Effect of Early Peripheral Parenteral Nutrition Support in an Enhanced Recovery Program for Colorectal Cancer Surgery: A Randomized Open Trial

Luis Sánchez-Guillén 1*, Leticia Soriano-Irigaray 2,2*, Francisco López-Rodríguez-Arias 1, Xavier Barber 3,1, Ana Murcia 2, M José Alcaide 1, Verónica Aranaz-Ostáriz 1, Álvaro Soler-Silva 1, Andrés Navarro-Ruiz 2 and Antonio Arroyo 1

Abstract: Background: Peripheral parenteral nutrition allows repletion of acute nutrient deficiencies and could prevent further nutrition deficits before and after colorectal surgery. A randomized open study was performed to evaluate the effect of perioperative peripheral parenteral nutrition (PPN) support on postoperative morbidity after colorectal cancer surgery within an enhanced recovery program. Methods: Patients were randomized into two groups: peripheral parenteral nutrition (PPN) (with Peri-Olimel N4-E) versus conventional fluid therapy (FT). Ninety-day postoperative complications, laboratory parameters, length of hospital stay, and compliance with the ERAS protocol were assessed. Results: A total of 158 patients were analysed. The overall 90-day complication rate was 38.6% (61 patients), and 24 patients had major complications (Clavien–Dindo III–V) (15.2%).

1. Introduction

Colorectal cancer (CRC) is still among the most frequently diagnosed cancers, accounting for 1.14 million new cases in 2020, and surgery continues to be the main pillar of treatment [1]. The multimodal enhanced recovery after surgery (ERAS) programs implemented in the last decade have led to substantial improvements in the care of patients undergoing elective colorectal surgery [2]. Designed to reduce perioperative stress, maintain physiological function postoperatively, and promote faster recovery, the widely accepted protocol includes clear recommendations from preoperative to postoperative management. However, postoperative complications remain common and about a third of patients suffer them, with an impact on the length of the hospital stay, costs, and income associated with increased mortality [3,4].
Perioperative nutritional care is one of the pillars of evidence-based ERAS programs, as patients undergoing oncological surgery present an increased risk of malnutrition. Surgical stress and the consequent increase in energy expenditure, weight loss, eating difficulties, and poor appetite decrease nutritional status. Although it is an underestimated value, 10–20% of patients with CRC are malnourished before surgery. Preoperative malnutrition should be corrected or at least improved preoperatively, as it can reduce infectious complications and improve the immune status of the patient [5,6]. Additionally, postoperative nutritional support is crucial in maintaining nutritional status during the catabolic postoperative period, and ERAS protocols support early postoperative feeding within hours after surgery. It has been demonstrated that early oral feeding can improve tissue healing and shorten the postoperative hospital stay, improving clinical outcomes, readmissions, and costs of care [7–11].

However, nutritional therapy during the postoperative recovery period, especially in older patients, is challenging. Decreased appetites, persistent nausea and vomiting, opioid-induced constipation, postoperative ileus, and lack of education about how to optimize their diet lead many patients to not achieving adequate nutritional requirements during the first postoperative days. Because of that, the use of parenteral nutrition (PN) should be considered, as it allows the repletion of acute nutrient deficiencies and prevents further nutrition deficit development and has demonstrated to be safe and effective. Preoperative PN, even 12 h before surgery, has proven to be valuable in stimulating both protein transcription and translation, reducing autophagy and lysosomal degradation, and augmenting the immune system, promoting lymphocyte proliferation in patients undergoing abdominal surgery, and could be beneficial for all patients [12–15].

Considering the different options for delivering PN, peripheral parenteral nutrition could narrow the nutritional gap in patients before surgery and those recovering after the procedure.

The aim of this study was to evaluate the effect of perioperative peripheral parenteral nutrition (PPN) support in patients undergoing elective CRC surgery versus conventional fluid therapy, improving overall complication rates and shorter stays in the context of an ERAS program.

2. Materials and Methods

2.1. Study Design and Participants

A single-centre, open, pragmatic, randomized controlled trial was performed comparing the influence of peripheral parenteral nutrition (PPN) (with Peri-Olimel N4-E) versus conventional fluid therapy (FT) on postoperative complications in colorectal surgery patients. Patients with a diagnosis of colorectal cancer between October 2016 and September 2019 treated in a university hospital (designated a Centre of Excellence in ERAS programs) were selected for inclusion. All patients diagnosed with a colorectal tumour scheduled for surgery with preoperative T1-T3NxM0 were included. Patients at severe nutrition risk by one of the ESPEN guidelines criteria (weight loss > 10–15% within 6 months, BMI < 18.5 kg/m², SGA grade C, or NRS > 5, and preoperative serum albumin < 30 g/L (without evidence of liver or kidney dysfunction)) were excluded [8,16]. Additional exclusion criteria were emergency surgery, an American Society of Anaesthesiologists (ASA) physical status IV, renal failure defined as necessitating haemodialysis, hepatic failure, allergy or sensitivity to egg or soy protein, severe bleeding disorder, congenital abnormality of amino acid metabolism, hyperlipidaemia, and inability to comply with the ERAS protocol.

All eligible patients provided written informed consent before undergoing study-related procedures. The study protocol was registered in the NCT register as NCT03606863 and approved by the Ethics Commission of the Elche University Hospital and performed in accordance with the Declaration of Helsinki (World Medical Association, 2013).
2.2. Randomization and Masking

Using online randomization software, patients were randomly assigned (1:1) into two parallel groups: the control group (conventional FT) or the experimental group (PPN with Peri-Olimel N4-E). Randomization was done by an external statistician. The investigators, surgeons, patients, and statisticians were unmasked to the group in which the patient was randomly allocated.

2.3. Procedures

All patients were admitted the day before surgery, and patients were preoperatively prepared with only a low fibre diet for three days before surgery. The ERAS bundles used were based on previously published protocols [2]. All the procedures of our ERAS pathway are described in Figure 1. Furthermore, it was required that the patients receive carbohydrate-rich beverages the day before and 2 h before surgery. The control group received conventional FT the day before surgery. The experimental group was treated with peripheral parenteral nutrition (PPN) Peri-Olimel N4E for 4 days (the day before the scheduled surgery and 3 days after surgery). Both groups received antithrombotic therapy and intravenous tobramycin 300 mg and metronidazole 1.5 g at the time of anaesthetic induction. All patients underwent surgery by colorectal surgeons.

