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Immediate Oral Refeeding in Patients with Mild and Moderate Acute Pancreatitis: A Multicenter, Randomized Controlled Trial (PADI trial)

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Conflict of Interest

The authors declare no conflicts of interest

Running head

Immediate diet in acute pancreatitis

Registration

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Elena Ramírez-Maldonado and Rosa Jorba participated in all phases of the study with the help other authors in the different parts.

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MINI-ABSTRACT

Optimal timing for refeeding in mild or moderate acute pancreatitis was investigated in this multicenter randomized trial, demonstrating that compared with conventional refeeding, administering an immediate low-fat oral diet to patients reduce hospital length of stay (primary endpoint), hospital costs and complications.

STRUCTURED ABSTRACT

Objective: To establish the optimal time to start oral refeeding in mild and moderate acute pancreatitis (AP) in order to reduce hospital length-of-stay (LOS) and complications.

Summary Background Data: Oral diet is essential in mild and moderate AP. The greatest benefits are obtained if refeeding starts early; however, the definition of 'early' remains controversial.

Methods: This multicenter, randomized, controlled trial (NCT03829085) included patients with a diagnosis of mild or moderate AP admitted consecutively to four hospitals from 2017 to 2019. Patients were randomized into two treatment groups: immediate oral refeeding (IORF) and conventional oral refeeding (CORF). The IORF group (low-fat-solid diet initiated immediately after hospital admission) was compared to CORF group (progressive oral diet was restarted when clinical and laboratory parameters had improved) in terms of LOS (primary endpoint), pain relapse, diet intolerance, complications, and, hospital costs.

Results: One hundred-thirty-three patients were included for randomization. The mean LOS for the IORF and CORF groups was 3.4 (SD±1.7) and 8.8 (SD±7.9) days, respectively ($p<0.001$). In the CORF group alone, pain relapse rate was 16%. There were fewer complications (8% vs 26%) and health costs were twice as low, with a savings of 1325.7€/patient in the IORF than CORF group.

Conclusions: IORF is safe and feasible in mild and moderate AP, resulting in significantly shorter LOS and cost savings, without causing adverse effects or complications.

INTRODUCTION

Acute pancreatitis (AP) is the third cause of hospital admission for gastrointestinal disease. In the United States, it represents an annual cost of 2.5 billion dollars. Recent studies have recorded an increase in the worldwide incidence of this disease[1-8].

During an AP episode, hydroelectrolytic enzymes, toxins, and cytokines are released, which can result in organ failure caused by systemic and metabolic dysregulation. This cascade of events leads to hypermetabolism and a negative energy balance making nutritional support indispensable[8].

Despite the importance of nutrition in the management of patients with AP, it remains a controversial topic[8-33]. Traditionally, the "pancreatic rest" concept was considered as the initial treatment of AP to avoid pain and pancreatitis relapse. Nevertheless, a recent evidence-based review[34] about nutritional support in AP demonstrated that fasting may induce intestinal atrophy, loss of epithelial barrier function, and changes to the intestinal flora which could derive, in some patients, in a systemic inflammatory response leading to a high risk of sepsis and organ failure[7-10,34].

Although the Pancreatitis, very early compared with normal start of enteral feeding - PYTHON study[35] may question the beneficial effects of early enteral nutrition on the gut mucosa, several studies have shown that an early oral diet in cases of mild AP or early enteral nutrition in cases of severe AP is associated with substantial pain reduction, reduced opioid use, and shorter hospital length-of-stay (LOS) in AP patients[8-12].

Current clinical guidelines[2,3] propose that oral refeeding (ORF) can be started early when certain and varied conditions are met, such as absence of pain and the improvement of laboratory parameters. However, the definition of "early" is not clearly established due to the lack of a consensus on its definition[26,27]. This controversy may explain why the conventional ORF (CORF), including fasting during the first 24-48 h until clinical and analytical improvement and gradual intake increase over 5-7 days, continues to be the treatment of choice for mild AP patients[36].

To address this issue and based on the benefits of early ORF, the aim of this study was to evaluate the outcomes of immediate ORF (IORF) in mild and moderate AP compared to CORF. We hypothesized that providing IORF to patients with mild or moderate AP would decrease the LOS (primary endpoint) and hospital expenses, without increasing the risk of complications.

