

Early ERCP in acute biliary pancreatitis: 20 years of dispute

A. Beltsis, D. Kapetanos

SUMMARY

Biliary is the most common form of acute pancreatitis and is believed to result from transient obstruction of the bile and pancreatic ducts. The severity of the disease is determined by the extent and the intensity of the ensuing local and systemic inflammatory reaction, which depends on multiple factors possibly including the persistence of obstruction. Early ERCP with endoscopic sphincterotomy and disobstruction of the common bile duct has been proposed as a procedure to improve the outcome of acute pancreatitis. Over the last 20 years a number of clinical trials and meta-analyses have addressed the issue of early ERCP in acute pancreatitis producing conflicting results. Inconsistencies in the various clinical trials and meta-analyses should be interpreted within the context of several limitations, namely the difficulties in excluding patients with concurrent cholangitis and the unavailability of a reliable and accurate scoring system to predict the severity of acute pancreatitis early in the course of the disease. Reviewing the clinical trials and meta-analyses we conclude that, at present, strong evidence supports early ERCP in acute biliary pancreatitis only in the presence of cholangitis or persistent obstruction of the common bile duct when the predicted outcome of the disease is severe.

Key Words: Acute Pancreatitis, Acute Biliary Pancreatitis, Endoscopic Retrograde Cholangio-Pancreatography (ERCP), Early ERCP, Endoscopic Sphincterotomy, Common Bile Duct Stones, Common Bile Duct Obstruction

Gastroenterology Department, "G. Papanikolaou" Hospital, Thessaloniki, Greece

Author for correspondence:

D. Kapetanos, Gastroenterology Department "G. Papanikolaou" Hospital, Exohi, Thessaloniki, e-mail: dkapetan@otenet.gr

INTRODUCTION

Acute pancreatitis is a disease with multiple etiologies and a wide spectrum of outcomes, ranging from mild, self-limited illness, to severe, decapacitating and life threatening disease. The most common form of the disease, at least in populations without high prevalence of alcohol abuse, is "biliary" pancreatitis, believed to result from transient obstruction of the bile and pancreatic ducts, causing reflux of bile and duodenal content into the pancreatic duct and/or increase of hydrostatic pressure in the pancreatic duct.¹ The severity of the disease is determined by the extent and the intensity of the ensuing local and systemic inflammatory reaction, which depends on multiple factors, some of which may be genetic. Animal models and human studies suggest that the duration of obstruction is a critical factor affecting severity, with pancreatic necrosis developing more often when it exceeds 48 hours.²⁻⁵ Obstruction can be constant (as by an impacted stone in the ampulla) or intermittent (multiple stones passing through the ampulla). Early resolution of the obstruction would therefore, at least in theory, affect the outcome of the disease. The introduction of therapeutic endoscopic retrograde cholangio-pancreatography (ERCP) in clinical practice in the 1980s provided the potential of a pathogenetic treatment for biliary pancreatitis. However the procedure is not without risks, with a rate of complications such as post-ERCP pancreatitis, perforation and heamorrhage of 5-10%.^{6,7} Futrhermore, performing ERCP in the setting of acute pancreatitis can be especially challenging because the patient's duodenum and ampulla are swollen and physical condition compromised. Over the last 20 years, the role of early ERCP in acute billiary pancreatitis remains disputed with a number of clinical trials and meta-analyses producing conflicting results.

Randomized Trials & Meta-Analyses on Early ERCP in Acute Biliary Pancreatitis

In 1988, Neoptolemos et al studied 121 patients with probable biliary pancreatitis stratified for severity according to modified Glasgow criteria.⁸ The trial was performed in a single center (Leicester, UK). Patients assigned to the study group underwent ERCP within 72 hours of admission, while ERCP was withheld for at least 5 days in the control group receiving conservative treatment. Ten patients (6 study group, 4 controls) were excluded after randomization because of an alternate diagnosis. Patients with predicted severe pancreatitis had fewer complications if they underwent ERCP within 72 hours of admission (24% vs 61%, $p < 0.05$). When patients with concurrent acute cholangitis (who would obviously benefit from early ERCP) were excluded, the difference remained significant (15% vs 61%, $p = 0.003$) for patients with predicted severe pancreatitis. Mortality was not significantly different in the two groups.

