# NON-INFERIORITY COMPARATIVE CLINICAL TRIAL BETWEEN EARLY ORAL REFEEDING VERSUS USUAL ORAL REFEEDING IN MILD ACUTE PANCREATITIS PATIENTS

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## Abstract

**Background** The aim of the study is to compare the onset of oral feeding in the first 24 hours after hospital admission and determine if this influences the recurrence of pain or alters the blood levels of pancreatic enzymes, compared to usual oral refeeding in patients with mild acute pancreatitis

**Methods** This Non-Inferiority Randomized controlled trial was carried out between September 2018 and June 2019, prior authorization from the ethics committee in health research. Patients with diagnosis of mild acute biliary pancreatitis, were divided into: Group A (early oral refeeding) and Group B (usual oral refeeding). Outcome measures were lipase pancreatic, systemic inflammatory response (concentrations of leukocytes) were used as marker for it, feasibility evaluated by abdominal pain recurrence, presence and recurrence of gastrointestinal symptoms and length of hospital stay.

**Results** Two patients of the EOR group had pain relapse (3.2%) and four of the UOR group (6.77%) after oral refeeding (p= 0.379). The presence of nausea or vomiting after onset of oral refeeding does not show differences (p= 0.293). The start time of the oral refeeding was approximately 48 h longer in the UOR group. Hospital length was 5 days in the group EOR and 8 days for the UOR group (p = 0.042); and this difference was also manifested in the hospital cost being higher in the group UOR p = 0.0235

**Conclusion** The early oral refeeding is safe in mild acute pancreatitis patients, without adverse gastrointestinal events, and reduce the hospital stay and cost compared with usual oral refeeding.

**Trial registration: Local Committee 1001 registration number 17 CI 11020146 CPFEPRIS. Trial registration number R-2018-1001-074 August 28, 2018.**

**Keywords**

**Mild acute pancreatitis**

**Oral refeeding**

**Non inferiority clinical trial**

**Nil per oral**

## BACKGROUND

Acute pancreatitis (AP) is an inflammatory pancreatic process, presents different severity degrees [1]. Over the last two decades, there has been a paradigm shift in the management, from surgical to "step up" approach using percutaneous or endoscopic catheter drainage followed by minimally invasive necrosectomy [2]. As no curative therapy is currently available for AP, early treatment consists of supportive care which includes adequate fluid resuscitation, pain management and enteral nutrition [3]. Pancreatic rest by Nil Per Oral (NPO) strategy was considered necessary in AP till abdominal pain get resolved and the levels of pancreatic and inflammatory markers decrease [4]. This trend has changed, now it is clear that the early oral refeeding for PA mild does not only provide adequate caloric intake, it may also improve clinical outcomes. It has been hypothesized that the combination of disturbed intestinal motility, microbial overgrowth and increased permeability of the gut can lead to bacterial translocation, thus causing infection of pancreatic necrosis [5,6].

The oral refeeding (OR) may reduce translocation by stimulating intestinal motility, reducing bacterial overgrowth and thereby maintaining mucosal gut integrity [7,8]. Also decrease infection complications, organ failure and mortality as compared with routine total parenteral nutrition [9,10]. In patients with (predicted) mild pancreatitis, numerous studies concluded that a normal oral diet can be resumed once the pain is decreasing [11-13], However, it remains unclear what the optimal time to do it is. There is still no consensus about the definition of "early" refeeding.

The aim of the present study is to compare the onset of oral feeding in the first 24 hours after hospital admission and determine if this influences the recurrence of pain or alters the blood levels of pancreatic enzymes, compared to usual oral refeeding in patients with mild acute pancreatitis.

## METHODS

### Patients

This Randomized controlled trial was carried out between September 2018 and June 2019, prior authorization from the ethics committee in health research. All patients admitted to the surgery services with diagnosis of acute biliary pancreatitis, whit mild episode criteria and symptom onset time less than 24 h, were screened for inclusion in the study. Patients with pancreatitis from another cause other than biliary, pregnant, history of chronic pancreatitis, under 18 or over 75 years, and with moderately severe or severe acute biliary pancreatitis were excluded. Written informed consent was taken from all patients.

