

Treatment strategy for gallstone pancreatitis and the timing of cholecystectomy

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Abstract

AIM: To reviewed the literature and evaluated the scope and timing of the application of endoscopic retrograde cholangiopancreatography (ERCP)/endoscopic sphincterotomy (ES) and cholecystectomy.

METHODS: A pooled odds ratio (OR) and a pooled mean difference with the 95%CI were used to assess the enumeration data of included studies. A pooled weighted mean difference (WMD) and a pooled mean difference with the 95%CI were used to assess the measurement data of included studies. Statistical heterogeneity was tested with the χ^2 test. According to forest plots, heterogeneity was not significant, so the fixed effect model was adopted. The significance of the pooled OR was determined by the Z test and statistical significance was considered at $P < 0.05$.

RESULTS: Data were collected from two studies (353 patients, 142 in the early cholecystectomy group and 211 in the delayed cholecystectomy group) regarding the length of hospital stay [The WMD was -2.87 (95%CI: -3.36--2.39, $P < 0.01$). Data were collected from four studies (618 patients, 211 in the early cholecystectomy

group and 408 in the delayed cholecystectomy group) regarding perioperative complications (OR = 0.94, 95%CI: 0.41-2.12, $P > 0.05$). Data were collected from four studies (618 patients, 211 in the early cholecystectomy group and 408 in the delayed cholecystectomy group) on the number of patients who underwent ERCP± ES postoperatively (OR = 0.80, 95%CI: 0.45-1.41, $P > 0.05$).

CONCLUSION: Cholecystectomy offers better protection than ES against further bouts of pancreatitis in patients with gallstone pancreatitis, although ES is an acceptable alternative.

Key words: Gallstone pancreatitis; Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy; Cholecystectomy

Core tip: In this study we reviewed the literature and evaluated the scope and timing of the application of endoscopic retrograde cholangiopancreatography (ERCP)/endoscopic sphincterotomy (ES) and cholecystectomy. We also carried out a meta-analysis regarding the timing of cholecystectomy and found that early cholecystectomy administered to patients with mild gallstone pancreatitis could reduce the length of hospital stay with no increase in perioperative complications or the incidence of postoperative ERCP ± ES.

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INTRODUCTION

Acute pancreatitis is associated with considerable morbidity and mortality^[1]. In fact, approximately 20% of patients with acute pancreatitis will present a severe disease

course, with a 10%-30% mortality rate^[2]. The most common causes of acute pancreatitis include gallstones and alcohol abuse which together account for more than 80% of cases, and gallstones alone cause 30%-75% of cases^[3,4]. Apart from these two main causes, hyperlipidemia, medication use, hypercalcemia, trauma, familial pancreatitis, and other rare origins also can lead to pancreatitis^[5].

The theories of pathogenesis of gallstone pancreatitis (GSP) are still controversial now. The common channel theory proposes that a stone lodged at the ampulla of Vater creates a common channel between the bile and pancreatic ducts, which allows bile reflux into the pancreatic duct (PD) and subsequent activation of pancreatic enzymes^[6]. In contrast, the duodenal reflux theory postulates that the passage of biliary stones creates incompetence of the sphincter of Oddi, which results in the reflux of duodenal contents into the PD and subsequently leads to the activation of pancreatic proenzymes and the development of pancreatitis^[7]. The third prominent theory is the obstruction theory, which holds that a gallstone or inflammation with edema consequent to gallstone passage may impact or transiently obstruct the common bile duct (CBD) and PD at the level of the ampulla of Vater, which leads to extravasation of digestive enzymes into the gland parenchyma^[8]. Recently, many studies have reported that inflammatory mediators, including cytokines, interleukins (IL-6 and IL-8), platelet activating factor, and tumor necrosis factor (TNF- α), also play an important role in the systemic complications of acute pancreatitis^[9,10].

