

June 15, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: wjg-2013-3653 .doc).

Title: Effect of early enteral combined with parenteral nutrition on patients undergoing pancreaticoduodenectomy

Author: Xin-Hua Zhu, Ya-Fu Wu, Yu-Dong Qiu, Chun-Ping Jiang, Yi-Tao Ding

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 3653

The manuscript has been improved according to the suggestions of reviewers:

1. Revision has been made according to the suggestions of the three reviewers.

Reviewer 1

(1) Postoperative total enteral feeding is associated with complications such as diarrhea, abdominal distention, and abdominal cramps. These symptoms worsened with increasing caloric intake and finally lead to discontinuance of total enteral feeding. On the basis of our experience and the findings of previous studies, we believe that parenteral nutrition combined with early enteral nutritional support might be the optimal nutritional method for patients that received PD.

(2) We have added some comments in the conclusion to alert the readers that a RCT might be necessary to identify the correct application of PN and EN for patients received PD.

Reviewer 2

(1) Because the format for title should be less than 12 words, we would not change the title according to the reviewer's comments.

(2) We have explained the PAB in the abstract.

(3) The exact p values in the abstract have been provided.

(4) Two references have been added for the complications with total enteral feeding in the introduction part.

(5) We have checked the results of the decreases of TP and PAB in Table 3. Compared with the results of the TPN group, a significant difference was seen in the extent of decrease in PAB ($P=0.02$) in the EEN/PN group. However, no significant difference of TP was seen between the two groups ($P=0.076$).

Reviewer 3

(1) Numerous studies have suggested that EN has several advantages over TPN. So a randomized, controlled clinical study on the effect of early enteral combined with parenteral nutrition rather than just parenteral nutrition on patients undergoing PD couldn't be approved by the ethical committee of the Affiliated Drum Tower Hospital. Because of this reason, we investigated the effect of early enteral nutrition combined with parenteral nutritional support for patients received PD with a retrospective controlled clinical trial.

(2) All patients in this study underwent PD to remove biliary obstruction, so the ALT, AST, TB, DB and LDH were significantly reduced. Numerous studies have revealed that cholestatic jaundice is the major complication of total parenteral nutrition. Lack of enteral feeding has several metabolic and endocrine consequences for intestinal and liver function. Experimental studies have shown that the fasted state reduces the secretion of several gastrointestinal hormones, such as cholecystokinin, gastrin and peptide YY. These hormones are instrumental in stimulating bile flow and gallbladder contraction, and maintaining intestinal motility. And EN could also stimulate hepatic circulation and ameliorate liver function. This is the reason for a significant difference was seen in the extent of the decrease in TB and DB in the EEN/PN group compared with the results of the TPN group.

(3) The differences of rate of postoperative pancreatic fistula (POPF) might be related to the variability of the definitions used. The amylase content is well recognized as an integral and unavoidable biochemical definition of POPF, and there do not seem to be any data suggesting a reliable cutoff value for absolute amylase activity. Based on the consensus of the international study group (ISGPF), we thought a broadly inclusive value of more than 3 times the normal serum value to firstly suspect the POPF, and later we graded the POPF.

We did the amylase examination of drainage liquid for each patient in this study on POD 5 and POD 8. There were totally 6 patients with amylase content more than 3 times of normal serum value, and we listed the detail data of amylase examination of drainage liquid in the following table.

Table The detail data of amylase examination of drainage liquid in patients with POPF

Group	Patient No.	Amylase level on POD 5(u/L)	Amylase level on POD 8(u/L)
TPN group	1	1295	3763
	2	8923	12041
EEN/PN group	1	4836	3228
	2	260	802
	3	7552	9015
	4	3116	5130

(4) Intraperitoneal haemorrhage occurring in the first week following PD is described as early and if it occurs later is defined as delayed haemorrhage. The main cause of early intraperitoneal haemorrhage is bleeding from small vessels in the area of the superior mesenteric vessels. The main cause of delayed haemorrhage, especially with the presence of pancreatic or bile leak or sepsis, is the rupture of arterial pseudoaneurysms in the operating field. There are nine patients with intraperitoneal bleeding in this study, including 5 cases with early bleeding and 4 cases with late bleeding. Reoperation was necessary in 4 patients, and the causes of reoperation were early bleeding (1 case in TPN group and 2 cases in EEN/PN group), late bleeding (1 case in EEN/PN group).

(5) Standard parenteral nutrition solutions after PD contain 60–75% of energy as dextrose, whereas standard tube feeding solutions contain 40–55% of energy as dextrose. Metabolic alterations that accompany the stress response result in more endogenous glucose production and reduce the capacity to oxidize plasma glucose directly. Excessive glucose loads that are superimposed on the stress response in parenteral nutrition caused the higher incidence of hyperglycemia.

(6) We have verified P value in the format.

(7) The paper has received language editing by *Dr. Ma's Office for Editing SCI Papers in Medicine*, and some typographical and minor word errors are corrected.

2. Revision has been made according to the editor's suggestions.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Xin-Hua Zhu, MD, PhD

Yi-Tao Ding, Professor

Dept. of Hepatobiliary Surgery
Affiliated Drum Tower Hospital
Medical School of Nanjing University
University
Zhongshang Road 321
Nanjing, China
Fax: +86-25-8331-7056
E-mail: drzhuxh@hotmail.com

Dept. of Hepatobiliary Surgery
Affiliated Drum Tower Hospital
Medical School of Nanjing
Zhongshang Road 321
Nanjing, China
Fax: +86-25-8331-7056
E-mail: drzhuxh@163.com