Perioperative Immunonutrition in Patients Undergoing Cancer Surgery

Results of a Randomized Double-blind Phase 3 Trial

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Hypothesis: Perioperative administration of a supplemented enteral formula may reduce the rate of postoperative infections.

Design: Prospective, randomized, double-blind clinical trial.

Setting: Department of surgery at a university hospital.

Patients: Two hundred six patients with neoplasm of colorectum, stomach, or pancreas.

Intervention: Patients were randomized to drink 1 L/d of either a control enteral formula (n = 104) or the same formula enriched with arginine, RNA, and ω3 fatty acids (n = 102) for 7 consecutive days before surgery. The 2 diets were isoenergetic and isonitrogenous. Jejunal infusion with the same formulas was started 6 hours after operation and continued until postoperative day 7.

Main Outcome Measures: Rate of postoperative infectious complications and length of hospital stay.

Results: Both groups were comparable for age, sex, weight loss, Karnofsky scale score, nutritional status, hemoglobin level, duration of surgery, blood loss, and rate of homologous transfusion. Intent-to-treat analysis showed a 14% (14/102) infectious complication rate in the supplemented group vs 30% (31/104) in the control group (P = .009). In the eligible population, the postoperative infection rate was 11% (9/85) in the supplemented group vs 24% (21/86) in the control group (P = .02). The mean ± SD length of postoperative stay was 11.1 ± 4.4 days in the supplemented group and 12.9 ± 4.6 in the control group (P = .01).

Conclusion: Perioperative administration of a supplemented enteral formula significantly reduced postoperative infections and length of stay in patients undergoing surgery for cancer.


Despite several reports1-7 that the early postoperative administration of enteral diets enriched with arginine, ω3 fatty acids, and nucleotides resulted in improved host defense mechanisms, the effectiveness of postoperative immunonutrition in terms of clinical benefit is a matter of debate.1,7-18 This is probably because the amount of substrates delivered in the first days after operation may not be sufficient to stimulate a prompt burst of the immune response. In fact, in patients fed supplemented formulas, the up-regulation of the immune system becomes evident only some days after operation, while the impairment of the host defense mechanisms occurs immediately after major surgery.2,5

In a recent phase 2 trial, Braga et al19 reported that when the provision of immunonutrients was anticipated before surgery the early postoperative immune impairment was effectively controlled, the postoperative inflammatory response was modulated, and gut microperfusion and oxygen metabolism were up-regulated. However, data supporting translation of these biologic benefits to clinical advantages are warranted. Thus, a phase 3 trial was designed to evaluate whether the perioperative administration of immunonutrition could reduce postoperative infections after major surgery for cancer. Both well-nourished and malnourished patients were included in the study because the immunoenhancing diet was not given perioperatively to simply provide energy and proteins but mainly to counteract the postoperative immune and metabolic alterations that also occur in well-nourished patients.1,5,19

RESULTS

Six patients (4 in the supplemented group and 2 in the control group) who did not
PATIENTS AND METHODS

This was a prospective, randomized, double-blind clinical trial. Enrolled in the study were 206 consecutive patients of both sexes, aged between 18 and 75 years, with neoplasm of colorectum, stomach, or pancreas and who were candidates for elective curative surgery. Exclusion criteria were alterations of the pulmonary, cardiovascular, renal, or hepatic function; history of recent immunosuppressive therapy (including preoperative radiochemotherapy) or immunological diseases; ongoing infection; emergency operation; and preoperative evidence of widespread metastatic disease, as previously described. Patients were required to sign a written informed consent after the details of the protocol were fully explained. The protocol was approved by the Ethical Committee of the San Raffaele Institute, Milan, Italy.

By means of sealed envelopes, patients were randomized to drink 1 L/d for 7 consecutive days of either a supplemented liquid diet (Impact; Novartis Nutrition, Bern, Switzerland) or a control isonitrogenous, isocaloric liquid diet. In addition to the 2 liquid diets, the patients of both groups were advised to consume standard food as desired. One liter of Impact contains the following: 12.5 g of arginine, 3.3 g of ω3 fatty acids, and 1.2 g of RNA. The kilojoule-to-milliliter ratio is 1:1. The preoperative treatment was carried out as outpatient therapy. Hospital admission was scheduled 2 days before surgery. The preoperative diets were provided by the manufacturer in powder form, to be mixed with water before drinking. The envelopes containing the two different powders were coded with 2 different letters. To ensure the double-blind nature of the study, the 2 formulas were prepared to obtain a liquid suspension with the same taste and appearance. The control diet was specially formulated to meet those characteristics and it was not commercially available.