A total number of 124 patients were randomized in this study. The sample size was calculated according to the formula published by Bouemn et all 2015 [14], in which a percentage of success was estimated with the standard treatment of 90% compared to the experimental management of 85%, with a margin of no less than 10%, with an alpha for a tail of 0.05%, and a beta of 20 %, with a percentage of estimated losses of approximately 10%, a total of 62 patients per group was obtained.

**Definitions**

The diagnosis of AP was established when the patient presents two or more of the following three findings: typical abdominal pain, elevation of serum pancreatic enzymes (amylase and/or lipase) at more than three times the upper limit of the normal value, and imaging study (ultrasonography or computed tomography) suggestive of AP [15].

Severity Assessment

Severity assessment of AP was done based on the revised Atlanta classification into mild, moderately severe and severe. Absence of organ failure or local or systemic complications was labelled as mild AP; of was defined using the modified Marshall scoring system [16]; and only the patients whose complete these severity criteria were randomized for the study.

**Protocol**

Once the diagnosis of acute biliary pancreatitis was confirmed and the course was mild, corresponding informed consent signed.

Patients were divided into: Group A (early oral refeeding) and Group B (usual oral refeeding) through a table of random numbers generated with the commercial program IBM SPSS statistics number 25 (The numbers generated by the program were from the experimental group)

Due to the characteristics of the study, only a simple blinding was possible (the doctor who performed the statistical analysis)

Both groups were given medical management in the same manner as marked in the IAP and APA guidelines [17].

*Fluid therapy* with crystalloid solution (Hartmann), initial bolus of 10 mL / kg and followed by infusion for 24 h of 1.5 mL / kg / h.

*Pain management* with opioid weak tramadol 50mg every 6 hours and paracetamol 1 gram every 8 hours with continuous evaluation of the analogue numerical scale to determine the need for extra doses

*Oral refeeding*

Group A: Early oral refeeding (EOR) Once the patient had a score of 1-3 of the analogue numerical scale (ENA), he was interrogated about symptoms such as nausea or vomiting, if he did not have them, then receives diet indicated between 16 and 24 hours after admission.
Group B: usual oral refeeding (UOR) Once the attending physician decided according to his clinical judgment to restart the oral feeding.

*Type of Diet*:
In both groups, their initial diet was the same so that this did not influence the results to be measured.
The soft diet consisted of one of 900 Kcal per day, with 86.7% carbohydrates (190 g), 13.3% protein (30 g) and 0% lipids (0 g); during 24 h.
When the diet was adequately tolerated and there was no evidence of clinical complications or deterioration, normal diet was indicated, and the follow-up continues.

*Endpoints*
Outcome measures were amylase and lipase pancreatic-specific, systemic inflammatory response (concentrations of leukocytes) were used as marker for it, feasibility evaluated by abdominal pain recurrence, presence and recurrence of gastrointestinal symptoms and length of hospital stay.

*Data Collection*:
Laboratorial data, such as leukocytes, amylase and lipase were collected after inclusion in the study and after 24 and 48 h of oral refeeding. Clinical data records include age, gender, time from onset of pain baseline, Marshall score at admission and after start the oral feeding, gastrointestinal symptoms, abdominal pain, days until solid food intake, pain relapse, complications, length of hospital stay and readmissions.

*Statistical analysis*
Date are presented as frequency and percentage, comparisons between groups were using the $\chi^2$ test for binary data or Fisher´s exact test. Continuous variables are presented as median and range interquartile range and were compared using the Mann-Whitney U-test or t student test if they meet normal criteria. p-Values of less than 0.05 were considered significant. Statistical analyses were performed with SPSS version 25.0.0. Analysis by intention to treat was used.

**RESULTS**

A total of 120 patients were included in this study (61 in the EOR group and 59 in the group UOR). One patient from the EOR group was excluded because due to persistence of pain and for this reason he could not receive the oral refeeding. Three patients of the UOR group were excluded because: one patient had no pain improvement; tomography was performed and peripancreatic collections were demonstrated; two patients were operated without starting the oral refeeding. These four patients not included in the study represent 3.2% of losses.

The demographic data and clinical parameters of patients at admission are presented in the table 1. There was not statistically significance difference in both groups.

