Gut and Liver
https://doi.org/10.5009/gnl250110
pISSN 1976-2283 eISSN 2005-1212

Original Article

Early Oral Refeeding in Patients with Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Randomized Controlled Trial

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Article Info
Received March 6, 2025
Revised June 11, 2025
Accepted July 2, 2025
Published online August 25, 2025

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Background/Aims: To assess the safety and efficacy of early oral refeeding (ERF) versus delayed refeeding (DRF) in patients with mild post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP).

Methods: Eligible patients were randomly assigned in a 1:1 ratio to the ERF or DRF group. Eligible patients were randomly assigned in a 1:1 ratio to the ERF or DRF group. In the ERF group, feeding began 24 hours after the diagnosis of PEP; in the DRF group, feeding commenced once normal bowel sounds returned and pain had decreased to a visual analog scale score of <2. The diet was advanced from clear fluids to soft foods according to patient tolerance. Refeeding was temporarily halted if the visual analog scale score reached ≥5 points or if intake was refused due to pain. Resumption required normal amylase/lipase levels, pain relief, and bowel movement restoration. Discharge criteria included patient well-being >24 hours post-diet. The primary outcome was PEP hospitalization duration, and secondary outcomes were the incidence of severe acute pancreatitis, readmission rate (<30 days), and PEP-related mortality rate.

Results: A total of 80 patients (40 in each ERF and DRF group) were enrolled across nine referral centers. Baseline characteristics, procedural parameters and initial PEP severity were not significantly different between the two groups. Four ERF and three DRF patients had refeeding interruptions. ERF significantly reduced PEP hospitalization duration compared to DRF (2.93±1.59 days vs 3.78±1.97 days: relative risk, 0.75; 95% confidence interval, 0.59 to 0.97; p=0.026). Rates of severe acute pancreatitis, readmission, and mortality/morbidity related to PEP were similar between the two groups.

Conclusions: ERF effectively shortens hospitalization in mild PEP patients without increasing safety risks (ClinicalTrials.gov identifier NCT04750044). **(Gut Liver, 2025;19:900-908)**

Key Words: Endoscopic retrograde cholangiopancreatography; Pancreatitis; Feeding method

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a widely used technique for diagnosing and treating bile duct diseases.[1] Post-ERCP pancreatitis (PEP), which affects 5% to 10% of patients undergoing ERCP,[2] presents clinical challenges with potential morbidity and prolonged hospitalization.[3] Among the strategies aimed at improving post-ERCP patient outcomes, the optimal timing and type of refeeding after pancreatitis onset remain undetermined.

While fasting in patients with PEP rests the pancreas and reduces pancreatic stimulation,[4] recent studies suggested that early oral refeeding (ERF) for acute pancreatitis (AP) may lead to faster recovery, reduced hospital stay, and improved overall patient well-being.[5-8] These results challenge the conventional practice of prolonged fasting and support more proactive approach that minimizes the adverse effects of fasting while ensuring patient safety. Despite these potential benefits, data in patients with PEP remain limited due to the scarcity of randomized controlled trials in this specific population.[5,9]

Therefore, we investigated the safety and efficacy of ERF compared with that of delayed refeeding (DRF) in patients with mild PEP. This trial aimed to improve patient outcomes and reduce PEP burden by providing evidence-based insights to guide clinical decision-making and optimize patient management.

MATERIALS AND METHODS

1. Study design

This randomized, prospective, controlled, open-label, multicenter clinical trial was performed at nine Korean hospitals. The clinical trial was registered at ClinicalTrials.gov (NCT04750044) on February 11, 2021, and conducted from February 2021 to September 2022. The first patient was enrolled on February 18, 2021. The study was conducted in accordance with the principles of the International Conference on Harmonization of Good Clinical Practice and reviewed by the institutional review boards of all participating institutions (No. 4-2020-1237). All participants provided written informed consent prior to randomization.

