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Short-term preoperative supplementation of an immunoenriched diet does not improve clinical outcome in well-nourished patients undergoing abdominal cancer surgery

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ABSTRACT

Objective: A recent study suggested that the anti-inflammatory effect of immunonutrition starts after only two d. We therefore investigated the effect of an immunoenriched oral diet administered for three d preoperatively.

Methods: In this prospective, randomized, double-blind, placebo-controlled study, well-nourished patients (Nutrition Risk Screening 2002 <3) with gastrointestinal cancer who were scheduled for major elective abdominal cancer surgery were randomly assigned to either 750 mL of an immunoenriched formula (IEF group) or 750 mL of an isocaloric, isonitrogenous placebo diet (Con group) for 3 consecutive d preoperatively.

Results: A total of 108 patients (IEF group: n = 55; Con group: n = 53) were randomized. The two groups were comparable for all baseline and surgical characteristics. The overall mortality was 2.8% and not significantly different between the two groups (IEF group: 3.6% vs. Con group: 1.9%, $P = 1.00$). Intention-to-treat analysis showed no difference for the incidence of postoperative overall (IEF group: 29% vs. Con group: 30%; $P = 1.00$) and infectious (IEF group: 15% vs. Con group: 17%; $P = 0.79$) complications. Length of hospital stay was 12 ± 4.9 d in the IEF group and 11.6 ± 5.3 d in the Con group ($P = 0.68$).

Conclusions: Preoperative oral supplementation with an immunoenriched diet for 3 d preoperatively did not improve postoperative outcome compared with the placebo in well-nourished patients with elective gastrointestinal cancer surgery.

Introduction

Major surgery is a powerful stimulus for systemic inflammatory response, which represents, if excessive and uncontrolled, a risk factor for a state of hypermetabolism with rapid consumption of endogenous energy stores and immunological dysfunction, eventually leading to postoperative complications, including deterioration of organ function [1,2]. Patients undergoing surgery for gastrointestinal or pharyngeal cancer are often malnourished, rendering them vulnerable for postoperative complications, prolonged hospitalization, and increased health care costs. Among the proposed strategies to reduce such sequelae is the use of enteral diets enriched with specific nutritional compounds such as arginine, glutamine, omega-3 fatty acids (fish oil), and/or ribonucleic acid (RNA), which has been defined as *immunonutrition*. Immunonutrition is supposed to alter immune function and cytokine production, thereby

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limiting the undesirable perioperative excessive stimulation of the immune and inflammatory cascades [3]. Several randomized studies found that the perioperative (before and after surgery) use of such diets in malnourished cancer patients significantly decreases the incidence of infectious complications, length of hospital stay (LOS), and hospital costs compared with a control enteral formula [4–7]. Preoperative oral feeding with an immune-enhancing diet for 5 d in well-nourished cancer patients undergoing abdominal surgery has been shown to decrease postoperative infectious complications, length of hospital stay, and health care costs [8]. Although guidelines recommend supplementation with an immunoenriched diet for 5 consecutive d before visceral surgery [9], there is neither clear evidence about the exact length of preoperative supplementation, nor about the required minimum amount of immunonutrients needed for improving clinical outcome.

In a recent pilot study, we have shown that the positive effect an immunoenriched diet on markers of inflammation starts after only 2 d of preoperative supplementation [10]. On the basis of this observation, we performed a trial in well-nourished visceral cancer patients to find out whether preoperative supplementation with an immunoenriched diet for 3 d is superior to placebo concerning postoperative outcome.

Patients and methods

Between January 2006 and May 2008, we conducted a prospective, randomized, double-blind, placebo-controlled multicenter study in six different tertiary referral centers for abdominal cancer surgery in Switzerland (Hospitals in Fribourg, St. Gallen, Aarau, Liestal, Baden, and Schaffhausen). The study protocol was approved by all local ethic committees. All study personnel and participants were blinded to treatment assignment for the duration of the study. Only the data monitoring committee saw unblinded data, but none of its members had any contact with study participants. The study protocol is summarized in Figure 1.

Well-nourished patients, defined by a total score <3 on the nutritional risk screening tool (NRS 2002 [11]), of both genders with histologically documented adenocarcinoma of the upper or lower gastrointestinal tract who were candidates for elective surgery were assessed. Exclusion criteria were clinically relevant pulmonary (FEV1 <0.8 L/s), cardiovascular (Goldmann classification class >3), renal (serum creatinine level >165 μmol/L), hematological (Hb level <80 g/L; circulating neutrophils $<2.0 \times 10^9$/L), or hepatic (Child-Pugh Class B or C) alterations. Further, patients were also excluded for pregnancy, severe mental disorders, age younger than 18 y, uncontrolled ongoing infection, intestinal obstruction, any concomitant dietary supplements containing omega 3-fatty acids, any immunomodulationg therapy, other oral supplements, and/or an Eastern Cooperative Oncology Group (ECOG) performance status >2 [12].

