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Original Article

The immunomodulating enteral nutrition in malnourished surgical patients – A prospective, randomized, double-blind clinical trial

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SUMMARY

Background & aim: The immunomodulating nutrition was supposed to reduce the incidence of complications in surgical patients, but many authors have questioned its value recently. The aim of the study was to assess the impact of enteral immunonutrition in postoperative period.

Methods: Between January 2003 and December 2009, 305 malnourished patients (123 F, 182 M, m. age 60.8) undergoing resection for pancreatic or gastric cancer, after preoperative 14 days of parenteral feeding, were randomized in double-blind manner to receive either postoperative immunomodulating enteral diet (IMEN) or standard oligopeptide diet (SEN). Outcome measures of the intend-to-treat analysis were: number and type of complications, length of hospitalization, mortality, and vital organ function.

Results: Median postoperative hospital stay was 17.1 days in SEN and 13.1 days in IMEN group ($p = 0.006$). Infectious complications were observed in 60 patients (39.2%) in SEN and 43 (28.3%) in IMEN group ($p = 0.04$). Differences were also observed in overall morbidity (47.1 vs 33.5%, $p = 0.01$) and mortality (5.9 vs 1.3%, $p = 0.03$), but the ratio of surgical complications, organ function, and treatment tolerance did not differ.

Conclusions: The study proved that postoperative immunomodulating enteral nutrition should be the treatment of choice in malnourished surgical cancer patients.

The Clinical Trials Database registry number: NCT00576940.

1. Introduction

Malnutrition represents a factor, which can significantly affect the outcome of surgery in many ways, such as complication of wound healing or delaying the recovery. Its detrimental influence is a result of the suppression of the immune function, the exaggeration of a stress response and organs' dysfunction.

Nutritional therapy has been used in the struggle against malnutrition for over forty years, since its invention by team of Dudrick, Vars and Rhoads, who used the new technique in surgical patients.[1] Intravenous admixtures helped surgical patients to recover after major surgery and changed the whole concept of perioperative care irretrievably. Twenty years later, studies of Buzby et al. and VA trial showed drawbacks of parenteral route and questioned the value of intravenous feeding in all surgical patients, showing its drawbacks and limited effectiveness – the reduction of postoperative complications was observed only in malnourished patients and did not exceed 10–20%.[2,3] Since then, parenteral nutrition became less popular and the use of enteral feeding instead of intravenous was encouraged in surgical wards.

The surgical guidelines for enteral nutrition published by European Society for Nutrition and Metabolism in 2006 (ESPEN), unanimously described the positive role of preoperative enteral feeding and recommended its use in all malnourished patients.[4] Late nineties abounded with attempts to improve the nutritional intervention and to create formulas influencing other vital organs. Much consideration was paid to new admixtures, not only providing energy and proteins, but also modifying the immune system's response. Those diets, initially called immunostimulating, than immunomodulating or immunoenhancing, included arginine, glutamine, omega-3-fatty acids, vitamins C, E, and nucleotides. Some authors showed their positive impact on the outcome of surgery.[6,7] For the last decade, however, some controversies have occurred and the real impact of immunomodulating formulas has been questioned because the positive effects of immunonutrition observed in experimental models were often denied by clinical results.[7,8,9] For example, Lobo et al. demonstrated that immunodiets showed no benefit over standard enteral nutrition when

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peptide-based diet was used, and other authors observed similar results.[7,9,10] Those results were however difficult to compare because of the heterogeneity of study groups, sample numbers and differences in analytical approach. Some studies performed in well-nourished patients failed to prove the clinical effectiveness of immunomodulating diets.[11,12]

To address those ambiguities and to assess the actual clinical significance of enteral immunonutrition, a randomized, prospective clinical trial was conducted.

2. Methods

2.1. Study design and settings

The study was a two-arm, randomized, controlled clinical trial conducted to assess the impact of enteral nutrition on post-operative complications in patients undergoing gastrectomy and pancreatoduodenectomy for cancer. The trial was set at the tertiary surgical center – the 1st Department of General Surgery, Jagiellonian University in Cracow and was carried out between January 2003 and December 2009. The study was designed to test the hypothesis that immunomodulating enteral nutrition would reduce the incidence of surgical and non-surgical complications following upper gastrointestinal surgery when compared to standard, isocaloric and isonitrogenous oligopeptide diet. The secondary objective of the study was to evaluate the effect of nutritional intervention on overall morbidity and mortality rates, the length of hospital stay, liver, kidney and immune function.