2.3.1. Outcome Measures

The primary endpoint was the incidence of postoperative complications, according to the Clavien–Dindo criteria [17]. Minor complications were defined as Clavien–Dindo grades I–II, and major complications were defined as Clavien–Dindo grades III–V. The following variables were analysed as possible risk factors for postoperative complications: demographic data (age, sex), comorbidities (American Society of Anaesthesiologists (ASA) score, oral anticoagulants, smoking habit, high blood pressure, and diabetes), preoperative nutritional status (serum total protein), surgical details (surgical approach, type of anastomosis, perioperative transfusions), and characteristics of the disease (tumour location and TNM stage). Complications and mortality were evaluated at 90 days after surgery using the Clavien–Dindo score. Pathological details were evaluated (TNM system). Analytical (urea, creatinine, haemoglobin, leukocytes, lymphocytes, procalcitonin, and C-reactive protein) and nutritional (serum total protein, albumin, prealbumin, transferrin, and zinc) variables were determined before intervention and daily postsurgery (for the four days after surgery and the day of hospital discharge).

Our ERAS pathway includes a set of interventions from the ERAS protocol (Figure 1). The data on compliance were obtained during the postoperative hospital stay and, in cases of missing data, by a review of patients’ electronic medical charts. Compliance was assessed similarly to Gustafsson et al. [2], including elements before and during the postoperative period. Oral intake and early mobilization were considered crucial interventions for an early diagnosis of postoperative complications during the early postoperative days. Intraoperative ERAS elements and those for whom compliance was nearly 100% were excluded from analysis. A compliance rate ≥ 70% was considered an acceptable level of compliance. Any missing data (written information) about the duration or termination of ERAS interventions were considered noncompliant.

The patients were discharged following the criteria in ERAS, and they were followed for at least 90 days postoperatively. A confidential database was prepared for the collection of data.

2.3.2. Statistical Analysis

The sample size was calculated to compare the incidence of postoperative complications in the control group (patients receiving traditional fluid therapy) versus the intervention group (patients who received early nutritional support with peripheral parenteral nutrition (Peri-Olimel N4-E)). With a confidence level of 95% (alpha = 0.05) and a power of 80% (beta = 0.2) in a bilateral contrast, 170 subjects are required; 85 in the first group and
85 in the second to detect the difference between two proportions as statistically significant, which, for the control group, is expected to be 0.35 and, for the intervention group, is expected to be 0.17, assuming a 10% loss.

**Table 1. Enhanced recovery program.**

| Day of surgery (preoperative period) | **Hospital admission** |
|--------------------------------------|------------------------|
| Preoperative counseling and stoma education and marking (if necessary) | Preoperative counseling and stoma education and marking (if necessary) |
| Anaemia optimization (if necessary) | Anaemia optimization (if necessary) |
| Liquids on demand. Nutricia preop two shakes at 16:00 and 20:00 | Liquids on demand. Nutricia preop two shakes at 16:00 and 20:00 |
| Control the vital signs and blood pressure optimization | Control the vital signs and blood pressure optimization |
| Cleasing enema at 11 p.m | Cleasing enema at 11 p.m |
| Preoperative antithrombotic prophylaxis: Tinzaparine 3500 UI | Preoperative antithrombotic prophylaxis: Tinzaparine 3500 UI |
| Showering and shaving the surgical area | Showering and shaving the surgical area |
| Two shakes of Nutricia preop at 05:00 Remove at 06:30. | Two shakes of Nutricia preop at 05:00 Remove at 06:30. |
| Antibiotic prophylaxis 30–60 min before the first incision: Metronidazole 1.5 gr + Tobramicina 300 mg. | Antibiotic prophylaxis 30–60 min before the first incision: Metronidazole 1.5 gr + Tobramicina 300 mg. |
| Intraoperative goal-directed fluid therapy and avoidance of hypothermia | Intraoperative goal-directed fluid therapy and avoidance of hypothermia |
| Intraoperative pneumatic legs compression | Intraoperative pneumatic legs compression |
| Minimally invasive surgical access when feasible | Minimally invasive surgical access when feasible |
| Avoidance of drainage when possible under surgeon criteria | Avoidance of drainage when possible under surgeon criteria |
| Multimodal analgesia, abdominal wall blockade, epidural catheter in selected cases, and prevention of postoperative nausea and vomiting | Multimodal analgesia, abdominal wall blockade, epidural catheter in selected cases, and prevention of postoperative nausea and vomiting |
| Avoidance of nasogastric tubes | Avoidance of nasogastric tubes |
| Early oral feeding (meaning 6–8 h after surgery) with water, teas, and other beverages | Early oral feeding (meaning 6–8 h after surgery) with water, teas, and other beverages |
| Monitorization of vital signs and diuresis each 8 h. If diuresis is <500 cc in 24 h, notify the doctor on ward | Monitorization of vital signs and diuresis each 8 h. If diuresis is <500 cc in 24 h, notify the doctor on ward |

**Figure 1.** Enhanced recovery program.

Data were collected prospectively, and patients were followed up per protocol with individual case report forms. Continuous variables were reported using the median and interquartile range, while categorical variables were reported using the number of patients and percentage. Differences in the duration of hospitalization between the different groups were analysed with the Kruskal–Wallis test. A univariate analysis was carried out to assess
the association between the study variables (major AF, mortality, and morbidity) and the
different independent variables: continuous and categorical variables were analysed using
the Mann–Whitney U test and \( \chi^2 \) tests, respectively. After univariate analysis, we put
the variable into a logistic regression model to determine the independent risk factors
for a two-level response variable or ordinal logistic regression for categorical ordered
response. \( p < 0.05 \) was considered to indicate statistical significance (two-tailed test). For
the multivariate analysis of the response variable, we used two classification methods:
(i) logistic regression with a stepwise selection variable method and (ii) regression trees
with recursive partitioning for selection variables.

We performed all analyses using R software and the rpart package [18,19].

3. Results
3.1. Pre- and Perioperative Clinical and Laboratory Features

A total of 170 consecutive patients were allocated for the trial, but 12 were excluded
from the analysis according to the pre-established criteria. Figure 2 shows the CONSORT
flowchart for the study. Thus, 158 patients were analysed, 83 in the peripheral parenteral
nutrition group (PPN) versus 75 patients in the conventional fluid therapy group (FT).
Baseline characteristics were similar in both groups. The demographic, preoperative,
surgical, and pathological data for the entire sample are detailed in Table 1.

