ORIGINAL ARTICLE

Pre-operative total parenteral nutrition improves post-operative outcomes in a subset of Crohn's disease patients undergoing major abdominal surgery

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Abstract

Background: Despite major advances in the medical management of Crohn's disease (CD), a significant proportion of patients will require surgery within 5 years of diagnosis. Malnutrition is an independent risk factor for adverse post-operative outcomes following gastrointestinal surgery. Data on the value of pre-operative total parenteral nutrition (TPN) in CD patients are mixed and there is a paucity of data in the biologic era. We aimed to define the role of pre-operative TPN in this population.
Methods: This was a retrospective cohort study conducted at a tertiary referral center. CD patients who underwent major abdominal surgery were identified. Patients receiving pre-operative TPN were compared to controls. We compared the incidence of 30-day infectious and non-infectious post-operative complications between the two groups.
Results: A total of 144 CD patients who underwent major abdominal surgery between March 2007 and March 2017 were included. Fifty-five patients who received pre-operative TPN were compared to 89 controls. Twenty-one (14.6%) patients developed infectious complications (18.2% in TPN group vs 12.3% in non-TPN group, $P = 0.34$) and 23 (15.9%) developed non-infectious complications (14.5% in TPN group vs 16.9% in non-TPN group, $P = 0.71$). In a multivariate analysis, controlling for differences in baseline disease severity and malnutrition between groups, patients receiving pre-operative TPN for ≥ 60 days had significantly lower odds of developing non-infectious complications (odds ratio 0.07, 95% confidence interval: 0.01–0.80, $P = 0.03$). Weight loss of >10% in the past 6 months was a significant predictor of post-operative complications.
Conclusions: In a subset of malnourished CD patients, TPN is safe and allows comparable operative outcomes to controls. Pre-operative TPN for ≥ 60 days reduced post-operative non-infectious complications without associated increase in infectious complications.

Key words: Crohn's disease; total parenteral nutrition; pre-operative malnutrition; post-operative complications

Introduction

Despite major advances in the medical management of Crohn's disease (CD) in past decades, 25–33% of patients ultimately require surgery within 5 years of diagnosis [1]. Post-operative complications represent a major source of morbidity for patients and are estimated to occur in about 21% of CD patients undergoing major abdominal surgery [2]. Malnutrition, impacting up to 70% of CD patients [3, 4], is an independent risk factor for adverse post-operative outcomes following gastrointestinal surgery [5]. Nutritional optimization has been shown to improve surgical outcomes in this patient population. Frequently, disease complications such as intestinal obstruction or fistula formation lead to the use of total parenteral nutrition (TPN) for nutritional optimization. Studies on the effects of TPN on post-operative outcomes in CD are limited and have yielded inconsistent results. Importantly, the relative impact of TPN on post-operative complications in the era of biologic therapy has not been fully studied in the literature. We therefore investigated the impact of pre-operative TPN on 30-day post-operative complications in CD patients undergoing major abdominal surgery.

Patients and methods

This was a single-center retrospective cohort study conducted at the University of Florida. Subjects were identified utilizing a search of the Integrated Data Repository using Informatics for Integrating Biology and the Bedside (i2b2), which is an NIH-funded National Center for Biomedical computing program available for use at the University of Florida. Manual chart review was utilized to obtain data after identifying the initial patient cohort. Institutional review board (IRB) approval was obtained to evaluate the electronic medical record of patients identified in the i2b2 search (IRB201700894).

A total of 159 patients with a diagnosis of CD who underwent major abdominal surgery between March 2007 and March 2017 were identified. Of these, 15 patients were excluded (4 pediatric patients, 4 underwent no bowel resection, 4 without post-operative follow-up, 2 underwent emergency surgery for immediately life-threatening conditions and 1 patient underwent robotic surgery). As such, 144 patients were included in the final analysis. A retrospective review of their baseline patient characteristics, radiology, endoscopy, operative and pathology reports as well as inpatient and outpatient provider notes was performed.

