## **Articles**

# Early endoscopic retrograde cholangiopancreatography in mild gallstone pancreatitis with deranged liver function test

## A 7-year experience in central Saudi Arabia

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## ABSTRACT

**الأهداف**: لإقرار استخدام اختبارات وظائف الكبد، كاداة انتقاء لإجراء تصوير الطرق الصفراوية والبنكرياس عبر التنظير بالطريق الراجع ما قبل العمل الجراحي لمريض التهاب البنكرياس الخفيف الحصوي المنشأ .

الطريقة: دراسة استعادية لجميع مرضى التهاب البنكرياس الحفيف، الحصوي المنشأ مع اضطراب وظائف الكبد، المقبولين في مدينة الملك سعود الطبية، الرياض، المملكة العربية السعودية، من يناير 2006م ولغاية فبراير 2013م. حيث تم تجميع وتحليل البيانات السكانية للمرضى، الأعراض السريرية، الاختبارات المخبرية، الدراسات الشعاعية، نتائج تصوير الطرق الصفراوية والبنكرياس عبر التنظير بالطريق الراجع، الاختلاطات وعلاجها، التداخل الجراحي، الموجودات أثناء وما بعد العمل الجراحي، الوفيات، المتابعة في العيادات الخارجية.

النتائج: تمت الدراسة على 245 مريض بالتهاب بنكرياس خفيف، حصوي المنشأ مع اضطراب وظائف الكبد في يوم الدخول. تصوير الطرق الصفراوية والبنكرياس عبر التنظير بالطريق الراجع ما قبل العمل الجراحي. اجري في نفس يوم الدخول ل 74 مريض، وظائف الكبد ( المجموعة أ ). كانت نتيجة التنظير طبيعي ل 65 مريض، تم كشف حصيات ل 5 مرضى ، وطحل ل 4 مرضى. وتعرض 6 مرضى لاختلاطات نتيجة التنظير .تم تأجيل المظار الراجع ل 171 مريض، مع إجراء يومي لتحاليل وظائف الكبد لفترة 4-3 أيام. وظائف الكبد بقيت عالية باستمرار لدى 8 مرضى، حيث أجري لهم التنظير الراجع وتبين وجود حصيات لدى 5 مرضى وطحل لدى 3 مرضى، أما المرضى الذين أصبحت وظائف الكبد لديهم طبيعية ( 163 ) مريض، أما يم المرضى الذين أصبحت ما قبل العمل الجراحي . ولكن 3 مرضى من هؤلاء، قدم بعد سنتين من استئصال المرارة بمضاعفات .

الخاتمة: من المفضل عدم اجراء تصوير للطرق الصفراوية والبنكرياس عبر التنظير بالطريق الراجع لمرضى التهاب البنكرياس الخفيف الحصوي المنشأ المترافق باضطراب في وظائف الكبد لغاية التاكد من استمرار ارتفاع التحاليل المتكررة لوظائف الكبد لفترة 4–3 أيام. وبهذا نكون قد قللنا من نسبة ومضاعفات الاجراء غير الضروري لهذا التنظير.

**Objectives:** To determine the use of liver function tests (LFTs) as a selection tool for preoperative endoscopic retrograde cholangiopancreatography (ERCP) in patients with mild gallstone pancreatitis.

**Methods:** All patients admitted with mild gallstone pancreatitis with deranged LFTs in King Saud Medical City, Riyadh, Kingdom of Saudi Arabia between January 2006 and February 2013 were studied retrospectively. Patients' demography, symptoms, laboratory values, imaging studies, ERCP findings, complications and its treatment, surgical intervention, intraoperative and postoperative findings, mortality, and outpatient follow up were collected and analyzed.

**Results:** A total of 245 patients were admitted as mild gallstone pancreatitis with admission day deranged LFTs. Pre-operative ERCP was performed in 74 patients based on admission day LFTs (Group A). Endoscopic retrograde cholangiopancreatography was normal in 65 patients, revealed stones in 5, and sludge in 4 patients. Six patients developed ERCP complications. Endoscopic retrograde cholangiopancreatography was deferred in 171 patients (Group B) until the LFTs were repeated in 3-4 days. Liver function tests remained persistently high in 8 patients. They were submitted to preoperative ERCP, which revealed stones (n=5) and sludge (n=3). Patients with normalized LFTs (n=163) were not submitted to ERCP. Three of them developed gallstone related complications.

**Conclusion:** Patients admitted with predicted mild gallstone pancreatitis, deranged LFTs, and no evidence of cholangitis should not be submitted to ERCP unless a repeat LFT within 3-4 days shows persistently deranged LFTs. This will reduce unnecessary ERCP and its complications.