METHODS

Study design and participants

This was a multicenter, randomized, controlled clinical trial consisting of two treatment groups (NCT03829085). This study was in accordance with the Declaration of Helsinki guidelines and approved by the Ethics Committee of the "Unió Catalana d'Hospitals" (code CEIC 17/05). Patients were recruited from four secondary and tertiary care hospitals (Consorci Sanitari Garraf - Coordinating Hospital, Clinic Hospital, University of Barcelona,

Moisés Broggi Hospital and University Hospital of Tarragona Joan XXIII) from March 1, 2017 to January 31, 2019.

All patients admitted to the emergency department at any of the centers who met at least two of the three AP diagnostic criteria were included in the study. The three diagnostic criteria included: acute abdominal pain, elevated serum amylase and/or lipase levels (≥three-fold above the upper reference limit), and evidence of AP on ultrasound and/or computed tomography. Pancreatitis severity was assessed based on the Modified International Multidisciplinary Classification[37-39]. Systemic inflammatory response syndrome (SIRS) was used to predict severe AP at admission and persistent SIRS at 48 h[2]. Organ failure (OF) was defined according to Marshall's modified scoring system (persistent OF>48 h, and transient OF<48 h)[7].

The inclusion criteria were >18 years old, with mild or moderate AP, randomization <12 h from hospital admission, and adequate cognitive capacity. The exclusion criteria were as follows: pregnancy or breastfeeding, poor oral intake for reasons other than AP, abdominal pain lasting >96 h prior to admission, pancreatic neoplasm, surgery, trauma or endoscopic retrograde cholangiopancreatography as AP etiology, chronic pancreatitis, short bowel syndrome, and severe or critical AP on admission.

Randomization and interventions

Randomization was performed using a computer-generated random code and stratified by center. Each random code, with the assigned treatment strategy, was placed in a sealed and opaque envelope and distributed to each center by the study monitor. Surgeons on call at the different centers were responsible for enrollment and treatment allocation according to each sequentially numbered envelope. Enrollment was unblinded for patients and physicians due to the type of intervention. To reduce bias, the investigators assessing the outcome did not participate in the follow-up or discharge of patients. All patients received detailed written information about their diagnosis and hospital treatment plan.

After obtaining informed consent, the patients were admitted and randomly allocated to either the IORF (experimental) or CORF (control) group. Patients in the IORF group were started on a low-fat solid diet immediately upon hospital admission, regardless of symptoms or laboratory parameters, even if they were in the emergency room waiting for a hospital bed. For patients in the CORF group, oral diet was reintroduced in a stepwise manner from fasting, then to clear liquids, and finally, a low-fat solid diet when the patients met the following criteria: absence of abdominal pain and presence of peristalsis, pancreatic enzymes two-fold below the reference limit, blood leukocyte level <15000/mm^3, and decreased C-reactive protein level.

Patient management, except their diet, followed the recommendations of the International Association of Pancreatology (IAP)/American Pancreatic Association (APA) evidence-based guidelines[2]. Patients received adequate intravenous fluid resuscitation based on their individual hemodynamic parameters and fluid balance, correction of hydroelectrolytic imbalances and treatment of organ failure and analgesia according to individual requirements (oral, intravenous, continuous intravenous infusion, or opioids). All patients were monitored

upon arrival at the emergency room and during admission, three times per day, for vital signs, total intake, urine output, gastrointestinal symptoms, peristalsis and abdominal pain using the visual analog pain scale (VAS) (the highest VAS value per day was selected). Indications for assessment imaging, interventions or intensive care unit admission also followed the guidelines[2].

Diet tolerance was defined as the patient's ability to ingest >50% of each meal. Conversely, diet intolerance was considered as the inability to ingest ≤50% of the meals at any time during admission due to the following criteria: abdominal pain not controlled with conventional analgesics, nausea or vomiting not alleviated by antiemetics, AP relapse, and abdominal pain relapse.

LOS was calculated from the day of admission to the day of discharge and based on the number of nights spent in hospital, with a one-night minimum. The criteria for hospital discharge were as follows: diet tolerance ≥75% of the diet, absence of nausea or vomiting and analgesic-controlled pain (VAS≤2). In cases of LOS prolongation due to cholecystectomy scheduling, medical conditions independent of AP itself, or waiting for a convalescence center space, the discharge date was instead established by meeting the medical criteria for discharge. A clinical and analytical follow-up, was conducted one to three months from hospital discharge.

Study endpoints

The primary endpoint of the trial was LOS. Secondary endpoints included complications, abdominal pain relapse, laboratory findings, diet intolerance, and hospital costs.

Data collection

Blood samples collected upon hospital admission, on refeeding day and discharge day were analyzed by each institution's labs and standardized for the database. Blood samples and VAS scale on admission and refeeding day being the same day for IORF group.

