Retrospective Study

Early enteral nutrition vs parenteral nutrition following pancreaticoduodenectomy: Experience from a single center

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Abstract

AIM: To analyze and compare postoperative morbidity between patients receiving total parenteral nutrition (TPN) and early enteral nutrition supplemented with parenteral nutrition (EEN + PN).

METHODS: Three hundred and forty patients receiving pancreaticoduodenectomy (PD) from 2009 to 2013 at our center were enrolled retrospectively. Patients were divided into two groups depending on postoperative nutrition support scheme: an EEN + PN group (n = 87) and a TPN group (n = 253). Demographic characteristics, comorbidities, preoperative biochemical
parameters, pathological diagnosis, intraoperative information, and postoperative complications of the two groups were analyzed.

RESULTS: The two groups did not differ in demographic characteristics, preoperative comorbidities, preoperative biochemical parameters or pathological findings \((P > 0.05\) for all). However, patients with EEN + PN following PD had a higher incidence of delayed gastric emptying \((16.1\% \text{ vs } 6.7\%, P = 0.016)\), pulmonary infection \((10.3\% \text{ vs } 3.6\%, P = 0.024)\), and probably intraperitoneal infection \((18.4\% \text{ vs } 10.3\%, P = 0.059)\), which might account for their longer nasogastric tube retention time \((9 \text{ d vs } 5 \text{ d}, P = 0.006)\), postoperative hospital stay \((25 \text{ d vs } 20 \text{ d}, P = 0.055)\) and higher hospitalization expenses \((USD10397 \text{ vs } USD8663.9, P = 0.008)\), compared to those with TPN.

CONCLUSION: Our study suggests that TPN might be safe and sufficient for patient recovery after PD. Postoperative EEN should only be performed scrupulously and selectively.

Key words: Pancreaticoduodenectomy; Postoperative complications; Enteral nutrition; Parenteral nutrition; Delayed gastric emptying

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Core tip: Although most studies have shown that early enteral nutrition (EEN) seems to be superior to total parenteral nutrition (TPN) in postoperative outcomes, the optimal nutritional support route choice after pancreaticoduodenectomy (PD) remains debatable. In this retrospective study, we investigated postoperative outcomes between patients undergoing TPN and EEN + PN after PD. The results demonstrated that the EEN + PN group had an increased morbidity of delayed gastric emptying and pulmonary infection, which might account for their longer nasogastric tube retention time, postoperative hospital stay and higher hospitalization expenses. In our opinion, EEN should only be performed cautiously and selectively.

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INTRODUCTION

Since its introduction by Whipple in 1935, pancreaticoduodenectomy (PD) has been considered an irreplaceable treatment choice for carcinoma of the periampullary region and some benign lesions\(^1\). Preoperatively, many candidates for PD are in a state of disease/comorbidities-associated malnutrition; aggravating this situation, surgery causes disorganization of the digestive arrhythmic and absorptive functions, leading to worsening postoperative indigestion and malabsorption, which accounts for the high morbidity rate of PD-related complications\(^2\), and this is combined with the difficulty of the nil per os period during the first days after surgery. Hence, appropriate nutritional therapy is of great significance for postoperative rehabilitation following PD.

Nutrition support strategies have undergone tremendous evolution in the decades following the first application of total parenteral nutrition (TPN) in postoperative patients\(^3\). Recent studies have elaborated that early enteral nutrition (EEN) could improve immune capability, maintain intestinal barrier function, and potentially moderate metabolic stress reactions caused by surgical intervention, thereby reducing the incidence of postoperative complications\(^4-8\). Moreover, EEN is thought to be a more reliable and economic solution for postoperative nutritional support compared with parenteral nutrition (PN)\(^6-7\). Currently, this is the mainstream view. Some studies, however, have claimed that EEN is insignificant or even negative in decreasing complication morbidity rates after abdominal surgery\(^9-17\); thus, the role of EN remains debatable. On the other hand, with improvements in central venous catheter care and progress in energy supply (isocaloric or hypocaloric formulas), PN-associated morbidity has significantly decreased in high-volume centers. Because decided evidence in respect of the first-rank nutrition strategy following PD remains absent, feeding route decision relies prevalently on the surgeon’s subjective perspective. The objective of our research was to compare the incidence of postoperative complications between patients undergoing TPN and EEN by placing a nasojejunal catheter combined with additional PN [considering the universally recognized adverse effects of total enteral nutrition (TEN) such as diarrhoea, abdominal tympany, and abdominalgia].