Adult patients aged 20 to 80 years who developed PEP and met the following inclusion criteria simultaneously to define PEP were included: serum amylase or lipase levels three times higher than the upper normal range at 4 hours after ERCP or the following morning and new or worsening abdominal pain compatible with pancreatitis, arising 4 hours after ERCP or the following morning. In general, computed tomography is not commonly performed to diagnose mild PEP, which is why it was not featured in the inclusion criteria. The exclusion criteria included: incomplete intended procedure; occurrence or suspicion of complications; suspicion of severe AP with multi-organ failure (based on the Atlanta criteria);[10] need for additional imaging tests and endoscopy for diagnosis of underlying disease or treatment of complications; cases wherein fasting was necessary, regardless of this study; history of chronic pancreatitis; and pregnancy or lactation. Patients who developed signs of persistent organ failure or systemic/local complications were excluded from the final analysis to ensure the inclusion of only clinically mild PEP cases.

Clinical symptoms, signs, laboratory findings, and serum amylase and lipase levels were measured in all patients at baseline (before ERCP), 4 hours after ERCP, and on the following morning. PEP onset was defined as the time when both clinical and laboratory diagnostic criteria (abdominal pain and amylase/lipase ≥3× ULN) were first met. Patients were randomly assigned in a 1:1 ratio to either the ERF or DRF group. Randomization was performed using a table of computer-generated random numbers prepared by a biomedical statistician who was not involved in ERCP. The allocation was concealed in a sealed opaque envelope and provided to the endoscopist at the time of PEP diagnosis.

2. Dietary protocols

In the ERF group, an oral diet was initiated 24 hours after PEP diagnosis, whereas in the DRF group, it was initiated after the restoration of normal bowel sounds and a reduction in abdominal pain to a visual analog scale score of <2. The oral diet was started with sips of water and built sequentially to clear liquid to soft diet, considering the patient's tolerability. Oral refeeding was interrupted if patient's pain increased to ≥5 points or the patient refused a diet owing to abdominal pain or other reasons. After a refeeding interruption, the diet was resumed once the amylase or lipase level had fallen below the upper limit of normal, abdominal pain had resolved, and bowel movements had returned. The patient met the discharge criteria if they continued to feel well for >24 hours post-diet buildup completion. Patients were excluded from the DRF group if symptoms persisted for >96 hours, requiring continued fasting, parenteral nutrition, or withdrawal from the trial at the researchers' discretion.

3. ERCP procedures and PEP management

All ERCP procedures were performed by an expert endoscopist who had performed >500 ERCP procedures. As a precautionary measure against PEP, 20 mg nafamostat

mesilate was dissolved in 500 mL of 5% DW and infused 24 hours after ERCP. No other pharmacological agents were permitted for PEP prophylaxis. Post-procedure, the endoscopist recorded the total procedure time (defined as the time interval from endoscope insertion to endoscope withdrawal), difficult cannulation (>5 cannulation attempts), pancreatic duct (PD) cannulation or stenting, and interventions such as endoscopic sphincterotomy, endoscopic pneumatic balloon dilatation, or stent placement, if performed. After PEP diagnosis, patients fasted and were provided sufficient crystalloid fluid (Hartmann's solution) according to the AP treatment guidelines.[4] If needed, total parenteral nutrition or nutritional supplementation was administered. Serum amylase and lipase levels were measured during hospitalization.

4. Outcome measurements and definitions

Study outcome analyses were based on the intention-to-treat population, defined as patients who received randomization after a PEP diagnosis, regardless of the completion of the diet protocol. The primary outcome was the hospitalization period for PEP. PEP was considered improved and patients were discharged if they remained well for >24 hours after initiating a soft diet (abdominal pain improvement and a decrease in amylase or lipase levels to less than twice the upper limit of normal). "Hospitalization period for PEP" was the period from the time-point of PEP diagnosis to satisfaction of discharge criteria. Secondary outcomes were mortality rates related to PEP during hospitalization, incidence of severe AP and necrotizing pancreatitis up to 30 days after ERCP, and readmission rate within 30 days after discharge.

