Original Article

Enteral nutrition is superior to total parenteral nutrition for pancreatic cancer patients who underwent pancreaticoduodenectomy

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Objective: To determine the effects of total parenteral nutrition (TPN) and enteral nutrition (EN) on biochemical and clinical outcomes in pancreatic cancer patients who underwent pancreaticoduodenectomy. Methods: From the year 2006 to 2008, 60 patients who underwent pancreaticoduodenectomy in Tianjin Third Central Hospital were enrolled in this study. They were randomly divided into the EN group and the TPN group. The biochemical and clinical parameters were recorded and analyzed between the two groups. Results: There was no significant difference in the nutritional status, liver and kidney function, and blood glucose levels between the TPN and EN groups on the preoperative day, the 1st and 3 rd postoperative days. However, on the 7th postoperative day, there was significant difference between the two groups in 24 h urinary nitrogen, serum levels of, total protein (TP), transferrin (TF), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyl transpeptadase (GGT), blood urea nitrogen (BUN) and creatinine (Cr). On the 14th postoperative day, there was a significant difference between the two groups in terms of urinary levels of 24 h nitrogen, TP, TF, retinol binding protein, ALT, AST, ALP, GGT, total bilirubin, direct bilirubin, BUN, Cr, and glucose. The incidence of delayed gastric emptying in the EN and TPN groups was 0% and 20%, respectively. Moreover, the incidence of pancreatic fistulas and hemorrhages in the EN group were 3.6% and 3.6%, versus 26.7% and 30% in the TPN group, respectively. Conclusions: EN is better than TPN for pancreatic cancer patients who received pancreaticoduodenectomy.

Key Words: EN, TPN, pancreaticoduodenectomy, biochemical parameter, complication

INTRODUCTION

Pancreatic cancer is one of the most common malignant disorders of the digestive system, and pancreaticoduodenectomy (PD) proves effective in the curative therapy of pancreatic cancer.[1,2] However, this surgical procedure is accompanied by a high postoperative incidence of various complications, including pancreatic fistulas, delayed gastric emptying (DGE), and infections, and increase medical costs.[3,4]

Adequate nutrition is a basic factor for the successful treatment of cancer patients. Malnutrition during the postoperative period of surgery constantly affects normal wound-healing and increases the risk of various complications.[5,6] Perioperative nutrition supplements, including enteral nutrition (EN) and total parenteral nutrition (TPN), have been proven to be effective in improving the clinical outcomes of many kinds of surgical treatments and diminishing the incidence of postoperative complications.[7,8] Studies have demonstrated that perioperative nutritional support for pancreatic cancer patients who underwent PD could ameliorate clinical outcomes. Furthermore, most studies suggested that EN is superior to TPN.[9-12] However, other studies indicated that EN did not provide as much benefit in medical treatment as expected,[13] and it is still unclear whether EN or TPN is more effective in reducing complications and enhancing postoperative recovery.[14,15]

So far, clinical experience on postoperative nutrition supplement after PD is limited. Patients of these studies have different disease profiles. In order to clarify the benefits of EN and TPN for pancreatic cancer patients who received a PD, we evaluated the influence of EN and TPN on the clinical and biochemical parameters, and compared the clinical outcomes between the two feeding manipulations.

MATERIALS AND METHODS

Patients

From the year 2006 to 2008, 60 pancreatic cancer patients were enrolled in this study. All of them underwent standard PD surgery and antecolic gastrointestinal reconstruction

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by our group. They were divided into two groups randomly according to the smallest imbalance index scheme, which was achieved by balancing the parameters such as age and body mass index (BMI). One group was fed only by EN postoperatively, and the other group were provided with TPN. The definition of postoperative period was from the first day after a PD until discharge from the hospital. The protocol for this research has been approved by the constituted Ethics Committee of Tianjin Third Hospital and informed consent received from all participants. Patients' characteristics are listed in Table 1.

Criteria of inclusion

Blood loss during operation was less than 400 ml. All patients received at least 6 days of nutritional support postoperatively. They were all confirmed as pancreatic adenocarcinoma by pathologic procedures postoperatively. Patient age ranged from 18-80 years, and the average age was 46. BMI ranged from 16-30 kg/m^2.

Criteria of exclusion

Those who suffered from any of the following diseases or symptoms would be excluded from this research, including endocrinal disease or abnormal fat metabolism, such as hyperthyroidism, diabetes with pharmaceutical therapy, hypertriglyceridemia, liver dysfunction, such as hepatitis and chronic liver disease, HIV infection, severe respiratory dysfunction, cardiac arrest, severe kidney dysfunction, and instable vital sign. Those on cortisol, cytotoxic drugs and immunosuppressive agents during two weeks preoperatively, or allergic to the nutrient supplement were also excluded.