Parenteral and non-parenteral nutrition groups

For the purposes of this study, patients who received pre-operative TPN (TPN group) were compared to those who did not (non-TPN group). Only patients who received TPN for at least 7 days continuously prior to surgery were included in the TPN group. Initiation of TPN was decided upon jointly by the gastroenterologist and colorectal surgeon based on patient characteristics deemed to indicate malnutrition (physical examination, weight loss in past 6 months, albumin levels [<3 g/dL], prealbumin levels [<15 mg/dL] and indication for surgery) as well as passing a standard hospital TPN qualification checklist.

Patients received an individualized total parenteral nutrition formula in a 2-in-1 fashion through a central venous catheter. Macronutrients were based on body weight with 1.5 g/kg of amino acids, 2 mg/kg/min of 70% dextrose and 250–500 mL of lipids. The Harris–Benedict equation was used to estimate the daily basal metabolic rate for each patient. A specialized parenteral nutrition pharmacist implemented daily micronutrient and electrolyte adjustments based on individual patient requirements.

Determination of nutritional status

Patients were deemed to be at 'severe nutritional risk' if they met one of the following criteria in accordance with the European Society for Clinical Nutrition and Metabolism consensus guidelines [6, 7]:

- weight loss >10–15% within 6 months;
- body mass index $<18.5 \, \text{kg/m}^2$;
- serum albumin <3 g/dL (with no evidence of hepatic or renal dysfunction).

Description of pre-operative, operative and post-operative variables

We collected data on pre-operative variables including age, gender, race, smoking history, comorbidities, American Society of Anesthesiologists (ASA) class, body mass index (BMI) at time of surgery, percent weight loss in past 6 months, albumin, prealbumin and C-reactive protein (CRP) levels. We also collected details of pre-operative medication use including steroids, immunomodulators and/or biologics. We defined and collected 'a priori' two variables that reflected the severity of disease in our patient population: hospitalization in the year prior to surgery for a CD exacerbation (aside from hospitalization for initiation of TPN) and failure to achieve disease control on two prior biologic therapies [1, 2]. Disease-related variables collected were pre-operative Harvey Bradshaw Index (HBI) scores, pre-operative quality of life via the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) score and duration of disease.

Surgical variables collected included the urgency of surgery (with urgent surgery defined as surgery for non-immediately life-threatening complications performed during an unplanned admission), type of surgery, use of laparoscopic vs open approach, total operative time, total operative blood loss, length of small-bowel resection, creation of a primary anastomosis or diverting ostomy.

The incidence of infectious and non-infectious complications up to 30 days post-operatively was assessed. Infectious complications included skin and soft-tissue infection (SSI), intra-abdominal abscess formation, urinary-tract infection, line-associated infection, bacterial pneumonia. Non-infectious complications included anastomotic leak, bowel obstruction, deep venous thrombosis (DVT), pulmonary embolism and acute renal failure. The presence of post-operative complications was determined by a combination of provider notes supported by laboratory or imaging findings. Only complications occurring in the first 30 days post-operatively were included in the analysis.

Statistical analysis

Comparisons of categorical variables were performed using Pearson's chi-square or Fisher's exact test, as appropriate. Continuous parametric variables were compared with Student's *t*-test and non-parametric variables with the Mann–Whitney U test. The multivariate analysis was conducted through logistic regression. A *p*-value <0.05 was considered statistically significant and all tests were two-tailed. Stata version 15.0 (Stata Corp, College Station, TX) was used for all statistical analysis.

Table 1. Baseline and clinical characteristics of the total parenteral nutrition (TPN) group and the non-TPN group