Due to the variability in hospital costs, cost analysis was performed only at the study's coordinating hospital. The financial department provided cost data. The total cost per treatment group was based on their mean LOS.

Data on each patient were collected in a standard form by the research coordinator at each center and sent to the coordinating hospital at the end of the study. Data were monitored by the Research and Innovation Department of the Consorci Sanitari Garraf and were included in a database using IBM-SPSS Statistical Software version 25 (IBM Corporation, Armonk, NY, USA).

Sample size and statistical analysis

In the coordinating hospital, the median LOS was 5 days (range 3-10 days). To detect a 2-day reduction in LOS, a minimum sample size of 60 patients for each study group was required, with 90% power and a p-value of 0.05. A dropout rate of approximately 10% was assumed. An intention-to-treat analysis was conducted, with the exclusion of patients AP diagnosis was deemed incorrect or who met any exclusion criteria (decided before any analysis by the data monitoring committee, whose members were unaware of treatment assignments).

Differences between groups were analyzed using Fisher's exact test for categorical variables and ANOVA for quantitative variables. P-values <0.05 were considered significant. For variables that were not normally distributed, p-values were obtained through a permutation test. Multiple comparisons were conducted using Wilcoxon's nonparametric test with a false discovery rate correction. For categorical variables, Fisher's and McNemar's tests were used to analyze the resulting contingency tables.

To analyze LOS, a linear regression model was applied, after logarithmic transformation of the response variables. Variables that showed a significant association with the response in univariate analysis were used as initial predictor variables. Subsequently, the final model was obtained by selecting the predictor variables using the Lasso method. All statistical analysis (including sample size calculation) were performed by an external statistician.

RESULTS

Selected patients and clinical characteristics

In accordance with the clinical guidelines of the Consolidated Standards of Reporting Trials (CONSORT)[40], Figure 1 shows the patient selection scheme. A total of 142 patients with AP diagnosis were initially randomized. After monitoring, 11 patients were excluded from the analysis for not meeting the requirements of the study protocol (Figure 1). Finally, 131 patients were included in the study, 71 in the IORF group and 60 in the CORF group. Six patients were lost during follow-up, though none were withdrawn from the analysis. Table 1 shows the descriptive analysis of the groups. Demographic, anthropometric, and laboratory data at the time of hospital admission were comparable in the two groups (Table 1).

Primary endpoint

LOS was significantly shorter in the IORF than CORF group (mean ± standard deviation [SD], 3.4±1.7 days vs 8.8±7.9 days, p<0.001). The average LOS reduction for an IORF patient was 51% (95% confidence interval 40.5-59.6). The treatment group variable was a significant factor in multivariate analysis for LOS prediction (Table 2, Figure 2).

Secondary Endpoints

Abdominal pain

The VAS score was significantly higher in the IORF group than the CORF group on refeeding day (admission day for IORF group, p<0.001; Table 3). The requirement for analgesics or opioids was lower in the IORF group than in the CORF group (p<0.001). The abdominal pain relapse rate was 0% and 16% in the IORF and CORF groups, respectively (Table 2).

Diet intolerance

In the IORF group, 99% of patients tolerated the diet from the beginning of refeeding; just one patient was intolerant to the diet due to persistent vomiting. In the CORF group, 21% of patients had diet intolerance due to abdominal pain, vomiting, or hyporexia (Table 2).

Analytical inflammatory and biochemical parameters

On the refeeding day, mean serum amylase and leukocyte levels had not normalized in the IORF group due to the admission and refeeding day being the same day for this group (Table 1 y 3). Leukocyte and amylase levels on the refeeding day were statistically higher in the IORF than in the CORF group ($p=0.03$ and $p<0.001$, respectively; Table 3).

Complications

Significantly fewer complications developed in the IORF group than in the CORF group ($p=0.01$). The IORF group included three patients (4%) with complications ranging from transient organ failure to peripancreatic collections. Eleven CORF patients (18%) presented with organ failure, peripancreatic collection, and infected pancreatic necrosis. Mortality and hospital readmissions were not significant. Zero and six patients in the IORF and CORF groups, respectively, progressed to severe or critical AP ($p=0.006$; Table 2).

Interventions

In the IORF group, no patients required radiological or surgical intervention or intensive care unit admission. In contrast, in the CORF group, two patients (4%) required radiological drainage of a peripancreatic collection, one patient (1.6%) required surgical intervention for infected pancreatic necrosis, and four patients (6.6%) were admitted to the intensive care unit with a total stay of 45 days (Table 2).

