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RAPID COMMUNICATION

Comparison of early enteral nutrition in severe acute pancreatitis with prebiotic fiber supplementation versus standard enteral solution: A prospective randomized double-blind study

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Abstract

AIM: To compare the beneficial effects of early enteral nutrition (EN) with prebiotic fiber supplementation in patients with severe acute pancreatitis (AP).

METHODS: Thirty consecutive patients with severe AP, who required stoppage of oral feeding for 48 h, were randomly assigned to nasojejunal EN with or without prebiotics. APACHE Ⅱ score, Balthazar's CT score and CRP were assessed daily during the study period.

RESULTS: The median duration of hospital stay was shorter in the study group [10 ± 4 (8-14) d *vs* 15 ± 6 (7-26) d] ($P < 0.05$). The median value of days in intensive care unit was also similar in both groups [6 ± 2 (5-8) d *vs* 6 ± 2 (5-7) d]. The median duration of EN was 8 ± 4 (6-12) d *vs* 10 ± 4 (6-13) d in the study and control groups, respectively ($P > 0.05$). Deaths occurred in 6 patients (20%), 2 in the study group and 4 in the control group. The mean duration of APACHE Ⅱ normalization (APACHE Ⅱ score < 8) was shorter in the study group than in the control group (4 ± 2 d *vs* 6.5 ± 3 d, $P < 0.05$). The mean duration of CRP normalization was also shorter in the study group than in the control group (7 ± 2 d *vs* 10 ± 3 d, $P < 0.05$).

CONCLUSION: Nasojejunal EN with prebiotic fiber supplementation in severe AP improves hospital stay, duration nutrition therapy, acute phase response and overall complications compared to standard EN therapy.

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Key words: Severe acute pancreatitis; Prebiotics; Enteral nutrition; Treatment

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disorder of variable severity including multiorgan failure (MOF), and high mortality in severe cases (15%-40%). In the first phase of the disease, the initial local inflammatory process in the pancreas leads to cytokine release and subsequent systemic inflammatory response syndrome (SIRS)[1]. The standard therapeutic approach to the management of AP involves the reduction of pancreatic exocrine secretion by pancreatic rest achieved *via* stopping oral feeding. This concept has evolved since the last decade that gives nutrients beyond Treitz ligament, the post-pyloric feeding, and decreases pancreatic stimuli, thus improving the overall outcome. However, post-pyloric feeding could decrease pancreatic stimuli and improve the overall outcome[2]. Controlled trials comparing total parenteral nutrition (TPN) versus enteral (jejunal) nutrition (EN) in acute AP have revealed a significant benefit for the enteral nutrition groups in the length of hospital stay, morbidity, complications and in some studies, decreased mortality[3]. The logic behind the EN in acute AP is restoration of commensal bacterial flora, which dramatically alters early in the disease process[4,5]. The supplementation of synbiotics (combination nutritional supplements comprised of probiotics and prebiotics) to patients with severe AP has so far only been reported in one study[6]. Although there were fewer complications related to severe AP in symbiotic-supplemented group, the study has received criticism for having several methodological shortcomings[7,8]. Therefore, pre-pro or symbiotic-supplemented enteral nutrition is a challenging area in the treatment of severe AP. The multicenter Dutch study formulated PROPATRIA in order to evaluate whether administration of probiotics in a large study group is able to reduce the infective complications in

severe AP and this study is still in progress[9]. The aim of the present study was to determine the beneficial effects of prebiotic fiber-supplemented EN on the clinical course of severe AP in comparison with standard EN.

MATERIALS AND METHODS

Study design

This study was a randomized prospective double-blind controlled clinical trial which compared the effect of a special prebiotic fiber-supplemented enteral diet with that of a control standard formula in patients with severe AP. Patients were treated in the Division of Gastroenterology, Faculty of Medicine, Gazi University. The local institutional ethical board approved the study protocol and all patients gave their written informed consent before inclusion into the study. Randomization was done by computer-generated numbers and the sequence was implemented using numbered containers. Both patients and investigators were blind to the therapy.

