Original Article

Parenteral nutrition combined with enteral feeding improves the outcome of cancer patients

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Background and Objectives: This study investigated whether total parenteral nutrition combined with enteral nutrition is associated with improved biochemical and clinical outcomes in cancer patients with gastrointestinal dysfunction. **Methods and Study Design:** From January to December 2014, the clinical data of 68 patients in a cancer ward were retrospectively collected, and these patients were classified into two groups according to nutrition delivery, through parenteral nutrition, combined with enteral nutrition more (group A) or less (group B) than 250 kcal/day. The following variables were analyzed: the route and percentage of nutritional support, total caloric intake, age, gender, body weight, body mass index, diagnosis at admission, complications of intestinal failure, modified Glasgow Prognostic Score, co-morbidities, duration of total parenteral nutrition support, performance status scale, and plasma nutritional markers. **Results:** A significant difference was observed between the two groups in functional capacity, including the Karnofsky index, World Health Organization/Eastern Cooperative Oncology Group score, body-weight loss, and serum albumin levels. However, no significant difference was observed in the modified Glasgow Prognostic Score. **Conclusions:** Cancer patients receiving total parenteral nutrition who were fed enterally more than 250 kcal/d exhibited more favorable clinical outcomes than those who were fed enterally less than 250 kcal/d. Enteral nutrition should be considered for these severely ill patients.

Key Words: performance status (PS) scale, enteral nutrition (EN), total parenteral nutrition (TPN), oncology, modified Glasgow Prognostic Score (mGPS)

INTRODUCTION

Cancer has been the leading cause of death in Taiwan for 31 consecutive years, according to the Ministry of Health and Welfare (MHW).[1] According to the MHW, each year, approximately 28% of deaths in Taiwan are related to cancer. Adequate nutrition is essential for the successful treatment of cancer patients. Malnutrition is common among cancer patients, and is caused by various factors, including decreased food intake, adverse effects from anticancer treatment, and wasteful metabolic processes.[2] Cancer-associated malnutrition has many consequences, including an increased risk of infection, reduced wound healing, reduced muscle function, and poor skin turgor resulting in skin breakdown.[3]

Nutritional supplements, including enteral nutrition (EN) and total parenteral nutrition (TPN), have been proven to be effective in improving the clinical outcomes of many types of cancer treatments and in reducing the incidence of chemotherapy complications.[4] Studies have demonstrated that appropriate nutritional support for patients diagnosed with cancer can ameliorate clinical outcomes.[5] Furthermore, most studies have suggested that EN is superior to TPN.[6-8] The preferred route of nutritional support for cancer patients is enteral, however, in most cases, EN alone cannot meet the energy needs of these patients because of gastrointestinal (GI) intolerance, which induces protein-energy malnutrition and poorer clinical outcomes.[9] At admission, these patients usually require TPN.[10]

Since its introduction by Dudrick et al[11] in the late 1960s, PN support has been considered the standard nutritional supplement for hospitalized patients requiring aggressive treatment.TPN is an effective method of delivering nutrients into the bloodstream, bypassing the usual process of eating and digestion.TPN has been proven to be lifesaving for patients diagnosed with conditions involving chronic, severe GI insufficiency, such as radiation enteritis, and whose cancer is cured or non progressive. However, TPN is reportedly associated with hyperglycemia, the development of mucosal atrophy, the loss of epithelial carrier function, an impaired immune system, and an increased risk of infection in critically ill patients.[12]

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Early EN after GI dysfunction has gained much attention in recent years. [13] A study by Sagar et al[14] in 1979 was the earliest study to compare the administration of an enteral diet during the early GI insufficiency period, against conventional therapy after major GI dysfunction.[14] However, other studies have indicated that EN is not as beneficial as expected.[15,16] It is still unclear whether EN or TPN is more effective in reducing complications and enhancing GI recovery.[17] Some authors have suggested that, regardless of the route and formula of nutrition delivery, supplying adequate nutrition is critical in severely ill patients.[18] To date, clinical experiments on TPN nutritional supplements combined with EN for cancer patients have been limited. This study investigated whether TPN combined with EN was associated with improved outcomes in cancer patients with GI dysfunction.

