Original Article

Efficacy and safety of pectin-supplemented enteral nutrition in intensive care: a randomized controlled trial

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Background and Objectives: Enteral nutrition (EN) can improve clinical outcomes as an important treatment in critically ill patients. However, when patients suffer from gastrointestinal function disorders, intestinal intolerance occurs and EN administration may be delayed and even fails to perform. Pectin, a structural heteropolysaccharide, could protect gastrointestinal function from disorders in many gastrointestianl diseases. The present study aimed to determine whether pectin-supplemented EN was safe and improved clinical outcomes in intensive care unit (ICU) patients. **Methods and Study Design:** Patients enrolled in ICU from August 2014 to January 2015 were randomized to EN group and pectin-supplemented EN group (PEC/EN group). Both group received isonitrogenous, isocaloric EN support within 36 hours after ICU admission, and last for 6 days. The primary endpoints were 30-day mortality and gastrointestinal intolerance. **Results:** There were 125 patients included in this study (63 in EN group, and 62 in PEC/EN group). The results showed that the 30-day mortality was 4.8% in EN group and 1.61% in PEC/EN group (p=0.317). PEC/EN group had a smaller gastrointestinal intolerance rate than EN group (41.3% vs 27.4%, p=0.04). Furthermore, there were shorter times to reach full EN (13.0±5.12 vs 9.99±1.91, p=0.05), length of ICU stay (17.9±9.72 vs 13.8±8.59, p<0.001), and length of hospital stay (32.9±19.0 vs 23.4±13.2, p<0.001) in EN group than those in PEC/EN group. **Conclusions:** These results revealed that pectin-supplemented EN was safe, and could improve clinical outcomes in ICU patients.

Key Words: enteral nutrition, pectin, intensive care unit, gastrointestinal function, randomized controlled trial

INTRODUCTION

Enteral nutrition (EN) can improve clinical outcomes as an important treatment in critically ill patients. However, when patients suffer from gastrointestinal function disorders, intestinal intolerance occurs and EN administration may be delayed and even fails to perform.[1] Delayed EN support is often followed by many complications in critically ill patients. It could cause colonic bacteria reflux to the ileum and jejunum, lead to ischemic necrosis or colon perforation,[2] and increase the incidence of various adverse events.[3] Therefore, methods to protect gastrointestinal function and enhance recovery after critical disease are popular pursuits in critical medicine.

Dietary fiber (DF) plays an important role in gastrointestinal function. It undergoes partial or total fermentation in the distal small bowel and colon, leading to the production of short chain fatty acids (SCFA) and gas.[4] It helps to conduct a slower and delayed gastroenterology absorption, and reduce luminal flow.[5] Previous studies have showed that DF-supplemented EN could reduce the incidence of gastrointestinal dysfunction, especially the colonic dysfunction, in non-intensive care unit studies.[6] Pectin, a representative DF, is a gelatinous substance derived from the cell walls of fruits and plants.[7] Much research has revealed that pectin could enhance gastrointestinal function, and improve clinical outcomes in many gastrointestinal diseases.[8,9]

Therefore, in the present study, we designed a prospective randomized controlled trial to determine whether pectin-supplemented EN was safe and could improve clinical outcomes in intensive care unit (ICU) patients.

METHODS

Informed consent

Investigators from two ICU of Jinling hospital, Nanjing University enrolled patients in this randomized controlled trial. The protocol and accompanying documents were approved by Nanjing University Clinical Ethics Committee. Each patient or his/her legally authorized representative provided written informed consent before randomization. The study was registered at ClinicalTrial.gov, number NNSF81270884.

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Patient population

Between August 2014 and January 2015, patients who were at least 18 years enrolled in ICU were randomly assigned to either a EN or a pectin-supplemented EN (PEC/EN) feeding using a computer generated randomization system. Patients were excluded if they: (1) could not be fed through enteral route; (2) had received EN in the past 2 months; (3) had a colectomy or jejunostomy in situ; (4) had severe colonic disease such as ulcerative colitis and crohn's disease; (5) were pregnant; and (6) belonged to a group who had a taboo on EN.