Most of the patients with gallstone pancreatitis demonstrate mild to moderate clinical disease, and some can recover with conservative management. The conservative management of gallstone pancreatitis includes bowel rest, fluid resuscitation, total parenteral nutrition or enteral nutrition, and parenteral analgesia, which is similar to the management approach for any form of pancreatitis. However, in contrast to other forms of pancreatitis, for instance, gallstone pancreatitis often requires surgery. According to the pathogenesis of gallstone pancreatitis, we know that removing the gallstones and resolving the obstruction of CBD and PD is the key point for management, although the optimal method for removing the gallstones and resolving the obstruction remains controversial. In particular, the application and timing of endoscopic retrograde cholangiopancreatography (ERCP)/endoscopic sphincterotomy (ES) or cholecystectomy remain the subject of current debate.

Publication search

To assess the method and timing of surgical treatment for gallstone pancreatitis, we searched the relevant literature from the Cochrane Library and the MEDLINE and EMBASE databases up to September 20th, 2013. The search strategy included the following MESH terms: "gallstone pancreatitis" and "endoscopic retrograde cholangiopancreatography" and "cholecystectomy".

MATERIALS AND METHODS

The inclusion criteria were as follows: (1) study popula-

Table 1 Chief characteristics of the included trials

Ref.	Group	POT	No. of patients	LOS	ERCP \pm ES postoperative	Complications
Aboulian <i>et al</i> ^[44] , 2010	Early	35.1	25	3.5 \pm 2.04	6	0
	Delayed	77.8	25	5.8 \pm 5.35	4	0
Rosing <i>et al</i> ^[42] , 2007	Early	48	43	4	2	2
	Delayed	120	177	7	24	9
Taylor <i>et al</i> ^[43] , 2004	Early	43.2	26	3.5	6 (1)	3
	Delayed	55.2	20	4.7	7 (2)	2
Falor <i>et al</i> ^[45] , 2012	Early	< 48	117	3.4 \pm 2.20	19 (12)	5
	Delayed	> 48	186	6.3 \pm 2.08	51 (19)	9

POT: Preoperative time, hours; LOS: Length of hospital stay, days; ERCP: Endoscopic retrograde cholangiopancreatography; ES: Endoscopic sphincterotomy.

tion: patients with mild gallstone acute pancreatitis (less than 3 Ranson criteria); (2) intervention: ERCP with or without ES *vs* cholecystectomy; (3) outcome measures: the length of hospital stay, the incidence of perioperative complication and the mortality; and (4) study design: randomized controlled trial. The exclusion criteria were as follows: (1) patients with severe gallstone pancreatitis (3 or more Ranson criteria); (2) pancreatitis from other causes; (3) suspected concomitant acute cholangitis; and (4) articles reporting non-comparative studies.

Statistical analysis

For statistical analysis, Review Manager (RevMan) software Version 4.2 was used (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). A pooled odds ratio (OR) and a pooled mean difference with the 95%CI were used to assess the enumeration data of included studies. A pooled weighted mean difference (WMD) and a pooled mean difference with the 95%CI were used to assess the measurement data of included studies. Statistical heterogeneity was tested with the χ^2 test. According to forest plots, heterogeneity was not significant, so the fixed effect model was adopted. The significance of the pooled OR was determined by the Z test and statistical significance was considered at $P < 0.05$.

RESULTS

Eligible studies

We found no randomized controlled trial or retrospective study concerning the application of ERCP with or without ES *vs* cholecystectomy. Therefore, we reviewed the previously published literature for studies evaluating ERCP/ES and cholecystectomy and then assessed the scope of the application of ERCP/ES and cholecystectomy.