MATERIALS AND METHODS

Patients

This study retrospectively reviewed the clinical data of 68 patients admitted to the cancer care ward of Taichung Chung Shan Medical University Hospital, from January to December 2014, who required TPN supply owing to GI dysfunction. Furthermore, this study was conducted according to the guidelines in the Declaration of Helsinki, and all procedures involving subjects and patient recruitment were approved by the Ethical Committee of the Medicine Faculty of Chung Shan Medical University Hospital (CSMUH No: CS15122). All participants underwent standard Clinical Nutrition Support Team assessment. They were divided into two groups according to the combination of supplemental PN and EN: Group A was fed more than 250 kcal/d by EN, and Group B was fed less than 250 kcal/d by EN. The route of nutrition (enteral or parenteral) and the number of nutrient calories prescribed for each patient were recorded.

Inclusion criteria

TPN was administered to a cancer patient if the patient could not tolerate EN owing to GI dysfunction or complications for more than 5 days, or if 60% of caloric requirements could not be met through the enteral route. All patients received at least 7 days of TPN support. Patient ages ranged from 18 to 80 years, and the average BMI ranged from 16 to 26 kg/m^2.

Exclusion criteria

The exclusion criteria were HIV infection, instable vital signs, and pregnant and breastfeeding women. Patients less than 18 years old, and those who received TPN for fewer than 7 days, were also excluded.

EN and TPN

PN was infused through a central venous catheter 18–20 h/d. The total calories were determined using the Harrise–Benedict equation.[19] TPN consists of dextrose, amino acids and lipids, as well as vitamin and mineral supplements, and provides full nutritional requirements. A non-protein calorie-to-nitrogen (protein) ratio of 100–150 kcal/g of nitrogen should be maintained to ensure that amino acids are available for use as an energy source for tissue healing and repair. TPN formulations include 5–8 g/kg/d of dextrose, 0.8–2 g/kg/d of amino acids, and 1–1.3 g/kg/d of lipids. Moreover, 50% dextrose provides 3.4 kcal/g, 20% lipid emulsion provides 9 kcal/g, and 10% amino acid solution provides 4 kcal/g.

EN was administered to patients who could tolerate it. A clinical dietitian provided medical nutrition therapy and the energy intake of patients was recorded by the dietitian, whilst the dietary intake was assessed using dietary records (DRs). The 68 patients were divided into two groups that each received an EN intake more or less than 250 kcal/d.

Biochemical parameters

Several aspects reflecting the nutritional states and organ functions of the cancer patients were evaluated by analyzing specific parameters. Nutritional parameters included total protein (TP), transferrin (TF), albumin (Alb), prealbumin, and hemoglobin (Hb). Functional capacity parameters included the Karnofsky index and the World Health Organization/Eastern Cooperative Oncology Group (ECOG) score. Patients were repartitioned according to the modified Glasgow Prognostic Score (mGPS). Changes in body weight were also measured.

Postfeeding complications

The incidence of common complications, such as intestinal failure (IF), including intestinal fistulas, extensive small-bowel disease, intestinal dysmotility, and mechanical obstruction, were recorded and compared between the two groups. Table 1 lists the definitions of the complications.[20]

Statistical analyses

Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Data are presented as means and standard deviations and categorical variables as percentages. The Student's t-test and chi-square test were used to compare continuous variables and proportions. Distributions of patients per grade were compared between groups by using Fisher's exact test and compared between the first day of TPN and the last day of TPN by using the McNemar–Bowker test. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Out of a total of 72 patients, four discontinued the intervention because they could not maintain a complete food record each day and were excluded from this study. The data of the remaining 68patients were collected, and the patients were divided into two groups. Table 2 presents the patient characteristics. No significant differences were observed between the two groups regarding age, gender, diagnosis at admission, complications of IF, comorbidities, BMI, duration of TPN (d), and total daily calories (kcal/d). Patients were encouraged to take nutrition orally if they could tolerate EN. Patients in group B were provided with fewer EN calories (kcal/d) than those in group A ($p<0.005$), and patients in group A were provided with fewer TPN calories (kcal/d) than those in group B ($p<0.005$).

