Original Article

Does early postoperative enteral ecoimmunonutrition enhance intestinal function in gastric cancer?

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Background and Objectives: We assessed the effect of enteral ecoimmunonutrition (enteral nutrition involving probiotics and immune nutrients) on gastric cancer in the postoperative period. **Methods and Study Design:** In total, 60 patients with gastric cancer were randomized into an enteral ecoimmunonutrition group or an enteral nutrition group. Information on postoperative complications; hospitalization length; time to first bowel movement and first flatus; and differences between preoperative and postoperative nutritional status, inflammatory reactions, and immune function was collected. **Results:** No significant between-group differences in nutritional status and complications were observed. C-reactive protein concentrations were lower in the enteral ecoimmunonutrition group than in the enteral nutrition group on postoperative day 7 ($p<0.001$) and $CD4^+$ concentrations were significantly higher ($p=0.01$). The enteral ecoimmunonutrition group had a significantly shorter time to first flatus than the enteral nutrition group ($p=0.03$). **Conclusions:** Early postoperative enteral ecoimmunonutrition significantly improved immune function, reduced inflammatory responses, and promoted intestinal function recovery in patients with gastric cancer undergoing gastrectomy.

Key Words: gastric cancer, ecoimmunonutrition, enteral nutrition, early nutrition support, surgery

INTRODUCTION

Gastric cancer (GC) is one of the most common upper gastrointestinal malignancies, the fifth most common type of cancer, and the third leading cause of cancer deaths worldwide.[1] In China, GC ranks as the second most common type of cancer and the third leading cause of cancer deaths.[2] Patients with malignant tumors demonstrate varying degrees of malnutrition. In GC, the rate can be as high as 87%.[3] Malnutrition can suppress immune function, alter inflammatory reactions, and increase the postoperative complication incidence and hospitalization length. Therefore, comprehensive nutrition therapy is critical in patients with GC and malnutrition.

According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, nutrition therapy is considered a crucial component of anticancer therapy[4] and early postoperative enteral nutrition (EN) therapy is recommended. EN therapy could include nutritional elements such as probiotics, ω-3 fatty acids, glutamine (Gln), and arginine (Arg). Enteral immunonutrition (EIN) and enteral econutrition (EEN) has shown to protect the intestinal barrier, modulate immune function, induce inflammatory responses, and prevent postoperative complications (Figure 1).[5-9] In general, immunonutrition includes at least two nutrients of Arg, ω-3 fatty acids, Gln, and nucleotides. Because probiotics are potential immunomodulators, some experts suggest that they are immunonutrients.[10] However, whether enteral ecoimmunonutrition (EEIN) -EN therapy involving probiotics and immune nutrients -is superior to other therapies is unclear. Few studies have investigated the postoperative EEIN application in patients with GC. Thus, this clinical trial was conducted to assess the effect of EEIN on GC in the postoperative period.

METHODS

Patient qualifications

This study included 60 patients with GC who underwent radical gastrectomy with D2 lymphadenectomy in the Department of Gastrointestinal Surgery of Sichuan Cancer Hospital in China between June 2018 and June 2019. The study was approved by the independent Ethics Committee of Sichuan cancer hospital (SCCHEC-02-2018-048). Signed informed consent was obtained from each patient before surgery according to the principles of the Declaration of Helsinki. Exclusion criteria comprised previous abdominal radiotherapy; preoperative chemotherapy; pulmonary, cardiovascular, renal, or hepatic disease; and diabetes.

