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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

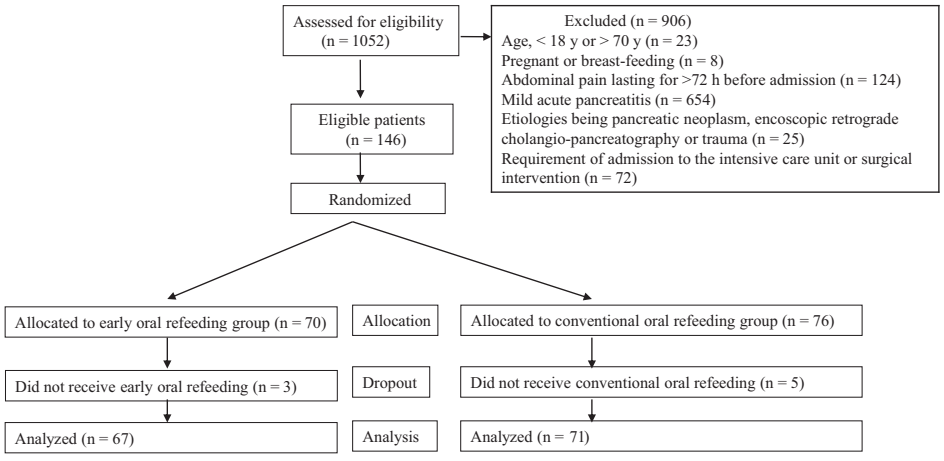

Fig. 1. Participant screening, enrollment, randomization, and result.

treatment, including PN, antibiotics, gabexate mesylate, somatostatin, and TCM (Table 2).

Outcome measures before and after oral refeeding

On the day of oral refeeding, mean serum amylase and lipase levels had not normalized in the EORF group, and all biochemical markers except serum triglyceride and cholesterol levels and hematocrit value were significantly higher in the EORF group than in the CORF group (Table 3). At the final measurement before discharge, there was no statistically significant difference between the two groups in any major biochemical parameter other than mean blood glucose level, which was higher in the EORF group than in the CORF group (Table 4).

Total LOS was significantly shorter in the EORF group than in the CORF group (13.7 ± 5.4 d versus 15.7 ± 6.2 d; $P = 0.0398$), and the duration of fasting after the onset of abdominal pain was shorter (8.3 ± 3.9 d versus 10.5 ± 5.1 d; $P = 0.0047$). However, there was no difference in LOS after reinitiating oral feeding between the two groups (5.4 ± 2.4 d in the EORF group versus 5.3 ± 2.9 d in the CORF group; $P = 0.7404$). There were no differences between the two groups in terms of abdominal pain relapse, abdominal distension, organ failure, and occurrence of local or systemic complications before discharge from hospital (Tables 5 and 6).

Table 1
Baseline patient characteristics*

	EORF (n = 67)	CORF (n = 71)	*P*-value
Female	24 (35.8)	28 (39.4)	0.9177
Age (y)	51 (24–72)	48 (21–74)	
Etiology			
Biliary	13 (19.4)	16 (22.5)	0.6517
Alcoholic	12 (17.9)	14 (19.7)	0.7861
Hyperlipidemia	33 (49.3)	29 (40.9)	0.3210
Miscellaneous	9 (13.4)	12 (16.9)	0.5707
WBC count ($\times 10^9$/L)	12.87 ± 5.94	12.99 ± 3.56	0.8850
Hematocrit	0.39 ± 0.44	0.40 ± 0.55	0.9066
Serum amylase (IU/L)	1523 ± 584	1357 ± 689	0.1302
Serum lipase (IU/L)	1024 ± 315	945 ± 358	0.1720
Ranson score	3.4 ± 1.8	3.9 ± 1.1	0.0966
CT severity index	4.7 ± 1.8	5.1 ± 1.8	0.1652
Severity			
Moderate	45 (67.2)	56 (78.9)	0.1207
Severe	22 (32.8)	15 (21.1)	0.1207
First onset of acute pancreatitis	59 (88.1)	64 (90.1)	0.6946
Duration of APPTA, days	1.7 ± 1.3	1.5 ± 1.2	0.3490

APPTA, abdominal pain before admission; CORF, conventional oral refeeding; CT, computed tomography; EORF, early oral refeeding; WBC, white blood cell
* Data are n (%), median (range), or mean ± SD.

Discussion

Moderate and severe AP often causes complications and/or organ failure, leading to high-catabolic, hypermetabolic, and hyper-dynamic stress with high morbidity and mortality. Over the past decade, nutritional support has become a key element in the treatment of moderate and severe AP. Specialized nutrition is indicated from admission, with EN preferred over PN [1,13]. However, there is insufficient information on the optimal criteria for oral refeeding in AP patients. The usual criteria for reinitiating oral feeding are the absence of abdominal pain, nausea and vomiting, and the restoration of appetite and normalization of laboratory findings including serum amylase and lipase levels.