The fish oil was encapsulated in microcaplets to avoid its smell or taste in the experimental diet. Palliative surgery for intraoperative evidence of metastatic disease or unresectable primary tumor, and the lack of preoperative feeding were considered protocol violations.

Eight days before surgery (day −8), the following baseline measures were determined in all patients: plasma levels of albumin, retinol-binding protein, prealbumin, transferrin, cholinesterase activity, hemoglobin, and C-reactive protein. Serum levels of interleukin 6 (IL-6) were measured in the first 60 patients by a commercially available enzyme-linked immunosorbent assay (Genzyme Diagnostics, Cambridge, England). Patients with weight loss of 10% or more of usual body weight were considered as malnourished. Performance status was assessed in all patients according to the Karnofsky scale. Baseline measures were reassessed 1 day before surgery (−1) and 1 (+1) and 8 (+8) days after surgery.

Intestinal washout with an iso-osmotic solution (3 L) was carried out the day before operation in patients undergoing colorectal surgery. The evening before and the morning of operation, patients were also treated with enema. These patients received antibiotic prophylaxis with a single intravenous dose (2 g) of cefotetan disodium 30 mg F. The preoperative diet regimen was interrupted permanently.

Table 2 describes the distribution of the adverse effects in the 2 groups. The daily mean postoperative volume infused was 1038 ± 352 mL in the control group vs 1060 ± 309 mL in the supplemented group (P = .58).

The intent-to-treat analysis of postoperative infections and the results of the eligible patients are shown in Table 3. The intent-to-treat analysis included the 6 patients who did not complete the preoperative diet regimen (2 in the control group and 4 in the control group) and the 15 patients with anastomotic leak. In the eligible population (171 patients), 31 infections occurred in a total of 30 patients (17.5%). There was a significantly lower number of patients who developed postoperative infections in the supplemented group (9/85; 11%) than in the control group (21/86; 24%) (P = .02; \( \chi^2 = 4.801 \)). The mean duration of antibiotic therapy needed to treat postoperative infections was 6.7 ± 1.7 days in the supplemented group vs 9.0 ± 2.5 days in the control group (P = .001). The mean length of postoperative stay was significantly shorter in the patients receiving the supplemented formula than in the control group (11.1 ± 4.4 days vs 12.9 ± 4.6 days, respectively; P = .01). The post hoc analysis of postoperative infections in both well-nourished and malnourished patients showed that the administration of the supplemented diets significantly reduced the rate of postoperative infections regardless of the baseline nutritional status (Figure).

Table 4 shows the distribution of postoperative noninfectious complications. No significant difference was...
observed between the 2 groups. Reoperation was necessary in 3 patients (2%) (1 in the supplemented group for gastrointestinal tract bleeding and 2 in the control group—1 for fascial dehiscence and 1 for hemoperitoneum).

Postoperative mortality was 0.6% (1 patient in the control group died of septic shock secondary to pneumonia).

Table 5 reports the variations of nutritional values, C-reactive protein, and IL-6. The IL-6 and C-reactive protein plasma levels sharply rose on day +1 in both groups but rose to a lesser extent in the supplemented group. On day +8, the IL-6 concentration returned to similar preoperative values in the supplemented group and remained elevated in the control group. None of the nutritional values were affected by the preoperative feeding. Surgical trauma caused a decline in all measures, although preoperative transferrin values were not significantly different compared with preoperative values. Eight days after operation the concentration of both prealbumin and retinol-binding protein were significantly higher in the supplemented group than in the control group.

**COMMENT**

In the last years, standard enteral preparations have been modified by adding immunonutrients, such as arginine, glutamine, ω-3 fatty acids, nucleotides, and others. These substrates have been shown to up-regulate host immune response, to control inflammatory response, and to modulate nitrogen balance and protein synthesis after injury. All of these substrates, tested separately or in different combinations, improved septic morbidity and mortality in animal models.

