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Perioperative immunonutrition in normo-nourished patients undergoing laparoscopic colorectal resection

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Abstract
Objective To determine whether the joint implementation of immunonutrition and a laparoscopic approach improves morbidity, mortality, and length of stay (LOS) compared with dietary advice.
Background Despite progress in recent years in the surgical management of patients with colorectal cancer, postoperative complications are frequent. Nutritional supplements enriched with immunonutrients have recently been introduced into clinical practice. However, the immunonutrition benefits in patients undergoing colorectal laparoscopic surgery are unknown.
Methods This study was a prospective, randomized trial with two parallel treatment groups receiving an immune-enhancing dietary supplement for 7 days before colorectal resection and 5 days postoperatively or dietary advice.
Results A total of 128 patients were randomized. At baseline, both groups were comparable with respect to age, sex, surgical risk, comorbidities, and analytical and nutritional parameters. The median postoperative LOS was 5 days and was not significantly different between the groups. Wound infection differed significantly between the groups (11.50 vs. 0.00 %, $p = 0.006$). No other differences between the groups were identified.
Conclusions The joint use of laparoscopy and supplementation with immunonutrients reduces surgical wound infection in patients undergoing colorectal surgery.
Trial registration This study is registered with ClinicalTrial.gov: NCT0239396.

Keywords Laparoscopic · Immunonutrition · Surgical complication

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Laparoscopic colorectal surgery results in a faster return of gastrointestinal function, less postoperative pain, a shorter hospital length of stay (LOS), lower complication and readmission rates, and lower total health care utilization compared with open surgery [1–6].

Although the minimally invasive approach attenuates the risk of global complications, postoperative infections remain among the major complications that follow colorectal surgery. It is difficult to anticipate when such complications occur because their causes are varied. Furthermore, immunosuppression caused by surgical stress is one of the most important factors in complication development [7].

In recent years, standard nutritional formulas have been modified by the addition of arginine, omega-3 fatty acids, glutamine, and other components, which may increase immune responses by modulating inflammatory responses or enhancing protein synthesis after surgery. The potential effects of these immunonutrients include reducing infectious and other postoperative complications [8].

The aim of this study was to examine whether the joint implementation of immunonutrition with a laparoscopic approach improves morbidity, mortality, and LOS compared with the absence of supplementation. To date, few studies have investigated the role of immunonutrition in laparoscopic colorectal surgery.

Materials and methods

Patients treated at the University Hospital of Elche with a preoperative diagnosis of colorectal cancer were included.

Study design

This study was a prospective, randomized trial with two parallel treatment groups that received an immune-enhancing dietary supplement (IEF)-ATEMPERO® produced by Vegenat® for 7 days prior to colorectal resection and for 5 days postoperatively or received no supplements (WS group). The patients were randomized using the following Web site: http://www.randomization.com.

Dietary regimens

Patients who completed a staging workup and were deemed suitable candidates for colorectal resection with a laparoscopic approach were randomized to either the WS group or IEF group. The contents of the dietary supplement are listed in Table 1.

The patients in the IEF group were asked to consume two cartons (400 ml) of their assigned supplement per day for 7 days prior to surgery and to keep daily records of the volume consumed in a dedicated "compliance diary." This dietary supplement was consumed in addition to normal food intake. No patient received total parenteral nutrition during the preoperative period of the trial. Postoperatively, the patients were asked to consume two cartons (400 ml) of supplement each day for 5 days. The WS patients received only dietary advice.

Table 1 Composition of diet

Constituents (per 100 mL)	ATEMPERO®
Energy (kcal)	151
Protein (g), of which	8.3
Arginine	1
RNA	0.2
Carbohydrate (g), of which	13.3
Sugars	1
Fat (g)	5
Omega-3 fatty acids	0.77
Fiber (g)	1.7
Osmolarity (mOsm/l)	366
Sodium (mg)	100
Potassium (mg)	250
Chloride (mg)	100
Calcium (mg)	120
Magnesium (mg)	31
Phosphorus (mg)	115
Iron (mg)	1.7
Zinc (mg)	2.2
Copper (µg)	169
Manganese (mg)	0.27
Iodine (µg)	18
Fluorine (µg)	0.21
Chromium (µg)	3.9
Molybdenum (µg)	8.1
Selenium (µg)	7.1
Vitamin A (µg)	200
Vitamin D (µg)	3.3
Vitamin E (mg)	4.5
Vitamin K (µg)	7.9
Vitamin B_1 (mg)	0.33
Vitamin B_2 (µg)	0.33
Niacin (mg)	2.2
Vitamin B_6 (µg)	0.33
Vitamin B_{12} (µg)	1
Pantothenic acid (mg)	1.2
Biotin (µg)	6
Folic acid (µg)	41
Vitamin C (mg)	33
Choline (mg)	55

Inclusion and exclusion criteria

Inclusion criteria

All of the patients were required to be at least 18 years of age, to be scheduled for surgery for colorectal cancer with a laparoscopic approach, to be normo-nourished, and to provide written consent.

