Enhanced Recovery in Mild Acute Pancreatitis

A Randomized Controlled Trial

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Objectives: Acute pancreatitis (AP) is a leading cause of hospitalization for a gastrointestinal illness in the United States. We hypothesized that enhanced recovery approaches may lead to earlier time to refeeding in patients with AP.

Methods: We performed a double-blind, randomized controlled trial of patients admitted with mild AP from July 2016 to April 2017 at a tertiary medical center. Participants were randomly assigned to receive either enhanced recovery consisting of nonopioid analgesia, patient-directed oral intake, and early ambulation versus standard treatment with opioid analgesia and physician-directed diet. Primary study end point was time to oral refeeding on an intent-to-treat basis. Secondary end points included differences in pancreatitis activity scores, morphine equivalents, length of stay, and 30-day readmissions.

Results: Forty-six participants enrolled. Median age was 53.1 years, and 54.3% were female. There was significant reduction in time to successful oral refeeding in the enhanced recovery versus standard treatment group (median, 13.8 vs 124.8 hours, $P < 0.001$). Pancreatitis activity scores trended lower at 48 to 96 hours among patients assigned to enhanced recovery (mean, 43.6 vs. 58.9, $P = 0.32$). No differences found in length of stay or 30-day readmissions.

Conclusion: In this randomized controlled trial, enhanced recovery was safe and effective in promoting earlier time to refeeding in patients hospitalized with AP.

Key Words: acute pancreatitis, opiates, enhanced recovery, nutrition

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Acute pancreatitis is one of the most common reasons for hospitalization related to a gastrointestinal illness in the United States. It accounts for almost 250,000 hospitalizations in the United States annually, leading to direct costs of more than $2 billion each year.[1] Although significant advances have occurred in understanding related to pathophysiology and management of complications related to severe forms of this disease, relatively little progress has been made in the standard treatment of acute pancreatitis.

The current treatment paradigm for acute pancreatitis centers on analgesia, intravenous fluid resuscitation, and bowel rest. However, it is conceivable that certain aspects of this approach to caring for patients with acute pancreatitis may actually present barriers to recovery. The use of opiates may lead to delays in gut motility, contributing to undesirable effects such as ileus and opioid-induced bowel dysfunction. Prolonged bowel rest may lead to delayed restoration of gut function, as well as increased intestinal permeability due to compromised integrity of the gut mucosa.[2] The use of opiates in conjunction with intravenous fluids has also been shown to significantly increase gastrointestinal dysmotility in patients with acute pancreatitis.[3]

Patients recovering from major intra-abdominal surgery have similar needs for parenteral analgesia and intravenous fluid requirements and are limited due to bed rest. Enhanced recovery after surgery (ERAS) strategies have been developed over the last few decades to help postsurgical patients overcome these barriers to facilitate expedited recovery. Enhanced recovery after surgery is a multidisciplinary, multimodal care pathway based on evidence-based approaches that have transformed perioperative surgical care. Enhanced recovery after surgery strategies encourage use of nonopioid adjunctive analgesia, early mobilization, and early initiation of oral diet to promote recovery. Implementation of ERAS care bundles has been shown to reduce care time and complications by up to 50% in patients undergoing colorectal surgery.[4] Data from systematic reviews assessing ERAS performance in pancreatic surgery have also shown favorable outcomes with regard to decreasing length of stay and complications without compromising patient safety.[5,6]

We hypothesized that application of ERAS strategies may help expedite recovery in patients with mild acute pancreatitis. Our study aim was to evaluate impact of an enhanced recovery protocol compared with standard of care on time to refeeding in patients with mild acute pancreatitis.

MATERIALS AND METHODS

Study Design and Setting

The study was a double-blind, 1:1 parallel group randomized controlled trial conducted at Kaiser Permanente Los Angeles Medical Center from July 2016 to April 2017. Kaiser Permanente Los Angeles Medical Center is a 528-bed tertiary care center located in Los Angeles, Calif. This study protocol was approved by the institutional review board. The trial was registered with http://clinicaltrials.gov NCT02813876 and is reported in accordance with the CONSORT guidelines. All patients completed

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written informed consent before study participation. All study authors had access to the data and approved the final manuscript.

Study Participants

Patients 18 years or older who were directly admitted with a diagnosis of acute pancreatitis were eligible for study participation. Diagnosis was confirmed by the presence of 2 or more of the following criteria: (1) epigastric abdominal pain, (2) elevation in serum lipase and/or amylase greater than 3 times the upper limit of normal, and/or (3) confirmatory findings of acute pancreatitis on cross-sectional imaging.