Interventions

Patients enrolled in this trial were all given a nasojejunal tube (Nutricia, the Netherlands) before EN started. The detailed nutritional support program is shown in Figure 1. Briefly, in both groups, EN administration started within 36 hours after ICU admission, and lasted for 6 days. For the EN group, 5% glucose at a rate of 25 mL/h was given on day 1, followed with initial amount of EN (31.3 g peptisorb dissolved in 250 mL water) at 12.5 mL/h on day 2. From day 3 to day 6, EN with 62.5 g peptisorb dissolved in 250 mL water was administrated at 12.5 mL/h. For the PEC/EN group, the nutritional support program was the same as EN group except that an additional amount of pectin was administrated once 4 hours ahead of EN from day 2 to day 6 (24 g every day). For both group, after day 7, EN was advanced to the goal energy target as quickly as possible, adhering to the protocol described by Rice.[10] After reaching full EN, nutrition support was continued until transition to oral feeding. Of note, for extubated patients, EN was restarted and clinical data were re-started when the reintubation was performed.[11]

Clinical outcomes

The primary outcomes were 30-day mortality and gastrointestinal intolerance. The secondary outcomes included the duration of organ support, frequency of treated infectious, noninfectious complications, gastric residual volumes, time to reach full EN, length of ICU stay, and length of hospital stay.

Statistical analysis

We did all analyses using SPSS version 17. Variables were summarized as frequencies and percentages, mean±standard deviation (SD), or median±interquartile range (IQR) as appropriate. Continuous variables were compared with a student's t test when distributed normally, or otherwise using a Mann-Whitney U test. The χ^2 test was used for comparison of categorical variables. $p<0.05$ was considered statically significance.

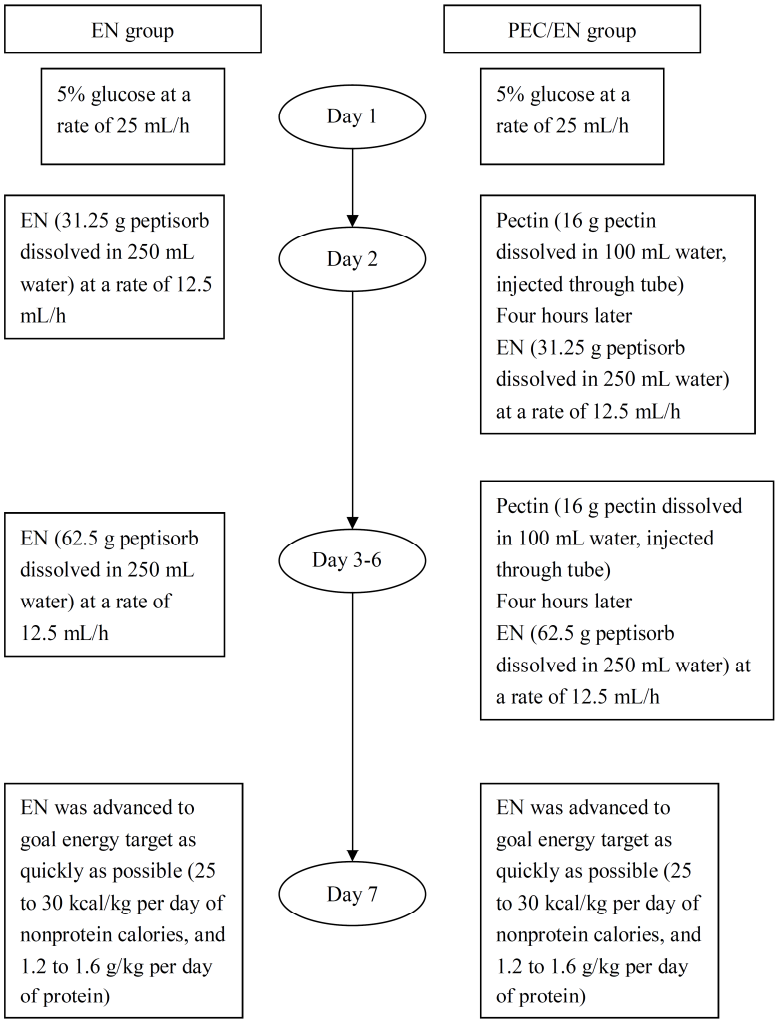

Figure 1. Nutritional support step.

RESULTS

Subjects

From August 2014 to January 2015, we screened to accrue 1,825 critically ill patients at our site (Figure 2). Of these patients, 1,659 were excluded from the study on the basis of exclusion criteria, which resulted in an intention-to-treat participant of 166 patients (87 were randomly assigned to EN group and other 79 in PEC/EN group). Eleven participants (6 EN group, 5 PEC/EN group) withdrew after randomization, but before starting nutrition support because of the burden of participation. There were also 30 participants (18 in EN group, 12 in PEC/EN group) excluded in analysis forvarious reasons. Finally, a total of 63 patients in EN group and 62 in PEC/EN group were involved in this study.

