• CLINICAL RESEARCH •

Clinical study on nutrition support in patients with severe acute pancreatitis

Gang Zhao, Chun-You Wang, Fang Wang, Jiong-Xin Xiong

Gang Zhao, Chun-You Wang, Jiong-Xin Xiong, Pancreatic Surgery Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei Province, China
Fang Wang, Department of Pharmacology, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China
Correspondence to: Dr. Gang Zhao, Pancreatic Surgery Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei Province, China. zhaogang1427@yahoo.com.cn
Telephone: +86-27-85726273
Received: 2003-03-20   **Accepted:** 2003-04-22

Abstract

AIM: To investigate the effect of nutritional support therapy on severe acute pancreatitis (SAP).

METHODS: A total of 96 patients with severe acute pancreatitis were divided randomly into control and treatment groups. The former group received total parenteral nutrition (TPN) via central venous infusion, while parenteral nutrition (PN) and enteral nutrition (EN) therapies were applied in different phases for the latter group. The nutrition status, acute phase responses, pancreas lesions, enteric mucosa penetrability and immune functions were monitored.

RESULTS: Body weight and prealbumin concentration were increased in treatment group, compared to those in the control group, but albumin concentration did not change significantly. Acute physiology and chronic health evaluation II (APACHE II) scores decreased after 7 d of treatment, whereas the scores of the control group decreased on the 11th day. Concentrations of tumor necrosis factor-α (TNF-α), interleukine-6 (IL-6) and serum C reactive protein (CRP) dropped earlier in the treatment group (on the 4th day) than that in the control group (on the 7th day). No difference was observed in pancreatic lesions between the control and treatment groups. Concentration of endotoxin and lactulose/manicol (L:M) ratio of urine did not change in treatment group, but those in the control group were elevated markedly. Compared with the treatment group, CD4:CD8 T cells ratio and immunoglobulin G (IgG) concentration in the control group decreased significantly.

CONCLUSION: Compared to TPN, the combined therapy of EN and PN could improve the nutrition status and moderate the acute phase response obviously. Moreover, the integrity of enteric mucosa and immune function were protected more effectively in treatment group than in the control one. On the other hand, EN did not simulate the excretion of pancreas and avoid exaggerating the inflammation of pancreas. Thus, appropriate application of PN and EN appears to be more effective for patients with SAP.

INTRODUCTION

Severe acute pancreatitis (SAP) is characterized by a diffuse inflammatory process of the pancreas with variable involvement of adjacent tissues and dysfunction of remote organs[1]. The metabolic alterations of SAP are involved in a classical stress state, as proposed for sepsis, including hyperdynamic changes, hypermetabolism and hypercatabolism. Thus, artificial nutritional support should be a suitable treatment[2-4]. The clinical nutritional management of pancreatitis has changed from total parenteral nutrition (TPN) to enteral nutrition (EN). However, it remains to be clarified whether EN is the best approach or not[5-8]. The purpose of this observation was to evaluate different nutrition therapies for SAP.

MATERIALS AND METHODS

Patients

A total of 96 patients with SAP admitted to the Pancreatic Surgery Center of Union Hospital (Wuhan, China) between February 2000 and October 2002 were recruited to the randomized study. The severity of pancreatitis was defined according to the Atlanta classification system for acute pancreatitis. Criteria for this observation were the acute physiology and chronic health evaluation II (APACH II) score higher than 8, and no indication for operation temporarily[9, 10]. These patients consisted of 58 males and 38 females with a mean age of 47.8 years (range 24-68 years). After 48 hours of common management including active liquid resuscitation and organ function protection[11,12], the patients were divided randomly into control and treatment groups. No significant differences of male:female ratio (15.6:16.7) and average age (48.2 and 46.7) were found between the two groups.

Study protocol

The 41 patients in control group were commenced on TPN via central venous infusion. In the treatment group, PN and EN were carried out by three stages for 55 patients. At first, the patients of treatment group only received glutamine-supplemented PN. When the paralysis was relieved, EN and PN were applied at the same time. EN was administrated via a nasojejunal feeding tube under endoscopy or X-ray. Following the study period, the volume and speed of enteral feeding were adjusted depending on the individual tolerance. Deficiency of energy was compensated through glutamine-supplemented PN. At last, the enteric feeding reached approximately 2 000 ml in 5-7 d, and PN was ceased.

