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Timing of cholecystectomy after acute biliary pancreatitis

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1. Introduction

Acute pancreatitis is a common gastrointestinal disorder and in the majority of patients the etiology is either alcohol-associated or biliary, i.e. caused by gallstones or sludge (37, 40). The incidence of acute biliary pancreatitis is increasing worldwide, possibly due to an increased risk of gallstone disease due to nutritional and lifestyle factors and obesity (34, 41). The economic burden of acute pancreatitis is high; In the United States alone, the annual costs of acute pancreatitis currently exceed $2.2 billion (10). The majority of patients with acute pancreatitis (80%) have a mild course of their disease, but 20% of patients develop severe pancreatitis, which is associated with high morbidity and mortality (4). Once biliary pancreatitis is resolved, cholecystectomy is indicated to reduce the risk of recurrent gallstone-related complications such as acute pancreatitis, cholecystitis, cholangitis or gallstone colics (32, 38). A much discussed question is when during the course of pancreatitis the gallbladder should be removed.

High complication and mortality rates after early cholecystectomy in patients with severe pancreatitis have prompted guidelines recommending delaying cholecystectomy until all signs of inflammation have resolved (i.e. interval cholecystectomy) (17, 22, 38). After mild biliary pancreatitis early cholecystectomy is advised by current guidelines (11, 38, 39). However, no consensus exists between these guidelines about the exact definition of ‘early’. The British Society of Gastroenterology recommend cholecystectomy within 2 weeks after discharge, whereas the International Association of Pancreatology (IAP) and the American Gastroenterological Association recommend that all patients with mild biliary pancreatitis should undergo cholecystectomy as soon as the patient has recovered from the attack (32, 38, 39). However, in contrast with these guidelines, in daily practice cholecystectomy after mild biliary pancreatitis is often postponed for several weeks after hospital discharge (interval cholecystectomy). Nationwide audits from Europe and the United States have shown that laparoscopic cholecystectomy is usually performed around 6 weeks after discharge from hospital admission for mild biliary pancreatitis (3, 5, 9, 18, 24-26, 29, 33). A perceived danger of perioperative complications in early cholecystectomy after acute pancreatitis is the main reason for this delay in cholecystectomy (21, 24). It is believed that distorted biliary tract anatomy by inflammation and edema may complicate dissection with a higher risk of conversion and surgical complications, such as bile duct injury (16, 17, 31). Another reason is that a delayed approach facilitates surgical

scheduling, as emergency theatre capacity is often limited (21).

In patients with mild biliary pancreatitis, the role of endoscopic sphincterotomy is limited when cholangitis is not present (38). However, large nationwide studies from the United Kingdom and United States still show a relatively high percentage of patients with mild biliary pancreatitis undergoing endoscopic sphincterotomy (14, 16, 24). Several retrospective studies have suggested that patients do not need to undergo early cholecystectomy after sphincterotomy (13). However, a recent meta-analysis on prophylactic cholecystectomy after sphincterotomy for gallstone-related complications other than pancreatitis still suggests that a cholecystectomy should be performed even after sphincterotomy to further reduce recurrent biliary events (19).

In severe pancreatitis, some have advocated the use of endoscopic sphincterotomy as a bridge to cholecystectomy (13, 27). This issue has not been addressed in prospective trials and needs further study in patients with severe biliary pancreatitis.

The drawback of the present practice of postponing cholecystectomy until several weeks after discharge is that during this period patients are at risk of developing recurrent biliary events (e.g. recurrent biliary pancreatitis, cholecystitis, symptomatic choledocholithiasis and biliary colics). This risk is substantial and has been reported to occur in up to 60% of patients in observational studies (2, 36). It is thought that the lack of high quality evidence may attribute to the reported low adherence to guidelines (9, 14, 16, 18, 24).

Three main questions will be discussed in this review:

1. Does early cholecystectomy reduce recurrent biliary events compared to interval cholecystectomy?
2. Is early cholecystectomy technically more difficult to perform than interval cholecystectomy?
3. Are patients in whom early cholecystectomy is performed more at risk for complications than patients who undergo interval cholecystectomy?

In the next paragraphs we will discuss available studies on timing of cholecystectomy and try to answer the above mentioned three questions.