MATERIALS AND METHODS

Patient selection

From February 2009 to January 2013, patients receiving classic PD and Child’s reconstruction were retrospectively enrolled in this study at Xi’an Jiaotong University First Affiliated Hospital. Exclusion criteria included preoperative ongoing infection, inflammatory bowel disease, severe renal insufficiency and history of previous gastrointestinal surgery. In order to avoid the interference of variable PD patterns, patients subjected to pylorus-preserving PD, total PD, or Roux-en-Y choledochojejunostomy were also excluded. Finally, 340 patients undergoing PD were enrolled in this study. Data including patients’ demographic characteristics,
laboratory results, pathological diagnosis of resected lesions, intraoperative information and postoperative complications were registered on specific forms. The study was reviewed and approved by the First Affiliated Hospital of Xi’an Jiaotong University ethics committee.

**Surgical procedures**

All operations were performed by six experienced senior surgeons. 87 and 253 cases received EEN + PN and only TPN, respectively. Preoperatively, nurses introduced a nasojejunal nutrition tube (NJT) [10/F, Nutricia Pharmaceutical (Wuxi) Co., China] through the nasal cavity, together with a nasogastric tube (NGT) [10/F, Nutricia Pharmaceutical (Wuxi) Co., China]. The decision to place an intraoperative jejunum feeding tube was more frequently determined by the surgeon’s discretion rather than the patient’s preoperative status. Child’s procedures were standardized, with pancreateojunostomy performed initially, and pancreatic duct stent was used as occasion demands. Interrupted jejunal muscularis serosa-pancreas sutures were made at the outer layer. Endo-side cholangioenterostomy was performed 15–20 cm distal to the pancreateojunal anastomotic stoma, and gastrojejunostomy 45-55 cm distal to the cholangioenteral anastomosis. The NJT was then positioned 25-30 cm distal to the gastrointestinal anastomosis by surgeons, and attached to the nose wing with surgical silk thread (4-0) and tape. Before abdominal closure, two rubber drainage tubes were routinely placed into the abdominal cavity (behind the pancreateojunal and cholangioenteral anastomosis, respectively), with their external openings linked to anti-reflux negative-pressure drainage bags.

**Postoperative management**

Barring special circumstances (such as serious complications or comorbidities in need of strict monitoring), patients remained in the ICU for the first postoperative 24-48 h. Unless sustained antibiotic treatment was necessary (like for severe sepsis, etc.), prophylactic antibiotics were discontinued after the first 24-48 h. Both groups began parenteral nutrition through a central venous catheter on the first postoperative day. Then, the EEN + PN group was administered enteral nutrition through the NJT from the second day after surgery, with an initial volume of 500 mL (1 Kcal/mL, protein 4.5 g/100 mL, carbohydrate 14.3 g/100 mL, lipid 2.8 g/100 mL). The total calories and protein intake for both groups were maintained at 25-30 Kcal/(kg·d) and 1.2-1.5 g/(kg·d), respectively. The initial delivery rate was 30 mL/h, increasing gradually to normal intake in 48 h depending on patients’ condition. Once the patient had passed flatus, the nasogastric tube was clipped and an oral liquid diet was gradually started, beginning with small volumes. The volume of liquid diet via NJT or TPN was gradually decreased once the patient could tolerate oral intake, and was finally discontinued once the patient could eat regularly, followed by removal of the nasogastric tube and NJT. If the patient experienced abdominal distension, nausea or vomiting, the nasogastric tube was re-aspirated and the feeding was slowed or stopped temporarily.

The character and volume of the abdominal drainage fluid were observed twice a day, and the drainage fluid amylase was examined if a pancreatic fistula was suspected. Routine ultrasound was used to detect any fluids in the abdominal cavity before removal of the drainage tubes.

**Postoperative morbidity**

The definition and classification of delayed gastric emptying (DGE) were based on International Study Group of Pancreatic Surgery (ISGPS) recommendations as follows: Grade A, demanding an NGT intubation or reinsertion between postoperative day (POD) 4 and POD 7 or intolerance to a solid diet by POD 7; Grade B, demanding an NGT intubation or reinsertion between POD 8 and POD 14 or intolerance to a solid diet by POD 14; and Grade C, demanding an NGT intubation or reinsertion after POD 14 or intolerance to a solid diet by POD 21[18]. The definition of pancreatic fistula was based on ISGPS criteria as calculable intraperitoneal drainage volume on or after POD3 with concentration of amylase at least 3 times the serum normal upper limit[19,20]. Definition of bile leakage was based on the International Study Group of Liver Surgery as a bilirubin content of the drainage fluid 3 times or greater than the serum content on or after POD3 or requiring imaging or surgical treatment arising from choleperitonitis or bile collections[21].

