Selected Summaries

Urgent endoscopic retrograde cholangiopancreatography for acute biliary pancreatitis: Few answers and more questions

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SUMMARY

In this multicentre randomized study from the Netherlands, patients with acute biliary pancreatitis (ABP) predicted to have a severe course were randomized to receive urgent endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy or conservative therapy. The study randomized these patients within 24 hours of presentation and the patients with cholangitis were excluded from the study. The primary end-point was a combination of death or major complications (post-ERCP persistent organ failure, cholangitis, other infectious complications, pancreatic necrosis or insufficiency). Of the 232 patients in the intention-to-treat analysis, 118 were randomized to the urgent ERCP group. The primary end-point was noted to occur in 38% of patients in the ERCP group and in 44% of those in the conservative group (p=not significant). Except for cholangitis, which was less frequent in the ERCP group, no differences in individual end-points were noted between the two groups. The authors suggest that a conservative strategy is appropriate to predict severe acute gallstone pancreatitis in the absence of cholangitis.

COMMENT

Acute gallstone pancreatitis is the most common cause of acute pancreatitis globally and the incidence is increasing because of the rising prevalence of obesity and gallstone disease.[1] Impacted stones in the common bile duct or ampulla are believed to be the initiating and propagating event in biliary pancreatitis.[2] Hence, it has been presumed that urgent biliary decompression may ameliorate and modify the disease course, especially vis-à-vis the severity of the disease. The literature has shown variable results of biliary decompression, especially in unselected patients of ABP (Table I).[3–10] Pooled data of these randomized controlled trials show a clear advantage of ERCP in patients with concomitant cholangitis and persistent cholestasis but not in the case of unselected patients with ABP.[11] Various guidelines suggest urgent (<24 hours) ERCP in the presence of concomitant cholangitis and early (<72 hours) ERCP in those with persistent cholestasis in ABP. Guidelines also suggest a lack of benefit of ERCP in case of mild disease.[12–15] In patients with predicted severe pancreatitis, limited literature is available. Previous studies had many lacunae such as small sample size, heterogeneous inclusion, variable timing of ERCP and sphincterotomy rates in this group of patients.[3,6,8]

The present randomized trial by the Dutch pancreatitis group has attempted to address these lacunae. The trial has certain strengths as it is the largest trial in patients with predicted severe ABP, a well-designed study with clearly defined criteria for cholestasis. All the ERCPs were done early in the course of the disease (<24 hours) and endoscopic sphincterotomy was done in all the patients who underwent ERCP. While this recent trial on the role of urgent ERCP in ABP provides evidence for a conservative approach in the absence of cholangitis, there are concerns regarding the generalizability

TABLE I. Randomized trials for endoscopic retrograde cholangiopancreatography for acute gallstone pancreatitis

Authors (year)	Study design, number of patients	ERCP timing, sphincterotomy	Inclusion (I), exclusion (E)	Outcome
Fan *et al*. (1993)[6]	RCT, 97 patients in the ERCP arm *v*. 98 patients in the conservative arm	Urgent (<24 hours), papillotomy in 37 patients with CBDS in the ERCP arm	(I) Patients with mild and severe AP, also patients with cholangitis	Less cholangitis/septic complications/mortality in the ERCP arm
Lee *et al*. (2018)[10]	RCT, 39 patients in the urgent ERCP arm *v*. 34 in the early ERCP arm	Urgent (<24 hours) *v*. early ERCP (<72 hours), no comment on sphincterotomy	(I) Patients with cholestasis (E) Patients with cholangitis	No difference in hospital stay and complications
Acosta *et al*. (2006)[5]	RCT, 30 patients in the study group, 31 in the control group	ERCP <48 hours in the study group and >48 hours in the control group; 13 patients in the study group underwent sphincterotomy	(I) Acute gallstone pancreatitis with ampullary obstruction (severe and continuous epigastric pain, bile-free gastric aspirate, and elevated serum bilirubin level)	Shorter period of biliary obstruction and lower rate of immediate complications in the study group
Neoptolemos *et al*. (1988)[3]	RCT, 121 patients, 59 in the ERCP arm and 62 in the conservative arm	Early ERCP (<72 hours), not all patients underwent sphincterotomy (exact number not mentioned)	(I) All patients with acute gallstone pancreatitis including cholangitis Predicted severe AP defined as modified Glasgow score ≥3	Fewer complications and shorter hospital stay in the ERCP group, especially in predicted severe AP
Fölsch *et al*. (1997)[7]	RCT, 126 patients in the ERCP arm and 112 in conservative arm	Early ERCP (<72 hours), papillotomy done only in 58 patients with CBDS in the ERCP group	(I) Patients with mild and severe acute gallstone pancreatitis (E) Patients with cholangitis and persistent cholestasis (biliary >5 mg/dl)	Mortality and complications were similar; however, the ERCP group had more severe complications
Oría *et al*. (2007)[4]	RCT, 51 patients in both arms	Early ERCP (<72 hours), sphincterotomy only in 38 patients in the ERCP group (34 had CBDS, 4 incomplete biliary drainage)	(I) Patients with mild and severe pancreatitis with persistent biliary obstruction (E) Patients with cholangitis	No difference in mortality, organ failure scores, CTSI, local complications
Van Santvoort *et al*. (2009)[8]	Prospective multicentre study, 81 patients in the ERCP arm and 72 in the conservative arm	Early ERCP (<72 hours), papillotomy in 69 patients	(I) Only patients with predicted severe acute gall stones (E) Patients with cholangitis Patients with/without cholestasis were analysed separately	Patients with cholestasis: lower complications Patients without cholestasis: no difference in complications No difference in mortality in both the arms with/ without cholestasis
Chen *et al*. (2010)[9]	RCT, 53 patients, 21 in the ERCP group, 32 in the conservative group	Early ERCP (<72 hours), papillotomy done in 17 patients	(I) Acute severe pancreatitis and persistent ampullary obstruction	In the ERCP group, considerable decrease in APACHE II score on day 10
Study being commented upon	RCT, 232 patients, 118 in the ERCP arm, 114 in the conservative arm	Urgent ERCP (<24 hours), technical success in 81% patients, sphincterotomy in all patients in the ERCP arm	(I) Only patients with predicted severe acute gallstone pancreatitis (E) Patients with cholangitis	No difference in composite end-points (mortality and complications) at 6 months

