

Recurrent acute biliary pancreatitis: the protective role of cholecystectomy and endoscopic sphincterotomy

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Abstract

Background Recurrent attacks of acute biliary pancreatitis (RABP) are prevented by (laparoscopic) cholecystectomy. Since the introduction of endoscopic retrograde cholangiopancreatography (ERCP), several series have described a similar reduction of RABP after endoscopic sphincterotomy (ES). This report discusses the different treatment options for preventing RABP including conservative treatment, cholecystectomy, ES, and combinations of these options as well as their respective timing. **Methods** A search in PubMed for observational studies and clinical (comparative) trials published in the English language was performed on the subject of recurrent acute biliary pancreatitis and other gallstone complications after an initial attack of acute pancreatitis.

Result Cholecystectomy and ES both are superior to conservative treatment in reducing the incidence of RABP. Cholecystectomy provides additional protection for gallstone-related complications and mortality. Observational studies indicate that cholecystectomy combined with ES is the most effective treatment for reducing the incidence of RABP attacks.

Conclusion From the literature data it can be concluded that ES is as effective in reducing RABP as cholecystectomy but inferior in reducing mortality and overall morbidity. The combination of ES and cholecystectomy seems superior to either of the treatment methods alone. A prospective randomized clinical trial comparing ES plus cholecystectomy with cholecystectomy alone is needed.

Keywords Acute biliary pancreatitis · Cholecystectomy · Endoscopic sphincterotomy · ERCP · Recurrent

Acute biliary or gallstone pancreatitis (ABP) is an inflammatory condition of the pancreas induced by gallstones [1]. The initial treatment of ABP can be either conservative or interventional. The coexistence of cholangitis is an accepted indication for the performance of endoscopic retrograde cholangiopancreatography (ERCP). However, whether this procedure is performed for patients with ABP depends on local expertise and guidelines, as is the decision to perform an endoscopic sphincterotomy (ES) [2–5].

After patients have recovered from their first attack of ABP, most guidelines advocate a cholecystectomy to prevent a recurrent attack or other gallstone-related disorders such as symptomatic choledocholithiasis, cholecystitis, gallstone ileus, jaundice, and cholangitis [2–5]. “Recurrent” symptomatic choledocholithiasis after an initial attack of ABP may be preexisting common bile duct (CBD) stones not detected at the time of the primo episode or stones that migrated from the gallbladder into the CBD after initial stone clearance. Choledocholithiasis also may have developed newly within the bile duct after cholecystectomy.

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Table 1 Recurrent acute biliary pancreatitis (ABP)

Study ^a	Recurrent ABP % (n)	Recurrent ABP after ES % (n)	Recurrent ABP after cholecystectomy % (n)	Recurrent ABP after cholecystectomy and ES % (n)
Kaw, Billi, Hammarstrom, Vazquez-Iglesias, Gislason [7, 8, 22–24]		0.9–6.4		
Uomo [6]	57 (7)	5 (19)		
Kaw [7]		2.9 (34)	2.4 (83)	
Billi [22]		6.4 (47)		
Hammarstrom [8]	12.5 (16)	2 (49)	19 (16)	0 (15)
Vazquez-Iglesias [23]		2.2 (88)		
Paloyan [21]	48 (64)			
Kahaleh [79]		2.1 (96)		3.0 (66)

ES endoscopic sphincterotomy

^a All studies are prospective, observational, and nonrandomized

The incidence of recurrent acute biliary pancreatitis varies widely, from 0% to 57%, depending on the population studied, the initial treatment, and the follow-up time (Table 1). Recently, observational studies point toward a reduction in recurrent ABP attacks and other gallstone complications when ES is performed for selected groups of patients [6–10]. Based on whether a patient has undergone ES, cholecystectomy, or both, the post-ABP-status of a patient can be classified into four categories: 1 (no ES and no cholecystectomy), 2 (no ES with cholecystectomy), 3 (ES without cholecystectomy), or 4 (ES with cholecystectomy).

To date, no studies have compared any combination of these conditions (Table 1). The current report reviews additional medical interventions to determine which are most effective for preventing recurrent medical problems after an attack of ABP.

