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Efficacy and safety of immediate oral intake in patients with mild acute pancreatitis: A randomized controlled trial

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ABSTRACT

Objectives: Early enteral nutrition is recommended for patients with severe acute pancreatitis (AP); however, nutritional management strategies for patients with mild AP have not been established. The aim of this study was to evaluate the benefits and safety of immediate oral intake of low-fat solid food in patients with mild AP who were allowed to take opioid analgesics.

Methods: In this single-center randomized study, the immediate feeding (IMF) group was permitted immediate oral intake of low-fat (15 g/d) solid food. In the standard food (STF) group, patients received gradually increasing amounts of dietary fat. Twenty-six patients were randomized, with 13 allocated to each group. The primary outcome was the period between diagnosis and recovery from AP. The cost and rate of progression to severe disease were evaluated as secondary outcomes.

Results: The IMF group (mean recovery days: 2 ± 1) recovered significantly earlier (mean difference in recovery days: 6.3; 95% confidence interval [CI], 4.8–7.9; $P < 0.001$) than the STF group (mean recovery days: 8.3 ± 2.3), with a lower overall treatment cost (mean difference in costs: −$460; 95% CI, −$880 to −$40; $P = 0.034$). The IMF group showed a lower rate of progression to severe AP (IMF, 0%; STF, 15.3%; $P = 0.48$).

Conclusion: The initial treatment strategy for mild AP should be altered from the gradual introduction of oral feeding upon the absence of pain to immediate oral nutrition with opioid analgesics, to improve treatment efficacy and reduce treatment cost.

Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal hospital discharge diagnoses (~280 000 admissions in 2014) and is associated with an annual aggregate treatment cost >$2.7 billion in the United States [1]. AP has three grades of severity, according to the revised Atlanta classification (mild, moderately severe, and severe), with around 80% cases being of the mild type [2,3]. The use of early enteral nutrition (EN) primarily depends on the severity of the pancreatitis. The European Society for Clinical Nutrition and Metabolism guidelines for pancreatic treatment recommend that patients with mild pancreatitis be fed orally after a short period of starvation if the pain stops and that oral nutrition be increased continuously if the patient tolerates the diet well [4]. For severe AP, however, EN should be initiated as early as possible because early EN improves the course of the disease and enables the use of analgesics [4].

Recent studies have shown the benefits of early oral refeeding for non-severe AP [5–9]. A systematic review and meta-analysis demonstrated that, compared with standard oral refeeding, early oral refeeding reduced the hospital length of stay (LOS) for patients with AP [10]. However, in mild AP, answers to questions, such as how early the refeeding should begin, what type of food should be given to initiate refeeding, and whether patients should eat while receiving opioid analgesics, remain

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unclear [11]. Moreover, although the intervention has the potential to expedite the resolution of pancreatitis or conversely to impede recovery by inducing abdominal pain recurrence, its ultimate effect on the outcome is still not clearly known. Therefore, we conducted this study to evaluate the benefits and safety of the immediate oral intake of low-fat solid food in patients with mild AP who were allowed to use opioid analgesics.

Material and methods

Study design, setting, and patient characteristics

This was a single-blind (assessors were blinded) randomized, controlled superiority study with a 1:1 allocation (parallel group). Ethical approval was obtained from the Ethics Review Committee of Keio University School of Medicine. The study was preregistered with the University Hospital Medical Information Network Center. Written informed consent was obtained from the participants before group allocation. The inclusion and exclusion criteria are presented in Table 1. When patients were diagnosed with mild gallstone pancreatitis, the gallstones were examined for incarceration. If there was incarceration caused by gallstones, they were treated with endoscopic retrograde cholangiopancreatography before allocation to the study. Patients were recruited from August 4, 2015 to September 14, 2017, and the final patient follow-up occurred on December 14, 2017. The study ended after the required number of participants were enrolled.

Randomization and masking

Random allocation of the participants to either an immediate feeding (IMF) or a standard feeding (STF) group was performed after the diagnosis of mild AP. The block size of randomization was four or six and was concealed from all researchers except the data analyst. The randomization sequence was stored by independent staff who were not involved in the study, and randomization was done at the individual level. The assessors (the nurses, measuring the oral intake, and the data analyst) were concealed from the allocation.

Interventions

IMF group

Patients in the IMF group were permitted oral intake of low-fat (15 g/d) solid food (Supplementary Fig. 1; Fig. 1) within 1 d of diagnosis. Eating with the concurrent use of opioid analgesics was allowed. If the patients experienced aggravated abdominal pain or tenderness (Wong-Baker face ≥6) [12] owing to their diet and requested an additional opioid analgesic, one meal was omitted. If this occurred three times, these patients were considered to have dropped out of the study and went on to receive the same treatment as the STF group.