2. Studies Addressing the Timing of Cholecystectomy in Mild Biliary Pancreatitis

In 2011, Bakker et al. published a retrospective multicenter study which evaluated recurrent biliary events as a consequence of delayed cholecystectomy following mild biliary pancreatitis (3). Patients with mild biliary pancreatitis who were candidates for cholecystectomy were registered prospectively in 15 Dutch hospitals from 2004 to 2007. Recurrent biliary events requiring admission were evaluated before and after cholecystectomy, as well as for a subgroup of patients who underwent endoscopic sphincterotomy. Of 308 patients with mild biliary pancreatitis, 267 had an indication for cholecystectomy. An early cholecystectomy was performed in 18 patients (7%) and late in 188 patients after a median of 6 weeks (76%). Before cholecystectomy was performed, 34 patients (14%) were readmitted for biliary events, including 24 patients with recurrent biliary pancreatitis. During the initial admission, endoscopic sphincterotomy had been performed in 108 patients. Among these patients, eight patients (7%) suffered from recurrent biliary events after endoscopic sphincterotomy and before cholecystectomy. In the group of patients who did not undergo endoscopic sphincterotomy, 26 of 141 patients (18%) had recurrent biliary events, which was significant compared to the group of patients who did have an endoscopic sphincterotomy (risk ratio 0·51, 95% confidence interval 0·27 to 0·94; P = 0.015). It was concluded that an interval cholecystectomy after mild biliary

pancreatitis carries a substantial risk of recurrent biliary events. Endoscopic sphincterotomy reduces the risk of recurrent biliary pancreatitis but not of other biliary events. Shortcomings of this study were: 1) the study was not primarily designed to analyse safety of cholecystectomy, and 2) the study design was not a randomized clinical trial comparing early versus interval cholecystectomy.

In 2012, van Baal et al. published a systematic review on the timing of cholecystectomy after mild biliary pancreatitis (35). The objective was to determine the risk of recurrent biliary events in the period after mild biliary pancreatitis but before interval cholecystectomy and to determine the safety of cholecystectomy during the index admission. A systematic search in PubMed, Embase, and Cochrane for studies published from January 1992 to July 2010 was performed. Cohort studies of patients with mild biliary pancreatitis reporting on the timing of cholecystectomy, number of readmissions for recurrent biliary events before cholecystectomy, operative complications (e.g., bile duct injury, bleeding), and mortality were included. Also study quality and risks of bias were assessed. From 2413 screened studies, 8 cohort studies and 1 randomized trial were included, in total describing 998 patients. An early cholecystectomy was performed in 483 patients (48%) without any reported readmissions **(Table 1)**. An interval cholecystectomy was performed in 515 patients (52%) after a median of 40 days (interquartile range: 19 – 58 days). Before the interval cholecystectomy was performed 95 patients (18%) were readmitted for recurrent biliary events (0% vs. 18%; P < 0.0001).

Table 1 Patient outcomes in cholecystectomy after mild biliary pancreatitis

	Number of patients		Time between discharge and cholecystectomy (days)		Readmissions for biliary events		Complications	
Study	Early	Interval	Early	Interval	Early	Interval	Early	Interval
Schachter et al.(28)	-	19	-	Mean > 56	-	0	-	0
McCullough et al.(20)	74	90	0	Mean 40	0	18 (20%)	11	16
Cameron et al.(7)	-	58	-	Mean 93, Median 68	-	11 (19%)	-	0
Griniatsos et al.*(12)	-	20	-	Median 14	-	0	-	1
Griniatsos et al.*(12)	-	24	-	Median 60	-	1 (4%)	-	1
Clarke et al.(8)	110	92	0	Mean 23	0	8 (9%)	4	5
Ito et al.(15)	162	119	0	Median45	0	39 (33%)	37	34
Nebiker et al.(23)	32	67	0	Mean > 14	0	15 (22%)	2	5
Sinha et al.(30)	81	26	0	Mean > 42	0	3 (12%)	0	0
Aboulian et al.(1)	24	-	0	-	0	-	0	-
Total	483	515	0	Median 40	0	95 (18%)	17 (4%)	29 (6%)

This table was adapted from the original manuscript of van Baal et al (35). *In one study, 2 different groups of interval cholecystectomy were described.

Forty-three patients (8%) were readmitted due to recurrent biliary pancreatitis, 17 patients (3%) with acute cholecystitis and 35 patients (7%) with biliary colics. Fewer recurrent biliary events were present in patients who had an endoscopic sphincterotomy (10% vs. 24%; P = 0.001), with especially less recurrent biliary pancreatitis (1% vs. 9%). No differences were found in operative complications, conversion rate (7%), and mortality (0%) between early and interval cholecystectomy. Baseline characteristics were often missing and only reported in 26% of patients, so subgroups could not be compared. It was concluded that interval cholecystectomy after mild biliary pancreatitis is associated with a high risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis. Furthermore, early cholecystectomy for mild biliary pancreatitis appears to be safe. The main shortcomings of this systematic review were: 1) all included studies were of relatively low quality, and 2) selection bias could not be excluded.

