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原　著

The effects of early enteral nutrition in the postoperative management of pancreatoduodenectomy

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Abstract

Background : The usefulness of early enteral feeding after surgery has recently been reported. This prospective study was conducted to examine whether enteral nutrition just after pancreatoduodenectomy would protect the intestinal mucosa and reduce complications.

Methods : This study included 34 patients who underwent pancreatoduodenectomy at our hospital between April 2011 and May 2013. For postoperative nutrition, the patients were randomly assigned into 2 groups preoperatively : total parenteral nutrition (n=18) and enteral nutrition (n=16) groups. Postoperative outcomes were compared between both groups, including incidence of complications and duration of hospital stay, nutritional status, parameters of inflammation and cytokines, and plasma diamine oxidase levels (as a marker of intestinal mucosal injury).

Results : Postoperative clinical outcomes did not differ between the 2 groups. Diamine oxidase levels were significantly higher in the enteral than in the total parenteral nutrition group on postoperative days 5 and 14. In addition, serum levels of aminotransferase were significantly higher on postoperative days 5 and 7 in the total parenteral nutrition group.

Conclusion : Our findings suggest that early enteral nutrition after pancreatoduodenectomy significantly reduces atrophy of the intestinal mucosa, as indicated by the higher diamine oxidase levels, although no apparent clinical benefit was observed.

Key Words : pancreatoduodenectomy, enteral nutrition, diamine oxidase

Introduction

Total parenteral nutrition (TPN) improves nutritional status during the perioperative period in gastrointestinal (GI) surgery and reduces postoperative complications[1]. On the other hand, complications associated with central venous catheter insertion, poor glycemic control and intestinal mucosal atrophy are potential problems of TPN[2]. Recently, nutritional management by early commencement of oral intake after surgery has been reported as being useful[3]. However, in patients after GI surgery or in those with a poor preoperative general condition, oral intake soon after surgery is difficult, resulting in inadequate nutrient intake.

Administration of enteral nutrition (EN) can provide adequate nutrition soon after surgery. In addition, it has been reported that EN early after highly invasive surgery can reduce the incidence of postoperative complications[4,5]. Pancreatoduodenectomy (PD), which is a major abdominal surgery involving resection and reconstruction of multiple organs, including the upper GI tract, is associated with several PD-specific complications, such as worsening glucose tolerance, delayed gastric emptying and pancreatic fistulas. For these reasons, TPN is commonly prescribed during the postoperative management of these patients[3].

Diamine oxidase (DAO) is an enzyme found mainly in the villus epithelial cells of the small intestinal mucosa. DAO is involved in biological defense by regulation of cell proliferation and catabolism of toxic polyamines and histamine[6]. In addition, intestinal DAO activity significantly correlates with plasma DAO activity. Intestinal, and thus, plasma DAO activity decreases in the

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presence of intestinal mucosal injury. Hence, plasma DAO activity can serve as a marker of small intestinal mucosal integrity and maturity[6)~9)].

We conducted a prospective pilot study based on the hypothesis that EN early after PD may reduce atrophy of the intestinal mucosa and improve postoperative recovery. In this study, we compared the incidence of postoperative complications and adverse events, duration of postoperative hospital stay, nutritional parameters, changes in cytokine levels, glycemic control (required insulin doses) and DAO activity between an EN group and a TPN group.

Methodos

1) Patients

Patients who were scheduled to undergo PD at our hospital between April 2011 and May 2013 were eligible for inclusion in the study. The PD procedures were standardized using the same methods. Modified Child's reconstruction was performed in all patients. For postoperative nutrition, the patients were randomly assigned preoperatively, using a sealed envelope technique, into a total parenteral nutrition (TPN) group and enteral nutrition (EN) group. All subjects provided written, informed consent for participation in the study. This study was approved by the Ethics Committee at Ehime University School of Medicine (approval code : 1101006).