In the present study, we investigated an alternative approach to reinitiating feeding that was based on hunger, without the remission of abdominal pain or normalization of pancreatic amylase and lipase. Our results demonstrated that EORF based on this approach decreased the duration of both fasting and hospitalization. These benefits are clearly in accord with the European Society for Clinical Nutrition and Metabolism guidelines, which state that "oral food intake should be tried as soon as possible" [1].

Data to support EORF without normalization of serum parameters are increasingly convincing. The results of an open randomized multicenter trial suggested that normalization of

Table 2
Therapeutic data*

	EORF (n = 67)	CORF (n = 71)	*P*-value
Parenteral nutrition	65 (97)	69 (97.2)	0.6536
Antibiotics	66 (98.5)	71 (100)	0.9768
Gabexate mesylate	17 (25.4)	29 (40.8)	0.0540
Somatostatin analogs	16 (23.9)	26 (36.6)	0.1041
Narcotic drug	29 (43.3)	30 (42.3)	0.9027
TCM oral intake	62 (92.5)	68 (95.8)	0.6535
TCM enema	57 (85.1)	66 (93)	0.1370

EORF, early oral refeeding; CORF, conventional oral refeeding; TCM, Traditional Chinese Medicine
* Data are n (%).

Table 3
Laboratory parameters before oral refeeding*

	EORF (n = 67)	CORF (n = 71)	*P*-value
Serum amylase (IU/L)	512 ± 558	304 ± 402	0.0128†
Serum lipase (IU/L)	596 ± 615	367 ± 518	0.0192†
WBC count ($\times 10^9$/L)	15.2 ± 6.8	12.1 ± 5.2	0.0030†
Hematocrit	0.36 ± 0.05	0.37 ± 0.05	0.2424
Blood glucose (mmol/L)	9.3 ± 3.5	8.1 ± 3.4	0.0462†
Serum triglyceride (mmol/L)	2.7 ± 2.3	3.6 ± 5.5	0.2036
Serum cholesterol (mmol/L)	4.0 ± 2.1	4.2 ± 2.5	0.5574

EORF, early oral refeeding; CORF, conventional oral refeeding; WBC, white blood cell

* Data are mean ± SD.

† Significance of the differences between EORF and CORF.

serum lipase levels is not obligatory before reinitiating EN in patients with mild AP [6], and an RCT showed that nasogastric tube feeding commenced within 24 h of hospital admission was well tolerated in patients with mild to moderate AP [14]. Furthermore, it has been reported that immediate oral refeeding is feasible and may accelerate recovery without adverse GI events, at least in patients with mild AP [15]. Our previous study also showed that EORF based on subjective feelings of hunger rather than CORF guidance was a safe approach in the treatment of patients with mild AP [8].

There is also evidence that EORF may be beneficial for patients with in severe AP. A multicenter RCT showed that immediate oral feeding (<24 h) in patients with mild AP was feasible and significantly shortened the LOS compared with traditional fasting (4 versus 6 d; $P < 0.05$) [16]. In this study, we used a moderated reinitiation protocol based on hunger in patients with moderate and severe AP. Our results showed that this EORF protocol based on hunger was safe and effective, and decreased the duration of fasting and the total LOS by approximately 2 d. This may suggest that subjective feelings of hunger reflected recovery of GI dysfunction and indicated that patients were ready for a trial of food. Clinical data strongly support the concept that early EN can decrease complications, LOS, and mortality in patients with AP [14,17,18]. Therefore, EORF based on hunger may be appropriate for the management of AP, and hunger may be a useful indicator for reinitiation of oral intake.

Compared with CORF, EORF had no major adverse effects on most biochemical parameters, with the exception of blood glucose levels. After the initiation of oral feeding, mean blood glucose levels and the percentage of patients with hyperglycemia were higher in the EORF group than in the CORF group, suggesting that EORF may have been harmful to glucose control in patients with severe AP. This finding contradicted our previous study on patients with mild AP, where EORF was beneficial for blood glucose control [19]. Hyperglycemia is a common metabolic complication of AP, particularly severe AP. One recent systematic review showed that patients with AP often develop prediabetes and/or diabetes mellitus after discharge from hospital, and have a greater than twofold increased risk for diabetes mellitus over 5 y [20]. Although it has been proposed that excessive nutrition in EORF can cause excessive glucose intake and lead to hyperglycemia, this view is somewhat rebutted by recent systematic reviews [21,22]. For example, when compared with both late EN and PN, early EN was associated with improved blood glucose control and a significantly decreased incidence of hyperglycemia in patients with AP [19,20]. Some evidence suggests that in human pancreatitis the injured pancreas may be less responsive to stimulation by food [23,24]. Therefore, the seriously injured pancreas in severe AP may respond poorly to EORF, more readily resulting in hyperglycemia compared with mild AP. This may explain the different influence of EORF on blood glucose levels in severe and mild AP. Although early resumption of enteral feeding may result in higher glucose levels, stricter glucose-control protocols can be used to manage this risk. Further research is required to clarify this issue.