2.2. Inclusion and exclusion criteria

341 adults aged 18–85 years undergoing subtotal and total gastric resection with lymphadenectomy and pancreatoduodenectomy and/or total pancreatectomy with lymphadenectomy were initially assessed to participate in the trial. The inclusion criteria included: malnutrition (defined as one of the following unintentional weight loss by at least 10% or body mass index (BMI) < 18), good general status (Karnofsky Performance Index > 80, Eastern Cooperative Oncology Group (ECOG) grade 0 or 1); no confirmed neoplastic dissemination, no severe concomitant disease (heart, lung, kidney, liver failure, chronic obstructive pulmonary disease [COPD], coronary aortic bypass graft [CABG], etc.), no history of known allergies or drug intolerance to analyzed substances. Patients well nourished or with metastatic disease, pregnant, in poor general status (Karnofsky < 80, Eastern Cooperative Oncology Group (ECOG) > 1), with recent history of severe heart, lung, kidney or liver failure, with history of allergies or drug intolerance were excluded. Patients' characteristics were presented in Table 1.

2.3. Randomization and allocation of patients

Following recruitment, after signing the informed consent, all participants who met eligibility criteria were randomly assigned after operation either of the treatment groups: SEN group – standard enteral nutrition; IMEN group – immunomodulating enteral nutrition, using according to a computer generated randomization list managed by an external person not involved in the study. The CONSORT diagram shows the flow of participants through the study [Fig. 1].

2.4. Clinical management

All patients received standard parenteral nutrition for 14 days before surgery. Protein and energy requirements were calculated using the nitrogen to body mass ratio (0.15 g N/kg b.w.) and the Q quotient ($Q = 150$ kcal/g N). The 10% amino acid solutions, 10–40% glucose and 10–20% lipid emulsions, trace elements (Aminoplasmal, Glucose and Lipofundin MCT/LCT B and Tracutil, B Braun, Germany), vitamins (Cernevit, Baxter, USA) and electrolytes solutions were used to prepare All-in-One admixtures in the hospital pharmacy. No immunomodulating substances were added. The central venous catheter was inserted in subclavian or jugular vein by an anesthesiologist before the start of the treatment. The placement was confirmed afterwards or during procedure by the chest X-ray. The spontaneous oral intake did not exceed 100 kcal/day in case of each patient.

The selection of parenteral intervention instead of the enteral preoperative feeding, which is recommended nowadays, was the result of the lack of those guidelines at the time when study design was prepared, that was 2001 and 2002. At that time the parenteral nutrition was greatly favored in all surgical units in Poland, its tolerance was satisfactory, hence the choice of intravenous route. If the study had been designed today, the enteral nutrition would have been selected as its value was clearly proven.[4]

During resective procedure (gastrectomy or pancreatoduodenectomy) enteral feeding tube (Flocare Nutricia Ltd., 140 cm length) was inserted into the first jejunal loop 15–20 cm below the lowest intestinal anastomosis by a surgeon in cooperation with an anesthesiologist. The surgical team included at least two surgeons experienced in the field of general and oncological surgery, and anesthesiology team included 4 persons.

Table 1
Baseline patient characteristics.

	SEN ($n = 153$)	IMEN ($n = 152$)	P value
Age, years (mean (SD))	61.5 (11.8)	60.2 (12.4)	0.347
Gender, M:F	89:62	92:60	0.353
% Weight loss (mean (SD))	18.8 (4.9)	18.3 (4.4)	0.484
BMI (mean (SD))	17.9 (2.8)	17.9 (2.8)	0.838
Type of surgical operation			0.755
subtotal gastrectomy	29 (18.95%)	27 (17.76%)	
total gastrectomy	40 (26.14%)	49 (32.24%)	
pancreaticoduodenectomy	42 (27.45%)	37 (24.34%)	
total pancreatectomy	9 (5.88%)	6 (3.95%)	
surgical bypass	33 (21.57%)	33 (21.71%)	
ASA score			0.138
1	10 (6.54%)	20 (13.16%)	
2	135 (88.24%)	123 (80.92%)	
3	8 (5.23%)	9 (5.92%)	
Blood transfusion (mean (SD))	1.7 (1.3)	1.6 (1.3)	0.420

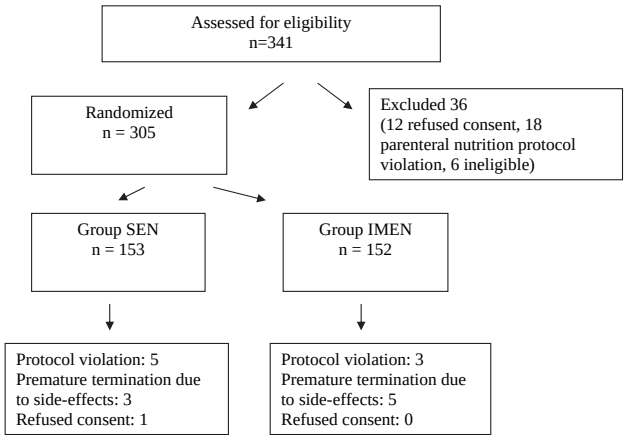

Fig. 1. CONSORT diagram showing the flow of participants through each stage of the trial.