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Early oral refeeding based on hunger in moderate and severe acute pancreatitis: A prospective controlled, randomized clinical trial

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ABSTRACT

Objective: Early enteral nutrition is beneficial for acute pancreatitis (AP), but the optimal timing and criteria remain unclear. The aim of this study was to explore the feasibility and safety of early oral refeeding (EORF) based on hunger in patients with moderate or severe AP.
Methods: In a prospective, single-center, controlled, randomized clinical trial (ChiCTR-TRC-12002994), eligible patients with moderate or severe AP were randomized to either EORF or conventional oral refeeding (CORF). Patients in the EORF group restarted an oral diet when they felt hungry, regardless of laboratory parameters. Those in the CORF group restarted an oral diet only when clinical and laboratory symptoms had resolved. Clinical outcomes were compared between the two groups.
Results: In all, 146 eligible patients with moderate or severe AP were included and randomized to the EORF (n = 70) or CORF (n = 76) group. There were eight dropouts after randomization (three in EORF group; five in CORF group). The groups had similar baseline characteristics. The total length of hospitalization (13.7 ± 5.4 d versus 15.7 ± 6.2 d; $P = 0.0398$) and duration of fasting (8.3 ± 3.9 d versus 10.5 ± 5.1 d; $P = 0.0047$) were shorter in the EORF group than in the CORF group. There was no difference in the number of adverse events or complications between the two groups. The mean blood glucose level after oral refeeding was higher in the EORF group than in the CORF group ($P = 0.0030$).
Conclusions: This controlled, randomized clinical trial confirmed the effectiveness and feasibility of EORF based on hunger in patients with moderate or severe AP. EORF could shorten the length of hospitalization in patients with moderate or severe AP.

Introduction

Acute pancreatitis (AP) is a leading cause of hospitalization worldwide, and nutritional support is an essential part of its management. Early enteral nutrition (EN) is vital to maintain the mucosal integrity of the gastrointestinal (GI) tract, and helps prevent bacterial translocation and the infection of sterile pancreatic necrosis [1,2]. A recent meta-analysis compared the efficacy of total EN and total parenteral nutrition (TPN), and demonstrated that, in patients with predicted severe AP, total EN was associated with lower mortality, fewer infectious complications, decreased organ failure, and a lesser need for surgical intervention than TPN [3]. The international consensus guidelines on nutrition therapy for AP make a few key proposals [4]. First, nutrition support therapy is generally not required for patients with mild to moderate AP, and can be reserved for patients with severe AP. Second, EN is preferred to PN, with PN used only when EN is contraindicated or not feasible. These guidelines further highlight the importance of early nutrition support therapy in patients with severe AP [1,4].

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The decision to recommence oral feeding is commonly based on resolution of abdominal pain and normalization of laboratory findings, including pancreatic amylase and lipase [5]. However, emerging data from recent studies suggest that normalization of serum lipase level is not a necessary prerequisite for recommencing oral feeding [6,7]. In an earlier prospective randomized controlled trial (RCT), we found that early oral refeeding (EORF) based on hunger in patients with mild AP was safe and reduced the hospital length of stay (LOS) [8]. Patients recommenced oral feeding when they were hungry, without the remission of symptoms or normalization of biochemical markers. However, the effectiveness of EORF based on hunger in patients with moderate or severe AP remains unclear. Therefore, the aim of this study was to determine the feasibility and safety of EORF based on hunger in patients with moderate or severe AP by comparing EORF with conventional oral refeeding (CORF).

Materials and methods

Study design and setting

This was a single-center, prospective, RCT. The study protocol was approved by the institutional review board (Ethics and Human Research) of our institution. The registration number of the trial was ChiCTR-TRC-12002994. The study was conducted at the Department of Integrative Medicine, West China Hospital, Sichuan University. The Department of Integrative Medicine is the research center for pancreas disease in Sichuan province and is the national key construction unit on pancreas disease in China.

All eligible adult patients admitted to the Department of Integrative Medicine with AP between January 1, 2011 and December 31, 2012, were considered for inclusion in the study, and written informed consent was obtained from all participants. All authors had full access to all study data, and have reviewed and approved the final manuscript.