Table 1
Inclusion and exclusion criteria

Inclusion criteria

• Diagnosis of acute pancreatitis required the presence of two of the following features:
  ◦ Acute onset of upper abdominal pain often radiating through to the back
  ◦ Serum amylase or lipase activity greater than three times the upper limit of the normal range
  ◦ Findings from cross-sectional abdominal imaging consistent with acute pancreatitis [2]
• Mild acute pancreatitis was defined as patients with no organ failure (Modified Marshall score <2) [2] and patients with two or fewer prognostic factors according to the Japanese Ministry of Health, Labour and Welfare study group criteria for acute pancreatitis severity (2008) [16].
• The lower age limit was 16 y, and the upper age limit was 95 y.

Exclusion criteria
• Current complications of cholangitis • Pancreatitis caused by trauma • Pancreatitis caused by malignancy • History of concomitant diseases capable of weakening deglutition (e.g., bulbar paralysis) • Inability to eat solid food due to a disturbance of consciousness • Computed tomography or ultrasound findings indicating paralytic ileus involvement (e.g., expansion of the intestinal tract or the presence of a "keyboard" sign) • Regular use of analgesics due to pain from chronic pancreatitis • Lack of consent to participate in this study

STF group

Patients in the STF group were given a gradually increasing amount of dietary fat after a fast in accordance with the Japanese guidelines [13], which state that the initiation of oral feeding should be determined based on the remission of abdominal pain and the serum pancreatic enzyme level [13] (Fig. 1). Oral water intake was allowed if the patients met all of the following conditions without analgesia:

- No nausea, vomiting, abdominal pain, or tenderness (Wong-Baker face ≥6) [12].
- They felt hunger.
- Serum amylase or pancreatic amylase activity was lower than twice the upper limit of the normal range [13,14].

The step-up protocol is shown in Figure 1.

Both groups

All patients received adequate intravenous fluids during the early stage of pancreatitis [13,15]. Intravenous pentazocine (15 mg), an opioid analgesic, was administered up to four times daily if the patients reported abdominal pain or tenderness (Wong-Baker face ≥6) [12].

Follow-up

A blood test was performed during hospitalization on days 0 (day of diagnosis), 2, and 5. The severity of pancreatitis was assessed daily for ≥5 d from admission or until the day of discharge [2,16].

Patients made follow-up visits at 2, 6, and 12 wk after discharge, and the need for rehospitalization as a result of pancreatitis recurrence was evaluated over 3 mo after discharge. Patients who missed a follow-up visit were contacted by telephone.

Outcome measures

The number of days until recovery from pancreatitis was the primary outcome. Patients were deemed to have recovered when.

- The average amount of food consumed in three consecutive low-fat (15 g/d) solid-food meals was ≥50% of the prescribed amount per meal; and
- There were no abdominal symptoms for 24 h after starting the low-fat (15 g/d) solid food regimen.

The average oral intake of three consecutive meals (breakfast, lunch, and dinner) per day was ascertained by nurses blinded to the intervention. Each day, patients were assessed for aggravated abdominal pain or tenderness (Wong-Baker face ≥6) [12] related to their diet and were asked if they wished to have analgesia. The assessment of recovery from pancreatitis, based on the criteria just described, was made by an independent data analyst blinded to the intervention. If a patient died before recovery, the day of recovery was considered as not evaluable. The secondary outcomes are shown in Table 2.

Statistical analysis

The sample size was calculated by a statistician at the Center for Clinical Research at Keio University School of Medicine and was based on the number of days until recovery from pancreatitis. At our institution, the average hospital LOS for patients with mild AP between 2012 and 2014 was 12.6 d, and the SD was 5.1 d. The number of days to recovery was predicted to be 10 d for the STF group because the patients in our institution are discharged after 1 to 3 d of recovery, and the number of days of recovery was predicted to be 4 for the IMF group when they were treated according to the protocol. The mean difference of 6 d was calculated on the assumption that about 90% of patients treated according to the protocol would have no abdominal pain or symptoms. The sample size necessary to demonstrate this expected difference with a two-sided significance level of 5% and a statistical power of 80% was 13 patients for each group, allowing for a 5% dropout rate.

Primary and secondary analyses were conducted for all randomized patients (an intention-to-treat analysis). The primary outcome was compared using the two-sample t test. For the secondary outcomes, continuous variables were compared using the two-sample t test, and categorical outcomes were analyzed using the χ^2 test or Fisher exact test, depending on the expected value. Changes in the serum concentrations of various markers were compared using the two-sample t test. $P < 0.05$ was considered statistically significant. All the analyses were conducted using JMP (R) statistical software version 11.2 (SAS Institute, Inc., Cary, NC, USA).