Clinical outcomes

Baseline demographics and disease characteristics were compared between two groups (Table 1). No statistically significant differences were observed between two groups. There was no difference with regard to the primary end point, death within 30 days was 4.8% in EN group and 1.61% in PEC/EN group (p=0.317); including free of specified organ support days (Table 2a). Participants in PEC/EN group had fewer infectious complications events compared with EN group, but there was no statistically significant difference (9 (14.3%) vs 7 (11.3%); p=0.13). The most common noninfectious event was gastrointestinal intolerance (26 (41.3%) vs 17 (27.4%); p=0.04). For most symptoms, there were significant differences between two groups, such as in the percentage of diarrhea (16 (25.4%) vs 7 (11.3%); p<0.001), constipation (7 (11.1%) vs 2 (3.2%); p<0.001), or regurgitation (5 (7.9%) vs 3 (4.8%); p<0.001). Patients in EN group consumed more given antidiarrheal agents (3 (4.8%) vs 1 (1.6%); p<0.001) and prokinetic agents (11 (17.4%) vs 6 (9.7%); p< 0.001) (Table 2b). Specifically, patients in PEC/EN group also spent fewer days in time to reach full EN (13.0±5.12 vs 9.99±1.91 days, p=0.05). There were also significant differences in the duration of ICU stays (17.9±9.72 vs 13.8±8.59 days, p<0.001), and length of hospital stay (32.9±19.0 days vs 23.4±13.2 days; p<0.001)

Nutritional support

Energy intake is summarized in Figure 3. Two groups shared nearly the same trend on the amount of daily energy intake. The target nutritional value of 25 kcal per kilogram per day was not achieved for the majority of patients in the two study groups. The patients in PEC/EN group took more energy everyday compared with that in EN group, also in their goal caloric percentage (p>0.05 in most days, except p=0.03 at day 11 for daily energy received, and p<0.05 at day 9 and 11 for daily percentage of caloric goal). Mean plasma glucose values were higher in EN group during the first 12 days as shown. When the both groups increased to full feeding, glucose values in pectin start group had a smaller fluctuation (p>0.05).