**Statistical analysis**

Quantitative variables are presented as the mean ± SE or median, and percentages for qualitative variables. The Mann-Whitney U test or Student’s t-test was applied for quantitative variables, and the χ² test or Fisher’s exact test for qualitative variables. Statistical analyses were completed with SPSS 21.0 software (Chicago, IL, United States). P-values less than 0.05 were defined statistically significant.

**RESULTS**

**Patient characteristics**

Table 1 shows the comparison of patients’ demographic characteristics, comorbidities, and preoperative serum biochemical levels between the two groups. There were no significant differences in all the baseline characteristics between the two groups.

**Pathological variables**

The postoperative pathological diagnosis results of the two groups are shown in Table 2. Pancreatic adenocar-
cinoma, bile duct adenocarcinoma and duodenal/ampullary adenocarcinoma were the top three common pathological patterns, accounting for 91.9% in the EEN + PN group and 88.7% in the TPN group. No significant differences existed in pathological types between the two groups (P > 0.05 for all).

**Operation details and postoperative recovery**

Table 3 shows the details of intraoperative information and postoperative recovery. There were no differences between the two groups in maximum tumor diameter, pancreatic/bile duct diameter, intraoperative bleeding volume, proportion of retrocolic choledochojejunostomy or combined vascular resection. However, the nasogastric tube retention time in the EEN + PN group was significantly longer (9 ± 0.2 d vs 5 ± 0.1 d, P = 0.006). The overall and postoperative hospitalization time in the EEN + PN group tended to be longer than those of the TPN group, although these were not significantly different (32 ± 2 d vs 27 ± 1 d, P = 0.074; and 25 ± 2 d vs 20 ± 1 d, P = 0.055). Finally, the results showed that the total costs were significantly higher in the EEN + PN group (USD10397.0 ± 861.2 vs USD8663.9 ± 239.2, P = 0.008).

**Postoperative complications**

Table 4 presents postoperative complications. The morbidity of pulmonary infection and DGE was significantly higher in the EEN + PN group (10.3% vs 3.6%, P = 0.024 and 16.1% vs 6.7%, P = 0.016, respectively). In addition, the incidence of abdominal cavity infection seemed to be higher in the EEN + PN group (18.4% vs 10.3%, P = 0.059). No significant differences were shown in other surgery-related complications, involving bile leakage, pancreatic fistula, intraperitoneal bleeding, gastrointestinal bleeding, pulmonary embolism, chylos leakage or wound infection (P > 0.05 for all). Four of 87 (4.6%) patients in the EEN + PN group underwent unplanned second operation for intraperitoneal hemorrhage (1 case), severe choleperitonitis (2 cases) and intraperitoneal bleeding combined with severe bile leakage (1 case),
and eventually, 2 of these patients died of multiple organ dysfunction syndrome (MODS). Seven of 253 (2.8%) patients in the TPN group underwent unexpected reoperation due to intraperitoneal bleeding (3 cases), severe bile leakage (2 cases), complicated anastomotic failure (1 case) and wound dehiscence (1 case), and 4 of these patients died from MODS and serious systemic infection. There were no significant differences in the incidence of unplanned reoperation or in-hospital mortality ($P = 0.482$ and $P = 0.204$, respectively).

Moreover, 28 (32.2%) patients in the EEN + PN group developed EN-related complications, including abdominal distention (17 cases), abdominal cramps (15 cases), vomiting (10 cases) and diarrhea (9 cases), most of which were attenuated by decreasing the enteral feeding infusion speed or by administering prokinetic agents, and no discontinued enteral feeding occurred in these patients.

**DISCUSSION**

Despite the fact that mortality following PD at many pancreatic centers has decreased to less than 4%, the incidence rate of postoperative complications remains high, ranging from 34% to 50%\cite{12,22}. Considering the fact that preoperatively most patients undergoing PD have significant weight loss or even cachexia due to anorexia and malabsorption, and even considering the postoperative deficient oral intake duration as long as 10 d\cite{29}, nutritional debilitation might greatly contribute to the high rate of complications, making perioperative appropriate nutrition therapy necessary.

