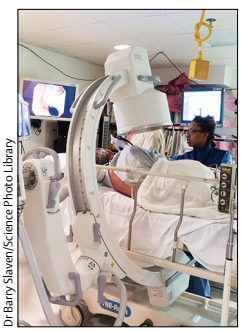
Judicious use of ERCP in gallstone pancreatitis



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In *The Lancet*, Nicolien Schepers and colleagues[1] report the results of a multicentre, assessor-masked, randomised controlled superiority trial comparing urgent endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy versus conservative management in adult patients with predicted severe acute gallstone pancreatitis. The investigators conclude that urgent ERCP with sphincterotomy did not reduce the composite endpoint of major complications or mortality. The study addresses the clinical dilemma encountered when patients present with severe gallstone pancreatitis with no associated cholangitis.

Neoptolemos and colleagues[2] were the first to describe the role of early ERCP in patients with severe gallstone pancreatitis, and in a subsequent study, Fan and colleagues[3] showed that biliary sepsis (cholangitis, acute cholecystitis) was more common in patients with predicted severe disease treated conservatively than in those assigned to emergency ERCP with or without endoscopic papillotomy. Fan and colleagues concluded that all patients, regardless of severity, should undergo early ERCP to prevent biliary sepsis. However, only a fraction of the patients in the study had predicted severe disease at randomisation, and all causes of pancreatitis were included in the analysis. In 1997, a randomised controlled trial by Fölsch and colleagues[4] showed no benefit of early ERCP, with an associated increased rate of severe complications including respiratory failure in the intervention group compared with the conservative treatment group. Their findings were unchanged when further classified by disease severity. A 2012 Cochrane review of seven clinical trials involving 757 patients provided the strongest evidence and found that early routine ERCP did not have a significant effect on complications or mortality in patients with biliary pancreatitis without cholangitis, regardless of disease severity.[5]

This new multicentre trial in *The Lancet* by Schepers and colleagues[1]—the largest randomised controlled trial to date, to our knowledge, in patients with predicted severe disease—is therefore welcomed. Schepers and colleagues cast a wide net with the study design, thereby increasing patient diversity, and in turn, reliability. All patients (aged ≥18 years) who presented with acute biliary pancreatitis to 26 centres in the Netherlands were screened for eligibility. Only those with predicted severe disease (Acute Physiology and Chronic Health Evaluation II score ≥8, Imrie score ≥3, or C-reactive protein concentration >150 mg/L) were eligible for randomisation. Of note, acute biliary pancreatitis was diagnosed if one of the following conditions was met: pancreatitis plus confirmed cholelithiasis, a dilated common bile duct, or an alanine aminotransferase concentration of more than twice the upper limit of normal. Patients were excluded from randomisation if they had a history of chronic pancreatitis, pancreatitis due to other causes, a history of previous ERCP with sphincterotomy, or presented with suspected cholangitis—a patient population known to benefit from the intervention in question. Cholangitis was defined as fever in combination with documented common bile duct stones, a dilated common bile duct, or progressive cholestasis. Over 4 years, 232 participants (127 [55%] men; mean age 70 years [SD 13]) were randomly assigned (1:1) to either urgent ERCP with sphincterotomy within 24 h after hospital presentation, or conservative treatment.

The primary endpoint, a composite of mortality or major complications (new-onset persistent organ failure, cholangitis, bacteraemia, pneumonia, pancreatic insufficiency, or pancreatic parenchymal necrosis) within 6 months, occurred in 45 (38%) of 117 patients in the urgent ERCP with sphincterotomy group and in 50 (44%) of 113 patients in the conservative treatment group (risk ratio 0·87, 95% CI 0·64–1·18; p=0·37). However, the only component of the primary endpoint that differed significantly between treatment groups was cholangitis, occurring more frequently in patients treated conservatively (two [2%] of 117 in the urgent ERCP group *vs* 11 [10%] of 113 in the conservative treatment group; p=0·010). In a subgroup analysis involving only patients with confirmed cholestasis at randomisation, the primary composite endpoint occurred in 20 (32%) of 63 patients in the urgent ERCP group, compared with 29 (43%) of 67 patients in the conservative treatment group (p=0·18). Although cholangitis was more common in the conservative treatment group, the investigators concluded that the lack of statistically significant increased rates of mortality or the other serious complications meant that conservative treatment had no net negative impact on the overall outcome.

