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ORIGINAL ARTICLE

Early postoperative glutamine-supplemented parenteral nutrition *versus* enteral immunonutrition in cancer patients undergoing major gastrointestinal surgery

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Summary

Purpose: *The aim of this study was to determine whether the type of postoperative feeding, glutamine-supplemented parenteral nutrition or enteral immunonutrition, can modify morbidity and outcome in malnourished cancer patients undergoing major surgery in the gastrointestinal tract.*

Patients and methods: *Twenty-nine consecutive malnourished patients undergoing major elective surgery for carcinoma of the stomach (n=8), pancreas (n=8), liver (n=1), and colon (n=12), were randomly assigned to receive from the first postoperative day either enteral immunonutrition or glutamine-supplemented parenteral nutrition, for at least 5 consecutive days. Postoperative major and minor morbidity and mortality were recorded. Data analysis was done using the Fisher's exact test.*

Results: *Fifteen patients received glutamine-supplemented parenteral nutrition and 14 received enteral immunonutrition. The overall incidence of postoperative complications was 33.3% in the parenteral nutrition group versus 50% in the enteral nutrition group (p=0.2). Subdividing postoperative complications into different types, the rates of major complications were similar in both groups of patients (13.3 and 21.4% respectively, p=0.4). Similarly, there were no significant differences between the two groups considering minor postoperative noninfectious complications, infectious complications, and mortality.*

Conclusion: *In malnourished cancer patients undergoing major gastrointestinal surgery, morbidity and mortality are not significantly influenced by the type of postoperative feeding.*

Key words: complications, enteral immunonutrition, glutamine, surgery, total parenteral nutrition

Introduction

Malignancy of the gastrointestinal tract is frequently associated with malnutrition which predisposes to postoperative complications such as increased incidence of infection, anastomotic leakage, delayed wound healing, and increased length of hospital stay and cost of care [1]. Conventional treatment after major abdominal operations entails starvation for at least 4-5 days, with administration of intravenous fluids until passage of flatus. However, even this relatively short period of starvation aggravates the preexisting malnutrition and may conduct to detrimental effects [2]. Enteral nutrition (EN) is considered to be better than total parenteral nutrition (TPN) for providing feeding in various clinical settings because it is less expensive, safer, and maintains the nutritional, metabolic, immunological and barrier function of the intestine [3-5]. Moreover, it has been recently shown that patients fed via EN after abdominal surgery for trauma and severe acute pancreatitis developed fewer septic complications than patients who received TPN [6-9]. However, controversy exists about the use of EN, compared to TPN, in patients undergoing major abdominal surgery, although there is some evidence that early postoperative EN with immune-enhancing diets may reduce morbidity and improve outcome.

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The aim of this study was to compare the efficacy of early postoperative glutamine-supplemented TPN (Glu-TPN) *versus* enteral immunonutrition (EIN) on the outcome of malnourished cancer patients undergoing major elective abdominal surgery. The primary objective was to determine whether the type of postoperative feeding can modify major and minor morbidity, mortality, or both in such patients, and, especially, if EIN is really better than Glu-TPN.

Patients and methods

Patients undergoing non-emergency major abdominal surgery were considered. They were screened at admission for the presence of malnutrition according to the Nutritional Risk Index [10]; all patients with an index less than 90% were potentially eligible for the study, and they were randomly assigned to receive postoperatively either EIN or Glu-TPN. Patients randomized to the Glu-TPN group, in the presence of large and accessible peripheral veins, received the nutrient admixture through a fine-bore (22 G) venous catheter inserted in the largest palpable vein of the forearm; patients with unsuitable peripheral veins received the nutrient admixture via a central venous catheter inserted the day before surgery. In all the patients randomized to receive EIN, a nasojejunal feeding tube was inserted intraoperatively in the proximal jejunum, with the surgeon verifying the position. Glu-TPN or EIN were initiated on the first postoperative day and continued for at least 5 consecutive days, or until normal diet was possible. The feeding regimens were determined by the patient's metabolic requirements using the Harris - Benedict equation to calculate energy expenditure, which was then multiplied by an appropriate stress/injury factor to determine the actual energy expenditure. The TPN formula consisted of aminoacids with an average range of 1-1.4 g/kg/day, L-alanyl-L-glutamine at a dose of 0.3 g/kg/day (Dipeptiven®, Fresenius-Kabi), and non-protein calories provided by glucose and fat in a ratio 60/40, with supplemental electrolytes, trace elements and vitamins, according to individual patient's requirements. The EIN formula used was Impact (Novartis), providing 1 kcal/ml, enriched with arginine, omega-3 fatty acids and nucleotides, which began as a full - strength formula introduced at 20 ml/h, and increased gradually, depending on tolerance, to reach the target rate of 25 kcal/kg/day, comparable with that of the Glu-TPN group, within 48 h.

In all the patients, oral fluids started on passage of flatus and increased to normal diet over 48 - 72 h. Glu-TPN and EIN were stopped when oral intake was resumed with at least 1000 kcal per day.

All patients received perioperative antibiotic prophylaxis and a subcutaneous injection of low molecular weight heparin sodium daily as deep venous thrombosis prophylaxis.

A record was made of the type of surgery, postoperative complications, and mortality. Complications were classified as major or minor, and as infectious or noninfectious. Data analysis was done by the Fisher's exact test, with a level of statistical significance of $p < 0.05$.

