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Original Article

Unrecognized necrosis at same admission cholecystectomy for pancreatitis increases organ failure and infected necrosis

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ABSTRACT

Background and aims: Guidelines recommend same admission cholecystectomy (SAC) in the management of mild acute gallstone pancreatitis (AGP) with a recent randomized trial supporting this recommendation. However, the push for early cholecystectomy will lead a subset of patients with evolving, unrecognized necrotizing pancreatitis (NP) to undergo laparoscopic cholecystectomy (LC) with unknown consequences. With concerns about potentially serious outcomes, we studied the outcomes in patients with unrecognized NP who underwent SAC and identified predictors of unrecognized NP at the time of SAC.

Methods: Retrospective study of patients who appeared to have mild AGP but subsequently discovered to have unrecognized NP after SAC (study group). Outcomes were compared to a similar cohort with necrotizing AGP who did not undergo SAC (control group 1). Predictors for unrecognized NP at the time of SAC were identified through logistic regression using a second control group with truly mild AGP undergoing SAC.

Results: Patients in the study group ($N = 46$) undergoing SAC demonstrated higher rates of persistent organ failure ($p = 0.0003$), infected necrosis ($p = 0.02$), and length of hospital stay ($p = 0.049$) compared to a similar group ($N = 48$) with necrotizing AGP who did not undergo SAC. Persistent SIRS ($p < 0.0001$) and WBC $>12 \times 10^9$/L ($p < 0.0001$) on the day of cholecystectomy were associated with evolving/unrecognized NP.

Conclusions: Unrecognized NP at the time of SAC is associated with increased rates of subsequent persistent organ failure, infected necrosis, and length of hospital stay. Persistent leukocytosis and SIRS at the time of proposed cholecystectomy are predictive of unrecognized NP and should prompt contrast enhanced CT prior to proceeding with LC.

1. Introduction

The optimal timing of cholecystectomy for acute gallstone pancreatitis (AGP) has been debated for several decades [1,2,3,4]. Recurrences of gallstone related adverse events occur in 30% of patients not undergoing same admission cholecystectomy (SAC) and the minimally invasive nature of the operation are reasons for increasing rates of SAC in mild AGP [5]. Recent from the American College of Gastroenterology, International Association of Pancreatology, and American Pancreatic Association all recommend laparoscopic cholecystectomy (LC) during the initial hospitalization for mild AGP and recommend delayed LC in the setting of necrotizing pancreatitis (NP) [6,7]. Two randomized trials including the recent PONCHO trial have reported that SAC can be safely performed with regards to surgical complications [3,4]. However, these trials were not powered to detect uncommon complications related to pancreatitis which can be clinically significant especially if SAC approach becomes widely adopted.

A potential danger of SAC is subjecting patients with evolving, unrecognized NP to an additional inflammatory insult of surgery which could increase the risk of subsequent organ failure, infection,

Abbreviations: AGP, acute gallstone pancreatitis; BMI, body mass index; BUN, blood urea nitrogen; CT, computed tomography; IQR, interquartile range; LC, laparoscopic cholecystectomy; MRI, magnetic resonance imaging; NP, necrotizing pancreatitis; ROC, receiver operator characteristic; SAC, same admission cholecystectomy; SIRS, systemic inflammatory response syndrome; SD, standard deviation; WBC, white blood cell count.

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or death. The outcomes of LC in the setting of NP has not been well studied. One study reported two deaths out of 12 patients with NP who underwent LC during their initial hospitalization [8]. Unlike organ failure which is easily recognized, NP can be clinically silent and imaging may take up to 5 days to reveal necrosis [7]. There are no reliable predictors of necrosis in the first few days if imaging fails to demonstrate necrosis [7]. With SAC becoming increasingly common in accordance with guidelines, it seems inevitable that a subset of patients who appear to have mild pancreatitis, yet harbor unrecognized NP, will undergo LC. The evolving NP then can manifest with more serious outcomes in subsequent days, due to the added insult of surgery. There is no data in the literature regarding this scenario which is likely to become increasingly recognized. A clinical trial powered to detect this complication would require several hundred patients in the SAC arm and will be hard to accomplish.

The aim of this study is to determine the clinical outcomes of patients with unrecognized NP who underwent SAC. Additional aims are to estimate the magnitude of this problem among patients who undergo SAC for AGP and also identify predictors for undiagnosed NP prior to SAC.