EN and TPN

Nutritional agents were provided by the Nutricia company. According to the criteria of the Beth Israel Deaconess Medical Center of Harvard University, both the TPN and EN patients were treated with isonitrogenous and isocaloric nutrients. Intake of calories was 113 KJ (27 kcal)/kg/d, and the intake of nitrogen was 0.2 g/kg/d. The ratio of nitrogen to calories was 1:130. For the EN patients, a tube was employed and placed into the jejunum through a jejunostomy. On the first day after surgery, nutrients were provided with 50% of the total volume, while full volume nutrient supplement was initiated from the second day postoperatively. The EN formulas mainly contained omega-3 fatty acid, saturated fatty acid, protein, lactose, dietary fiber, mineral matters, microelements and vitamins. EN would last at least 6 days postoperatively, and the patients would be considered poor-tolerance if nausea and vomiting emerged, or the patients suffered from abdominal pain and diarrhea, or the volume of gastric residual for 6hours was more than 200 ml. For TPN patients, a transfusion apparatus was applied and nutrients were delivered intravenously through the central venous catheter 18-20 h/d, and the transfusion speed was 1-2 ml/kg/d. On the first day after surgery, nutrients were provided with 50% of the total volume, while full volume nutrient supplement was implemented from the second day postoperatively. Main content of the TPN formulas were glucose, alanine, aspartic acid, phenylalanine, glutamic acid, glycine, histidine, isoleucine, lysine, methionine, praline, serine, threonine. The patients in TPN group were given fluid diet from about 7 days after operation, until the TPN was completely replaced by oral intake. For DGE patients, oral intake began from about 7 days after operation, depending on the patients' status.

Table 1. Patients characteristics

	TPN (n=30)	TEN (n=28)	*p*
Body mass index	22.9±0.76	22.5±1.05	0.316
Arm circumference, cm	28.3±1.6	27.9±2.1	0.187
Age	60.5±11.9	59.7±11.2	0.275
Male/female	17/13	16/12	0.971

Biochemical and parameters

Several aspects reflecting the nutritional state, and organ functions of the PD patients were evaluated by analyzing specific parameters. Nutritional parameters included: 24 h nitrogen, total protein (TP), transferrin (TF), and retinol binding protein (RBP). Liver function parameters included aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transpeptadase (GGT), total bilirubin (TBil), direct bilirubin (DBil). Kidney function parameters included blood urea nitrogen (BUN) and creatinine (Cr). Blood glucose level was also measured.

Postoperative complications

The incidence of common complications was recorded and compared between the two groups, such as biliary fistulas, pancreatic fistulas, delayed gastric emptying, hemorrhages and infective complications. The definitions of the complications were listed in Table 2.

Statistical analysis

Statistical analyses were performed with SPSS version 16.0. A Student's t-test was used for the comparison of biochemical parameters and hospital stays between the two groups. Fisher exact test was used for the comparison of incidences of postoperative complications, including intra-abdominal infection, liver dysfunction, biliary fistula and lung infection. Continuity corrected Chi-Square test was used to compare the incidences of upper gastrointestinal hemorrhage, delayed gastric emptying and pancreatic fistula. A *p-value* <0.05 was considered statistically significant.

RESULTS

Two patients in the EN group discontinued intervention because they could not tolerate the feeding method; they converted to TPN afterward, and were excluded from the study. All 30 patients in the TPN group tolerated the feeding method well, and there were no discontinued cases.

The effects of TPN and EN on liver and kidney function

On the preoperative day and the 1st and 3rd postoperative days, there was no significant difference in the liver and kidney function and blood glucose level between the two groups (Table 3). However, on the 7th postoperative day, the serum levels of ALT, AST, ALP, GGT, BUN and Cr in the EN group significantly decreased, while the same

