ESGE STUDY EUROBIL 1

Biliary pancreatitis: sphincterotomy within 48 hours of symptoms onset versus conservative treatment. A randomized controlled trial

Introduction

Acute pancreatitis remains a disease with high morbidity (~40%) and mortality (~10%). It is a process of autodigestion due to the premature transformation of zymogenes to active proteolytic enzymes within the pancreas. The cascade of molecular mechanisms which initiate enzymatic activation are still under investigation. The current treatments are therefore still mostly supportive.

Gallstone migration can trigger acute pancreatitis, probably by causing mechanical obstruction at the ampulla of Vater. The stone is spontaneously evacuated in the duodenum in two thirds of the cases, but a number of severe complications can be attributed to the persistence of the obstruction or the repeated passage of stones or even to biliary sludge. Experimental data in the opossum have shown that early decompression of the ductal system prevents progression of the disease (Runzi). A clinical study also suggests that duration of obstruction is correlated with the severity of acute pancreatitis (Acosta).

Several studies have compared an invasive approach, involving rapid decompression of the biliary duct, to a more conservative attitude, with decompression only in cases of adverse evolution. Neoptolemos et al (1988) compared endoscopic retrograde cholangiopancreatography (ERCP) within 72 hours of admission, with or without endoscopic biliary sphincterotomy (EBS) and gallstone extraction (if present) to a more conservative approach, where ERCP was performed after 5 days if judged necessary. This study showed that in patients with severe acute pancreatitis, as determined upon admission, the group receiving urgent ERCP suffered fewer complications. Fan et al (1993) compared ERCP within 24 hours of admission with or without EBS and gallstone extraction (if present) to a conservative approach where ERCP is done in all cases after the acute phase, and earlier in case of adverse evolution. This study shows decreased sepsis of biliary origin in patients receiving rapid intervention, but no difference in complications of pancreatitis per se. Both studies seem to show an advantage for rapid ERCP, with EBS and stone extraction if necessary, in case of acute biliary pancreatitis. In a 1995 abstract, Nowak et al show the advantage, in terms of morbidity and mortality, of early ERCP+EBS in all cases of acute biliary pancreatitis, even in the absence of obstructing stones and even in mild pancreatitis.
The superiority of early endoscopic intervention has been recently questioned by Fölsch et al (1997) who compared ERCP within 72 hours of pain onset (ERCP ± EBS) to conservative management where ERCP was performed if deemed necessary. This study's main weakness is the high number of patients excluded (101 of 339 consecutive patients) because undelayed ERCP was indicated. Exclusion criteria included fever >= 39°C, bilirubin > 5 mg/dL, and "biliary cramps" distinct from pancreatic pain. Though this study does not show an advantage for early intervention in terms of complications, this conclusion is hard to interpret knowing that more than 30% of the patients described had urgent ERCP after being excluded.

Despite the fact that it is customary to proceed with EBS only in cases of visible gallstones (in view of stone extraction), it has been shown that a number of "idiopathic" cases of pancreatitis are associated with the presence of biliary sludge (Lee). In these cases, EBS, even in the absence of visible stones, may be beneficial. Experimental data are also in favor of rapid decompression of the ductal system, the extent of pancreatic damage being correlated to the duration of the obstruction (Runzi). Furthermore, it is presumable that the severity of pancreatitis is determined very early after the initiation of the inflammatory process. It is therefore possible that an "urgent" intervention, by conventional standards within 72 hours, may in fact be too late to improve outcome.

The following hypothesis for a randomized trial is based on the subsequent counts : 1. A "therapeutic window" of 24-48 hours exists from the onset of symptoms during which the inflammatory response is developing and determines the severity of the disease (animal and clinical studies). 2. Early relief of ampullary obstruction decreases the severity of the disease (animal studies) and complications (clinical studies). 3. ERCP is not a 100% sensitive tool to diagnose gallstone pancreatitis (sludge, microcalculi) and therefore, should not be the gold-standard to decide whether a biliary sphincterotomy should be performed or not. 4. Functional obstruction of the ampulla may still exist even if the stone has passed into the duodenum (edema related to "forced" papilla). 5. From published studies, it would be today unethical to leave patients with signs of biliary sepsis or severe biliary pancreatitis untreated endoscopically 72 hours after admission.

Hypothesis

In the context of acute gallstone pancreatitis, the current evidence-based strategy is to perform an ERCP with EBS and stone extraction (if seen during the procedure) within 24 to 72 hours of admission if there are signs of severe pancreatitis or biliary sepsis.
The purpose of this study is to randomly assign all patients with gallstone pancreatitis to either current standard treatment (see above) or very early EBS to all patients within the "therapeutic window"(onset of symptoms within 48h).

Primary end-points: development of severe pancreatitis, complications rates,

Secondary end-points: costs and mortality

Patients and Methods

Inclusion criteria

- Inclusion via the Emergency Room of consecutive cases of suspected acute biliary pancreatitis.