Four studies showing that early cholecystectomy for mild gallstone pancreatitis may decrease hospital stay without increasing morbidity or mortality were identified; among these studies, 1 was a randomized controlled trial study and 3 were retrospective studies. All of these studies were single-center studies, and their main characteristics are listed in Table 1. Based on these 4 studies, we

Review: Early cholecystectomy vs Delayed cholecystectomy on the patients with gallstone pancreatitis
 Comparison: 01 early cholecystectomy vs Delayed cholecystectomy in terms of length of hospital stay
 Outcome: 01 the length of hospital stay

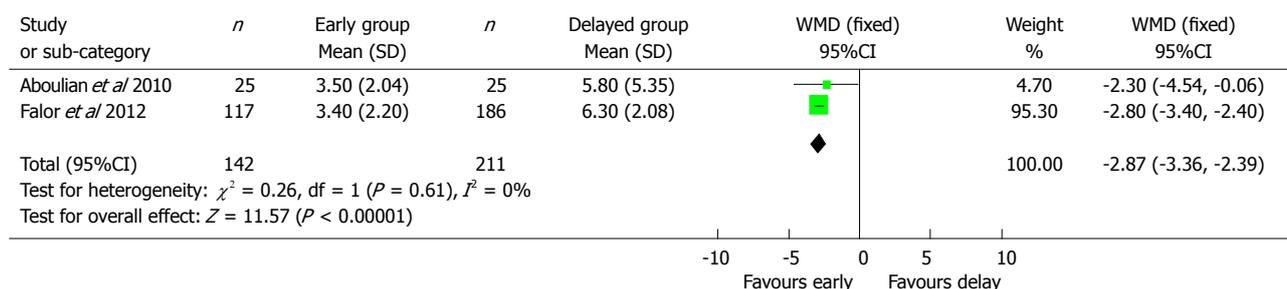


Figure 1 Forest plot comparing early cholecystectomy vs delayed cholecystectomy in terms of length of hospital stay. WMD: Weighted mean difference.

Review: Early cholecystectomy vs Delayed cholecystectomy on the patients with gallstone pancreatitis
 Comparison: 02 early cholecystectomy vs delayed cholecystectomy in terms of perioperative complications
 Outcome: 01 the number of patients who had perioperative complications

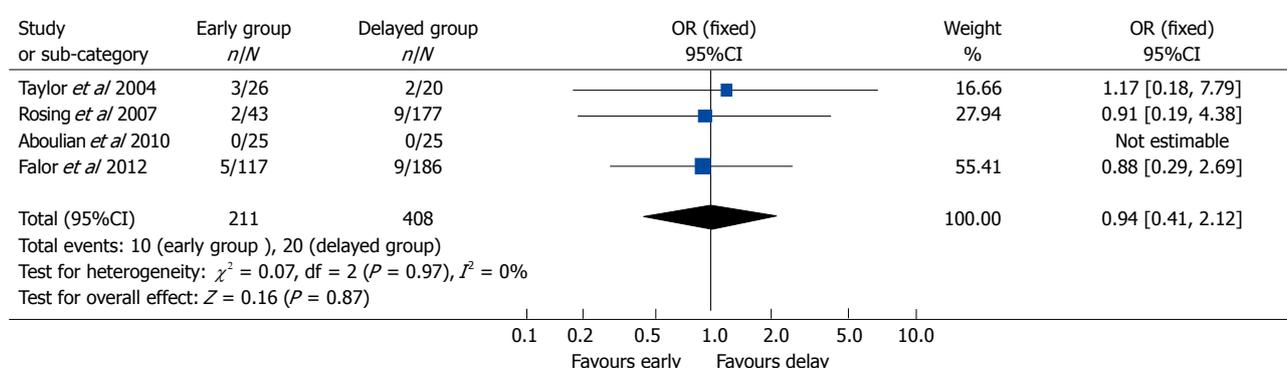


Figure 2 Forest plot comparing early cholecystectomy vs delayed cholecystectomy in terms of perioperative complications.

