Original Article

Perioperative enteral immunonutrition with probiotics favors the nutritional, inflammatory, and functional statuses in digestive system surgery

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Background and Objectives: This study aimed to evaluate the effects of enteral immunonutrition (EIN) on the nutritional status of patients during the perioperative period of digestive system surgery. **Methods and Study Design:** The clinical data of 102 patients who underwent gastrointestinal surgery between August 2017 and February 2021 were retrospectively analyzed. According to the nutritional support regimen, the patients were divided into an enteral nutrition (EN) group (50 patients) and an EIN group (52 patients). **Results:** The times (in hours) to return of the first bowel sound, first postoperative flatus, and first bowel movement, as well as the length of postoperative hospital stay were shorter in the EIN group than in the EN group (p<0.05). The concentrations of hemoglobin, prealbumin, albumin, and transferrin, as well as the concentrations of immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), complement C3, and complement C4 were higher in the EIN group than in the EN group at 1 and 7 days after surgery (p<0.05). The concentrations of endotoxins, D-lactic acid, and diamine oxidase were lower in the EIN group than in the EN group (p<0.05). The tolerance to enteral feeding was better in the EIN group than in the EN group (p<0.05). The incidence of complications was lower in the EIN group (5.77%) than in the EN group (10.0%) (p>0.05). **Conclusions:** EIN can promote gastrointestinal function recovery, improve the nutritional status, enhance the humoral immune function, regulate intestinal flora balance, improve intestinal permeability, prevent enteral feeding intolerance, and reduce complications in patients undergoing surgery for digestive system diseases.

Key Words: digestive system surgery, microbial immune enteral nutrition, nutritional status, immune function, intestinal flora

INTRODUCTION

Patients often experience varying degrees of immunosuppression and malnutrition due to reduced nutrient intake, abnormal catabolism, absorption and digestive dysfunctions, and changes in the anatomical and physiological structures of the digestive tract. Moreover, surgical stress can cause bacterial/endotoxin translocation and intestinal mucosal atrophy, further aggravating the dysfunction of the immune system.[1-3] Therefore, providing timely immune regulation and nutritional support is particularly crucial in improving the nutritional status of patients during the perioperative period, as well as in reducing complications and accelerating recovery.

Parenteral nutrition is a traditional mode of nutritional support after digestive system surgeries. Although it can meet the nutritional needs of patients, long-term parenteral nutrition can destroy the intestinal mucosal barrier because of the lack of food in the intestines, leading to intestinal mucosal atrophy and inflammation in the body.[4,5] Enteral nutrition (EN) can maintain the integrity of the intestinal mucosa, protect the intestinal barrier function, increase visceral blood flow, promote the normal growth of the intestinal flora, and enhance the function of gut-associated lymphoid tissues.[6] Meanwhile, enteral immunonutrition (EIN) can regulate the activity of the immune system during the perioperative period. Microbial EIN combines an enteral nutrient solution with probiotics, arginine, glutamate, and other nutritional components to regulate the intestinal flora. As a result, it can enhance the immune response, regulate the release and production of cytokines, inhibit intestinal flora imbalance, maintain growth, and reduce systemic inflammation.[7,8] A meta-analysis found that EIN can regulate the inflammation level, improve the cellular immune function, and reduce postoperative complications in patients undergoing radical gastrointestinal cancer surgery.[9] An animal experiment study reported that it can effectively inhibit the inflammatory response in rats with acute pancreatitis, and its mechanism of action is related to the regulation of the Janus kinase 2/signal transducer and activator of transcription 3 signaling pathway.[10] This study aimed to

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investigate the effects of EIN on the nutritional status, immune function, intestinal flora, and intestinal permeability of patients during the perioperative period of digestive system surgery.