Patients

Thirty consecutive patients with severe AP admitted to our department between September 2004 and May 2006, who required stoppage of oral feeding for 48 h, were included. Acute pancreatitis was defined as acute abdominal pain associated with elevated levels of serum amylase or serum lipase (> 5 times upper limit of normal) and ultrasound or computed tomographic evidence of acute pancreatitis[10]. Severe pancreatitis was defined as APACHE Ⅱ score > 8 or CT score > 7 or a C-reactive protein (CRP) level in excess of 150 mg/L[11-14]. Patients were excluded if (1) there was a delay between onset of symptoms and refeeding of over 30 d, (2) the patient was already on oral feeds at presentation, (3) the patient had an acute exacerbation of chronic pancreatitis, (4) if the patient needed surgery for complications of acute pancreatitis, (5) patients with paralytic ileus. APACHE Ⅱ score and CRP were assessed daily after admission in order to monitor inflammatory response during the study period. Contrast-enhanced CT of the abdomen was performed 72 h after the onset of acute pancreatitis and the severity of pancreatitis according to Balthazar's score was recorded[15].

Enteral nutrition

A nasojejunal (NJ) feeding tube (size 8F Flocare® polyurethane feeding tube, Nutricia Ltd) was inserted endoscopically under fluoroscopical guidance with its position checked by aspiration and pH measurement. Where aspiration was unsuccessful, a plain abdominal radiograph was performed. The patients started feeding after the position of the tube was rechecked with a plain abdominal radiograph 12 h after the procedure. If the tube was dislodged on the radiograph, the tube was repositioned immediately before starting feeding. Feeds were commenced at full strength and a rate of 30 mL/h increasing to 100 mL/h over 24-48 h. The caloric target was 2000 kcal/d, which was chosen over an individually calculated target in an attempt to simplify administration. The diets in the two groups were identical in caloric (125 kcal/100 mL), lipid (35%) and protein (20%) content. Study group received additional multifibers including 0.7 g/100 mL soluble fibers and 0.8 g/100 mL insoluble fibers, a total of 1.5 g/100 mL (24 g per day) multifiber supplement as a prebiotic. All patients received adjuvant peripheral parenteral nutrition with a standard solution containing 120 g/L glucose, 50 g/L aminoacid, 20% lipid (Aminomix 2®, Fresenius-Kabi, Hamburg-Germany).

Table 1 Demographic features and baseline biochemical, prognostic indices in study and control groups

	Study group (n = 15)	Control group (n = 15)	P
Mean age (SD)	47.3 (16.8)	44.9 (11.2)	NS
Sex (Male:Female)	6:9	8:7	NS
Body mass index mean (SD)	24.7 (7.8)	27.1 (9.5)	NS
Interval between onset of symptoms and admission (days) median (range)	2 (1-9)	1 (1-6)	NS
Etiology (n, %)			
Biliary	11 (73.3)	12 (80)	NS
Post-ERCP	2 (13.3)	2 (13.3)	NS
Hyperlipidemia	1 (6.6)	1 (6.6)	NS
Idiopathic	1 (6.6)	0 (0)	NS
At admission			
Serum amylase, mean (SD) IU/L	545 (232)	498 (277)	NS
Serum lipase, mean (SD) IU/L	554 (167)	396 (187)	NS
Serum CRP, mean (SD) mg/L	232 (97)	244 (104)	NS
Serum prealbumin, mean (SD) mg/L	17.6 (4.5)	19.1 (6.7)	NS
APACHE Ⅱ score, mean (SD)	9.4 (3.7)	9.6 (3.8)	NS
Balthazar CT score, mean (SD)	8.5 (4.6)	9.1 (5.2)	NS

ERCP: endoscopic retrograde cholangiopancreaticography; CRP: C-reactive protein; CT: computerized tomography; SD: standard deviation; NS: not significant.

Statistical and power analysis

Data were expressed as mean or percentage. Continuous data were compared using two-sample t test (parametric) or Mann-Whitney test (non-parametric), and comparison of categorical variables was made using chi-square test or Fischer's exact test. $P < 0.05$ was considered statistically significant. Statistical analysis was done with SPSS 8.0 software (SPSS, Inc, Chicago, Ⅲ). A power calculation revealed that 30 patients were required to show a 25% difference in CRP concentrations with a 0.05 alpha value and 80% statistical power.