The comparison of outcome variables between two groups as present in the table 2. Two patients of the EOR group had pain relapse (3.2%) and four of the UOR group (6.77%) after oral refeeding (p= 0.379). Another characteristic that determines tolerance to the OR is the presence of gastrointestinal symptoms, so the presence of nausea or vomiting after onset of oral refeeding does not show differences (p= 0.293).

The lipase serum level could demonstrate recurrence, in the EOR group did not increase after the onset of the OR compared to the levels of admission. In the UOR group, decrease lipase serum level was observed comparing the baseline levels against the after start of OR levels, but it is expected, in fact was an inclusion criterion for this group.

The systemic inflammatory response was evaluated with leukocyte levels, the behavior was very similar to that described in lipase levels, in the EOR group did not increase after the onset of the OR compared to the levels of admission

The length of hospital and follow up as present in the table 3. The start time of the oral refeeding was approximately 48 h longer in the UOR group. Hospital length was 5 days in the group EOR and 8 days for the UOR group (p = 0.042); and this difference was also manifested in the hospital cost being higher in the group UOR p = 0.0235

## DISCUSSION

For decades, pancreatic rest by Nil Per Oral (NPO) strategy was considered necessary in AP till abdominal pain get resolved and the levels of pancreatic and inflammatory markers normalize. This trend has changed now, early enteral feeding is accepted in the treatment of AP, but still have not consensus about of definition of early oral refeeding.

The concept of the early oral refeeding includes the time between admission and the start the diet, and the presence of adverse event, that includes abdominal pain relapse and gastrointestinal symptoms (nausea and vomiting).

In this study we found that the EOR is safe within the first 24 h after hospital admission, that there is no difference in the presence of abdominal pain relapse, nausea or vomiting compared with standard oral refeeding in mild acute pancreatitis.

An unclear concept is the criteria for EOR, Eckerwall GE 2007 [11] report as criteria of starting OR "immediately allowed to drink" and the diet start time for his patients was one day. Teich N 2010 [13] it does not have a criterion; it was according to the randomization and the start time for his patients was two days. Li J 2013 [1] report as criteria of starting OR "feeling of hunger" and the start time for his patients was five days. Larino-Noia 2014 [18] report as criteria of starting OR "normal bowel sounds" and the diet start time for his patients was two days. Our criteria were the objective measurement of symptoms, the pain with a score of 3-10 on visual analogue scale, and the absence of symptoms like nausea or vomiting, these criteria allowed the OR to begin in the first 24 h, with a 95% success rate.

Once start time of diet is defined, the next point to clarify is the type of diet. The meta-analysis conducted by Meng et al 2011[19], showed that in comparation with the clear liquid diet, the early oral refeeding with a solid diet might provide better outcomes and is safe for patients with AP. Based on these results we started with a solid diet in both groups, so the diet type did not influence the results of the study, and shows that this type of diet can be started without complications.

Masayasu H et al 2016 [20] in a systemic review and meta-analysis reported that early oral refeeding reduces the hospital stay length without significant differences in adverse events. In our study, the hospital stay was shorter for the EOR group 5 vs 8 days ($p= 0.042$), this also led to the lower hospital cost in the EOR group 2089 vs 3310 dollars ($p= 0.0235$), this cost represents total hospital stay expenses. The results of this study might impact treatment strategy and potentially reduce the cost of hospitalization in these patients.

Eckerwall GE 2007 [11], analyzed the recurrence and systemic inflammatory response, measured values of pancreatic-specific amylase serum levels and CRP concentrations, there observed any significant difference between groups in any of those biochemical markers for amylase of systemic inflammatory response for any days evaluated. In our study we measured lipase serum levels and leukocytes as parameters of recurrence and systemic inflammatory response; we found that the beginning of the OR did not influence the modification of these parameters, so it did not affect the natural history of the disease.

The strengths of this study were that all patients had the same cause of acute pancreatitis (biliary), had at least 24 h of evolution and everyone started orally with the same type of diet, that confers homogeneous groups. Another strength is the clear and objective criteria for start the diet.

A limitation of the present study is that design did not include blinding. The nature of the intervention (EOR vs UOR) make it obvious that the patients and medical staff are informed of the groups. Another limitation was the use of leukocytes but not CRP as marker of systemic inflammatory response.