METHODS

Clinical data

The clinical data of 102 patients who underwent gastrointestinal surgery at our hospital between August 2017 and February 2021 were retrospectively analyzed. The patients were divided into an EN group (50 patients) and an EIN group (52 patients) according to the specific nutritional support regimen. The EN group consisted of 29 male and 21 female patients with an average age of 53.7±8.12 years (range, 28–76 years) and an average body mass index of 21.5±2.58 kg/m^2. Their diagnoses were as follows: cancer (n=31) (esophageal cancer, n=8; gastric cancer, n=9; colorectal cancer, n=8; and bladder cancer, n=6) and benign lesions (n=19) (intestinal perforation, n=6; intestinal obstruction, n=9; esophageal stenosis, n=3; and intestinal necrosis, n=1); educational level: junior middle school or below (n=18), senior high school or technical secondary school (n=20), and junior college or above (n=12); residence: urban areas (n=38) and rural areas (n=12); payment methods for medical expenses: medical insurance (n=35), new rural cooperative medical care system (n=10), and own expense (n=5); and underlying disease: hypertension (n=10), coronary heart disease (n=8), diabetes (n=7), stroke (n=2), and fatty liver (n=2). Their average preoperative Nutritional Risk Screening 2002 (NRS-2002) score was 4.56±0.52 points; hemoglobin (Hb) concentration, 126±13.2 g/L; prealbumin (PA) concentration, 266±28.2 mg/L; albumin (ALB) concentration, 35.3±3.02 g/L; and transferrin (TRF) concentration, 2.46±0.29 g/L on admission. Meanwhile, the EIN group consisted of 30 male and 22 female patients with an average age of 54.1±7.46 years (range, 25–75 years) and an average body mass index of 22.0±2.49 kg/m^2. Their diagnoses were as follows: cancer (n=28) (esophageal cancer, n=7; gastric cancer, n=7; colorectal cancer, n=9; and bladder cancer, n=5) and benign lesions (n=24) (intestinal perforation, n=8; intestinal obstruction, n=10; esophageal stenosis, n=4; and intestinal necrosis, n=2); educational level: junior middle school or below (n=17), senior high school or technical secondary school (n=21), and junior college or above (n=14); residence: urban areas (n=37) and rural areas (n=15); payment methods for medical expenses: medical insurance (n=33), new rural cooperative medical care system (n=9), and own expense (n=10); and underlying disease: hypertension (n=9), coronary heart disease (n=7), diabetes (n=8), stroke (n=3), and fatty liver (n=1). Their preoperative NRS-2002 score was 4.63±0.38 points; Hb concentration, 126±13.0 g/L; PA concentration, 266±27.2 mg/L; ALB concentration, 36.2±2.97 g/L; and TRF concentration, 2.51±0.33 g/L on admission. The types of surgery in the EIN group were as follows: partial gastrectomy or subtotal gastrectomy (n=12), esophagectomy (n=14), partial colectomy or colon segmental resection (n=11), pancreaticoduodenectomy (n=11), and other surgeries (n=4). The general data of the patients were comparable between the EIN and EN groups (p>0.05). The study design and conceptual framework are shown in Figures 1 and 2.

Selection criteria

The inclusion criteria were as follows: preoperative NRS-2002 score of ≥3 points, age of ≥18 years, indications for nutritional support, clear consciousness and no communication or mental disorders, and voluntarily signed informed consent form. The exclusion criteria were as follows: preoperative infection; requirement for emergency surgery; comorbidities, including Addison's disease, hyperthyroidism, or hypothyroidism; radiotherapy and chemotherapy upon admission; surgery time of >6 h and intraoperative blood loss amount of >500 mL; use of immunosuppressant and glucocorticoid therapy; immune system disease; and severe heart, lung, kidney, and liver insufficiencies before surgery. This study was approved by the Ethics Committee of The Ninth People's Hospital of Chongqing.

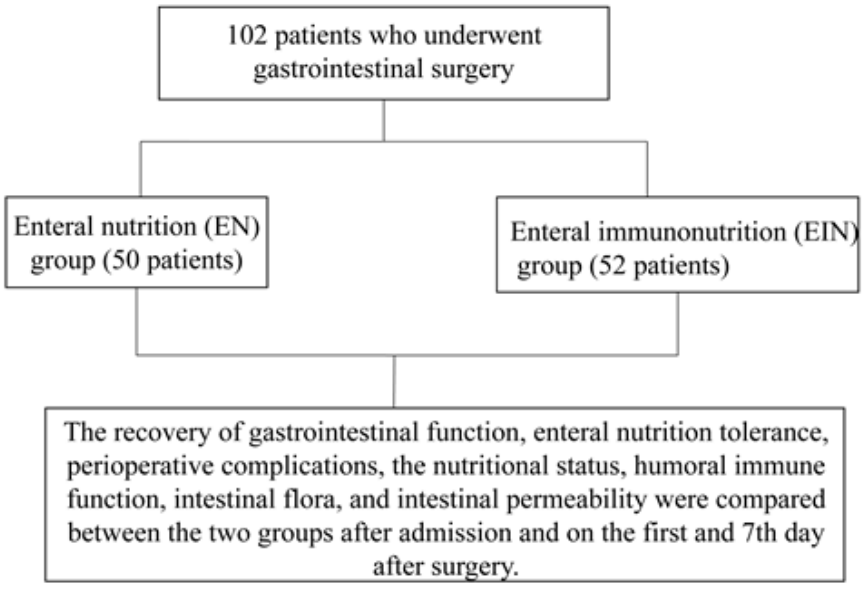

Figure 1. Study design of the study.