![CONSORT Flow Diagram](image)

Figure 2. Flowchart of patient in the study.
| Table 1. Demographic, preoperative, surgical, and pathological data of study population. | FT (N = 75) (%) | PPN (N = 83) (%) | TOTAL (N = 158) | p-Value |
|-------------------------------|----------------|----------------|----------------|---------|
| **Age (mean SD)**             | 67.8 (11.6)    | 71.4 (11.0)    | 69.7 (11.4)    | 0.049   |
| **Sex**                       |                |                |                |         |
| Male                          | 46 (47.4)      | 51 (52.6%)     | 97 (61.4)      | 1.000   |
| Female                        | 29 (47.5)      | 32 (52.5%)     | 61 (38.6)      |         |
| **ASA score**                 |                |                |                |         |
| 1                             | 10 (71.4)      | 4 (28.6%)      | 14 (8.9)       | 0.139   |
| 2                             | 38 (47.5)      | 42 (52.5%)     | 80 (50.6)      |         |
| 3                             | 27 (42.2)      | 37 (57.8)      | 64 (40.5)      |         |
| **Surgical approach**         |                |                |                |         |
| Open                          | 9 (52.9)       | 8 (47.1%)      | 17 (10.8)      | 0.845   |
| Laparoscopic                   | 66 (46.8)      | 75 (53.2)      | 141 (89.2)     |         |
| **Type of procedure**         |                |                |                |         |
| Abdominoperineal excision     | 13 (72.3)      | 5 (27.7)       | 18 (11.4)      | 0.551   |
| Left hemicolectomy            | 4 (40)         | 6 (60%)        | 10 (6.3)       |         |
| Subtotal colectomy            | 2 (50)         | 2 (50%)        | 4 (2.5)        |         |
| Total colectomy               | 0 (0)          | 1 (100)        | 1 (0.6)        |         |
| Hartmann                       | 1 (50)         | 1 (50)         | 2 (1.3)        |         |
| Right hemicolectomy           | 25 (46.3)      | 29 (53.7)      | 54 (34.2)      |         |
| ULAR                          | 2 (50)         | 2 (50)         | 4 (2.5)        |         |
| Anterior resection            | 19 (43.18)     | 25 (56.82)     | 44 (27.8)      |         |
| Sigmoidectomy                 | 9 (42.85)      | 12 (57.15)     | 21 (13.3)      |         |
| **Stoma**                     |                |                |                |         |
| 0                             | 53 (44.9)      | 66 (55.1)      | 119 (75.4)     | 0.402   |
| 1                             | 22 (56.5)      | 17 (43.5)      | 39 (24.6)      |         |
| **Type of stoma**             |                |                |                |         |
| Colostomy                     | 16 (64)        | 9 (36)         | 25 (15.8)      | 0.307   |
| Ileostomy                     | 5 (35.7)       | 9 (64.3)       | 14 (8.9)       |         |
| **Baseline disease**          |                |                |                |         |
| Left colon cancer             | 6 (42.8)       | 8 (57.2)       | 14 (8.9)       | 0.651   |
| Right colon cancer            | 19 (41)        | 27 (59)        | 46 (29.1)      |         |
| Transverse colon cancer       | 4 (66.7)       | 2 (33.3)       | 6 (3.8)        |         |
| Rectal cancer                 | 35 (52.2)      | 32 (47.8)      | 67 (42.4)      |         |
| Sigmoid colon cancer          | 11 (44)        | 14 (56)        | 25 (15.8)      |         |
| **Anastomosis configuration** |                |                |                |         |
| Side to side                  | 25 (48.1)      | 27 (51.9)      | 52 (32.9)      | 0.280   |
| End to side                   | 0 (0)          | 3 (100)        | 3 (1.9)        |         |
| End to end                    | 36 (43.4)      | 47 (53.6)      | 83 (52.5)      |         |
| No anastomosis                | 14 (70)        | 6 (30)         | 20 (12.7)      |         |

Ninety-seven patients (61.4%) were men and 61 were women, with a median age of 72 years and mainly ASA II (50.6%) and III (40.5%). All patients underwent scheduled surgery, and the laparoscopic approach was performed in 89.2% of the patients. The most frequent procedures were right hemicolectomy in 54 patients (34.2%) and anterior rectal resection in 44 (27.8%). A stoma was performed in 39 patients (24.6%), of whom 25 underwent a colostomy and 14 underwent an ileostomy. The most frequent type of anastomosis was end-to-end anastomosis in 83 patients (52.5%).

At the time of recruitment, serum total protein, albumin, prealbumin, transferrin, haemoglobin, and zinc and all laboratory parameters were comparable between the two groups, and there were no significant differences between them (Table 2).
Table 2. Values of the parameters analyzed before and after surgery.

