The effects of multi-oil fat emulsion on older patients with gastric cancer.

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Abstract

Objective: To explore the effect of Multi-oil Fat Emulsion (SMOF) in perioperative parenteral nutritional support on older patients with gastric cancer.

Methods: 120 patients with gastric cancer were evenly and randomly assigned to Control, Intralipid and SMOF group. Nutritional status, immune function and liver function in three groups were compared among 0 dpo (day post operation), 3 dpo and 7 dpo. Complications, length of stay and hospital costs were analyzed, as well.

Results: Significant differences were observed in nutritional status, immune function and liver function among three groups during perioperative period. After surgery, ALB, PAB, TF in Intralipid and SMOF group were significantly higher than in that Control group (P<0.01). CD3, CD4, CD4/CD8, IgA, IgG, IgM levels after surgery in SMOF group were significantly higher than in that Control and Intralipid group (P<0.05). CRP and IL-6 and TBIL levels of 7 dpo in SMOF group were significantly lower than other two groups, especially Intralipid group (P<0.01). SMOF group had the lowest complication incidence (P<0.05).

Conclusion: SMOF in perioperative parenteral nutritional support contributes to older gastric cancer patients with significantly improved immune function, reduced complications and without increasing hospital costs. A Cohort study with greater patient numbers is needed.

Keywords: Multi-oil fat emulsion, Older patients, Parenteral nutritional support, Gastric cancer, Immune function, Complications.

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Introduction

Gastric cancer is the second most frequent cause of cancer death and the fourth most common cancer, which used to be developed from initial chronic gastritis, atrophy, intestinal metaplasia and even dysplasia [1]. According to the International Agency for Research on Cancer (IARC), gastric cancer accounted for an estimated 700,000 deaths and 934,000 new cases per year in 2002 (8.6% of new cancer cases) [2]. Gastric cancer has been reported to correlate with several environmental factors, such as, excessive intake of salt, bile reflux, N-nitroso compounds, a deficiency of antioxidants, and Helicobacter pylori [3]. Recent study illustrated that Helicobacter pylori was a major cause of gastric cancer, which was responsible for 5.2% of the 12.7 million total cancer cases worldwide in 2008 [4]. Though the incidence and mortality rate have been decreasing over recent decades [5], the real cause of gastric carcinogenesis is yet not fully understood.

To date, nutritional support has become a standard of care for hospitalized patients, with decreasing postoperative morbidity and decreasing mortality [6-8], especially the older patients. More than two thirds of gastrointestinal cancers and 70% of all deaths from malignant tumors occurred in patients ≥ 65 years [5,9]. Parenteral nutritional support is better tolerated than enteral nutritional support [8] and highly efficacious in reversing those events attributed to simple starvation [10]. Moreover, one of the main aims of perioperative nutrition is the boost of the immune response through administration of specialized nutrients, even in well-nourished patients [11]. However, conclusions on lipid emulsion were inconsistent.

In the present study, we aimed to investigate the effect of Multi-oil Fat Emulsion in perioperative parenteral nutritional support on older gastric cancer patients. Nutritional status, immune function and liver function during perioperative period, complications, length of stay and hospital costs were analyzed in patients with different nutritional support.

Materials and Methods

Subjects

The present study was approved by the ethics committee of the First Affiliated Hospital of Fujian Medical University, performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient before enrollment. One hundred and twenty older patients (>65 years) with gastric cancer were recruited in our study from January 2014 to December 2015. All patients are in accord with criteria, as follows.

Inclusion criteria:

- 1. Every patient was screened by nutritional risk assessment after admission and has a mean score ≥ 3 .
- 2. Patients with normal kidney and liver function before operation.
- 3. Patients didn't receive any hormones, immunostimulants, immunosuppressants, radiotherapy or chemotherapy treatment six month before operation.
- 4. Patients at stage II or III in accord with the 2014 National Comprehensive Cancer Network guidelines and diagnosed by endoscopy, CT and pathological examination.