In another single centre trial published in 1993, Fan et al studied 195 patients with suspected biliary pancreatitis stratified for severity according to Ranson's criteria.⁹ Patients in the study group underwent ERCP within 24 hours of admission and those in the control group were offered conservative management which however included ERCP if acute cholangitis developed. In the subgroup of patients with biliary stones (a stone located in any part of the biliary tract) and predicted severe pancreatitis, those who underwent early ERCP had fewer complications (13% vs 54%, $p = 0.002$). Criticism of this study has been aroused by the fact that only 66% of the study population actually had biliary pancreatitis and no provisions were made to exclude patients with concurrent cholangitis but all patients were offered ERCP if cholangitis developed, resulting in about half the patients in the control group to eventually undergo ERCP.

Trying to avoid the pitfalls of previous studies originating from the inclusion of patients with overt or latent concurrent cholangitis, Fölsch et al designed a multi-center study excluding patients with bilirubin level higher than 5mg/dL.¹⁰ Two-hundred and thirty-eight patients with suspected biliary pancreatitis were originally recruited in the trial and stratified for severity according to modified Glasgow criteria. Patients assigned to the study group underwent ERCP within 72 hours from the onset of pain and patients assigned to the control group were offered conservative management including ERCP if signs of cholangitis developed. Thirty-two patients (16 from each group) were excluded after randomization. The study was prematurely terminated because interim analysis revealed that the

primary goal (superiority of ERCP) could not be reached. Morbidity and mortality were similar between the groups. An alarming finding was an estimated 8% mortality for patients with predicted mild pancreatitis in the ERCP group, compared to 5.4% in the control group ($p = 0.7$), but much higher than that of other studies.¹¹ Furthermore, there was a significant increase in the rate of respiratory failure in the ERCP group, a finding not explained by the authors.

In an effort to identify the subgroup of patients who would benefit from early ERCP, Acosta et al tested the hypothesis that it is the duration of bile duct obstruction that determines the outcome of biliary pancreatitis and hence the need for ERCP.¹² The hypothesis was based on findings from an older retrospective study that revealed that more patients with severe pancreatitis had bile duct stones 72 hours after the attack (61% vs 35%) than patients with mild pancreatitis ($p < 0.01$).¹³ Acosta et al studied 61 patients with biliary pancreatitis and ampullary obstruction who were randomized to receive ERCP within 48 hours if signs of obstruction persisted for over 24 hours (study group, 30 patients) or conservative treatment and selective ERCP after 48 hours (control group, 31 patients). Indications of obstruction were severe persistent epigastric pain, bile free gastric aspirate and elevated serum bilirubin, while relief of pain, decrease of bilirubin or reappearance of bile in the gastric aspirate were considered signs of spontaneous relief of obstruction. Fourteen patients in the study group underwent ERCP (16 disobstructed spontaneously) and impacted stones were extracted in 79%. Patients in the study group had a lower incidence of immediate complications (3% vs 26%, $p = 0.026$). Furthermore, patients with obstruction lasting ≤ 48 hours regardless of treatment group had significantly fewer immediate complications than those whose obstruction persisted for > 48 hours (4% vs 78%, $p < 0.001$).

A similar study by Orva et al reached different conclusions.¹⁴ The group from Buenos Aires randomized within 48 hours from the onset of biliary pancreatitis 103 patients with a distal bile duct measuring ≥ 8 mm and total bilirubin ≥ 1.2 mg/dL to receive either ERCP or conservative treatment, excluding patients with coexisting cholangitis. No significant differences were found between the two groups in mean organ failure score ($p = 0.87$), mean CT severity index ($p = 0.88$), incidence of local complications ($p = 0.99$), overall morbidity ($p = 0.8$) and mortality ($p = 1$). Furthermore, bile duct stones were eventually found in 72% of patients with predicted mild and 73% of patients with predicted severe pancreatitis using the APACHE II score for stratification, challenging the hypothesis of persistent obstruction as a predisposing factor for severe pancreatitis.