Table 2. Definition of complications

Domplications	Definition
Pancreatic fistula	Pancreatic fluid drainage >100 ml/d; drainage amylase >10,000 U/L
Biliary fistula	bile drainage >100 ml/d
Upper gastrointestinal hemorrhage	>100 ml/d fresh blood drained ; vomiting fresh blood or melena
Delayed gastric emptying	Nausea and vomiting after food intake; gastric retention as diagnosed by gastroscope; the volume of gastric residual for 24h was >800 ml
Liver dysfunction	Jaundice aggravated; ascites formed or increased; hepatorenal syndrome emerged; the Child-Pugh grade decreased
Lung infection	Toxemia, cough, pus and blood sputum, white blood cell count increased, neutrophil increased and shift to the left; chest X-Ray or CT scan revealed that lung segment or lobes consolidated, or foliolar infiltration; definite diagnosis was achieved by bacteriological examination, and the pathogenic bacteria was found by sputum bacterial culture.
Abdominal infection	Diffused peritonitis and abdominal pain thatlasted more than 48 hrs, with evident sepsis symptoms and/or organ dysfunction; body temperature and white blood cell count increased; B-ultra sound or CT scan showed formulation of peritoneal abscess.

Table 3. Liver and kidney functions and glucose level of the patients on the preoperative , 1st and 3rd postoperative days

	Preoperative day			1st postoperative day			3rd postoperative day		
	TPN	EN	*p*	TPN	EN	*p*	TPN	EN	*p*
ALT (U/L)	155±12.5	169±14.7	0.066	137±10.8	118±12.4	0.127	73.5±7.9	66.6±8.4	0.122
AST (U/L)	72.6±8.8	88.3±9.6	0.322	81.1±9.2	77.9±8.3	0.223	65.1±2.5	58.8±3.6	0.134
ALP (U/L)	399±40.5	414±38.7	0.177	263±19.2	249±24.5	0.421	199±17.1	182±16.8	0.324
GGT (U/L)	421±55.3	443±50.1	0.127	343±30.1	357±28.8	0.165	289±17.3	281±17.2	0.432
TBiL (μmol/L)	273±23.5	276±27.1	0.135	195±20.4	198±18.9	0.134	232±23.1	208±21.6	0.566
DBiL (μmol/L)	183±20.1	172±18.6	0.543	128±10.6	127±12.1	0.631	150±14.2	134±12.7	0.387
BUN (mmol/L)	5.0±0.8	5.2±0.6	0.639	6.1±0.8	5.6±0.6	0.553	6.2±0.5	5.5±0.3	0.323
Cr (μmol/L)	58.1±6.5	57.3±5.4	0.371	59.1±6.8	55.8±5.9	0.175	55.8±7.4	50.6±6.3	0.628
Glucose (mmol/L)	5.8±0.7	6.9±0.8	0.564	10.2±0.9	11.3±0.8	0.331	7.8±0.8	8.1±0.9	0.253

Table 4. Liver and kidney functions and blood glucose level of the patients on the 7th and 14th postoperative days

	7th postoperative day			14th postoperative day		
	TPN	EN	*p*	TPN	EN	*p*
ALT (U/L)	71.4±5.1	59.0±6.4	0.012	62.6±7.1	50.7±6.8	0.031
AST (U/L)	53.5±3.1	38.4±3.3	0.033	47.3±3.2	34.3±4.0	0.035
ALP (U/L)	188±12.1	167±13.2	0.026	176±18.2	149±21.5	0.018
GGT (U/L)	203±18.5	155±11.4	0.039	172±17.2	130±13.3	0.048
TBiL (μmol/L)	181±10.3	164±9.6	0.077	104±9.1	74.7±7.9	0.022
DBiL (μmol/L)	74.0±8.3	80.4±9.7	0.121	70.3±8.6	47.9±4.5	0.043
BUN (mmol/L)	6.0±0.8	4.8±0.6	0.036	5.6±0.3	4.5±0.6	0.013
Cr (μmol/L)	58.7±5.2	50.5±4.5	0.045	54.6±5.2	49.2±4.3	0.003
Glucose (mmol/L)	7.6±0.9	7.2±1.3	0.068	6.8±0.4	5.2±0.6	0.024

trend for TBil and DBil levels was not observed. Meanwhile, there was no difference in blood glucose level between the EN and TPN groups. On the 14th postoperative day, there was a significant difference in liver and kidney function parameters and blood glucose between the two groups (Table 4).

The effects of TPN and EN on nutritional status

On the preoperative day and the 1st and 3rd postoperative days, there was no significant difference in the parameters of nutritional status between the two groups (Table 5). In contrast, on the 7th postoperative day, the serum levels of TP and TF significantly increased, while the urinary level of 24 h nitrogen decreased in EN group. Meanwhile, there was no difference in RBP level between the EN and TPN groups. On the 14th postoperative day, there was a significant difference in all parameters of nutritional status between the two groups (Table 6).