- Criteria for Acute Biliary Pancreatitis (all necessary)
  1. Acute upper abdominal pain
  2. lipase > 2 x N (upper limit of normal)
  3. gallstones/sludge suspected on ultrasound in the gallbladder or ducts
     - OR increased ALAT (> 2 x N)
     - OR increased alkaline phosphatase not caused by liver disease
     - OR increased total bilirubin (> 1.2 mg/dL or > 17 mmol/L)

- Other inclusion criteria (all necessary)
  1. abdominal pain onset <48 hours before admission
  2. informed consent
  3. age >= 18 years
  4. no other obvious cause of pancreatitis (ex: alcohol, drug-induced pancreatitis)

Exclusion criteria:

1. abdominal pain onset >48 hours before admission
2. unability to perform ERCP within the 48 h of symptoms onset
3. age<18 years
4. pregnancy
5. other obvious cause of pancreatitis (alcohol abuse, drugs-induced pancreatitis as corticosteroids and aziathoprin)
6. past-history of biliopancreatic and gastric surgery (including cholecystectomy)
7. underlying chronic liver disease
8. Abnormal coagulation tests (PTT< 75% or INR> 1.5 or APTT >35) and/or treatment with clopidogrel (or similar drugs).
9. severe cholangitis (septic shock) (Urgent EBS is indicated in these patients)
10. immunocompromized patients

Classification

- Classification of the pancreatitis according to Imrie: " mild " (< 3 criteria) or " severe " (≥ 3 or more criteria)
  1. age>55 years
  2. WBC>15000/mm³
  3. glucose>180 mg/dL (> 10mmol/l) except pre-existing diabetes mellitus
  4. urea>45 mg/dL (> 16 mmol/l)
  5. albumin<3.2 g/dL (< 32 g/l)
  6. calcium <8 mg/dL (< 2 mmol/l)
  7. LDH>600 UI (> 600 IU/l)
  8. PaO2<60 mm Hg (< 8 kPa)

Randomization process

Secured web-based randomization: 24h/24 access to a specific website (www.live-endoscopy.com) which provides the randomization group taking into account a stratification by center.

- Group 1: ERCP+EBS : immediate call to endoscopist on duty and urgent ERCP with EBS in all cases is performed within 48 hours of onset of symptoms.
- Group2: ERCP±EBS within 24-72h : supportive treatment, admission. ERCP on next working day. Criteria for performing EBS: visible stone in common bile duct or cholangitis or severe acute pancreatitis based on the Imrie criteria.

Statistical analysis:

According to most series, severe acute pancreatitis occurs in 30% of the patients. This is characterized by a protracted clinical course, a high incidence of local complications and a high mortality rate. If we intend to reduce the rate of acute severe pancreatitis to 20% by applying very early endoscopic management, within the therapeutic window, 186 patients would be needed in each group in order to demonstrate a significant difference with an α error of 0.05 and a power of 80%.

Standard medical treatment:

Apply to all patients included in the study

Antibiotic Prophylaxis

- for patients with CRP > 12 mg/dL (48h after the onset of symptoms) and/or pancreatic enhancement of less than 30 Hounsfield Units on CT scan
- use of cephalosporin or fluoroquinolone

Enteral Nutrition

- To be preferred to iv parenteral nutrition in the absence of intestinal ileus

Data collection:

- Emergency Room:

- History
  1. other possible causes of pancreatitis: alcohol, drugs (corticoids, etc.)
  2. time of pain onset (as precise as possible)
  3. time of hospital admission
  4. biliary and pancreatic history
  5. liver disease

- Physical Examination
- ASA grouping
- Abdominal ultrasound: gallbladder, biliary tract (considered dilated if diameter >=6 mm with gallbladder in place, if diameter >= 8mm if post cholecystectomy), stones
- Standard blood tests: cell counts (WBC), hemoglobin, electrolytes, urea, creatinin, AST/ALT, alkaline phosphatase, LDH, total bilirubin, glucose, calcium, CRP, triglycerides, ethanol, albumin, 5cc of plasma (EDTA tube, to be frozen at -25°c after separation of RBCs) to retrospectively evaluate cytokine levels and 5cc of whole blood to be frozen at -80°c for analysis of genetic polymorphisms)
- Arterial blood gases: Pa02
- Abdominal CT scan + iv contrast (within 48 hours of admission, if possible before ERCP)
  1. Estimation of pancreatic gland enhancement (Hounsfield Units) following intravenous contrast injection. Radiological classification of severity of pancreatitis (Balthazar)
  2. Evaluation of biliary tract and gallbladder

- ERCP data:

- Date, time
- Impacted stone, CBD stone, sludge…
- Ease of the procedure
  1. Schutz classification
  2. Time elapsed from scope insertion to scope extraction
- Number of unsuccessful cannulation attempts
- Pancreatic injections (number, acinarization)
- Method of EBS: Needle knife on impacted stone ("pregnant papilla" +/- completion with conventional sphincterotome
- Complications of EBS (bleeding, perforation)
- Need for additional procedure (mechanical litho, naso-biliary catheter, precut for access, stent)
- Bile sampling for bacteriological assessment and search for microcristals

- until the end of hospital stay

- daily clinical evaluation
- CT scan with intravenous contrast injection on day 8
- Imrie severity criteria at 48 hours
- blood tests on days 2, 3, 5, 7 and 14, and upon discharge: cell counts (WBC), hemoglobin, electrolytes, urea, creatinin, ASAT/ALAT, alkaline phosphatase, LDH, total bilirubin, glucose, calcium, CRP and 5cc of plasma to retrospectively evaluate cytokine levels (day 1 and 2)

- 1 month, 3 months and 6 months later:

- clinical follow-up
- morbidity, mortality

Evaluation of outcome

- Local complications
- Systemic complications

- Hospital stay: total and ICU
- Mortality

Informed consent

Simple and clear explanations will be given to the patient and his or her family concerning the disease, the possible therapeutic approaches, and the rationale of the present study. The risks inherent to medical intervention (i.e. endoscopy) will be summarized. If participation in the study is refused, usual management will be suggested, that is, in our center, urgent ERCP and EBS.

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