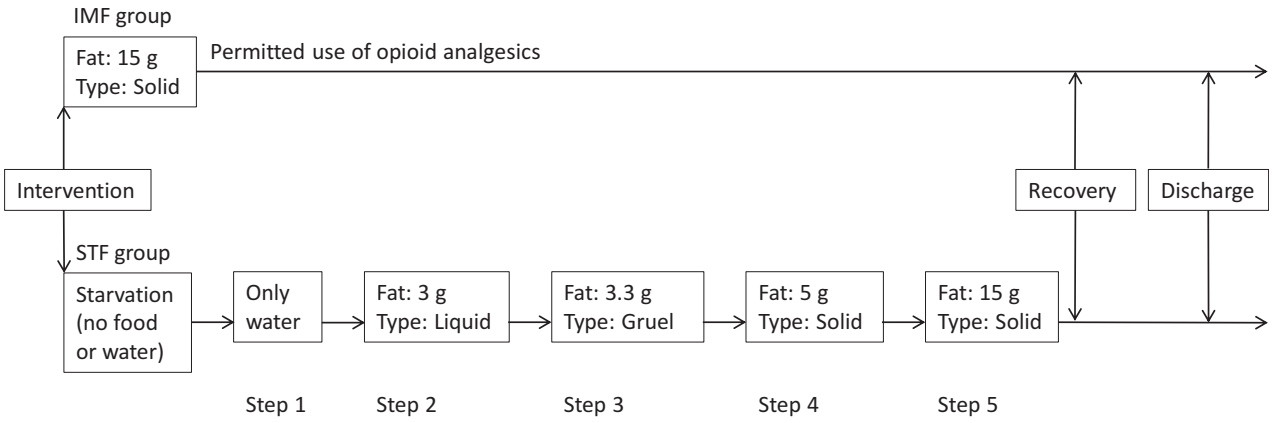

Fig. 1. Treatment strategies for the IMF and STF groups. For the STF group, patients progressed from one step to the next when all the following conditions were met: (1) Patients had no nausea, vomiting, abdominal pain (Wong-Baker face ≥6) [12] or tenderness (Wong-Baker face ≥6) [12]. (2) Patients felt hunger. (3) Serum amylase or pancreatic amylase activity was lower than twice the upper limit of the normal range. (4) The average intake of three consecutive meals was ≥50% of a prescribed meal. IMF, immediate low-fat solid food; STF, standard food.

Results

Study population

The study diagram is shown in Figure 2. We screened 90 patients with AP and enrolled 26 (with 13 in each group). None of the patients received treatment different from the protocol after allocation. The median time between diagnosis and the first intervention was 19 h (interquartile range [IQR], 6.5–24.5 h) in the IMF group and 12 h (IQR, 3–22 h) in the STF group. We were able to evaluate the number of days until recovery and the hospital LOS for 25 patients with AP. These values were not evaluable for one patient who died after admission. All other patients were followed up for ≥3 mo after discharge, and the follow-up rate was 96.2% (25 of 26). The characteristics of the groups are presented in Table 3.

Efficacy

In terms of the primary outcome, the IMF group recovered from AP significantly earlier than the STF group ($P < 0.001$; Fig. 3 and Table 4). The median number of days until recovery from pancreatitis was 2 in the IMF group (IQR, 1–3 d) and 8 in the STF group (IQR, 7–9 d). Furthermore, the hospital LOS in the IMF group was significantly shorter ($P = 0.0004$; Fig. 3 and Table 4). The median LOS was 4 d in the IMF group (IQR, 3–7 d) and 10 d in the STF group (IQR, 8.5–14.5 d). The treatment costs were significantly lower for the IMF group ($P = 0.034$; Table 4). The changes in C-reactive protein and calcium values from day 0 to day 2 did not significantly differ between the groups ($P = 0.26$ and $P = 0.21$, respectively; Table 4).

Table 2
Patient outcomes

Primary outcome Number of days until recovery
Secondary outcomes
• Hospital LOS in patients who survived and were discharged • Difference in serum amylase, pancreatic amylase, lipase, calcium, and CRP levels before (day 0) and after (day 2) intervention • Rehospitalization rate owing to pancreatitis recurrence within 3 mo of hospital discharge and the period until rehospitalization • Rate of exacerbation of abdominal pain or abdominal symptoms during hospitalization after starting the dietary regimen • The proportion of patients in which mild AP progressed to moderately severe or higher AP, assessed according to the revised Atlanta classification [2] • Proportion of patients with progression from mild to severe AP, according to the Japanese Ministry of Health, Labour and Welfare study group criteria for AP severity (2008) [16] • Total dropout rate (for any reason) • Cost of hospital treatment

