

ERCP in acute biliary pancreatitis

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Abstract

The role of urgent endoscopic retrograde cholangiopancreatography (ERCP) in acute biliary pancreatitis is for many years a subject for disagreement among physicians. Although the evidence seemed to be in favor of performing ERCP, endoscopists usually hesitate to conform to the guidelines. ERCP is an invasive procedure, with complications which can affect patients' outcome. Recent evidence suggests that we should probably modify our policy, recruiting less invasive procedures, like magnetic resonance cholangiopancreatography and endoscopic ultrasound, before conducting ERCP in patients with acute biliary pancreatitis. In this editorial the different aspects regarding the role of ERCP in acute biliary pancreatitis are discussed.

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INTRODUCTION

The pathogenesis of acute biliary pancreatitis is attributed to transient obstruction of the bile and pancreatic duct, which causes reflux of bile and duodenal content in the pancreatic duct or/and increases the hydrostatic pressure in the pancreatic duct^[1]. The severity of pancreatitis is determined by the size of the following local and systemic inflammatory reaction that depends on the interaction of multiple factors probably including genetic predisposition. It has been suggested by animal models and human studies that the duration of bile duct obstruction is a critical factor contributing to the severity of pancreatitis^[2-5]. Pancreatic necrosis develops more often when the duration of obstruction exceeds 48 h. This obstruction may be constant, due to an impacted stone, or intermittent, when a stone remains in the bile duct or multiple stones try to pass the ampulla.

Initial surgical attempts to decompress the bile duct soon after the diagnosis of pancreatitis failed, because they were associated with increased mortality in the urgent surgery group^[6,7]. Endoscopic retrograde cholangiopancreatography (ERCP) is a less invasive method to clear the bile duct, so it could favorably affect the severity of biliary pancreatitis if utilized properly. On the other hand, it is difficult to perform ERCP in a patient with acute pancreatitis, because the duodenum and ampulla are swollen and the patients' physical condition is compromised. Thus, we should have strong evidence to attempt an urgent invasive procedure which is inconvenient for both the patient and the doctor.

Four randomized studies have been published the last twenty years and they will be reviewed in the light of two recent meta-analyses. We should address in advance that each of those studies focused in different populations, so the results must be interpreted within this context.

Neoptolemos *et al*^[8] studied patients with probable biliary pancreatitis, stratified according to severity based on the modified Glasgow criteria. They found that patients with predicted severe pancreatitis had fewer complications if they underwent ERCP within 72 h (24% vs 61%, $P < 0.01$). When patients with acute cholangitis were excluded

the difference remained (15% *vs* 60%, $P = 0.003$). It is reasonable to exclude patients with acute cholangitis from the studied population because the coexistence of acute pancreatitis and cholangitis is accompanied by higher rate of complications, therefore these patients are the most probable to benefit from early ERCP^[9].

A few years later Fan *et al*^[10] published a similar study in a mixed population, but only 66% of them had biliary pancreatitis. The pancreatitis severity was predicted by serum urea and plasma glucose levels, a system with disputed value^[11]. ERCP was performed within 24 h after admission. In the subgroup with biliary stones (a stone located in any part of the biliary tract) the authors from Hong Kong also found, in agreement with the Leicester study, that the early ERCP group with predicted severe pancreatitis had fewer complications (13% *vs* 54%, $P = 0.002$), although one half of the conservative treatment group eventually underwent ERCP (median time 60 h). Patients with cholangitis were not excluded in that study but were offered ERCP irrespectively of the assigned group.

The results of those studies suggested that patients with predicted severe acute biliary pancreatitis should have urgent ERCP.

IS THIS TRUE OR THE FAVORABLE RESULTS COME FROM THOSE PATIENTS WITH IMPACTED COMMON DUCT STONES AND PERSISTING OBSTRUCTION?

The study of Folsch *et al*^[12] tried to answer this question by excluding patients with bilirubin level higher than 5 mg/dL. The modified Glasgow criteria were used to predict severity and ERCP was performed within 72 h after the onset of pain. This study was prematurely terminated because an interim analysis found that the primary goal (superiority of ERCP treatment) could not be reached. The rate of morbidity and mortality was similar between the invasive and conservative treatment group. Mortality in the severe pancreatitis group was 6/26 in the ERCP arm and 2/20 in the conservative arm ($P = 0.44$)^[13]. A worrying finding was an estimated 8% mortality in the mild pancreatitis group who underwent ERCP (5.4% in the conservative treatment group, $P = 0.7$) which was much higher than that observed in other studies^[13]. The rate of respiratory failure was significantly higher in the ERCP group, which could not be explained by the authors. This study highlights that ERCP is an invasive procedure, with complications that can affect patients' outcome.

IS THERE A SUBGROUP OF PATIENTS WITH ACUTE BILIARY PANCREATITIS WHO COULD BENEFIT FROM EARLY ERCP?

Twenty years ago Neoptolemos *et al*^[14] found in a retro-

spective study that more patients with severe pancreatitis had bile duct stones 72 h after the attack (61% *vs* 35%) and even 3-30 d after the attack (50% *vs* 24%) than patients with mild pancreatitis ($P < 0.01$). In a randomized study Acosta *et al*^[15] tested the hypothesis that it is the duration of bile duct obstruction that determines the outcome of biliary pancreatitis and not the presence of stones *per se*. The authors subjected to ERCP the patients enrolled in the intervention arm, if signs of obstruction persisted over 24 h. Indications of obstruction were severe and continuous epigastric pain, bile free gastric aspirate and elevated serum bilirubin, while relief of pain, decrease of bilirubin level and reappearance of bile in the gastric aspirate were signs of spontaneous termination of obstruction. Half of the patients in the intervention group eventually underwent ERCP. When discontinuation of the obstruction occurred spontaneously or after ERCP in less than 48 h, the rate of complications was lower than in cases with obstruction lasting more than 48 h (8% *vs* 78%, $P < 0.001$).