	TPN group ($n = 55$)	Non-TPN group ($n = 89$)	P-value
Baseline characteristics			
Age, years	41.3 ± 15.6	40.4 ± 16.6	0.78
Female	30 (54.5%)	49 (55.1%)	0.95
African American	5 (9.1%)	5 (5.6%)	0.43
Active smoking	11 (20.0%)	10 (11.2%)	0.15
ASA classification	2 [2–3]	3 [2–3]	0.23
BMI at time of surgery, kg/m^2	24.7 ± 6.1	25.2 ± 5.8	0.63
BMI $<18.5 \, kg/m^2$	6 (10.9%)	7 (7.9%)	0.54
Albumin, g/dL	3.6 ± 0.6	3.9 ± 0.6	<0.01
Albumin <3 g/dL	21 (38.2%)	12 (13.5%)	<0.01
Pre-albumin, mg/dL	19.4 ± 8.2	18.6 ± 9.9	0.57
CRP, mg/L	21.8 [2.0–43.5]	8.8 [1.2–18.8]	0.06
Weight loss >10% in past 6 months	10 (18.2%)	12 (13.5%)	0.45
Disease characteristics			
Steroid use[a]	9 (16.4%)	11 (12.4%)	0.51
Biologic use[b]	42 (76.4%)	68 (76.4%)	0.85
HBI[c]	5.5 [3–14]	6 [3–12]	0.96
SIBDQ	40 [26–52]	41 [33–52]	0.45
Hospitalized for Crohn's in 12 months prior to surgery	49 (89.1%)	50 (56.2%)	<0.01
Duration of disease in years	6 [2–20]	7.6 [2.4–15.6]	0.63
Operative characteristics			
Urgent surgery[d]	11 (20.0%)	14 (15.7%)	0.51
Length of small-bowel resection, cm	23 [10–37]	16 [11–27]	0.32
Operative blood loss, mL	100 [50–150]	50 [30–150]	0.05
Operative time, minutes	154 [129–202]	131 [91–200]	0.07
Laparoscopic surgery	29 (52.7%)	41 (46.1%)	0.44
Converted to open	3 (10.3%)	2 (4.9%)	0.37
Primary anastomosis	42 (79.2%)	71 (83.5%)	0.52
With proximal diversion	6 (14.3%)	20 (28.2%)	
Without proximal diversion	36 (85.7%)	51 (71.8%)	
No primary anastomosis	11 (20.8%)	14 (16.5%)	0.52
End ileostomy	7 (63.6%)	8 (57.1%)	
End colostomy	4 (36.4%)	6 (42.9%)	

Values presented as mean $\pm$ standard deviation, median [interquartile range] or N (%).

ASA, American Society of Anesthesiology; BMI, body mass index; CRP, C-reactive protein; HBI, Harvey Bradshaw Index; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.

[a]Steroid use defined as more than 40 mg daily use of prednisone in the 2 weeks pre-operatively.

[b]Biologic use defined as use of a biologic in the past 8 weeks pre-operatively.

[c]As assessed during a clinic visit within 30-days pre-operatively.

[d]Defined as surgery during an unplanned admission.

Results

Baseline and nutritional characteristics

Overall, 144 adult patients with a diagnosis of CD who underwent major abdominal surgery at the University of Florida Hospital between March 2007 and March 2017 were included. Mean age was 40.9 years (range 18–77), 78 (54.2%) were females; 55 (38.2%) received TPN (TPN group) for at least 7 days pre-operatively (median 73 days, interquartile range 30–138) and 89 patients did not (non-TPN group). Of those in the TPN group, 23 (41.8%) patients received TPN for <60 days pre-operatively and 32 (58.2%) for ≥ 60 days. The TPN group had a significantly higher proportion of patients with albumin level <3 g/dL at the time of surgery (38.2 vs 13.5%, $P < 0.01$), a lower overall mean albumin level (3.6 vs 3.9 g/dL, $P < 0.01$) and a higher CRP level (21.8 vs 8.8, $P = 0.06$) (Table 1). The two groups were otherwise similar.

TPN composition characteristics

Overall, mean daily protein intake was 108 ± 24.7 grams (range 50–170). This represented a mean of 1.7 ± 0.2 grams of protein/

kg of body weight (range 1–2). A mean of 295 ± 50.6 grams of dextrose was administered per day (range 190–430). As for lipids, a mean of 415 ± 105 mL of lipids was administered (range 250–500). On average, the TPN formula provided a mean of 1881 ± 301 calories per day (range 859–2530), representing a mean of 30.6 ± 5.2 kcal/kg (range 18–45).