AP, acute pancreatitis; CRP, C-reactive protein; LOS, length of stay

Safety

There was no significant difference in the adverse events between the groups (Table 4). Although no patients dropped out of the IMF group, three dropped out of the STF group as a result of progression to severe AP, as assessed according to the Japanese AP severity criteria (2008). The absolute risk reduction (ARR) for IMF compared with STF for progression was 23.1%. After receiving a diagnosis of severe AP, all three patients started EN immediately. Severe AP according to the revised Atlanta classification developed in two of the three patients. The ARR for the IMF group compared with the STF group for progression to severe AP was 15.4%. One of the two patients died as a result of multiple organ failure 70 d after the intervention (starvation) was initiated. The ARR of death in the IMF group compared with the STF group was 7.7%

Only one patient in the STF group had exacerbated abdominal pain or symptoms after starting refeeding and was treated through fasting in accordance with the protocol. After the second fast, the patient recovered without any further exacerbation of abdominal pain or symptoms. The ARR for exacerbation was 7.7% in the IMF group compared with the STF group. No patients in either group experienced AP recurrence within 3 mo. There was no significant difference in amylase, pancreatic amylase, or lipase values between day 0 and day 2 ($P = 0.18$, $P = 0.42$, and $P = 0.51$, respectively; Table 4).

Discussion

The patients with mild AP who were fed a low-fat solid diet immediately after diagnosis and allowed to use opioid analgesics (the IMF group) recovered more quickly than those who received gradually increasing amounts of dietary fat after short-term starvation (the STF group). Moreover, the mean total cost of treatment for the IMF group was significantly lower than that for the STF group.

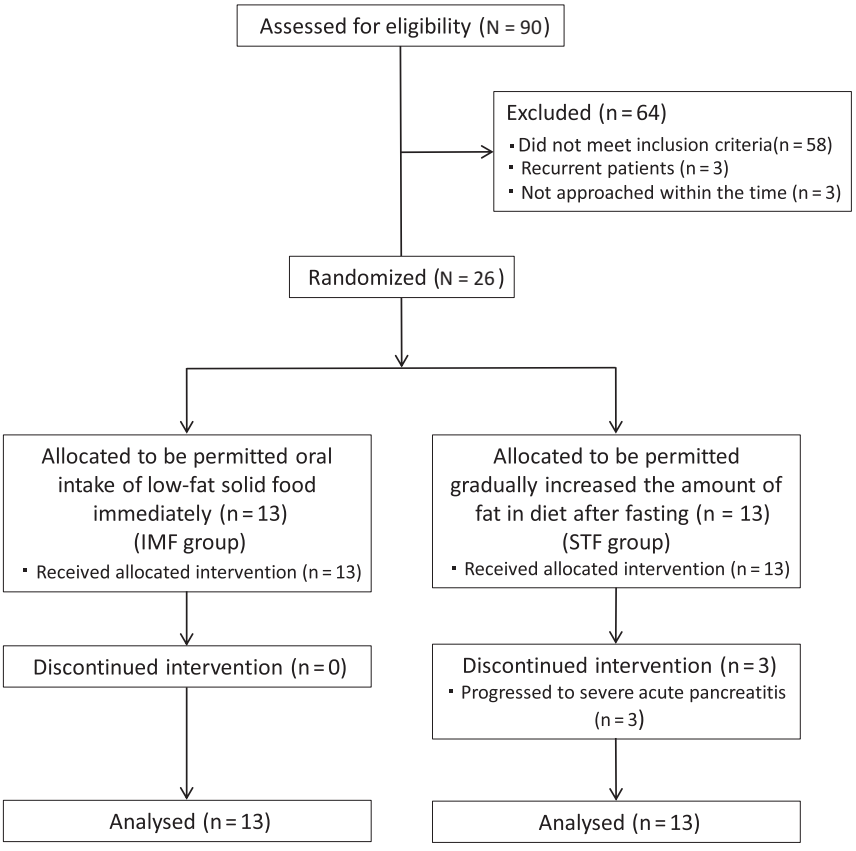

Fig. 2. Study flow.

To our knowledge, this was the first randomized controlled trial (RCT) to examine the oral intake of food with concurrent use of opioid analgesics in patients with AP. Previous RCTs on early or immediate oral feeding permitted feeding if the patients were able to tolerate it without the use of opioid analgesics [5–9]. The American Gastroenterological Association (AGA) guidelines, which recommend initiating early oral feeding if tolerable to the patient, state that this strategy is sometimes unsuccessful because of pain, vomiting, or ileus [3]. Several other guidelines also recommend that oral feeding in patients with mild pancreatitis be restarted once abdominal pain decreases [13,17]. Thus, initiating early oral feeding as soon as the patient experiences a decrease in pain without analgesics is a general nutritional strategy. However, our first attempt demonstrated that immediate oral intake with the use of opioid analgesics may be conducive to early recovery from AP.