Patients were excluded from participation if they met any of the following criteria: known history of severe cardiovascular, respiratory, renal, gastrointestinal/hepatic, hematologic/oncologic, or immunologic disease defined as (1) greater than New York Heart Association class II heart failure, (2) active myocardial ischemia, (3) chronic kidney disease with serum creatinine greater than 2.0 mg/dL, (4) chronic obstructive pulmonary disease with requirement for supplemental oxygen, (5) gastrointestinal motility disorder or inflammatory bowel disease, (6) history of cirrhosis, and (7) malignancy other than nonsquamous skin cancer not in remission.

Individuals with a history of chronic pancreatitis or chronic pain syndrome requiring use of narcotic analgesics, or recent opioid prescription within 30 days before hospitalization were excluded. Those who had undergone abdominal surgery within 60 days before hospitalization were also excluded.

Patients who presented with severe acute pancreatitis defined as the presence of any of (1) organ failure (oxygen saturation less than 90% on room air, mean arterial pressure less than 70 mm Hg, requirement for vasopressor or inotropic support, serum creatinine greater than 2.0 mg/dL, Glasgow coma score less than 15) or (2) suspected or confirmed infected pancreatic necrosis (fever, leukocytosis in the setting of suspicious findings on cross-sectional imaging [gas within necrotic collection], or confirmed infection on fine needle aspirate) were excluded from enrollment. Patients with active evidence of the systemic inflammatory response syndrome at the time of recruitment were excluded from participation. Patients were also excluded if they were transferred from an outside hospital, had a documented allergy to hydromorphone or acetaminophen, or were pregnant at the time of enrollment.

Study Interventions

Participants were randomized in a 1:1 fashion to either (1) standard treatment or (2) enhanced recovery protocol. Those assigned to standard treatment were started on lactated Ringer's intravenous fluid resuscitation at a rate of 3 $mL \cdot kg^{-1} \cdot h^{-1}$ for a period of 24 hours then transitioned to a rate of 1.5 $mL \cdot kg^{-1} \cdot h^{-1}$ until discharged or discontinued by the primary medical team.[7] Parenteral analgesia was dosed at 0.2, 0.4, and 0.6 mg of intravenous hydromorphone as needed for mild (1–3), moderate (4–6), or severe (7–10) pain scales, respectively. Diet, antiemetics, and activity orders were determined by the primary medical team.

Patients assigned to the enhanced recovery protocol were immediately allowed a low-fat, solid diet. They were started on lactated Ringer's intravenous fluid resuscitation at a rate of 3 $mL \cdot kg^{-1} \cdot h^{-1}$ for a period of 24 hours. After the first 24 hours, if the patient was tolerating a solid diet, the intravenous fluids were discontinued; however, if not, they were transitioned to a rate of 1.5 $mL \cdot kg^{-1} \cdot h^{-1}$ until tolerating diet or discontinued by the primary medical team.

Patients were started on standing infusions of intravenous acetaminophen 1 g every 6 hours for the initial 24 hours (held in the setting of elevated liver transaminases >3 times upper limit normal). They also received intravenous ondansetron 4 mg every 6 hours for 24 hours. After 24 hours, intravenous ondansetron was available on an as needed basis.

Parenteral analgesia was provided as needed for mild to moderate pain (numeric rating scale, 1–6; ketorolac 30 mg) and severe pain (numeric rating, 7–10; morphine 2 mg). Early ambulation was encouraged for these patients; nursing orders were placed for the patients to be out of bed on day of hospital admission, followed by ambulation 5 times a day with nursing assistance the subsequent hospital days. Supplemental oxygen via nasal cannula at a rate of 2 L/min was provided for the first 24 hours as well.

Recruitment Procedures

Potentially eligible patients were identified in real time by a direct paging system from the clinical laboratory based on elevation in lipase values. A study physician confirmed the diagnosis of acute pancreatitis. All potentially eligible patients were required to be screened and enrolled within 12 hours of admission to the general medical ward to be randomized. Patients were approached either in the emergency department or in the medical ward for study participation. All participants completed written informed consent before randomization.

Randomization

Sequence Generation

Randomization was performed in random, permuted blocks through an online service (Sealed Envelope Ltd. 2017. Simple randomisation service. [Online] Available at: https://sealedenvelope.com/simple-randomiser/v1/. Accessed September 14, 2017.)