Disease characteristics

Patients undergoing surgery had fistulizing disease in 58 (40.3%), stricturing disease in 53 (36.8%), with evidence of intra-abdominal abscess in 20 (13.9%), with evidence of bowel obstruction in 20 (13.9%) and perforation in 3 (2.1%). Overall, 20 (13.9%) patients had used an equivalent of ≥ 40 mg of daily prednisone in the 2 weeks prior to surgery and 110 (76.4%) patients were on biologic therapy in the 8 weeks prior to their operation. Of 110 patients on biologics pre-operatively, 81 (73.6%) patients were on tumor necrosis factor (TNF) inhibitors, 13 (121.8%) were on vedolizumab, 6 (5.5%) on ustekinumab, 6 (5.5%) on natalizumab and 4 (3.6%) on tofacitinib. Forty-two (38.2%) patients were on simultaneous therapy with an immunomodulator

Table 2. Surgical procedures of the total parenteral nutrition (TPN) group and the non-TPN group

	TPN group (*n* = 55)	Non-TPN group (*n* = 89)	P-value
Colonic resection	34 (61.8%)	50 (56.2%)	0.50
Ileo-colectomy	18 (32.7%)	23 (25.8%)	
Left-sided/sigmoid colectomy	6 (10.9%)	5 (5.6%)	
Low anterior resection	1 (1.8%)	7 (7.9%)	
Segmental colectomy	9 (16.4%)	15 (16.9%)	
Small-bowel resection	9 (16.4%)	20 (22.5%)	0.46
Combined small-bowel and colonic resection	10 (18.2%)	15 (16.9%)	0.83
Other	2 (3.6%)	4 (4.5%)	0.80

(azathioprine [*n* = 17], 6-mercaptopurine [*n* = 10], methotrexate [*n* = 9], tacrolimus [*n* = 6]).

As expected, patients in the TPN group appeared to have more severe disease. This was suggested by a significantly higher number of patients in the TPN group failing to respond to more than two biologic therapies in the past (for reasons other than immediate medication intolerance) (40.7 vs 23.9%, $P = 0.03$). In addition, a significantly higher proportion of patients in the TPN group required hospitalization related to their CD in the past year (89.1 vs 56.2%, $P < 0.01$). Median HBI score for the overall sample was 6 (interquartile range [IQR], 3–12) and median SIBDQ score was 41 (IQR, 29.5–52) and both were comparable between groups. Notably, steroid use immediately pre-operatively was comparable between the two groups. The median duration of disease pre-operatively was 7.1 years (IQR, 2.1–16.1) and was also comparable between groups (Table 1).

Operative characteristics

Surgery was performed urgently in 25 patients (17.4%); among them, seven patients had severe colitis refractory to medical therapy, seven had fistulizing disease leading to intra-abdominal abscess not amenable to conservative therapy, seven had bowel obstruction refractory to medical therapy and four had bowel perforation not responding to conservative therapy. Seventy (48.6%) patients underwent a laparoscopic procedure, with 7.1% converted to an open procedure (Table 1). Colonic resection was the most commonly performed procedure (*n* = 84, 58.3%), followed by small-bowel resection (*n* = 29, 20.1%) and combined small-bowel and colonic resection (*n* = 25, 17.4%). Six (4.2%) patients underwent miscellaneous procedures (four underwent exploratory laparotomy with extensive adhesiolysis and stricturoplasty; two underwent exploratory laparotomy with revision of prior jejunostomy) (Table 2). Primary anastomosis was performed in 113 patients (81.8%), with 26 patients (23.0%) requiring proximal diversion. Of the 25 patients for whom primary anastomosis was not performed, 15 had an end ileostomy and 10 had an end colostomy. The two groups were comparable with respect to operative characteristics with notably no difference in the need for an operative ostomy (20.8% in TPN group vs 16.5% in control, $P = 0.52$). There was a non-significant increase in operative blood loss and mean operative time in the TPN group (Table 1).

Post-operative complications

Forty patients (27.8%) had at least one complication in the 30-day post-operative period. There was no difference in the incidence of overall complications between the TPN and the non-TPN groups on univariate analysis (29.1% in TPN group vs 26.9% in non-TPN group, $P = 0.78$) (Figure 1). Twenty-one patients

(14.6%) suffered infectious complications (18.2% in TPN group versus 12.3% in non-TPN group, $P = 0.34$) and 23 (16.0%) suffered non-infectious complications (14.5% in TPN group vs 16.8% in non-TPN group, $P = 0.71$). The overall rate of anastomotic leak was low, with only four leaks (3.6% in TPN group vs 2.2% in non-TPN group, $P = 0.63$) (Table 3).

