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# Impact of additional parenteral nutrition given early versus late in patients having abdominal surgery: A clinical study using randomization

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**Abstract**
**Important:** The effect of and optimal timing for initiating supplemental parenteral nutrition (SPN) remain unclear after major abdominal surgery for patients in whom energy targets cannot be met by enteral nutrition (EN) alone.
**Objective:** To examine the effect of early supplemental parenteral nutrition (E-SPN) (day 3 after surgery) or late supplemental parenteral nutrition (L-SPN) (day 8 after surgery) on the incidence of nosocomial infections in patients undergoing major abdominal surgery who are at high nutritional risk and have poor tolerance to EN.
**Design, setting, and participants:** A clinical trial was conducted in Sri Rama Krishna Institute of Medical Science from December, 2020 to July 2021, in the general surgery department of 11 hospitals in Kolkata, India. Participants were those undergoing major abdominal surgery with high nutritional risk and poor tolerance to EN (30% of energy targets from EN on postoperative day 2, calculated as 25 and 30 kcal/kg of ideal body weight daily for women and men, respectively) and an expected post-operative hospital stay longer than 7 days.
**Interventions:** Random allocation to E-SPN (starting on day 3 after surgery) or L-SPN (starting on day 8 after surgery).
**Main outcomes and Measures:** The primary outcome was the incidence of nosocomial infections between postoperative day 3 and hospital discharge.
**Results:** A total of 230 patients (mean [SD] age, 60.1 [11.2] years; 140 men [61.1%]; all patients were of India in kolkatta, India were randomized (115 to the E-SPN group and 115 to the L-SPN group). One patient in the L-SPN group withdrew informed consent before the intervention. The E-SPN group received more mean (SD) energy delivery between days 3 and 7 compared with the L-SPN group (26.5 [7.4] vs 15.1 [4.8] kcal/kg daily; $p$<.001). The E-SPN group had significantly fewer nosocomial infections compared with the L-SPN group (10/115 [8.7%] vs 21/114 [18.4%]; risk difference, 9.7%; 95% CI, 0.9%-18.5%; P = .04). No significant differences were found between the E-SPN group and the L-SPN group in the mean (SD) number of noninfectious complications (31/115 [27.0%] vs 38/114 [33.3%]; risk difference, 6.4%; 95% CI, −5.5% to 18.2%; P = .32), total adverse events (75/115 [65.2%] vs 82/114 [71.9%]; risk difference, 6.7%; 95% CI, −5.3% to 18.7%; P = .32), and rates of other secondary outcomes. A significant difference was found in the mean (SD) number of therapeutic antibiotic days between the E-SPN group and the L-SPN group (6.0 [0.8] vs 7.0 [1.1] days; mean difference, 1.0 days; 95% CI, 0.2-1.9 days; P = .01).
**Conclusion and Relevance:** In this randomized clinical trial, E-SPN was associated with reduced nosocomial infections in patients undergoing abdominal surgery and seems to be a favorable strategy for patients with high nutritional risk and poor tolerance to EN after major abdominal surgery.

**Keywords:** Randomization, abdominal surgery, enteral nutrition (EN), parenteral nutrition

## Introduction
The estimated prevalence of malnutrition in patients after major abdominal surgery ranges from 20% to 70% [1, 2] and is associated with increased morbidity, such as impaired wound healing, hospital-acquired infection, postoperative complications, prolonged hospital stay, and increased mortality [3-5]. It is well documented that the catabolic response to surgery causes the depletion of essential nutrients, resulting in an increased risk of postoperative complications, particularly infectious complications. Therefore, timely and adequate energy supply is essential for maintaining optimal cell and organ function, promoting wound repair, and decreasing infectious complications after surgery.