Nutrition formulas

Conventional TPN was based on an amino acid solution providing 0.25 g nitrogen/(kg· d) with lipid emulsion and glucose. Half of the non-protein calories were provided by lipid. The total calorie was 30 kcal/(kg· d) and the calorie to nitrogen ratio was 120:1 in each patient. Electrolytes, trace elements and vitamins were added to maintain requirements [13].

PN in treatment group was based on the same elements as TPN but with supplement of 0.22 g glutamine/kg. EN formula was Peptide-2000 (Nutricia, Holland) semi-elementary diet

(2.9 g nitrogen and 500 kcal non-protein calorie/500 ml), with supplement of glutamine tablets to increase the intake of glutamine[14,15].

Experimental protocols

Body weight, albumin and prealbumin concentrations were determined to evaluate the nutrition status once of a week. APACH II scores, serum C reactive protein (CRP), tumor necrosis factor-α (TNF-α) and interleukine-6 (IL-6) were quantified every three days to assess the acute phase response. Pancreatic and peripancreatic necrosis were detected by contrast-enhanced CT scan once a week. These results of CT scan were scored with a modified Balthazar scoring system. Permeability of gastrointestinal mucosa was evaluated by concentration of endotoxin and lactulose/manicol (L:M) ratio of urine. CD4:CD8

ratio of T cell and concentration of immunoglobulin G (IgG) were quantified to assess immunological function.

Statistical analysis

All data were expressed as the mean ± standard deviation. Student's t test was used to analyze the difference. A value of P<0.05 was considered statistically significant.

RESULTS

Nutrition status

Compared to the control group, body weight and plasma prealbumin concentration were increased in the treatment group after two weeks of treatment (P<0.05), whereas plasma albumin concentration did not change (Table 1).

Table 1 Changes of body weight, plasma albumin and prealbumin concentrations in two groups

	1 d		7 d		14 d		21 d	
	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment
Weight (kg)	66.5±13.4	65.7±13.1	56.9±13.1	55.4±13.5	55.7±12.9	60.4±13.4[a]	58.81±4.2	63.2±13.2[a]
Albumin (g/L)	38.7±5.2	38.8±3.9	33.4±4.1	33.8±3.7	35.2±4.3	36.5±2.9	37.3±4.5	38.7±5.1
Prealbumin(g/L)	12.6±3.2	12.7±5.2	8.4±2.9	11.1±2.2[a]	9.6±4.1	12.5±5.1[a]	11.9±6.1	12.7±5.9

[a]P<0.05 vs control.

Table 2 Changes of APACHE II scores and concentration of TNF-α, IL-6 and CRP in two groups

	1 d		4 d		7 d		11 d		15 d	
	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment
APACH II	8.2±0.7	8.3±0.6	8.4±0.9	7.9±0.6[a]	7.1±0.8	5.7±0.7[a]	5.2±0.7	3.7±0.8[a]	1.6±0.4	1.5±0.5
TNF-α(pg/ml)	63.5±15.2	68.4±13.5	55.6±16.3	47.4±11.6[a]	43.9±9.7	34.2±7.6[a]	34.6±7.5	14.2±3.2[a]	16.5±9.6	15.4±5.3
IL-6(pg/ml)	43.3±11.4	46.7±12.4	39.8±9.2	31.4±8.5[a]	34.3±9.2	22.5±7.6[a]	13.2±58	21.7±9.4[a]	11.5±4.7	12.3±3.8
CRP(mg/L)	77.3±13.5	75.4±14.5	67.3±18.6	54.8±11.2[a]	54.3±9.6	41.2±8.5[a]	37.5±9.8	24.7±9.8[a]	21.3±8.6	19.7±6.4

[a]P<0.05 vs control.