In 2010, a randomized clinical trial on the timing of cholecystectomy after mild biliary pancreatitis was published by Aboulian et al (1). The authors hypothesized that a laparoscopic cholecystectomy performed within 48 hours after admission for mild biliary pancreatitis would result in shorter hospital stay. Patients with mild pancreatitis (defined as a Ranson score ≤ 3) were randomized to early laparoscopic cholecystectomy (within 48 hours of admission) or to control laparoscopic cholecystectomy, performed after resolution of abdominal pain and normalizing trend of laboratory enzymes. In this single centre study at interim analyses, 25 patients were randomized to early cholecystectomy and 25 patients to the control group who subsequently would undergo cholecystectomy after resolution of abdominal pain and normalization of laboratory values. Median duration of symptoms was 2 days upon presentation with a median Ranson score of 1. Duration of hospital stay was 1 day shorter in the early cholecystectomy group with a median of 3 days (interquartile range 2 – 4) compared with the control group with a median of 4 days (interquartile range 4 – 6; P = 0.0016). There were no statistically significant differences between both groups for conversions to an open procedure or in perioperative complications. It was concluded that a laparoscopic cholecystectomy performed within 48 hours after admission (very early cholecystectomy) results in shorter hospital stay and appears to be safe and not more technical demanding. Shortcomings of this study were: 1) the study was not powered to detect differences in clinically relevant outcomes such as recurrent biliary events, and 2) cholecystectomy within 48 hours after admission in gallstone pancreatitis is controversial because patients may still develop pancreatic necrosis or organ failure during this phase of the disease, which both are considered contraindications for early surgery.

These three studies all show a benefit of early cholecystectomy in mild biliary pancreatitis, which appears a safe strategy without an increase in difficulty of the cholecystectomy. However, the quality of the evidence in these studies and their study design was not particularly high. It appeared that a well-designed randomized clinical trial was needed to resolve the issue of timing of cholecystectomy in mild biliary pancreatitis.

In 2012, the study protocol for a randomized controlled trial titled: pancreatitis of biliary origin, optimal timing of cholecystectomy (PONCHO trial) was published by Bouwense et al (6). The hypothesis for this trial is: early laparoscopic cholecystectomy minimizes the risk of recurrent biliary events in patients with mild biliary pancreatitis without increasing the difficulty of dissection and the surgical complication rate compared with interval laparoscopic cholecystectomy. PONCHO is a randomized controlled superiority multicenter trial in which patients are randomly allocated to undergo early laparoscopic cholecystectomy, within 72 hours after randomization, or interval laparoscopic cholecystectomy, 25 to 30 days after

randomization. Patients are randomized during their index admission when all signs of the disease have been resolved and patients are expected to be discharged within 1 – 2 days. In 18 Dutch hospitals a total of 266 patients were enrolled. The primary endpoint is a composite endpoint of mortality and acute readmissions for biliary events (e.g. recurrent biliary pancreatitis, acute cholecystitis, symptomatic/obstructive choledocholithiasis requiring endoscopic retrograde cholangiopancreaticography including cholangitis (with/without endoscopic sphincterotomy), and uncomplicated biliary colics) occurring within 6 months following randomization. Secondary endpoints include the individual endpoints of the composite endpoint, surgical and other complications, technical difficulty of cholecystectomy and costs. The results of the PONCHO trial are expected to be published at the end of 2015. This trial will provide the high level of evidence needed to finally close the debate on timing of cholecystectomy in mild biliary pancreatitis.

3. Conclusion

In patients with severe biliary pancreatitis, it is generally accepted to perform an interval cholecystectomy. In mild biliary pancreatitis, although advocated by current guidelines, patients frequently do not undergo an early cholecystectomy, resulting in a high percentage of hospital readmissions due to recurrent biliary events. All published studies are of medium to low methodological quality and the results of the first randomized controlled clinical trial comparing early versus interval cholecystectomy in patients with mild biliary pancreatitis is expected at the end of 2015. The role of endoscopic sphincterotomy is still under debate, although it is generally accepted that endoscopic sphincterotomy in patients without cholangitis is not indicated. It is thought that endoscopic sphincterotomy will reduce the number of recurrent biliary events, but will not prevent all events.

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