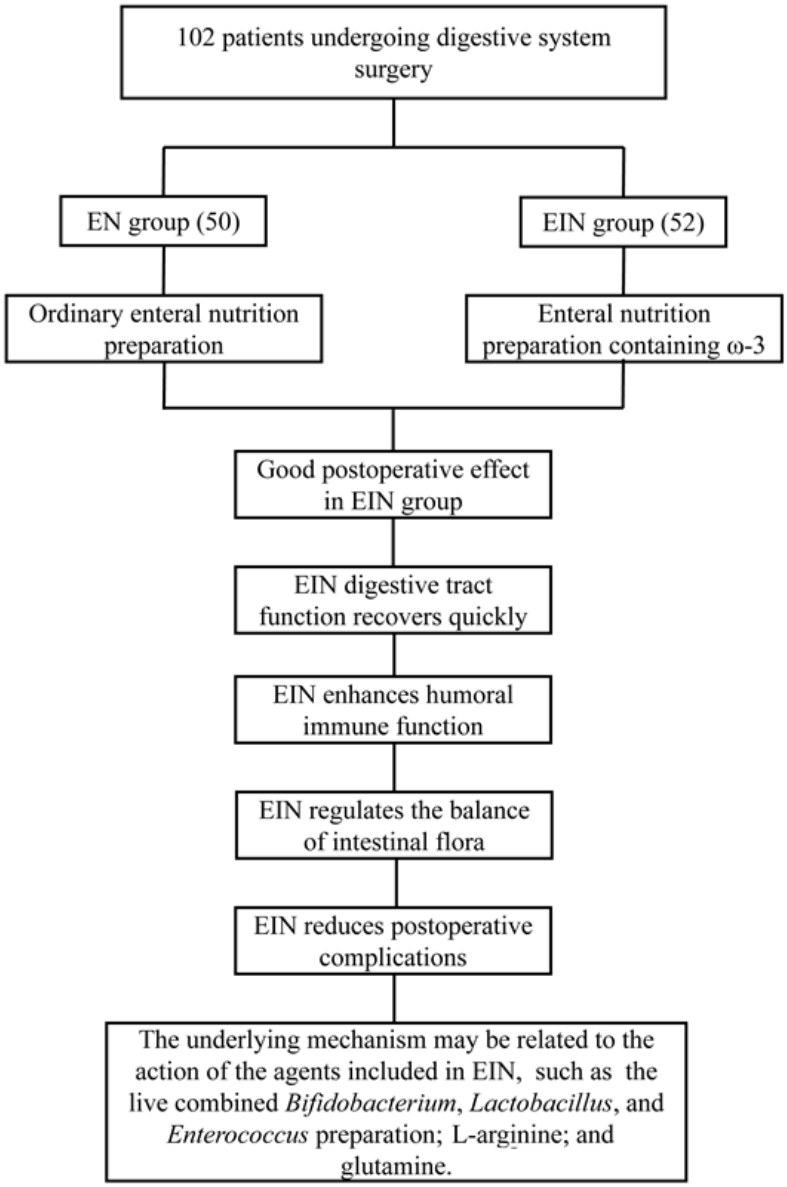

Figure 2. Conceptual framework of the study.

Methods

All patients were provided with 25 kcal/kg EN 3 days before surgery, and the intervention was discontinued 6–8 h before surgery. After 6 h, the stability of the patients' vital signs was checked, and EN was administered via a gastric tube. The EIN group was administered an EN preparation containing omega-3 fatty acids (Ruidai, Huarui Pharmaceutical Co., Ltd.). In addition, 6 g/day live combined *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* preparation; 0.25 g/(kg·day) L-arginine; and 0.4 g/(kg·day) glutamate were administered three times a day. The EN group received common enteral nutrient preparations (Ruidai, Huarui Pharmaceutical Co., Ltd.).

