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Pancreatitis, very early compared with selective delayed start of enteral feeding (PYTHON) trial

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Registration date 28/02/2008	**Overall study status** Completed	
Last Edited 30/12/2020	**Condition category** Digestive System	

Plain English summary of protocol
Not provided at time of registration

Study website
http://www.pancreatitis.nl

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
Pancreatitis, very early compared with selective delayed start of enteral feeding (PYTHON) trial: a randomised controlled multicentre trial - Dutch Pancreatitis Study Group

Acronym
PYTHON Trial (Pancreatitis, verY early compared wiTH selective delayed start Of eNteral feeding Trial)

Study objectives
Please note that the following amendments have been made to the Interventions field as of 14 /07/2008:

1. Changes to the interventions for Group A:

Current interventions for Group A: Very early EN, i.e. within 24 hours
Patients will receive a nasojejunal feeding tube (Nutricia, the Netherlands) within the first 24 hour after admission.

Previous interventions for Group A: Very early EN, i.e. within 24 hours
Patients will receive a nasogastric feeding tube (Nutricia, the Netherlands) on the emergency department or within the first 24 hour after admission, if not admitted through the emergency department. Nasogastric feeding is shown to be safe in patients with predicted severe acute pancreatitis in two recent RCTs.

2. The following text was transferred from the Interventions field as nasogastric tube will not be used:

Reasons to change nasogastric tube for nasojejunal tube:
a. In case of gastric fluid retention >250 ml (on Intensive Care [IC] gastric fluid retention is measured every 6 hours, on the ward gastric fluid retention is only measured in case of nausea), the nasogastric tube will be replaced by a nasojejunal tube. Note: Erythromycin is not allowed to promote gastric emptying because erythromycin is an antibiotic potentially influencing the risk of infectious complications (primary endpoint). There is no evidence in support for erythromycin in the treatment of delayed gastric emptying in AP.
b. Repeated vomiting (nasogastric feeding not tolerated)
c. Lowered consciousness (Glasgow Coma Scale [GCS] 14 or lower) in a patient that is not intubated (risk of aspiration)

Study hypothesis:
Acute Pancreatitis (AP) runs a severe clinical course with the occurrence of pancreatic necrosis and peripancreatic necrosis in 20% of patients. In necrotizing pancreatitis, secondary infection of (peri) pancreatic necrosis occurs in 33%, with mortality of 34% in the Netherlands, accounting for 80% of mortality in all patients with acute pancreatitis. Two recent meta-analysis have shown that prophylactic use of systemic antibiotics does not prevent infectious complications or mortality. In severe acute pancreatitis, disturbed gastrointestinal motility leads to bacterial

overgrowth and failure of the structural mucosal barrier leads to increased gut permeability. These processes result in bacteria crossing the gastrointestinal mucosal barrier to the systemic compartment and pancreatic necrosis - a phenomenon called bacterial translocation. Experimental and clinical research has shown that these phenomena already take place in AP within a few hours after onset of symptoms. This implies that there is only a very narrow therapeutic-window for preventing bacterial translocation and subsequent infections.

Nutritional support plays an important role in the therapy of patients with documented severe AP (organ failure and/or necrosis). There are two options for nutritional support: Total Parental Nutrition (TPN) and Enteral Nutrition (EN). EN is superior to TPN in patients with predicted severe AP, as it has been shown that TPN is associated with an increased risk of bacterial translocation and subsequent infectious complications and mortality as compared to EN.

In clinical practice, patients with predicted severe AP are kept at a 'nil per mouth' regimen until it becomes clear that the patient will not be able to tolerate oral intake for a prolonged period of time. According the recent Practice Guidelines in Acute Pancreatitis of the American College of Gastroenterology, this assessment should be made within 3-4 days after hospital admission, after which nutritional support should be instituted. In a recent nationwide randomised controlled trial performed by the Dutch Pancreatitis Study Group (DPSG) the trial protocol stated that EN should be started as soon as possible. Despite intense monitoring by nurses and trial physicians, EN was started a median of 2.5 days after admission in patients with predicted severe AP.

There is strong support from studies in other diseases that a very early start of EN is beneficial. In a recent meta-analysis of 15 randomised trials in critically ill patients with (other than AP), EN within 24 hours after admission was associated with a lower incidence of infectious complications (relative risk reduction 0.45; 95% confidence interval, 0.300.66; p <0 .001) if compared with delayed EN. The relation between moment of starting EN and the optimal effect of EN in terms of prevention of infection in patients with predicted severe AP remains unknown.