2) Treatment plan

1. TPN group

On postoperative day (POD) 1, intravenous fluids including 5% glucose were continued. On POD 2, Elneopa No. 1® (Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan, 2,000 mL : glucose 240 g, free amino acids 40 g, nitrogen 6.27 g, electrolytes, vitamins, and trace elements ; total calories : 1,120 kcal) was started at the rate of 20 kcal/kg/day via a central venous catheter. On POD 3, Elneopa 1 was replaced with Elneopa No. 2® (2,000 mL : glucose 350 g, free amino acids 60 g, nitrogen 9.40g, electrolytes, vitamins, and trace elements ; total calories : 1,640 kcal) and adjusted to deliver 30 kcal/kg/day. Patients were allowed to start drinking water on day 3 and eating food on day 5.

2. EN group

EN was provided through an intestinal fistula. A jejunostomy catheter (Nippon Covidien Ltd., Tokyo, Japan) was used as the enteral tube. This was inserted into the jejunum during surgery, about 40 cm distal to the gastrojejunal anastomosis site. On POD 1, a 5% glucose solution was infused through the fistula at 20 mL/hr. On POD 2, a semi-solid for enteral use (Racol®, Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan) (100 kcal/100 mL : protein 4.38 g, fat 2.23 g, carbohydrate 15.62 g, vitamins, trace elements) was started at the rate of 20 kcal/20 mL/hr (480 kcal/day). On POD 3, this was continued at 40 kcal/40 mL/hr (960 kcal/day), and on POD 4, this was continued at 60 kcal/60 mL/hr (1,440 kcal/day). In general, this was continued until POD 7, but depending on the amount of oral intake, it was continued as needed after that time. Intravenous fluids were also continued until EN was adequate, and total administered calories/kg/day were comparable between the 2 groups. As in the TPN group, patients were allowed to start drinking water on day 3 and eating food on day 5.

3) Parameters evaluated and statistical analysis

The incidence of postoperative complications, including pancreatic fistulas (PF), systemic inflammatory response syndrome [SIRS] and surgical site infection [SSI], and duration of postoperative hospital stay (days) were compared between groups. Major complications were defined as those ≥ Grade IIIa according to the Clavien-Dindo classification[10)]. The definition of postoperative pancreatic fistula (POPF) was adopted from the report by the International study group on postoperative pancreatic fistula (ISGPF)[11)]. The definition of SIRS was adopted from the report by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference[12)]. SSI was diagnosed according to the Centers for Disease Control (CDC) definition of SSI[13)]. Blood tests were performed to evaluate nutritional status (serum albumin, prealbumin, retinol-binding protein), inflammation and immunity (WBCs, lymphocyte, platelets, CRP, IL-6, IL-10), and liver function (AST, ALT, total bilirubin). The amount of insulin required to

maintain blood glucose levels between 100 and 200 mg/dl was also assessed. In addition, plasma DAO activity levels were measured as a marker of intestinal mucosal activity. DAO activity was assayed as described by Takagi et al[9]. All laboratory tests were performed preoperatively and on POD 1, 3, 5, 7 and 14.

Values were expressed as median and range. Continuous variables were evaluated by the Wilcoxon signed-rank test and categorical variables by Fisher's exact test. Statistical analysis of the data was performed using JMP software (SAS Institute Inc.). The level of statistical significance was set at $p<0.05$.

Results

In total, 34 patients (18 in the TPN group, and 16 in the EN group) were included in the present study. Another 4 patients who had been scheduled to receive PD were excluded from the study due to changes in operative procedures (total pancreatectomy 1, partial resection of duodenum 1, palliative bypass 1, exploratory surgery 1).

The patient preoperative and operative profiles are shown in Table 1. Age, male/female ratio and weight did not differ significantly between the TPN and EN groups. In addition, no significant differences between the groups were observed in operative time and blood loss.

Except for 1 patient who developed apparent pancreatic fistula on POD 4, the EN protocol was completed without any particular problems in the EN group. With regard to patient outcome (Table 2), there was no in-hospital mortality in either group. Pancreatic fistulas of grade B or C occurred in 5 patients (31.2%) in the EN group and 3 patients (16.7%) in the TPN group ($p=0.429$). There were no significant differences in the incidence of major postoperative complications, SIRS on POD 5, or SSI. Postoperative duration of hospital stay and dose of insulin required during the first postoperative week also did not significantly differ between the groups.