| Parameter                          | FT (N = 75)                  | PPN (N = 83)                  | p-Value  |
|------------------------------------|------------------------------|------------------------------|----------|
|                                   | Before surgery               | First day after surgery      | Three day after surgery |
| GLUCOSE, mean (SD)                 | 106.798 (28.075)             | 118.422 (21.159)             | 96.641 (18.586)         |
|                                   | 108.406 (25.622)             | 136.079 (36.321)             | 116.073 (30.522)        |
|                                   | 0.706                         | <0.001                       | <0.001                |
| UREA, mean (SD)                    | 41.199 (17.823)              | 31.678 (13.25)               | 34.105 (18.152)         |
|                                   | 44.319 (15.473)              | 38.243 (15.492)              | 37.944 (20.903)         |
|                                   | 0.239                         | 0.005                        | 0.220                 |
| CREATININE, mean (SD)              | 0.836 (0.272)                | 0.74 (0.256)                 | 0.796 (0.336)           |
|                                   | 0.846 (0.255)                | 0.777 (0.296)                | 0.774 (0.424)           |
|                                   | 0.795                         | 0.404                        | 0.729                 |
| TOTAL PROTEINS, mean (SD)          | 7.108 (0.603)                | 5.644 (0.589)                | 5.998 (0.694)           |
|                                   | 6.944 (0.648)                | 5.522 (0.609)                | 5.528 (0.63)            |
|                                   | 0.102                         | 0.203                        | 0.508                 |
| ALBUMINE, mean (SD)                | 4.058 (0.404)                | 3.145 (0.394)                | 3.039 (0.493)           |
|                                   | 3.956 (0.484)                | 3.053 (0.433)                | 2.996 (0.441)           |
|                                   | 0.153                         | 0.168                        | 0.554                 |
| PREALBUMIN, mean (SD)              | 22.128 (5.728)               | 16.535 (3.669)               | 13.998 (3.919)          |
|                                   | 21.236 (5.052)               | 16.807 (3.965)               | 14.472 (3.606)          |
|                                   | 0.298                         | 0.655                        | 0.429                 |
| HEMOGLOBIN, mean (SD)              | 12.748 (1.639)               | 11.221 (1.759)               | 11.168 (1.859)          |
|                                   | 12.82 (1.949)                | 11.414 (1.819)               | 11.203 (1.647)          |
|                                   | 0.802                         | 0.497                        | 0.900                 |
| TRANSFERRINE, mean (SD)            | 257.348 (54.15)              | 201.16 (42.743)              | 185.008 (43.717)        |
|                                   | 271.33 (65.302)              | 214.134 (46.386)             | 192.315 (49.159)        |
|                                   | 0.146                         | 0.069                        | 0.325                 |
| ZINC, mean (SD)                    | 63.94 (16.692)               | 43.074 (10.037)              | 59.705 (15.865)         |
|                                   | 64.774 (14.079)              | 35.422 (14.203)              | 48.058 (16.313)         |
|                                   | 0.298                         | <0.001                       | <0.001                |
| WBC, mean (SD)                     | 6.039 (2.322)                | 9.22 (2.94)                  | 7.152 (2.893)           |
|                                   | 6.189 (2.125)                | 10.964 (3.692)               | 7.498 (2.567)           |
|                                   | 0.673                         | 0.001                        | 0.426                 |
| % NEUTROPHILS, mean (SD)           | 64.514 (8.692)               | 80.241 (5.627)               | 74.029 (9.402)          |
|                                   | 63.887 (9.46)                | 81.135 (6.161)               | 72.927 (8.522)          |
|                                   | 0.665                         | 0.342                        | 0.439                 |
| LYMPHOCYTES, mean (SD)             | 22.91 (7.928)                | 11.634 (4.513)               | 14.857 (7.235)          |
|                                   | 23.366 (8.923)               | 10.876 (5.381)               | 15.487 (7.135)          |
|                                   | 0.734                         | 0.340                        | 0.581                 |
| PLATELETS, mean (SD)               | 230.802 (117.353)            | 215.17 (102.572)             | 213.432 (97.272)        |
|                                   | 230.108 (72.006)             | 212.811 (66.995)             | 203.345 (73.989)        |
|                                   | 0.964                         | 0.863                        | 0.461                 |
| FIBRINOGEN, mean (SD)              | 412.79 (120.087)             | 445.295 (119.332)            | 642.406 (181.08)        |
|                                   | 379.33 (115.917)             | 440.461 (114.263)            | 654.873 (203.599)       |
|                                   | 0.076                         | 0.794                        | 0.685                 |
| RCP, mean (SD)                     | 14.71 (29.005)               | 60.982 (37.77)               | 114.501 (95.885)        |
|                                   | 11.017 (22.532)              | 63.545 (45.955)              | 95.086 (67.622)         |
|                                   | 0.369                         | 0.703                        | 0.140                 |
| PROCALCITONINE, mean (SD)          | 0.634 (3.664)                | 0.545 (1.054)                | 1.631 (3.636)           |
|                                   | 0.164 (0.129)                | 0.963 (1.687)                | 1.751 (7.424)           |
|                                   | 0.245                         | 0.066                        | 0.899                 |

WBC: white blood cells, RCP: reactive C protein.
3.2. Postoperative Changes in Laboratory Parameters

Postoperative changes in laboratory parameters were also comparable between the two groups (Table 2). For both groups, the postoperative serum total protein, albumin, pre-albumin, transferrin, haemoglobin, and zinc levels were substantially decreased compared with the preoperative levels. However, there were no significant differences between the groups, and only glucose was higher in the PPN group (118.422 in FT vs. 136.079 in PPN on the first day after surgery \( p < 0.001 \), and 96.641 in FT vs. 116.073 in PPN on the third day after surgery \( p < 0.001 \)).

3.3. Postoperative Complications and Mortality

The median compliance with the measures programmed in the protocol and within the multimodal rehabilitation programs during the preoperative and intraoperative period was 98.6%.

The overall morbidity rate was 38.6% (61 patients), including any deviation in the postoperative course. Thirty-seven patients (23.4%) suffered minor complications (Clavien–Dindo I–II), and 24 patients suffered major complications (Clavien–Dindo III–V) (15.2%). The most frequent complications were anastomosis-related complications (17.7%) followed by surgical site infections (SSIs) (12.6%). Major anastomotic leak was diagnosed in 18 patients (11.4%). The mortality rate was 1.3% (two patients). The median postoperative hospital stay was 6 days (25th–75th percentile: 5–8 days) for the entire group and was lower in the PPN group (6 days (5–8) vs. 7 days (5–9) in the FT group) \( p = 0.19 \) (Table 3).

Table 3. Postoperative morbidity details for the whole group of patients.

|                          | FT \( N = 75 \) (%) | PPN \( N = 83 \) (%) | \( p \)-Value |
|--------------------------|---------------------|----------------------|--------------|
| Postoperative complications | 33 (0.44)           | 28 (33.7)            | 0.186        |
| Major complications       | 14 (18.7)           | 10 (12)              | 0.001        |
| (C–D III–V)               |                     |                      |              |
| Minor complications       | 19 (25.3)           | 18 (21.7)            | 0.001        |
| (C–D I–II)                |                     |                      |              |
| Anastomotic leak          | 15 (20)             | 13 (15.6)            | 0.062        |
| Major leak                | 12 (16)             | 6 (7.2)              | 0.001        |
| Minor leak                | 3 (4)               | 7 (8.4)              | 0.001        |
| Postoperative ileus       | 12 (16)             | 13 (15.7)            | 0.954        |
| Surgical site infections (SSI) | 11 (14.6)       | 9 (10.8)             | 0.47         |
| Other complications       | 7 (9.3)             | 5 (6)                | 0.433        |
| Length of hospital stay (LOS) | 7 (5–9)           | 6 (5–8)              | 0.19         |

PPN: parenteral peripheral nutrition, FT: fluid therapy, C–D: Clavien–Dindo. Chi-Square was used for determined the association of variables under study (bilateral significance).

The variables associated with morbidity in the univariate analysis are expressed in Table 4. In the univariate analysis, first day mobilization, first day tolerance for oral feeding, and type of oral feeding on the third postoperative day were related to postoperative morbidity. In the multivariate analysis, the intervention (PPN vs. FC) showed a protective effect against postoperative complications \( p = 0.0031, \) OR = 0.2 (CI: 0.08–0.87), with an 80% lower risk of complications in the group that received PPN.