Exclusion criteria

All of the patients who did not meet the inclusion criteria were excluded. Other exclusion criteria included the need for emergency surgery, an American Society of Anesthesiologists (ASA) physical status of IV, renal failure defined via hemodialysis, patients on nutritional supplements, the inability to consume food orally (dysphagia, esophageal stricture, and pyloric stenosis), psychiatric disorders, human immunodeficiency virus (HIV), pregnancy, bowel obstruction, undergoing colostomy or ileostomy, and uncontrolled infection.

Enhanced recovery after surgery (ERAS) protocol All patients were treated according to the ERAS protocol. The ERAS interventions used were based on previously published protocols [9–11], which required that, during the preoperative period, the patients be given advice and that they receive intravenous iron supplementation in cases of preoperative anemia and no preparation of the colon regardless of the surgery being performed (diet low in fiber and enemas before surgery). It also required that the patients receive four carbohydrate-rich drinks (800 ml) 1 day prior to surgery and two additional drinks (400 ml each) on the morning of surgery. During surgery, goal-directed fluids were administered using esophageal Doppler monitoring, hypothermia and drainages were avoided, and epidural anesthesia was used. After surgery, nasogastric tubes were not used; rather, early mobilization was practiced, opioid-free pain control and prophylactic medication for nausea and vomiting was used, and oral fluids were administered early.

Protocol for the prevention of surgical site infection All patients were treated according to this protocol, and it was based on the previously published study [12]. The protocol included an antiseptic shower with chlorhexidine soap the same day of the intervention, preoperative preparation of the skin with chlorhexidine/alcohol solution, intravenous surgical antimicrobial prophylaxis (metronidazole and tobramycin) administered 30 min before incision, perioperative glucose levels <200 mg/dl, glove change every 90 min, perioperative maintenance of patient normothermia, and no bowel preparation. The incisions were closed using buried triclosan-coated polydioxanone antimicrobial sutures (PDS® Plus Antibacterial Suture; Ethicon, Inc., Somerville, NJ, USA) and irrigated with chlorhexidine solution. The incision was coated with cyanoacrylate tissue adhesive (Dermabond®; Ethicon, Inc., Somerville, NJ, USA).

Outcome measures

Patient baseline characteristics at the time of surgery (age, gender, ASA status, and major comorbidities) were obtained from each patient.

The 30-day postoperative complications were recorded. Complications were defined as any deviation from the normal postoperative course and were divided into minor and major complications. Minor complications included minor risk events, such as wound infections opened at the bedside, urinary tract infection, and postoperative ileus (Clavien-Dindo I–II) [13]. Major complications included potentially life-threatening complications and complications requiring surgical, endoscopic, or radiological intervention, such as an anastomotic leakage, an abdominal abscess, or pneumonia (Clavien-Dindo III–IV) [13]. Wound infection was defined as spontaneous drainage of purulent material from the wound or from the surgeon's deliberate revision and a positive culture of drained serous fluid. LOS and rates and causes of readmissions were also documented.

Nutritional (total protein, albumin, prealbumin, transferrin, and zinc) variables were assessed before nutritional supplementation, and normally nourished patients were enrolled in the study.

Ethics

The study was presented to the Hospital Ethical Board and was accepted as an interventional and randomized study. The research was conducted in accordance with the Declaration of Helsinki and local legislation. The patients provided informed consent to participate in the study. This study has been registered in the NCT register as NCT0239396.

Sample size calculation

We hypothesized that immunonutrition would reduce the wound infection rate. The sample size calculation was based on the detection of significant differences in the primary endpoint parameter of the trial. We assumed a postoperative wound infection rate of 25 % in the WS group according to the rates found in several studies in the literature. With an expected wound infection rate of 5 % in the IEF group, the trial sample size necessary for a power of 80 % and a one-sided significance level of 0.05 was calculated to be 58 patients per group. An assumed 10 % dropout rate in this trial (due to non-compliance and intolerance) increased the sample size to 64 patients per group. Therefore, at least 128 patients had to be included in the trial.

