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ORIGINAL ARTICLE

Effect of early intrajejunal nutrition on pancreatic pathological features and gut barrier function in dogs with acute pancreatitis

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Abstract—Background: In patients with major trauma and burns, total enteral nutrition (TEN) significantly decreases the acute phase response and incidence of septic complications when compared with total parenteral nutrition (TPN). Traditionally, it was believed that early intrajejunal nutrition (EIN) in severe acute pancreatitis (SAP) may exacerbate the clinical pathological features, lead to recurrence of symptoms and delay complications.
Objective: To compare the effect of EIN vs TPN on the pancreatic pathological features and gut barrier function in dogs with acute pancreatitis (AP).
Methods: Fifteen dogs (surviving over 7 days, the death rate being 32%, 7/22) were divided into parenteral nutrition (PN) group ($n = 7$) and EIN group ($n = 8$). SAP model was induced by injecting 1 ml/kg of combined solution of 2.5% sodium taurocholate and 8000–10,000 BAEE units trypsin/ml into the pancreas via the pancreatic duct. Nutrients were delivered to the EIN group by catheter via a jejunostomy feeding 24 h postoperatively. The two groups were isocaloric and isonitrogenous. Systemic blood samples were obtained before and 1, 4, 7 d following AP, and cultured by aerobic as well as anaerobic bacterial growth. Systemic plasma and portal vein endotoxin levels were quantified by the chromogenic limulus amebocyte lysate (LAL) technique. Portal vein blood and specimens of tissue from mesenteriolum and mesocolon lymph nodes, lung, pulmonary portal lymph nodes and pancreas were adopted before the experiment was finished. Aliquots of the homogenata were cultured as blood mentioned above. Serum glucose, calcium, amylase and lysosomal enzymes were determined. All dogs were injected with 50 μCi ^{125}I-BSA 4 h at the 7th day before being sacrificed. The ^{125}I-BSA indexes of the pancreas/muscle and pancreas/blood were measured, and pancreatitic pathological scores (PPSs) of the different partial pancreas were observed. The content of mucosa protein, DNA and the villi, the thickness of mucosa and the whole bowel wall of the ileum and transverse colon were measured.
Results: The study showed that serum glucose in the PN group was higher than in the EIN group after SAP 3 d; the levels of systemic plasma endotoxin and the magnitude of bacterial translocation to the portal and systemic blood and distant organ reduced significantly in the EIN group $P < 0.01$. There were no differences between the two groups in the data of serum calcium, amylase and lysosomal enzymes, $P > 0.05$; the ^{125}I-BSA index of pancreas/muscle and pancreas/blood, and PPS of the head, body, tail and total pancreas did not reach significant difference between the two groups, $P > 0.05$. The contents of protein and DNA, the height of villi, the thickness of mucosa and the whole bowel wall of the ileum and transverse colon in the EIN group were higher than that in the PN group, $P < 0.01$.
Conclusion: Our results suggested that EIN was safe and effective to be adopted by intrajejunal delivery of nutrients in SAP dogs, did not make SAP clinical pathological features deteriorate, and decreased the occurrence rate of endotoxin and gut bacterial translocation.

Key words: early intrajejunal nutrition; parenteral nutrition; acute pancreatitis pathological features; bacterial translocation

Introduction

Total parenteral nutrition (TPN) has been the standard practice for providing exogenous nutrients to patients with acute pancreatitis (AP) in order to improve nutritional status and at the same time avoid pancreatic stimulation. However, TPN is associated with certain disadvantages. In particular, there is an increased risk of central catheter infection, severe hyperglycemia, and other metabolic and electrolyte disturbances and a possible exacerbation of metabolic disturbances. TPN may also promote gut barrier alterations due to increased intestinal permeability (1–3).