The incidence of various complications in TPN and EN groups

As shown in Table 7, there was no difference in the incidence of intra-abdominal infections, liver dysfunctions, biliary fistulas and lung infections between the TPN and EN groups. However, compared to the TPN group, the incidence of upper gastrointestinal hemorrhages, delayed gastric emptying and pancreatic fistulas was significantly reduced in the EN group. Shortened hospital stays were observed in the EN group, but there was no significant difference (Table 7).

DISCUSSION

Numerous studies have suggested that EN has several advantages over TPN. Enteral nutrition could preserve the gut flora architecture, prevent gastrointestinal mucosa atrophy, and exert trophic effect on the gastrointestinal tract to inhibit microbial translocation from the gut to the

Table 5. Nutritional status of the patients on the preoperative, 1st and 3rd postoperative days

	Preoperative day			1st postoperative day			3rd postoperative day		
	TPN	EN	*p*	TPN	EN	*p*	TPN	EN	*p*
24h urinary nitrogen (g/24h)	6.7±0.7	6.3±0.6	0.173	15.5±1.2	15.2±1.1	0.122	11.2±0.7	10.9±0.8	0.221
TP(g/L)	64.8±5.9	64.2±6.2	0.136	59.9±5.3	58.3±5.6	0.362	60.3±5.4	60.9±5.6	0.143
TF (mg/dl)	281±24.6	271±22.1	0.543	260±21.1	259±22.3	0.291	262±21.9	268±22.8	0.382
RBP (mg/L)	59.5±3.4	63.5±5.7	0.213	47.8±3.8	49.6±4.2	0.453	45.5±3.1	47.9±3.5	0.273

Table 6. Nutritional status of the patients on the 7th and 14th postoperative days

	7th postoperative day			14th postoperative day		
	TPN	EN	*p*	TPN	EN	*p*
24h urinary nitrogen (g/24h)	12.4±1.2	9.1±0.9	0.022	8.7±0.8	6.5±1.2	0.018
TP (g/L)	64.9±5.8	66.8±5.4	0.043	65.6±4.9	68.0±5.1	0.037
TF (mg/dl)	263±21.7	275±20.4	0.037	260±21.3	281±22.5	0.029
RBP (mg/L)	50.9±2.9	55.7±2.8	0.065	52.8±2.8	60.8±3.1	0.014

Table 7. Incidence of postoperative complications and hospital stay times of the patients

	TPN (n=30)	EN (n=28)	*p*
Intra-abdominal infection	2	1	1
Liver dysfunction	1	0	1
Biliary fistula	2	2	1
Lung infection	2	1	1
Upper gastrointestinal hemorrhage	9	1	0.021
Delayed gastric emptying	6	0	0.039
Pancreatic fistula	8	1	0.039
Hospital stay	19.2±1.3	17.8±1.1	0.375
Mortality	0	0	-

blood stream.[12,16] However, hepatobiliary complications related to artificial nutrition were reported, and less frequently in patients receiving EN than in patients treated with TPN.[17] This difference may be due to the fact that EN could also stimulate hepatic circulation and ameliorate liver function.[18] In our study, liver and kidney functions were not improved significantly until the 7th postoperative day in the EN group. However, on the 14th postoperative day, liver and kidney functions and blood glucose level were fully ameliorated in the EN group, compared to TPN group. The results suggest that EN is more effective at ameliorating liver and kidney functions, blood glucose level as well as the nutritional status of pancreatic cancer patients during the late postoperative days. It is still unclear why there was no difference in liver and kidney functions and blood glucose level on the 1st and 3rd postoperative days, which may be partly related to the pathophysiological processes during stress shortly after operation.

Surprisingly, Ronald *et al*. reported that TPN did not provide any benefit to the patients, but instead did harm. Compared with patients who did not receive any nutritional support, the TPN patients were more prone to suffer from complications.[19] We examined the role of both TPN and EN in improving the nutritional status of PD patients, and found that although there was no significant difference in the nutritional status between the EN and TPN groups on the 1st and 3rd postoperative days, the nutritional status of PD patients in the EN group significantly improved after the 7th postoperative day, with regard to the outcomes of liver and kidney functions.

In addition, we found that the incidence of intra-abdominal infections, liver dysfunctions, biliary fistulas and lung infections was low in both EN and TPN groups and exhibited no difference between the groups. Several reasons may explain this. First, all the patients were treated with antibiotics for 5 days postoperatively. Second, the inclusion criteria of our study was so strict that most patients were in relatively good health condition. In addition, it has been suggested that immune-enhancing formulas that contained special ingredients such as arginine, glutamine, and omega-3 fatty acids could improve nutritional status and ameliorate the postoperative immune depression.[8,9] In the present study, EN nutrients were commercial immune-enhancing formulas.

