STUDY PROTOCOL

PADI

PAncreatitis and DIet

Randomized multicenter prospective clinical trial to compare the effectiveness of starting early oral diet versus Nil Per Oral in patients with acute pancreatitis

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Introduction

Acute pancreatitis (AP) is a common condition in emergency services worldwide. Approximately 85% of AP are mild and the patients usually recover within 1 to 2 weeks, not requeiring any critical care and organ support. The management of mild AP conventionally involves fasting, intravenous hydration and adequate analgesia until pain improves in order to prevent stimulation and allow the pancreas gland to rest. (1-7)

The current guidelines recommend the oral food intake should be tried as soon as possible, and beneficial effects or early enteral nutrition with mild AP have been reported in literature. (7-13)

Then, arly oral refeeding (EOR) after mild and moderate acute pancreatitis (AP) is beneficial, but the optimal timing and starting criteria are unclear. Even now, refeeding after mild and moderate AP is typically started until clinical symptoms have resolved and pancreatic enzymes are decreasing, in a successively increasing manner. We aim to evaluate length of hospital stay and clinical findings for early refeeding with immediately full caloric intake in patients with mild and moderate AP.

Methods

Trial Design

This is prospective, randomized, controlled, multicentre trial. Patients with mild and moderate AP will be randomly assigned to groups A (EOR with low fat solid diet (LFSD), administration starting since admission in hospital) and B (fasting, until the symptoms, signs, inflammatory parameters of AP have resolved).

Study population

All patients diagnosed with AP with inclusión criteria and not exclusion criteria, will be informed of the possibility of taking part in the PADI study. After consent form (Annex 1) is signed, the patient will be randomize (Figure 1).
The diagnosis and severity of AP will be establish according to the Modified Determinant-Based Classification.

Inclusion criteria

The inclusion criteria are: 1) diagnosed of AP by at least two of these three criteria: compatible abdominal pain, amylase or lipase level superior in three-fold respective laboratory baseline levels, and suitable findings in imaging techniques (CT, ultrasound or MRI); 2) age > 18 years, sign consent form.

Exclusión criteria

The exclusion criteria are: 1) pregnant o breastfeeding women; 2) abdominal pain lasting >96 horas before admission; 3) the possibility of poor oral intake for reasons other than AP; 4) Pancreatic neoplasm, endoscopic retrograde cholangiopancreatography or trauma etiology; 5) Chronic pancreatitis; 6) Randomization greater the 12 hours after admission.

Sample size

Given that historically the duration of hospitalization for mild AP at two hospitals is 7 days, a sample size of 120 patients (60 in each group)will be necessary to be recruited using a 10% drop-out rate, 80% power and 95% significance level to detect a two-day difference in total length of hospital stay between the study groups.

Randomisation
In each centre participants will be divided into two groups receiving one of the two study treatments. The allocation of participants to the different groups will be carried out based of predefined randomization lists created separately for each recruiting centre. The randomization lists will be prepared with a block size of 2 and with an allocation ratio of 1:1.

Duration
The planned starting date of the study is June 1st, 2017 and the planned finishing date of the study is December 31st, 2018.

Intervention
Based on the currently available guidelines, oral refeeding can be started early for patients with mild and moderate AP. Additionally, with an LFSD appeared safe and provided more calories.Therefore, both groups can be regarded as being treated within accepted practice recommendations. In this study, EORF with LFSD will be the intervention. Patients will be randomized to group A or PADI diet (EORF with LFSD) or fasting group.

Groups
In group A (PADI), the oral refeeding will be started after admission. Patients will receive a low fat solid diet with more and less 1500 calories, 35 g fat day.
In group B (fasting), the oral diet will be reintroduced in a traditional stepwise manner until the symptoms, signs, inflammatory parameters of AP have resolved.

General patient management
General treatment intimater by the IAP / APA guideline will be used.
All patients will receive adequate intravenous fluid resuscitation based on their individual hemodynamic parameters and fluid balanced. The patients will be monitored daily for gastrointestinal symptoms, abdominal pain, total intake/output, nutritional parameters, and laboratory findings.

Endpoints
The primary endpoint is length of hospitalization. Several secondary endpoints such as pain, the duration of fasting, tolerance to food, relapse rate, degree of transitional abdominal dissension and/or abdominal pain and/or vomits after the first ingestion of oral food, multiorgan failure, pancreatic infection, hyperglycemia, nutricional parameters, mortality and quality of life will be determined to elucidate more detailed differences between the groups. The feasibility, safety and quality checks required for high quality evidence will be adhered.