ERCP endoscopic retrograde cholangiopancreatography RCT randomized controlled trial CBDS common bile duct stone AP acute pancreatitis
CTSI computed tomography severity index

of these findings. The primary outcome used in this study was a composite of mortality and complications at 6 months as in other trials by the group. This end-point has benefits as it assesses the effect of intervention with respect to multiple parameters and the fact that assessment is up to 6 months since acute pancreatitis can be associated with late mortality. However, the trend to use this composite outcome at a time gap from the actual intervention and this 'one size fits all' approach is of concern.[16] Benefits from early ERCP would be derived from a change in the course of disease and should accrue early in the course of the disease. Over 6 months, other factors such as infection of the local complications could impact outcomes and cloud the actual benefit from the intervention. Assessment at shorter duration (at 1–2 weeks) with parameters such as development of severe pancreatitis (persistent organ failure), worsening systemic inflammatory response syndrome (SIRS) and organ failure, as used in previous trials, may have been more meaningful.[4,9] Nevertheless, given the null hypothesis of this

trial (i.e. early sphincterotomy may reduce disease severity in predicted severe acute necrotizing pancreatitis), the use of composite measure at 6 months is acceptable as it provides a complete assessment of severity during the entire course of acute pancreatitis.

The use of elevated alanine transaminase as the sole criterion to diagnose biliary pancreatitis in a considerable number of patients is also of concern. Previous studies included these criteria along with the presence of other evidence of gallstone disease including either elevated serum bilirubin or alkaline phosphatase when imaging failed to show evidence of gallstone/sludge.[7,8] Further, patients in the ERCP group had higher SIRS scores and C-reactive protein (CRP) at admission. These baseline differences could have masked the possible benefit of ERCP as sicker patients were included in the intervention arm, which might impact the results. This is especially so because in a substantial number of patients (19%) in the ERCP group, the procedure could not be done. The reason for technical failure was large periampullary diverticulum in 3 patients and complications of pancreatitis including periampullary oedema and respiratory failure in 7 patients. Eventually, in the ERCP arm, there was imbalance for these two reasons: failure to complete the procedure and higher SIRS rates that could have impacted the primary outcome. In such a situation, a per-protocol analysis should also have been done. The authors had committed this in the statistical plan, but this analysis was not provided.

In view of these concerns, we believe that the final word on the role of early ERCP in acute pancreatitis has not yet been said. Future studies should address these concerns about patient selection and selection of appropriate outcome measures before the role of ERCP in this group of patients can be defined.

Conflicts of interest. None declared

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Future pharmacotherapy for non-alcoholic steatohepatitis

Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, Sanyal AJ, Sejling A-S, Harrison SA. (National Institute for Health Research, Biomedical Research Centre at University Hospitals Birmingham NHS Foundation Trust and the Centre for Liver and Gastrointestinal Research, Institute of Immunology and Immunotherapy, University of Birmingham, and the Liver Unit, University Hospitals Birmingham NHS Foundation Trust, Birmingham, and the Radcliffe Department of Medicine, University of Oxford, Oxford—all in the United Kingdom; Novo Nordisk, Søborg, Denmark; Division of Endocrinology, Diabetes, and Metabolism, University of Florida, Gainesville, USA; Department of Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, Japan; Institute of Cardiometabolism and Nutrition, Sorbonne Université, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, INSERM Unité Mixte de Recherche Scientifique 1138 Centre de Recherche des Cordeliers, Paris, France; Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA.) A placebo-controlled trial of subcutaneous