RESULTS

Thirty severe AP patients were divided into two groups and the study group received additional prebiotic supplementation. The demographic features of the patients are shown in Table 1. The most common etiology was gallstones in the study and control groups (73.3% *vs* 80%) , respectively. The median age, sex distribution, mean body mass index, distribution of etiological factors, mean interval between onset of symptoms and admission to hospital, mean value of baseline serum amylase, lipase, CRP, prealbumin and APACHE Ⅱ, Balthazar CT scores were similar between the two groups (Table 1). All patients started EN within 24 h of admission. The enteral feeding was well tolerated. The median duration of hospital stay

Table 2 Clinical course of patients in the study and control groups

	Study group	Control group	*P*
Median duration of hospital stay ± (range)	10 ± 4 (8-14)	15 ± 6 (7-26)	< 0.05
Median value of days in ICU ± (range)	6 ± 2 (5-8)	6 ± 2 (5-7)	NS
Median duration of EN ± (range)	8 ± 4 (6-12)	10 ± 4 (6-13)	NS
Median duration (days) of serum amylase or lipase normalization ± (range)	7 ± 2 (6-9)	8 ± 3 (6-11)	NS
Complications			
Multiorgan failure (*n*)	1	2	
Cholangitis (*n*)	1	0	
Sepsis (*n*)	1	2	
Pseudocyst (*n*)	2	1	
Number of deaths (*n*)	2	4	
Overall complications (%)	7/15 (46.6)	9/15 (60%)	< 0.05

ICU: intensive care unit; EN: enteral nutrition; NS: not significant.

Table 3 Time (days) for normalization of CRP, APACHE Ⅱ and CT scores in the study and control groups, (mean ± SD)[1]

Items	Study group	Control group	*P*
CRP mg/L	7 ± 2	10 ± 3	< 0.05
APACHE Ⅱ score	4 ± 2	6.5 ± 3	< 0.05
CT score	12 ± 4	16 ± 3	< 0.05

[1]Normal values: APACHE Ⅱ < 8, CT score = 0-1, CRP negative. CRP: C-reactive protein; CT: computerized tomography.

was shorter in the study group [10 ± 4 (8-14) d *vs* 15 ± 6 (7-26) d] ($P < 0.05$). Seven patients in the study group and 6 patients in the control group were admitted to the Intensive Care Unit (46.6% *vs* 40%, $P > 0.05$). The median value of days in Intensive Care Unit was also similar in both groups [6 ± 2 (5-8) d *vs* 6 ± 2 (5-7) d]. All of these patients required assisted ventilatory therapy for respiratory failure. There were no complications associated with the tube insertion in both groups. In the control group, only one patient had removal of the NJ tube intentionally and the tube was re-inserted by endoscopy. In the study group, three patients had bloating and gas symptoms in the first 48 h of feeding. However, the symptoms subsided in the following days. The median duration of EN was 8 ± 4 (6-12) d *vs* 10 ± 4 (6-13) d in the study and control groups, respectively ($P > 0.05$). Deaths occurred in 6 patients (20%), 2 in the study group and 4 in the control group (Table 2).

Early diagnostic endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) was carried out in 10 patients in the study group and 11 patients in the control group. All of these patients had biliary pancreatitis. ERCP was not performed in only one patient with biliary pancreatitis for his severe cardiovascular collapse. All prognostic indices normalized earlier in the study group than in the control group (Table 3). The mean duration of CRP normalization was also shorter in the study group (7 ± 2 d *vs* 10 ± 3 d, $P < 0.05$). The mean duration of APACHE Ⅱ normalization (APACHE Ⅱ score < 8) was shorter in the study group than in the control group (4 ± 2 d *vs* 6.5 ± 3 d, $P < 0.05$). The mean duration of CT score normalization (CT score = 0 or 1) was also shorter in the study group than in the control group (12 ± 4 d *vs* 16 ± 3 d, $P < 0.05$).

DISCUSSION

A significant reduction in the commensal flora occurs early in the disease process, because of both disease and pharmaceutical treatment in severe acute pancreatitis. It has been observed in experimental pancreatitis that anaerobic bacteria and lactobacilli are significantly reduced within 6-12 h after induction both in the distal small bowel and in the colon. These alterations lead to significant overgrowth with potentially pathogenic microorganisms, such as *E coli*, and dramatic increases in mucosal barrier permeability (lumen to blood) and in endothelial permeability (blood to tissue), associated with increased pathogenic microbial colonization, translocation, microbial growth in mesenteric lymph nodes and finally pancreatic tissue[5,16,17]. Although translocation of pathogenic bacteria from gut lumen to lymph nodes is a well-documented entity, its presence and clinical significance in human beings are not clearly defined. A recent study indicated the importance of gut barrier function rather than the virulence of microorganisms, in the bacterial translocation process[18]. For this reason, we do not exactly know the underlying mechanisms of bacterial translocation-related distant infections (if it exists) in human beings. The early supplementation of synbiotics to severe AP patients has so far been reported only in one study[6], in which patients were supplemented daily with either 1 billion live or 1 billion heat-killed Lactobacillus plantarum 299 plus 10 g oat fibers during the first week. Infected pancreatic necrosis and abscesses were seen in one out of 22 patients (4.5%) supplied live Lactobacillus versus seven out of 23 (30%) of those supplied heat-killed Lactobacillus ($P = 0.023$). A much larger dose of Lactobacilli (2 × 40 billion per day) and four different fibers (20 g per day) could lead to a significant reduction ($P < 0.05$) in systemic inflammatory response syndrome and multiple organ failure, as eight out of 33 treated patients (24%) developed the syndrome compared with 14 out of 29 control patients (48%)[1]. Severe attacks of acute pancreatitis are strongly associated with the priming and subsequent over-activation of leukocytes, which contribute to the production of inflammatory mediators and the induction of distant organ failure[19]. The degree of oxidative stress and neutrophil activation are also of great importance for outcomes[20]. Severe AP patients have a documented deficit in antioxidants, flora, and the supply of fiber and nutrients, especially micronutrients which should be compensated for[1,21]. Patients in intensive care units usually have lost their entire Lactobacillus flora[22]. The colonic mucosa normally obtains most of its calories and antioxidants from the lumen and most of the absorbed nutritive substances are either produced by or released from microbial fermentation of plant fibers[23].