Statistical analyses

Statistical analyses of any differences between the two groups were performed using SPSS version 22 (SPSS Inc. Chicago, IL, USA). The data are presented as the mean ± standard deviations or as medians and interquartile ranges where appropriate. For dichotomous outcomes, the treatment groups were compared using the χ^2 test. The Mann–Whitney U and Kruskal–Wallis tests were used for continuous, non-normally distributed outcomes. For continuous, normally distributed data, analysis of variance (ANOVA) was used.

Results

Patients

Figure 1 shows the CONSORT flowchart for the study. Of the 128 patients who were randomized, two did not receive

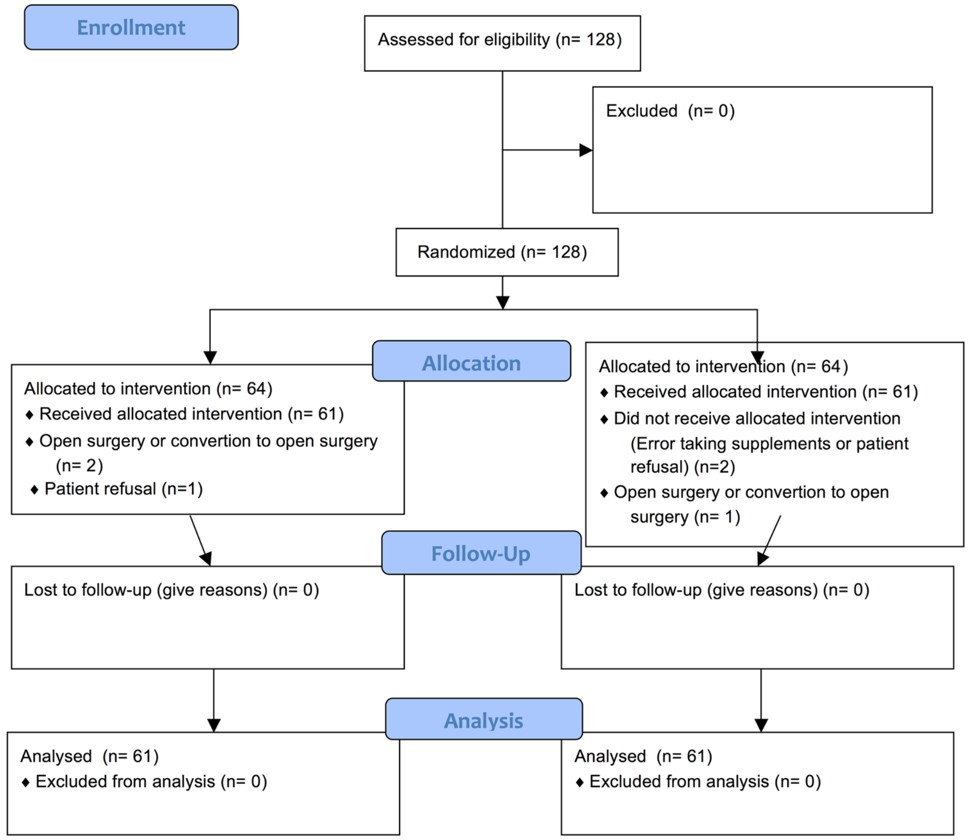

Fig. 1 Flow diagram for the trial

the intervention, one chose not to participate after the study started, and three either did not undergo laparoscopy or underwent conversion to open surgery. Thus, 122 patients were recruited to the trial over an 18-month period (WS, $n = 61$; IEF, $n = 61$).

At baseline, the two groups were comparable with respect to age, sex, surgical risk, comorbidity, and diagnosis (Table 2).

Results after seven days of preoperative nutritional supplementation

Patient enteral nutritional supplementation compliance and tolerance

All of the patients completed the preoperative nutritional treatment with a consumption of 400 ml per day. Preoperatively, the nutritional supplement drinks did not reduce the patients' normal dietary intake .

Surgery, postoperative treatment, and postoperative nutritional supplementation

Sigmoidectomy and right hemicolectomy comprised the majority of the procedures performed (64.7 %). There were no significant differences between the two groups with respect to the operative time or estimated intraoperative blood loss. Table 2 shows the surgical procedures that were performed. Postoperative nutritional supplementation tolerance is summarized in Table 3.

Postoperative hospital stay and readmission rate

The median length of the postoperative hospital stay was 5 days (range 3–22 days), 5 days for the WS group (range 3–22 days) and 5 days for the IEF group (range 3–19 days), with no difference between the groups ($p = 1.000$). Of all the patients, 2.46 % (three patients, two in the WS group and one in the IEF group) were readmitted following discharge for medical or surgical reasons, with no significant between-group differences. One patient presented with febrile syndrome, one presented with an abdominal wall abscess, and one presented with vomiting.