5. Sample size calculation and randomization

Our main objective was to assess the superiority of ERF over DRF. The sample size was based on the estimated differences in hospital days of patients with PEP with ERF and DRF of 8.4±1.8 and 10.2±2.0 days, respectively, as previously reported.[11] Overall, 62 patients (31 per group) were needed to show the superiority of ERF, achieving a power of 95% with a two-sided alpha level of 0.05 and an allocation ratio of 1:1. Considering a possible dropout rate of 20%, 80 patients (40 per group) were included in the estimated sample size.

Patients were randomly assigned in a 1:1 ratio to the early or delayed feeding groups according to a randomization list (with a predefined block size of 4) generated by an independent statistician.[12,13] A blocked randomization method was applied to ensure a balanced intergroup assignment. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used to create random numbers and develop a random allocation list. A random allocation sequence was generated by a medical statistician at the Department of Biomedical Systems Informatics of the Yonsei University College of Medicine. Patient allocation was performed by nurses who were not involved in other aspects of the study.

6. Statistical analysis

A random-effects regression model was used to account for the heterogeneity of multicenter data. For the primary outcome, hospital stay was analyzed using a mixed-effects Poisson regression.[13] For the secondary outcomes, linear regression was used for continuous outcomes and logistic regression for binary outcomes. For baseline characteristic comparisons, continuous and categorical variables are presented as means with standard deviations and frequencies with proportions, respectively. Categorical variables were analyzed using the chi-square or Fisher's exact test, and continuous variables were analyzed using the Student's t-test or the Mann–Whitney U test. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at $p<0.05$.

RESULTS

1. Study population and baseline characteristics

From February 2021 to September 2022, 80 patients diagnosed with PEP were enrolled in nine referral centers and randomized to the ERF (n=40; males: 18 [45%]; mean age: 65.9±16.7 years) and DRF (n=40; males: 20 [50%]; mean age: 67.1±16.2 years) groups (Fig. 1). In the ERF group, 36 patients completed the diet without interruption, while refeeding was interrupted in four patients due to abdominal pain (n=2), nausea/vomiting (n=1), and melena (n=1). In the DRF group, 37 patients completed the diet without interruption, with refeeding interrupted in three patients due to abdominal pain (n=2) and post-endoscopic sphincterotomy bleeding (n=1). Table 1 summarizes the baseline characteristics of the enrolled patients. There were no significant intergroup differences in the baseline characteristics. Pre-ERCP laboratory findings did not differ between the groups.

2. Procedure-related findings

Procedure-related findings are presented in Table 2. There were no significant differences between the groups with regard to procedural parameters. The total procedure time, total cannulation attempts, and rate of difficult cannulation did not differ between the groups ($p>0.05$). The most common cannulation procedure used a standard

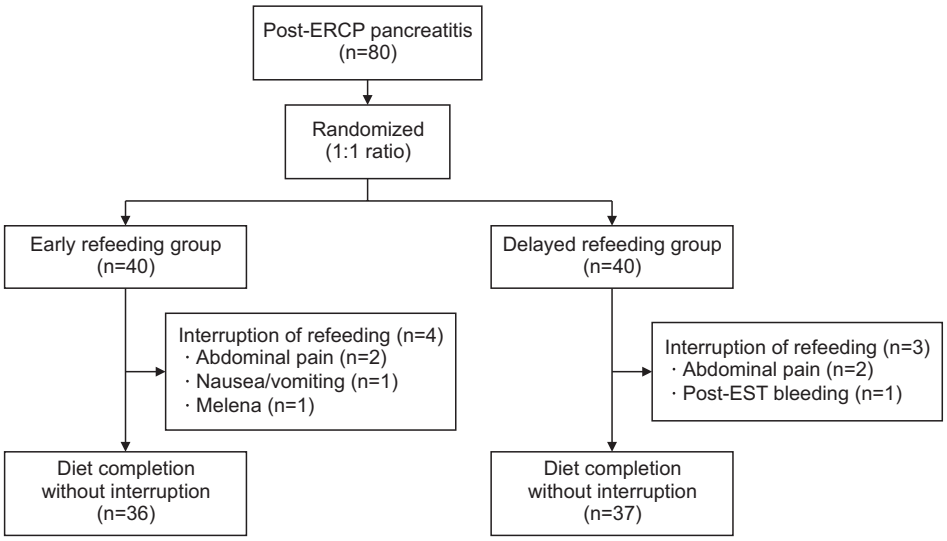


Fig. 1. Study flowchart. Eighty patients with post-ERCP pancreatitis were enrolled in the study. Patients were randomly assigned in a 1:1 ratio to the early or delayed refeeding groups. ERCP, endoscopic retrograde cholangiopancreatography; EST, endoscopic sphincterotomy.