Exclusion criteria:

- 1. Patients with hemoglobin (HGB <90 g/L) or albumin (ALB <25 g/L).
- 2. Patients with serious complications, such as, pyloric obstruction, gastrointestinal bleeding and electrolyte imbalance.
- 3. Patients with cirrhosis, portal hypertension or hypersplenism.
- 4. Patients with severe cardiovascular disease, including heart failure, hypertension with pressure more than 160/100 and so on.
- 5. Patients with severe diabetes, poor perioperative glycemic control.
- 6. Patients with chronic diseases and other allergic diseases.
- 7. Patients with BMI >28.
- 8. Patients with operative time >3 h and intraoperatve blood loss>800 ml.
- 9. Patients with spleen resection.

Grouping and nutritional support

The study is a prospective, randomized and single-blinded trial. In accordance with the random number table, all individuals (n=120) were evenly divided into Control group, Intralipid group and SMOF group. Control group received no nutritional support before operation. Intralipid group and SMOF group were given 20% intralipid and 20% SMOF with equal energy by subclavian vein catheterization 7 days before operation, respectively. Three groups were given same nutritional support with 20% intralipid on 2 to 7 dpo. Different nutritional support programs with a total energy 105 KJ•kg-1•d-1 (fat emulsion 40% and glucose 60%) and amino acids in accordance with hot nitrogen ratio 418 KJ: 1g were carried out in three groups. During hospitalization, all patients were given electrolytes, water-soluble fat-soluble vitamins or trace elements, as appropriate.

Sampling and measurement of chemical parameters

Venous blood samples were collected on the first day of admission, 0 dpo, 3 dpo and 7 dpo. Alanine aminotransferase (ALT), total bilirubin (TBIL), blood albumin (ALB) and interleukin (IL-6) were measured by automatic biochemical analyzer (Model OLMPUS AU2700, OLMPUS, Tokyo, Japan). Prealbumin (PAB), Transferrin (TF), C-reactive protein (CRP), immune proteins (IgA, IgG and IgM) were measured by Special protein analyzer (Model Array360, Beckman-Coulter, USA). T lymphocyte subsets (CD4, CD8, CD3 and CD4/CD8) were analyzed by flow cytometry (Beckman-Coulter Epics XL, Beckman-Coulter, USA).

Statistical analysis

Statistical analysis was performed using SPSS (version 16.0). Data were expressed as means \pm standard deviation (SD). Comparisons of the quantitative data among groups were conducted using One-way analysis of variance (ANOVA) followed by SNK test. Measurement data before and after treatment in one group were compared using the t test. Comparisons of the enumeration data were conducted using χ^2 or Fisher's exact test as appropriate. A P value, P \leq 0.05 or P \leq 0.01, was considered as statistically significant.

Results

Clinical data analysis of older gastric cancer patients

To figure out patients' health status, clinical data of gastric cancer patients in three groups were collected on the first day of admission (Table 1). As shown, there were no significant differences in sex, age and BMI among three groups (P>0.05). Mean age in patients of Control, Intralipid and SMOF group was 70.78 \pm 4.13, 69.48 \pm 3.11, 71.33 \pm 4.80 years, respectively. No significant differences were observed in nutritional status parameters (ALB, PAB, TF), liver function parameters (CD3, CD4, CD8, CD4/CD8, IgA, IgG, IgM, CRP, IL-6), as well (P>0.05).

Table 1. Clinical parameters analysis in older patients with gastric cancer.

	Control	Intralipid	SMOF	P value
Male/Female	26/14	24/16	23/17	0.78
Age	70.78 ± 4.13	69.48 ± 3.11	71.33 ± 4.80	0.12
BMI	20.57 ± 1.00	20.09 ± 1.54	19.84 ± 1.56	0.60
PAB (mg/L)	204.01 ± 51.02	199.6 ± 43.0	205.35 ± 44.61	0.68
TF (g/L)	1.88 ± 0.47	1.85 ± 0.54	1.90 ± 0.57	0.86
ALB (g/L)	32.52 ± 4.34	32.63 ± 4.88	32.18 ± 4.04	0.56
ALT (U/L)	22.69 ± 7.40	24.33 ± 7.59	22.05 ± 7.68	0.41
TBIL (mmol/L)	13.84 ± 6.34	13.75 ± 4.91	14.33 ± 5.59	0.90