Outcome measurements

1. Gastrointestinal function recovery. The times (in hours) to the first postoperative flatus and first bowel movement, and the length of postoperative hospital stay were recorded.
2. Sample collection. Fasting cubital venous blood (5 mL) was collected from all patients after admission and at 1 and 7 days after surgery. The blood samples were allowed to stand at room temperature for 30 min and centrifuged thereafter for 10 min (R=6 cm, 3500 r/min). The serum was separated and refrigerated at -80℃.
3. Nutritional status. The serum Hb, PA, ALB, and TRF concentrations were measured using an automatic biochemical analyzer (Atellica CH930, Shanghai Jumu Medical Instruments Co., Ltd.).
4. Humoral immune function. The serum immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), complement C3, and complement C4 concentrations were determined using an enzyme-linked immunosorbent assay kit (Guangdong Gukang Biotechnology Co., Ltd.).
5. Intestinal flora. After admission and at 1 and 7 days after surgery, 5–8 g fresh stool specimens were collected and cultured for bacteria. *Lactobacillus*, *Bifidobacterium*, *Escherichia coli* (*E. coli*), *Staphylococcus*, and *Enterococcus faecalis* were enumerated using the plate count technique.
6. Intestinal permeability. Enzyme-linked immunosorbent assay was used to determine the endotoxin

concentrations; enzymatic spectrophotometry (Shanghai Fantai Biotechnology Co., Ltd.) was used to measure the dextro-lactate dehydrogenase concentrations; and colorimetry (Amictech Co., Ltd.) was used to determine the diamine oxidase (DAO) concentrations.

7. Enteral feeding tolerance. Patients who were able to tolerate the target enteral nutrient solution, without obvious unfavorable reactions, were considered to have complete tolerance. Patients who experienced mild adverse reactions and received more than one-half of the target volume of the enteral nutrient solution after slowing down the administration were determined to have partial tolerance. Patients who developed abdominal pain, abdominal distension, and other adverse reactions; received less than one-half of the target volume of the enteral nutrient solution; had watery stool that occurred more than four times within 24 h; or developed a sore throat were considered to have intolerance to enteral feeding.
8. Complications. The occurrence of deep vein thrombosis, incisional infection, abdominal cavity infection, urinary tract infection, anastomotic leakage, reflux pneumonia, and other complications was recorded.

Statistical analysis

The SPSS software (version 24.0) was used for all statistical analyses. Measurement data were reported as means ± standard deviations (means ± SDs). The independent t-test and paired t-test were used for comparisons between the groups. Count data were expressed as rates and examined using the chi-square test. Statistical significance was set at $p<0.05$.

RESULTS

Gastrointestinal function recovery

The times (in hours) to return of the first bowel sound, first postoperative flatus, and first bowel movement, as well as the length of postoperative hospital stay were shorter in the EIN group than in the EN group ($p<0.05$); this indicates that EIN could promote an earlier recovery of the gastrointestinal function after surgery in patients with digestive system diseases (Table 1).

Nutritional status

The concentrations of the nutritional indices after admission were not significantly different between the two groups ($p>0.05$). However, the concentrations of Hb, PA, ALB, and TRF were higher in the EIN group than in the EN group at 1 and 7 days after surgery ($p<0.05$), indicating that EIN could improve the perioperative nutritional status of patients with digestive system diseases (Figure 3).

Humoral immune function

The concentrations of the humoral immune indices after admission did not significantly differ between the EIN and EN groups ($p>0.05$). However, the concentrations of IgA, IgG, IgM, complement C3, and complement C4 were higher in the EIN group than in the EN group at 1 and 7 days after surgery ($p<0.05$), indicating that EIN could enhance the postoperative humoral immune function of patients with digestive system diseases (Figure 4).

Intestinal flora

The intestinal flora indices after admission were not significantly different between the EIN and EN groups ($p>0.05$). However, the *Lactobacillus* and *Bifidobacterium* counts were higher in the EIN group than in the EN group at 1 and 7 days after surgery, whereas the *E. coli*, *Staphylococcus*, and *Faecococcus* counts were lower in the EIN group than in the EN group ($p<0.05$); this indicates that EIN could regulate the balance of the intestinal flora, supplement beneficial bacteria, and inhibit the growth of pathogenic bacteria after surgery in patients with digestive system diseases (Table 2).

Intestinal permeability

The concentrations of the intestinal permeability indices after admission were not significantly different between the two groups ($p>0.05$). However, the endotoxin, D-lactate, and DAO concentrations were lower in the EIN group than in the EN group at 1 and 7 days after surgery ($p<0.05$), indicating that EIN could improve intestinal permeability in patients with digestive system diseases (Table 3).