Monitored parameters during hospitalisation
There will be a large variety of parameters monitored during the study: medical history, physical examination, laboratory test, diagnostic imaging, therapy, complications, interventions. The data collection will be done in the form A. This form will contain parameters collected on admission, parameters every day during hospital admission and contain parameters 1 month after hospital discharge.

Data management and statistical analyses
The investigator will ensure that the data in the form A are accurate, complete and legible. Detailed data flow will be described in a Data Management Plan. Data from completed form A will be validated under direction of the Data Manager according to a Data Cleaning

Plan. Any missing, or inconsistent recordings in the form A will be referred back to the investigator of each centre. The Data manager is a biostatistician.

Study populations
Three analysis populations will be defined:
Safety Analysis Set (SAS): all patients enrolled in the study.
Per Protocol Set (PPS): all enrolled patients who finished the study conforming to the requirements of the study protocol.
Intention to Treat (ITT): all randomized participants who start on a treatment, excluding consent withdrawals.

Withdrawal of a subject from Per Protocol Set
Any participants / investigators and Data manager can submit recommendations for dropouts from the PPS group with reasons given to the coordinator. The coordinator will discuss all the recommendations all the information and, if the alteration in the protocol would be expected to have any bearing on the interventions and outcomes of the study, the patient will not be included in the final pre-protocol analysis. Automatic dropout from per-protocol group shall be ordered if: 1) any of the exclusion criteria are diagnosed during the course of AP; 2) parameters for answering the primary endpoints are missed; or 3) serious medical reasons nor related to pancreatitis occur.

Applied software
Statistical analysis will be performed using SPSS 21 statistical packages. Pages Mac will be used for reporting.

Statistical methods
Baseline patient and disease characteristics will be analyzed using descriptive analysis. Demographic and baseline characteristics will be summarized for the overall study population. Continuous variables will be described by mean, median, SD and ranges and categorical variables will be described by absolute and relative frequencies. A graphical presentation of efficacy variables will be prepared. Descriptive statistics for both the primary and secondary parameters will be analyzed similarly. Mean changes (with 95% CI) from baseline to end-of-study visit will be presented. Chi-quadrate test will be applied to compare proportions between the different groups. Survivals will be investigated using the Kaplan-Meier analysis method, while subgroup comparisons will be performed using the Chi-quadrate or Fisher's exact test, as appropriate. For safety data, descriptive statistics and individual listing of adverse events will also be presented.

Centres
The trial will start in six centres:
1. Consorci Sanitari del Garraf - Hospital Residencia San Camil
2. Hospital Universitari Joan XXIII de Tarragona
3. Hospital Clinic de Barcelona

In all centre the coordinator will make an audit of the centre and will report to Data Manager.

Publication policy
Centres providing more than 20 patients can provide one authors to the authorship list. Every additional 20 patients will give the opportunity to nominate an additional author.

Feasibility and safety
The diet is a general protocol for the treatment of AP.
Since no unknown drugs/therapy are used in the study, no adverse or serious adverse events are expected that would be attributable to the intervention during the trial.

Discussion

We report a prospective, randomized, controlled trial to study the effects of EORF with LFSD in AP. The current studies and meta-analysis suggest that EORF should be beneficial but we don´t know the optimal timing and starting criteria. Our main hypothesis is that EORF with LFSD is well tolerated and leads to a shorter total length of hospitalization. The aim of the study will be evaluated the efficacy and feasibility of immediate oral feeding as compared to traditional fasting in patients with mil and moderate pancreatitis.

Ethics

The study has been approved by the relevant organization: Comitè Ètic de'investigació d'la Fundació Union Catalana d´Hospitals. Codi CEIC 17/05.

Dissemination

This study will provide strong evidence as to whether EOR with LFSD is beneficial in the clinical management of mild and moderate AP. The results of this trial will be published in an open access way and disseminates among medical societies.

Conclusion

This study provides the stronger evidence concerning the optimal timing and starting criteria for EORF with LFSD.

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Annex 1. Informed consent form

Title:

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Principal investigator

Elena Ramírez-Maldonado, Consorci Sanitari del Garraf, Hospital Residencia San Camil.

Study: PADI (Acute Pancreatitis and Diet)

I,(name surname)…….

- I have read the information that the investigator has been given to me
- I was able to ask questions about the study
- I have received satisfactory answers to my questions
- I have received enough information about the study and I have understood it
- I have spoken with (name and surname of the researcher

……..……..

- I understand that my participation is voluntary
- I understand that I can withdraw from the study
  - Whenever I want
  - Without having to explain
  - However, this has no repercussions for anyone.
- I freely give my consent to participate in the study and receive a copy of this document

....
(Date) (patient's signature)

....
(Date) (researcher's signature)