Results

Twenty-nine patients identified as eligible for the study were randomly assigned to the Glu-TPN (n=15) or the EIN group (n=14). Table 1 lists the diseases of the 29 patients, and Table 2 lists the operative procedures as well as the type of postoperative feeding. The overall incidence of postoperative complications was 33.3% in the Glu-TPN group *versus* 50% in the EIN group (p=0.2). Subdividing complications into different types, the rates of major postoperative complications were similar in the two groups: 2 (13.3%) of the 15 patients receiving Glu-TPN and 3 (21.4%) of the 14 patients of the EIN group had such complications (p=0.4). Similarly, the rates of minor postop-

Table 1. Malignant diseases of the 29 patients

Disease	*No. of patients*
Gastric carcinoma	8
Pancreatic carcinoma	8
Hepatocellular carcinoma	1
Colon carcinoma	12

Table 2. Operative procedures and type of postoperative feeding

Operative procedure	*No. of patients*	*Glu-TPN*	*EIN*
Gastrectomy	8	3	5
Whipple operation	2	2	
Left pancreatectomy	1		1
Choledocho-duodenal anastomosis and gastro-enteroanastomosis	5	2	3
Liver resection	1	1	
Colectomy	12	7	5

erative complications were comparable in the Glu-TPN and EIN groups (3 patients in the Glu-TPN and 4 patients in the EIN group, p=0.4). The individual complications are presented in Table 3. As it is shown in Table 3, the rates of major postoperative infectious complications were also similar in the two groups (one patient in the Glu-TPN and one patient in the EIN group, p=0.7), as well as mortality (one patient in each group, p=0.7).

Discussion

In Europe and North America, 40 - 50% of hospitalized patients are at risk of malnutrition, which tends to worsen during hospitalization [1]. Malignancy is frequently associated with malnutrition, resulting in increased morbidity and mortality [11]. Also, experimental data suggest that the absence of nutrients within the lumen of the intestine results in intestinal mucosal atrophy, rapid and severe atrophy of the gut-associated lymphoid tissue (GALT), bacterial overgrowth, increased intestinal permeability, and translocation of bacteria and/or bacterial products into the portal circulation [12-15]. Clinically, the enteral delivery of nutrients appears to improve host defenses and reduce the incidence of septic complications in some patient populations, such as those undergoing surgery for trauma and severe acute pancreatitis, compared with parenteral feeding [7-9]. Moreover, recent clinical studies suggest that the use of immune-enhancing enteral nutrition in certain circumstances is associated with significant improvement of the immune function, improvement of nitrogen balance and protein synthesis, and overall improved clinical outcome, especially in critically ill patients [16,17]. However, the efficacy of such immune-enhancing nutrients in patients undergoing major gastrointestinal surgery has not been yet consistently confirmed; for example, some studies have shown that this type of postoperative feeding is associated with an improved clinical outcome, usually through reduction in septic complications and shortening of hospital stay [18-21], whereas other studies have not shown any benefit deriving from the use of such nutrients compared with TPN [22,23]. On the other hand, a recent meta-analysis of 11 randomized controlled trials comparing EIN *versus* standard EN has shown that provision of EIN resulted in a decrease in infectious complications and reduction in overall hospital stay, but there were no differences between patient groups for either pneumonia or death [24]. Finally, no study to date shows any difference regarding postoperative mortality [24,25].

Glutamine has attracted great interest in the last few years because of its role in gut mucosal preservation and immune function, and recent studies suggest that glutamine-supplemented TPN appears to be more beneficial than TPN without glutamine in various patient populations [26-28]. However, there are not clinical studies to date comparing Glu-TPN with EIN; in other words, there is no answer to the question if EIN is better than Glu-TPN in patients undergoing major surgery. As in a considerable percentage of patients early postoperative EIN is not well tolerated, TPN enriched with glutamine could be a suitable alternative for feeding such patients in the early postoperative period with the same or, eventually, better results.

In this study, our primary objective was to determine whether the type of postoperative feeding, Glu-TPN or EIN, can modify major and minor morbidity and mortality in malnourished cancer patients undergoing major elective gastrointestinal surgery, and, consequently, if EIN is better than Glu-TPN. The results showed no significant reduction of morbidity and mortality when postoperative EIN was compared with postoperative Glu-TPN. Even when subdividing postoperative complications into different types (major and minor, infectious and noninfectious), we did not observe statistically significant differences between the two groups.

Table 3. Postoperative complications and mortality

Complication	*Glu-TPN patients (n=15)*	*EIN patients (n=14)*	*p-value*
Major			0.4
catheter-related sepsis	1		
dehiscense of surgical wound	1		
intractable diarrhea		1	
pneumonia		1	
bowel necrosis, reoperation		1	
Minor			0.4
peripheral vein thrombophlebitis	3		
abdominal distension and cramps		1	
dislodgment of the feeding tube		2	
occlusion of the feeding tube		1	
Infectious			0.7
catheter-related sepsis	1		
pneumonia		1	
Mortality	1	1	0.7

In conclusion, this study failed to demonstrate that immediate EN with immune-enhancing formulas following major gastrointestinal surgery reduces postoperative complications and mortality when compared with glutamine-supplemented TPN. According to these data and keeping in mind that EN is less expensive than TPN, it appears that in patients unable to tolerate enteral feeding, glutamine should be a constituent of parenteral foods; however, more well - designed studies comparing EIN with Glu-TPN are required to confirm these results.

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