Delayed gastric emptying occurred in 6 (20%) patients in the TPN group while no cases (0%) suffered from DGE in the EN group. The underlying mechanism of DGE after PD is unclear and several factors including pancreatic fistulas, and bleeding have been Implicated.[20,21] In addition, recent studies suggested that gastrointestinal reconstruction plays an important role in the occurrence of DGE. The incidence of DGE in the antecolic duodenojejunostomy group was lower than that in the retrocolic reconstruction group.[22-24] Given that all the patients were treated with antecolic reconstruction, this could partially explain why the incidence of DGE was low in our study. Furthermore, the bleeding volume of the patients during operation was small (<400 ml).[25]

Pancreatic fistulas are another common complication in PD patients, with rates up to 20% in specialized centers.[26,27] In our study, there were 8 pancreatic fistula cases

in the TPN group, accounting for 26.7%. Surprisingly, there was only 1 patient with a pancreatic fistula in the EN group. The difference is statistically significant. Meticulous maneuvers acted to prevent pancreatic fistulas and postoperative hemorrhages. However, the underlying mechanism by which EN reduces the incidence of pancreatic fistulas remains unclear and requires further study. The average hospital stay time in EN group was a little shorter than that in the TPN group. However, the difference was not significant.

Another surprising finding from our study is that no patient in either group died of any complication. Pancreatic fistulas and postoperative hemorrhages are major causes of postoperative death for PD patients. As such, patients always need interventional assistance or repeated operations. However, in our study, 10 hemorrhages and 9 pancreatic fistula cases were all treated successfully with conservative measures. We believe that the strict inclusion criteria account for the good result. Moreover, while pancreaticogastrostomy has been proposed as a safer method than pancreaticojejunostomy following a PD, with significantly lower rate of pancreatic leakage, surgical morbidity, and mortality,[28,29] we adopted pancreaticojejunostomy in all the patients and none died. This suggests that the pancreaticojejunostomy is also safe and effective in PD surgery.

It is important to notice that our study had some disadvantages. First, the cohort number was relatively small. Second, we did not take the disease information into account, such as tumor size and TNM stage. As a result, the risk factors for complications were not fully explored in our study.

In conclusion, for pancreatic cancer patients who underwent a PD, EN is superior to TPN in improving nutritional status, liver and kidney functions and reducing postoperative complications. Larger scale trials are necessary in the future to identify the correct application of TPN and EN in well-selected patients, and future studies should stratify the patients for enrollment according to pathological features of the diseases and clinical characteristics of the patients.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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對胰十二指肠切除的胰腺癌患者給予肠内营养优於全肠外营养

目的：本前瞻性研究的目的，在于比较全肠外营养和肠内营养，在胰腺癌胰十二指肠切除的患者之生化及临床指标方面的优劣。方法：从 2006 年到 2008 年间在天津第三中心医院接受胰十二指肠切除术的 60 名患者，随机分为两组，一组为肠内营养组，另一组为全肠外营养组。记录并分析两组的生化及临床指标差异。结果：术前 1 天及术后第 1 及第 3 天，全肠外营养组和肠内营养组患者在营养状态、肝肾功能和血糖方面无明显差异。但是术后第 7 天，两组之间在 24 小时尿氮，血清总蛋白、转铁蛋白、丙氨酸转氨酶、天冬氨酸转氨酶、碱性磷酸酶、γ-谷氨酰转肽酶及血尿素氮、肌酐有明显差异。术后第 14 天，两组患者在 24 小时尿氮，血清总蛋白、转铁蛋白、视黄醇结合蛋白、丙氨酸转氨酶、天冬氨酸转氨酶、碱性磷酸酶、γ-谷氨酰转肽酶、总胆红素、直接胆红素、血尿素氮、肌酐和血糖方面均存在显著性差异。肠内营养组和全肠外营养组，胃排空延迟的发生率分别为 0%和 20%。再者，胰瘺和出血的发生率，在肠内营养组分别为 3.6%和 3.6%，在全肠外营养组则為 26.7%和 30%。结论：在胰腺癌胰十二指肠切除的患者中，肠内营养优于全肠外营养。

关键词：肠内营养、全肠外营养、胰十二指肠切除术、生化指标、并发症