Cholecystectomy versus conservative treatment

Evidence that a cholecystectomy actually reduces the incidence of recurrent ABP is scarce. The evidence that does exist originates mainly from older retrospective studies that observed no recurrent ABP after a cholecystectomy compared with a 25% to 61% rate of ABP recurrence with conservative management [11–17]. From a retrospective population-based cohort study, it was concluded that a cholecystectomy reduces the risk of a recurrent or de novo ABP almost to the same level as found in the general population [18]. The overall age- and sex-adjusted incidence of acute pancreatitis before cholecystectomy was 6.3 to 14.8 per 1,000 patient years. Cholecystectomy for patients without a prior ABP attack reduced the relative risk for the development of acute pancreatitis to 2 (0.65 per 1,000 person years). The

recurrence rate for acute pancreatitis of cholecystomized patients was 2.7 per 1,000 patient years. However, none of these had a biliary origin. Importantly, 13% to 14% of all patients presenting with ABP have a history of a prior cholecystectomy without having undergone ERCP and ES [19, 20].

Endoscopic sphincterotomy versus conservative management

Uomo et al. [6] prospectively investigated the effect of ES on patients after a first attack of ABP who were considered unfit for surgery. In the ES group, the observed rate of recurrent ABP was 5% compared with 57% in the conservative group after a mean follow-up period of 30 and 23.8 months, respectively. Paloyan et al. [21] confirmed this rate of ABP recurrence after conservative treatment with their rate of 48%. However, Hammarstrom et al. [8] observed a 12.5% rate of ABP recurrence in noncholecystomized patients during a median follow-up period of 79 months. Other prospective observational studies with various follow-up times showed ABP recurrence rates of 0.9% to 6.4% for patients treated with ES alone [7, 8, 22–24].

Intraoperative choledocholithiasis is present in 13% to 24% of patients undergoing cholecystectomy and bile duct exploration for symptomatic gallstone disease [25–29], including ABP [29, 30]. In 3% to 6% of the patients in whom CBD stones were detected, the stones were asymptomatic without preoperative indicators, negative abdominal ultrasound findings, or laboratory parameters [25, 29, 31]. It is believed that about 15% of these asymptomatic patients eventually will become symptomatic and require further interventional treatment [32].

Table 2 Incidence of common bile duct (CBD) stones in acute biliary pancreatitis (ABP) in relation to time [33–37]

Time from admission	CBD stones (%)
Admission	50–70
<24 hours	45
<48 hours	27
2–3 days	23.1
4–5 days	25
6–7 days	12.5
>7 days	8

Evaluation of the CBD for a planned cholecystectomy to decide on CBD exploration should be scheduled with a tight interval because the prevalence of CBD stones may change in time. In fact, multiple studies have shown that the prevalence of CBD stones in relation to admission time decreases because of spontaneous stone migration [33–37] (Table 2). Conversely, when a CBD is found to be free of stones at admission, this might be not representative for the time of surgery because migration of gallbladder stones into the CBD may have occurred just before the operation.

From a clinical management point of view, patients referred to the surgeon for a laparoscopic cholecystectomy after an attack of ABP can be classified as follows according to what is known about the presence of CBD stones: 1 (cleared CBD after ERCP/ES), 2 (no CBD stones on previous imaging investigations including ultrasound, magnetic resonance cholangiopancreatography [MRCP], endoscopic ultrasound [EUS], and ERCP), or 3 (unknown CBD stone status). Hence, perioperative CBD stone clearance is of great importance.

Clayton et al. [38] performed a metaanalysis to compare endoscopic removal of CBD stones and cholecystectomy with cholecystectomy and intraoperative removal of CBD stones in terms of morbidity and mortality. They concluded that both approaches had similar outcomes and that treatment should be determined by local resources and expertise.