Table 1. Pathophysiological classification of intestinal failure

Condition	Primary mechanism of intestinal failure	Concomitant mechanisms
Intestinal fistula	Bypass of large areas of the absorptive mucosal surface	• Increased intestinal loss of fluids and electrolytes • Disruption of the enterohepatic cycle • Restricted oral/enteral nutrition or total fasting (bowel rest) to decrease fistula output • Impaired intestinal peristalsis and increased metabolic demand related to concomitant sepsis and inflammation
Extensive small-bowel mucosaldisease	Inefficient absorptive and/or nutrient-losing mucosal surface.	• Increased intestinal loss of fluids and electrolytes • Restricted oral/enteral nutrition • Disease-related hypophagia
Intestinal dysmotility	Restricted oral/enteral nutrition or total fasting from intolerance due to feeding-related exacerbation of digestive symptoms or episodes of nonmechanical intestinal obstruction	• Malabsorption due to small bowel bacterial overgrowth • Increased intestinal secretion of fluids and electrolytes in the obstructed segments • Increased intestinal loss of fluids and electrolytes due to vomiting, gastric drainage, and/or diarrhea
Mechanical obstruction	Incomplete or total fasting (bowel rest)	• Increased intestinal secretion of fluids and electrolytes in the obstructed segments • Increased intestinal loss of fluids and electrolytes due to vomiting or gastric drainage

Definition of gastrointestinal complications from L. Pironi et al (2015).[20]

Table 2. Demographic data of cancer patients receiving TPN at baseline (n =68)

	Group A TPN+EN ≥250 kcal (N=34)	Group B TPN+EN<250 kcal (N=34)	*p*
Age (y)	66.0±10.4	62.3±13.0	0.190
Male (%)	14 (41.2)	17 (50.0)	0.313
Admission diagnosis (%)			
Cancer types			
Colon ca.	8 (23.5)	12 (35.3)	0.213
Esophageal ca.	7 (20.6)	7 (20.6)	0.617
Gastric ca.	5 (14.7)	4 (8.8)	0.355
Others	14 (41.2)	11 (32.4)	0.308
Complications of intestinal failure (%)			
Intestinal fistulas	3 (8.8)	2 (5.9)	0.500
Extensive small bowel disease	4 (11.8)	1 (2.9)	0.178
Intestinal dysmotility	10 (29.4)	14 (41.2)	0.223
Mechanical obstruction	17 (50.0)	17 (50.0)	0.596
Comorbid condition (%)			
DM	13 (38.2)	13 (38.2)	0.598
Hypertension	10 (29.4)	8 (23.5)	0.392
CKD	4 (11.8)	7 (20.6)	0.256
COPD	2 (5.9)	3 (8.8)	0.500
Nutritional parameters			
BMI (kg/m^2)	19.9±4.22	21.4±4.58	0.171
Duration of TPN (days)	17.9±10.6	17.4±11.6	0.853
Total daily calories (kcal/d)	1659±165	1571±217	0.065
TPN calories (kcal/d)	1355±168	1496±208*	0.003
EN calories (kcal/d)	306±75.5	75.0±72.0*	0.0001

DM: diabetes mellitus; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; TPN: total parenteral nutrition; EN: enteral nutrition.
Data are presented as n or means±SD.
*p<0.05.

Effects of TPN and EN on nutritional status

Patient compliance with the nutritional intervention was assessed using plasma nutritional markers (Table 3). Albumin levels were significantly higher in group A than in group B (p<0.05), and significantly increased between Db (day beginning; first day of TPN) and De (day end; last day of TPN) in group A (p<0.05), but significantly decreased between Db and De in group B (p<0.05). TP significantly increased between Db and De only in group A (p<0.05). Pre-albumin significantly increased between Db and De in group A (p<0.05), but significantly decreased between Db and De in group B (p<0.05). Hemoglobin significantly decreased between Db and De only in group B (p<0.05).