Table 1. Baseline Characteristics

Characteristic	Early refeeding group (n=40)	Delayed refeeding group (n=40)	p-value
Age, yr	65.9±16.7	67.1±16.2	0.743
Sex			
Female	22 (55)	20 (50)	0.654
Male	18 (45)	20 (50)	
BMI, kg/m^2	23.4±3.6	22.2±4.9	0.194
Smoking history	4 (10)	6 (15)	0.499
Alcohol history	4 (10)	6 (15)	0.499
Pancreatitis history	3 (8)	1 (3)	0.615
Comorbidities			0.321
None	25 (63)	24 (60)	
Cardiovascular	14 (35)	10 (25)	
Cerebrovascular	0	2 (5)	
Renal	1 (3)	3 (8)	
Hepatic cirrhosis	0	1 (3)	
ERCP indication			0.370
CBD stone	23 (58)	30 (75)	
Biliary stricture	8 (20)	6 (15)	
Pancreatic mass	2 (5)	1 (3)	
Others	7 (18)	3 (8)	
Laboratory findings			
Hemoglobin, g/L	12.3±1.7	12.3±1.7	0.902
Hematocrit, g/dL	36.5±5.1	36.4±5.3	0.957
Platelet, 10^3/μL	233±83	213±69	0.255
AST, U/L	120±177	108±125	0.733
ALT, U/L	120±157	154±245	0.461
Total bilirubin, mg/dL	3.07±4.93	2.99±4.03	0.936

Data are presented as mean±SD or number (%).
BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

catheter, followed by pull-type sphincterotomy, precutting, the double-guidewire technique, PD septotomy, and infundibulotomy. No statistical difference was found between the groups (p=0.343). Endoscopic sphincterotomy was performed in 31 (78%) and 32 (80%) patients, and endoscopic pneumatic balloon dilatation was performed in five (13%) and 10 (25%) patients in the ERF and DRF groups, respectively, with no significant difference (p>0.05). There was no significant difference in the rate of biliary stent insertion or type of stent used between the groups

Table 2. Procedural Parameters

Variable	Early refeeding group (n=40)	Delayed refeeding group (n=40)	p-value
Total procedure time, min	23±9	23±14	0.798
Total cannulation attempts	3.5±2.5	4.0±5.0	0.521
Difficult cannulation*	14 (35)	13 (33)	0.813
Cannulation method			0.343
Standard catheter	13 (33)	18 (45)	
Pull-type sphincterotome	13 (33)	11 (28)	
Precutting	7 (18)	5 (13)	
Infundibulotomy	0	2 (5)	
Double-guidewire technique	6 (15)	2 (5)	
PD septotomy	1 (3)	2 (5)	
EST	31 (78)	32 (80)	0.785
EPBD	5 (13)	10 (25)	0.152
Biliary stent	16 (40)	15 (37)	0.708
Plastic	14 (35)	13 (33)	
Metal, uncovered	1 (3)	0	
Metal, covered	1 (3)	2 (5)	
Unintended PD cannulation	16 (40)	14 (35)	0.644
Unintended PD cannulation times	0.6±1.0	1.0±1.0	0.778
PD dye injection	9 (23)	7 (18)	0.576
PD stent	14 (35)	8 (20)	0.133

Data are presented as mean±SD or number (%).
PD, pancreatic duct; EST, endoscopic sphincterotomy, EPBD, endoscopic pneumatic balloon dilatation.
*Cannulation attempts >4 times.