CD3 (%)	50.12 ± 11.05	50.88 ± 9.51	52.14 ± 8.72	0.84
CD4 (%)	31.51 ± 5.52	31.32 ± 6.36	32.88 ± 4.72	0.46
CD8 (%)	22.61 ± 5.03	21.88 ± 5.89	22.18 ± 4.89	0.55
CD4/CD8	1.38 ± 0.45	1.44 ± 0.44	1.53 ± 0.44	0.46
IgA (g/L)	1.30 ± 0.59	1.28 ± 0.60	1.24 ± 0.66	0.79
lgG (g/L)	7.76 ± 2.26	7.53 ± 2.21	7.20 ± 2.34	0.39
IgM (g/L)	0.88 ± 0.41	0.87 ± 0.39	0.86 ± 0.41	0.88
CRP (mg/L)	4.71 ± 2.01	4.57 ± 1.86	5.36 ± 2.45	0.24
IL-6 (pg/L)	4.18 ± 2.29	4.68 ± 2.34	4.92 ± 2.59	0.49

Note: Multi-oil Fat Emulsion (SMOF), Body Mass Index (BMI), Prealbumin (PAB), Transferrin (TF), Blood albumin (ALB), Alanine aminotransferase (ALT), total bilirubin (TBIL), T lymphocyte subsets (CD4, CD8, CD3), Immune proteins (IgA, IgG and IgM), C-reactive protein (CRP), Interleukin (IL-6).

Comparison of nutritional status parameters and liver function-related factors during perioperative period

To figure out effect of different nutritional support programs on patients, nutritional status and liver function related parameters were measured on 0 dpo and 3 dpo and 7 dpo (Table 2).

Table 2. Comparison of nutritional status parameters.

		0 dpo	3 dpo	7 dpo
	PAB (mg/L)	208.63 ± 52.17	178.65 ± 32.20**	202.4 ± 32.93 ^{&&}
	TF (g/L)	1.92 ± 0.48	1.57 ± 0.31**	$1.69 \pm 0.37^{*}$
Control	ALB (g/L)	33.25 ± 4.44	27.83 ± 3.09**	30.55 ± 2.95**&&
	ALT (U/L)	23.2 ± 7.57	25.88 ± 10.59	23.38 ± 13.23
	TBIL (mmol/L)	14.15 ± 6.48	16.53 ± 6.14	21.7 ± 8.14**&&
	PAB (mg/L)	231.83 ± 31.37 [△]	210.60 ± 37.29 ^{**∆∆}	236.25 ± 42.35 ^{&&∆∆}
	TF (g/L)	1.91 ± 0.42	1.81 ± 0.39 ^{∆∆}	1.88 ± 0.28 [△]
Intralipid	ALB (g/L)	32.85 ± 4.39	30.85 ± 3.17 ^{*∆∆}	34.3 ± 3.44 ^{&&∆∆}
	ALT (U/L)	24.48 ± 6.13	30.18 ± 16.86 ^{*∆}	34.8 ± 23.32 ^{**∆}
	TBIL (mmol/L)	15.03 ± 5.12	21.73 ± 12.52 ^{**∆}	32.58 ± 20.37 ^{**&& ∆∆}
	PAB (mg/L)	234.55 ± 31.67 ^{∆∆}	220.1 ± 31.2 ^{*∆∆}	238.53 ± 43.83 ^{*∆∆}
	TF (g/L)	1.94 ± 0.47	1.91 ± 0.29 ^{∆∆}	2.00 ± 0.29 ^{∆∆}
SMOF	ALB (g/L)	33.45 ± 3.80	31.4 ± 3.22 ^{*∆∆}	34.8 ± 4.01 ^{**∆∆}
	ALT (U/L)	23.75 ± 6.34	27.48 ± 12.28	25.05 ± 12.92##
	TBIL (mmol/L)	14.38 ± 6.23	17.68 ± 7.94 [*]	19.48 ± 8.14 ^{*&&##</sup></td></tr></tbody></table>}

Note: Multi-oil Fat Emulsion (SMOF), Prealburnin (PAB), Transferrin (TF), Blood alburnin (ALB), Alanine aminotransferase (ALT), total bilirubin (TBIL). *P<0.05 vs 0 dpo; **P<0.01 vs 0 dpo; [&]&P<0.01 vs 3 dpo; ^ΔP<0.05 vs Control group; ^{ΔΔ}P<0.01 vs Control group; ##P<0.01 vs Intralipid group.