Blood test results were compared between the 2 groups (Table 3). Inflammatory parameters, including WBCs, lymphocyte counts, platelets, CRP and cytokine levels, did not differ significantly between the 2 groups. With regard to postoperative liver function, AST on POD 5 and ALT on POD 5 and 7 were significantly lower in the EN group. Nutritional parameters, including albumin, prealbumin and retinol-binding protein, reached a nadir on POD 3, followed by a gradual increase. There were no significant differences in the levels of these parameters between the EN and TPN groups.

DAO activity reached a nadir on POD 3 and then gradually improved in both the EN and TPN groups. By POD 14, DAO activity almost returned to baseline levels in the EN group, whereas it still remained low in the TPN group. On POD 5 and 14, DAO activity was significantly higher in the EN group than in the TPN group (Table 3).

Table 1. Baseline patient characteristics

	EN group (n=16)	TPN group (n=18)	P value
Age (yrs) [median (range)]	75 (41-89)	70 (49-82)	0.284
Gender, male: female	9 : 7	9 : 9	0.745
Weight (kg) [median (range)]	53.5 (46.7-72.8)	57 (44-78)	0.407
Disease			0.574
PIDC	4	8	
IPMN	4	3	
BDC	7	4	
VC	1	3	
Procedure (Modified Child method)			0.330
PD (including SSPPD)	8	5	
PPPD	8	13	
Operating time (min) [median (range)]	610 (390-775)	598 (470-765)	0.512
Operative blood loss (mL) [median (range)]	1015 (370-2250)	1170 (400-2680)	0.904

EN: enteral nutrition; TPN: total parenteral nutrition; PIDC: pancreatic invasive ductal carcinoma; IPMN: intraductal papillary mucinous neoplasm; BDC: bile duct carcinoma; VC: papilla of Vater carcinoma; PD: pancreatoduodenectomy; SSPPD: substomach-preserving pancreatoduodenectomy; PPPD: pylorus-preserving pancreatoduodenectomy.

Table 2. Comparison of postoperative complications in the enteral nutrition (EN) and total parenteral nutrition (TPN) groups after pancreatoduodenectomy

	EN group (n=16)	TPN group (n=18)	P value
Mortality	0 (0%)	0 (0%)	
PF Grade B/C (percentage of total)	5/0 (31.2%)	2/1 (16.7%)	0.429
Grade III or more complications, except PF	4 (25%)	4 (22.2%)	1.000
SIRS on POD 5	2 (12.5%)	3 (16.7%)	1.000
SSI	3 (18.8%)	6 (33.3%)	0.448
Duration of postoperative hospital stay (days) [median (range)]	35.5 [16-105]	35 [26-95]	0.641
Required insulin dose during the 1st week [median (range)]	0 [0-110]	8 [0-52]	0.430

PF: pancreatic fistula; SIRS: systemic inflammatory response syndrome; POD: postoperative day; SSI: surgical site infection.

Table 3. Comparison of laboratory parameters between enteral nutrition (EN) and total parenteral nutrition (TPN) groups