Table 3 Changes of serum amylase, urine amylase and CT scores in two groups

	1 d		4 d		7 d		11 d		15 d	
	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment
Serum amylase (IU)	672±83	640±79	869±96	821±87	621±69	585±72	432±47	445±39	124±27	135±31
Urine amylase (IU)	1327±324	1521±284	2227±357	2312±312	1413±315	1486±274	924±189	945±157	522±114	547±142
CT score	2.5±0.8	2.3±0.7			3.8±1.1	3.7±0.9			2.1±0.5	2.1±0.6

Table 4 Changes of endotoxin concentration and L:M ratio of urine in two groups

	1 d		7 d		15 d		21 d	
	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment
Endotoxin (pg/ml)	–	–	5.9±1.1	2.4±0.7[a]	8.3±3.2	1.9±0.8[a]	8.4±1.6	1.7±0.6[a]
L:M	0.047±0.019	0.052±0.021	0.097±0.023	0.063±0.011[a]	0.143±0.046	0.061±0.027[a]	0.156±0.032	0.057±0.028[a]

[a]P<0.05 vs control.

Table 5 Changes of CD4:CD8 ratio and IgG concentration in two groups

	1 d		7 d		15 d		21 d	
	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment
CD4:CD8	1.82±0.02	1.85±0.04	1.54±0.05	1.72±0.06[a]	1.64±0.07	1.82±0.04[a]	1.78±0.03	1.87±0.05[a]
IgG (mg/L)	12.3±1.7	11.8±1.1	9.8±0.9	11.4±0.7	10.8±0.6	11.8±0.7[a]	11.0±0.5	12.2±0.6[a]

[a]P<0.05 vs control.

Acute phase responses

APACH II scores decreased earlier in the treatment group (on the 4th day) than those in the control group (on the 7th day). Moreover, the concentration of serum CRP, TNF-α and IL-6 in treatment group decreased earlier too (Table 2).

Pancreas lesions

The concentrations of serum and urine amylase in both groups decreased on the 7th day, and there were no significant differences between these two groups. Similar changes were observed in the CT scores (Table 3).

Enteric mucosal permeability

Few endotoxins were detected in the treatment group on the 7th day, and the urine L:M ratio remained unchanged. Endotoxin concentration and urine L:M ratio in control group elevated gradually and were much higher than those in the treatment one ($P<0.05$) (Table 4).

Immune function

CD4:CD8 T cell ratio and serum IgG concentration did not change in the treatment group. In control group, CD4:CD8 T cell ratio and serum IgG concentration decreased continuously and were markedly lower than those in the treatment group ($P<0.05$) (Table 5).

DISCUSSION

Infected pancreatic necrosis is the most severe complication in patients with SAP. Its occurrence is associated with systemic inflammatory response syndrome (SIRS), sepsis, and multiple organ failure (MOF). Failure of intestinal barrier function is probably responsible for the occurrence of these phenomena[16-19]. Experimental models have shown that infection of necrotic pancreas is caused by translocated intestinal bacteria. Bacterial endotoxins and antigens invade the portal circulation and generate cytokines, causing multiple organ failure syndrome (MODS). Enteral feeding has been proved to be beneficial in burn patients and major trauma victims. Theoretically, EN should help preserve intestinal barrier function in patients with SAP[20-23].

It is worth considering which factors contribute to the failure of gut barrier function in acute pancreatitis. Some of these factors are consequences of the disturbance of peristalsis caused by paralysis and disturbance of perfusion caused by hypotension. The most important factor is the deficiency of oxygen and substrate supply for enteric mucosae. Atrophy and apoptosis of intestinal mucosae occur after several days of PN, and the permeability of intestinal wall increases[24-26]. The increased permeability of intestinal wall allows macromolecules, bacteria, endotoxins, and antigens to enter into the portal circulation and adjacent tissues. This invasion elicits an inflammatory response by stimulating the macrophages and neutrophil granulocytes and by inflammatory cytokines (IL-1, 2, and 6 and TNF). These inflammatory mediators may be responsible for the development of SIRS and MODS[27-29]. Our study indicated that inflammatory mediators (CRP, IL-6 and TNF-α) in the treatment group decreased earlier (on the 4th day) than those in the control group (on the 7th day). Similarly, APACH II scores in the treatment group declined earlier (on the 7th day) than those in the control group (on the 11th day). These results suggest that the combined therapy of EN and PN could avoid the excess production of inflammatory mediators, and then alleviate SIRS and acute phase response.