The Indian Society for Parenteral and Enteral Nutrition (ISPEN) and the Enhanced Recovery After Surgery (ERAS) Society guidelines [2, 6-9] recommend that enteral nutrition (EN) should be implemented for patients after surgery as soon as possible if the gastrointestinal tract works. Compared with parenteral nutrition (PN), a meta-analysis and several randomized clinical trials [10-13] reported that EN is associated with lower postoperative infections, mortality, and length of stay in patients undergoing major abdominal surgery. However, in many cases, energy delivery in postsurgical patients using EN alone is less than the estimated requirements for various reasons. To supplement insufficient EN, PN is a strategy that can increase energy delivery more closely to the estimated energy requirements. However, recommendations for its use differ, and the evidence is controversial [2, 14-19]. Current clinical guidelines for PN support in surgical patients are largely based on expert opinion and differ substantially across continents [2, 14, 20]. The ISPEN guidelines recommend that surgeons consider initiating PN if the energy requirements of the patient have not been met by EN for more than 7 days [2]. The Indian Society for Parenteral and Enteral Nutrition guidelines recommend that PN should be initiated within 3 to 5 days for patients who are at nutritional risk and unlikely to achieve a desired oral intake or with insufficient EN.

Infectious risk related to PN has been a concern when compared with EN. However, this concern has been challenged in recent trials that investigated PN in critically ill patients or those undergoing abdominal surgery. One randomized trial17 found that early supplemental PN in critically ill patients with insufficient EN can significantly reduce nosocomial infections, and another [18] found a trend to reduce newly acquired infections in nutritionally at-risk, critically ill patients. Many observational studies have suggested an association between higher energy delivery and improved clinical outcomes in critically ill patients. However, there is still a lack of large randomized clinical trials on the timing of supplemental parenteral nutrition (SPN) initiation for patients undergoing abdominal surgery. The objective of this randomized clinical trial was to evaluate the effects of initiating early SPN (E-SPN) (day 3 after surgery) or late SPN (L-SPN) (day 8 after surgery) on the incidence of nosocomial infections in patients undergoing major abdominal surgery who were at nutritional risk and intolerant to EN.

## Methods

### Study Design and Participants

A clinical trial was conducted in Sri Rama Krishna Institute of Medical Science from December, 2020 to July 2021, in the general surgery department of 11 territory hospitals in Kolkata, India. A total of 1560 patients were screened. The trial protocol and the statistical analysis plan are available in Supplement 1. The trial protocol was approved by the Indian Hospital Ethics Committee and was registered at ClinicalTrials.gov. All participating patients provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The inclusion criteria were as follows: adults patients who underwent elective gastric, colorectal, hepatic, and pancreatic resections (both benign and malignant disease) without traumatic reasons; were at risk of malnutrition defined as a Nutritional Risk Screening 2002 (NRS-2002) score of 3 or higher30; were expected to have a postoperative hospital stay longer than 7 days; and had received 30% or less of the energy target by EN on day 2 after surgery (e Appendix in Supplement 2). Detailed exclusion criteria are described in the trial protocol.

### Randomization and Masking

Randomization was performed using a permuted block design, with stratification of different clinical centers (Supplement 2). The random allocation sequences were computer generated. Allocation concealment was implemented by sequentially numbered, sealed, opaque envelopes. After being deemed eligible for enrollment, patients were randomized in a 1:1 ratio to the E-SPN group or the L-SPN group. Investigators and participants were not masked to the treatment assignment, but the follow-up assessments were performed by trained physicians and nurses who were blinded to the patient's assignment. The statisticians were blinded to the treatment group during the data analysis.

### Screening and Baseline Measurements

Patients' preoperative baseline characteristics, including sex, age, weight, height, body mass index, NRS-2002 score, comorbidities, disease diagnosis, and type of tumor (if applicable) were collected. The duration of surgery, operative blood loss, operative characteristics, and the amount of homologous blood transfusions were recorded. Furthermore, preoperative baseline levels of C-reactive protein, white blood cells, albumin, and prealbumin as well as hepatic and kidney function were measured by laboratory testing.

### Procedures

Enteral nutrition was started within 24 hours after abdominal surgery according to standard procedures based on ESPEN guidelines.2Energy targets were calculated as 30 kcal/kg of ideal body weight for men and 25 kcal/kg of ideal body weight for women, and the protein requirements were 1.2 g/kg of ideal body weight. A trained clinician developed personalized nutritional plans to reach the energy target. These plans were initially based on EN supplements. After the randomization, both groups received nutrition support for a minimum of 5 days, until 80% of the energy target had been reached via EN, or until hospital discharge. Enteral nutrition products were routinely prescribed at all hospitals and contained 1 kcal/mL of energy (16% proteins, 35% lipids, and 49% carbohydrates). Enteral nutrition was performed by tube feeding. Parenteral nutrition formulas consisted of 0.88 kcal/mL of energy (15% proteins, 40% lipids [20% long-chain triglycerides], and 45% carbohydrates) and supplemental vitamins and minerals. Parenteral nutrition was administered via peripheral or