Univariate and multivariate analyses of predictors of non-infectious complications

Univariate and multivariate analyses were conducted utilizing variables defined a priori to control for differences in baseline disease severity and malnutrition between groups and while stratifying patients by duration of TPN pre-operatively into two groups (<60 days, ≥60 days). In univariate analysis, weight loss of >10% in the past 6 months was significantly associated with post-operative non-infectious complications (odds ratio [OR] 7.81, 95% confidence interval [CI]: 2.44–25.03, $P < 0.01$). In multivariate analysis, patients receiving pre-operative TPN for ≥60 days had significantly lower odds of developing post-operative non-infectious complications (OR 0.07, 95% CI: 0.01–0.88, $P = 0.03$) (Table 4). Weight loss of >10% in the past 6 months continued to be significantly associated with increased odds of non-infectious complications (OR 15.55, 95% CI: 3.28–73.44, $P < 0.01$). Finally, a history of failing more than two biologic therapies was also found to be significantly associated with non-infectious post-operative complications (OR 5.30, 95% CI: 1.30–21.55, $P = 0.02$). Figure 2 shows the overall incidence of non-infectious complications in the non-TPN group compared to patients who received TPN for ≥60 days.

Univariate and multivariate analyses of predictors of infectious complications

In univariate analysis, only weight loss of >10% in the past 6 months was found to be significantly associated with infectious complications (OR 3.60, 95% CI: 1.25–10.34, $P = 0.01$). This significant association persisted on multivariate analysis (OR 3.64, 95% CI: 1.13–11.61, $P = 0.03$). Importantly, TPN was not associated with an increased odds of infectious complications on univariate as well as multivariate analysis (Table 5).

Discussion

In our retrospective study of 144 CD patients undergoing major abdominal surgery, we found that patients receiving TPN pre-operatively had comparable outcomes in terms of post-operative complications compared to controls, despite having more severe disease and malnutrition. We also show that patients receiving TPN for ≥60 days pre-operatively were found to have a significantly lower risk of 30-day non-infectious post-
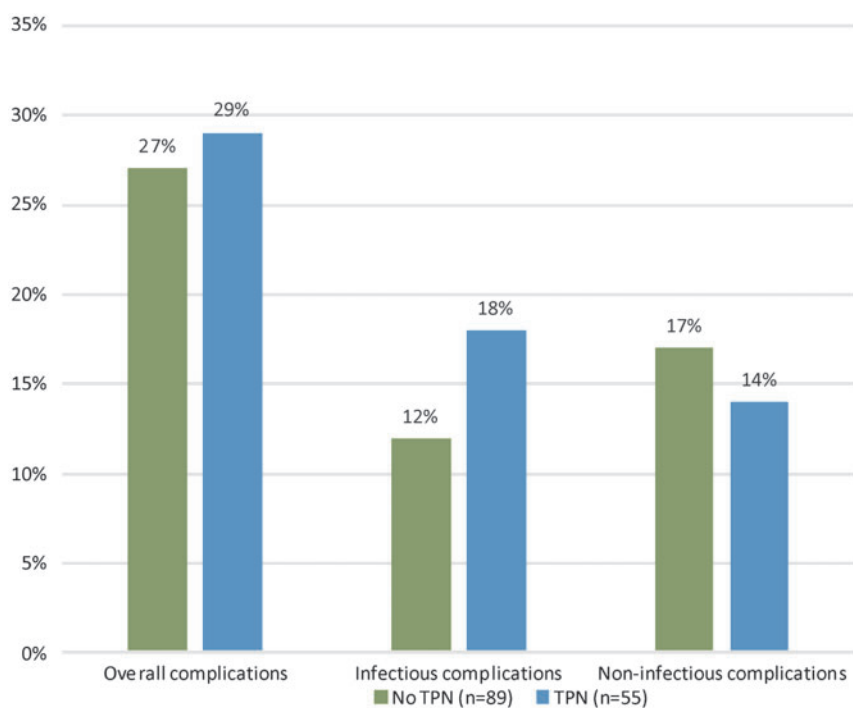
Figure 1. Incidence of post-operative complications comparing patients who received total parenteral nutrition (TPN) to controls.