Benefits from the use of total enteral nutrition (TEN) have been noted in a number of other disease states, such as burns, trauma, and sepsis. In comparison with

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TPN, the use of TEN reduces nosocomical infection, multiple organ failure (MOF), and length of hospitalization (3, 4). The use of early enteral feeding for nutritional support in patients with AP has not been evaluated systematically. The commonly encountered problems of gastric atony and outlet obstruction have limited the successful delivery of enteral formulas to patients with severe acute pancreatitis (SAP). In addition, many surgeons think scrupulously about the fact that enteral nutrition (EN) may exacerbate the clinical pathological features and lead to recurrence of symptoms and delayed complications (5). However, these problems may be overcome if EN were to be delivered to the distal ileum far away from Treize's ligament and avoiding stimulation of the cephalic and gastric phases, and those effects are not as pronounced when nutrients are delivered directly into the jejunum. Therefore, it is necessary to investigate the efficiency of early intrajejunal nutrition (EIN) on pancreatitic clinicopathology changes in AP dogs.

Materials and methods

Animal model

Twenty-two dogs weighing 18–22 kg were allowed ad libitum intake of water. After 12–14 h fasting, all dogs were induced anesthesia by intramuscular injection of ketamine 10 ml/kg, and then were subjected to dauernarcosis by intravenous injection of sodium pentobarbital 30 mg/kg. Under sterile conditions, a middle laparotomy and duodenotomy were performed. AP model was induced by injecting 1 mg/kg of combined solution of 2.5% sodium taurocholate and 8000–10,000 BAEF units trypsin/ml into pancreas via pancreatic duct with pressure 30 cmH_2O, the common biliary duct was clamed, the model was finished, duodenum and the abdomen were closed. A catheter via jejunostomy was set far away from Treitz's ligament by 30 cm. The neck regions of the dogs were shaved and prepared in a sterile manner for catheterization. A silastic catheter (1.0 mm inner diameter, 1.5 mm outer diameter) was inserted through the external jugular vein to reach the superior vena cava. The catheter was fixed to connect the infusion solution. Fifteen dogs with AP survived over 7 days and the death rate was 32% (7/22). The trial was approved by our institutional animal committees.

Experimental groups and nutritional solution prepared

Fifteen dogs over 7 days with SAP were allocated randomly to two groups: parenteral nutrition (PN) group ($n = 7$) and EIN group ($n = 8$). The two groups were isocaloric and isonitrogenous. The PN solutions consisted of 7% Vamin (SSPC, 9.4 g/1000 ml) and 20% Intralipid (SSPC) and 50% glucose (GS). Non-protein calories were 50 kcal (209.2 kJ/kg) and nitrogen was 0.3 g/kg/d. The total volume of the solution infused was 70 ml/kg/d. Energy index supported with glucose and fat emulsion was 1:1. Multivitamins and electrolytes were also included in TPN solutions. Natural saline was infused by 250 ml/kg during operation time and 8 h postoperatively, and then infused with 125 ± 25 ml/kg. The nutrient solution was infused at a constant infusion rate by a pump (100–120 ml/h).

The EIN solution was Nutrison (Nutricia). After SAP induced 24 h, the jejunum was infused with 250 ml Nutrison and 500 ml NS through a jejunostomy catheter; after SAP 48 h, 500 ml Nutrison and 250 ml NS were infused and the duration time was 5 d. The infusion rate was controlled by a microcomputer pump (Nutricia). During EIN supporting, the insufficiency of calories and nitrogen were supplemented by partial PN (Table 1).

Laboratory tests, ^{125}I-BSA index and pancreatic pathology

Serum glucose, calcium, amylase and lysosomal enzymes (according to Kit's indication) were determined before

Table 1 The calories, nitrogen and liquid supplemented between two groups (according/20 kg)

Groups		PN group		EIN group			
Calories (50 kcal/kg/d)				PPN		EIN Nutrison (1 kcal/ml)	
		1–7 d				1 d	
	20% Intralipid	227 ml	500 kcal	170 ml	375 kcal	250 ml	500 kcal
	50% GS	250 ml	500 kcal	187.5 ml	375 kcal	Nutrison GS (5/g500 ml)	
N	0.3 g/kg/d					Nutrison (3.2/g500 ml)	
	Vamin (9.4 g/l	640 ml	6.0 g	468 ml	4.4 g	250 ml	1.6 g
						2–7 d	
	20% Intralipid			113.6 ml	250 kcal	500 ml	500 kcal
	50% GS			125 ml	250 kcal	Nutrison (3.2 g/500 ml	
N	Vamin (9.4 g/l)			298 ml	2.8 g	500 ml	3.2 g
Liquid		GNS + NS 2500 ml		GNS + NS 2000 ml		NS + Nutrison 1000 ml	
Total		35–400 ml		3500–4000 ml			