Enteral feeding tolerance

The enteral feeding tolerance was better in the EIN group than in the EN group ($p<0.05$), indicating that EIN could improve the enteral feeding tolerance in patients with digestive system diseases (Table 4).

Complications

Although the difference was not significant, the incidence of complications was lower in the EIN group (5.77%) than in the EN group (10.0%) ($p>0.05$), indicating that EIN is a safer regimen than EN (Table 5).

Table 1. Comparison of the gastrointestinal function

	EN group (n=50)	EIN group (n=52)
Time to return of the first bowel sound (h)	40.2±6.12	35.9±5.12***
Time to the first postoperative flatus (h)	54.1±7.25	45.8±6.25***
Time to the first bowel movement (h)	65.3±6.25	58.8±4.16***
Duration of postoperative hospital stay (d)	11.0±2.64	8.31±2.46***

EN: enteral nutrition; EIN: enteral immunonutrition.
Data are presented as means ± SDs.
***$p<0.001$ vs the EN group.

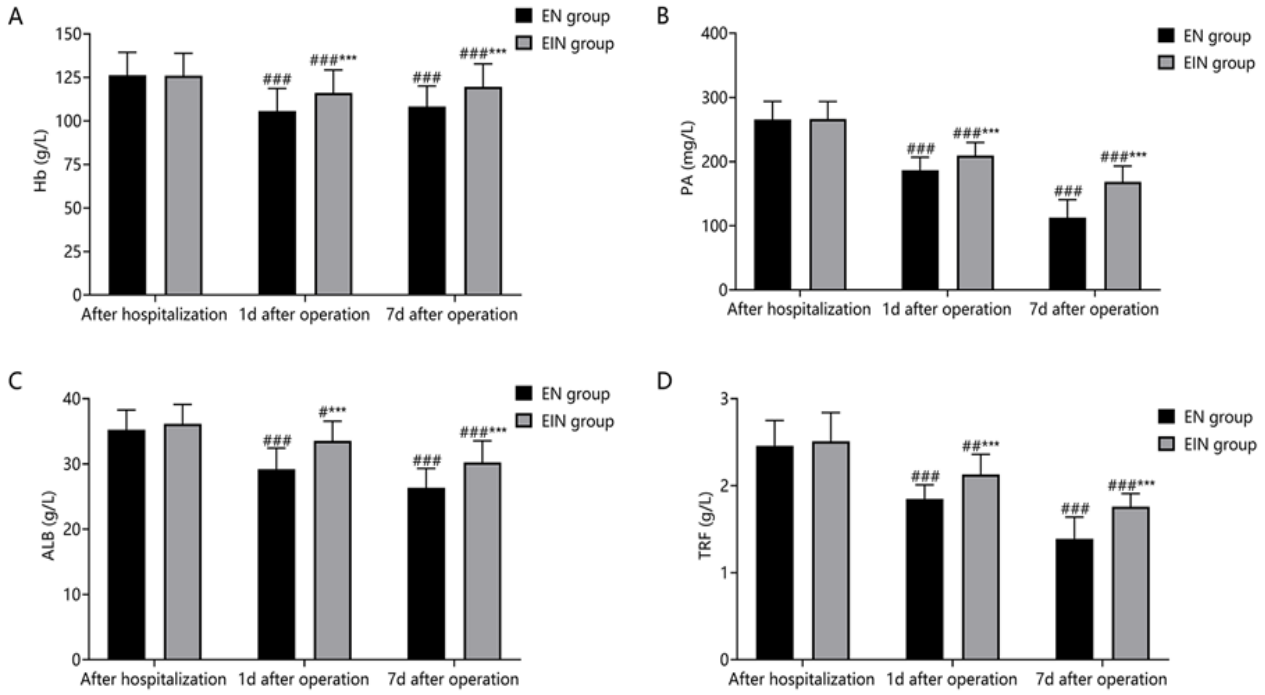

Figure 3. Comparison of the nutritional indicators between the two groups. (A) The Hb concentrations were significantly higher in the EIN group than in the EN group at 1 and 7 days postoperatively. (B) The PA concentrations were significantly higher in the EIN group than in the EN group at 1 and 7 days postoperatively. (C)The ALB concentrations were significantly higher in the EIN group than in the EN group at 1 and 7 days postoperatively. (D) The TRF concentrations were significantly higher in the EIN group than in the EN group at 1 and 7 days postoperatively. $^{\#}p<0.05$, $^{\#\#}p<0.01$, and $^{\#\#\#}p<0.001$ vs after admission; $^{***}p<0.001$ vs. the EN group; Hb: hemoglobin; EIN: enteral immunonutrition; EN: enteral nutrition; PA: prealbumin; ALB: albumin; TRF: transferrin.