Allocation Concealment Mechanism

After a participant agreed to enroll, a study physician would input the data into the online randomization service, which would generate a coded treatment assignment. A physician member of the trial group would consent, enroll, and implement the appropriate order set for each participant.

Blinding

Patients were blinded to their treatment assignment. To maintain investigator blinding, a separate study staff member blinded to treatment assignment performed assessments of all patient outcomes after randomization.

Outcome Assessment

The primary study end point was time to successful oral refeeding, which was defined as tolerance of solid diet without nausea, vomiting, or abdominal pain. Ascertainment of the primary study end point was performed prospectively by a blinded study staff member through administration of daily questionnaires in which patients were asked to rate their pain control, diet intake, and degree of ongoing gastrointestinal symptoms.

Secondary end points included differences in pancreatitis activity scores (PASS),[8] average morphine requirements, length of stay, 30-day readmission rates, and patient satisfaction. The PASS score was calculated at 12-hour intervals for all study participants. Morphine equivalents were calculated as the mean intravenous morphine equivalents used over 12-hour intervals. Overall patient satisfaction was assessed through the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) patient satisfaction survey. All analyses were conducted on an intent-to-treat

basis. There were no changes to the trial outcomes after the commencement of the trial.

With respect to safety, all study participants were monitored for evidence of clinical deterioration, that is, worsening of pancreatitis, including necrosis, organ failure, and mortality. Feeding intolerances and any further adverse events were assessed prospectively on a daily basis up to 7 days after randomization.

Sample Size Estimation

In regard to the primary efficacy end point, we estimated that a total of 46 patients, 23 per arm, were needed to achieve a 24-hour reduction in time to successful oral refeeding from a historical average of 4 to 3 days, with 80% power at $\alpha = 0.05$.

Statistical Analysis

Primary End Point

Time to successful oral refeeding was analyzed as time to event/survival analysis (log-rank test), with patients censored at discharge.

Secondary End Points

PASS Scores

We compared average PASS scores during the recovery period, 48 to 96 hours across the treatment arms (*t* test).

Pain Control and Morphine Requirements

Mean pain scores and morphine equivalents were compared between the 2 treatment arms during the recovery period of 48 to 96 hours (*t* test).

Patient Satisfaction

After discharge, patients were mailed the HCAHPS survey. Responses to the HCAHPS survey with emphasis on satisfaction with pain management were compared across study arms (*t* test).

RESULTS

One hundred seventy-two patients were assessed for eligibility, and 126 were excluded. A total of 46 patients were randomized, 24 to enhanced, and 22 to the standard arm (Fig. 1). All patients were analyzed on intent-to-treat basis. There were no protocol deviations. Baseline demographics of the study population can be found in Table 1. The average age of the collective group was 53.1 years, with 54.3% women. Most patients were Hispanic (n = 29 [63%]). There were no significant differences in age, sex, or race/ethnicity between the 2 groups. The most common etiology overall for acute pancreatitis in this study was gallstones (n = 28 [60.9%]). Seventeen subjects (37%) underwent abdominal computed tomography imaging at some point during their hospitalization.

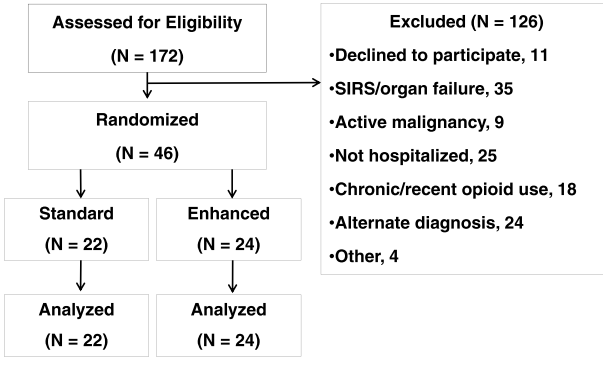

FIGURE 1. CONSORT diagram.

The primary end point for our study was defined as time to successful oral refeeding after hospital admission. There was a significant reduction in time to oral refeeding in participants assigned to enhanced recovery (median time of 13.8 hours compared with standard treatment median of 124.8 hours, $P < 0.001$; Fig. 2).