Table 3. Plasma nutritional markers post TPN intervention combining different EN support

	Group A TPN+EN ≥250 kcal (N=34)		Group B TPN+EN <250 kcal (N=34)	
	Db	De	Db	De
Albumin (g/dL)	2.64±0.60[§]	2.87±0.51[‡]	2.85±0.68	2.54±0.58[‡†]
Total protein (g/dL)	5.42±1.01	5.99±0.90[‡]	6.37±2.51	6.00±1.28
Prealbumin (mg/dL)	11.6±5.39	14.4±5.69[‡]	13.9±9.24	11.6±6.72[‡]
Transferrin (mg/dL)	123±48.3	127±47.9	126±57.2	107±42.3
Hb (g/dL)	10.7±1.59	10.5±1.74	10.6±2.09	9.94±1.70[‡]

Db: day beginning (first day of TPN); De: day end (last day of TPN); Hb: hemoglobin.
[†]Group A versusgroup B, unpaired t-test between periods, $p<0.05$.
[‡]Db versus De, paired t-test for each group, $p<0.05$.
[§]Results are expressed as means±SD.

Table 4. Repartition of patients by modified Glasgow Prognostic Score (mGPS)

	Group A TPN+EN ≥250 kcal (N=34)		Group B TPN+EN <250 kcal (N=34)	
	Db	De	Db	De
Grade 0	22[†]	24	20	20
Grade 1	1	1	1	1
Grade 2	11	9	13	13

Db: day beginning (first day of TPN); De: day end (last day of TPN).
The risk of malnutrition and/or inflammation was evaluated using the modified Glasgow Prognostic Score (mGPS), as follows: grade 0, C-reactive protein (CRP) serum level ≤10 mg/L; grade 1, CRP >10 mg/L and albumin ≥35 g/L; grade 2, CRP >10 mg/L and albumin <35 g/L.
[†]Results are expressed as number of patients. Distributions of patients per grade were compared using Fisher's exact test between groups (group Aversusgroup B; $p=0.713$) and McNemar–Bowker test (Db versus De; $p=0.560$) for group A.

Repartition of patients according to mGPS

The distribution of patients per grade of mGPS tended to be modified in group A (Db vs De, $p=0.560$), whereas the distribution in group B was unexpectedly maintained. No significant difference was observed between the groups (group A vs B, $p=0.713$) (Table 4).

Functional capacity evaluation

Functional capacities deteriorated between Db and De in group B, as reflected by an increased WHO/ECOG score (2.41±0.5 vs 3.15±0.70, $p<0.05$) and a decreased Karnofsky index (58.2±7.96 vs 44.1±13.7, $p<0.05$). Thus, as shown in Figure 1, at the end of nutritional support, group A exhibited a lower WHO/ECOG score and a higher Karnofsky index than that ofgroup B (WHO/ECOG score: 1.98±0.52 vs 3.15±0.70, $p<0.05$; Karnofsky index: 60.9±9.00 vs 44.1±13.7, $p<0.05$).

Changes in body weight

As shown in Figure 2, the significant mean weight gain in group A was 0.816 kg ($p=0.068$), and the significant mean weight loss in group B was 1.47 kg ($p<0.001$).

DISCUSSION

Cancer patients inevitably experience malnutrition owing to poor GI function. IF was first defined in 1981 by Fleming and Remington as "a reduction in the functioning gut mass below the minimal amount necessary for adequate digestion and absorption of food."[21] Table 1 summarizes the pathophysiological mechanisms of IF in our study population, and no difference was observed between the two groups (Table 2). EN alone usually cannot fulfill the energy requirements of cancer patients. PN is recommended in patients with severe mucositis or severe radiation enteritis (grade C).[22] However, TPN requires the placement of a central venous catheter, which entails risks and inconvenience to patients, and it is unclear whether parenteral nutritional support improves the outcomes of patients or results in more complications. Potential predisposing factors related to clinical outcomes include the administration route, the number of calories, and the types of nutrients provided. Numerous studies have suggested that EN possesses several advantages over TPN. EN can preserve gut flora architecture, prevent GI mucosal atrophy, and exert a trophic effect on the GI tract to inhibit microbial translocation from the gut to the bloodstream.[8,23] However, hepatobiliary complications related to artificial nutrition have been reported, and these complications occur less frequently in patients receiving EN than in those receiving TPN.[24] In this study, patients in the two groups received the same number of calories, however, those in group A received more calories from EN(more than 250 kcal/d), and those in group B received fewer calories from EN (less than 250 kcal/d). A significant difference was observed (Table 2) for cancer patients with GI dysfunction who require TPN for nutritional support, however the benefit of additional EN is unclear.