Inclusion and exclusion criteria

The diagnosis and severity of AP were established according to the 2012 revision of the Atlanta classification [9]. Briefly, mild AP is characterized by the absence of organ failure and the absence of local and systemic complications. Moderately severe AP is characterized by the presence of transient organ failure (<48 h) and/or local or systemic complications in the absence of persistent organ failure. Severe AP is characterized by persistent organ failure (>48 h). Organ failures were defined by the Modified Marshall Scoring System [9]. Local complications were peripancreatic fluid collections, pancreatic and peripancreatic necrosis, pseudocysts, and walled-off necrosis. Systemic complications included exacerbation of underlying heart disease, chronic diabetes, obstructive lung disease, and chronic liver disease. The inclusion criteria were acute abdominal pain accompanied by elevated serum amylase and/or lipase levels (≥3-fold above the upper reference limit) and unequivocal evidence of AP on ultrasound and computed tomography. The exclusion criteria were:

1. Age <18 y or >70 y;
2. Abdominal pain lasting >72 h before admission;
3. Mild AP;
4. Pregnant or breastfeeding;
5. Pancreatic neoplasm, endoscopic retrograde cholangiopancreatography, or trauma etiology;
6. The possibility of poor oral intake or prolonged hospitalization for reasons other than pancreatitis, such as gastroparesis or surgical intervention;
7. Admission to the intensive care unit for intubation; and
8. Surgical intervention for infected pancreatic necrosis or pancreatic hemorrhage.

Although some patients with chronic pancreatitis had multiple flare-ups during the study period, each patient only participated once during the study period, and the patients involved in the study had no complications during last episode that could affect oral refeeding in the present study. An adverse event was defined as abdominal pain and distention relapse or other evidence of AP.

Study protocol

Eligible patients were consecutively enrolled and randomized to one of the two groups. Randomization was based on a computer-generated randomization list generated by an independent statistician who was not involved in the rest of the study, and took place in a consultation before the initiation of oral-feeding preparation on the same day that patients agreed to participate in the study. Only the investigators were blinded to the refeeding regimen. The clinician was not blinded to the regimen because of obvious trial indexes. All patients received conservative treatment according to their individual conditions, including limited PN if they were in malnutrition and EN was contraindicated or not feasible, prophylactic antibiotics if they were at risk for infection, glucose control (insulin or acarbose oral) if they were at risk for hyperglycemia, treatment to maintain the homeostasis, appropriate fluid resuscitation therapy, and Traditional Chinese Medicine (TCM) formulation. TCM, such as Da-Cheng-Qi decoction, is widely used for the treatment of AP in China and has been used for several decades [10,11]. The severity of AP and nutritional status were assessed on admission and at frequent intervals thereafter. PN was given after adequate fluid resuscitation and when the patient had achieved full hemodynamic stabilization (usually 48–72 h after admission). Adequate protein delivery (1.2–2.0 g/kg daily) and calories (15–30 kcal/kg daily) were given to patients according to their individual condition [1,12]. The volume of PN was gradually reduced after oral refeeding (usually 12–24 h after the first oral intake). The decision for administering these treatments was made by a multidisciplinary team.

Patients in the EORF group recommenced oral feeding once they felt hungry regardless of laboratory parameters. Patients in the CORF group recommenced oral refeeding once their abdominal pain resolved and biochemical markers had normalized. The diet was gradually progressed from clear liquid to a low-fat solid diet that comprised foods such as porridge and vegetables in the early stage, then steamed bread and rice, and finally an ordinary diet. Hospital discharge was planned on the basis of the resolution of clinical symptoms and the patient's tolerance of a solid diet for at least 24 h. All patients were monitored daily for vital signs, fluid intake, urinary output, food intake, and GI symptoms. Serum lipase, amylase, albumin, and blood glucose levels and leukocyte count were determined before and after the initiation of oral refeeding or at the time of suspected disease recurrence. The investigators were blinded to the refeeding regimen.

Outcome measures

The primary outcome measure was hospital LOS. The secondary outcome measures were the duration of fasting (determined from the onset of abdominal pain) and the subjective tolerance to food, including the relapse rate and the degree of transitional abdominal distension and/or abdominal pain after the first ingestion of orally consumed food, which were evaluated by an independent assessor who did not know the group assignment. Laboratory findings and complications were also measured.

Statistical methods

All data entry, data management, and analyses were performed at the Department of Integrative Medicine, West China Hospital, Sichuan University. All outcomes were analyzed with the Package for Encyclopaedia Medical Statistics 3.1 for Windows medical statistics software, which was provided by the Department of Health Statistics, West China School of Public Health, Sichuan University. Continuous variables were expressed as mean ± SD if they were normally distributed, and median and interquartile range if they were non-normally distributed. Categorical variables are expressed as frequency count. We used t test or χ^2 test in our study. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

We screened 1052 potential candidates with AP for inclusion in the study, and 146 eligible patients with moderate or severe AP were included in the randomization (Fig. 1). The main reason for exclusion was mild AP (n = 654, 62.2%; Fig. 1). Eight patients dropped out after randomization (three in the EORF group and five in the CORF group) due to refusal to follow the prescribed oral refeeding protocol. In all, 138 patients (13%) were available for final analysis: 67 in the EORF group and 71 in the CORF group (Fig. 1). The two groups were comparable in terms of sex, age, disease etiology, disease severity, and duration of abdominal pain before hospital admission (Table 1). White blood cell count, hematocrit, and serum amylase on admission also were similar in the two groups (Table 1). All patients received similar