Table 3. Post-operative complications of the total parenteral nutrition (TPN) group and the non-TPN group

	TPN group ($n = 55$)	Non-TPN group ($n = 89$)	P-value
Overall complications	16 (29.1%)	24 (26.9%)	0.78
Infectious complications	10 (18.2%)	11 (12.3%)	0.34
Intra-abdominal abscess formation	3 (5.5%)	5 (5.6%)	0.97
Bacterial pneumonia	1 (1.8%)	0 (0.0%)	0.20
Urinary-tract infection	3 (5.5%)	5 (5.6%)	0.37
Skin and soft-tissue infection	4 (7.3%)	5 (5.6%)	0.69
Line infection	2 (3.6%)	1 (1.1%)	0.31
Non-infectious complications	8 (14.5%)	15 (16.9%)	0.71
Anastomotic leak	2 (3.6%)	2 (2.2%)	0.64
Bowel obstruction	5 (9.1%)	11 (12.4%)	0.54
Acute renal failure	3 (5.5%)	5 (5.6%)	0.98
Deep venous thrombosis/pulmonary embolism	2 (3.6%)	2 (2.2%)	0.62

operative complications when controlling for severity of malnutrition and disease severity. Despite having a higher proportion of patients with severe disease and severe malnutrition, as well as the inherent infectious risks of TPN use, patients in the TPN group did not have higher rates of post-operative infectious complications.

Our study adds to the existing literature in being the largest to date on pre-operative TPN in CD patients, particularly since the advent of widespread biological use. Our findings are novel, since the benefits in post-operative outcomes were noted despite controlling for underlying disease severity and malnutrition. While we were not able to demonstrate a benefit in post-operative infectious complications, the absence of significantly higher infectious complications in the TPN group is notable, since these patients were significantly more malnourished with more severe disease. Moreover, despite the requirement for administration of TPN via a central catheter, the TPN group did not have a demonstrably higher incidence of post-operative line infections or venous thrombosis. Overall, our findings indicate a positive

role for TPN in allowing comparable operative outcomes in malnourished CD patients as compared to controls.

CD patients undergoing intestinal resection are at a significant risk for post-operative complications. A US study of 130 CD patients undergoing surgical treatment prior to the widespread use of biologic therapy reported a post-operative complication rate of 30% [8]. A more recent multi-center French study concluded that around 21% of patients undergoing intestinal resection developed post-operative complications [2]. Our cohort developed post-operative complications at a rate of 27.7%, in line with previously reported figures. Efforts aimed at decreasing this relatively high complication rate are prudent. Differing factors predicting post-operative complications have been identified in different studies of surgical CD patients, including a history of smoking, intra-abdominal sepsis and pre-operative use of steroids, among others [9, 10]. Pre-operative poor nutritional status has been uniformly identified as a predictor of poor post-operative outcomes across multiple studies [9–12]. While albumin level is commonly used to guide pre-operative
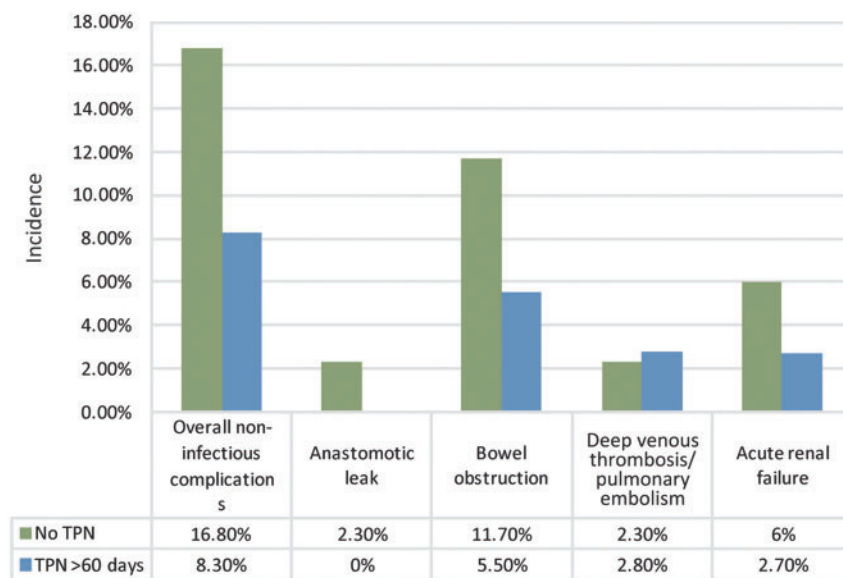
Figure 2. Incidence of non-infectious post-operative complications comparing patients who received total parenteral nutrition (TPN) for ≥60 days to patients who did not receive TPN.