and 1, 4, 7 d following SAP. All dogs were injected with 50 μCi ^{125}I-BSA 4 h at the 7th day before being sacrificed. The ^{125}I-BSA volume in the pancreas (/g), muscle of the right leg (/g) and blood (/ml) were tested by r-accounter radioimmunology analyzer. The ^{125}I-BSA indexes of the pancreas/muscle and pancreas/blood were measured. A fixed section of the pancreatic head, body, tail and the total pancreas was taken off to observe the histological change. Pancreatitic pathological scores (PPSs) were taken by the extent of pancreas tissue edema, inflammation, hemorrhage and necrosis according to score 1, 2, 3, 4 and PPSs of the different pancreas partial were determined.

Changes of DNA, protein and histological observations of ileum and transverse colon

Systemic blood samples before and 1, 4, 7 d following AP and the portal vein blood before the experiment finished were adopted. Systemic plasma endotoxin was quantified by the chromogenic limulus amebocyte lysate (LAL) technique. The bacterial volumes in systemic blood and portal vein were tested by aerobic as well as anaerobic bacterial culture.

When the experiment was finished, the dogs were placed on a sterile field, the chest and the ventral abdomen were cleaned with 70% isopropyl alcohol and opened with sterile instruments. Several tissues such as lung, pulmonary portal lymph nodes (PPLNs) and several mesenteric lymph nodes (MLNs) and pancreatitic tissue were isolated, weighed and put into sterilized glass tissue grinders. Two hundred microliters of the homogenate by five full up-and-down strikers of motorized glass-Teflon homogenizer were plated onto general agar plates, and agar plates with 5% sheep's blood. Aliquots of the homogenata were incubated as blood mentioned above. Following several tissue excisions, 20-cm segments of ileum and transverse colon were rapidly excised, and 10-cm segments were opened along the antimesenteric border; the mucosa was blotted with tissue paper and then weighed. All samples were immediately frozen at −70°C. The mucosae of the ileum and transverse colon segments were scraped off from the specimens with a glass slide and homogenized in a blender at 30,000 rpm for 30 s. The homogenates were centrifuged for 15 min at 3000 × *g* and the supernatants assayed spectrophotometrically for protein DNA (6). Values were expressed per gram of gut tissue. Another 10 cm segments of the ileum and transverse colon were cut, pinned flat onto wax, and fixed in Boin's solution. Tissues were subsequently embedded in paraffin, and 5-μm sections were taken and stained with hematoxylineosin. All slides were coded and morphologically interpreted in a 'blind' fashion. The villi, the thickness of mucosa and the whole bowel wall of the ileum and transverse colon were determined.

Statistical analysis

Analysis of bacterial translocation was performed using χ^2 analysis, these specimen measures were expressed as means ± SEM of the sample and comparison between two groups was made using one-way analysis of variance. *P* value below 0.05 was considered the statistically significant difference.

Results

General observation

There is no difference in CVP, respiratory, artery blood gas analysis, or WBC between the PN group and the EIN group. Their differences did not reach the statistically significant difference, $P > 0.05$.

Changes of serum glucose, calcium, amylase and lysosomal enzymes

After the AP model was finished, serum glucose in the PN group was in a higher level as compared with the EIN group during the whole experimental period. Serum calcium markedly decreased after SAP was induced, and there was no difference in the changes of serum calcium between the two groups in the later days. Serum amylase and lysosomal enzymes increased and gradually decreased in the later days during the