Nutritional therapy has evolved over decades. Parenteral nutrition, which initially prevailed and was preferred, was replaced by enteral feeding in the early 1990s. Hyperalimentation evolved into iso- or even hypoalimentation, and standard formulas were superseded by individually optimized ones, such as immunonutrition. Nutritional feeding strategies have switched from having a role as a primary provider of basic substrates into a sustainer of optimal postoperative metabolic and immune status\cite{24}. Nevertheless, there remains no agreement in studies concerning the optimal postoperative PD feeding strategy, so the ideal nutrition support mode remains controversial. Enteral feeding after PD is proposed applied routinely by European nutritional guidelines\cite{25}, however not for American guidelines\cite{26}.

Few research studies have evaluated the efficacy and complications related to the nutrition pathway (EEN + PN vs TPN) of the feeding strategies on postoperative recovery following standard PD procedures. In the present study, nasojejunal feeding tube placement was performed as the best enteral nutrition pathway, because any unnecessary enterotomy is a potential source of cumbersome complications. Whether to implement EEN + PN or TPN depended on the surgeon’s preference instead of the patient’s condition. There was no difference in patients’ general features, preoperative comorbidities existing before surgery, or general conditions between the EEN + PN and TPN groups, thus making the potential selection bias negligible. Moreover, the current series results suggested a homogeneous histological pattern, lesion condition, surgical technique, postoperative management, and most complications. Based on our study, patients with EEN + PN following PD had a higher incidence of DGE, pulmonary infection, and probably intraperitoneal infection, which might account for longer nasogastric tube retention time, longer hospital stay and higher hospitalization expenses, compared to administration of TPN.

DGE was originally described as “gastroparesis” following pylorus-preserving PD. DGE is not lethal, but invariably prolongs the hospital stay duration significantly and increases hospital costs. According to the ISGPS classification, grade A DGE was not taken into account in our study due to our postoperative protocol for preserving NGT for 3-7 d until NGT became uncomfortable and the patient tolerated a liquid diet intake. Our results indicated that postoperative grades B and C DGE occurrence rate was 9.1%. Whether added EEN would consequently lower postoperative DGE following PD remains unascertained. In our study, patients dealt with EEN + PN following PD had a higher incidence of DGE, pulmonary infection, and probably intraperitoneal infection, which might account for longer nasogastric tube retention time, longer hospital stay and higher hospitalization expenses, compared to administration of TPN.

**Table 4  Postoperative complications a (%)**

|                      | EEN + PN (n = 87) | TPN (n = 253) | $P$ value |
|----------------------|-------------------|-------------|-----------|
| Bile leakage         | 7 (8.0)           | 12 (4.7)    | 0.280     |
| Pancreatic fistulas   | 13 (14.9)         | 27 (10.7)   | 0.334     |
| Intraperitoneal infection | 16 (18.4)    | 26 (10.3)   | 0.059     |
| Intraperitoneal bleeding | 1 (1.1)        | 10 (4.0)    | 0.301     |
| Gastrointestinal bleeding | 4 (4.6)        | 11 (4.3)    | 1.000     |
| Pulmonary infection   | 9 (10.3)          | 9 (3.6)     | 0.024     |
| Pulmonary embolism    | 0                 | 1 (0.4)     | 1.000     |
| Chylous leakage       | 1 (1.1)           | 3 (1.2)     | 1.000     |
| Wound infection       | 8 (9.2)           | 23 (9.1)    | 1.000     |
| Delayed gastric emptying | 14 (16.1)    | 17 (6.7)    | 0.016     |
| Grade B              | 9 (10.3)          | 11 (4.3)    |            |
| Grade C              | 5 (5.7)           | 6 (2.4)     |            |
| Unplanned reoperation | 4 (4.6)          | 7 (2.8)     | 0.482     |
| In-hospital death     | 2 (2.3)           | 4 (1.6)     | 0.024     |
| EN-related complications | 28 (32.2) | -           |          |
| Abdominal distention  | 17 (19.5)         | -           |          |
| Abdominal cramps      | 15 (17.2)         | -           |          |
| Vomiting              | 10 (11.5)         | -           |          |
| Diarrhea              | 9 (10.3)          | -           |          |

EEN: Early postoperative enteral nutrition; PN: Parenteral nutrition; TPN: Total parenteral nutrition.
In this retrospective controlled series, postoperative surgery decreased motility of the gastrointestinal system after pressur by digestive inadaptation to the complications were principally due to edema induced EEN + PN developed these complications. These the present study, 28 of 87 (32.2%) patients with which were named “EN-related complications” as diarrhoea, abdominal tympany, and abdominalgia, postoperative EEN tended to trigger complications such as digestive inadaptation to the nutrients, as evidenced by a decrease in motility, impaired respiratory mechanics, and postoperative mobility.