After applying these exclusion criteria, the study was explained to potential participants who then signed a consent form before randomization. Patients were randomized by means of sealed envelopes. Each envelope was bearing a number on the outside and contained a card indicating if the patient were to be a TT (IEF group; Impact RTD, Novartis Consumer Health, Berne, Switzerland) or a RR case (Con group; isocaloric and isonitrogenous placebo). The study products were blinded for color, taste, consistency, and appearance, and were served in identical packages labeled RR or TT. Patients received a total of 750 mL of Impact RTD (IEF group) or the same amount of an isocaloric and isonitrogenous placebo (Con group) for 3 consecutive d before surgery. A daily dose of Impact RTD (750 mL) contains 16.72 g of arginine, 3.3 g of omega-3 fatty acids, and 1.32 g of RNA with a kilocalorie-to-milliliter ratio of 1.4:1.

Generally, oral supplementation was performed as an outpatient therapy. All patients kept a written record of the daily amount of supplemented diet consumed. Furthermore, gastrointestinal side effects related to supplementation were also documented. All patients were advised to consume regular meals in addition to the supplements as recommended by the producer of Impact RTD. Bowel preparation was selectively used for rectal cancer patients or patients with small colon cancer or polyps scheduled for laparoscopic surgery. Antegrade bowel cleansing started the d before surgery. Supplement intake during that d started after the end of bowel preparation in the early afternoon and ended at the same evening. During bowel cleansing, oral intake of clear liquids and fruit juices was allowed.

In the postoperative course, the patients were given intravenous fluids and electrolytes based on their individual demands until they resumed adequate oral intake. Realimentation by oral feeding was started as soon as possible after the surgical intervention, based on clinical decisions by the medical staff.

Single-shot antibiotics (1.5 g cefuroxime IV and, in case of colorectal surgery, additionally 500 mg metronidazole IV) were routinely used for infection prophylaxis and were given at least 30 min before surgery and repeated every 4 h during surgery, if necessary. Antegrade intestinal wash out was performed only selectively, e.g., in patients with rectal cancer. Patients were kept nil per mouth the night before surgery. Prophylaxis for deep venous vein thrombosis was performed by weight-adapted low-molecular weight heparin.

Seven d preoperatively (d −7), the following parameters were recorded: a full physical examination, body weight (kg), height (m), body mass index (kg/m^2), and NRS 2002 and ECOG performance status. All comorbidities existing preoperatively were recorded. A full white blood count (WBC), red blood count (RBC), liver and kidney function tests, albumin, prealbumin, total protein, glucose, C-reactive protein (CRP), and serum electrolytes were determined 7 d and 1 d before surgery. Type and duration of surgery and operative blood loss, as well as rate and amount of homologous blood transfused were registered. Concomitant medication, antibiotic therapy, and all perioperative complications were recorded for a follow-up period of 30 d postoperatively. Infectious complications were defined according to the recommendations of the Center of Disease Control [13].

Statistical analysis

The primary outcome measure was the overall rate of postoperative complications. We assumed an overall complication rate of 30% in the Con group. A reduction by 20% in the IEF group was considered to indicate the efficacy of treatment [8]. With 73 patients in each group, we obtained a power of 80% to detect such a reduction with an alpha level of 0.05 (two-sided). Therefore, we planned to include 75 patients in each group. Secondary parameters measured in this study were the incidence of postoperative infectious complications, incidence of noninfectious complications, length of intensive and/or intermediate care unit (ICU/ICU), length of hospital stay (LOS), and postoperative antibiotic use. All patients were analyzed on an intention-to-treat basis. Descriptive results are expressed as mean values ± SD or number of observations (%). Fisher's exact test was used to compare discrete variables. All P values are two-sided and statistical significance was accepted at a P value <0.05. The SAS Software (Version 9.1.3, SAS Institute, Carry, NC, USA) was used for statistical analysis.

Results

With the assumption that preoperative oral short-term feeding of an immunoenriched diet would decrease the infectious complications by 20%, 75 patients into each group would provide 80% power to detect such an effect (alpha level of 0.05 [two-sided]). Because an interim of 108 patients (IEF group: n = 55; Con group: n = 53) analysis found no difference for any of the analyzed parameters in this study, the data monitoring committee decided to close the trial at an earlier stage.

Figure 1 shows the diagram of the trial according to the CONSORT statement [14]. During the study period, 254 patients were investigated. Of these, 146 (57.4%) patients did not meet the inclusion criteria and were excluded. One hundred eight patients were randomized into either the immunoenriched (IEF group: n = 55) or placebo group (Con group: n = 53). During the preoperative period, three patients withdrew their informed consent before oral supplement intake (IEF group: n = 1; Con group: n = 2). The mean amount of liquid food of the 105 patients who started oral supplementation was not different between the two groups (IEF group: 640 mL/d; Con group: 660 mL/d). A total of 99 patients (IEF group: n = 50; Con group: n = 49) had an adequate preoperative intake of oral supplementation (>500 mL/d).

Table 1 lists the preoperative characteristics and type of surgical pathology of the randomized patients. The two study arms were well balanced for all parameters without significant differences for gender, age, weight, NRS-score, ECOG performance status, and surgical pathology. No differences were furthermore observed for serum albumin and prealbumin, WBC and RBC, CRP, electrolytes, and liver and kidney parameters before food supplementation on d −7 to d −5 as well as 1 d before surgery (data not shown).

As shown in Table 2, the overall frequency of adverse events reported by the patients during oral supplementation was