APACHE Ⅱ scores and serum CRP normalized earlier in the study group (4 ± 2 *vs* 6.5 ± 3 d and 7 ± 2

vs 10 ± 3 d, respectively, $P < 0.05$). These findings show that prebiotic fiber-supplemented EN improves acute phase response earlier than standard enteral solutions. The median duration of hospital stay was shorter in the study group than in the control group. This may be due to a consequence of early suppression of inflammatory response by prebiotic fiber supplementation. However, suppression of inflammation by probiotic and/or prebiotic fibers is still a speculative issue and further research is needed in order to clarify the mechanisms behind.

Although the median duration of EN was similar between groups, the rate of overall complications related to pancreatitis was higher in the control group. In contrast to probiotics, which beneficially affect the host by improving its intestinal microbial balance[24], the principle of prebiotics involves ingestion of a substance that selectively induces microbial growth and metabolic activity as opposed to direct administration of bacterial cells as dietary supplements. Thus, prebiotics encompass a wider range of products than probiotics. In addition, since probiotics produce a temporary alteration in the composition of gut microbiota, changes are not maintained upon discontinuation of supplementation[25-29]. In the present study, since we did not use probiotics in EN, this is the first randomized study comparing the beneficial effects of prebiotics without probiotics on severe AP.

One of the limitations of our study is the lack of bacterial count measurements in the stool of patients to see if there was a difference between the two groups. This might have added more information about the mechanisms behind the beneficial effects of prebiotics.

In conclusion, nasojejunal EN with prebiotic fiber supplementation in severe AP improves hospital stay, duration of nutrition therapy, acute phase response and overall complications compared to standard EN therapy.

COMMENTS

Background

The standard therapeutic approach to the management of AP involves the reduction of pancreatic exocrine secretion achieved *via* stopping oral feeding. This concept has evolved since the last decade that feeding beyond Treitz ligament decreases pancreatic stimuli. The addition of probiotics was shown to have beneficial effects. Prebiotics (non-absorbable fibers) enhances microbiota and has theoretical advantages over mucosal and systemic immunity.

Research frontiers

Recent studies indicate that lowered morbidity is related to post-pyloric feeding in severe acute pancreatitis. Few studies have mentioned the role of probiotics in this area. Prebiotics are not studied as an adjuvant therapy for acute pancreatitis.

Related publications

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16167471&query_hl=30&itool=pubmed_docsum.

Innovations and breakthroughs

Nasojejunal EN with prebiotic fiber supplementation in severe AP improves hospital stay, duration of nutrition therapy, acute phase response and overall complications compared to standard EN therapy.

Applications

Post-pyloric feeding strengthened with prebiotics improves clinical status and decreases the duration of hospital stay. The amount of prebiotics and further subgroups of prebiotics should be investigated in future clinical trials.

Terminology

Prebiotic: Food substances that intend to promote the growth of certain bacteria in the intestines. Probiotic: Dietary supplements containing potentially beneficial bacteria or yeast, with lactic acid bacteria (LAB) as the most common microbes used. LAB have been used in the food industry for many years, because they are able to convert sugars (including lactose) and other carbohydrates into lactic acid. Synbiotic: Combinant nutritional supplements comprised of probiotics and prebiotics.

Peer review

The peer reviewers represent the characteristics, values and significance of the article, thus allowing the readers to have an objective point of view toward the article.

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