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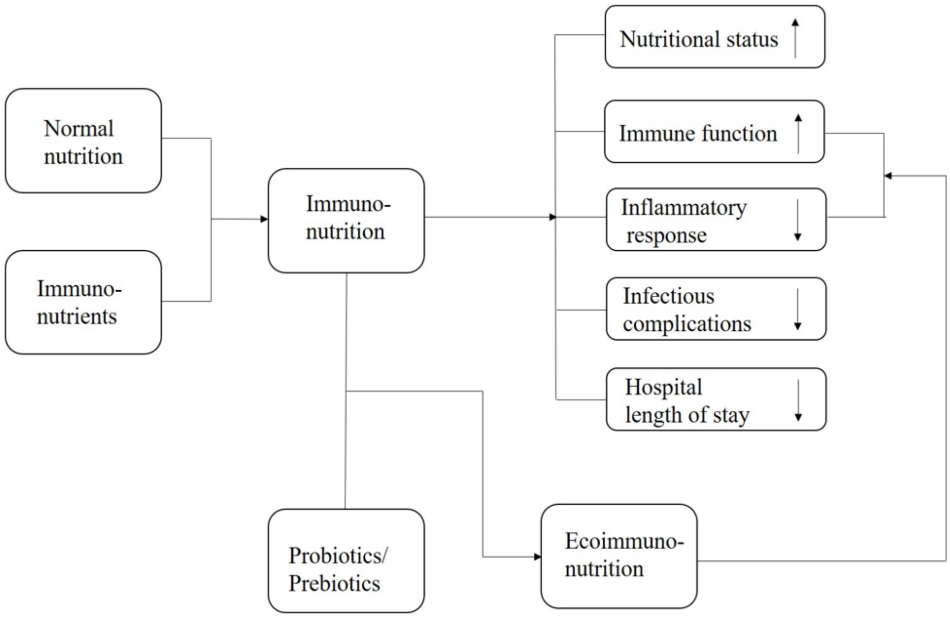

Figure 1. Effects of immunonutrition and ecoimmunonutrition.

Patient management

Patients who met the inclusion criteria were randomized into the EEIN or EN (control) group (30 patients each). Each patient received preoperative education and were allowed to intake clear fluids and solids until 2 and 6 h before induction of anesthesia, respectively.[11] During surgery, a 140-cm-long enteral feeding tube (Nutricia Flocare, the Netherlands) was inserted into the first intestinal loop, 15–20 cm below the lowest anastomosis. The daily energy allowance for all patients was set at 125.52 kJ/kg (≈30 kcal/kg). The EEIN group received the nutrients through a nasojejunal feeding tube for 7 consecutive days after surgery. The EN group received a regular diet without nutritional supplementation. Enteral tube feeding was initiated 8 h after surgery with administration of a 5% glucose solution. EN was administered at rates of 25, 50, 75, and 100 mL/h on days 1, 2, 3, and 4 through 7, respectively. Table 1 presents the intervention details.

Clinical assessment

The assessed clinical data included patients' age, sex, weight, body mass index, nutritional status, and tumor–node–metastasis (TNM) stage, according to the eighth edition of "TNM Classification of Malignant Tumors" by American Joint Committee on Cancer/Union for International Cancer Control.[12] On the preoperative day and on the postoperative days 2 and 7, peripheral blood was collected to assess nutritional status, immune function, and inflammatory reaction. Data on hospitalization length, time to first bowel movement and first flatus, and postoperative complications during hospitalization, defined according to the criteria established by the American College of Chest Physicians, were recorded.[13]

Statistical analysis

Statistical analysis was performed on IBM SPSS (version19; IBM Corp., Armonk, NY, USA), and measurement data are presented as means ± standard deviations. The t test and chi-square test were used to examine the quantitative and categorical data, respectively. Differences at $p<0.05$ were considered statistically significant.