Costs

Table 4 shows the costs calculation for each group, according to the mean LOS and intensive care unit admission. Hospital costs were twice as low in the IORF group, with savings of 1325.7€/patient.

DISCUSSION

The optimal timing for refeeding in AP was investigated in this multicenter, randomized study, demonstrating that administering an immediate oral low-fat solid diet to mild or moderate AP patients significantly reduced LOS and hospital costs without increasing the risk of complications when compared to CORF. Due to current variability in the timing of refeeding studies and the persistent use of CORF treatment in many hospitals, this study provides high-level scientific evidence to help in the decision-making process of the management of these patients.

The most recent clinical guidelines regarding nutritional support for AP patients include recommendations according to severity. In mild AP patients, "early" oral diet is preferred, although the conditions for defining the ideal time for refeeding are highly variable. First, the *IPA/APA guidelines*[2] recommend that "diet in predicted mild AP can be restarted once abdominal pain is decreasing and inflammatory markers are improving." Second, the *American College of Gastroenterology guidelines*[4] describe that "the diet can be started immediately if there is no nausea or vomiting, and abdominal pain has resolved." Finally, the most recent update from the *American Gastroenterological Association guidelines*[5]

recommend “an early (within 24 h) oral feeding as tolerated rather than keeping the patient nil per os.”

These differences in clinical guideline recommendations may explain why the antiquated dogma of “pancreatic rest” remains in clinical practice. A high percentage of patients admitted with mild AP are treated conventionally with fasting to minimize pancreatic stimulation and the risk of worsening abdominal pain. A 2015 Canadian study, which evaluated hospital compliance with the guidelines for AP, found that a significant proportion of the cost for this disease was attributed to the unjustified application of the old dogma in about 80.6% of patients[36].

We designed this study to address the timing of diet in AP based on the differences of standards in previous studies of EORF in patients with mild AP (Table 5)[19-24] and in line with the conclusions of a recent review[41], which highlighted the lack of solid evidence regarding the onset of diet in AP. We hypothesized that administering a low-fat solid diet immediately upon hospital admission in mild or moderate AP patients would reduce LOS, hospital costs, and complications.

CORF management was based on "pancreatic rest", which is still the most common treatment strategy despite the recommendations of current clinical guidelines. Traditionally, it consists of starting a gradual diet when pancreatic enzymes levels drop, peristalsis is present, and patients do not have abdominal pain or fever. The oral diet moves progressively from clear liquids to solids. Although it could be considered a bias, a blood leukocyte level <15000/mm^3 was included to conform to previous studies where it was part of the conditions of the conventional arm[22]. We also specified conditions for refeeding in each group and for hospital discharge, thus avoiding bias driven by subjective opinion of the treatment team in this unblinded study. The unblinded study design may be considered a limitation, but the nature of the interventions carried out (immediate oral diet vs. fasting) made it obvious to patients and physicians which was the assigned treatment group.

LOS was our primary endpoint. According to other similar studies (Table 5) we found a 51% reduction in LOS in the IORF group. This result was achieved by administering a low-fat solid diet upon hospital admission.

For patients in the IORF group (refeeding and admission day were the same), the pain level and laboratory measurements (amylase and leucocyte levels and all beochemical markers were the same on admission) were taken at the time of emergency consultation, and they were able to start the diet (Table 1 and 3). In this group, starting and tolerating the diet was possible with conventional analgesics and antiemetic treatments. These findings concur with those reported in other studies[19,20,23].

Therefore, in our experience, it is possible to start an oral diet without waiting for reductions in abdominal pain, peristalsis to begin, or appetite recovery. Furthermore, there is no need to apply analytical restrictions such as amylase, leukocytes or C-reactive protein levels to start the diet in mild or moderate AP patients (Table 3).

Several studies (Table 5)[28-29,31], a meta-analysis[32], and the present study show a reduction in LOS in patients receiving a non-liquid diet. A study by Moraes et al.[30] compared three treatment branches (A: a hypocaloric clear liquid diet; B: a hypocaloric soft diet; C: a full solid diet) for refeeding in mild AP. No differences in abdominal pain relapse or LOS were found between treatment branches, with no adverse effects produced by a normal fat diet. Despite these results, we opted to use a low-fat solid diet because we did not want to introduce any confounders between abdominal pain relapse and possible biliary colic.