Table 2. Comparison of the gastrointestinal function

	EN group (n=50)	EIN group (n=52)
Lactobacillus		
After admission	8.03±0.46	7.96±0.52
1 d postoperatively	8.06±0.43	8.68±0.56$^{\#*}$
7 d postoperatively	7.56±0.39	9.67±0.48$^{\#\#\#***}$
Bifidobacterium		
After admission	7.16±0.65	7.11±0.64
1 d postoperatively	7.20±0.56	7.95±0.55$^{\#***}$
7 d postoperatively	6.95±0.37	8.92±0.66$^{\#\#\#***}$
Escherichia coli		
After admission	7.59±0.46	7.82±0.55
1 d postoperatively	7.62±0.52	6.85±0.32$^{\#**}$
7 d postoperatively	8.02±0.51	6.38±0.38$^{\#\#***}$
Staphylococcus		
After admission	4.12±0.49	4.28±0.38
1 d postoperatively	4.13±0.51	3.49±0.52$^{\#**}$
7 d postoperatively	4.08±10.5	3.32±0.38$^{\#\#***}$
Enterococcus faecalis		
After admission	7.63±0.86	7.82±0.89
1 d postoperatively	7.56±0.56	6.89±0.35$^{\#\#**}$
7 d postoperatively	7.69±0.67	6.68±0.39$^{\#\#\#***}$

EN: enteral nutrition; EIN: enteral immunonutrition.
Data are presented as means ± SDs in log colony-forming units/g.
$^{\#}p<0.05$, $^{\#\#}p<0.01$, and $^{\#\#\#}p<0.001$ vs after admission.
$^{**}p<0.01$ and $^{***}p<0.001$ vs the EN group.

DISCUSSION

The metabolic response to stress induced by surgical trauma can alter the Ig synthesis and intestinal mucosal barrier function and damage immune cells. An impaired intestinal mucosal barrier can lead to an uncontrolled release of inflammatory cytokines and excessive production of inflammatory mediators, further disrupting the ecological balance of the intestinal flora and the immune homeostasis and increasing the permeability of the intestinal mucosal barrier.[11, 12] Enteral microecological nutrition can balance the intestinal flora, and EN can enhance the immune function. Meanwhile, EIN can provide both benefits through its synergistic effects.[13]