RESULTS

Demographic and baseline clinical data

Of the 60 patients enrolled, 30 (22 men and 8 women) were in the EEIN group, whereas 30 (25 men and 5 wom-

Table 1. Nutritional interventions

Time	Nutrients	EEIN	EN
POD 1	5% GNS	500 mL	500 mL
	Probiotics‡	4 g	-
	Glutamine	2 g	-
POD 2–3	Enteral nutrition†	500 mL	500 mL
	Probiotics‡	4 g	-
	Glutamine	2 g	-
POD 4–7	Enteral nutrition†	1000 mL	1000 mL
	Probiotics‡	4 g	-
	Glutamine	2 g	-

POD: postoperative day; EEIN: enteral ecoimmunonutrition; EN: enteral nutrition; GNS: glucose normal saline.
†EN: An elemental diet composed of short peptides (486 kcal/500 mL) obtained from Zhejiang Hailisheng Biotechnology, China.
‡Probiotics: Combined *Bifidobacterium* and *Lactobacillus* tablets obtained from Inner Mongolia Shuangqi Pharmaceutical, Hohhot, China

en) were in the EN group. The participants were well matched for age, sex, weight, body mass index, nutritional status, and TNM stage. Table 2 presents demographic and clinical characteristics of the groups are.

Effects on nutritional status

No significant between-group differences were observed on the preoperative day and postoperative days 2 and 7 in the nutritional variables -weight and concentrations of albumin, prealbumin, and hemoglobin (Table 3).

Effects on inflammatory reaction

As Table 4 shows, C-reactive protein concentrations were lower in the EEIN group than in the EN group on postoperative day 7 (p=0.00). Between-group differences in neutrophil, platelet, C-reactive protein, and procalcitonin concentrations on the preoperative day or on postoperative days 2 and 7 were nonsignificant.

Effects on immune function

The cellular immunity data showed that postoperative $CD3^+$, $CD4^+$, and human leukocyte antigen–DR isotype concentrations increased in both groups between postoperative days 2 and 7. However, only $CD4^+$ concentrations in the EEIN group were significantly higher than those in the EN group on postoperative day 7 (p=0.01; Table 5).

Effects on recovery

Patients in the EEIN group had a significantly shorter time to first flatus than those in the EN group (p=0.03). No significant between-group differences were found for postoperative complication incidence and hospitalization length (Table 6).

DISCUSSION

GC is a common malignancy. In China, where surgery remains the firstline treatment for this disease, most patients with GC are diagnosed at advanced stages.[14]

Table 2. Baseline clinical characteristics of patient groups

	EEIN (N=30)	EN (N=30)	p value
Age (y) †	57.7±9.27	60.5±8.62	0.23
Sex, n (%)			0.53
Male	22 (73.3)	25 (83.3)	
Female	8 (26.7)	5 (16.7)	
Smoking, n (%)			0.43
Smoker	19 (63.3)	15 (50)	
Nonsmoker	11 (36.7)	15 (50)	
Drinking, n (%)			1.00
Drinker	9 (30)	10 (33.3)	
Nondrinker	21 (70)	20 (66.7)	
Weight (kg)*	57.9±7.50	60.6±13.1	0.33
PG-SGA score, n			0.79
>3	19	17	
≤3	11	13	
TNM stage, n (%)			0.30
I-II	15 (50)	11 (36.7)	
III	15 (50)	19 (63.3)	

EEIN: enteral ecoimmunonutrition; EN: enteral nutrition; TNM: tumor–node–metastasis; PG-SGA: Patient-Generated Subjective Global Assessment.
†Values are presented as means ± standard deviations.

Table 3. Nutritional variables†

	EEIN	EN	p value
ALB (g/L)			
Pre Op	40.3±4.36	40.3±3.86	0.98
POD 2	30.8±2.97	32.4±3.44	0.07
POD 7	34.4±3.82	33.6±3.07	0.43
PAB (mg/L)			
Pre Op	208±61.1	208±39.5	0.98
POD 2	115±27.8	124±32.9	0.24
POD 7	149±46.9	138±34.8	0.31
HB (g/L)			
Pre Op	125±24.8	127±26.6	0.71
POD 2	117±15.2	120±21.5	0.52
POD 7	110±16.0	113±18.3	0.43
Weight (kg)			
Pre Op	57.9±7.50	60.6±13.1	0.33
Post Op	56.1±7.03	57.6±11.3	0.54

EEIN: enteral ecoimmunonutrition; EN: enteral nutrition; Pre Op: preoperation; POD: postoperative day; Post Op: postoperation; ALB: albumin; PAB: prealbumin; HB: hemoglobin.
†All values are presented as means ± standard deviations.