Traditionally, one of the most feared adverse effects of oral refeeding in AP patients is abdominal pain relapse, which prolongs LOS and requires additional health care resources[21]. Petrov et al[11] reported that 22% of patients suffered abdominal pain relapse after oral refeeding. Although the pathophysiology of abdominal pain relapse in AP is not clear[11], studies have shown that diet has no interaction with pain or other adverse effects. The present study identified no relapse in the IORF group and only a 16% abdominal pain relapse rate in the CORF group, which influenced LOS duration. It is noteworthy that pain control was better with conventional analgesia in the IORF group than in the CORF group. In fact, the CORF group more frequently required opioids or continuous analgesic perfusion during their hospital stay.

Another adverse effect is diet intolerance, which can occur in 50% of patients[44], leading to a prolonged LOS with greater costs and risk of readmissions. In this study, only 1% of the IORF group showed diet intolerance compared with >20% in the CORF group. In the IORF group, only one patient had intolerance caused by vomiting which was adequately treated with antiemetics, eventually allowing the patient to continue with the diet. Patients in the CORF group also received adequate treatment of symptoms that presented before and after refeeding.

Previous studies[19-24] have found that EORF causes no adverse effects in patients with AP, with no significant differences compared to CORF. In our experience, since our study evaluated all possible adverse effects (Table 5), the IORF group had a lower percentage of abdominal pain relapse, diet intolerance, complications, intensive care unit admissions, progression to severe or critical AP, and hospital readmissions (although not significant), than the CORF group. For these remarkable and significant findings, there is no clear clinical or pathophysiological explanation despite having evaluated inflammatory parameters, such as C-reactive protein and leukocyte levels, and nutritional status through triglycerides, cholesterol, glycemia, albumin and prealbumin levels. It would be interesting to carry out other studies to try to explain these findings.

One of the main goals when designing a treatment strategy is to reduce hospital costs and increase the efficiency of healthcare systems. AP is one of the most common gastrointestinal causes of hospital admission, with worldwide increases in incidence and very notable annual hospital costs[1-8,34,42-44], specially when current guidelines are not complied with[36,45]. In our study, IORF reduced health costs by almost 50% with a LOS reduction of 51% in comparison to CORF. However, a major limitation of our study was the lack of assessment of complication and intervention costs due to the variability of health costs at each hospital.

In summary, this study answers the previously posed questions: IORF with low-fat solid diet administered by the treatment team as a nutritional management strategy reduced LOS and hospital costs in mild and moderate AP patients. This study contributes further evidence to existing literature that will permit greater adherence to clinical guidelines by medical treatment teams.

CONCLUSIONS

The administration of immediate oral low-fat solid diet to patients with mild and moderate AP is safe and feasible. IORF was associated with a significant reduction in LOS and hospital costs without increasing the risk of complications. Although the timing of refeeding is now established, future studies should compare low and normal-fat diets and should be sufficiently powered to identify differences in adverse effects and complications.

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FIGURE LEGENDS

Figure 1. CONSORT flow diagram. IORF: Immediate Oral Refeeding, CORF: Conventional Oral Refeeding

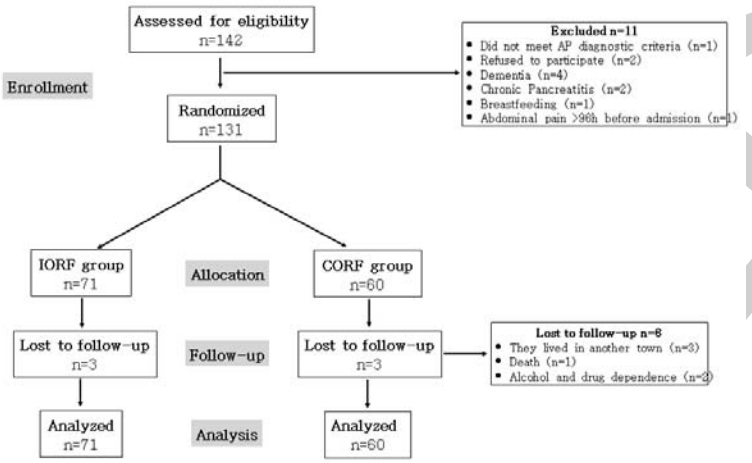

Figure 2. Analysis of hospital length of stay. 2A. Lasso regression. 2B. Kaplan-Meier analysis. IORF: Immediate Oral Refeeding, CORF: Conventional Oral Refeeding