		Pre-op	POD1	POD3	POD5	POD7	POD14
WBC (/μL)	EN	5450 [3200-7400]	8250 [5400-15900]	8650 [3600-17600]	6900 [4000-12200]	9000 [5800-22900]	7250 [4800-24000]
	TPN	5150 [2400-9800]	8700 [5900-14900]	8500 [5100-15300]	7650 [4200-12500]	8200 [4300-12500]	7500 [3200-19000]
Lymphocyte count (/μL)	EN	1300 [730-3050]	590 [130-1360]	790 [470-1810]	830 [230-1310]	800 [140-2270]	870 [360-2110]
	TPN	1460 [580-3090]	630 [320-1890]	710 [120-1300]	880 [230-1550]	810 [320-1630]	1140 [330-1960]
Plt ($\times10^4$/μL)	EN	23.2 [10.7-36.8]	13.5 [9.7-30.5]	13.8 [7-23.9]	17.0 [7.4-37.2]	23.1 [8.6-40.6]	37.2 [23.7-76.3]
	TPN	18.5 [8.7-34.7]	15.5 [6.4-22.3]	13.4 [5.4-21.3]	17.2 [8.4-33.6]	21.0 [9.6-32.4]	34.8 [20.2-63.5]
TP (/dL)	EN	6.5 [3.7-7.7]	4.55 [3.9-5.6]	5.05 [4.4-6.1]	5.1 [4.6-6.2]	5.4 [4.7-6.5]	6.05 [4.6-7.7]
	TPN	6.35 [3.7-7.4]	4.4 [3.3-5.8]	4.85 [4-6.4]	5.4 [4.3-6.2]	5.35 [4.1-6.2]	5.95 [3.8-7.6]
Alb (g/dL)	EN	3.55 [1.9-4.0]	2.7 [2-3.5]	2.75 [2-3.2]	2.65 [2.3-3.4]	2.7 [2-3.3]	2.7 [2.2-3.6]
	TPN	3.55 [2.1-4.5]	2.7 [1.9-4.4]	2.75 [2-4.2]	2.7 [2-3.9]	2.6 [1.8-3.3]	2.8 [1.3-3.4]
AST (U/L)	EN	28 [12-381]	85 [33-348]	53 [21-136]	36 [17-86] *	29 [17-95]	25 [11-313]
	TPN	27 [18-222]	82 [33-810]	41 [25-247]	51 [20-139] *	44 [16-95]	27 [15-78]
ALT (U/L)	EN	25 [8-525]	58 [12-366]	56 [16-232]	48 [15-158] *	38 [21-144] *	30 [9-223]
	TPN	40 [10-364]	81 [37-920]	57 [26-593]	76 [25-365] *	101 [26-294] *	51 [21-157]
T-Bil (mg/dL)	EN	1.1[0.4-6.8]	1.5[0.5-7]	1.2[0.4-6.9]	0.9[0.3-6.2]	0.8[0.2-5.6]	0.6[0.2-4.5]
	TPN	0.9[0.2-7.2]	1.3[0.5-7]	1.2[0.5-3.9]	1.0[0.4-2.2]	0.7[0.1-1.4]	0.5[0.2-1.0]
CRP (mg/dL)	EN	0.16 [0.01-1.8]	9.58 [1.12-12.95]	12.75 [5.7-24.81]	3.27 [0.84-18.96]	2.06 [0.36-20.4]	1.32 [0.07-7.38]
	TPN	0.1 [0.01-3.6]	8.54 [2.47-11.07]	14.62 [2.12-30.69]	6.15 [0.16-20.53]	4.47 [0.05-19.45]	3.99 [0.04-14.3]
IL-6 (pg/ml)	EN	0 [0-19.03]	184.70 [5-3305.13]	18.56 [0-459.42]	9.29 [0-147.95]	8.12 [0-7505.76]	2.1 [0-22.61]
	TPN	0 [0-4.15]	226.58 [2.5-784.83]	7.8 [0-198.92]	4.84 [0-53.53]	4.92 [0-51.52]	3.39 [0-157.75]
IL-10 (pg/ml)	EN	0 [0-12.9]	22.4 [0-1419.3]	5.4 [0-251.1]	1.3 [0-336.7]	8.7 [0-413.66]	0 [0-45.6]
	TPN	0 [0-343]	13.0 [0-1049.4]	6.2 [0-546.8]	3.0 [0-167.2]	2.4 [0-128.9]	2.5 [0-178.2]
Prealbumin (mg/dL)	EN	21 [6.9-37]	10.5 [5.5-16]	8.3 [4.5-17]	13 [7.8-17]	14 [7.7-31]	13 [7.8-32]
	TPN	21 [14-37]	12 [7.6-16]	9.6 [6.6-13]	12 [6.2-19]	13.5 [5.2-24]	13.5 [3.2-21]
Retinol Binding Protein (mg/dL)	EN	2.85 [1.7-6.0]	1.35 [1-2.3]	1.45 [1-2.7]	2 [1.4-2.6]	2.35 [1.5-4.7]	1.9 [1.4-4.6]
	TPN	3.3 [2.1-5.8]	1.3 [1-2.2]	1.3 [1-1.8]	1.9 [1-2.5]	2.15 [1-2.9]	2 [1-5.8]
Zn (μg/dL)	EN	68 [42-99]	27 [21-45]	44 [30-52]	56 [33-70] *	60 [35-78]	78 [56-116]
	TPN	81 [59-128]	30 [24-92]	48 [33-89]	64 [35-90] *	71 [36-98]	85 [35-117]
Fe (μg/dL)	EN	76 [21-170]	12.5 [8-52]	25 [14-73]	24 [8-40]	28 [12-43]	30.5 [14-73]
	TPN	77 [13-110]	12.5 [8-85]	20 [8-74]	33 [16-57]	24 [12-67]	27 [8-67]
Cu (μg/dL)	EN	106 [71-170]	62 [28-95]	80 [55-110]	81 [59-121]	77 [55-119]	92 [46-135] *
	TPN	103 [79-168]	65 [36-80]	84 [68-109]	93 [59-109]	84 [68-119]	111 [81-155]
DAO (U/ml)	EN	3.34 [0-7.34]	1.43 [0-4.32]	0.6 [0-2.06]	0.63 [0-2.8] *	0.6 [0-3.71]	1.95 [0-10.77] *
	TPN	1.09 [0-5.43]	2.17 [0-5.83]	0 [0-2.06]	0 [0-2.11] *	0.03 [0-2.13]	0.53 [0-7.05]