Following ordinal regression, the risk of postoperative morbidity was established in levels (no complications, minor complications, or major complications). The OR for PPN showed a protective effect, being 73% less likely to develop complications or to move from minor to major complications if the patients received PPN versus the group receiving FT. Additionally, patients with early oral tolerance also were 78% less likely to develop complications or move from minor to major complications (Table 5).
Table 4. Association of categorical variables related to the patient, the surgery, and the tumor with morbidity at univariate analysis (χ² test) and evaluation of independent risk factors for morbidity by multivariate analysis (logistic regression) with a Wald test for global variable significance.

| Variables                  | Patients without Complications | Patients with Any Complications | p-Value ¹ | Odds Ratio ² | 95 % CI ² | p-Value ² |
|----------------------------|--------------------------------|---------------------------------|-----------|--------------|-----------|-----------|
| Age (<65)                  | 36 (37.1)                     | 19 (31.1)                       | 0.7133    | 1.0000       | (0.43, 2.31) | 0.4326    |
| Age (65–75)                | 25 (25.8)                     | 16 (26.2)                       | 0.77      | 1.0000       | (0.43, 2.31) | 0.4326    |
| Age (>75)                  | 36 (37.1)                     | 26 (42.6)                       | 0.77      | 1.0000       | (0.43, 2.31) | 0.4326    |
| Gender Female              | 35 (36.1)                     | 26 (42.6)                       | 0.5129    | 1.0000       | (0.43, 2.31) | 0.4326    |
| Gender Male                | 62 (63.9)                     | 35 (57.4)                       | 1.0000    | 1.0000       | (0.43, 2.31) | 0.4326    |
| ASA score I–II             | 58 (59.8)                     | 36 (59)                         | 0.6188    | 1.0000       | (0.43, 2.31) | 0.4326    |
| ASA score III              | 39 (40.2)                     | 25 (41)                         | 1.0000    | 1.0000       | (0.43, 2.31) | 0.4326    |
| PPN No                     | 42 (43.3)                     | 33 (54.1)                       | 0.2461    | 1.0000       | (0.43, 2.31) | 0.4326    |
| PPN Yes                    | 55 (56.7)                     | 28 (45.9)                       | 0.2461    | 1.0000       | (0.43, 2.31) | 0.4326    |
| Surgical approach Open     | 7 (7.2)                       | 10 (16.4)                       | 0.1215    | 1.0000       | (0.43, 2.31) | 0.4326    |
| Surgical approach Laparoscopy No | 90 (92.8)                  | 51 (83.6)                       | 0.1215    | 1.0000       | (0.43, 2.31) | 0.4326    |
| Surgical approach Laparoscopy Yes | 79 (81.5)                  | 40 (65.6)                       | 0.1215    | 1.0000       | (0.43, 2.31) | 0.4326    |
| 1st day mobilization No    | 16 (16.5)                     | 25 (41)                         | 0.1215    | 1.0000       | (0.43, 2.31) | 0.4326    |
| 1st day mobilization Yes   | 81 (83.5)                     | 36 (59)                         | 0.1215    | 1.0000       | (0.43, 2.31) | 0.4326    |
| 1st day tolerance No       | 7 (7.2)                       | 20 (32.8)                       | 0.1215    | 1.0000       | (0.43, 2.31) | 0.4326    |
| 1st day tolerance Yes      | 90 (92.8)                     | 41 (67.2)                       | 0.1215    | 1.0000       | (0.43, 2.31) | 0.4326    |
| 2nd day diet Clear liquid/Full liquid diet | 72 (74.2)                  | 42 (68.9)                       | 0.5813    | 0.619       | (0.38, 0.96) | 0.0575    |
| 2nd day diet Pureed food/soft food diet | 25 (25.8)                  | 19 (31.1)                       | 0.5813    | 0.619       | (0.38, 0.96) | 0.0575    |
| 3rd day diet Clear liquid/Full liquid diet | 24 (24.7)                  | 25 (41)                         | 0.5813    | 0.619       | (0.38, 0.96) | 0.0575    |
| 3rd day diet Pureed food/soft food diet | 73 (75.3)                  | 36 (59)                         | 0.5813    | 0.619       | (0.38, 0.96) | 0.0575    |

¹ univariate analysis; ² multivariate analysis. ASA: American Sociecity of Anesthesiology, PPN: peripheral parenteral nutrition.

Table 5. Multivariate ordinal logistic regression for complication response variable taking account the order for non-complication vs. minor vs. major complications. Proportional odds ratios are shown.

| Variables                  | OR (95% CI) |
|----------------------------|-------------|
| Age (<65)                  | 0.51 (0.13–1.8) |
| Age (65–75)                | 1.15 (0.32–4.11) |
| Age (>75)                  | 1.0000       |
| Gender Female              | 1.92 (0.75–4.92) |
| Gender Male                | 1.0000       |
| ASA score I–II             | 0.63 (0.20–1.86) |
| ASA score III              | 1.0000       |
| PPN No                     | 0.27 (0.09–0.72) |
| PPN YES                    | 1.0000       |
| Surgical approach Open     | 0.66 (0.17–2.57) |
| Surgical approach Laparoscopy No | 1.0000     |
| Surgical approach Laparoscopy Yes | 1.0000     |
| 1st day mobilization No    | 1.14 (0.29–4.82) |
| 1st day mobilization Yes   | 1.0000       |
| 1st day tolerance No       | 0.22 (0.05–0.98) |
| 1st day tolerance Yes      | 1.0000       |
| 3rd day diet Clear liquid/Full liquid diet | 1.17 (0.43–3.38) |
| 3rd day diet Pureed food/soft food diet | 0.64 (0.20–2.00) |

OR: odds ratio, ASA: American Society of Anesthesiology, PPN: peripheral parenteral nutrition.

Through decision trees, the risk of complications according to the degree of compliance with the ERAS programs during the first postoperative day was established. Patients with no tolerance to oral feeding on the first postoperative day showed a 73% higher risk of...
postoperative complications. If early postoperative mobilization was not achieved, the risk of postoperative complications increased by 50%. In these cases, with poor compliance during the first postoperative day, PPN showed a protective effect, preventing 28% of postoperative complications (Figure 3).

4. Discussion

To the best of our knowledge, this is the first trial that shows that PPN supplementation and early compliance with ERAS programs can reduce postoperative morbidity. Patients receiving PPN had a lower risk of complications than those who received conventional FT, and PPN decreased the chance of worsening complications or developing major postoperative complications by 73%. Compliance with ERAS bundles has a summative impact, decreasing complications, and PPN has shown a protective effect for patients who cannot truly fulfill ERAS protocols because of any deviation in the postoperative course.