According to the above results it would be reasonable to assume that patients with persisting biliary obstruction could benefit from urgent ERCP. In a study that could be regarded supplementary to that of Folsch *et al*^[12], Oria *et al*^[16] randomized patients with signs of obstruction (main bile duct diameter ≥ 8 mm and total serum bilirubin ≥ 1.20 mg/dL) without cholangitis, to urgent ERCP within 72 h after the onset of the attack or to conservative treatment. The incidence of complications was similar between the two groups. Bile duct stones were found in 72% of patients with predicted mild pancreatitis (APACHE II score) and in 73% of patients with predicted severe pancreatitis. These results intrigued the results by Neoptolemos *et al*^[14].

A Cochrane meta-analysis of the first three trials (Neoptolemos *et al*^[14], Fan *et al*^[10] and Folsch *et al*^[12]) concluded that early ERCP decreases significantly the rate of complications in patients with predicted severe pancreatitis^[17]. A recent meta-analysis from Italy included the aforementioned studies and added the study of Oria *et al*^[16] and one study from China with disputable randomization^[18-20]. The authors reached the same conclusions with the Cochrane meta-analysis. They also stated that excluding the Chinese study the results would be similar^[19]. Another meta-analysis, which was published concurrently, approached this issue excluding patients with acute cholangitis^[21]. Petrov *et al*^[21] included the trials by Neoptolemos *et al*^[14], Folsch *et al*^[12] and Oria *et al*^[16] and excluded the study by Fan *et al*^[10] because it did not provide separate data on acute cholangitis. This meta-analysis failed to prove a substantial benefit from early ERCP even in patients with predicted severe pancreatitis. The authors noted that even in the case they had included the study by Fan *et al*^[10], the results would not differ.

Each of the previous studies and consequently the meta-analyses should be interpreted within the context of several limitations: First, the diagnosis of acute cholangitis in a patient with inflammatory reaction due to acute pancreatitis is cumbersome and until recently there

were no specific criteria^[22]. Second, the criteria used for prediction of pancreatitis' severity (APACHE II, Glasgow) have low positive predictive value (50%-60%), which means that about half of those predicted to have severe pancreatitis actually prove to have mild pancreatitis. How could someone evaluate the effectiveness of a given intervention, if half of the patients would probably not benefit and the intervention itself may affect morbidity and mortality in both ways? Third, stones were eventually found in only half of the patients who underwent ERCP, which means that ERCP would not benefit half of those in whom an indication for the intervention was determined and the procedure could possibly deteriorate their clinical condition.

The UK guidelines for the management of acute pancreatitis advocate urgent therapeutic ERCP in every patient with suspected gall stone etiology and predicted severe pancreatitis or when there is cholangitis, jaundice or a dilated common bile duct^[23]. The indications for early ERCP in the AGA Institute review on acute pancreatitis are more restricted^[24]. According to these guidelines, early ERCP should be performed in patients with cholangitis or when there is suspicion of persistent common bile duct stone (a dilated common bile duct or visible common bile duct stone, or jaundice or persistently abnormal liver chemistry values). Urgent ERCP in predicted severe pancreatitis without concomitant cholangitis or high suspicion of a persistent common bile duct stone is controversial.

Medical community appears reluctant to conform to these guidelines as clearly shown in a recent study from UK^[25]. Physicians complied with all the UK guidelines except for urgent ERCP for severe acute pancreatitis. Only 48% of patients with this indication finally underwent ERCP within 72 h. Difficulties in transferring patients to specialized centers capable to perform ERCP and in providing ERCP out of hours may have contributed to these results. It was obvious that urgent ERCP was reserved for patients with severe gallstone pancreatitis who had biliary obstruction or cholangitis. Nevertheless this policy did not increase the mortality of acute pancreatitis. The same viewpoint is also encountered in the USA^[26].

According to the Tokyo guidelines a definite diagnosis of cholangitis is reached when there are two or more of the following i.e. (a) history of biliary disease, (b) fever and/or chills, (c) jaundice (d) upper abdominal pain and in addition, laboratory evidence of inflammatory response and abnormal liver function tests and imaging findings of biliary dilatation or of specific etiology (e.g. a stone, in the case of pancreatitis)^[22]. The diagnosis of cholangitis in a patient with severe acute biliary pancreatitis with systemic inflammatory response syndrome (SIRS) could be problematic. From the aforementioned criteria only the imaging finding of an impacted stone could differentiate superimposed cholangitis on acute pancreatitis from pancreatitis with SIRS.

MRCP is useful in the diagnosis of biliary obstruction, although it should not be recommended in a patient with

unstable condition who could not be monitored in the MRCP chamber^[27]. Endoscopic ultrasound (EUS) can also detect biliary obstruction, at least equally to MRCP^[28,29]. These procedures could be applied before ERCP, if they are available, therefore ERCP would be reserved for patients with strong evidence of biliary obstruction.

CONCLUSION

In conclusion, (1) early ERCP should be reserved for patients with acute cholangitis superimposed to acute pancreatitis; (2) There is no indication for urgent ERCP in patients with mild pancreatitis without cholangitis; and (3) In cases with severe biliary pancreatitis the differential diagnosis between acute cholangitis and pancreatitis with SIRS may be difficult. In those patients every effort should be made to identify biliary obstruction, including MRCP and EUS when accessible, before resorting to ERCP.

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