Review: Early cholecystectomy vs Delayed cholecystectomy on the patients with gallstone pancreatitis
 Comparison: 03 Early cholecystectomy vs delayed cholecystectomy according to the number of patients who underwent postoperative ERCP ± ES
 Outcome: 01 the number of patients who underwent postoperative ERCP ± ES

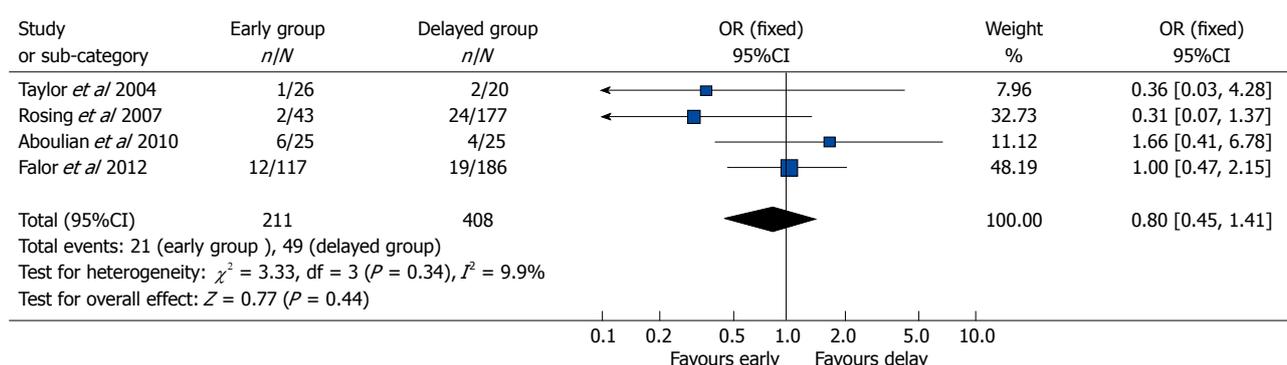


Figure 3 Forest plot comparing early cholecystectomy vs delayed cholecystectomy according to the number of patients who underwent postoperative endoscopic retrograde cholangiopancreatography ± endoscopic sphincterotomy. ERCP: Endoscopic retrograde cholangiopancreatography; ES: Endoscopic sphincterotomy.

carried out a meta-analysis regarding the timing of cholecystectomy in patients with mild gallstone pancreatitis.

Meta-analysis results

Length of hospital stay: Data were collected from two studies (353 patients, 142 in the early cholecystectomy

group and 211 in the delayed cholecystectomy group) regarding the length of hospital stay (LOS). The overall meta-analysis (Figure 1) indicated that early cholecystectomy for the patients with mild gallstone pancreatitis could significantly decrease the LOS compared with delayed cholecystectomy; the WMD was -2.87, (95%CI:

-3.36--2.39, $P < 0.01$).

Perioperative complications: Data were collected from four studies (618 patients, 211 in the early cholecystectomy group and 408 in the delayed cholecystectomy group) regarding perioperative complications. The overall meta-analysis (Figure 2) showed that the effect of early cholecystectomy on perioperative complications in patients with mild gallstone pancreatitis was inconclusive (OR = 0.94, 95%CI: 0.41-2.12, $P > 0.05$).

Postoperative ERCP ± ES: Data were collected from four studies (618 patients, 211 in the early cholecystectomy group and 408 in the delayed cholecystectomy group) on the number of patients who underwent ERCP ± ES postoperatively. The overall meta-analysis (Figure 3) indicated that the effect of early cholecystectomy on the number of patients who underwent ERCP ± ES postoperatively was also inconclusive (OR = 0.80, 95%CI: 0.45-1.41, $P > 0.05$).

DISCUSSION

ERCP/ES is one of the most technically challenging endoscopic procedures performed by gastroenterologists and surgeons with special training. This approach is well suited for the evaluation of diseases of the bile ducts and pancreas. However, it has been reported that the rate of complications due to ERCP ranges from 5% to 7%, with pancreatitis and bleeding as the most common complications^[11-14]. Moreover, death directly related to the procedure occurs in approximately 0.4% of cases in large prospective studies^[13,14]. Therefore, many surgeons do not advocate for use ERCP/ES as the preferred treatment strategy for gallstone pancreatitis. A meta-analysis conducted by Uy *et al*^[15] showed a trend that the mortality of patients receiving early ERCP with or without sphincterotomy in the setting of acute gallstone pancreatitis without cholangitis was higher than that of patients who received conservative management (RR = 1.92, 95%CI: 0.86-4.32 $P = 0.11$). A study conducted by Sees *et al*^[6] also suggested that in patients with mild to moderate gallstone pancreatitis, preoperative ERCP/ES led to a higher rate of postoperative pancreatitis and an increased length of hospitalization, especially in patients with choledocholithiasis. In addition, numerous other studies have also shown that in patients with acute biliary pancreatitis who received early ERCP/ES presented more severe complications and did not benefit from the procedure^[17-19].

