https://doi.org/10.1016/j.hpb.2018.03.016 HPB

ORIGINAL ARTICLE

Index versus delayed cholecystectomy in mild gallstone pancreatitis: results of a randomized controlled trial

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Abstract

Background: Delayed cholecystectomy is associated with increased risk of biliary events. The objectives of the study were to confirm the superiority of index cholecystectomy over delayed operation in mild gallstone pancreatitis.

Methods: Patients with mild gallstone pancreatitis were randomized into index–or delayed cholecystectomy (IC vs. DC). IC was performed within 48 h from randomization provided a stable or improved clinical condition. The primary outcome was gallstone-related events. Secondary outcomes were rates of cholecystectomy complications, common bile duct stones (CBDS) detected at cholecystectomy and patient reported quality-of-life and pain.

Results: Sixty-six patients were randomized into IC (n = 32) or DC (n = 34) between May 2009 and July 2017. There were significantly higher rates of gallstone-related events in the DC compared with the IC group (nine patients vs. one patient, p = 0.013). No statistically significant differences could be demonstrated in cholecystectomy complications (p = 0.605) and CBDS discovered during cholecystectomy (p = 0.302) between the groups. Pain and emotional well-being measured by SF-36 were improved significantly in the IC group at follow-up.

Conclusions: Delayed cholecystectomy in mild gallstone pancreatitis can no longer be recommended since it is associated with an increased risk for recurrent gallstone-related events and impaired patient's reported outcomes.

Trial registration number: clinicaltrials.gov (ID: NCT02630433).

Received 9 February 2018; accepted 30 March 2018

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Introduction

Gallstones are one of the leading causes of acute pancreatitis with an estimated etiologic role of up to 50%.[1] Given the general agreement that the gallstone containing gallbladders have to be removed in patients presenting with gallstone pancreatitis (GSP) to avoid recurrent biliary events, a number of issues remain related to the adoption of such management concepts in routine clinical practice. There are diverging opinions on the optimal timing of the treatment. In patients with severe GSP accepted clinical practice is to wait until the patient has recovered from the initial inflammation before performing cholecystectomy and/or endoscopic retrograde cholangiopancreatography (ERCP) in severe GSP with systemic or local complications.[1,2] However, the international recommendations are less clear when it comes to patients with mild biliary pancreatitis. The British Society of Gastroenterology and American Gastroenterological Association guidelines recommend cholecystectomy within two to four weeks after the initial episode.[3–5] A safety aspect was portrayed by the retrospective study by Sinha *et al.*, which implied more complex dissection during cholecystectomy when carried out 6

Please cite this article in press as: Noel R, et al., Index versus delayed cholecystectomy in mild gallstone pancreatitis: results of a randomized controlled trial, HPB (2018), https://doi.org/10.1016/j.hpb.2018.03.016

weeks after mild GSP.[6] There are considerable variations in the adherence to current guidelines, probably due to the lack of evidence for the optimal timing of the intervention.[7] A study published by Creedon *et al.* on mild GSP in a single teaching hospital-setting showed that only 32% of patients underwent cholecystectomy in accordance with the British Society of Gastroenterology guidelines. In addition, they showed a difference in the proportion of admitted patients that underwent cholecystectomy under a hepatobiliary specialty compared to others.[8] In a nationwide study from the United States, only about 50% of patients underwent cholecystectomy during the same admission. Furthermore, ethnicity affected the rates of cholecystectomy.[9] On the other hand, recently published studies from the United States and Sweden demonstrated higher adherence rates; 78% within 30 days from index episode and 68% at index, respectively.[10,11]

In 2015, a multicenter randomized controlled trial, cholecystectomy before discharge for mild GSP was shown not only to be safe but also advisable in terms of offering prevention from biliary events.[12] Accordingly, postponing surgery carries an 18% risk for readmission due to recurrent biliary events; including 8% for recurrent GSP, 3% for acute cholecystitis and 7% for biliary colic.[2] Therefore, the aim of the present study was to compare gallstone-related events following cholecystectomy performed before discharge (index cholecystectomy) or delayed at least 6 weeks after the initial episode.

Material and methods

Study design

The study was conducted as a single center randomized clinical trial with two parallel arms with a superiority design. Patients with mild gallstone pancreatitis were randomized to undergo cholecystectomy during their index admission (Index Cholecystectomy – IC) or delayed for cholecystectomy at least 6 weeks after the index admission (Delayed Cholecystectomy – DC).

Data source

Patients admitted to the surgical department at the Karolinska University Hospital in Huddinge between May 2009 and July 2017 aged 18–80 years with first episode of GSP were eligible for inclusion. Pancreatitis was diagnosed when at least two out of three criteria were met; acute abdominal pain, elevated serum amylase level three times (>3 μkat/L) above the upper normal limit and/or evidence of pancreatitis on imaging modality, e.g. computerized tomography (CT) of abdomen. The biliary genesis was verified by abdominal ultrasonography showing one or more gallstones and/or biliary sludge in the gallbladder and/or in the bile ducts. Mild pancreatitis was defined by the absence of persistent organ failure (more than 48 h) and local complications.[13] In addition, a rapidly improving clinical course together with a serum C-reactive protein less than 150 mg/L during the first 24 h from admission were compatible with mild GSP.[14] Patients with multiple organ failure, concurrent cholangitis or cholestasis requiring intervention, pregnancy and alcohol induced pancreatitis were excluded.

Randomization

All eligible patients obtained verbal and written information by the surgeon in charge. Patients were included after a consent was obtained. Owing to the invasive nature of the intervention and the logistics involved to do the procedures, neither the trial participants nor the investigators could be masked to group allocation. The randomization was performed through a sealed envelope by the same surgeon who informed the patient. Randomization was planned within 72 h from admission according to the study protocol. Patients randomized to IC- were assigned to cholecystectomy within 48 h after randomization. Patients in both groups were managed according to a local standardized program for acute pancreatitis, including regimes of intravenous fluids and analgesia. Patients were discharged as soon as their clinical condition allowed. Patients randomized to DC were scheduled for cholecystectomy at least 6 weeks after primary discharge.

Interventions-cholecystectomy and intraoperative endoscopic retrograde cholangiopancreatography (ERCP)

The laparoscopic cholecystectomy was performed with standard 4-ports laparoscopic technique. Standardized pre-, intra- and postoperative surgical care was provided. No preoperative ERCP was performed in any patients as the routine policy of the hospital to manage concurrent common bile duct stones is intraoperative cholangiography and intraoperative rendezvous ERCP if stones are encountered.[15] No antibiotics were administered routinely during cholecystectomy unless ERCP was warranted in which case a single dose of 4 g Piperacillin/Tazobactam was given intravenously before the start of the ERCP. In case of penicillin allergy, one dose of Ciprofloxacin 500 mg intravenously was given instead. To ensure the surgeons adherence to the study protocol and interventions, a retrospective review of the included patients was conducted.

Ethics

The study was approved by the regional ethical committee of Stockholm (ID: 2008/1030-31/3). An independent Safety Committee was established to monitor the study participants for unintentional risks that may have arisen because of randomization. The safety committee was established in 2010 and the final report was presented in 2017. Due to slow inclusion rate, the study was ended after the inclusion of 66 patients. The study was registered at clinicaltrials.gov (ID: NCT02630433).

Outcomes

The primary endpoint was gallstone-related events, including recurrent acute pancreatitis, cholecystitis, cholangitis or biliary

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