatty acids could produce two kinds of lipid regulators, protectins

and resolvins, with strong anti-inflammatory and tissue repair promoting activity. This study showed that the levels of CRP and hs-CRP had a downward trend in both groups after treatment. The decrease of PCT, CRP and hs-CRP in the observation group was more significant than the control group ($P < 0.05$), indicating that omega-3 fatty acids could reduce the production and release of inflammatory mediators in critically ill cancer patients and thus reduce their inflammatory responses.

Lymphocytes are important immune cells in the body. When peripheral blood lymphocytes, CD4 cells and CD4/CD8 are low, multiple opportunistic infections or tumours may occur. In this study, as the treatment time prolonged, the levels of TLC, CD4, and CD4/CD8 showed an upward trend with no significant change of CD8, but the increase of TLC, CD4, and CD4/CD8 of the observation group was more significant than the control group ($P < 0.05$). However, the meta-analysis by MANZANARES *et al.* (12) suggested that the addition of omega-3 fatty acids didn't benefit critically ill patients, and may even increase additional damage and increase mortality. Consequently, in the 2016 International Treatment Guidelines for Sepsis and Septic Shock, omega-3 fatty acids were not recommended as the immunity enhancer for patients with sepsis (13,14). Therefore, for cancer patients with sepsis, caution should be exercised when using omega-3 fatty acids to enhance immune function.

In recent years, there have been many studies on whether omega-3 fatty acids can improve the prognosis of critically ill patients. A foreign meta-analysis by Sabater *et al.* (15) showed that supplementation with omega-3 fatty acids could reduce ICU stay and mechanical ventilation, but it didn't significantly affect mortality. The study by HOFMAN *et al.* (16) compared medical patients receiving immunomodulatory nutritional therapy and those receiving high-protein nutritional therapy. The results showed that though there was no significant difference in the 28-day mortality, the immunonutrition group had a significantly better performance than the normal diet group in the 6-month mortality. This study showed that the ICU stay of the observation group was significantly shorter than the control group ($P < 0.01$). The ICU mortality and infectious complication rates in the observation group were also lower than the control group, though without significant differences. The results were similar to recent studies. The reason why the length of ICU stay was shortened but the ICU mortality was not improved or even rose was unclear. The possible mechanism was that in the early stage of the transfer to the ICU, some patients who had been already highly immunosuppressed after the use of omega-3 fatty acids suffered excessive inhibition of inflammation as well as persistent inflammation, immunosuppression, and catabolism syndrome (PICS) which brought chronic inflammation, acquired immunosuppression and secondary nosocomial infection, etc., resulting in unimproved or even higher mortality. Focusing on patients' fatty acid levels, Piper *et al.* (17) tested the serum-free fatty acid profile of sepsis patients using fish oils and found that the eicosapentaenoic acid (EPA) level in patients' serum increased significantly while the arachidonic acid (AA) level decreased. However, due to the small sample size, whether it can increase or decrease the survival rate still

needs further clinical research.

There are more and more studies testing the fatty acid profile in the blood of various types of patients to explore its association with various diseases (18,19). Adding omega-3 fatty acids to patients with different ratios of the fatty acids profile may lead to different clinical outcomes. Due to limited experimental conditions, this study didn't monitor the fatty acid profile in critically ill cancer patients, and subsequent studies are needed. In addition, the sample size of this study is not large enough, and the single-center study may have a partial impact on the results, so large-sample-size and multi-center systematic research are still needed for further verification.

In this study, we looked at the effects of omega-3s on cancer treatment. Therefore, it should be noted that due to the genetic and environmental nature of cancer agents, it is necessary to examine the genetic and nutritional factors and other fatty acids (20-24). Also, omega-3 comes in a variety of forms and can also be obtained from plant sources such as *Camelina sativa* (, other omega-3s from plant sources, especially *C. sativa*, need to be considered (25-32).

In summary, the use of omega-3 fatty acid parenteral nutrition can improve the malnutrition status in critically ill cancer patients, reduce inflammation, regulate immune function, and reduce ICU stay, but it has no significant effect on ICU mortality and infectious complication rate. For the question about how to use omega-3 fatty acid-based parenteral nutrition according to the serum fatty acid profile of critically ill cancer patients, further basic and clinical studies are still needed to determine.

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