Although ERCP/ES has limitations related due to potential morbidity and mortality, ERCP/ES also has its incomparable advantage. For example, a recent large-sample retrospective cohort study conducted by Hwang *et al*^[20] analyzed the risk of developing recurrent gallstone pancreatitis in patients who never received a cholecystectomy. In this study, a total of 1119 patients were identified, including 802 who received no intervention and 317 who received ERCP. After a median follow-up of 2.3 years, the risk of recurrent pancreatitis was 8.2% and 17.1% in

patients who received ERCP and those who received no intervention, respectively ($P < 0.001$). The median time to recurrence was also longer in the ERCP group (11.3 *vs* 10.1 mo), and the recurrence rates at 1, 2 and 5 years in the ERCP group were all lower than those in the non-intervention group (5.2%, 7.4%, 11.1% *vs* 11.3%, 16.1%, 22.7%). These results suggested that ERCP could mitigate the risk of recurrent pancreatitis and should be considered during initial hospitalization if cholecystectomy was not performed. Kaw *et al*^[21] also found that the recurrence of pancreatitis after ERCP with ES alone for the treatment of gallstone pancreatitis was rare and the complication rate, as well as the rate of serious complications, was higher in comparison to cholecystectomy but not significant. Also recently, the most acceptable range for the use of ERCP was shown to be in high-risk surgical patients and the elderly^[22-25], as cholecystectomy may lead to a higher rate of morbidity and mortality in these patients. Another condition for which ERCP/ES is recommended is severe gallstone pancreatitis, and it is reported that up to 25% of patients with gallstone pancreatitis experienced severe pancreatitis^[6]. In addition to intensive care monitoring for the management of associated systemic complications, most of these patients are initially managed with ERCP and ES if common bile duct stones are found. Moreover, surgery is delayed for approximately 3 wk because numerous studies have shown that early cholecystectomy is associated with increased morbidity and mortality^[10,26-28]. There are also other conditions that may benefit from ERCP/ES, such as cholangitis or obstructive jaundice associated with gallstone pancreatitis^[29,30].

The United Kingdom guidelines for the management of gallstone pancreatitis published by the British Society of Gastroenterology in 1998^[31] and 2005^[32] suggest that all patients with mild GSP should be offered definitive treatment, *i.e.*, cholecystectomy, if they are fit for surgery. Several studies have also reported that cholecystectomy can reduce the risk of recurrence or further attack for patients with GSP^[33-36]. Moreover, cholecystectomy is a lower-risk procedure, and the biliary complications attributable to gallstones in the gallbladder, such as cholecystitis, are avoided^[37]. Therefore, for the treatment of GSP, it is generally agreed that all patients with acute GSP who are sufficiently fit should undergo cholecystectomy.

Recent reports have also presented controversial findings regarding the timing of surgery. According to several experts cholecystectomy for GSP can be delayed from the inciting pancreatitis. In their opinion, postponing cholecystectomy 6-8 wk may reduce the acute inflammation and decrease the technical difficulty of cholecystectomy and possibly lower the conversion rate^[38]. However, in the last decade, the standard timing for cholecystectomy has supported earlier intervention. For example, a large-sample (8631 patients) observational study in 2009 divided study patients into four groups according to the treatment policy: cholecystectomy during index stay (group 1); cholecystectomy within 30 d of index admission (group 2); sphincterotomy, but not cholecystectomy within 30 d of index admission (group 3); and neither

cholecystectomy nor sphincterotomy within 30 d of index admission (group 4). The results showed that group 1 required a slightly longer length of stay in the hospital compared to group 2, although these patients had had much fewer readmissions for biliary complications. Similar to the study mentioned above, several observational studies have supported the use of doing cholecystectomy within 2 wk of index admission to prevent gallstone pancreatitis recurrence^[39,40].