central veins. Eligible patients were randomly assigned to the E-SPN group or the L-SPN group (Supplement 2). For patients in the E-SPN group, SPN was initiated on day 3 after surgery to reach the energy target, whereas SPN was initiated on day 8 after surgery for patients in the L-SPN group. The energy target of combined EN and SPN was 100% of the energy requirement. When enteral feeding comprised 80% of the energy goal, SPN was reduced and eventually discontinued. The energy target in both groups was verified every 24 hours throughout the study period by a trained clinician based on the daily nutritional information records. Daily nutritional information was recorded for a maximum of 12 days or until patients could resume a normal oral diet or discharge. The daily and cumulative energy postoperative results from nutritional products and no nutritional fluids (eg., glucose for drug dilution and lipids from propofol) were also recorded. We routinely performed blood glucose monitoring on each patient during the hospital stay, especially at SPN initiation. The patients were monitored for postoperative complications by trained experienced physicians not associated with the surgical teams. According to previously described criteria, complications were classified as major or minor and infectious or noninfectious (Supplement 2).

**Outcomes**

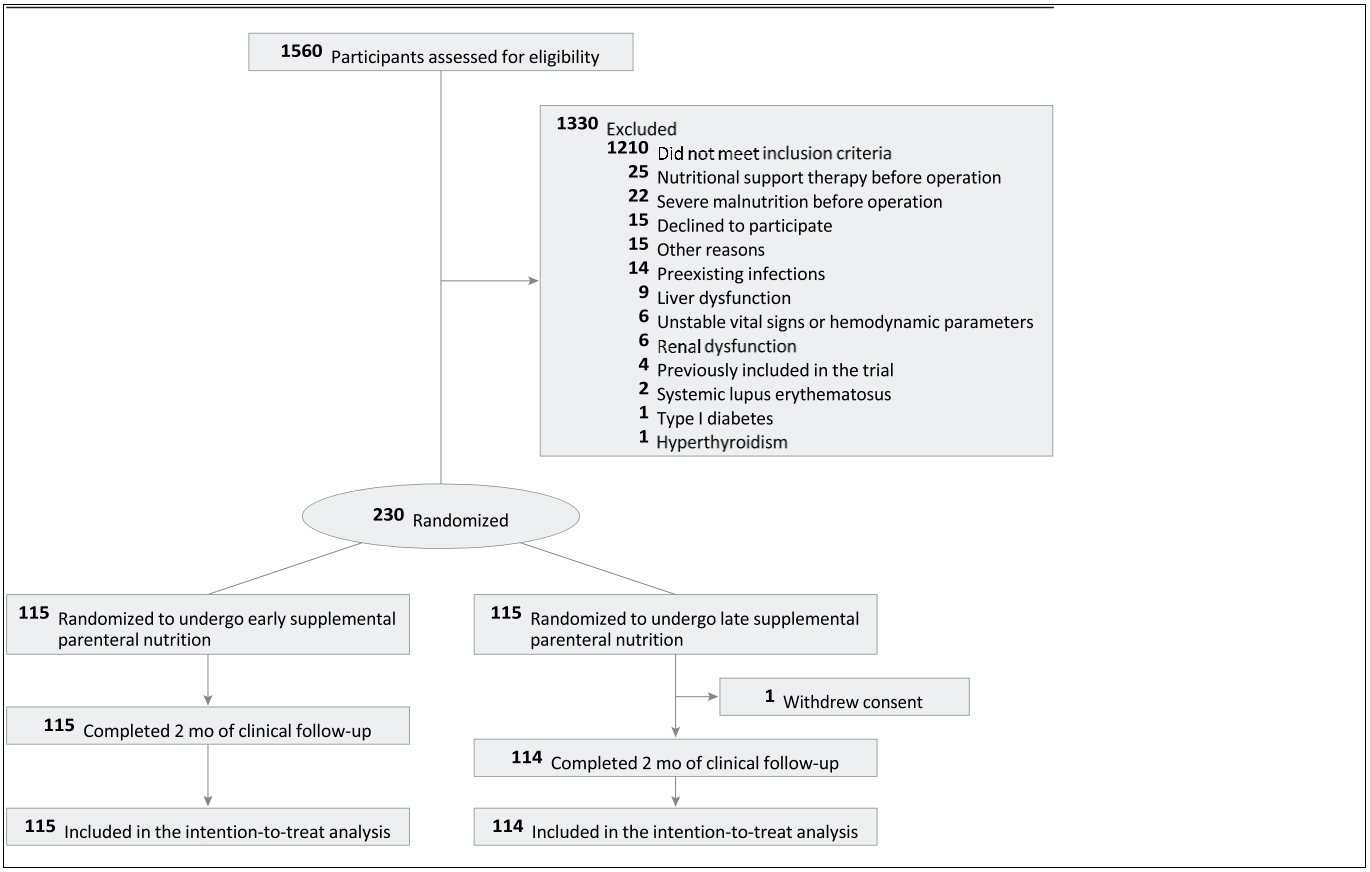
The primary outcome was the occurrence of nosocomial infections between postoperative day 3 and discharge. The following infections were defined according to the Centers for Disease Control and Prevention: bloodstream infections, pneumonia, urinary tract infections, surgical site infections, abdominal infections, and other infections (Supplement 2). The secondary outcomes included the actual energy and protein intake (including EN and PN), postoperative noninfectious complications, incidence of gastrointestinal intolerance, PN-related complications, length of hospital stay, hospitalization expenses, therapeutic antibiotic days (defined as days from postoperative day 3 to discharge during which a patient received at least 1 dose of antibiotics for actual nosocomial infection), prophylactic antibiotic days (defined as days antibiotics were used for prophylaxis [no infection]),mechanical ventilation, mortality within 2 months after randomization, and laboratory tests at discharge, including white blood cell count, C-reactive protein level, albumin level, prealbumin level, hepatic function, and kidney function.