For nutritional status, PAB levels of 0 dpo in SMOF group (P<0.01) and Intralipid group (P<0.05) were significantly higher than Control group, but no significant differences were observed in ALB and TF levels of 0 dpo in three groups. ALB and PAB levels of 3 dpo were significantly decreased in Control group (P<0.01), Intralipid and SMOF group (P<0.05) than that of 0 dpo. Compared with 3 dpo, ALB and PAB levels of 7 dpo were increased in Control and Intralipid group (P<0.01). No significant differences were observed in ALB and PAB levels between 3 dpo and 7 dpo in SMOF group (P>0.05). TF levels only showed significant differences in Control group (P<0.05) and there were no significant differences in Intralipid and SMOF group during perioperative period. Moreover, PAB and TF levels of 3 dpo and 7 dpo all showed the highest levels in SMOF group, followed by Intralipid group, which were significantly higher than that in Control group (P<0.01).

For liver function, ALT levels during perioperative period in Control group and SMOF group showed no significant differences, but showed a gradually increase profile in Intralipid group with the highest level 34.8 U/L on 7 dpo and 1.4 times than that 0 dpo. There were TBIL levels of 7 dpo in three groups were the highest, which significantly higher than 0 dpo (P<0.05). Meanwhile, TBIL levels in SMOF and Control group were significantly lower than that in Intralipid group (P<0.01).

Analysis of immune function in older gastric cancer patients during perioperative period

In order to figure out immune function changes, immunerelated factors were all analyzed in gastric cancer patients during perioperative period (Table 3). There were no significant differences in immune function of 0 dpo in patients of three groups (P>0.05) and in CD8 and IgM during perioperative period (P>0.05). Patients in Control group and Intralipid group showed similar immune function during perioperative period. Levels of CD3, IgA and IgG in Control and Intralipid group were both significantly decreased on 3 dpo than 0 dpo (P<0.01) and no significant differences were observed in SMOF group (P>0.05). Control and Intralipid group had no differences in levels of CD4 and CD4/CD8 during perioperative period (P>0.05), which were significantly decreased on 7 dpo in SMOF group than 0 dpo (P<0.05). Levels of IgA were significantly decreased in Control and Intralipid group on 7 dpo than 0 dpo (P<0.01) but significantly increased in SMOF group (P<0.05). Interestingly, CRP and IL-6 levels of 3 dpo during perioperative period were all the highest in three groups, followed by levels of 7 dpo, which were still higher than that of 0 dpo (P < 0.01).

Table 3. Analysis of immune function in older patients with gastric cancer.

		0 dpo	3 dpo	7 dpo
	CD3 (%)	51.25 ± 11.30	43.82 ± 10.18**	45.42 ± 8.47 [*]
	CD4 (%)	32.22 ± 5.64	29.82 ± 7.11	31.15 ± 6.36
	CD8 (%)	23.12 ± 5.14	24.41 ± 5.45	24.70 ± 5.13
	CD4/CD8	1.41 ± 0.46	1.25 ± 0.37	1.27 ± 0.40
Control	IgA (g/L)	1.33 ± 0.60	0.86 ± 0.44**	0.89 ± 0.41**
	lgG (g/L)	7.93 ± 2.31	6.02 ± 2.57**	7.15 ± 2.12 ^{&}
	IgM (g/L)	0.90 ± 0.42	0.73 ± 0.44	0.81 ± 0.44
	CRP (mg/L)	4.82 ± 2.06	27.35 ± 22.19**	24.83 ± 22.18**
	IL-6 (pg/L)	4.27 ± 2.34	25.86 ± 18.65**	20.56 ± 12.18**
Intralipid	CD3 (%)	51.87 ± 7.76	46.56 ± 10.68**	48.68 ± 9.48
	CD4 (%)	32.10 ± 6.83	31.92 ± 6.41	33.84 ± 5.47∆
	CD8 (%)	22.39 ± 4.48	22.2 ± 5.22	21.98 ± 4.95∆
	CD4/CD8	1.45 ± 0.42	1.46 ± 0.40∆	1.55 ± 0.49 ^{∆∆}
	lgA (g/L)	1.35 ± 0.51	0.92 ± 0.33**	$0.96 \pm 0.46^{**}$