Glutamine is an amino acid rich in the plasma and intracellular free amino acid pool. It is essential for a wide variety of physiologic processes, in particular, the growth and function of enteric mucosae and immune cells including lymphocytes and macrophages[30-32]. In SAP, glutamine is in condition of excess utilization and endogenous glutamine production may not adequate. In our present study, glutamine was added into the elements of PN and EN. The results showed that endotoxin concentration and urine L:M ratio in the treatment group did not have any change, but elevated markedly in the control group. It was indicated that intestinal epithelial cells and immune cells received nutrients especially glutamine from the gut and reins in the treatment group. Furthermore, intestinal motility adjusted the secretion of enteral hormones and enhanced blood flow. Therefore, the combined therapy of PN and EN can prevent mucosae from atrophy and apoptosis effectively. Meanwhile, the results of CD4:CD8 ratio of T cells and serum IgG concentration indicated that the immune function in the treatment group was protected effectively. The combined therapy of PN and EN protected mucosal barrier and immune function, which could prevent the translocation of bacteria effectively.

Several investigations have emphasized that early EN should be beneficial to patients with SAP. However, too early EN or intragastric nutrition would increase the exocrine of pancreas, which aggravates pancreatitis. Our criteria for the enteral feeding are to alleviate the acute phase response, stabilize the organs function and limit the local necrosis tissue and exudates. Nutritional tube must be placed in the superior segment of jejunum, so enteric feeding will not increase the amount of pancreatic secretions[33, 34]. Because the gut failed to function in patients with SAP and the nutritional tube couldnot peristalsize, the tube should be pushed with endoscopy or under X-ray to the superior segment of the jejunum[35]. In this study, CT scores and the concentration of amylase indicated that EN did not simulate the excretion of pancreas, and thus could avoid exaggerating the inflammation of pancreas.

In summary, the results of our study provide evidences that combined therapy of EN and PN can significantly modulate acute phase response and improve the mucosal barrier and immune defense. Thus, appropriate application of PN and EN appears to be more effective for patients with SAP.

REFERENCES

1   **Zazzo JF**. Nutrition in acute pancreatitis. *Schweiz Med Wochenschr* 1999; **129**: 1617-1625
2   **Schneider H**, Boyle N, McCluckie A, Beal R, Atkinson S. Acute severe pancreatitis and multiple organ failure: total parenteral nutrition is still required in a proportion of patients. *Br J Surg* 2000; **87**: 362-373
3   **Lobo DN**, Memon MA, Allison SP, Rowlands BJ. Evolution of nutritional support in acute pancreatitis. *Br J Surg* 2000; **87**: 695-707
4   **Clancy TE**, Ashley SW. Current management of necrotizing pancreatitis. *Adv Surg* 2002; **36**: 103-121
5   **Everitt NJ**. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *Br J Surg* 1998; **85**: 716
6   **Kale-Pradhan PB**, Elnabtity MH, Park NJ, Laus M. Enteral nutrition in patients with pancreatitis. *Pharmacotherap.* 1999; **19**: 1036-1041
7   **Sahin M**, Ozer S, Vatansev C, Akoz M, Vatansev H, Aksoy F, Dilsiz A, Yilmaz O, Karademir M, Aktan M. The impact of oral feeding on the severity of acute pancreatitis. *Am J Surg* 1999; **178**: 394-398
8   **Rao MP**, Mulleague L. Nutritional support in acute pancreatitis: the enteral vs parenteral dilemma. *Hosp Med* 2001; **62**: 580
9   **Ribeiro MD**, Paiva JA, Landeiro N, Duarte J. Patients with severe acute pancreatitis should be more often treated in an Intensive Care Department. *Rev Esp Enferm Dig* 2002; **94**: 523-532
10   **Chen QP**. Enteral nutrition and acute pancreatitis. *World J Gastroenterol* 2001; **7**: 185-192

11   **Mao EQ**, Tang YQ, Zhang SD. Effects of time interval for hemofiltration on the prognosis of severe acute pancreatitis. *World J Gastroenterol* 2003; **9**: 373-376

12   **Slavin J**, Ghaneh P, Sutton R, Hartley M, Rowlands P, Garvey C, Hughes M, Neoptolemos J. Management of necrotizing pancreatitis. *World J Gastroenterol* 2001; **7**: 476-481

13   **Abou-Assi S**, O' Keefe SJ. Nutrition support during acute pancreatitis. *Nutrition* 2002; **18**: 938-943

14   **Windsor AC**, Kanwar S, Li AG, Barnes E, Guthrie JA. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut* 1998; **42**: 431-435