Postoperative morbidity/mortality

Table 4 summarizes the complications encountered. Approximately 80 % of the patients had an uneventful postoperative course without complications.

Table 2 Characteristics and surgical procedures of the two groups

Patient characteristics	Without perioperative immunonutrition ($N = 61$)	With perioperative immunonutrition ($N = 61$)	p value
Age (years)	68 (45–92)	69 (51–85)	0.469
Sex			0.586
Female	34 (55.7 %)	31 (50.8 %)	
Male	27 (44.3 %)	30 (49.2 %)	
Surgical risk: ASA			1.000
ASA I	21 (34.9 %)	21 (34.9 %)	
ASA II	32 (52.2 %)	32 (52.2 %)	
ASA III	8 (13.1 %)	8 (13.1 %)	
Morbidity			
Diabetes	8 (13.1 %)	8 (13.1 %)	1.000
Hypertension	27 (44.3 %)	19 (31.1 %)	0.135
Heart disease	7 (11.5 %)	10 (16.4 %)	0.433
Respiratory disease	6 (9.8 %)	6 (9.8 %)	1.000
Surgical procedure			0.984
Right hemicolectomy	19 (31.1 %)	19 (31.1 %)	
Left hemicolectomy	4 (6.6 %)	3 (4.9 %)	
Sigmoidectomy	20 (32.8 %)	21 (34.4 %)	
High anterior resection	12 (19.7 %)	10 (16.4 %)	
Low anterior resection	5 (8.2 %)	7 (11.5 %)	
Subtotal colectomy	1 (1.6 %)	1 (1.6 %)	

Quantitative variables are expressed as medians plus minimum and maximum values; qualitative variables are expressed as absolute numbers and percentages

Table 3 Postoperative nutritional supplementation tolerance

Number of bricks	Postoperative day 0	Postoperative day 1	Postoperative day 2	Postoperative day 3	Postoperative day 4	Postoperative day 5
0	13	4	4	6	7	7
0.5	10	12	14	6	6	0
1	22	25	22	14	9	0
1.5	7	9	11	15	11	0
2	9	11	10	20	28	54

The most common complications were surgical (12.30 %; 15 patients) followed by infectious complications (17.70 %; 13). The most common surgical complications were paralytic ileus (7.20 %; 9) and anastomosis leakage (4.10 %; 5). Finally, the most common infectious complications were wound infections (5.25 %; 7), respiratory infections (3.30 %; 4), and venous catheter infections (2.45 %; 3). Five patients (4.10 %) required repeat surgery, all due to anastomotic leakage. No patient died during the hospital stay or following discharge.

Table 4 shows the differences between the groups. There were fewer infectious complications in the IEF group than in the WS group, primarily due to a significant decrease in the wound infection rate (11.50 vs. 0.00 %, $p = 0.006$). Wound infection rate according to surgical procedure is summarized in Table 5.

Discussion

Our trial showed that immunonutrient supplements reduce surgical site infection even with the laparoscopic approach. Patients receiving immunonutrients preoperatively and postoperatively had fewer surgical site infections than those who received dietary advice.

Table 4 Complications

Outcome variable	Without perioperative immunonutrition ($N = 61$, %)	With perioperative immunonutrition ($N = 61$, %)	RR (95 % CI)	p value
Percentage with any complications[a]	21.30	18.00	1.231 (0.503–3.014)	0.649
Percentage with any surgical complications[a]	11.50	13.10	0.859 (0.291–2.536)	0.783
Anastomotic leak	3.30	4.90	0.655 (0.106–4.067)	0.648
Ileus	6.20	8.20	0.786 (0.201–3.079)	0.729
Others	1.60	1.60	1.000 (0.061–16.360)	1.000
Percentage with any infectious complications[a]	14.80	6.60	2.466 (0.716–8.491)	0.142
Wound infection	11.50	0.00	**0.470 (0.387–0.570)**	**0.006**
Pneumonia	3.30	3.30	1.000 (0.136–7.337)	1.000
Venous catheter infection	1.60	3.30	0.492 (0.043–5.569)	0.559
Mortality	0	0		
Reoperation rate	3.30	4.90	0.655 (0.106–4.067)	0.648

RR, relative risk with 95 % confidence interval in ()

Bold values indicate statistical significance ($p = 0.006$)