Table 4. Inflammatory variables †

	EEIN	EN	*p* value
NEUT (10^9/L)			
Pre Op	3.81±1.27	3.32±1.14	0.12
POD 2	11.4±4.94	12.5±5.20	0.37
POD 7	6.26±2.19	7.38±2.92	0.10
PLT (10^9/L)			
Pre Op	195±62.9	188±58.6	0.69
POD 2	162±48.4	179±53.3	0.21
POD 7	272±112	275±83.1	0.91
CRP (mg/L)			
Pre Op	5.05±11.91	2.70±1.57	0.29
POD 2	107±48.9	129±72.1	0.17
POD 7	26.5±18.6	48.3±28.4	0.00
PCT (ng/mL)			
Pre Op	0.11±0.02	0.11±0.03	0.92
POD 2	1.30±1.59	1.32±1.09	0.97
POD 7	0.31±0.25	0.34±0.23	0.61

EEIN: enteral ecoimmunonutrition; EN: enteral nutrition; Pre Op: preoperation; POD: postoperative day; NEUT: neutrophils; PLT: platelets; CRP: C-reactive protein; PCT: procalcitonin.
†All values are presented as means±standard deviations.

Table 5. Immune function variables †

	EEIN	EN	*p* value
$CD3^+$ (%)			
Pre Op	68.6±8.21	66.6±10.9	0.43
POD 2	67.6±8.04	62.7±12.1	0.07
POD 7	69.2±9.10	63.6±13.9	0.07
$CD4^+$ (%)			
Pre Op	40.7±8.28	36.9±7.89	0.08
POD 2	38.4±7.97	34.9±10.6	0.15
POD 7	43.2±6.86	36.7±10.5	0.01
$CD8^+$ (%)			
Pre Op	25.9±7.46	28.8±11.4	0.25
POD 2	27.4±8.36	25.9±11.1	0.56
POD 7	25.0±7.30	25.3±11.9	0.93
HLA-DR (%)			
Pre Op	98.9±1.27	99.1±1.58	0.54
POD 2	88.3±12.9	85.4±12.9	0.38
POD 7	96.4±4.92	93.8±9.82	0.20

EEIN: enteral ecoimmunonutrition; EN: enteral nutrition; Pre Op: preoperation; POD: postoperative day; HLA-DR: human leukocyte antigen–DR isotype.
†All values are presented as means±standard deviations.

Most patients with GC have malnutrition, the severity of which increases after gastrectomy.[15] Moreover, surgical trauma often causes impaired immune defense mechanisms, altered inflammatory responses, and aggravated malnutrition, leading to poor clinical outcomes. Because deteriorated nutritional status is a key factor affecting surgical outcomes, appropriate nutritional intervention is essential.[16]

Early postoperative EN in patients with digestive tract cancers is essential; it is the nutritional therapy recommended by the ESPEN guidelines.[17,18] In the present study, EN was initiated 24 h after surgery. The American Society for Parenteral and Enteral Nutrition[19] suggests that EN should ideally begin within 24–48 h after surgery. Numerous studies have confirmed that early postoperative EN can improve nutritional status, bolster immune function, protect gut barrier function, reduce the occurrence of enterogenous infection, and promote early recovery of intestinal function after surgery.[20,21]

At present, the focus of nutritional therapy has shifted from the provision of necessary calories to the restoration of metabolic and immune responses.[22] EN that includes nutrients such as Arg, Gln, ω-3 fatty acids, and probiotics has gained increasing attention. Gln is used as a primary fuel source for enterocytes of the small bowel to protect mucosal cells from apoptosis, increase mucosal weight, and promote DNA and protein synthesis in intestinal epithelial cells. Furthermore, probiotics can effectively reconstruct the gastrointestinal barrier by increasing the activity of intestinal epithelial cells and reducing the absorption of harmful substances.[23,24] In combination, these mechanisms can promote growth in intestinal villi to increase nutrient absorption, thereby improving nutritional status and reducing postoperative complications. EIN may effectively improve nutritional status[25] and reduce postoperative complication risk;[26] however, these findings are controversial. In the present study, no differences were observed in nutritional status and complications between the groups. Differences in conclusions reached