Table 2 Effect on serum glucose, calcium amylase and lysosomal enzymes and endotoxin of different nutrition support methods

	glu (μmol/l)	Ca (mmol/l)	Amylase (SU)	LE (U)	Endotoxin (EU/l)
PN group					
Pre-AP	4.0 ± 0.5	2.50 ± 0.10	328 ± 96	22 ± 10	0.56 ± 0.13
P1	8.3 ± 0.8*	2.42 ± 0.11	636 ± 100*	53 ± 11*	1.88 ± 0.47*
P4	10.3 ± 1.0*	2.36 ± 0.13*	1150 ± 416*	45 ± 14*	3.61 ± 0.92*
P7	9.8 ± 1.1*	2.20 ± 0.11	1060 ± 260*	47 ± 13*	2.90 ± 0.64*
EIN group					
Pre-AP	4.7 ± 0.8	2.34 ± 0.16	400 ± 110	26 ± 9	0.56 ± 0.22
P1	8.4 ± 1.0*	2.39 ± 0.11	734 ± 164*	64 ± 17*	1.99 ± 0.68*
P4	6.7 ± 1.0	2.34 ± 0.15	1215 ± 416*	50 ± 19*	2.43 ± 0.65*$^{\#}$
P7	6.6 ± 0.7	2.30 ± 0.09	1169 ± 362*	52 ± 20*	2.08 ± 0.51*$^{\#}$

*$P < 0.05$ vs pre-SAP, $^{\#}P < 0.01$ vs PN group.
LME: lysosomal enzymes.

Table 3 Content of blood and tissues (10^5 CFU/ml or/g)

	PN group	EIN group
Systemic blood	9.45±2.54	4.04±0.12*
Portal vein blood	14.29±2.65	1.23±0.30*
Lung tissue	22.34±10.02	8.09±3.09*
PPLN	28.91±13.27	9.88±5.38*
Pancreas	55.37±33.72	28.23±22.17*
MLN	41.45±21.17	8.54±3.89*

*$P<0.01$ vs PN group.
Note: PPLN, pulmonary portal lymph nodes, MLN, mesocolon lymph nodes.

experimental period, but there were no difference between the two groups, $P>0.05$ (Table 2).

^{125}I-BSA index and PPSs

The ^{125}I-BSA index of pancreas/muscle and pancreas/blood in the EIN group (4.22±0.18 cpm/g, 0.22±0.03 cpm/ml) and the PN group (3.69±0.26 cpm/g, 0.17±0.02 cpm/ml) did not reach the statistically significant difference, $P>0.05$. PPSs of different sections including head, body, tail and total pancreas in the EIN group (1.40±0.24, 2.3±0.20, 2.1±0.20, 1.9±0.23) and the PN group (1.30±0.38, 2.4±0.22, 2.2±0.22, 1.9±0.06) did not reach the statistically significant difference, $P>0.05$.

Systemic endotoxin content and distal organ bacterial translocation

There is a decrease of endotoxin in the EIN group as compared with the PN group at 4, 7 d, $P<0.01$ (Table 2). The bacterial volume of the distal organs such as lung, PPLNs and several MLNs and pancreatitic tissue in the EIN group were lower than in the PN group, $P<0.01$ (Table 3).

Changes of DNA, protein and histological observations of ileum and transverse colon

The mucosal protein and DNA contents of ileum and transverse colon in the EIN group were improved as compared with the PN group, $P<0.01$ (Table 4). The bowel wall thickness, mucosa thickness and villus height in the EIN group were improved as compared with the PN group, $P<0.01$ (Table 5).

Discussion

Autodigestion of the pancreas is the main underlying pathophysiological mechanism of SAP. The conception of pancreatic rest stems from the belief that stimulation of pancreatic exocrine function in patients with AP releases large quantities of proteolytic enzymes which results in autodigestion of the inflamed pancreas and peripancreatic tissues, causing a deterioration in the patient's condition. The presence of food in the stomach and duodenum elicits gastropancreatic and duodenopancreatic reflexes that result in the stimulation of pancreatic exocrine secretions. Therefore, traditionally, EN could be considered to be adopted after PN support over 2–3 weeks. This means having a long time for the pancreas to rest and rehabilitate. However, these effects are not as pronounced when nutrients are delivered directly into the jejunum.

Windsor et al. (7) reported that SIRS, sepsis, organ failure, and ICU stay, were globally improved in the enterally fed patients with AP. the acute phase response and disease severity scores were significantly improved following EN (C-reaction protein, CRP: 156 (117–222) to 84 (50–141), $P<0.005$; APACHEII scores 8 (6–10) to 6 (4–8), $P<0.0001$) without change in the CT scan scores. In parenterally fed patients, these parameters did not change, but there was an increase in serum IgM antiendotoxin antibody (EndoCAb) levels and a fall in total antioxidant capacity (TAC). Enterally fed patients showed no change in the level of EndoCAb antibodies and an increase in TAC. Their results suggested that TEN moderated the acute phase response and improved disease severity and clinical outcome, despite unchanged pancreatic injury on CT scan. Reduced systemic exposure to endotoxin and reduced oxidant stress also occurred in the TEN group. Enteral feeding modulates the inflammatory and sepsis response in AP and is clinically beneficial (7–9).