Table 3. Post-ERCP Pancreatitis Profiles

Variable	Early refeeding group (n=40)	Delayed refeeding group (n=40)	p-value
Onset			0.576
4 hr after ERCP	31 (78)	33 (83)	
Next day after ERCP	9 (23)	7 (18)	
4 hr after ERCP			
Amylase, IU/L	628.0±885.5	621.0±436.0	0.966
Lipase, IU/L	1,561±2,721	1,963±1,677	0.475
Abdominal pain (VAS 0-10)	4.1±1.8	5.0±2.0	0.058
Next day after ERCP			
Amylase, IU/L	671.4±905.0	721.0±662.7	0.780
Lipase, IU/L	973±1,059	1,139±1,169	0.513
Abdominal pain (VAS 0-10)	3.2±2.0	4.0±2.0	0.356
BISAP score			0.337
0	11 (28)	9 (23)	
1	27 (68)	24 (60)	
2	2 (5)	6 (15)	
3	0	1 (3)	
SIRS	1 (3)	3 (8)	0.308
CRP, g/L	11.3±29.9	12.5±25.4	0.907
Interruption of refeeding	4 (10)	3 (8)	0.745
Time from PEP to refeeding, hr	23.9±4.2	51.4±17.3	<0.001

Data are presented as number (%) or mean±SD.
ERCP, endoscopic retrograde cholangiopancreatography; VAS, visual analogue scale; BISAP, bedside Index for Severity in Acute Pancreatitis; SIRS, systemic inflammatory response syndrome; CRP, C-reactive protein; PEP, post-ERCP pancreatitis.

(p=0.708). Unintended PD cannulation, the mean number of unintended PD cannulation, PD dye injection rate, and PD stent insertion rate did not differ between the ERF and DRF groups (p>0.05). These results confirm that potential confounding variables affecting PEP severity were well-controlled, indicating successful randomization.

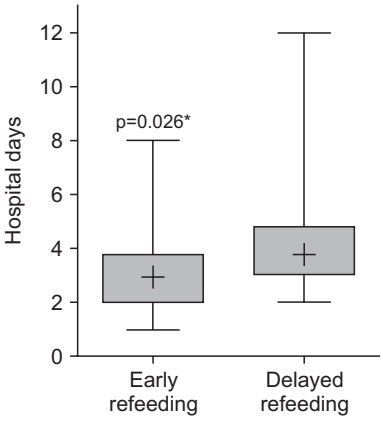
3. PEP profiles

PEP profiles are presented in Table 3. Most cases of PEP occurred 4 hours after ERCP in the ERF and DRF groups,

Table 4. Study Outcomes According to the Intention-to-Treat Analysis

	Early feeding group (n=40)	Delayed feeding group (n=40)	RR or OR (95% CI)	p-value
Primary outcome, mean±SD*				
Hospital days	2.93±1.59	3.78±1.97	0.75[§] (0.59–0.97)	0.026
Secondary outcomes, No. (%)				
Mortality[†]	1 (2.5)	0	0.71[‖] (0.04–infinity)	0.583
Readmission (<30 day)[‡]	3 (7.5)	1 (2.5)	2.95[‖] (0.28–31.34)	0.365
Severe acute pancreatitis	0	0	-	-
Necrotizing pancreatitis	0	0	-	-

RR, relative risk; OR, odds ratio; CI, confidence interval.
*Using Poisson regression with random effects; [†]One patient in the early refeeding group died from underlying pancreatic cancer, unrelated to pancreatitis. [‡]The causes of readmission were hematemesis, pancreatic cancer progression, biliary stent occlusion in the early refeeding group, and acute kidney injury in the delayed refeeding group;[§]RR; [‖]OR.