	IgG (g/L)	7.74 ± 1.90	$6.64 \pm 2.50^{*}$	7.20 ± 2.20
	IgM (g/L)	0.92 ± 0.42	0.85 ± 0.46	0.87 ± 0.40
	CRP (mg/L)	5.11 ± 1.61	24.1 ± 18.58**	22.11 ± 18.76**
	IL-6 (pg/L)	4.65 ± 2.73	22.11 ± 17.08**	19.65 ± 16.46**
	CD3 (%)	50.28 ± 8.14	50.31 ± 7.41 ^{∆∆}	52.71 ± 6.25 ^{∆∆#}
SMOF	CD4 (%)	32.93 ± 6.17	33.40 ± 4.75 ^{∆∆}	35.97 ± 4.58 ^{*&∆∆}
	CD8 (%)	21.26 ± 5.14	21.45 ± 4.69∆	21.00 ± 4.04 ^{∆∆}
	CD4/CD8	1.55 ± 0.45	1.58 ± 0.54 ^{∆∆}	1.72 ± 0.46 ^{*∆∆}
	IgA (g/L)	1.27 ± 0.63	1.07 ± 0.36∆	1.28 ± 0.53 ^{*&ΔΔ##}
	IgG (g/L)	7.36 ± 2.38	7.35 ± 2.19∆	8.68 ± 2.61 ^{*&ΔΔ}
	IgM (g/L)	0.87 ± 0.41	0.98 ± 0.50∆	1.12 ± 0.36 ^{&&∆∆##}
	CRP (mg/L)	5.10 ± 2.07	14.97 ± 15.44 ^{**∆∆#}	7.64 ± 7.32 ^{**&∆∆#}
	IL-6 (pg/L)	4.55 ± 2.38	13.77 ± 10.48 ^{**∆∆##}	8.26 ± 5.93 ^{**&∆∆##}

Note: Multi-oil Fat Emulsion (SMOF), T lymphocyte subsets (CD4, CD8, CD3), Immune proteins (IgA, IgG and IgM), C-reactive protein (CRP), Interleukin (IL-6). *P<0.05 vs 0 dpo; *P<0.01 vs 0 dpo; &P<0.05 vs 3 dpo; &&P<0.01 vs 3 dpo; &P<0.05 vs Control group; &AP<0.01 vs Control group; #P<0.05 vs Intralipid group; ##P<0.01 vs Intralipid group.

In addition, SMOF group showed significantly higher levels of CD3, CD4, CD4/CD8, IgA, IgG and IgM than Control group on 3 dpo and 7 dpo, respectively (P<0.01). Levels of CD8, CRP and IL-6 were significantly decreased in SMOF group than Control (P<0.01) and Intralipid group (P<0.05) on 3 dpo and 7 dpo, respectively.

Outcome analysis in older gastric cancer patients

As shown in Table 4, there were significant differences in complications among three groups (P<0.05). SMOF group showed the smallest complication rate of 10%, which was significantly lower than Control group with complication rate of 32.5%. One patient in Control group even had anastomotic fistula with abdominal infection after surgery. No significant differences were observed in length of stay and hospital costs among three groups (P>0.05).

Table 4. Comparison of complications, Length of stay and Hospital cost among three groups.

	Control	Intralipid	SMOF	P value
Complication (n, %)	13 (32.5)	8 (20)	4 (10)	0.50
Pulmonary infection	7	5	3	0.12
Abdominal infection	2	1	1	0.38
Septicopyemia	3	1	0	0.06
Incision infection	1	1	0	0.33
Anastomotic fistula	1	0	0	0.39

Length of stay (day)	18.98 ± 5.64	21.0 ± 2.68	20.3 ± 2.29	0.06
Hospital cost (dollar)	8468.67 ± 3675.37	8396.65 ± 1364.03	8823.90 ± 1152.60	0.69
Note: Multi-oil Fat Emulsion (SI	MOF)			

Discussion

The present study aimed to compare the effect of different nutritional support, especially SMOF on older gastric cancer patients during perioperative period. Our findings demonstrated that parenteral nutritional support of SMOF contributed to older gastric cancer patients with more moderate fluctuation when compared nutritional status, immune function and liver function, and even complications among three groups.