DISCUSSION

Critically ill patients who received pectin-supplemented

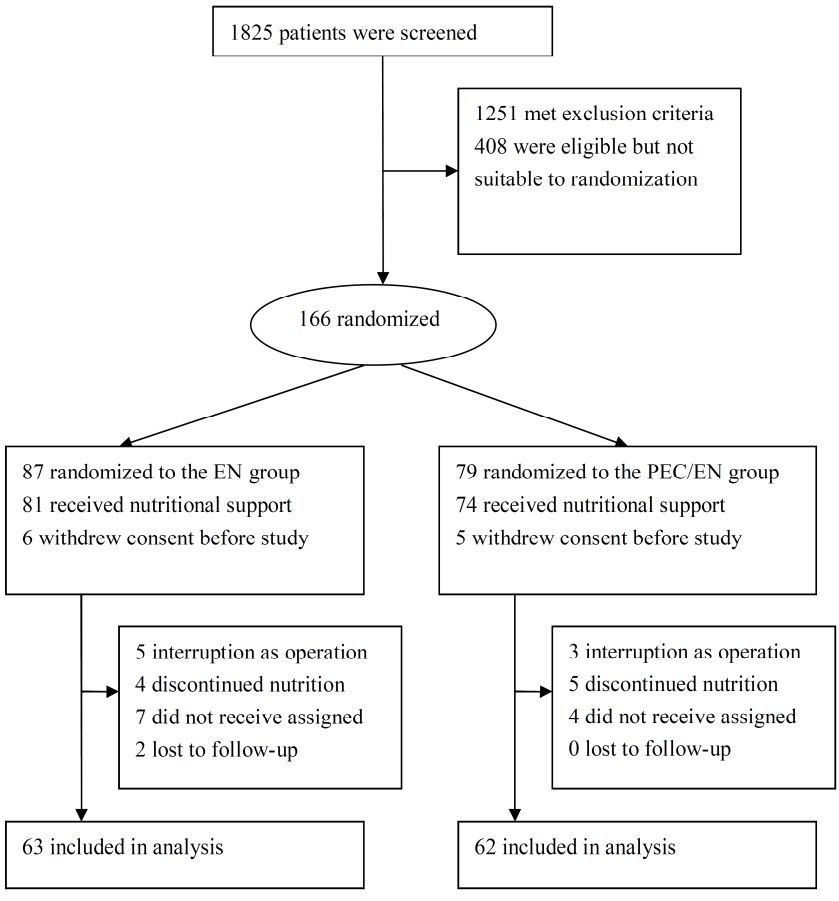

Figure 2. Trial profile

Table 1. Characteristics of subjects at baseline

	EN group (n=63)	PEC/EN group (n=62)	*p*-value
Age (years)	48.2±13.7	48.7±10.7	0.80
Men, n (%)	35 (55.6)	36 (58.1)	0.94
BMI score	22.0±2.28	22.1±1.58	0.79
APACHE II score*	12.0±2.36	12.3±2.75	0.66
Surgery <24 hours before ICU admission, n (%)	16 (25.4)	14 (22.6)	0.71
Hospitalization >7 days before ICU admission, n (%)	8 (12.7)	9 (14.5)	0.77
Mechanical ventilation, n (%)	53 (84.1)	50 (80.7)	0.92
Diabetes, n (%)	12 (19.1)	13 (21.0)	0.84
Baseline vasopressor use, n (%)	22 (34.9)	20 (32.3)	0.86
SOFA score	8.5±2.8	8.4±3.0	0.88
Albumin (g/L)	24.4±3.62	24.7±4.09	0.85
Total protein (g/L)	53.5±8.35	51.9±7.94	0.74

APACHE: acute physiology and chronic health evaluation; SOFA: scores on the sequential organ failure assessment; BMI: body mass index; ICU: intensive care unit; EN: enteral nutrition; PEC: pectin.

Table 2. Clinical outcomes of subjects

	EN group (n=63)	PEC/EN group (n=62)	*p*-value
Primary outcome, n (%)			
30-daydeath	3 (4.8)	1 (1.61)	0.317
Gastrointestinal intolerance*	26 (41.3)	17 (27.4)	0.04
Second outcomes:			
No. of days free of specified organ support (days)			
Respiratory support	19.4±2.3	21.3±1.7	0.68
Cardiovascular support	22.0±1.1	20.4±1.4	0.77
Renal support	22.6±2.0	21.6±0.9	0.84
Hepatic support	21.4±0.8	21.7±1.2	0.93
Coagulation support	24.7±1.0	23.8±1.1	0.82
Infectious complications, n (%)	9 (14.3)	7 (11.3)	0.13
Noninfectious complications, n (%)			
Episodes of hypoglycemia	13 (20.6)	5 (8.06)	<0.001
Elevated liver enzymes	7 (11.1)	5 (8.06)	0.06
Time to reach full EN (days)	13.0±5.12	9.99±1.91	0.05
Length of ICU stay (days)	17.9±9.72	13.8±8.59	<0.001
Length of hospital stay (days)	32.9±19.0	23.4±13.2	<0.001
Gastrointestinal intolerances, n (%)			
Vomiting	3 (4.8)	2 (3.2)	0.05
Diarrhea	16 (25.4)	7 (11.3)	<0.001
Abdominal distention or Cramping	5 (7.9)	4 (6.5)	0.18
Constipation	7 (11.1)	2 (3.2)	<0.001
Regurgitation	5 (7.9)	3 (4.8)	<0.001
Given antidiarrheal	3 (4.8)	1 (1.6)	<0.001
Given prokinetic agents	11 (17.4)	6 (9.7)	<0.001

ICU: intensive care unit; EN: enteral nutrition; PEC: pectin.

EN were less likely to have serious gastrointestinal intolerance, although there were no significant improvements compared with EN group in 30 days mortality. They got stable blood glucose levels and showed better adaption when EN was advanced to goal target. Our study results support pectin-supplemented EN as a new and potential non-pharmacological intervention for those patients with an unplanned ICU admission and EN could be provided through nasointestinal tube.

The concept and model of nutritional support in critically ill patients has changed for a long time. It aims to maximize clinical benefit while minimizing the potential risks for adverse events. Recently, some trials have suggested that patients who need early nutritional support may be those with depleted body stores due to malnutrition rather than all those who are at nutritional risk as a consequence of critical illness.[6] We did not believe it was feasible to receive no feeding at all, even though our usual practice indicated that many critically ill patients received no EN for many days. We chose to provide approximately 25% of estimated total caloric needs based on former studies;[8] our data also supported that a trophic amount of EN and late increase were in line with human physiological needs and may result in fewer infections, less gastrointestinal intolerance and improved mortality.[8]