**Statistical Analysis**

A previous systematic meta-analysis study12 found an overall infection rate of 10% to 30% in patients after abdominal surgery. That trial assumed an incidence of 25% of nosocomial infections in patients receiving PN after abdominal surgery. We postulated that E-SPN combined with EN might decrease the nosocomial infection rate by 15%. With a 2-tailed type I error rate of 5%, to detect such an effect with a statistical power level of 80%, a sample size of 110 patients would be required in each group. The sample size was increased to 230 to allow for withdrawal and loss to follow-up. The full analysis set was based on the intention-to-treat principle. Variables are reported as number (percentages), means (SDs), or medians (IQRs) as appropriate. We used the Shapiro Wilk test to assess whether continuous data were normally distributed. We performed a group comparison with the $\chi 2$ test or Fisher exact test for categorical variables and the 2-tailed ttest or Mann-Whitney U test for continuous variables when appropriate. The rate of nosocomial infections in a time-to-event analysis was reported using Kaplan-Meier plots, and the difference between the 2 groups was tested by log-rank test. A Cox proportional hazards regression model was used to estimate the hazard ratios and corresponding 95% CIs. We also performed subgroup analyses for the primary outcome, including the following variables: age (5 hours), and blood loss (≤500 vs >500mL). No data on primary outcomes were missing. Missing data for the other variables were not imputed. Statistical significance was set as a 2-sided $p< .05$. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

**Results**

Study Participants Of the 1560 screened patients, 230 eligible patients (mean [SD] age, 60.1 [11.2] years; 140male [61.1%]; all patients enrolled, with 115 randomized to the E-SPN group and 115 to the L-SPN group. One patient in the L-SPN group withdrew informed consent after randomization and thus did not receive the intervention. At baseline, the characteristics of the patients were similar in the 2 groups (Supplement 2).