Twelve prospective randomized studies have investigated the effects of immunonutrition on outcome either after major operation for cancer (6 trials) or after severe injury (4 trials of intensive care unit [ICU] patients and 2 trials of burn patients) (9,12–14). Gottschlich et al (burn patients) and Moore et al (ICU patients) reported a significant reduction of septic complications in immunonourished patients. In a large multicenter trial of ICU patients, Bower and colleagues found that the patients fed the supplemented diet had a substantial reduction of length of stay and significant reduction of frequency of acquired infections if the patients had septic complications on admission to the study; however, there

Side effects from enteral feeding, such as abdominal cramping, bloating, diarrhea (defined as more than 3 liquid stools per day), and emesis, were recorded. If any side effect appeared, jejunal infusion was reduced or discontinued for 4 hours and then resumed at a lower infusion rate.

The following postoperative infectious complications were recorded by the surgical staff who were not involved in the study: abdominal abscess, peritonitis, surgical wound infection, urinary tract infection, pneumonia, bacteremia, and sepsis, as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference; and overinfection of pancreatic fistula. Patients were followed up for infectious complications for 30 days after hospital discharge by serial in-hospital visits. Noninfectious complications were also recorded.

It was assumed that postoperative infections would occur in approximately 25% of the patients if not treated. A reduction of 50% in the incidence rate would be considered to indicate the efficacy of treatment. Detecting a difference of this magnitude admitting a type I error level of 0.05 and a power of 0.90 required the presence of 70 patients in each group. The Student t test and the Mann-Whitney U test were used to compare continuous variables, and the χ2 test and Fisher exact test were used to compare discrete variables. Values of P<.05 were considered to indicate statistical significance (2-tailed test). The SPSS 7.5 package for Windows (SPSS Inc, Chicago, Ill) was used for statistical analysis. Data are given as mean ± SD.
was no difference between treated and control groups in the intent-to-treat analysis. Conversely, no beneficial effects by immunonutrition were reported by Mendez et al\textsuperscript{18} (ICU patients) and by Saffle et al\textsuperscript{17} (burn patients). In cancer patients undergoing elective surgery, Daly et al reported, in 2 different studies\textsuperscript{1,7} a significant reduction of postoperative infections in patients who were given immunonutrition early after surgery. A multicenter study from Germany\textsuperscript{14} showed a slight reduction of overall postoperative complication rate in the immunonutrition group (22% vs 31% in the control group). When the authors grouped complications occurring before or after postoperative day 5, the immunonutrition group had a significantly less incidence of late postoperative complications, whereas no difference was found in the early postoperative complication rate. These results seem consistent with the hypothesis that some days of feeding are necessary to improve the host defense and subsequently to reduce infections. Heslin et al\textsuperscript{13} who studied 195 patients undergoing elective cancer surgery, did not find a significant difference in postoperative infectious and noninfectious complications by comparing groups treated with either an early postoperative immunoenhancing diet or simple crystalloid fluid replacement. However, in the immunonutrition group the average postoperative energy intake was 60% of the nutritional goal and only 30% was given with the immunoenhancing diet. In our experience\textsuperscript{11,12} the early postoperative administration of enteral immunonutrition compared with a control enteral diet significantly reduced both severity of infections and postoperative stay, while the reduction of postoperative infection rate was not significant.

The differences in results among these trials might be attributed to the different populations studied and to several other variables, but a constant that associates all these studies is that the amount of immunoenhancing substrates given in the first days following operation is quite limited and therefore it may be not sufficient to allow a prompt burst of the immune system and an effective bacterial clearance shortly after surgery.\textsuperscript{1-7} As any other substance with supposed pharmacological action, immunonutrients should reach suitable tissue and plasma concentration to be active. For this reason we believed that a key point could have been to anticipate the provision of immunonutrients before surgery to obtain adequate levels at the time of surgical stress when the need for stimulation of the immune system is maximal.