Group	Hospital days (SD)	RR (95% CI)	p-value
Early refeeding	2.93 (±1.59)	0.75 (0.59–0.97)	0.026
Delayed refeeding	3.78 (±1.97)		

Fig. 2. Length of hospitalization period. The hospitalization period for post-ERCP pancreatitis was 2.93±1.59 days in the early refeeding group and 3.78±1.97 days in the delayed refeeding group, with a significant difference (p=0.026). ERCP, endoscopic retrograde cholangiopancreatography; RR, relative risk; CI, confidence interval.

without a significant difference (78% and 83%, respectively, p=0.576). There were no significant differences in serum amylase/lipase levels or abdominal pain severity between the groups at 4 hours and the following day after ERCP. To evaluate PEP severity, intergroup Bedside Index for Severity in Acute Pancreatitis score, systemic inflammatory response syndrome score, and serum C-reactive protein level were compared. All patients had a Bedside Index for Severity in Acute Pancreatitis score of <3, and there were no statistically significant between-group differences (p=0.337). Systemic inflammatory response syndrome and C-reactive protein levels did not differ between the groups (p=0.308 and p=0.907, respectively). During refeeding, four and three patients in the ERF and DRF group, respectively, underwent refeeding interruption (p=0.745). The time duration from PEP to refeeding was significantly shorter in the ERF group than in the DRF group (23.9±4.2 hours vs 51.4±17.3 hours, p<0.001).

4. Study outcomes

For the primary outcome, the mean length of hospital stay was 2.93±1.59 days in the ERF group and 3.78±1.97 days in the DRF group (Table 4, Fig. 2). The ERF group had a significantly lower risk of prolonged hospitalization compared to the DRF group (relative risk, 0.75; 95% confidence interval, 0.59 to 0.97; p=0.026).

Table 4 presents the secondary outcomes. Mortality during hospitalization occurred in one patient (2.5%) in the ERF group (p=0.583). The cause of mortality was the progression of the underlying pancreatic cancer and was not related to pancreatitis. Readmission within 30 days after discharge was reported in three (7.5%) patients in the ERF group and one (2.5%) in the DRF group (p=0.365). Causes of readmission were hematemesis, pancreatic cancer progression, and biliary stent occlusion in the ERF group and acute kidney injury in the DRF group, without any evidence of a relationship with PEP. Severe AP or necrotizing pancreatitis within 30 days of ERCP was not observed in either group.

DISCUSSION

This is the first randomized controlled trial to compare ERF and DRF in patients with PEP, and it demonstrated that ERF could decrease hospitalization periods without safety issues. ERF in patients with PEP can aid patient recovery and reduce healthcare costs. This aligns with

emerging evidence from other studies that challenges the conventional practice of prolonged fasting in patients with AP.[6,8] PEP is an iatrogenic condition that makes physicians hesitant to change treatment strategies. This trial aims to provide evidence-based insights that can guide clinical decision-making and contribute to optimizing PEP management.

Pancreatitis is the most serious adverse post-ERCP event due to its high morbidity and mortality rates.[14] In the United States, the number of therapeutic ERCP procedures is increasing, along with the incidence of PEP and all-cause mortality associated with it.[2] Previous studies on PEP have reported several risk factors and prevention strategies.[14-19] Herein, we attempted to control the risk factors and prophylactic agents before ERCP. There were no between-group differences, which affect PEP incidence or severity, in the baseline characteristics, ERCP indications and procedure-related events. Therefore, the PEP profiles were not different between the groups with respect to disease onset, patient symptoms, and severity.

The hospitalization period, which was the primary outcome in this study, showed significant differences (2.9±1.6 and 3.8±2.0 days in the ERF and DRF groups, respectively); this is a reduction of approximately a day in hospitalization in the ERF group, which is similar to the previously reported result of about a 1- to 2-day decrease in mild/moderate AP.[7,9,11,20-22] Previous studies have reported various feeding routes and diet build-up plans for refeeding.[8] Some studies used time-based indications, whereas others used symptom- or laboratory-based indications to initiate ERF or DRF. The hospitalization period in this study tended to be shorter than that reported previously, which may be because of differences in the study design and exclusion of moderate-to-severe cases in this study.

Although the cause of PEP is inherently linked to the ERCP procedure itself, the exact physiological onset of PEP cannot be precisely determined. This variability likely reflects differences in individual patient susceptibility, procedural factors, and the degree of pancreatic irritation or injury. Our study aimed to evaluate the optimal timing for refeeding based on clinically detectable PEP, not the unobservable physiologic onset. To define diagnostic onset in a feasible and reproducible manner, we adopted a standardized protocol involving routine serum amylase/lipase measurement at 4 hours after ERCP and again the following morning, coupled with clinical assessment of abdominal pain. This approach minimized inter-individual variation and ensured consistency in applying the inclusion criteria and the definition of early refeeding. It also aligned the timing of the intervention and the primary outcome, hospitalization period, both of which were based on the time of PEP diagnosis rather than the time of ERCP.