**Nutrition Therapy**

Between days 3 and 7, patients in the E-SPN group received a mean (SD) energy intake of 26.5 (7.4) kcal/kg per day, whereas those in the L-SPN group received a mean (SD) energy intake of 15.1 (4.8) kcal/kg per day ($p$< .001) (Supplement 2). During the same period, the mean (SD) protein intake was 1.02 (0.28) g/kg per day in the E-SPN group and 0.48 (0.17) g/kg per day in the L-SPN group ($p$< .001 (Supplement 2). Meanwhile, no statistical differences were found in mean (SD) energy intake (28.8 [6.2] vs 29.6 [7.2] kcal/kg per day; P = .17) and mean protein intake (1.17 [0.25] vs 1.20 [0.28] g/kg per day; P = .35) between the E-SPN group and the L-SPN group during the 8 to 12 days after surgery (Supplement 2).

**Primary Clinical Outcome**

Overall, the total number of infectious complications in patients in the E-SPN group was significantly less than those in the L-SPN group (10/115 [8.7%] vs 21/114 [18.4%]; risk difference, 9.7%; 95% CI, 0.9%-18.5%; P = .04). KaplanMeier survival curves plotted with the nosocomial infection rates in the 2 groups also showed a statistically significant difference (hazard ratio, 2.07; 95% CI, 1.01-4.22; P = .04) (Supplement 2). This significant difference was mainly attributable to the number of major infectious complications, which was significantly lower in the E-SPN group compared with that in the L-SPN group (8/115 [7.0%] vs 18/ 114 [15.8%]; risk difference, 8.8%; 95% CI, 0.7%-17.0%; P = .04) No statistically significant difference was found in the number of minor infectious complications (2/115 [1.7%] vs 3/114 [2.6%]; risk difference, 0.9%; 95% CI, −2.9% to 4.7%; P = .68).

**Secondary Clinical Outcomes**

No significant difference was found in the incidence of noninfectious complications between the E-SPN group and the L-SPN group (total noninfectious complications: 31/115 [27.0%] vs 38/114 [33.3%]; risk difference, 6.4%; 95% CI, −5.5% to 18.2%; P = .32; major noninfectious complications: 14/115 [12.2%] vs 19/114 [16.7%]; risk difference, 4.5%; 95% CI, −4.6% to 13.6%; P = .35; minor noninfectious complications: 17/115 [14.8%] vs 19/114 [16.7%]; risk difference, 1.9%; 95% CI, −7.5% to 11.3%; P = .72) (Supplement 2). No significant difference was found in the total incidence of adverse events between the 2 groups (E-SPN vs L-SPN: 75/115 [65.2%] vs 82/114 [71.9%]; risk difference, 6.7%; 95% CI, −5.3% to 18.7%; P = .32) (Supplement 2). Patients in the L-SPN group had slightly increased gastrointestinal intolerance events, but this difference was not significant (E-SPN vs L-SPN: 67/115 [58.3%] vs 79/114 [69.3%]; risk difference, 11.0%; 95% CI, −1.3% to 23.4%; P = .10) (Supplement 2). The mean (SD) number of therapeutic antibiotic days was significantly lower in the E-SPN group than in the L-SPN group (6.0 [0.7] vs 7.0 [1.1] days; mean difference, 1.0; 95% CI, 0.2%-1.9%; P = .01). No significant differences were found between the 2 groups in any other secondary outcomes. Mean (SD) serum albumin and prealbumin levels at discharge were significantly higher in the E-SPN group than in the L-SPN group (albumin: 3.55 [0.76] vs 3.37 [0.45] g/dL; mean difference, 0.19 g/dL; 95% CI, 0.03-0.35 g/dL; P = .02 [to convert albumin to grams per liter, multiply by 10]; prealbumin: 15.84 [3.81] vs 13.0 [3.63]mg/dL;mean difference, 2.85mg/dL; 95% CI, 1.88-3.82 mg/dL; $p$< .001 [to convert prealbumin to milligrams per liter, multiply by 10]) (Supplement 2). No significant differences were found in the rest of the hematologic indicators between the 2 groups (Supplement 2).

**Subgroup Analyses**

Subgroup analyses of infections in the full analysis sets are shown in No significant differences were found in infectious complications among a priori defined subgroups. Results in all subgroups were comparable with those in the overall study population.

**Conclusions**

In this randomized clinical trial, E-SPN was associated with reduced nosocomial infections in patients undergoing abdominal surgery. Early SPN seems to be a favorable strategy for patients at high nutritional risk and with poor tolerance to EN after major abdominal surgery to reduce the number of nosocomial infections.

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