Table 4. Univariate and multivariate logistic regression analysis of predictors of non-infectious post-operative complications

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Duration of TPN pre-operatively						
No TPN		Reference			Reference	
<60 days	1.78	0.59–5.34	0.29	0.67	0.14–3.13	0.30
≥60 days	0.46	0.12–1.72	0.25	0.07	0.01–0.88	**0.03**
Albumin <3 g/dL	1.22	0.44–3.42	0.69	3.18	0.56–17.91	0.19
Pre-albumin <15 mg/dL	2.05	0.71–5.92	0.18	0.67	0.17–2.78	0.58
Weight loss >10% in past 6 months	7.81	2.44–25.03	**<0.01**	15.55	3.28–73.44	**<0.01**
BMI <18.5 kg/m^2	0.41	0.05–3.34	0.41	0.69	0.05–9.98	0.79
Failed more than two biologics in the past	1.57	0.62–3.98	0.33	5.30	1.30–21.55	**0.02**
Crohn's-related hospitalization in the past year	1.77	0.62–5.13	0.29	3.29	0.73–14.29	0.12

Significant P-values in bold. TPN: total parenteral nutrition, BMI: body mass index, OR: odds ratio, CI: confidence interval.

Table 5. Univariate and multivariate logistic regression analysis of predictors of infectious post-operative complications

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Duration of TPN pre-operatively						
No TPN		Reference			Reference	
<60 days	1.86	0.57–6.05	0.30	1.31	0.34–5.04	0.69
≥60 days	1.08	0.34–3.38	0.88	0.56	0.14–2.28	0.43
Albumin <3 g/dL	1.87	0.68–5.09	0.22	1.97	0.59–6.63	0.27
Pre-albumin <15 mg/dL	1.78	0.61–5.19	0.29	1.57	0.49–5.04	0.44
Weight loss >10% in past 6 months	3.60	1.25–10.34	**0.01**	3.64	1.13–11.61	**0.03**
BMI <18.5 kg/m^2	1.88	0.47–7.50	0.37	2.32	0.50–10.70	0.28
Failed more than two biologics in the past	1.16	0.43–3.11	0.77	1.66	0.54–5.01	0.37
Crohn's-related hospitalization in the past year	2.12	0.67–6.72	0.20	2.55	0.67–9.60	0.17

Significant P-values in bold. TPN, total parenteral nutrition; BMI, body mass index; OR, odds ratio; CI, confidence interval.

nutritional assessment, our univariate and multivariate analyses indicated that loss of more than 10% of body weight in the past 6 months pre-operatively was a stronger predictor of worse post-operative outcomes. Our findings support a more comprehensive nutritional assessment pre-operatively with attention given to weight loss rather than laboratory findings.

In patients with CD, enteral nutrition has been shown to promote mucosal healing [13], improve weight gain [14] and boost quality of life [15]. However, patient factors such as non-compliance due to the low palatability of enteral formulas [16], as well as disease complications such as intestinal obstruction and fistulization limit the applicability of enteral nutrition to all clinical scenarios. TPN, commonly administered via a central venous catheter, is an alternative method of pre-operative nutrition that has demonstrated variable benefits in surgical patients. Rapid improvement in nitrogen balance, quick recovery of lymphocyte function and ultimately improved wound healing have been demonstrated in patients receiving TPN pre-operatively [17]. A recent review by Grass et al. examined the pooled results of four meta-analyses on pre-operative TPN in general surgical patients and found that three out of the four meta-analyses demonstrated a reduction in post-operative complications in the TPN group [18]. A multi-center prospective randomized trial of 395 general surgical patients randomized to either total TPN or no TPN pre-operatively concluded that severely malnourished patients receiving TPN had fewer non-infectious post-operative complications than controls (5 vs 43%; $P = 0.03$) [19]. This benefit did not translate to those patients who were not severely malnourished, however, and patients in the TPN group had an overall higher incidence of infectious complications. In our cohort, patients in the TPN group did not have a significantly higher incidence of infectious complications, despite administration of TPN via a central catheter. This highlights the possibility that CD patients undergoing major abdominal surgery may represent a unique subgroup of surgical patients in this regard. This also may indicate the efficacy of central venous catheter 'care bundles' utilized at tertiary referral centers [20] including ours to decrease the incidence of line-associated infections and potentially thrombosis.