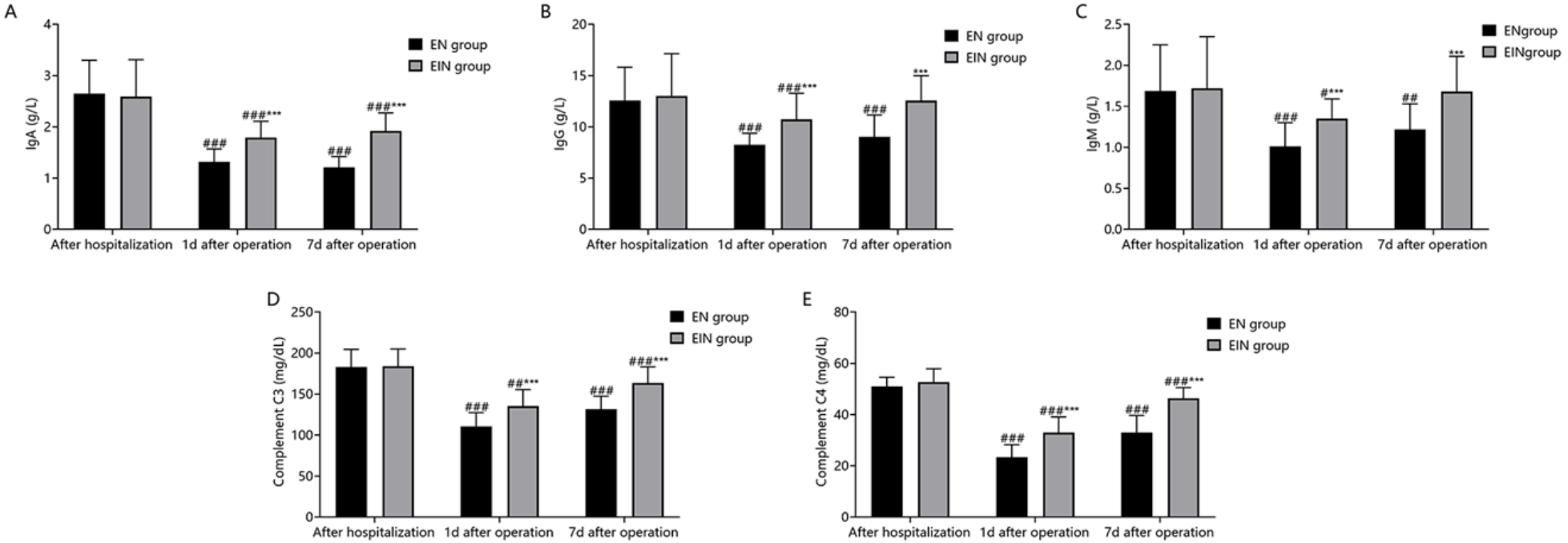

Figure 4. Comparison of the humoral immune function between the two groups. (A) The IgA concentrations were significantly higher in the EIN group than in the EN group at 1 and 7 days postoperatively. (B) The IgG concentrations were significantly higher in the EIN group than in the EN group at 1 and 7 days postoperatively. (C) The IgM concentrations were significantly higher in the EIN group than in the EN group at 1 and 7 days postoperatively. (D) The complement C3 concentrations were significantly higher in the EIN group than in the EN group at 1 and 7 days postoperatively. (E) The complement C4 concentrations were significantly higher in the EIN group than in the EN group at 1 and 7 days postoperatively. $^{\#\#}p<0.01$ and $^{\#\#\#}p<0.001$ vs. after admission; $^{***}p<0.001$ vs the EN group; Ig: immunoglobulin; EIN: enteral immunonutrition; EN: enteral nutrition.

Table 3. Comparison of the intestinal permeability

	EN group (n=50)	EIN group (n=52)
Endotoxin (pg/mL)		
After admission	1.52±0.31	1.29±0.29
1 d postoperatively	2.97±0.43$^{\#\#\#}$	2.02±0.37$^{\#\#\#**}$
7 d postoperatively	2.88±0.52$^{\#\#\#}$	1.25±0.33$^{\#\#\#***}$
D-lactate (μg/mL)		
After admission	15.4±3.25	16.0±3.86
1 d postoperatively	42.9±5.26$^{\#\#\#}$	36.5±4.19$^{\#\#\#***}$
7 d postoperatively	36.3±23.4$^{\#\#\#}$	19.6±5.28$^{\#\#\#***}$
DAO (mg/mL)		
After admission	40.3±3.85	41.1±4.19
1 d postoperatively	104±12.9$^{\#\#\#}$	86.7±5.94$^{\#***}$
7 d postoperatively	65.9±6.28$^{\#\#\#}$	53.7±5.98$^{\#\#\#***}$

DAO: diamine oxidase; EN: enteral nutrition; EIN: enteral immunonutrition.
Data are presented as means ± SDs.
$^{\#\#\#}p<0.001$ vs. after admission.
$^{**}p<0.01$ and $^{***}p<0.001$ vs the EN group.

Table 4. Comparison of the enteral feeding tolerance

	EN group (n=50)	EIN group (n=52)
Complete tolerance	18	32
Partial tolerance	25	19
Intolerance	7	1*

EN: enteral nutrition; EIN: enteral immunonutrition.
Data are presented as numbers of patients.
$^{*}p<0.05$ vs the EN group.

Table 5. Comparison of complications

	EN group (n=50)	EIN group (n=52)
Lower extremity deep vein thrombosis	0	1 (1.92)
Incisional infection	1 (2.00)	0
Abdominal infection	1 (2.00)	0
Urinary tract infection	1 (2.00)	1 (1.92)
Anastomotic fistula	1 (2.00)	1 (1.92)
Reflux pneumonia	1 (2.00)	0
Total	5 (10.0)	3 (5.77)

EN: enteral nutrition; EIN: enteral immunonutrition.
Data are presented as n (%).