2. Methods

2.1. Study group

This is a retrospective study of patients over 18 years of age treated at Mayo Clinic Rochester from January 2000 to August 2015 for AGP. Patients were retrospectively identified through a search of clinical databases including clinical notes, diagnosis codes, and procedure codes. The study group included consecutively admitted patients who had a presentation consistent with mild AGP and underwent SAC but were subsequently discovered to have (peri) pancreatic necrosis within 3 months of the diagnosis of AGP. Diagnosis of acute pancreatitis required 2 of the following 3 criteria: acute onset of upper abdominal pain consistent with pancreatic pain, amylase and/or lipase levels at least 3 times the upper limit of normal, or imaging evidence of pancreatic inflammation. A gallstone etiology was based on acute elevations of liver function tests and the presence of gallstones on ultrasound imaging. The assessment of mild pancreatitis was consistent with the revised Atlanta classification and included patients without evidence of organ failure, acute necrotic collections or acute peripancreatic fluid collections [9]. The definition of organ failure included acutely elevated creatinine greater than 2 mg/dL after fluid resuscitation or renal replacement therapy, a systolic blood pressure less than 90 mmHg after fluid resuscitation or pressor support, or requirement of high flow oxygen by facemask, positive airway pressure ventilation, or intubation. Severe pancreatitis was defined as persistent organ failure beyond 48 h. The diagnosis of NP was based on either contrast enhanced computed tomography or magnetic resonance imaging (MRI) performed with gadolinium. The timing of LC was at the discretion of the consulting surgeon but only patients undergoing SAC were included in the study group.

2.2. Control groups

Two control groups were created through a retrospective clinical database search of admitted patients to Mayo Clinic Rochester over the same time period. Control group 1 consisted of consecutively admitted patients with AGP who appeared to have mild pancreatitis within the first 48 h of presentation but were later discovered to have NP on imaging. These patients with NP did not demonstrate organ failure within the first 48 h and did not undergo LC during the same admission. Comparisons between the study group and control group 1 were performed to assess the effect of SAC on outcomes including length of hospital stay, development of persistent organ failure, infected necrosis, conversion to open cholecystectomy, need for intervention on (peri)pancreatic necrosis, and death during hospitalization. Control group 2 consisted of consecutively admitted patients with mild AGP who underwent SAC and were not diagnosed with NP at any point. Logistic regression analysis between the study group and control group 2 were performed to identify predictors of unrecognized necrosis in patients who present with what appears to be mild AGP.

2.3. Data collection

Medical records of patients included in this study were retrospectively reviewed and data regarding age, sex, BMI, vital signs, laboratory values, length of hospital stay, hospital readmission, persistent organ failure, infected necrosis, cholecystectomy technique, need for intervention for NP, and death were extracted.

2.4. Statistical analysis

Descriptive data is presented as median with interquartile ranges (IQR) or mean with standard deviations (SD) for continuous variables. Statistical analyses were performed using JMP and SAS statistical software (Cary, NC, USA). Wilcoxon rank-sum test was used for comparisons of continuous variables. χ^2 and Fisher's exact tests were used for comparisons of categorical variables. Univariate logistic regression analysis was performed to identify potential predictors of necrosis on the day of cholecystectomy. All reported *P* values are 2 sided with a $P < 0.05$ level of significance. Assessment of the predictive accuracy of potential predictors including SIRS and WBC were assessed by calculation of serial area under receiver operating characteristic (ROC) curves on day 1, day 2, and on day of cholecystectomy.

3. Results

3.1. Baseline patient characteristics

The study group included 46 patients with mild appearing AGP who underwent SAC and subsequently discovered to harbor unrecognized necrosis. Control group 1 included 48 similar patients with mild appearing AGP in the first 48 h and were subsequently discovered to have NP but did not undergo SAC. Control group 2 included 48 patients with mild AGP who underwent SAC and were not diagnosed with NP at any point. Clinical characteristics of patients are presented in Table 1.

3.2. Outcome comparisons

Outcome comparisons between the study group and control group 1 are provided in Table 2. The study group (unrecognized NP who underwent SAC) had a significantly longer length of hospital stay (median: 26 days, IQR 19–70) compared to control group 1 (unrecognized NP without SAC) (median: 24.5 days, IQR 16–33.5; $p = 0.049$). The study group had a higher rate of subsequent persistent organ failure (24%) compared to control group 1 (0%, $p = 0.0003$). Subsequent persistent organ failure in the study group was defined as organ failure with onset after cholecystectomy and persisting at least 48 h. Subsequent persistent organ failure in the control group 1 was organ failure with onset after the first 48 h of admission and persisting for at least 48 h. Patients in the study group demonstrated a higher rate of culture confirmed infected necrosis (52%) compared to control group 1 (27%, $p = 0.02$). There were no differences in the rates of intervention on necrosis,

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