Since parenteral nutrition used in clinical practice in 1960s, nutritional support has become a standard of care for hospitalized patients [12]. Adequate enteral based delivery of such nutrition is not possible in clinical settings, and total parenteral nutrition provides all of patient's nutritional needs intravenously and is lifesaving [13]. Due to its function of the reduction of glucose provision and the depletion of essential fatty acids, lipid emulsions used to be a highly dense energy source of parenteral nutrition and played a vital role in the resistance of inflammatory reaction, immune function, oxidative stress and coagulation functions [14]. The conventional emulsions, such as Intralipid (100% soybean oil), Liposyn II (50% soybean oil, 50% safflower oil), may consequently lead to an unbalanced fatty acid profile in cell membrane phospholipids and augment peroxidation, ultimately adversely affect immunologic functions and inflammatory events [15]. SMOF, a new type of balanced lipid emulsion with 30% medium chain triglycerides, 30% soybean oil, 25% olive oil, 15% fish oil, vitamin E and other antioxidants, should be a better parenteral nutrition for the critically ill patients, theoretically. Medium-chain triglycerides, fish oil or olive oil in various combinations may reduce negative effects of lipid emulsions on immune function and inflammation [16]. Moreover, ω -3 in SMOF lipid emulsion has been proved to effectively enhance immunologic function and reduce inflammation by affecting expression and signal pathways of cytokines [17,18], which was consistent with our findings. In our study, SMOF significantly improved percentage of T cell subsets, such as CD3, CD4 and CD8, and immunoglobulin levels, especially 7 dpo.

Though intensive studies have been carried out, conclusions on lipid emulsion used as nutrition support were inconsistent [14,15,19]. Some study suggested that SMOF used in parenteral nutrition support after surgery showed no significant differences with other medium and long chain fat emulsions, which could significantly reduce ALT, LDL and CRP levels [15]. Compared with medium and long chain fat emulsion, SMOF only significantly reduced glutamyl transpeptidase levels in Hallay's study [19]. Our finding demonstrated that SMOF application in SMOF group significantly promoted ALB, PAB, TF levels and reduced CRP, IL-6, ALT, TBIL levels, when nutritional status, liver function and immune function were analyzed. Moreover, lipid emulsion containing ω -3, for example SMOF, was helpful to reverse cholestasis and improve liver function [20]. In patients with intestinal dysfunction, ALT and TBIL levels were significantly improved after SMOF application for 4-weeks [21]. Different time treated with parenteral nutrition or different subjects may be the main causes resulting in the differences above. Older cancer patients may benefit more from long-term nutritional support [22]. Subjects in our study were all older patients with mean age >60 years. And SMOF application during perioperative period has a better therapeutic effect than Intralipid in older gastric cancer patients, which was consistent with previous studies [20,21].

Recently, total parenteral nutrition was reported to be associated with significant complications including gut atrophy and parenteral nutrition associated liver disease [13]. Acute cholecystitis was proved to be associated with the use of total parenteral nutrition after allogeneic stem cell transplantation [23]. Our present study showed a SMOF significantly improved liver function after operation. Calories trial offers confirmatory evidence that appropriate parenteral nutrition does not cause infectious complications and even could reduce postoperative complications in critically ill patients [24,25]. It is essential to explore appropriate parenteral nutrition programs for different populations.

Malnutrition is one of the significant risk factor for postoperative complications in major abdominal surgery, which correlates with perioperative morbidity and mortality [6,26,27]. The prevalence of malnutrition ranges from 30% to 50% in gastrointestinal surgery patients [26]. A low serum ALB level [6] or weight loss [28] has been considered an indicator of malnourished patient at risk of postoperative complications. Old individuals are susceptible to malnutrition and various diseases with different complications. Our results illustrated that parenteral nutrition (Intralipid and SMOF) significantly reduced perioperative complication morbidity, especially SMOF, which was consistent with previously study [29]. Moreover, nutrition intervention is predicted to be a costeffective approach in the prevention of pressure ulcer in at-risk patients [30]. No significant differences were observed in length of stay and hospital costs among three groups. Considering adverse effect of intralipid to immunologic functions and inflammatory events, all above illustrated that SMOF was an effective nutritional support in older gastric cancer patients during perioperative period. A Cohort study with greater patient numbers is needed to explore the latent effects of SMOF parenteral nutritional support on older patients.

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