[a] Note that a patient may experience more than one complication

Table 5 Wound infection rate according to the surgical procedure

Wound infection	Without perioperative immunonutrition	With perioperative immunonutrition	p value
Right hemicolectomy	3 (15.8 %)	0 (0 %)	0.071
Left hemicolectomy	0 (0 %)	0 (0 %)	
Sigmoidectomy	2 (10 %)	0 (0 %)	0.137
High anterior resection	2 (16.7 %)	0 (0 %)	0.176
Low anterior resection	0 (0 %)	0 (0 %)	
Subtotal colectomy	0 (0 %)	0 (0 %)	

Infectious complications remain one of the major complications that appear in colorectal surgery despite the development of antibiotics. It is difficult to anticipate when this complication should arise because its causes are varied. However, immunosuppression caused by surgical stress is one of the most important factors associated with its development [7, 14].

Despite the advances and improvements have emerged in recent years in the management of surgical patients, surgical site infections are still prevalent. The colorectal surgery has the highest rates, although in the literature, there is wide variability, with values between 10 and 40 %, depending on the series [15].

There are several measures that have been implemented to try to improve these results. Appropriate antibiotic prophylaxis, patient normothermia, strict glycemic control, preparation of the surgical field with alcoholic solution, postoperative hyperoxygenation, proper shaving of the hair, inter alia, have performed well when the application is in conjunction [12, 15–21]. However, wound infection is still common in our environment. Therefore, new lines of research should be valued.

In our study, in which patients with similar baseline characteristics in both groups were included, we found a decrease in surgical site infection in patients of the immunonutrients group. We can, therefore, conclude that immunonutrition must be included with other currently used strategies for reducing postsurgical infection. Much more, when we know that, surgery is a stressor for patients and induces changes in the activity of the immune system in both innate and adaptive immunity [22]. Immune system responses after surgery can be inappropriate in some cases (systemic inflammatory response syndrome). Major abdominal surgery and laparotomy cause a release of local and systemic cytokines, inducing a systemic inflammatory response syndrome [23–25]. Laparoscopic surgery has been shown to attenuate both local and systemic inflammatory responses [26–29], although complications are still frequent.

To modulate this response, patients have recently received traditional nutritional formulas containing certain immunonutrients, primarily arginine, glutamine, omega-3 fatty acids, and nucleotides. However, scientific evidence regarding the effectiveness of this supplementation is limited. Our results provide further evidence for the benefits of using these substances in surgical patients.

Few studies have focused on patients undergoing surgery for colorectal resection; many include various gastrointestinal surgeries and different approaches. Additionally, the published results are contradictory in some cases.

For example, Braga et al. [30, 31] demonstrated that immunonutrition supplementation induced an immune response, increased intestinal microperfusion and oxygenation, and reduced the rate of surgical site infection. Equally, Horie et al. [32] stated that preoperative immunonutrition can reduce the rate of surgical site infection. However, not all published results demonstrate the benefits of immunonutrients with respect to postoperative infection. Helminen et al. [33] studied patients who underwent elective gastrointestinal surgery for benign or malignant gastrointestinal illnesses and received nutritional supplementation with arginine, omega-3, and RNA, and they observed no benefit of routinely prescribed immunonutrition. Sorensen et al. [34] obtained similar results in a study in patients who underwent elective surgery for colorectal cancer.

One study that was similar to the present study was published by Finco et al. [35]. That study, wherein only patients undergoing colorectal cancer surgery performed laparoscopically were included (28 patients who underwent laparoscopic colorectal surgery), did not describe decreased complications using enriched immunonutrient supplements. Importantly, the number of patients included in that study was much lower than that included in the present study.

Our study has some limitations. First, the number of cases was insufficient to enable robust conclusions to be drawn. Second, our study was performed at a center with multidisciplinary teams that were fully dedicated to colorectal surgery and had proven experience in colorectal laparoscopy. Therefore, it may be difficult to reproduce our results in non-experienced groups.

Conclusions

Although the laparoscopic approach in colorectal resections has a decreased complication rate and yields an earlier recovery than traditional open surgery, we must continue to identify search tools that allow the improvement of our results. Based on the data from the present randomized study, the implementation of the laparoscopic approach and immunonutrient-enriched supplements reduces the surgical site infection rate among patients undergoing colorectal resection. However, further studies are needed to understand how immunonutrients improve the prognosis of patients with colorectal cancer.

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Compliance with ethical standards

Disclosures Pedro Moya, Elena Miranda, Leticia Soriano-Irigaray, Antonio Arroyo, Maria-del-Mar Aguilar, Marta Bellón, Jose-Luis Muñoz, Fernando Candela, and Rafael Calpena have no conflicts of interest or financial ties to disclose.

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