Some studies have even suggested that 2 wk after index admission is too long to wait, as patients presented with unacceptably high rates for recurrence of gallstone pancreatitis. For example, Ito *et al.*^[41], found that even following the guidelines that performing cholecystectomy within 2 wk of index admission (according to the guidelines), there remained a 33% rate of biliary related complications including a 13% recurrence rate for pancreatitis rate. As a result, so some experts have suggested that cholecystectomy should be performed within 48 h of admission for mild gallstone pancreatitis before serum pancreatic enzymes are normal and before abdominal pain has completely resolved. Indeed, some retrospective studies have confirmed that early cholecystectomy can shorten the length of hospital stay with no increase in complications or mortality or technical difficulty^[42-45].

The timing of cholecystectomy in patients with severe pancreatitis is different from that in patients with mild disease, as the former patients often have contraindications to surgery due to various physiologic derangements or the inflammatory response associated with severe pancreatitis. Thus, the treatment strategy for these patients is early ERCP/ES and cholecystectomy is delayed until the signs of lung injury and systemic disturbance have resolved, generally between 3 and 4 wk. Various studies have shown less controversy over the timing of cholecystectomy for these patients.

Our present meta-analysis also obtained the conclusion that early cholecystectomy in patients with mild gallstone pancreatitis could reduce the length of hospital stay with no increase in perioperative complications or the incidence of postoperative ERCP ± ES. However, there were some limitations to our meta-analysis. First, only four studies were included in our study, of which only one study was a randomized controlled trial and the other three were retrospective studies. Second, individual patient data were not used. Third, the publication bias may have been present because the quantity of the studies included was so small. Therefore, to confirm that early cholecystectomy is indeed both superior to delayed cholecystectomy and safe, a multicenter randomized controlled trial is needed.

In conclusion, cholecystectomy offers better protection than ES against further bouts of pancreatitis in patients with GSP, although ES is an acceptable alternative. Patients with mild to moderate gallstone pancreatitis should receive cholecystectomy during index admission, although patients with more severe disease will require early ERCP/ES and cholecystectomy should therefore be

delayed, depending on the clinical circumstances. For patients at a patients have high risk for surgery or the elderly, ERCP and ES should represent first-choice treatments.

COMMENTS

Background

Acute pancreatitis is associated with considerable morbidity and mortality. Approximately 30%-75% of cases are caused by gallstones and the management of gallstone pancreatitis remains challenging.

Research frontiers

The role and timing of endoscopic retrograde cholangiopancreatography (ERCP)/endoscopic sphincterotomy (ES) and cholecystectomy in the management of gallstone pancreatitis have been a subject of much debate in recent years.

Innovations and breakthroughs

In this study the authors reviewed the literature and evaluated the scope and timing of the application of ERCP/ES and cholecystectomy. The authors also carried out a meta-analysis regarding the timing of cholecystectomy and found that early cholecystectomy administered to patients with mild gallstone pancreatitis could reduce the length of hospital stay with no increase in perioperative complications or the incidence of postoperative ERCP ± ES.

Applications

For patients at a patients have high risk for surgery or the elderly, ERCP and ES should represent first-choice treatments.

Peer review

Hu *et al.* evaluated the management of gallstone pancreatitis. They demonstrated that cholecystectomy offers better protection than ES against further bouts of pancreatitis in patients with gallstone pancreatitis, but ES is an acceptable alternative. Patients with mild to moderate gallstone pancreatitis should have cholecystectomy during index admission, but patients with more severe disease will require early ERCP/ES and cholecystectomy should be delayed, depending on the clinical circumstances. If patients have high risk of surgery or the elderly, ERCP and ES is the first choice.

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