The role of peripheral parenteral nutrition in malnourished patients or patients who cannot tolerate oral or enteral nutrition is proven; however, the role of peripheral parenteral nutrition in well-nourished patients who are undergoing colorectal surgery has not yet been investigated. Several recent studies have evaluated the incidence of real malnutrition in well-nourished preoperative patients. Dolan et al. showed that, in patients undergoing CRC surgery, the incidence of sarcopenia is much higher than that described and treated preoperatively and could reach up to 50% [20]. In these patients, intensive perioperative nutrition therapy should be established, especially in fragile and elderly patients [21]. It is thus necessary to improve the nutritional status of these patients with short-term nutritional supplementation. PN provides an adequate and reliable amount of macronutrients and micronutrients, and the intravenous route of administration of nutrients may also allow for rapid improvement in nitrogen balance, increased muscle mass, faster recovery from surgery, improved immune function, and a decrease in the number of general and infectious complications [22]. Low preoperative serum levels of total proteins, albumin, prealbumin, or transferrin have been associated with increased surgical infections, increased morbidity and mortality, and increased hospital stay [23–25]. Fasting, reduced protein–calorie intake, and increased catabolic activity triggered by the stress of surgery are reflected in the decrease in analytical parameters such as urea and serum proteins. This decrease seems to be directly related to the degree of surgical stress to which the patient is subjected [26,27]. In our study, we only observed differences in glucose, urea, and zinc postoperative laboratory parameters between the PPN and FT groups in the short-term follow-up. As expected, we did not see differences in total protein and/or serum albumin levels. As serum proteins have a short half-life, they cannot be used to
predict changes in the nutritional status of patients in the short term after an intervention, as shown by Rinniella et al. [28]. Peri-Olimel N4-E is a PN emulsion for perfusion by the peripheral route and is composed of amino acids, lipids, and glucose, which can complement enteral and oral nutrition, until the patient has a normal tolerance and is able to reach the minimum daily requirements orally. The osmolarity of the admixture was 750 mOsm/l, which allowed its administration through a peripheral vein. Appropriate osmolarity reduces the risk of peripheral venous thrombophlebitis [29]. It also includes electrolytes (sodium, potassium, calcium, magnesium, phosphate) and can be added to a mixture of trace elements and vitamins. The lipid emulsion is based on olive oil, having a high oleic acid content, which could better preserve the immune response of the patient, decrease oxidative stress, and reduce inflammation, thus improving the healing process, the rate of postoperative infection, and the recovery of the patient [30]. Our results showed an important reduction in all complications, including both major and minor complications. These data suggest that early PPN may modulate the immune response to surgery and sustained postoperative immunosuppression and lead to reduced infectious complications. It is generally believed that major surgery is accompanied by increased catabolism and sustained postoperative immunosuppression, which potentially increases the risk for infectious complications, particularly in patients undergoing surgery for cancer [31]. Similarly, Williams et al. recently observed reduced postoperative major and minor complications with early oral nutritional supplementation (infectious complications ($p < 0.03$), pneumonia ($p < 0.04$), ICU admissions ($p < 0.04$), and gastrointestinal complications ($p < 0.05$) [11].

The importance of maintaining caloric–protein intake leading to better compliance with the ERAS protocol bundles was shown by a significant reduction in the risk of complications. In fact, the consumption of 60% or more of the protein needs during the first 3 postoperative days has been associated with a shorter hospital stay [32]. ERAS programs aim to reduce metabolic stress caused by surgical trauma while supporting early recovery of the patient. They are based on the fulfilment of different bundles (a package of four or five measures aimed at preventing an adverse event) at different moments of the operative process with a demonstrated effectiveness [33,34]. The optimization of nutritional status is an integral component of these programs, included in the bundles for the preoperative period (maintaining carbohydrate-loaded intake up to 2 h before surgery), intraoperative period (optimization of the infusion of fluids), and the postoperative period (early restart of oral nutrition). However, other bundles (minimally invasive surgery, early mobilization, removing all drains early, and so on) also have a summative effect when applied synergistically to obtain significantly better results than when implemented in isolation [35]. Early oral nutrition, especially within 24 h of surgery, improved the results of patients undergoing colorectal surgery with a statistically significant reduction in the length of hospital stay and in the risk of total postoperative complications, and should be proposed as the initial route for postoperative nutrition [7,11]. However, some patients deviate from the normal postoperative course and cannot follow ERAS protocols for various reasons. It is in these patients where we find the current challenge, as they cannot be nourished orally during the first postoperative days. In these patients who cannot tolerate oral feeding as established by the ERAS protocols, PPN has been shown to be a good alternative. The present results show how adding parenteral nutritional support during the immediate postoperative period together with oral feeding can reduce the risk of any kind of postoperative complication (minor and major complications). The rate of major complications and the risk of going from minor to major complications is lower in patients with NPP. Therefore, once the patients have been operated on, postoperative nutritional support should be considered, especially when it is difficult to predict postoperative oral intake. In this study, compliance with ERAS protocols during the early postoperative period allowed us to determine the risk of postoperative complications. Through decision trees, we can establish, during the first postoperative day, the risk of complications according to the degree of compliance with the ERAS programs and adding PPN, also decreasing the risk of postoperative morbidity. This could be an important support and a viable decision-
making system for increasing patient protection during the early postoperative days. It is also true that some of the most significant concerns about preoperative PN are catheter-related complications and PN-related complications. However, these complications are not common (overall catheter-related infection occurred in 0–10.7% of patients receiving preoperative PN, pneumothorax in 0–6.7% of patients, phlebitis in 0–1.8%, air embolus 0–1.6%, and thrombosis 0–0.5%) and they were relatively easy to detect and to treat. Appropriate catheter care is a measure to prevent infectious complications [36].

To the best of our knowledge, this study represents the largest randomized study analysing the perioperative effect of PPN in colorectal cancer published thus far. Even if limited by the fact of having been performed in a single centre and including all type of colorectal procedures, the study has strengths. Both groups were comparable, and nutritional supplementation was standardized. Performed in a referral hospital with a dedicated colorectal unit with excellence in ERAS programs and a close follow-up of patients, it offers a real picture of the outcome of ERAS compliance. We included all consecutive patients with colorectal cancer who fulfilled the inclusion criteria, thereby removing bias. In addition, risk factors for complications were evaluated, and confounding factors were removed by means of multivariable regression analysis. Clavien–Dindo scores have the advantage of being able to homogenize patients based on the severity of the complications developed. However, some differences about the type of complications are lost. Although this was a randomized study, we cannot identify the type of complications prevented, which allows to identify that the risk of developing some complication as well as major complications (Clavien–Dindo III–V) (those that require a new interventional procedure or that can be life-threatening and, therefore, the most potentially dangerous) is reduced. Further studies will be necessary to determine in which of these complications this therapy is most useful. Furthermore, this study provides decision trees representing a valuable tool for the early decision-making process evaluating ERAS compliance easily, allowing the addition of PPN in patients with a significant reduction in postoperative complications.