In patients with inflammatory bowel disease (IBD) requiring surgery, studies on pre-operative TPN have been more limited. To date, there have been no randomized–controlled trials and much of the literature on the subject originates from a small number of retrospective cohort studies. Some of the limitations of prior studies include small sample size and lack of control for disease and malnutrition severity [21–25]. Results have also been variable; the earliest cohort study by Rombeau et al. [21] comparing 22 patients who received pre-operative TPN to controls found a significant decrease in overall post-operative complications in the TPN group. In 1989, Lashner et al. [23] retrospectively compared 49 patients who received pre-operative TPN to 54 controls and found only a significant reduction in length of small-bowel resection but no difference in overall post-operative complications. Notably, the aforementioned studies were conducted prior to the advent and widespread use of biologic therapy, limiting applicability to current clinical practice. More recently, a retrospective study comparing 15 CD patients receiving pre-operative TPN to 105 controls selected from surrounding community hospitals by Jacobson [25] found a significant reduction in overall post-operative complications in the TPN group.

The optimal duration of TPN pre-operatively has been the subject of much debate. We demonstrate a benefit for TPN when it is administered for at least 60 days pre-operatively. In the study of TPN in CD patients undergoing surgery by Rombeau et al. [21], the longest duration of TPN administered was for 25 days; Jacobson [25] administered TPN for between 19 and 90 days pre-operatively and reported benefit in all 15 patients receiving TPN. Randomized–controlled trials of pre-operative TPN outside of CD have demonstrated benefits in patients receiving TPN for as little as 7 days pre-operatively [19, 26]. We note that the majority of our patients received TPN for ≥ 60 days, with a significantly smaller number receiving TPN for < 60 days. As a result, our study might lack the power to demonstrate benefits in patients receiving TPN less than 60 days pre-operatively.

Our study has a few limitations. The retrospective nature of our study makes it susceptible to unmeasured confounders; however, we attempted to control for these by a detailed description and comparison of baseline patient characteristics, including disease and surgical characteristics between groups. Our single-center design may limit the generalizability of our findings, although patients with complicated CD requiring surgery are often referred to tertiary centers. The inclusion of patients undergoing urgent surgery may have negatively affected outcomes, although we note that they represented a small portion of patients and were equally distributed between groups. The lack of a validated pre-operative nutritional assessment for all patients (such as the subjective global assessment [27]) is also a limitation, although we utilized a combination of laboratory values and weight measurements to assess patient nutritional status and used consensus guidelines to define malnutrition as accurately as possible [6, 7]. Finally, while being the largest study to date on the matter, our patient numbers (particularly those receiving TPN for < 60 days) may have limited our power to detect a benefit in all operative outcomes.

In conclusion, our study of patients undergoing major abdominal surgery for CD shows a reduction of non-infectious post-operative complications in patients receiving TPN for ≥ 60 days pre-operatively with no associated increase in infectious complications. We also show that patients receiving TPN had comparable post-operative outcomes to controls despite having more severe disease and malnutrition. Our findings illustrate that, when used in a select group of CD patients, TPN is safe and is associated with favorable operative outcomes. Larger prospective studies are needed to validate our findings.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

version to be submitted. S.T.: conception and design of the study; patient cohort identification; critical appraisal of manuscript drafts and revisions; approval of final version to be submitted. A.I.: conception and design of the study; patient cohort identification; critical appraisal of manuscript drafts and revisions; approval of final version to be submitted. E.M.Z.: conception and design of the study; revision of statistical analysis and methodology; critical appraisal of manuscript drafts and revisions; approval of final version to be submitted. S.C.G.: the conception and design of the study; patient cohort identification, and acquisition of data; critical appraisal of manuscript drafts and revisions, as well as final approval of the version to be submitted.

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