Malnutrition is a frequent complication in cancer patients and can negatively affect the outcomes of treatments.[25] Serum albumin has been proposed to be a critical predictor of the response to nutritional support and tolerance for EN in critically ill patients.[26] In our study, patients in group A presented higher serum albumin levels than those in group B on the last day of TPN (2.87±0.51

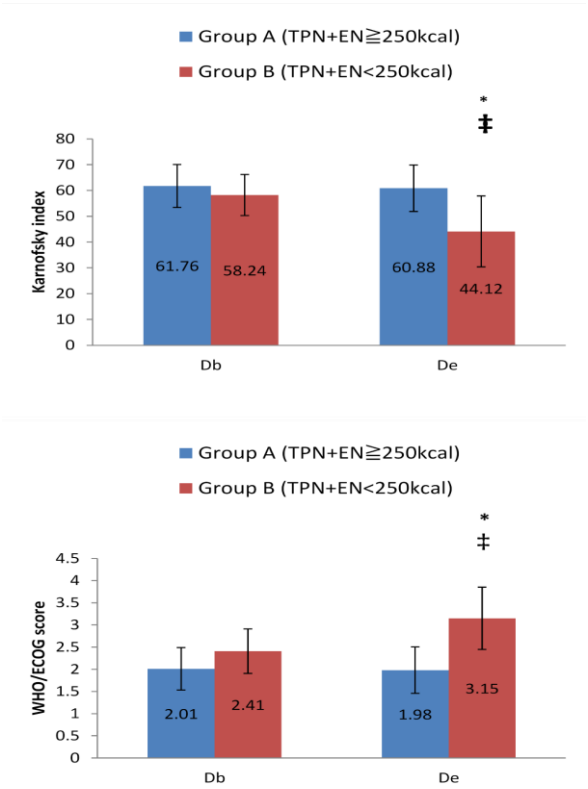

Figure 1. Evaluation of functional capacity. Functional capacity was evaluated using the Karnofsky index and WHO/ECOG score. Db: Day beginning(first day of TPN); De: Day end (last day of TPN). ‡p<0.05; Db vs De, paired t-test for each group; *p<0.05; group A versus group B, unpaired t-test between periods.

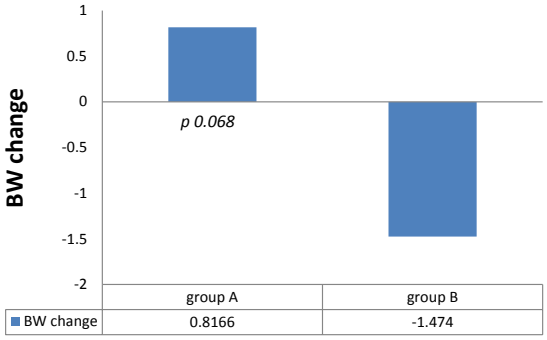

Figure 2. Changes in body weight, the mean body-weight gain in group A (TPN + EN ≥250 kcal), and significant mean body-weight loss in group B (TPN + EN <250 kcal) (p <0.001).

vs 2.54±0.58, p<0.05). A crucial observation is that although the two groups received the same number of calories, the albumin level was significantly higher in group A. Continual nutrition supply to the gut is preferred to parenteral feeding and is believed to prevent mucosal atrophy,[27]reduce endotoxin translocation, and maintain the gut barrier function, which may become compromised in patients receiving PN.[7] EN also avoids the abnormalities of liver and biliary function observed in patients receiving parenteral feeding.[7] In this study, serum albumin levels were significantly increased between Db and De in group A (2.64±0.60 vs 2.87±0.51, p<0.05) but significantly reduced between Db and De in group B (2.85±0.68 vs 2.54±0.58, p<0.05).