A major concern of EROF in AP is premature oral refeeding with intolerance to the reintroduced diet, which can cause AP relapse and prolonged hospital LOS. A meta-analysis and two prospective studies reported that intolerance to refeeding occurred in 21% to 25% of patients with AP [25–27]. Our study showed that there were no differences between EORF and CORF in terms of abdominal pain relapse, abdominal distension, organ failure, and local pancreatic complications, suggesting that the EORF based on hunger is feasible in patients with moderate or severe AP. These findings are consistent with a previous meta-analysis [22], which demonstrated that in comparison with

Table 4
Laboratory parameters before discharge*

	EORF (n = 67)	CORF (n = 71)	*P*-value
Mean WBC count ($\times 10^9$/L)	10.7 ± 4.9	8.8 ± 6.5	0.0632
Hematocrit	0.35 ± 0.04	0.35 ± 0.05	1.0000
Blood glucose (mmol/L)	7.8 ± 3.4	6.3 ± 2.2	0.0030†
Serum triglyceride (mmol/L)	3.7 ± 2.3	3.1 ± 3.4	0.2242
Serum cholesterol (mmol/L)	4.4 ± 7.6	43.7 ± 1.1	0.4623

EORF, early oral refeeding; CORF, conventional oral refeeding; WBC, white blood cell

* Data are mean ± SD.

† Significance of the differences between EORF and CORF.

Table 5
Clinical parameters before discharge*

	EORF (n = 67)	CORF (n = 71)	*P*-value
Biochemical parameters			
Serum amylase > ULOR	9 (13.4)	14 (19.7)	0.3221
Serum lipase > ULOR	32 (47.8)	23 (32.4)	0.0654
Blood glucose > ULOR	12 (17.9)	3 (4.2)	0.0098†
Serum triacylglycerol > ULOR	14 (21.0)	17 (24.0)	0.6681
Serum cholesterol > ULOR	0	1	0.9768
Clinical events			
Abdominal pain relapse	7 (10.5)	10 (14.1)	0.5159
Abdominal distention	8 (12.0)	8 (11.3)	0.9018
APTOR (d)	8.3 ± 3.9	10.5 ± 5.1	0.0047†
DHAOR (d)	5.4 ± 2.4	5.3 ± 2.9	0.7404
LOS (d)	13.7 ± 5.4	15.7 ± 6.2	0.0398†

APTOR, abdominal pain to oral refeeding; CORF, conventional oral refeeding; DHAOR, duration of hospitalization after oral refeeding; EORF, early oral refeeding; LOS, length of stay; ULOR, upper limit of reference

* Data are n (%) or mean ± SD.

† Significance of the differences between EORF and CORF.

Table 6
Complications*

	EORF (n = 67)	CORF (n = 71)	*P*-value
Persistent organ failure	22 (32.8)	15 (21.1)	0.1207
Transient organ failure	8 (11.9)	6 (8.5)	0.4974
Pancreatic necrosis	16 (23.9)	26 (36.6)	0.1041
Pancreatic fluid collection	37 (55.2)	49 (69.0)	0.0948
Pancreatic pseudocyst	11 (16.4)	10 (14.1)	0.7029
Pancreatic infectious	3 (4.5)	5 (7.0)	0.7795
Pleural effusion	20 (29.9)	27 (38.0)	0.3110
Gastrointestinal bleeding	2 (23.0)	1 (1.41)	0.9595
Pancreatic portal hypertension	3 (4.5)	2 (2.8)	0.9473

CORF, conventional oral refeeding; EORF, early oral refeeding

* Data are n (%).

late EN or TPN, EN within 48 h of admission improved the clinical outcomes of AP by decreasing complications such as infection and organ failure. It is possible that the recurrence of abdominal pain during the reinitiation of an oral diet is related to ingestion of a larger volume of food rather than the renewed release of enzymes [28]. In a typical oral-refeeding protocol, the diet is reintroduced gradually, starting with small amounts of clear liquids for the first 24 h. If tolerated, the diet is gradually changed to a soft, low-fat regimen followed by a solid diet.

Several limitations to our work should be recognized. First, the estimated daily energy intake may not have been accurate in every patient because the energy in porridge and vegetables is difficult to calculate accurately. However, apart from the time at which refeeding was initiated, the refeeding protocol and the PN protocol were similar in both groups. Second, this study was conducted in a single center. Although this center sees a large volume of patients with AP (>1000 patients/y), caution should be taken when generalizing our results.

Conclusions

In patients with moderate or severe AP, EORF based on hunger was safe and superior to CORF. EORF was associated with shorter hospital LOS and did not increase clinical complications. We believe that EORF based on hunger should be considered as a valid option in the management of AP. Although it may increase the risk for hyperglycemia, this could be attenuated by a strict glucose-control protocol. Further studies in multiple centers are necessary to confirm the reliability and generalizability of our findings.

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