Experimental studies demonstrated that the efficacy of immunonutrients was superior when they were given both before and after injury than solely in the postsurgery period\textsuperscript{20,29-31} In our recent randomized, double-blind trial\textsuperscript{19} the preoperative supplementation with an enteral diet enriched with arginine, ω3 fatty acids, and RNA prevented the early postoperative decline of both the

Table 1. Baseline and Surgical Characteristics of the 2 Groups*  

<table>
<thead>
<tr>
<th></th>
<th>Supplemented Group (n = 85)</th>
<th>Control Group (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.9 ± 11.9</td>
<td>60.8 ± 9.7</td>
</tr>
<tr>
<td>Male:female</td>
<td>50:35</td>
<td>56:30</td>
</tr>
<tr>
<td>Karnofsky scale, %</td>
<td>76 ± 12</td>
<td>78 ± 11</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.8 ± 10.9</td>
<td>67.6 ± 11.2</td>
</tr>
<tr>
<td>Malnourished patients, No.</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>125 ± 19</td>
<td>129 ± 17</td>
</tr>
<tr>
<td>Cancer site, No. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Colon</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Rectum</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Pancreas</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Time of surgery, min</td>
<td>234 ± 66</td>
<td>215 ± 82</td>
</tr>
<tr>
<td>Operative blood loss, mL</td>
<td>541 ± 410</td>
<td>605 ± 467</td>
</tr>
<tr>
<td>Transfused patients, No.</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Blood transfused, U</td>
<td>2.3 ± 1.0</td>
<td>2.8 ± 1.2</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD unless otherwise specified.

Table 2. Adverse Effects of Postoperative Enteral Feeding  

<table>
<thead>
<tr>
<th></th>
<th>Supplemented Group (n = 85)</th>
<th>Control Group (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal cramping</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Emesis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Inadvertent removal</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Overall</td>
<td>14 (16%)</td>
<td>18 (21%)</td>
</tr>
</tbody>
</table>

*P = .58 control group vs supplemented group.

Table 3. Distribution of Postoperative Infections  

<table>
<thead>
<tr>
<th></th>
<th>Intent-to-Treat Patients</th>
<th>Eligible Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supplemented Group (n = 102)</td>
<td>Control Group (n = 104)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Intra-abdominal abscess</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Overall infections</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>With any complications</td>
<td>14 (14%)</td>
<td>31 (30%)</td>
</tr>
</tbody>
</table>

*P = .008 (χ² = 6.908) control group vs supplemented group (intent to treat).
†P = .02 (χ² = 4.801) control group vs supplemented group (eligible).
phagocytosis ability and the respiratory burst of polymorphonuclear cells, significantly increased the nitric oxide plasma concentration and the CD4/CD8 ratio immediately after operation, reduced the synthesis of postoperative C-reactive protein, and improved both intestinal microperfusion, as directly measured by intraoperative laser Doppler flowmetry technique, and postoperative gut mucosal oxygen metabolism as measured by jejunal tonometry. In a similarly designed study, Wachtler et al\textsuperscript{34} reported that preoperative immunonutrition improved postoperative generation of leukotriene B\textsubscript{4} from peripheral neutrophils and reduced the leukotriene B\textsubscript{4}/leukotriene B\textsubscript{2} ratio.

The reduced production of IL-6 and C-reactive protein early after operation and the increased synthesis of prealbumin and retinol-binding protein in the supplemented group suggest a switch from the synthesis of acute-phase proteins to constitutive visceral proteins, probably as an effect of \( \omega-3 \) fatty acids on eicosanoid balance.\textsuperscript{35}

We speculate that the reduction of postoperative infections, which has been found in the supplemented group, is the translation of the immunologic and metabolic advantages reported in patients receiving perioperative supplementation with immunonutrition.\textsuperscript{19} The provision of immunoenhancing substrates before surgery appears to play a key role in reducing postoperative infections by a substantial activation of the immune response. Our data also suggest that perioperative immunonutrition is efficacious regardless of the baseline nutritional status of the patients. In fact, preoperative administration of immunoenhancing diets reduced postoperative infections also in well-nourished patients in whom a severe postoperative impairment of the host defense mechanisms has been reported.\textsuperscript{1,3,10}

In conclusion, the perioperative administration of the supplemented diet improved the synthesis of constitutive visceral proteins and significantly reduced the rate of postoperative infections and the length of stay in patients undergoing surgery for cancer.

The diets were generously provided by Novartis Nutrition, Bern, Switzerland.