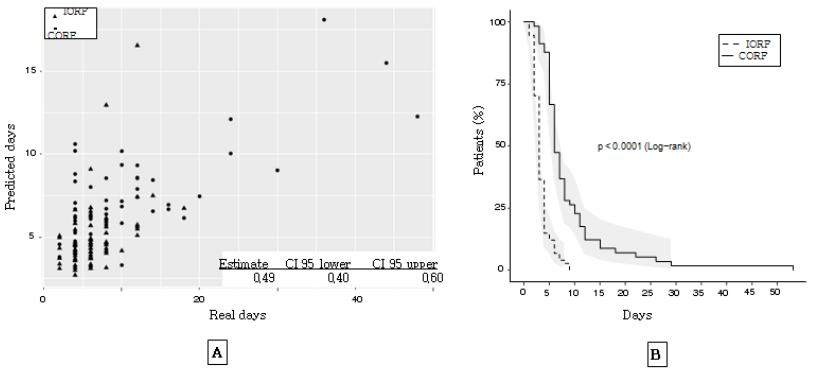

Table 1. Baseline characteristics of patients

Outcomes		Total	IORF group	CORF group	p-value
		n=131	n=71	n=60	<0.05
Age - years, mean (SD)		67.8 (17.2)	70.2 (16.4)	64.9 (17.9)	0.15
Sex - male, n (%)		67 (51.1)	37 (52.1)	30 (50.0)	1.0
ASA	I, n (%)	29 (22.1)	16 (22.5)	13 (21.7)	0.3
	II, n (%)	74 (56.4)	37 (52.1)	37 (61.7)	
	III, n (%)	23 (17.5)	15 (21.1)	8 (13.3)	
	IV, n (%)	5 (3.8)	3 (4.2)	2 (3.3)	
Weight - kg(SD)		74.8 (14.5)	75.7 (15.1)	73.7 (14.7)	1.0
BMI - kg/m^2(SD)		28.06 (4.9)	28.5 (4.7)	27.5 (5.2)	0.56
Etiology	Biliary, n (%)	96 (73.3)	54 (76.1)	42 (70.0)	0.18
	Alcoholic, n (%)	16 (12.2)	6 (8.4)	10 (16.7)	
	Miscellaneous, n (%)	19 (14.5)	11 (15.5)	8 (13.3)	
Days from onset of symptoms to admission -days (SD)		1 (1.5)	1 (1.3)	1 (1.7)	1.0
Signs and symptoms	Abdominal pain, VAS (SD)	6.8 (2.3)	6.2 (2.6)	7.2 (2.2)	0.12
	Pain and vomits, n (%)	50 (38.1)	26 (36)	24 (40.0)	0.47
	Peristalsis, n (%)	122 (93.1)	71 (100)	53 (88.3)	0.17
Glasgow scale <15		0	0	0	-
Serum amylase, U/L, mean (SD)$_a$		1421.6 (1424.0)	1339.9 (1341.1)	1527.6 (1530.6)	1.0
Serum lipase, IU/L, mean (SD)$_b$		4665.8 (4051.7)	4182.5 (4074.3)	5259.7 (4001.6)	0.16

Leukocytes, 10^9/L, mean (SD)	9.3 (0.4)	9.4 (0.3)	9.2 (0.4)	0.06
CRP, mg/dl, mean (SD)$_c$	10.0 (22.0)	10.5 (24.7)	9.4 (18.1)	1.0
Pre-Albumin, g/L, mean (SD)$_d$	0.22 (0.06)	0.20 (0.06)	0.24 (0.06)	0.02
Albumin, g/L, mean (SD)$_e$	34.7 (5.6)	34.2 (5.5)	35.5 (5.7)	0.94
Triglycerides, mg/dl, mean (SD)$_f$	153.1 (267.1)	167.7 (341.6)	133.6 (106.5)	1.00
Cholesterol, mg/dl, mean (SD)$_g$	168.5 (56.8)	169.7 (63.6)	166.9 (46.8)	0.69
Glycemia, mg/dl, mean (SD)$_h$	135.7 (51.5)	138.9 (57.6)	131.6 (42.6)	0.46
SIRS$_i$, n (%)	10 (7.6)	3 (4.2)	7 (11.7)	0.10

IORF: Immediate oral refeeding; CORF: Conventional oral refeeding; ASA:"American Society of Anesthesiologists" Physical status classification system; BMI: Body mass index; VAS: Visual analog pain scale; SIRS: Systemic Inflammatory Response Syndrome; CRP: C-reactive protein; SD: Standard deviation. $_a$Normal:20-104; $_b$Normal<393; $_c$Normal<1; $_d$Normal:0.2-0.4; $_e$Normal:34-48; $_f$Normal<150. $_g$Normal<200; $_h$Normal:65-110. $_i$SIRS definition: tat least 2 of the following 4 clinical criteria: Temperature: <38ºC or <36ºC; Respiratory rate: >20 breaths per minute or a PaCO2<32mmHg; Heart rate>90lpm; Leukocytes: >12 10^9/L o <4 10^9/L.