Secondary outcomes studied were the need and length of intensive care admission, length of hospital stay, readmission for gallstone-related events, quality of life, and societal costs within 6 months. Of the secondary outcomes studied, the only one of significance was an increased rate of readmission for recurrent gallstone pancreatitis in the conservative treatment group (ten [9%] patients) compared with the urgent ERCP group (no patients; p=0·0010).

One area of possible bias was the use of a stricter definition of common bile duct dilation than the commonly accepted norm. In the study, a dilated common bile duct was defined as more than 8 mm in patients aged up to 75 years, and more than 10 mm in patients older than 75 years. Since one of the definitions of cholangitis was fever in combination with a dilated common bile duct, it is reasonable to assume that some patients with cholangitis were randomly assigned when they otherwise would have been deemed ineligible. Nevertheless, this assumption would tend to favour rejection of the null hypothesis rather than acceptance, and therefore the impact of this potential bias is likely to be small.

The results of this trial support the judicious use of ERCP with sphincterotomy in patients admitted with severe acute biliary pancreatitis, with a convincing body of evidence that patients will not benefit from this invasive intervention.

We declare no competing interests.

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1 Schepers NJ, Hallensleben NDL, Besselink MG, et al. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. *Lancet* 2020; **396:** 167–76.
2 Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. *Lancet* 1988; **2:** 979–83.
3 Fan ST, Lai EC, Mok FP, Lo CM, Zheng SS, Wong J. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *N Engl J Med* 1993; **328:** 228–32.
4 Fölsch UR, Nitsche R, Ludtke R, Hilgers RA, Creutzfeldt W. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. *N Engl J Med* 1997; **336:** 237–42.
5 Tse F, Yuan Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database Syst Rev* 2012; **5:** CD009779.

The evolving clinical use of dexmedetomidine

In patients having cardiac and non-cardiac surgery, new-onset postoperative atrial fibrillation and postoperative delirium have been associated with several adverse long-term outcomes, including increased cardiovascular, renal, and cerebral complications, worsened postoperative cognitive function, increased mortality, longer length of stay in hospital, and increased medical costs.[1–3] Identifying effective therapies and modifiable factors that might reduce the incidence of postoperative atrial fibrillation and postoperative delirium is paramount.

The DECADE trial in *The Lancet* tested whether a perioperative dexmedetomidine infusion would reduce the incidence of postoperative atrial fibrillation or postoperative delirium within the fifth postoperative day in cardiac surgery patients.[4] As Alparslan Turan and colleagues[4] report, the trial failed to show a significant effect. Patients aged 18–85 years (20·4% women and 79·6% men), scheduled to have cardiac surgery with cardiopulmonary bypass, with no history of atrial fibrillation within 30 preoperative days, were recruited for this investigator-initiated, multicentre, double-blind, randomised controlled trial. Patients were randomised to receive dexmedetomidine infusion or a similar volume of saline infusion. Before skin incision, dexmedetomidine infusion was initiated—without a loading dose—at 0·1 μg/kg per h; after cardiopulmonary bypass the rate was increased to 0·2 μg/kg per h and further increased in the postoperative period to 0·4 μg/kg per h, and then continued for 24 h. Incidence of postoperative atrial fibrillation (121 [30%] in 397 patients in the dexmedetomidine group *vs* 134 [34%] in 395 patients in the placebo group; relative risk 0·90 [97·8% CI 0·72–1·15, p=0·34) and postoperative delirium (67 [17%] in the dexmedetomidine group *vs* 46 [12%] in the placebo group; 1·48 [0·99–2·23], p=0·026) was similar in patients who received dexmedetomidine or saline infusions. Given these findings, dexmedetomidine should be used cautiously in patients who have cardiac surgery to minimise the associated occurrence of intraoperative arterial hypotension and should not be given with the expectation of reducing atrial fibrillation or delirium. The lack of preoperative optimisation of modifiable postoperative atrial fibrillation and postoperative delirium risk factors and the non-standardised anaesthesiological


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