* : P <0.05 as compared to the other group at the same time point

WBC: white blood cell; Plt: platelet; TP: total protein; Alb: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; T-bil: total bilirubin.

CRP: C-reactive protein; IL-6: Interleukin-6; IL-10: Interleukin-10; Zn: zinc; Fe: iron; Cu: copper; DAO: Diamine Oxidase.

Discussion

PD is associated with a high incidence of postoperative complications, and an overall morbidity rate of 48% can be anticipated at major centers[14]. The high rate of complications is likely to be multifactorial and may include overall nutritional debilitation, as most patients requiring PD present with significant weight loss due to anorexia and malabsorption, and are expected to have a period of inadequate oral intake for up to 10 days after surgery[15]. Perioperative nutritional support can be beneficial in these patients, since it may reduce mortality and morbidity and duration of hospital stay[3].

Numerous studies have suggested that EN has several advantages over TPN. Early enteral feeding was shown in a meta-analysis of 8 prospective randomized trials to reduce postoperative septic complications and improve glucose tolerance, protein kinetics and wound healing. Furthermore, EN is safer and less expensive than PN[16,17]. However, postoperative total enteral feeding is associated with complications such as diarrhea, abdominal distension and abdominal cramps. These symptoms worsen with increasing caloric intake and can lead to discontinuance of enteral feeding[18,19].

In the present study, no serious complications or in-hospital mortality occurred in either group. The short-term postoperative outcomes, including the incidence of complications and duration of hospital stay, also did not significantly differ between the EN and TPN groups. Some previous studies have reported a significantly shorter duration of postoperative hospital stay with EN compared to TPN[20,21], or reduced weight loss and improved serum total protein and albumin levels with EN management after PD[22]. Such beneficial effects of EN treatment were not observed in our study. There are several possible reasons for this observed lack of a difference between the two groups, including small sample size, the study

protocol in which oral intake was started on POD 5 in both groups, and low calorie intake when EN was started.

The incidence of pancreatic fistulas tended to be higher in the EN group, although the difference was not statistically significant. This raises an issue for further investigation, namely, whether the incidence of pancreatic fistulas may differ because of the stimulation of pancreatic juice secretion by EN, and if so, whether there are differences based on the types of enteral feeding (e. g., elemental vs. semi-elemental).

DAO is an enzyme found mainly in the villus epithelial cells of the small intestinal mucosa. Although it is also present in the placenta, its activity is particularly high in the villus epithelium of the small intestine[23]. The major function of DAO, together with ornithine decarboxylase, is the metabolism of polyamines, which are essential for cell proliferation. Thus, DAO is involved in the regulation of cell proliferation. DAO also plays a role in biological defense by catabolizing toxic polyamines and histamine[6].

Intestinal DAO activity significantly correlates with plasma DAO activity[6),8)]. Plasma DAO activity has been reported as a marker of small intestinal mucosal integrity and maturity[8], and hence, attention has focused on DAO as a sensitive marker for intestinal mucosal injury. Moreover, decreased plasma DAO activity is a biomarker for intestinal mucosal injury due to anti-cancer drugs[24]. Plasma DAO levels may also be affected by liver dysfunction, GI stress due to surgery or chemotherapy, and by nutritional management. Thus, DAO activity has been investigated under various conditions[25)~27)].