Laparoscopic CBD duct exploration seems to be an ideal approach, but most surgeons still are uncomfortable and untrained with this technique. The potential drawback of finding CBD stones intraoperatively is that conversion to an open procedure sacrifices the advantage of the laparoscopic approach. However, a postoperative ERCP may be unsuccessful in clearing the CBD, necessitating a second surgical procedure. Adopting a wait-and-see policy is associated with additional interventions and increased morbidity [32, 39–41]. On the other hand, a “diagnostic” ERCP for detection and potential clearance of CBD stones before surgery is not justified because 76% to 87% of patients have no CBD stones, and the costs and potential

complications of such an invasive approach are considerable [25–29].

In light of these considerations, preoperative assessment of CBD stones by means of noninvasive and cost-effective procedures such as laboratory values, multi-item scores, and imaging methods is of great clinical relevance. A wide variety of multi-item scores are suggested to be useful, but no two studies have identified the same variables. Factors thought to be discriminative by some are found to be of little use by others [41–63].

Recently, two studies assessed the value of gamma-glutamyl-transferase (gGT) as a potential predictor for the presence of CBD stones. Peng et al. [64] investigated patients presenting with cholecystitis and found that there was a 33% chance of concomitant CBD stones with a gGT higher than 90 U/l and less than a 2% chance with a gGT lower than 90 U/l. In 1,002 patients undergoing laparoscopic cholecystectomy for any reason, Yang et al. [65] observed that abnormal gGT values had a sensitivity of 84.1%, a specificity of 72%, a positive predictive value of 22.4%, and a negative predictive value of 97.9% for detecting concomitant CBD stones before surgery.

Radiologic imaging techniques also can be used to detect CBD stones. Abdominal ultrasound is the safest, cheapest, and least invasive imaging method available for visualizing the biliary tree. Unfortunately, its performance in detecting CBD stones is disappointing, with a reported sensitivity of only 25% to 58% and a specificity of 68% to 91% [66]. The sensitivity of the CT scan for detecting CBD stones is about 40%, which is too low for it to be of clinical use [67]. However, MRCP is a very accurate method detecting CBD stones, with a reported sensitivity of 82% to 95%, a specificity of 97.5% to 100%, a positive predictive value of 95% to 100%, and a negative predictive value of 90% to 98% [33, 68–73].

In a systematic review of seven prospective trials, Ledro-Cano [74] compared the performance between MRCP ($n = 411$) and endoscopic ultrasonography ($n = 411$) in detecting choledocholithiasis. They concluded that both imaging methods had a comparable and very high accuracy in detecting CBD stones. Some individual studies suggest that MRCP has a slightly lower sensitivity for detecting stones than EUS because the sensitivity of MRCP decreases as follows when stones become smaller: 67% to 100% for stones larger than 10 mm, 89% to 94% for stones measuring 6 to 100 mm, and 33% to 71% for CBD stones smaller than 6 mm [69–72].

Endoscopic sphincterotomy and cholecystectomy

Hammarstrom et al. [8] followed 96 patients after an initial ABP event in an observational non randomized study for a

median of 79 months (range, 33–168 months). From this potentially biased study, it was concluded that ES without a cholecystectomy reduced the overall incidence of recurrent pancreatitis event (4.7% vs 9.4%; $p = 0.02$). Of those patients initially treated using ES, 35% required an additional cholecystectomy during the follow-up period.

It is reported that 2% to 33% of patients with symptomatic choledocholithiasis require an additional cholecystectomy, suggesting that patients with ABP are at greater risk for late gallstone-related complications [75–77]. This also is supported by the observation that 15% of the patients from the Hammarstrom study required an emergency cholecystectomy after ES, compared with only 4% to 6% of patients presenting with symptomatic gallstone disease but not ABP [8, 75]. Higher cholecystectomy rates probably are due to the risk of acute cholecystitis after ES, which alone does not have a clear etiology [8, 78].

In a prospective nonrandomized trial, Kahaleh et al. [79] investigated the rate of ABP recurrence after ES ($n = 96$) compared with ES and cholecystectomy ($n = 66$). The mean follow-up period was 1091 days. The observed rate of ABP recurrence was 2.1% compared with 3% ($p = 0.278$). Evidently, because of the nonrandomized study design, selection bias cannot be ruled out. Furthermore, this study has been published only in abstract form and other recurrent gallstone complications, for example, are not discussed.