15   **Ockenga J**, Borchert K, Rifai K, Manns MP, Bischoff SC. Effect of glutamine-enriched total parenteral nutrition in patients with acute pancreatitis. *Clin Nutr* 2002; **21**: 409-416

16   **Erstad BL**. Enteral nutrition support in acute pancreatitis. *Ann Pharmacother* 2000; **34**: 514-521

17   **Papapietro K**, Marin M, Diaz E, Watkins G, Berger Z, Rappoport J. Digestive refeeding in acute pancreatitis. When and how? *Rev Med Chil* 2001; **129**: 391-396

18   **Fang J**, DiSario JA. Nutritional management of acute pancreatitis. *Curr Gastroenterol Rep* 2002; **4**: 120-127

19   **Abou-Assi S**, Craig K, O' Keefe SJ. Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: results of a randomized comparative study. *Am J Gastroenterol* 2002; **97**: 2255-2262

20   **Olah A**, Pardavi G, Belagyi T, Nagy A, Issekutz A, Mohamed GE. Early nasojejunal feeding in acute pancreatitis is associated with a lower complication rate. *Nutrition* 2002; **18**: 259-262

21   **Dejong CH**, Greve JW. Nutrition in patients with acute pancreatitis. *Curr Opin Crit Care* 2001; **7**: 251-256

22   **Kotani J**, Usami M, Nomura H, Iso A, Kasahara H, Kuroda Y, Oyanagi H, Saitoh Y. Enteral nutrition prevents bacterial translocation but does not improve survival during acute pancreatitis. *Arch Surg* 1999; **134**: 287-292

23   **Qin HL**, Su ZD, Hu LG, Ding ZX, Lin QT. Effect of early intrajejunal nutrition on pancreatic pathological features and gut barrier function in dogs with acute pancreatitis. *Clin Nutr* 2002; **21**: 469-473

24   **Imrie CW**, Carter CR, McKay CJ. Enteral and parenteral nutrition in acute pancreatitis. *Best Pract Res Clin Gastroenterol* 2002; **16**: 391-397

25   **McClave SA**, Dryden GW. Issues of nutritional support for the patient with acute pancreatitis. *Semin Gastrointest Dis* 2002; **13**: 154-160

26   **Qamruddin AO**. Preventing pancreatic infection in acute pancreatitis. *J Hosp Infect* 2000; **44**: 245-253

27   **Lehocky P**, Sarr MG. Early enteral feeding in severe acute pancreatitis: can it prevent secondary pancreatic (super) infection? *Dig Surg* 2000; **17**: 571-577

28   **Foitzik T**. Pancreatitis and nutrition. Significance of the gastrointestinal tract and nutrition for septic complications. *Zentralbl Chir* 2001; **126**: 4-9

29   **Hallay J**, Kovacs G, Szatmari K, Bako A, Szentkereszty Z. Early jejunal nutrition and changes in the immunological parameters of patients with acute pancreatitis. *Hepatogastroenterology* 2001; **48**: 1488-1492

30   **De Beaux AC**, O' Riordain MG, Ross JA. Glutamine-supplemented total parenteral nutrition reduces blood mononuclear cell interleukin-8 release in severe acute pancreatitis. *Nutrition* 1998; **14**: 261-265

31   **Foitzik T**, Stufler M, Hotz HG, Klinnert J. Glutamine stabilizes intestinal permeability and reduces pancreatic infection in acute experimental pancreatitis. *J Gastrointest Surg* 1997; **1**: 40-47

32   **Yu JC**, Jiang ZM, Li DM. Glutamine: a precursor of glutathione and its effect on liver. *World J Gastroenterol* 1999; **5**: 143-146

33   **Olah A**, Belagyi T, Issekutz A, Gamal ME, Bengmark S. Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. *Br J Surg* 2002; **89**: 1103-1107

34   **Foitzik T**. Pancreatitis and nutrition. Significance of the gastrointestinal tract and nutrition for septic complications. *Zentralbl Chir* 2001; **126**: 4-9

35   **Berger Z**, Papapietro K. Long nasojejunal feeding tube: endoscopic method for placing and its use for enteral nutrition in acute pancreatitis. *Rev Med Chil* 1999; **127**: 53-58

Edited by Su Q and Wang XL