Klek et al found that EIN shortens the postoperative hospital stay, improves the perioperative nutritional status, and reduces the hospitalization costs.[14] Cui et al found that administration of EIN after surgery can modulate the inflammatory response and enhance the immune function of patients with gastric cancer.[15] In a randomized controlled trial, Suzuki et al observed that postoperative EIN prevented complications and promoted lymphocyte proliferation compared with total parenteral nutrition.[16] In our study, the times to return of the first bowel sound, first postoperative flatus, and first bowel movement were shorter in the EIN group than in the EN group, while the postoperative nutritional status, intestinal flora, intestinal permeability, and enteral feeding tolerance were better in the EIN group than in the EN group; these findings are consistent with those of the above-mentioned study, reaffirming the value of EIN in patients with gastrointestinal diseases. The underlying mechanism may be related to the action of the agents included in EIN, such as the live combined *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* preparation; L-arginine; and glutamine. The live combined *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* preparation contains probiotic bacteria, which can bind to the specific receptors of intestinal epithelial cells, prevent the invasion of other pathogenic bacteria, promote the recovery of the function and structure of the gastrointestinal tract, and enhance the function of the intestinal mucosal barrier. Moreover, they produce antimicrobial agents through metabolism, thus inhibiting or killing pathogenic microorganisms; directly replenish the normal flora of the intestine; aid the reproduction and growth of beneficial bacteria; and inhibit the reproduction of pathogenic bacteria, thus restoring the balance of the intestinal flora.[17,18] L-arginine is an essential mammalian amino acid and a precursor of nitric oxide that can be catalyzed by nitric oxide synthase into nitric oxide; it plays a role in stimulating immune cells, promoting wound healing, improving microvascular perfusion, and repairing tissues. Because trauma, surgery, and other stress-related factors cause negative nitrogen balance, the synthesis of amino acids cannot meet the demand of the body. In this situation, glutamine is consumed in great

quantity, which results in increased intestinal permeability, damaged intestinal mucosal epithelial cells, and impaired intestinal mucosal barrier. Supplementation with exogenous glutamine can maintain the intestinal mucosal structure, weight, and protein content; prevent intestinal mucosal atrophy; improve the intestinal immune function and cell activity; and avoid the translocation of intestinal bacteria/endotoxins.[19] Achamrah et al highlighted the beneficial effects of glutamine on gastrointestinal diseases, including maintenance of the integrity of the intestinal barrier and reduction of the intestinal permeability.[20] Kim and Kim found that glutamine regulates tight junction proteins, promotes enterocyte proliferation, inhibits pro-inflammatory signaling pathways, and protects cells from stress-induced apoptosis and that supplementation with exogenous glutamine attenuates muscle proteolysis, promotes protein synthesis, and improves nitrogen balance.[21]

In this study, the concentrations of IgA, IgG, IgM, complement C3, and complement C4 were higher in the EIN group than in the EN group at 1 and 7 days postoperatively, and no significant differences in the perioperative complications were observed between the two groups; these results indicate that EIN can enhance the postoperative humoral immune function in patients with digestive system diseases, with fewer complications. The underlying mechanism may be related to the following: (1) Omega-3 is integrated into the lipid bilayer of the endothelial cell membrane and T lymphocytes, which can affect the spatial composition of cell membrane receptors, improve the cell membrane composition, change the signal transduction processes, and regulate the expression of interleukins and fatty acids in the process of inflammation, thereby playing a role in regulating the immune function by inhibiting the synthesis of pro-inflammatory factors, such as interleukin-1, interleukin-6, tumor necrosis factor, and prostaglandin E2.[1,22] Plank et al found that preoperative administration of EN preparations containing omega-3 components for 7 consecutive days can maintain the immunity level, reduce the postoperative inflammatory response, and prevent the occurrence of postoperative infections in patients with gastric cancer.[23] (2) Probiotics can interact with dendritic cells and affect the differentiation of T cells into regulatory T cells or Th1 and Th2 cells, inhibit the production of pro-inflammatory factors, such as tumor necrosis factor-α, by monocytes, and play a role in regulating immune responses. Moreover, probiotics can regulate immune responses through dendritic cells and macrophages, regulate the secretion of cytokines by immune cells, stimulate the host immune response, and induce the immune function of the body.[24] (3) Glutamine helps promote the differentiation, mitosis, and proliferation of macrophages and lymphocytes, thus enhancing immune cell replication and protecting the function of immune cells.[25]

In conclusion, EIN can promote gastrointestinal function recovery, improve the nutritional status, enhance the humoral immune function, regulate intestinal flora balance, improve intestinal permeability, and prevent enteral feeding intolerance in patients with digestive system diseases, with few complications after surgery. Owing to the small sample size, short follow-up period, and single source of cases in our study, future studies with a larger sample size are warranted to further explore the possibility of improving the nutritional status and immune function of patients with gastrointestinal diseases.

AUTHOR DISCLOSURES

The authors declare that they have no conflicts of interest.

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