Secondary End Points

The PASS scores throughout hospitalization were compared between the 2 groups. During the recovery phase, hours 48 to 96 of hospitalization, there was no significant difference in PASS scores in the enhanced recovery mean PASS (43.6 [interquartile range [IQR], 22.5–64.5) compared with standard treatment (mean PASS, 58.9 [IQR, 34.6–83.2]; $P = 0.32$; Fig. 3). Morphine equivalents used were also not significantly different in the enhanced group (mean, 1.8 [IQR, 0.4–3.2]) compared with the standard group (2.5 [IQR, 0.7–4.4], $P = 0.51$) during the recovery phase of 48 to 96 hours (Fig. 4). There was no correlated increase in reported numerical pain scales between the 2 groups. Length of stay and 30-day readmission rates were not significantly different (Table 2).

Safety and Harms

No patients in the enhanced recovery arm had feeding intolerances, whereas 1 (4.5%) patient in standard treatment required enteral feeding. With regard to inpatient outcomes, 2 (9.1%) patients in the standard arm were found with pancreatic necrosis compared with 1 (4.2%) in the enhanced arm ($P = 0.51$). No patients developed organ failure during the study, and there were no deaths. There were no significant differences in adverse events. Two (9.1%) patients in the standard group had severe dizziness after administration of hydromorphone. One (4.2%) patient in the enhanced arm developed diarrhea (Table 2).

Regarding satisfaction with care (HCAHPS surveys), there were 13 (28%) respondents. Of those who responded, there was a significant difference in perception of pain management in response to the following question: During this hospital stay, how often did the hospital staff do everything they could to help you with your pain? (1, never; 2, sometimes; 3, usually; 4, always). The enhanced group had an average (standard deviation) answer of 4 (0) compared with standard treatment average (standard deviation) of 3 (0.5; $P = 0.028$).

DISCUSSION

In this prospective, randomized controlled trial, patients with mild acute pancreatitis on an enhanced recovery protocol safely resumed oral intake sooner compared with patients assigned to standard treatment. There were no significant differences in PASS scores or morphine equivalents used in patients undergoing enhanced recovery compared with standard care. There was increased satisfaction with regard to pain management for patients in the enhanced recovery arm. There also did not seem to be significant adverse events related to enhanced recovery.

To date, there has been limited evidence to guide recommendations for optimal supportive care for patients with acute pancreatitis. The present study evaluated 3 key components of care: pain management, nutrition, and activity.

The present study findings suggest that nonopioid-based analgesia may be effective approaches to pain control in patients with acute pancreatitis. This finding is consistent with previous literature. A Cochrane systematic review on pain management in acute pancreatitis evaluated 5 randomized controlled trials and concluded that there were no differences found in complications or adverse events in patients who received opiates compared with

TABLE 1. Baseline Demographics by Study Arm

	Standard Treatment, n = 22 (47.8%)	Enhanced Recovery, n = 24 (52.2%)	Total (n = 46)	*P*
Age at Admission, y				0.17
Mean (SD)	56.7 (19.71)	49.7 (16.93)	53.1 (18.44)	
18–<25	1 (4.5)	0 (0)	1 (2.2)	
25–<35	1 (4.5)	4 (16.7)	5 (10.9)	
35–<45	4 (18.2)	9 (37.5)	13 (28.3)	
≥45	16 (72.7)	11 (45.8)	27 (58.7)	
Sex, female	13 (59.1)	12 (50)	25 (54.3)	0.54
Race/ethnicity				0.20
White, non-Hispanic	4 (18.2)	4 (16.7)	8 (17.4)	
Black, non-Hispanic	0 (0)	3 (12.5)	3 (6.5)	
Hispanic	13 (59.1)	16 (66.7)	29 (63)	
Asian, non-Hispanic	4 (18.2)	1 (4.2)	5 (10.9)	
Other, non-Hispanic	1 (4.5)	0 (0)	1 (2.2)	
Neighborhood household income (in thousands)				0.34
n	17	14	31	
Mean (SD)	53.7 (24.79)	56.3 (32.39)	54.8 (28.00)	
<$25,000	1 (5.9)	0 (0)	1 (3.2)	
$25,000–$49,000	8 (47.1)	8 (57.1)	16 (51.6)	
$50,000–$99,999	7 (41.2)	3 (21.4)	10 (32.3)	
≥$100,000	1 (5.9)	3 (21.4)	4 (12.9)	
Disease etiology				0.28
Gallstones related	15 (68.2)	13 (54.2)	28 (60.9)	
Alcohol related	2 (9.1)	5 (20.8)	7 (15.2)	
Hypertriglyceridemia	4 (18.2)	2 (8.3)	6 (13)	
Other or unknown	1 (4.5)	4 (16.7)	5 (10.9)	
Charlson Comorbidity Index				0.05
0	7 (33.3)	13 (59.1)	20 (46.5)	
1–2	4 (19)	6 (27.3)	10 (23.3)	
≥3	10 (47.6)	3 (13.6)	13 (30.2)	
Underwent ERCP	2 (9.1)	6 (25)	8 (17.4)	0.18
Underwent cholecystectomy	9 (40.9)	6 (25)	15 (32.6)	0.27