Table 3
Group characteristics

	IMF group (n = 13)	STF group (n = 13)	*P*-value
Age, y, mean (SD)	50.1 (5.3)	60.8 (5.3)	0.17
Male	10 (76.9)	8 (61.5)	0.40
Etiology			
Alcohol	7 (53.9)	4 (30.8)	0.23
Post-ERCP	2 (15.4)	1 (7.7)	1.00
Abnormalities of the pancreas	1 (7.7)	2 (15.4)	1.00
Gallstones	0 (0)	2 (15.4)	0.48
Autoimmune	0 (0)	1 (7.7)	1.00
Drug	1 (7.7)	0 (0)	1.00
Hypertriacylglycerolmia	0 (0)	1 (7.7)	1.00
Post-FNA	1 (7.7)	0 (0)	1.00
Unclear	1 (7.7)	2 (15.4)	1.00
Use of opiate analgesia	8 (61.5)	10 (76.9)	0.40
Number of days after onset until diagnosis, mean (SD)	0.9 (0.9)	0.7 (0.9)	0.50
Hours from diagnosis to consent, mean (SD)	9.6 (15.4)	13 (9.9)	0.51
Fluid volume (mL) during 3 d after admission, mean (SD)	6460 (2108)	7433 (3363)	0.39
Antimicrobial prophylaxis	0 (0)	0 (0)	1

ERCP, endoscopic retrograde cholangiopancreatography; FNA, fine needle aspiration; IMF, immediate low-fat solid food; STF, standard food;
All values n (%), unless otherwise noted

To our knowledge, the present study was the first to assess an intervention consisting of the immediate (median number of hours fasting = 19 h) oral intake of low-fat solid food. Data from a previous RCT suggested that immediate oral intake of non-solid food (median number of days of fasting and solid food intake = 0 and 3 d, respectively) may accelerate recovery more safely than fasting [5]. Another RCT suggested that early, rather than immediate, oral intake of low-fat solid food (median number of fasting days = 2.5) may accelerate recovery more safely than intake administered in a stepwise manner [6,7]. Thus, we speculated that the combination of immediate refeeding with the intake of low-fat solid food may accelerate recovery to a greater degree than the immediate intake of non-solid food or early intake of low-fat solid food alone.

The AGA guidelines recommend initiating oral feeding early (within 24 h) based on the results of 11 RCTs that examined early versus delayed feeding [3]. However, the early feeding group included oral and enteral tube feeding; whereas the delayed feeding group included total parenteral nutrition [3,11]. Moreover, although enteral tube feeding was started within 24 h in some studies, none of the studies reported the initiation of oral feeding within 24 h [3,11]. Thus, whether the 24-h period is appropriate

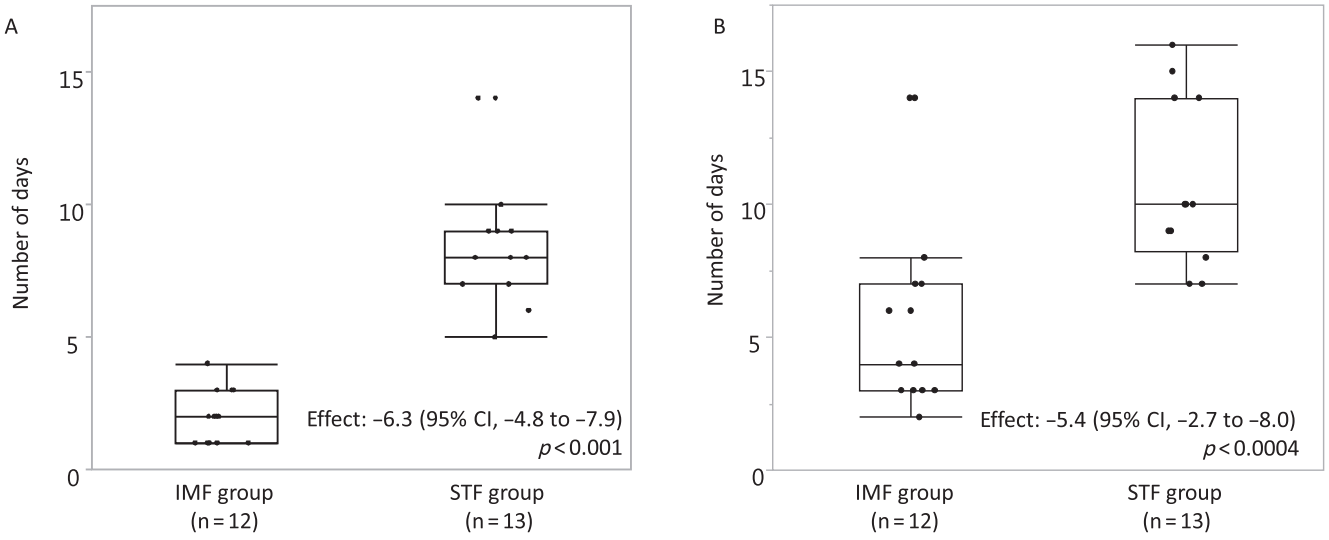

Fig. 3. (**A**) Recovery period and (**B**) hospital length of stay. IMF, immediate low-fat solid food; STF, standard food.

for the oral intake of food is still unclear. This study provides more solid evidence for the AGA guideline recommendation that oral intake should be started within 24 h. Although the guidelines state that starting with a clear liquid diet is not required, they do not clarify the appropriate type of food for starting refeeding [3]. We demonstrated that immediately starting a low-fat solid food regimen is a feasible dietary strategy.