To investigate whether early EN reduces infectious complications and mortality in AP, the DPSG will perform a nationwide randomised controlled parallel superiority trial comparing early EN with selective delayed EN in patients with predicted severe AP.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Submitted on the 17th of December 2007 to the Ethics Committee of the University Medical Centre Utrecht (ref: 07-292)

Study design
Randomised controlled parallel group superiority multicentre trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)

Not specified

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Acute pancreatitis

Interventions
A total of 208 patients will be randomised in 20 participating centres of the Dutch Pancreatitis Study Group (approximately 10 patients per centre).

Patients are randomised to Group A or Group B:

Group A: Very early EN, i.e. within 24 hours
Patients will receive a nasojejunal feeding tube (Nutricia, the Netherlands) within the first 24 hour after admission.

Group B: Selective delayed start of EN
During the first 72 hours after admission:
No artificial nutrition (EN or TPN) in all patients. If patient spontaneously requests food, introduce hospital food ad libitum (as much or as often as is wanted)

At 72 hours after admission:
a. Patients with organ failure: placement of a nasojejunal feeding tube and start of EN (see 'EN regime' section).
b. Patients without organ failure: offer oral food according to the patient's preference ad libitum. If not tolerated: food is offered again next morning. If still not tolerated: placement of nasojejunal feeding tube and start of EN.
c. If, at any time after the first 72 hours of admission, patients not yet on artificial nutrition suffer from organ failure a nasojejunal feeding tube is placed and EN is started (see EN regime section).

Method of placing nasojejunal feeding tube:
a. Placement either endoscopically or radiologically
b. Abdominal X-ray is performed after placement of nasojejunal feeding tube to check position

EN regimen:
Standard formula EN (Nutrison Standard®, Nutricia, the Netherlands) is started immediately after placement of feeding tube with a rate of:
a. First 24 hrs: 20 mL/hr
b. Between 24-48 hrs: 45 mL/hr
c. Between 48-72 hrs: increase to full nutrition
d. At 72 hrs and thereafter: Full nutrition

Full nutrition is defined as an energy target of 25 kcal/kg/day (ICU patients) and 30 kcal/kg/day (non ICU patients). At 72 hours after onset of enteral feeding, a dietician will evaluate the nutritional status and will change the type of EN accordingly (additional proteins, calories, fibers etc).

The patients is weighed twice a week during the first month after randomisation, and once a week until discharge from hospital thereafter. If nasojejunal feeding is not tolerated, EN is reduced by 50% and increased again gradually until tolerated. If after two attempts of reducing and re-increasing EN full nutrition cannot be reached with EN, TPN will be started, through a central venous catheter, to reach the required energy target.

Criteria to stop EN and remove feeding tube:
a. When a patient has reached full nutrition (so only after 72 after starting EN, in both arms of the study) and 1) abdominal pain is resolved and 2) does not suffer from organ failure: remove nasojejunal feeding tube and introduce regular hospital food, increase ad libitum
b. When a patient has been on full nutrition >1 week: the EN is gradually decreased and hospital food gradually introduced according to local policy
c. Indication for restarting EN after initial removal of feeding tube
d. If after reintroduction of oral food abdominal pain relapses withholding the patient from oral feeding and/or organ failure occurs, EN is restarted through a nasojejunal feeding tube

General treatment regimen:
a. Supportive care: during the first 48 hours of admission vital signs and bedside oxygen saturation are monitored. Aggressive IV fluid resuscitation is performed to guarantee a urinary output of at least 0.5 ml/kg/hr. Parenterally administered narcotics are provided to relieve abdominal pain. Patients are transferred to the ICU in case of organ failure.
b. CT scan: All patients will undergo baseline contrast enhanced CT within day 5-7 after admission. When CT is performed on admission, it will be repeated at day 5-7 since CT the first 72 hours is not reliable in detecting pancreatic necrosis.
c. Antibiotics: Antibiotic therapy is administered based on culture results but not as prophylaxis in case of necrotizing pancreatitis without documented infection.
d.Infected necrosis: Operative intervention is preferably postponed until the (peri)pancreatic collections are demarcated as shown on CT-scan.

Discharge criteria:
Patients can be discharged from hospital when abdominal pain has resolved, infection parameters (leucocytes, CRP) levels have normalized, artificial feeding is no longer necessary and a normal oral diet is tolerated.

Please note that the sponsor details have been updated as of 14/07/2008. The previous details were as follows:
Nutricia
Postbus 1
Zoetermeer
2700 MA
Netherlands
The amendment is due to an error at time of registration and does not reflect a change of sponsor.

Intervention Type
Other

Phase
Not Specified

Primary outcome measure

Fraction of patients with an infectious complication or mortality during hospital admission and until 90 days postdischarge (composite endpoint). Re-admission within 10 days after discharge is considered as a continued hospital admission.