Data presented as n (%) unless otherwise indicated.

nonopiate analgesia.[9,10] A small randomized controlled trial in 2008 compared metamizole with morphine analgesia and showed a nonsignificant association with pain relief in patients receiving metamizole. The patients on metamizole also had shorter mean times to pain relief compared with those on morphine.[11]

Nutritional support has been primarily studied in severe forms of acute pancreatitis.[12] However, optimal timing and type of nutrition for patients with mild cases of acute pancreatitis have been unclear. A 2017 meta-analysis of 11 randomized controlled trials on timing of feeding in acute pancreatitis showed that early feeding (within 48 hours of hospitalization) did not increase adverse events and was associated with reduced length of hospitalization compared with delayed feeding.[13] Initiation of oral intake with a low-fat solid diet has been supported in randomized controlled trials to be safe and associated with shorter length of stay.[14–16] A retrospective analysis of patients with acute pancreatitis found that discharge before tolerance of a solid diet was a risk factor for early readmission.[17] The present study extends upon these findings by examining the role of patient-directed resumption of dietary intake, particularly among patients with milder forms of illness.

Activity level has been understudied in patients with acute pancreatitis. Currently, no guidelines exist on recommended level of activity and mobilization of patients hospitalized with acute pancreatitis. To our knowledge, this is the first study to

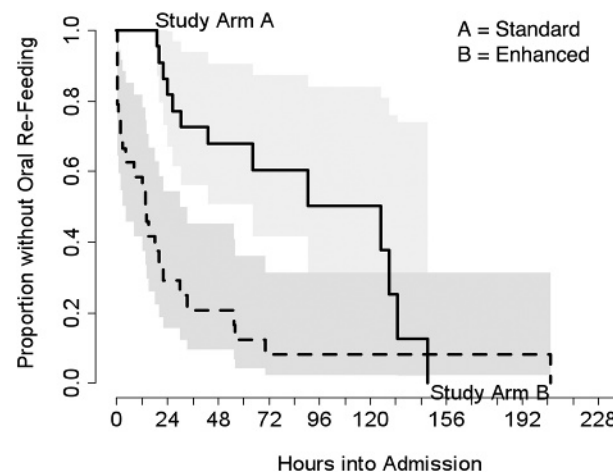

FIGURE 2. Time to oral refeeding.

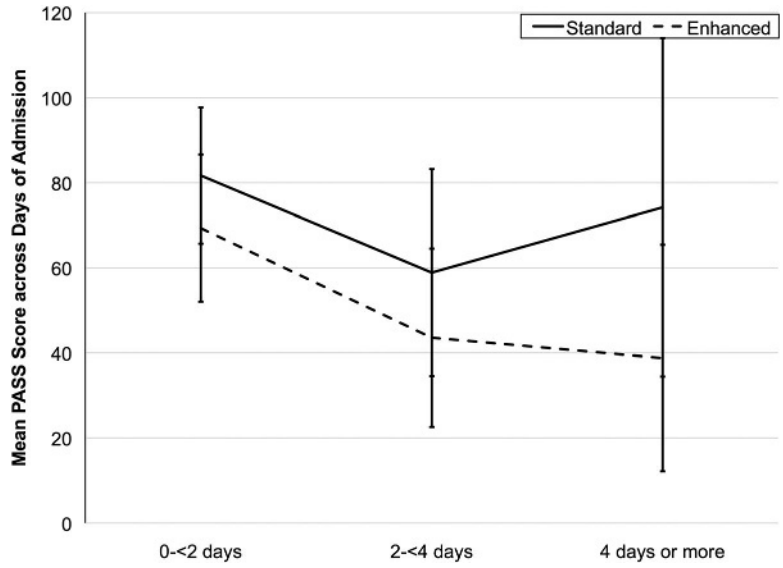

FIGURE 3. Mean PASS scores throughout hospitalization.

incorporate early mobility as a treatment intervention for patients with acute pancreatitis.