Meta-analyses have demonstrated that EN within 48 h of admission results in better clinical outcomes than either total parenteral nutrition or EN after 48 h in patients with severe AP [18,19]. One study reported that EN within 24 h of admission led to better clinical outcomes than EN after more than 24 h postadmission [20]. Earlier oral intake is also thought to achieve excellent outcomes similar to those in EN because both oral intake and EN preserve gut-associated lymphoid tissue, which is associated with immunoglobulin A and plays a vital role in intestinal immunity through maintaining the gut barrier function [21–24]. Injury to the intestinal mucosa leads to bacterial translocation, endotoxemia originating from the gut, and secondary infections of pancreatic tissue, causing systemic inflammatory response syndrome or multiple organ failure [25]. Thus, immediate oral intake may suppress the progression of AP by preventing injury to the intestinal mucosal barrier. Additionally, the form of food affects the outcomes. Oral intake of solid food suppressed intestinal mucosal injury significantly more than liquid EN in mice [26] and in pediatric patients with ileus [27–29]. An RCT demonstrated that the rates of infection and death did not significantly differ between enteral tube feeding (liquid) within 24 h of admission and an oral diet (standard solid food) >72 h after admission [30,31], suggesting that a late-phase oral diet has a similar beneficial effect to that of immediate enteral tube feeding. Thus, immediate oral intake of solid food may have a better outcome than intake in a stepwise manner (starvation, water, liquid, gruel, and solids). The present study also demonstrated that the risk for progression to severe AP was lower in the IMF group than in the STF group, although the difference was not significant ($P = 0.48$).

A systematic review of studies on early oral feeding demonstrated that the ideal primary outcome is the length of days until the resolution of pancreatitis rather than hospital LOS [10] because

Table 4
Group outcomes

	IMF group (n = 13)	STF group (n = 12)	*P*-value
Number of days until recovery (n = 13,12)	2 (1)	8.3 (2.3)	<**0.0001**
Hospital LOS, d (n = 13,12)	5.4 (3.2)	10.8 (3.2)	**0.0004**
Progression to severe pancreatitis; JSS, n (%)	0 (0)	3 (23.1)	0.22
Progression to moderately severe or severe pancreatitis; revised Atlanta Classification, n (%)	0 (0)	2 (15.4)	0.48
Progression to severe pancreatitis; revised Atlanta Classification, n (%)	0 (0)	2 (15.4)	0.48
Dropout rate, n (%)	0 (0)	3 (23.1)	0.22
Death, n (%)	0 (0)	1 (7.7)	1.00
Exacerbation of abdominal pain or symptoms, n (%)	0 (0)	1 (7.7)	1.00
Recurrence within 3 mo, n (%)	0 (0)	0 (0)	1.00
CRP, mg/dL (day 2 to day 0; n = 11, 13)	2.12 (6.7)	5.15 (6.1)	0.26
Calcium, mg/dL (day 2 to day 0; n = 10, 12)	−0.18 (0.42)	−0.44 (0.50)	0.21
Amylase, U/L (day 2 to day 0; n = 12, 10)	−492 (719)	−1120 (1370)	0.18
Pancreatic amylase, U/L (day 2 to day 0; n = 10, 8)	−546 (812)	−854 (764)	0.42
Lipase, U/L (day 2 to day 0; n = 6, 6)	−966 (1080)	−1990 (3570)	0.51
Total cost, USD	830 (340)	1340 (640)	**0.034**

CRP, C-reactive protein; IMF, immediate low-fat solid food; JSS: Japanese Ministry of Health, Labour and Welfare study group criteria for acute pancreatitis severity; LOS, length of stay; STF, standard food.
All values mean (SD), unless otherwise noted.
Bold values shows that there is a significant difference, namely p<0.05.

the discharge decision by a physician or medical team not only depends on the resolution of pancreatitis, but also other non-medical factors, such as the desire of the patients and their families. In the present study, recovery was defined before starting the study to avoid this type of bias. The primary outcome was also based on patient reports because the Food and Drug Administration announced that the primary endpoint of clinical trials should include items related to patients' subjective symptoms [32]. Our definition of recovery from AP was considered acceptable because no patient discharged after meeting the criteria relapsed within 3 mo of discharge.