EN infusion given prior to early recovery of lower gastrointestinal function can inevitably lead to bloating, nausea, vomiting and other gastrointestinal manifestations in different degrees, even serious aspiration pneumonia. Conventional EN formulations lack adequate amounts of adequate dietary fiber, only about 0-5 g/L, which is not enough to maintain a healthy gut microflora. It is currently recommended that at least 35 g of dietary fiber is needed per day. Therefore, adding a sufficient amount of die-

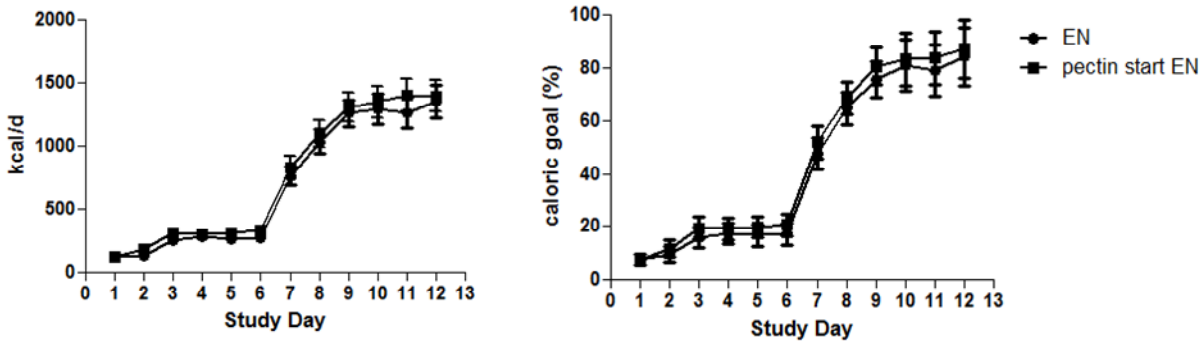

Figure 3. Mean daily energy received and mean daily percentage of caloric goal

tary fiber to recover the lower gastrointestinal function is important in critically ill patients, especially when gastrointestinal dysfunction occurred.

Pectin is a complex carbohydrate, which is found both in the cell walls of plants, and between the cell walls, helping to regulate the flow of water in between cells and keeping them rigid. Pectin is completely fermented in colon by microflora. Being a soluble diety fiber, pectin is reported to increase the transit time through gastrointestinal tract, fecal bulk, bile acid excretion and short chain fatty acid production.[12] Pectin is generally decomposed into SCFA by polysaccharase of bacteria in colon. SCFA provide colonic cells energy, promote cellular proliferation, improve blood supply of colon and ameliorate colonic motility by stimulating the autonomic nervous system. All these provide a good preparation for colon's best work and reduce associated complications. Patients in the PEC/EN group received pectin intake ahead of EN during the first 6 days. Therefore, pectin was more positive in relieving gastrointestinal dysfunction. Simultaneous use of proton pump inhibitors and antibiotics in critically ill patients would gradually lead to micro-ecological dysfunction,[13] however, pectin could reduce the destruction of colonic microflora, and balance microecological barriers in critically ill patients.[14] It is believed that the occurrence of EN-associated diarrhea is about 30%. But in PEC/EN group, we were surprised by the incidence of diarrhea and bloating. Gastrointestinal intolerances were all lower than that we expected. In addition, plasma glucose showed a steady and reduced trajectory over the course, which indicated that application of pectin may have also improved insulin resistance.

Although our trial was a small pilot, single-center study, the results are consistent with epidemiological data showing that dietary fiber in critically ill patients is associated with improved clinical outcomes.[8] This study does not address the efficacy or safety of parenteral nutrition (PN) in critically ill patients, as no PN was received in all patients during the whole study course. Some scientists strongly support the PN and they report supplementation by PN may be used when adequate EN calories cannot be provided in early stage, and occurrence of infections and other adverse events were not greatly due to different nutritional type.[8,15] Our future studies would include a larger group, and a dual-mode combined EN and PN with early pectin support would be tested in the early stage.

In summary, we believed that our results show that pectin-supplemented EN is safe, and could improve clinical outcomes in ICU patients. However, the evidence is limited by its small sample size. Future larger RCTs are needed to further assess the safety and efficacy of pectin-supplemented EN applied in ICU patients.

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AUTHOR DISCLOSURES

The authors declare that they have no competing interests. This study was supported by National Natural Science Foundation of China (81270884), Jiangsu Province Special Program of Medical science (BL2012006), Grant for 12th five-year plan major project (AWS11J03), Jiangsu Province's Key Medical Talent Program (RC2011128), and the Scientific Research Foundation of Graduate School of Nanjing University (2014CL02).

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