Some authors described (4, 10) an experience of early EN in severe AP using nasoenteral feeding, starting 36 h after admission. No patients developed relapse, hypertriglyceridemia or abnormalities of liver function, indicating that jejunal feeding can be used safely in AP without reactivation of the inflammatory process. Our experimental results showed that the changes of serum glucose, calcium, amylase did not reach the statistically significant difference between the two groups. It is known that the serum lysosomal enzymes are believed to be the gold standard for reflecting the extent of

Table 4 Ileum and transverse colon protein and DNA (mg/g)

Group	Ileum		Transverse colon	
	Protein	DNA	Protein	DNA
PN	141.62±37.90	10.20±3.48	183.67±65.33	17.82±3.68
EIN	161.79±36.75*	16.79±2.14*	222.44±78.21*	29.92±4.21*

*$P<0.01$ vs PN group.

Table 5 Results of intestinal and transverse colon pathology (μm)

Group	Ileum			Transverse colon		
	Total layer	Mucosa	Villi	Total layer	Mucosa	Villi
PN	605.77±57.63	519.60±69.31	322.57±63.09	1034.27±243.66	934.54±173.22	677.42±147.57
EIN	715.26±87.43#	674.55±80.02#	471.50±76.71#	1227.63±167.76	1179.33±181.34	803.29±108.43

#$P<0.01$ vs PN group.

pancreatic tissue necrosis and inflammation and to have attracted more attention in international medicine. Once the pancreatic tissue necrosis decreased, the volume of systemic lysosomal enzymes discharging from pancreatitis tissue would be attenuated. Our results indicated that serum lysosomal enzymes markedly increased after AP induced, but did not reach the statistically significant difference between the two groups. In addition, the ^{125}I-BSA index of pancreas/muscle and pancreas/blood reflected the permeability of the pancreas microcirculation. If this ^{125}I-BSA index decreased, microvessal permeability would be improved. Once the ^{125}I-BSA index in pancreatic tissue increased, the microvessal permeability elevated and deteriorated pancreatitis tissue to be further damaged. Our study showed that the changes of ^{125}I-BSA index did not reach statistically significant differences between the two groups. These results strongly suggested that the administration of EIN did not increase the serum lysosomal enzymes volume or deteriorate the course of AP. The PPSs of different segments including head, body, tail and total pancreas in the EIN and PN groups did not reach the statistically significant difference, $P>0.05$. Kalfarentzos reports (11) that EIN was well tolerated following AP and was of comparable efficacy to PN. It is a fact that EIN did not deteriorate pancreatitic pathology, and may be adopted safely in dogs with AP in our study.

It is frequently stated that TPN leads to mucosal atrophy and the assumption is made that this predisposes to bacterial translocation which may account for increased septic morbidity. So, some authors suggested that EIN was capable of maintaining the integrity and function of the intestinal mucosa (10, 11). Our results also showed that serum endotoxin in the EIN group was lower than that in the PN group at 4, 7 d, and the magnitudes of bacterial translocation to the portal, plasma and distant organ (mesenteriolum, mesocolon lymph nodes, lung, pulmonary portal lymph nodes and pancreas) in the EIN group were lower than that in the PN group. In addition, the EIN group improved mucosal protein and DNA contents and villus height, mucosal thickness and bowel thickness of the ileum and transverse colon. Considering these roles of EIN that it can restore normal gut structure and microflora, and aid the mucosa in withstanding challenges to these systems must be used.

In summary, EIN started at 24 h was as well tolerated, feasible and desirable as TPN in the management of disease with AP and failed to reveal any detrimental effect on the clinical pathologic features of AP. Therefore, EIN was helpful to maintain gut integrity and reduced bacterial and endotoxin translocation compared with TPN.

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