Table 2. Outcomes comparing groups

Outcomes		IORF Group n=71	CORF Group n=60	p-value
Length of hospital stay, days, mean (SD)		3.4 (1.7)	8.8 (7.9)	<0.001
Days from admission to refeeding, days, mean (SD)		0	2.8 (1.7)	<0.001
Days from refeeding to discharge, days, mean (SD)		3.4 (1.7)	5.4 (4.8)	<0.001
Need for opioids or analgesia infusión		0	5 (8.3)	<0.001
Intolerance diet n (%)		1 (1.4)	13 (21.6)	<0.001
Reasons for intolerance	Relapse of pain, n (%)	0	10 (16.7)	<0.001
	Nausea and vomiting, n (%)	1 (1.4)	2 (3.3)	0.37
	Anorexy, n (%)	0	1 (1.6)	0.44
Progression of acute pancreatitis, n (%)		0	6 (10.0)	<0.006
Complications, n (%)		3 (4.2)	11 (18.3)	<0.009
Interventions	Radiology, n (%)	0	2 (3.3)	0.19
	Surgery, n (%)	0	1 (1.6)	0.44
ICU admission, n (%)		0	4 (6.6)	0.03
Mortality, n (%)		0	1 (1.6)	0.44
Hospital readmission, n (%)		2 (2.8)	5 (8.3)	0.15

IORF: Immediate oral refeeding; CORF: Conventional oral refeeding; SD: Standard deviation; ICU: Intensive care unit

Table 3. Clinical situation at the refeeding day

Outcome	IORF group**	CORF group	p-value
	n=71	n=60	<0.05
Days from admission to refeeding, days, mean (SD)	0	2.8 (1.7)	<0.001
Abdominal pain, VAS (SD)	6.2 (2.6)	2.0 (0.3)	<0.001
Weight, kg (SD)	75.7 (15.1)	73.2 (13.8)	0.28
BMI, kg/m^2 (SD)	28.5 (4.7)	27.3 (5.2)	0.16
Serum amylase, U/L, mean $(SD)_a$	1339.9 (1341.1)	298.6 (13.8)	<0.001
Serum lipase, IU/L, mean $(SD)_b$	4182.5 (4075.3)	1388.8 (2080.7)	<0.001
Leukocytes, 10^9/L (SD)	9.4 (0.3)	9.09 (0.4)	0.03
CRP, mg/dl $(SD)_c$	10.5 (24.7)	14.6 (24.7)	0.56
Pre-Albumin, g/L $(SD)_d$	0.20 (0.06)	0.18 (0.12)	0.33
Albumin, g/L $(SD)_e$	34.2 (5.5)	31.3 (8.2)	0.04
Triglycerides, mg/dl $(SD)_f$	167.7 (341.6)	136.2 (80.9)	0.68
Cholesterol, mg/dl $(SD)_g$	169.7 (63.6)	151.4 (41.4)	0.08
Glycemia, mg/dl $(SD)_h$	138.9 (57.6)	112.8 (49.1)	0.01

**Refeeding day = admission day for IORF group. See table 1, values of admission day.

IORF: Immediate oral refeeding; CORF: Conventional oral refeeding; VAS: Visual analog pain scale; BMI: Body mass index; CRP: C-reactive protein; SD: Standard deviation; $_a$Normal:20-104; $_b$Normal<393; $_c$Normal<1; $_d$Normal:0.2-0.4; $_e$Normal:34-48; $_f$Normal<150. $_g$Normal<200; $_h$Normal:65-110

Table 4. Costs of treatment for each patient*

Outcome	IORF group		CORF group		Costs saving
	Cost	Total	Cost	Total	
Emergency department costs	343	343	343	343	0
Hospital admission costs					
Bed costs	167.47 x 3 days	502.41**	167.47 x 8 days	1339.76**	837.35
Physician	51.71		51.71		
Nurse	41.12		41.12		
Personal	92.83	92.83	92.83	92.83	0
Medical supplies	3.12	3.12	3,12	3.12	0
Drugs	15.26	15.26	15.26	15.26	0
Diagnosis tools	210.23	210.23	210.23	210.23	0
Personnel, administrative work	42.58	42.58	42.58	42.58	0
ICU admission costs	651.13 x 0 days	0***	651.13 x 0.75days	488.34***	488.34
Total costs		**1230.11**		**2555.80**	**1325.69**

IORF: Immediate oral refeeding; CORF: Conventional oral refeeding; ICU: Intensive care unit. *All values are in Euros for 2019: ** Bed costs according to the mean hospital stay per group, *** Bed cost calculated according to the mean ICU stay.