From the literature, the picture emerges that ES reduces the number of recurrent ABP events more than a cholecystectomy. Does this mean that we can skip performing a cholecystectomy after ABP? The answer is not straightforward. McAlister et al. performed a metaanalysis that included five prospective randomized trials [9, 80–83] showing the benefit of an additional cholecystectomy after ES in case of symptomatic gallstone diseases, including ABP [84]. An additional cholecystectomy resulted in a lower death rate (7.9% vs 14.1%; $p = 0.01$) even in studies that included patients from higher-risk American Society of Anesthesiology (ASA) classes. In the patients for whom a wait-and-see policy was adopted, 16% experienced the development of biliary type pain or cholecystitis (relative risk [RR], 14.56; confidence interval [CI], 4.95–42.78), and more patients experienced recurrent jaundice or cholangitis (RR, 2.53; CI, 1.09–5.87; $p = 0.03$), but no significant difference in recurrent ABP rates was observed (0.3% vs 1.3%; $p = 0.39$). Eventually, for 35% of the patients subjected to a wait-and-see policy, an additional cholecystectomy was performed, with median follow-up times ranging from 30 to 80 months.

From these data, it seems apparent that a cholecystectomy after an ABP event is beneficial and indicated. What about the timing of the operation? No scientific data exist to guide the timing of surgery. Expert opinion guidelines

are based on sound and practical reasoning. Windsor [17] proposed that a cholecystectomy should be performed within 1 month after the first episode of ABP because most recurrent ABP events occur within 1 month (if no additional ES was performed). When the initial episode of ABP is severe and accompanied by peripancreatic fluid collections or pseudocysts, cholecystectomy should be delayed until the pseudocysts have either resolved or persisted beyond 6 weeks, at which time pseudocyst drainage can safely be combined with cholecystectomy [85].

Hammarstrom et al. [8] investigated the effect of an additional ES after an initial cholecystectomy in preventing recurrent ABP events. Their data showed a 0% rate for recurrent ABP events after cholecystectomy plus ES compared with a 19% rate for recurrent ABP events after cholecystectomy alone and 2% after ES alone. These data were not confirmed by Kahaleh et al. [79], who observed no difference between ES and ES plus cholecystectomy in preventing recurrent ABP (2.1% vs 3.0%). Furthermore, the high rates of ABP recurrence after cholecystectomy in the Hammarstrom et al. [8] study were not confirmed by Kaw et al. [7], who reported a rate of 2.4%.

Boerma et al. [80] investigated the outcome of a cholecystectomy for patients whose symptomatic CBD stones, ABP, or both were treated by an ERCP and ES. The patients were randomized into two groups: group 1 (ERCP and ES plus cholecystectomy) and group 2 (ERCP and ES plus a wait-and-see policy). They observed significantly higher rates of conversion from laparoscopic to open procedure in the wait-and-see group than in the cholecystectomy group (55% vs 20%; $p = 0.01$). This also was observed by Allen et al. [86] in a prospectively collected database (25% vs 4%; $p < 0.01$). However, these observations were not confirmed in the metaanalysis by McAlister et al. described earlier.

Conclusion

Endoscopic sphincterotomy with or without an additional cholecystectomy offers better protection than cholecystectomy alone in terms of reducing the number of recurrent ABP events. An additional cholecystectomy after ES is indicated because studies suggest an added reduction in mortality and morbidity. The proper timing of the cholecystectomy has not been studied and is based on expert opinion. The current consensus is that surgery should be used for mild cases during the same hospital admission and severe cases after 6 weeks. To prevent recurrent ABP events or other gallstone-related disease, CBD stone clearance is an important issue. Therefore, diagnosing CBD stones to establish the proper indication for ERCP with ES and stone removal is an important and clinically

relevant item. For this, MRCP and EUS are instrumental. Randomized clinical trials comparing the long-term effects of cholecystectomy and ES versus cholecystectomy alone for APB are indicated.

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