## CONCLUSION

The early oral refeeding is safe in mild acute pancreatitis patients, without adverse gastrointestinal events, and reduce the hospital stay and cost compared with usual oral refeeding.

### Abbreviations

Acute pancreatitis (AP)

Oral Refeeding (OR)

Early oral refeeding (EOR)

Usual oral refeeding (UOR)

Visual analogue scale (VAS)

Neil per oral (NPO)

## Declarations

### Ethical approval and consent to participate

This clinical trial was approved by local committee in clinical research and ethics committee: Instituto Mexicano del Seguro Social. Coordination of investigation in health.

**Trial registration: Local Committee 1001 registration number 17 CI 11020146 COFEPRIS. Trial registration number R-2018-1001-074 August 28, 2018.**
Approval of all participating local hospital boards has been obtained

### Consent for publication

According to the study publication

### Availability of data and materials.

Database available for review

**Competing interests**

The authors declare that they have not competing interest

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**Authors 'contributions**

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### Contributions

EELH, the lead author, designed the study. OBG conducted all the interviews and alongside EELH, undertook the thematic analysis; EAJ, SVR, MCR took part in the schematic analysis. All authors have provided input into drafts of this article. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have read and approved the manuscript in its final state.

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EDUCATION UNIT, RESEARCH
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HEALTH RESEARCH COORDINATION
LETTER OF INFORMED CONSENT
(ADULTS)

| | |
|---|---|
| Study Name: | Non-inferiority Comparative Clinical Trial Between Early Oral Refeeding<br>Versus Usual Oral Refeeding in Mild Acute Pancreatitis Patients |
| External sponsor (if applicable): | Does not apply |
| Place and date: | LEON, GUANAJUATO. ____ de_____ de 2018 |
| Registry number: | R-2018-1001-074 |
| Rationale and objective of the study: | Compare whether early onset of the diet is safe compared to late onset of diet in patients with mild acute biliary pancreatitis. |
| Procedures: | Start the diet during the first 24 hours of admission to the emergency department with the diagnosis of mild acute biliary pancreatitis, a pain measurement will be made after the start of the diet as well as recording the presence or absence of nausea and vomiting. |
| Possible risks and inconveniences: | Abdominal pain, nausea, vomiting. |
| Possible benefits you will receive when participating in the study: | Decrease hospital stay time, decrease the risk of complications of mild acute biliary pancreatitis, decrease hospital stay time until cholecystectomy. |
| Information on results and treatment alternatives: | The results of this study will be carried out anonymously, guaranteeing not to mention the names of the participants. |
| Participation or withdrawal: | All patients who sign this consent will participate, and may withdraw at the time they decide. |
| Privacy and confidentiality: | The information obtained may be sent to an IMSS database, all information will be handled by the researcher and thesis, without access to any person outside the investigation. |

In case of biological material collection (if applicable):

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| ☐ | It does not authorize the sample to be taken. |
| ☐ | If I authorize the sample to be taken only for this study. |
| ☐ | If I authorize the sample to be taken for this study and future studies. |

| | |
|---|---|
| Availability of medical treatment in beneficiaries (if applicable): | |
| Benefits at the end of the study: | Prove that the onset of diet in patients with mild acute biliary pancreatitis in a tempana way is safe. |

In case of doubts or clarifications related to the study you can go to:

| | |
|---|---|
| Responsible Researcher: | Dr Edgard Efren Lozada Hernandez, Surgery investigator.<br>Phone: 4772745801 e-mail: edgardlozada@hotmail.com |
| Collaborators: | Dra Santa Romero Vazquez. Surgery Doctor.<br>Identification number: 10858598 |

In case of doubts or clarifications about your rights as a participant, you can go to: IMSS CNIC Research Ethics Commission: Cuauhtémoc 330 Avenue 4th floor Block "B" of the Congress Unit, Colonia Doctores. Mexico, D.F., CP 06720. Phone (55) 56 27 69 00 extension 21230, Email: comision.etica@imss.gob.mx

Name and signature of the subject

Name and signature of the person who obtains the consent

Witness 1
Name, address, relationship and signature

Witness 2

This format constitutes a guide that should be completed according to the characteristics of each research protocol, without omitting relevant information from the study.

Key: 2810-009-013