The prestigious Cochrane Collaboration published a meta-analysis of the trials by Neoptolemos et al, Fan et al and Fölsch et al concluding that early ERCP significantly decreases the rate of complications in patients with predicted severe pancreatitis.¹⁵ In 2008, Moretti et al performed another meta-analysis, incorporating the results of the study by Orva et al and a study by Zhou et al of disputable quality to the 3 previous studies, reaching the same conclusions.^{16,17} The authors claimed that excluding the data from the study by Zhou et al would not alter their results. Concurrent to Moretti et al, Petrov et al published their meta-analysis that excluded patients with cholangitis.¹⁸ The authors included the trials by Neoptolemos et al, Fölsch et al and Orva et al and failed to prove a substantial benefit from early ERCP, even in predicted severe pancreatitis. They also stated that even if they included the trial by Fan et al they would reach the same conclusion. In a complementary meta-analysis by Petrov et al focused on a unified outcome, local pancreatic complications, no benefit of early ERCP was revealed in either predicted mild or predicted severe pancreatitis groups.¹⁹ Finally, in an effort to completely exclude patients with even mild cholangitis Uy et al included only the trials by Fölsch et al and Orva et al and found no advantage of early ERCP, but instead a trend towards increased mortality from the procedure.²⁰

DISCUSSION

The Hippocratic principle “first do no harm” is at the core of the dilemma a physician treating a patient with acute biliary pancreatitis faces when he or she needs to decide whether early ERCP would be of benefit. Inconsistencies in the various clinical trials and meta-analyses can cause confusion and they should be interpreted within the context of several limitations. First, the diagnosis of concurrent acute cholangitis is difficult in patients with manifestations of inflammatory reaction due to acute pancreatitis, and only recently has a consensus been reached on the criteria of its diagnosis.²¹ Second, the numerous scoring systems for predicting the course of acute pancreatitis (Glasgow, APACHE II, Ranson’s) testify to the fact that we lack an efficient and accurate way of predicting the outcome of the disease. The positive predictive value of such systems is estimated at 50-60%, introducing an important misclassification error to the trials dividing their population to predicted mild and predicted severe subgroups.²² Third, stones were eventually found in only half the patients who underwent ERCP, thus exposing the rest to the dangers of the procedure without the prospect of benefit.

It is clear that better selection of patients for early ERCP needs to be made. The UK guidelines for the man-

agement of acute pancreatitis advocate urgent therapeutic ERCP in every patient with suspected gallstone etiology and predicted severe disease or concurrent cholangitis, jaundice or dilated common bile duct.²³ The AGA guidelines are more strict, proposing early ERCP only in patients with cholangitis or suspicion of persistent common bile duct stone (dilated common bile duct, visible common bile duct stone, jaundice or persistently abnormal liver biochemistry values).²⁴ In clinical practice however, physicians complied with the guidelines regarding early ERCP in only 48% of cases despite conforming with them in every other aspect as was shown in a recent study in the UK.²⁵ Nevertheless this lack of conformity did not result in an increase of mortality.

Persistent obstruction of the main bile duct for more than 48 hours is proposed as a much better indication for early ERCP in acute pancreatitis.²² This view is supported by evidence from retrospective studies and animal models as well as the aforementioned trial by Acosta et al.^{2-5, 12} However, the identification of a proper early indicator of biliopancreatic obstruction apart from cholangitis is still a matter of research. In another recent study, Acosta et al proposed severe unremitting pain, bile-free gastric aspirate and persistent or increasing levels of serum bilirubin as criteria for continuing obstruction, exhibiting high sensitivity and specificity in a dedicated hospital.²⁶ Furthermore, MRCP and EUS have shown excellent performance in diagnosing choledocholithiasis.^{27,28} In the setting of acute pancreatitis EUS was as sensitive (96% vs 96%) and specific (85% vs 92%) as ERCP in detecting choledocholithiasis.²⁹ These procedures could be applied prior to ERCP, provided their availability, restricting ERCP to patients with strong evidence of obstruction. EUS has the added advantage that it can be performed in pre-selected patients for ERCP immediately before the procedure.

In conclusion, early ERCP should be performed in patients with acute pancreatitis and concurrent cholangitis. Predicted severe pancreatitis should not be an indication for early ERCP per se, but only when there are indications of persistent biliary obstruction. Locally available modalities and expertise like MRCP and EUS can be used before resorting to ERCP.

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