Table 6. Postoperative outcomes †

	EEIN	EN	*p* value
Pneumonia	1	2	-
Abdominal infection	1	2	-
Lymphorrhagia	0	1	-
First flatus time (h) †	65.6±20.8	80.0±27.7	0.03
Length of hospital stay (d) †	12.9±3.82	12.0±3.59	0.35

EEIN: enteral ecoimmunonutrition; EN: enteral nutrition.
†Values are presented as means±standard deviations

by various studies may be due to differences in EIN regime composition and timing of administration. Although our data do not indicate the comparability between the two groups in nutritional status and complications, we observed a tendency of increase in albumin and prealbumin concentrations and reduction in weight loss and complication incidence in the EEIN group. Therefore, significant between-group differences in postoperative nutritional status and complications may emerge with longer follow-up.

After surgical trauma, patients may develop metabolic disorders and experience deteriorated nutritional status, intestinal barrier damage, and flora imbalance, exacerbating the inhibition of inflammatory responses and immune function. Some 90% of the normal anaerobic gut flora dissipate within 6h of trauma, and the pathobiome in turn increases.[27] A reasonable nutritional support program can alleviate such conditions. Multiple studies have found that EIN and EEN can aid in modulating inflammation and enhancing the immune system.[28-30] Gln has been called "the fuel of the immune system," and Gln metabolism and availability could influenced T cell differentiation and T regulatory subsets.[10] The present findings indicate that the EEIN group experienced quicker immune response recovery than did the EN group, with significant differences in $CD4^+$ T-cell concentrations observed 7 days after surgery (43.2%±6.86% vs 36.7%±10.5%, p=0.01). Decreasing trends in inflammation markers were more apparent in the EEIN group, which had significantly lower C-reactive protein concentrations 7 days after surgery than did the EN group (26.5±18.6 vs 48.3±28.4 mg/L, p=0.00). Gln is the most abundant conditionally essential amino acid and a immunonutrient type. Studies have found that low blood concentrations of Gln may damage immune cell function, leading to poor clinical outcomes and increased mortality.[31] In mice, Gln can change the proportion of intestinal flora that benefit Bacteroides growth in the intestinal wall and activate proinflammatory cytokines, antibacterial substances involved in activating nuclear factor kappa-light-chain-enhancer of activated B cells.[32] Thus, Gln can modify the intestinal microbiota and activate intestinal innate immunity. Probiotics can increase macrophages and lymphocyte activity, increase interleukin 10 production in the intestinal mucosa, reduce tumor necrosis factor-α and interferon-γ secretion, and suppress inflammatory reactions in the intestinal tract.[33] Because econutrition and immunonutrition have synergistic effects, EEIN can inhibit inflammatory reactions and benefit postoperative immune function.

EN can stimulate digestive fluid and gastrointestinal hormone secretion, increase visceral blood flow, and promote gastrointestinal function recovery. Liu et al[34] reported that EEIN could stimulate intestinal peristalsis by regulating its neuromuscular activity. Mochiki et al[35] suggested that Gln improves gastrointestinal motor activity after gastrectomy. In the present study, the EEIN group had a significantly shorter time to first flatus than the EN group (65.6±20.8 vs 80.0±27.7 h, p=0.03). This finding is consistent with the evidence that EEIN can promote intestinal function recovery after surgery.

In conclusion, EEIN can improve immune function, inhibit inflammatory responses, and promote intestinal function recovery in patients with GC undergoing gastrectomy.

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AUTHOR DISCLOSURES
The authors declare no conflicts of interest.

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