This study had several limitations. First, it was performed at a single institution. A multicenter study is needed to determine the generalizability of the findings. Second, although the calculated sample size was sufficient to demonstrate the efficacy of immediate oral food intake, it may be insufficient to demonstrate safety. The absence of any significant differences in the rate of adverse events between the groups may be due to the small sample size. The evidence is therefore too limited to permit any conclusions concerning safety. However, a systematic review suggested that early oral or enteral tube feeding (within 48 h) was not associated with any adverse effects [33]. Third, the median (2 d) time of recovery in the STF group in this study was close to the median hospital LOS in the United States (4 d) [1]. The cost reduction in the United States would be smaller than that in Japan, where the hospital LOS is 19.2 d (17.8 d in case of limited to mild acute pancreatitis) [34]. Furthermore, at this time, although no significant factors affecting recovery duration have been identified, this may be unclear owing to the small sample size and requires further consideration (examining age, etiology, use of opiate analgesia, etc.)

Conclusion

The present findings suggested that the initial treatment strategy for mild AP should be altered from the gradual introduction of oral feeding upon the absence of pain, to immediate oral nutrition with opioid analgesics. If the initial treatment strategy is changed, ~220 000 patients with mild AP per year in the United States should recover quickly and the medical cost should decrease [1,3]. However, large multicenter RCTs are required to confirm these findings.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Masayasu Horibe: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Eisuke Iwasaki:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Atsuo Nakagawa:** Conceptualization, Formal analysis, Methodology, Resources, Software, Supervision, Validation, Writing - original draft, Writing - review & editing. **Juntaro Matsuzaki:** Conceptualization, Formal analysis, Methodology, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Kazuhiro Minami:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Yujiro Machida:** Conceptualization, Data curation, Investigation, Writing - review & editing. **Hiroki Tamagawa:** Conceptualization, Data curation, Investigation, Writing - review & editing. **Yoichi Takimoto:** Conceptualization, Data curation, Investigation, Writing - review & editing. **Masahiro Ueda:** Conceptualization, Investigation, Writing - review & editing. **Tadashi Katayama:** Conceptualization, Investigation, Writing - review & editing. **Shintaro Kawasaki:** Conceptualization, Investigation, Writing - review & editing. **Misako Matsushita:** Conceptualization, Investigation, Writing - review & editing. **Takashi Seino:** Conceptualization, Investigation, Writing - review & editing. **Seiichiro Fukuhara:** Data curation. **Takanori Kanai:** Funding acquisition, Project administration, Resources, Supervision, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2020.110724.

References

[1] Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: Update 2018. Gastroenterology 2019;156:254–72.
[2] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11.
[3] Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN. American Gastroenterological Association Institute Clinical Guidelines C. American Gastroenterological Association Institute guideline on initial management of acute pancreatitis. Gastroenterology 2018;154:1096–101.
[4] Meier R, Ockenga J, Pertkiewicz M, Pap A, Milinic N, Macfie J, et al. ESPEN guidelines on enteral nutrition: pancreas. Clin Nutr 2006;25:275–84.
[5] Eckerwall GE, Tingstedt BB, Bergenzaun PE, Andersson RG. Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery—a randomized clinical study. Clin Nutr 2007;26:758–63.
[6] Teich N, Aghdassi A, Fischer J, Walz B, Caca K, Wallochny T, et al. Optimal timing of oral refeeding in mild acute pancreatitis: results of an open randomized multicenter trial. Pancreas 2010;39:1088–92.
[7] Larino-Noia J, Lindkvist B, Iglesias-Garcia J, Seijo-Rios S, Iglesias-Canle J, Dominguez-Munoz JE. Early and/or immediately full caloric diet versus standard refeeding in mild acute pancreatitis: a randomized open-label trial. Pancreatology 2014;14:167–73.
[8] Li J, Xue GJ, Liu YL, Javed MA, Zhao XL, Wan MH, et al. Early oral refeeding wisdom in patients with mild acute pancreatitis. Pancreas 2013;42:88–91.
[9] Zhao XL, Zhu SF, Xue GJ, Li J, Liu YL, Wan MH, et al. Early oral refeeding based on hunger in moderate and severe acute pancreatitis: a prospective controlled, randomized clinical trial. Nutrition 2015;31:171–5.
[10] Horibe M, Nishizawa T, Suzuki H, Minami K, Yahagi N, Iwasaki E, et al. Timing of oral refeeding in acute pancreatitis: a systematic review and meta-analysis. United European Gastroenterol J2016;4:725−32.
[11] Vege SS, DiMagno MJ, Forsmark CE, Martel M, Barkun AN. Initial medical treatment of acute pancreatitis: American Gastroenterological Association Institute Technical Review. Gastroenterology 2018;154:1103–39.
[12] Wong DL, Baker CM. Pain in children: comparison of assessment scales. Pediatr Nurs 1988;14:9–17.
[13] Yokoe M, Takada T, Mayumi T, Yoshida M, Isaji S, Wada K, et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. J Hepatobiliary Pancreat Sci 2015;22:405–32.
[14] Chebli JM, Gaburri PD, De Souza AF, Junior EV, Gaburri AK, Felga GE, et al. Oral refeeding in patients with mild acute pancreatitis: prevalence and risk factors of relapsing abdominal pain. J Gastroenterol Hepatol 2005;20:1385–9.