5. Conclusions

This randomized open trial demonstrates the benefits of proving early perioperative PPN in patients undergoing colorectal surgery. This is the first trial that shows that PPN supplementation and early compliance with ERAS programs can reduce postoperative morbidity. Patients receiving PPN had a lower risk of complications than those who received conventional FT, and PPN decreased the chance of worsening postoperative complications or developing major complications. It also revealed the importance of postoperative compliance with ERAS bundles during the first postoperative days. For patients who cannot truly fulfil ERAS protocols because of any deviation of the postoperative course, PPN has shown a protective effect on postoperative complications, defining a clear pathway that can help in these challenging patients.

Author Contributions: Conceptualization, L.S.-G., A.A., L.S.-I., F.L.-R.-A., A.M. and A.N.-R.; Formal analysis, L.S.-G., F.L.-R.-A., A.S.-S., X.B. and A.A.; Investigation L.S.-G., A.A., L.S.-I., F.L.-R.-A.; Methodology, L.S.-G., A.A., L.S.-I., F.L.-R.-A., A.S.-S., A.M., A.N.-R. and X.B.; Writing-Original draft preparation, L.S.-G., L.S.-I., F.L.-R.-A., VA.-O., A.S.-S. and A.A.; Writing-review and editing L.S.-G., L.S.-I., F.L.-R.-A., VA.-O., M.J.A., A.M., A.N.-R., X.B. and A.A. All authors have read and agreed to the published version of the manuscript.

Funding: This study was funded by an investigator-initiated grant from Baxter SL (Spain) to Antonio Arroyo via FISABIO (Foundation for the Promotion of Healthcare and Biomedical Research of the Autonomous Community of Valencia) in Hospital de Elche (Alicante). The sponsor (Baxter) did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Only the authors and investigators at Hospital de Elche participated in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.
Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Elche University General Hospital (protocol registered in the NCT register as NCT03606863).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2021, 71, 209–249. [CrossRef] [PubMed]
2. Gustafsson, U.O.; Scott, M.J.; Hubner, M.; Nygren, J.; Demartines, N.; Francis, N.; Rockall, T.A.; Young-Fadok, T.M.; Hill, A.G.; Soop, M.; et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations: 2018. World J. Surg. 2019, 43, 659–695. [CrossRef] [PubMed]
3. Sánchez-Guillén, L.; Frasson, M.; Pellino, G.; Fornés-Ferré, V.; Ramos, J.L.; Flor-Lorente, B.; García-Granero, Á.; Sierra, I.B.; Jiménez-Gómez, L.M.; Moya-Martínez, A.; et al. Nomograms for morbidity and mortality after oncologic colon resection in the enhanced recovery era: Results from a multicentric prospective national study. Int. J. Col. Dis. 2020, 35, 2227–2238. [CrossRef]
4. Damle, R.N.; Alavi, K. Risk factors for 30-d readmission after colorectal surgery: A systematic review. J. Surg. Res. 2015, 200, 200–207. [CrossRef]
5. Van der Kroft, G.; Bours, M.; Janssen-Heijnen, M.; van Berlo, C.; Konsten, J. Value of sarcopenia assessed by computed tomography for the prediction of postoperative morbidity following oncological colorectal resection: A comparison with the malnutrition screening tool. Clin. Nutr. ESPEN 2018, 24, 114–119. [CrossRef] [PubMed]
6. Kuppingler, D.; Hartl, W.H.; Bertok, M.; Hoffmann, J.M.; Cederbaum, J.; Küchenhoff, H.; Jauch, K.; Rittler, P. Nutritional screening for risk prediction in patients scheduled for abdominal operations. BJSS 2012, 99, 728–737. [CrossRef]
7. Herbert, G.; Perry, R.; Andersen, H.K.; Atkinson, C.; Penfold, C.; Lewis, S.J.; Ness, A.; Thomas, S. Early enteral nutrition within 24 hours of lower gastrointestinal surgery versus later commencement for length of hospital stay and postoperative complications. Cochrane Database Syst. Rev. 2019, CD004080. [CrossRef]
8. Weimann, A.; Braga, M.; Carli, F.; Hübner, M.; Klek, S.; Laviano, A.; Ljungqvist, O.; Lobo, D.N.; Martindale, R.; et al. ESPEN guideline: Clinical nutrition in surgery. Clin. Nutr. 2017, 36, 623–650. [CrossRef]
9. Willcuts, K.F.; Chung, M.C.; Erenberg, C.L.; Finn, K.L.; Schirmer, B.D.; Byham-Gray, L.D. Early Oral Feeding as Compared With Traditional Timing of Oral Feeding After Upper Gastrointestinal Surgery. Ann. Surg. 2016, 264, 54–63. [CrossRef]
10. Bliss, L.A.; Maguire, L.H.; Chau, Z.; Yang, C.J.; Nagle, D.A.; Chan, A.T.; Tseng, J.F. Readmission after resections of the colon and rectum: Predictors of a costly and common outcome. Dis. Colon. Rectum. 2015, 58, 1164–1173. [CrossRef]
11. Williams, D.G.A.; Ohnuma, T.; Krishnamoorthy, V; Raghunathan, K.; Sulo, S.; Cassidy, B.A.; Hegazi, R.; Wischmeyer, P.E. Impact of early postoperative oral nutritional supplement utilization on clinical outcomes in colorectal surgery. Perioper. Med. 2020, 9, 29. [CrossRef]
12. Ooi, S.-E.; Chen, G.-W.; Chou, C.-T. Adequate nourishment through total parental nutrition treatment may augment immune function in patients with colon cancer. Arch. Med. Res. 2004, 35, 289–293. [CrossRef] [PubMed]
13. Celaya P
14. Iresjö, B.-M.; Engström, C.; Lundholm, K. Preoperative overnight parenteral nutrition (TPN) improves skeletal muscle protein metabolism indicated by microarray algorithm analyses in a randomized trial. Physiol. Rep. 2016, 4, e12789. [CrossRef] [PubMed]
15. Iresjö, B.; Engström, C.; Smedh, U.; Lundholm, K. Overnight Steady-State Infusions of Parenteral Nutrition on Myosin Heavy Chain Transcripts in Rectus Abdominis Muscle Related to Amino Acid Transporters, Insulin-like Growth Factor 1, and Blood Amino Acids in Patients Aimed at Major Surgery. J. Parenter. Enter. Nutr. 2019, 43, 497–507. [CrossRef] [PubMed]
16. Braga, M.; Ljungqvist, O.; Soeters, P.; Fearon, K.; Weimann, A.; Bozzetti, F. ESPEN Guidelines on Parenteral Nutrition: Surgery. Clin. Nutr. 2009, 28, 378–386. [CrossRef]
17. Clavien, P.A.; Barkun, J.; De Oliveira, M.L.; Vauthey, J.N.; Dindo, D.; Schulick, R.D.; De Santibañes, E.; Pekolj, J.; Slankamenac, K.; Bassi, C.; et al. The Clavien-Dindo classification of surgical complications: Five-year experience. Ann. Surg. 2009, 250, 187–196. [CrossRef]
18. R Core Team. R: A Language and Environment for Statistical Computing; R Foundation for Statistical Computing: Vienna, Austria, 2020.
19. Therneau, T.; Atkinson, B. rpart: Recursive Partitioning and Regression Trees. R Package Version 4.1-15. Available online: https://cran.r-project.org/package=rpart (accessed on 12 February 2021).
Dolan, R.D.; Almasaudi, A.S.; Dieu, L.B.; Horgan, P.G.; McSorley, S.T.; McMillan, D.C. The relationship between computed tomography-derived body composition, systemic inflammatory response, and survival in patients undergoing surgery for colorectal cancer. *J. Cachexia Sarcopea Muscle* 2019, 10, 111–122. [CrossRef]