In PEP, the standard treatment involves fasting followed by refeeding after complete recovery. However, several studies have advocated for ERF in the clinical management of acute AP. While AP is theoretically similar to PEP, prescribing ERF for PEP without supporting clinical evidence remains challenging. Furthermore, some studies on dietary timing in AP have excluded patients with PEP.[6,20] This study is the first to provide clinical evidence supporting ERF in patients with PEP, demonstrating its potential for accelerating recovery safely.

Patients with ERF in this study had shorter hospitalization than those with DRF for several reasons. First, an early diet can promote recovery from PEP by reducing gut permeability and bacterial translocation by controlling the serum intestinal fatty acid-binding protein levels and endotoxin exposure.[23-26] However, the effects of decreased gut permeability and bacterial translocation may be limited to patients having AP with multi-organ failure, who were not included in this trial. Another possibility is that fasting was unnecessary in patients with mild PEP. In such cases, earlier refeeding allows patients to meet discharge criteria more quickly. The shortened hospitalization period in our study was almost equal to the time difference in starting the diet between the two groups (approximately 1 day). Further studies examining gut permeability and bacterial translocation before and after diet in patients with moderate-to-severe PEP are needed to confirm the mechanism by which early diet promotes recovery from PEP.

Although our study is the first to evaluate the safety and efficacy of ERF in patients with PEP, it has several limitations. First, the study focused exclusively on mild PEP, leaving the effects of ERF in moderate-to-severe cases unknown. As PEP is an iatrogenic condition, introducing treatments in clinical trials that could potentially worsen patient outcomes poses significant ethical challenges. Specifically, obtaining consent for ERF in such patients is difficult, as it may increase the risk of progressing to fatal AP. Additionally, previous studies on refeeding after AP have examined mild/moderate and severe cases separately, reflecting their distinct clinical courses.[8] Nevertheless, our findings on the safety of ERF in mild PEP could provide a foundation for future trials involving moderate or severe pancreatitis. Second, this was an open-label study; therefore, researcher subjectivity may have influenced the results. However, the open-label design was unavoidable, and previous refeeding timing studies on AP have obtained meaningful results with an open-label design. Third, although reportedly, rectal indomethacin has proven effective in preventing post-PEP, it could not be administered to patients in our study owing to its unavailability in Korea.[14]

Despite these limitations, our study provides valuable insights of post-PEP refeeding. ERF significantly reduced the hospital stay in patients with PEP compared with DRF and without increasing PEP-related safety issues. Therefore, we recommend that ERF 24 hours after PEP diagnosis should be considered in patients with mild PEP as it promotes recovery and reduce healthcare costs.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (grant numbers 2021R1A2C1006234 and RS-2024-00335625); the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant number HI22C047400); This paper was supported by Korea Evaluation Institute of Industrial Technology (KEIT) grant funded by the Korea Government (MOTIE) (grant number 20023781); and a faculty research grant from the Yonsei University College of Medicine (grant number 6-2023-0080).

AUTHOR CONTRIBUTIONS

Study concept and design: J.H.J., M.K.J., S.H.L. Data acquisition: J.H.J., J.M.L., D.K.J., J.W.C., S.Y.H., Y.H.C., E.J.K. Data analysis and interpretation: all authors. Drafting of the manuscript: J.H.J., M.K.J., S.H.L. Critical revision of the manuscript for important intellectual content: J.M.L., D.K.J., J.W.C., S.Y.H., Y.H.C., E.J.K., H.Y.K., S.H.L. Statistical analysis: H.Y.K. Administrative, technical, or material support: J.H.J., J.M.L., D.K.J., J.W.C., S.Y.H., Y.H.C., E.J.K., M.K.J. Study supervision: S.H.L. Approval of final manuscript: all authors.

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DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon request.

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