The cornerstones of ERAS address many of the same issues facing patients with acute pancreatitis. Specifically, patients recovering from surgery have needs related to pain management, nutrition, and assistance with mobilization. The principles developed for these patients in the ERAS pathway address all aspects of perioperative care.[18] The ERAS represents a paradigm shift by reexamining prior practices and implementing new evidence-based standards. The use of adjunctive nonopioid analgesia, early oral intake, cessation of intravenous fluids, and immediate mobilization of patients have been shown to reduce complication rates as well as overall length of hospitalization during postsurgical care.[4,5,19] This parallels with management of patients with acute pancreatitis, which, due to local inflammation from the injured pancreas, may mimic patients recovering from intra-abdominal surgery. This leads to downstream effects such as delay in gut function, which can be exacerbated by the use of opiates and prolonged bed rest.

There were limitations to the present study. Because this was an initial trial to assess feasibility, the sample size was limited to 46 participants. We excluded patients with severe disease and evidence of organ failure; thus, we are unable to generalize our results to those populations.

Although we did not see significant reductions in PASS scores or morphine equivalents, there was a nonsignificant trend toward reduced PASS score, as well as decreased morphine equivalents. These findings may have failed to reach statistical significance owing to our limited sample size. Larger studies are needed to assess differences in the 2 parameters. Furthermore, there was a large proportion of biliary disease seen in our study, which may have affected length of stay outcomes due to need for inpatient cholecystectomy. Finally, we were unable to perform prospective outreach to ascertain patient satisfaction because of institutional

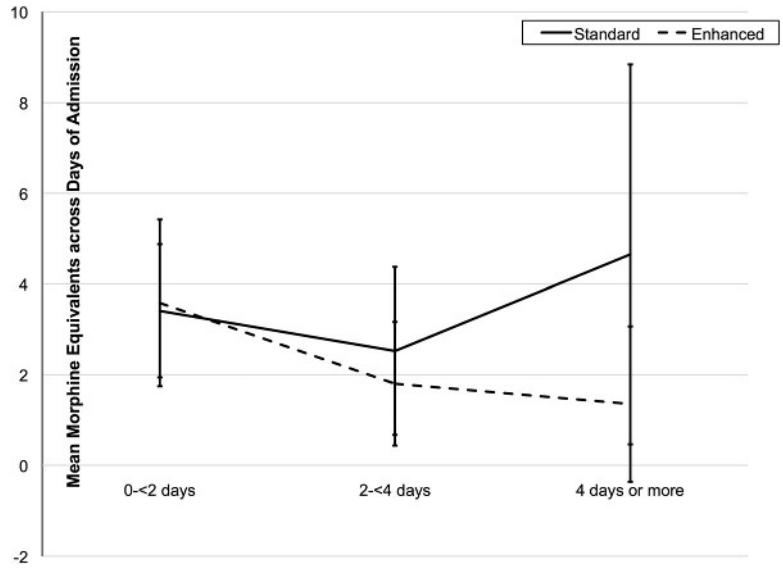

FIGURE 4. Mean morphine equivalents throughout hospitalization.

TABLE 2. Adverse Events and Additional Outcomes

	Standard, n = 22 (47.8%)	Enhanced, n = 24 (52.2%)	*P*
Length of stay, median (IQR), d	3 (2.0–4.2)	3 (2.5–4.1)	
30-d readmission, n (%)	2 (9.1)	1 (4.2)	0.51
Pancreatic necrosis, n (%)	2 (9.1)	1 (4.2)	0.51
Organ failure	0	0	
Mortality	0	0	
Adverse events, n (%)			
Dizziness after hydromorphone	2 (9.1)		
Enteral feeding	1 (4.5)		
Diarrhea		1 (4.2)	

policies to encourage return of HCAHPS, as well as to limit survey fatigue on behalf of study participants.

There are several potential implications of the present study findings. First, patient-directed resumption of oral intake seems to be safe and effective for patients with mild acute pancreatitis. Second, interventions such as early mobilization are feasible and may also help to promote earlier recovery. Finally, nonopiate-based approaches to analgesia are an important area of further study because the routine and widespread use of opiates in the care of patients with acute pancreatitis must be reconsidered in light of the current opioid epidemic across the United States.[20]

In summary, enhanced recovery approaches were safe and effective in promoting earlier time to refeeding in this randomized controlled trial of patients hospitalized for mild acute pancreatitis. Although certain aspects of the present treatment protocol such as patient-directed resumption of oral intake and early mobilization may be readily incorporated into current care pathways, further research is needed to establish effective nonopioid analgesic treatment regimens for patients with acute pancreatitis.

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