Ziś etalska, M.; Krawczyk-Lipiec, J.; Kraj, L.; Zaucha, R.; Małgorzewicz, S. Nutritional status assessment in colorectal cancer patients qualified to systemic treatment. *Współczesna Onkol.* 2017, 2, 157–161. [CrossRef]

Zhou, J.; Hiki, N.; Mine, S.; Kumagai, K.; Ida, S.; Jiang, X.; Nunobe, S.; Ohashi, M.; Sano, T.; Yamaguchi, T. Role of Prealbumin as a Powerful and Simple Index for Predicting Postoperative Complications After Gastric Cancer Surgery. *Ann. Surg. Oncol.* 2016, 24, 510–517. [CrossRef] [PubMed]

Haskins, I.N.; Baginsky, M.; Amund, R.L.; Agarwal, S. Preoperative hypoalbuminemia is associated with worse outcomes in colon cancer patients. *Clin. Nutr.* 2017, 36, 1333–1338. [CrossRef] [PubMed]

Junqueira, J.C.D.S.; Soares, E.C.; Filho, H.R.C.; Hoehr, N.F.; Magro, D.O.; Ueno, M. Nutritional risk factors for postoperative complications in Brazilian elderly patients undergoing major elective surgery. *Nutrients* 2019, 19, 321–326. [CrossRef]

Critselis, E.; Panagiotakos, D.B.; Machairas, A.; Zampelas, A.; Critselis, A.N.; Polychronopoulos, E. Risk and predictive factors of hypoalbuminemia in cancer patients following extensive abdominal surgery despite total parenteral nutritional support. *Int. J. Food Sci. Nutr.* 2011, 63, 208–215. [CrossRef]

Critselis, E.; Panagiotakos, D.B.; Machairas, A.; Zampelas, A.; Critselis, A.N.; Polychronopoulos, E. Postoperative Hypoproteinemina in Cancer Patients Following Extensive Abdominal Surgery Despite Parenteral Nutritional Support. *Nutr. Cancer* 2011, 63, 1021–1028. [CrossRef]

Rinninella, E.; Cintoni, M.; Raoul, P.; Pozzo, C.; Strippoli, A.; Bria, E.; Tortora, G.; Gasbarrini, A.; Mele, M.C. Effects of nutritional interventions on nutritional status in patients with gastric cancer: A systematic review and meta-analysis of randomized controlled trials. *Clin. Nutr. ESPEN* 2020, 38, 28–42. [CrossRef]

Lucia, P.E.O.; Liliana, V.V.M. Protocolo para el manejo de nutrición parenteral periérlica lista para usar en paciente quirúrgico. *Nutr. Hosp.* 2015, 31, 1003–1011. [CrossRef]

Cai, W.; Calder, P.C.; Curby-Boaventura, M.F.; De Waele, E.; Jakubowski, J.; Zaloga, G. Biological and Clinical Aspects of an Olive Oil-Based Lipid Emulsion—A Review. *Nutrients* 2018, 10, 776. [CrossRef]

Dąbrowska, A.M.; Slotwiński, R. The immune response to surgery and infection. *Cent. Eur. J. Immunol.* 2014, 39, 532–537. [CrossRef] [PubMed]

Yeung, S.E.; Hilkewich, L.; Gillis, C.; Heine, J.A.; Fenton, T.R. Protein intakes are associated with reduced length of stay: A comparison between Enhanced Recovery After Surgery (ERAS) and conventional care after elective colorectal surgery. *Am. J. Clin. Nutr.* 2017, 106, 44–51. [CrossRef] [PubMed]

IHI. What Is a Bundle? Disponibleen. Available online: http://www.ihi.org/resources/Pages/ImprovementStories/WhatIsABundle.aspx (accessed on 30 March 2021).

Dean, H.; King, E.; Gane, D.; Hocking, D.; Rogers, J.; Pullyblank, A. Introduction of a care bundle effectively and sustainably reduces patient-reported surgical site infection in patients undergoing colorectal surgery. *J. Hosp. Infect.* 2020, 105, 156–161. [CrossRef] [PubMed]

Tejedor, P.; Ayora, S.G.; López, M.O.; Arellano, M.L.; Guadalajara, H.; García-Olmo, D.; Pastor, C. Implementation barriers for Enhanced Recovery After Surgery (ERAS) in rectal cancer surgery: A comparative analysis of compliance with colon cancer surgeries. *Updates Surg.* 2021, 1–8. [CrossRef]

Burden, S.; Billson, H.A.; Lal, S.; Owen, K.A.; Muneer, A. Perioperative nutrition for the treatment of bladder cancer by radical cystectomy. *Cochrane Database Syst. Rev.* 2019, 5, CD010127. [CrossRef] [PubMed]