Another interesting result was a more frequent occurrence of pulmonary infection in the EEN + PN group than the TPN group (10.3% vs 3.6%, respectively, P = 0.024). Seven of nine patients diagnosed with pneumonia in the EEN + PN group had a prior history of vomiting, which could be exacerbated by DGE-vomiting or NJT placement-related presumed pulmonary aspiration. Moreover, impaired respiratory mechanics and postoperative mobility attributed to immediate postoperative jejunal feeding might also play a significant role in the incidence of pneumonia following PD.

Many clinicians have favored changes in nutritional strategies due to the insufficiency of evidence-based data. Some scholars have expressed their dissent concerning enteral feeding, arguing that compared with TPN, immediate postoperative EN failed to lower the postoperative morbidity rate. In contrast, it might be associated with an increased incidence of DGE and the development of chyle leakage, impaired respiratory mechanics, and postoperative mobility. Worse still, a number of cases of small bowel necrosis have occurred during enteral feeding after PD. Furthermore, it was acknowledged that postoperative EEN tended to trigger complications such as diarrhoea, abdominal tympany, and abdominalgia, which were named “EN-related complications”. In the present study, 28 of 87 (32.2%) patients with EEN + PN developed these complications. These complications were principally due to edema induced by digestive inadaptation to the colloid osmotic pressure between the adtevak and the gut cavity, and decreased motility of the gastrointestinal system after surgery.

CONCLUSION

In this retrospective controlled series, postoperative EEN + PN following PD was associated with an increased incidence of DGE and pneumonia, prolonged nasogastric tube retention and increased hospitalization expenses. Regardless of the mainstream view that postoperative EN has many desirable effects, clinical practitioners should be highly vigilant and aware of its harmful impacts, such as DGE and aspiration-related pneumonia. Discreet catheter care combined with an isocaloric nutrition supply of the TPN might neutralize the superiority of EN. Postoperative EN should only be performed scrupulously and selectively (such as for patients with a severe malnourished status). However, due to the restriction of this single center retrospective study, a sequence of RCTs should be implemented to evaluate the impact of EN on the postoperative morbidity rate and the optimal timing and dose according to a variable postoperative recovery period.

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COMMENTS

Background

Complications-related morbidity remains high after pancreaticoduodenectomy (PD), and this could be partly attributed to nutritional debilitation. An ideal nutrition support strategy remains controversial, and research evaluating the efficacy of early enteral nutrition accompanied by parenteral nutrition (EEN + PN) vs total parenteral nutrition (TPN) on postoperative recovery after PD is lacking.

Research frontiers

Although most studies have shown that EEN seems to be superior to TPN in enhancing immunocompetence, preserving intestinal structure and function, and attenuating dissimilatory stress reactions, some studies have demonstrated that EEN failed to lower the postoperative morbidity rate, and was even associated with an increased incidence of delayed gastric emptying (DGE) and chyle leakage, and impaired respiratory mechanics and postoperative mobility. Moreover, EN-related digestive symptoms (such as diarrhoea, abdominal tympany, and abdominalgia) could have a bad impact on caloric intake and might cause interrupted EN.

Innovations and breakthroughs

This study investigated the postoperative outcomes between patients undergoing TPN and EEN + PN after PD. The results suggest that EEN + PN is associated with a higher incidence of DGE and pulmonary infection morbidity, which might account for the longer nasogastric tube retention time, longer postoperative hospital stay and higher hospitalization expenses. In authors’ opinion, EEN should only be performed cautiously and selectively.

Applications

The results show that EEN + PN was associated with higher DGE and pulmonary infection morbidity, which might account for longer nasogastric tube retention time, longer postoperative hospital stay and higher hospitalization expenses. The conclusion is a wake-up call for surgeons to apply EEN cautiously and selectively following PD.

Peer-review

Well prepared and conducted retrospective study of postoperative nutrition and
energy management. Although it is controversial, this study well demonstrates that EEN + PN may have more postoperative complications compared with TPN after PD. Almost certainly, this effort will initiate controversy and launch prospective studies to evaluate the conclusions. This study is a good start to remind surgeons to pay more attention to postoperative management.

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