Table 5. Summary of Randomized Clinical Trials about refeeding in mild and moderate pancreatitis

	Studies	Group	n	Oral refeeding condition	Type of diet	LOHS days (p)		DI n (p)		APR n (p)		Complications n (p)		Readmission n (p)	
Oral refeeding time	**Eckerwall, 2007**[19] (2003-2005)	EORF	29	Immediately if tolerated	To eat freely as tolerated	4 (2-10)	<0.05	1	<0.3	1	<0.3	10	NR	2	NR
		CORF	30	No abdominal pain, decreased laboratory levels	Increased the intake during 3-7d	6 (2-14)		4		4		13		3	
	Teich, 2010[20] (2005-2008)	EORF	69	Patient chose	Low fat diet and tea	7 (5-10.5	0,315	NR		nd		NR		NR	
		CORF	74	Lipase below twofold upper limit	Low fat diet and tea	8 (5.75-12)									
	Li, 2013[21] (2009)	EORF	75	Subjective feeling of hunger	Progressed from CLD to LFSD	6.8 ± 2.1	<0.001	NR		6	0.31	NR		NR	
		CORF	74	No abdominal pain, decreased lipase <2-fold ULM	Progressed from CLD to LFSD	10.4 ± 4.1				3					
	Lariño-Noia, 2014[22] (2 years)	EORF	20	Bowel sounds were present	Stepwise increase kcal during 3d	6 (4-15)		3		1					
			17		Immediate intake 1767 kcal	5 (3-9)		1		0					
		CORF	17	Bowel sounds were present, no abdominal pain, no fever, decreasing lipase levels and blood leukocyte <15000/mm^3	Stepwise increase kcal during 3d	7 (4-16)	<0.001	1	1.0	1	0.58	NR		NR	
			18		Immediate intake 1767 kcal	7.5 (4-18)		3		0					
	Khan,	EORF	30	Feeding started in the	No characterist	7.8 ±	<0.0		NR		NR		NR		N

	2017[24] (2015-2016)	CORF	30	first 12 hours Feeding started in the first 12 hours	ics of the diet No characteristics of the diet	2.14 10.03 ± 1.75	01						R
	This study (2017-2019)	IORF CORF	71 60	Immediately Refeeding with conditions	LFSD Progressed from CLD to LFSD	3.4 (1.7) 8.8 (7.9)	<0.001	1 13	<0.001	0 10	<0.001	3 11	<0.001	2 5	0.15
	Jacobson, 2007[28] (1999-2005)	CLD LFSD	55 66	Until the medical team caring for the patient to resume oral feeding	CLD LSFD	4 (3-5) 4 (3-6)	0.72	4 6	0.51		NR		NR	6 3	0.51
	Sathiaraj, 2008[29] (2007-2008)	CLD SD	49 52	Abdominal pain, nausea and vomiting had subsided and bowel sounds had returned.	CLD LSFD	8.71 ± 4.995 5.92 ± 2.978	<0.001	7 4	nd	3 4	0.85		NR		NR
Oral refeeding type	**Moraes, 2010**[30] (2004-2008)	CLD LFSD SD	70 70 70	Absence of abdominal pain, normal bowel sounds and patient was hungry	CLD LSFD FSD	8.2 ± 2.6 8.2 ± 2.4 7.5 ± 3.5	0.32		NR	14 12 15	0.80		NR	1 1 1	nd
	Rajkumar, 2013[31] (2008-2010)	CLD SD	30 30	Complete absense of pain	CLD SD	6.91 ± 2.43 4.23 ± 2.08	<0.001	0 1	1.0	6 6	1.0		NR		NR
	This study (2017-2019)	IORF CORF	71 60	Inmediaterly Refeeding with conditions	LFSD Progressed from CLD to LFSD	3.4 (1.7) 8.8 (7.9)	<0,001	1 13	<0.001	0 10	<0.001	3 11	<0.001	2 5	0.15

IORF: Immediate oral refeeding; EORF: Early; CORF: Conventional; LFSD: Low fat solid diet; FSD: Fat solid diet; CLD: Clear liquid diet; SD: Solid diet; ULM: Upper limit measure; kcal: kilocalories; DI: Diet intolerance; APR: Abdominal pain relapse; nd: not differences; NR: Not reported