Our study found significantly higher DAO activity levels in the EN group on POD 5 and 14. This finding suggests that early EN after PD reduces postoperative atrophy of the intestinal mucosa. It is interesting that despite only a 4-day difference in the time that the GI tract was not used between the EN and TPN groups, DAO activity levels were still significantly different between the 2 groups on POD 14. It is thought that intestinal mucosal injury developing during the immediate postoperative period in the TPN group takes more than 2 weeks to recover. Although it is expected that maintaining the integrity of the intestinal mucosa can prevent bacterial translocation and the release of inflammatory cytokines, leading to the reduced incidence of SIRS, such protective effects were not observed in the EN group. It is likely that the preservation of intestinal mucosal integrity was not adequate to improve clinical outcomes in our study.

Changes in serum transaminase and bilirubin are the most important indices for evaluating liver function in patients after PD. In the present study, postoperative transaminase levels in both groups increased on POD 1 as compared to baseline, thereafter gradually improving towards normal. However, AST was significantly higher on POD 5 and ALT was significantly higher on POD 5 and 7 in the TPN group as compared to the EN group. It is thought that lack of enteral feeding in the TPN group might have several metabolic and endocrine consequences on intestinal and liver function. Experimental studies have shown that the fasting 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 for maintaining intestinal motility[28)~30)]. It has been also reported that EN can stimulate hepatic circulation and ameliorate liver dysfunction[31]. Therefore, early reduction of liver enzyme levels in the EN group in this study may be partly attributed to early use of the GI tract after surgery in this group.

Conclusion

The present study suggests that early EN after PD may reduce atrophy of the intestinal mucosa without adverse effects on the postoperative course. To achieve beneficial effects on clinical outcomes, such as a decreased complication rate or duration of hospital stay, the optimal calorie intake and type of enteral feed should be determined in future investigations.

Disclosure Statement

There are no conflicts of interest or research funding concerning this study.

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膵頭十二指腸切除術後における早期経腸栄養の効果と影響について

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要　旨

目的：近年，術後早期から腸管を使用することの有用性が報告されているが，膵頭十二指腸切除術（PD）のように大きな侵襲を伴う術後には，経口摂取が進まなかったり，合併症などの理由から絶食とせざるを得なくなることもある．

そうした場合には中心静脈栄養（TPN）や経腸栄養（EN）管理とすることが一般的である．

Diamine oxidase（DAO）は主に小腸粘膜の絨毛上皮細胞に分布する酵素で，小腸のintegrityと血中DAO活性値は有意に相関するため，小腸粘膜の障害の程度を鋭敏に反映する指標となる．

PD術後早期からEN管理した方が腸管粘膜の萎縮が軽度で，なおかつ合併症が少ないという仮説を立て，prospective pilot studyを計画し，その評価にDAO活性を用いた．

方法：2011年４月から2013年11月に当科でPDを予定した患者のうち，参加同意が得られ，実際にPDが施行された34症例を対象とした．

術前にTPN群とEN群に割り付け，TPN群は術後１日目は維持輸液とし，術後２日目より高カロリー輸液で管理した．

EN群は維持輸液に加え，術後１日目より５％糖液を手術時に造設した腸瘻から投与し，術後２日目より経腸栄養剤を投与した．

両群とも飲水は３日目，食事は５日目から開始した．

両群間の術後合併症や有害事象の発生率，術後在院日数，各種栄養学的指標，サイトカインの推移，インスリン使用量，DAO活性を比較検討した．

結果：EN群の術後５，14日目のDAO活性はTPN群に比較し有意に高値であった．

またALTはTPN群において術後５日，７日目に有意に高値であった．

両群間で栄養学的指標，炎症指標，合併症の発生率，術後在院日数には有意差を認めなかった．

結論：PD術後早期からの経腸栄養は，腸管粘膜の萎縮を抑制することが示唆されたが，臨床経過には有用性を認めなかった．

Key Words：膵頭十二指腸切除，経腸栄養，diamine oxidase（DAO）活性