Definition of infections:
a. Infected pancreatic necrosis = positive culture after first percutaneous drainage procedure of collection with (peri-) pancreatic necrosis or after first surgical necrosectomy
b. Positive blood culture = positive culture in 1 blood culture. In case of coagulase negative staphylococci or other non-virulent micro-organisms at least 2 blood culture bottles are mandatory
c. Pneumonia = coughing, dyspnoea, radiography with infiltrative abnormalities and positive culture in sputum. On the intensive care unit a positive endotracheal culture is mandatory.

Secondary outcome measures

Current secondary outcome measures as of 14/07/2008:
The following will be assessed during hospital admission and until 90 days postdischarge:
1. Individual components of the primary endpoint
2. Urinary tract infection (dysuria with bacteruria >10.000 Colony Forming Units [CFU]/mL)
3. Nutrition related complications: diarrhea, aspiration pneumonia, pneumothorax due to central TPN catheter placement
4. Need for conversion from EN to TPN
5. Days until intake of solid food
6. Use of antibiotics
7. Pain relapse, measured once daily during start of oral refeeding with the Visual Analogue Scale (VAS; 0 to 10, 0 = no pain, 10 = unbearable pain)
8. CRP and leukocytes as measures of systemic inflammation
9. Length of hospital stay
10. Need for ICU admission
11. New onset organ failure (onset, extent and duration, see definitions section)
12. Length of ICU stay
13. Need for percutaneous drainage
14. Need for surgical or endoscopical necrosectomy
15. Gastrointestinal permeability measured with the PolyEthylene Glycol (PEG) test
16. Hand grip muscular strength measured by the Jamar dynamometer
17. Quality of life will be measured using EQ-5D questionnaire
18. Total direct and indirect costs

Previous secondary outcome measures:
The following will be assessed during hospital admission and until 90 days postdischarge:
1. Individual components of the primary endpoint
2. Urinary tract infection (dysuria with bacteruria >10.000 Colony Forming Units [CFU]/mL)
3. Nutrition related complications: diarrhea, aspiration pneumonia, pneumothorax due to central TPN catheter placement
4. Need for conversion from nasogastric tube to nasojejunal feeding tube
5. Need for conversion from EN to TPN
6. Days until intake of solid food
7. Use of antibiotics
8. Pain relapse, measured once daily during start of oral refeeding with the Visual Analogue Scale (VAS; 0 to 10, 0 = no pain, 10 = unbearable pain)
9. CRP and leukocytes as measures of systemic inflammation
10. Length of hospital stay
11. Need for ICU admission

12. New onset organ failure (onset, extent and duration, see definitions section)
13. Length of ICU stay
14. Need for percutaneous drainage
15. Need for surgical or endoscopical necrosectomy
16. Gastrointestinal permeability measured with the PolyEthylene Glycol (PEG) test
17. Hand grip muscular strength measured by the Jamar dynamometer
18. Quality of life will be measured using EQ-5D questionnaire
19. Total direct and indirect costs

Overall study start date
01/03/2008

Completion date
31/12/2010

Eligibility

Key inclusion criteria
1. Diagnosis of acute pancreatitis, requiring 2 of the 3 following features:
1.1. Upper abdominal pain
1.2. Serum lipase and/or amylase levels 3 times the upper level of normal
1.3. Characteristic findings of acute pancreatitis on Computerised Tomography (CT) scan
2. Age 18 years or older
3. Written informed consent
4. Patients with predicted severe acute pancreatitis defined as Imrie score >2 or Acute Physiology And Chronic Health Evaluation II (APACHE-II) score >7 or C-Reactive Protein (CRP) level >150 mg/L (within 24 hours of admission to the hospital)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Current target number as of 14/07/2008: 208; Previous target number: 204

Total final enrolment
208

Key exclusion criteria
1. History of acute or chronic pancreatitis
2. Admitted to hospital >24 hours (either for AP or for other conditions)
3. Symptoms >96 hours (4 days)

4. AP due to malignancy
5. Diagnosis of AP during operation for acute abdomen
6. Post Endoscopic Retrograde CholangioPancreatography (ERCP) pancreatitis
7. Already on artificial nutrition (EN or PN)
8. Pregnancy

Date of first enrolment
01/03/2008

Date of final enrolment
31/12/2010

Locations

Countries of recruitment
Netherlands

Study participating centre
Department of Surgery
Utrecht
Netherlands
3508 GA

Sponsor information

Organisation
University Medical Centre Utrecht (Netherlands)

Sponsor details
PO Box 85500
Heidelberglaan 100
Utrecht
Netherlands
3508 GA

Sponsor type
University/education

ROR
https://ror.org/04pp8hn57

Funder(s)

Funder type
University/education

Funder Name
University Medical Centre Utrecht (Main funding body)

Funder Name
Nutricia Nederland B.V. (ref: 08/KR/AB/002)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	10/03/2011		Yes	No
Results article	results	20/11/2014	30/12/2020	Yes	No