[15] Buxbaum JL, Quezada M, Da B, Jani N, Lane C, Mwengela D, et al. Early aggressive hydration hastens clinical improvement in mild acute pancreatitis. Am J Gastroenterol 2017;112:797–803.
[16] Takeda K, Yokoe M, Takada T, Kataoka K, Yoshida M, Gabata T, et al. Assessment of severity of acute pancreatitis according to new prognostic factors and CT grading. J Hepatobiliary Pancreat Sci 2010;17:37–44.
[17] Working Group IAPAPAAPG. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13:e1–15.
[18] Li JY, Yu T, Chen GC, Yuan YH, Zhong W, Zhao LN, et al. Enteral nutrition within 48 hours of admission improves clinical outcomes of acute pancreatitis by reducing complications: a meta-analysis. PLoS One 2013;8:e64926.
[19] Feng P, He C, Liao G, Chen Y. Early enteral nutrition versus delayed enteral nutrition in acute pancreatitis: s PRISMA-compliant systematic review and meta-analysis. Medicine 2017;96:e8648.
[20] Bakker OJ, van Brunschot S, Farre A, Johnson CD, Kalfarentzos F, Louie BE, et al. Timing of enteral nutrition in acute pancreatitis: meta-analysis of individuals using a single-arm of randomised trials. Pancreatology 2014;14:340–6.
[21] Li J, Kudsk KA, Gocinski B, Dent D, Glezer J, Langkamp-Henken B. Effects of parenteral and enteral nutrition on gut-associated lymphoid tissue. J Trauma 1995;39:44–51. discussion −2.
[22] Kang W, Kudsk KA. Is there evidence that the gut contributes to mucosal immunity in humans? JPEN J Parenter Enteral Nutr 2007;31:246–58.
[23] Mestecky J, McGhee JR. Immunoglobulin A (IgA): molecular and cellular interactions involved in IgA biosynthesis and immune response. Adv Immunol 1987;40:153–245.
[24] Ottaway CA. Neuroimmunomodulation in the intestinal mucosa. Gatroenterol Clin N Am 1991;20:511–29.
[25] Zhang XP, Zhang J, Song QL, Chen HQ. Mechanism of acute pancreatitis complicated with injury of intestinal mucosa barrier. J Zhejiang Univ Sci B 2007;8:888–95.
[26] Fukatsu K, Kudsk KA, Zarzaur BL, Wu Y, Hanna MK, DeWitt RC. TPN decreases IL-4 and IL-10 mRNA expression in lipopolysaccharide stimulated intestinal lamina propria cells but glutamine supplementation preserves the expression. Shock 2001;15:318–22.
[27] Luk GD, Bayless TM, Baylin SB. Plasma postheparin diamine oxidase. Sensitive provocative test for quantitating length of acute intestinal mucosal injury in the rat. J Clin Invest 1983;71:1308–15.
[28] Tanaka Y, Mizote H, Asakawa T, Kobayashi H, Otani M, Tanikawa K, et al. Clinical significance of plasma diamine oxidase activity in pediatric patients: influence of nutritional therapy and chemotherapy. Kurume Med J 2003;50:131–7.
[29] Mennigen R, Bieganski T, Elbers A, Kusche J. The histamine-diamine oxidase system and mucosal proliferation under the influence of aminoguanidine and seventy percent resection of the rat small intestine. Agents Actions 1989;27:221–3.
[30] Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Boermeester MA, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. N Engl J Med 2014;371:1983–93.
[31] Bakker OJ, van Santvoort HC, Dutch Pancreatitis Study G. Reply: To PMID 25409371. Gastroenterology 2015;148:1478.
[32] US Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. Avaliable at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf. Accessed January 15, 2020.
[33] Vaughn VM, Shuster D, Rogers MAM, Mann J, Conte ML, Saint S, et al. Early versus delayed feeding in patients with acute pancreatitis: a systematic review. Ann Intern Med 2017;166:883–92.
[34] Murata A, Matsuda S, Mayumi T, Okamoto K, Kuwabara K, Ichimiya Y, et al. Multivariate analysis of factors influencing medical costs of acute pancreatitis hospitalizations based on a national administrative database. Dig Liver Dis 2012;44:143–8.