Prealbumin, also known as transthyretin, has a half-life of approximately 2 days in the plasma, which is much shorter than that of albumin. Prealbumin is therefore more sensitive than albumin to changes in protein-energy status, and prealbumin levels closely reflect recent dietary intake rather than overall nutritional status.[28] As a result of its short half-life, the prealbumin level decreases rapidly as a result of the decrease in its synthetic rate when there is reprioritization of synthesis toward acute-phase proteins such as C-reactive protein, fibrinogen, or α_1-acid glycoprotein. Moreover, similar to that of albumin, the prealbumin level in the plasma is affected by changes in transcapillary escape. Hence, the interpretation of plasma prealbumin is difficult in patients with infections, inflammation, or recent trauma.[29] Despite this difficulty, interest in prealbumin as a potential marker of the nutritional status in certain groups of patients led to the First International Congress on Transthyretin in Health and Disease in 2002.[30] In our study, no difference was observed in prealbumin levels between group A and group B. The prealbumin levels significantly increased between Db and De in group A (11.6±5.39 vs 14.4±5.69, p<0.05) but significantly decreased between Db and De in group B (13.9±9.24 vs 11.6±6.72, p<0.05).

Recently, mGPS was found to correlate with improved survival and clinical outcomes in a large cohort of cancer patients, and compared with other biochemical parameters, mGPS is a powerful prognostic factor and is independent of the tumor site in cancer patients.[31] In this study, mGPS indicated that the risk of inflammation could be stabilized between the groups (group A vs group B, p=0.713).

Several scales have been established to measure performance status (PS), among which the most widely used are the Karnofsky index,[32] and ECOGscore.[33] In this study, functional capacities (Karnofsky index and WHO/ECOG score) were maintained only in group A, and functional capacities deteriorated in group B patients during the end of TPN (p<0.05). Functional capacities were significantly improved in group A than in group B (p<0.05). The degradation in the Karnofsky index and WHO/ECOG score in group B over the course of treatment showed that patients were unable to pursue normal activities or work at the end of TPN. These findings are clinically relevant for guiding clinicians for administering EN as nutritional support for TPN to prevent functional capacity deterioration in patients.

Cancer patients exhibit highly variable changes in energy expenditure. Weight and tissue losses have been shown to influence PS in cancer patients.[34] Lean body mass and visceral protein depletion are characteristic in cancer patients with cachexia, and the degree of depletion may be associated with reduced survival.[35] Human studies have shown that in the absence of changes in food intake, hyper metabolism, characterized by elevated resting energy expenditure (REE), may be a contributing factor to weight loss in cancer.[36,37] Weight-losing and weight-stable cancer patients with various solid tumors exhibit similar dietary intakes; however, weight-losing patients exhibit higher REE, as determined by indirect calorimetry.[38] In the current study, patients in group A who received early EN exhibited a weight-gain of 0.8 kg, but the finding was not significant (p=0.068). Patients in group B with poor intake exhibited a significant weight loss of 1.4 kg (p<0.001). This finding showed that although both

groups had the same total calorie intake, group B (TPN combined with less EN feeding) had higher REE.

Cancer has a profound impact on the physical functioning of patients, and their nutrient levels and energy metabolisms are altered. The administration of oral nutritional supplements is a simple and noninvasive strategy to increase nutrient intake and is used whenever nutritional requirements cannot be met through counseling.[39] Owing to the use of the GI tract, EN maintains the immune responses of patients,[39] reduces the cost of treatment, and lowers the risk of infection in comparison with TPN.[40] In this study, patients receiving more calories from EN exhibited more favorable outcomes than patients receiving nutrition only from TPN.

Our study had some limitations. Due to its retrospective design, our study lacked detailed information on PN and EN, including the components of nutrition formulation, as well as detailed information on drugs or antibiotics used during hospital admission. Additional randomized controlled trials with larger samples should be conducted to elucidate the role of EN in critically ill patients who have moderately impaired GI function and require supplemental PN.

In conclusion, our study showed that in patients with cancer complications requiring TPN, patients fed enterally for more than 250 kcal/d of total calorie intake exhibited more favorable clinical outcomes than patients fed enterally for fewer than 250 kcal/d of total calorie intake during hospitalization. EN should be provided whenever possible to these severely ill patients.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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