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The triggering event for gallstone pancreatitis is biliopancreatic obstruction due to passing of biliary duct stones. In many cases, it causes transient obstruction and the offending stone passes rapidly into the duodenum. However, in the remainder bilio-pancreatic obstruction persists due to the continued presence of the bile duct stones or post stone passage ampullary edema. In most, the clinical course of the disease is mild, while in a few it may take a complicated course and result in morbidity and even mortality. Further attacks can be prevented by early cholecystectomy and bile duct stones clearance, once the acute stage of the disease has settled. Delaying definitive surgical treatment can put these patients at a higher risk of subsequent attacks of acute gallstone pancreatitis.1 Since the introduction of laparoscopic cholecystectomy (LC), bile duct stones clearance have usually been dealt with by preoperative endoscopic retrograde cholangiopancreatography (ERCP) in patients with deranged liver function tests (LFTs), dilatation of biliary tree, or bile duct stones seen in the imaging.<sup>2</sup> Endoscopic retrograde cholangiopancreatography has been defined as early when performed within 48-72 hours after onset of symptoms of acute biliary pancreatitis.<sup>3</sup> Methods of selection among these patients for preoperative ERCP remain a matter of debate. This retrospective study presents our experience over 7 years in the management of acute mild gallstone pancreatitis with deranged LFT, focusing on the use of LFTs as a selection tool for preoperative ERCP and follow up for long-term consequences in those patients in whom ERCP was not carried out.

**Methods.** All consecutive patients who were admitted with mild acute gallstone pancreatitis at King Saud Medical City, Rivadh, Kingdom of Saudi Arabia from January 2006 to February 2013 were included in this study. The diagnosis of acute gallstone pancreatitis was based on the presence of upper abdominal pain, a serum amylase level of >500 U/l (25-115 U/l), and gallstones on the trans-abdominal ultrasonography. Mild acute pancreatitis was defined as having 3 Ranson's score.4,5 Only patients who presented to the emergency department (ED) within 48 hours from the onset of acute pancreatitis and deranged LFTs (elevated bilirubin and alkaline phosphatase, alanine transaminase [ALT], aspartate aminotransferase

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[AST] elevation) on admission were included in the study. Patients were diagnosed to have cholangitis if they were febrile (>37.6°C) along with high bilirubin. Patients with normal LFTs, cholangitis, debilitating cardio-respiratory diseases, which made them high risk for anesthesia and surgery, were excluded from this study. The initial management included nil orally, fluids and electrolytes replacement, analgesia, oxygen administration and a selective nasogastric intubation. Oral feeding was commenced on clinical improvement and a decline in serum amylase. The LFTs were carried out on admission day and repeated on day 3-4 after admission. Preoperative ERCP was used as a diagnostic as well as a therapeutic tool. It was considered therapeutic if the common bile duct (CBD) was cleared of any stone or sludge. Timing of ERCP in these patients was based on the prevailing practice of the admitting surgical teams. Patients who were submitted to pre-operative ERCP based on admission day LFTs were placed in group A and those in whom decision for ERCP was deferred until a repeat LFTs results (3-4 days after hospital admission) were placed in group B. Endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy (ES) were performed a consultant gastroenterologist, using local by pharyngeal anesthesia and mild sedation. Laparoscopic cholecystectomy was performed on complete clinical resolution during the index admission. Magnetic resonant cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and intraoperative cholangiogram (IOC) were not carried out in any of these patients. After discharge from the hospital, all patients were followed up in the outpatient department (OPD) with an average of 2 OPD visits over 3-6 months. They were discharged from the OPD if they remained asymptomatic. The medical records were reviewed for age, gender, presenting symptoms, laboratory findings, imaging studies, ERCP timing and findings, ERCP related complications and its treatment, surgical intervention, intraoperative and postoperative findings, morbidity, and mortality. Ethical approval was obtained from the hospital research committee before commencement of this study. A MEDLINE search was used to retrieve the relevant literature in English.

*Statistical analysis.* The Statistical Package for Social Sciences Version 19.0 (IBM Corp., Armonk, NY, USA) was used to perform the data analysis. We presented mean±SD and range for quantitative variables of the laboratory results. Paired t-test was used to compare the quantitative variables at admission time and preoperative time. It was also used to compare admission time with pre-ERCP time variables. We used Chi-square

test to compare between group A and group B for nominal variables at admission time. Student t-test was used for independent groups to compare group A and group B for quantitative variables at admission time.

**Results.** A total of 245 patients were admitted with acute mild gallstone pancreatitis with deranged LFT. The female to male ratio was 4:1 (198 female and 47 male). The median age was 45 years (range 17-72). Transabdominal ultrasound revealed gallstones in all patients of both groups. No CBD stone was seen in any patient. However, mild CBD dilatation (7-9mm) was observed in 23 patients. There was no statistical difference between the 2 groups in terms of patient demographics and admission day LFTs results (Table 1). Group A patients (n=74) based on admission day deranged LFTs were submitted to ERCP ± ES within 72 hours from the onset of acute pancreatitis. Five patients were found to have CBD stones. All underwent ES, stone extraction, and bile duct clearance. One of them developed bleeding from sphincterotomy site, which was controlled endoscopically. One patient developed aggravation of pancreatitis (increased abdominal pain and elevated serum amylase level), which was treated conservatively. Four patients were found to have biliary sludge. Sixty-five patients had a normal ERCP, of whom 4 patients developed ERCP related complications. Two patients developed aggravation of pancreatitis, which responded to conservative management, one patient developed bleeding from the sphincterotomy site, which

**Table 1** - Patients demographic features and initial liver function tests(LFTs) values in the 2 groups.

Demographic features, severity score, and LFTS (normal values)	Group A (n=74)	Group B (n=171)	<i>P</i> -value						
	Mean admission±SD								
	(Rai	nge)							
Age (years)	47±5.1	44±14.1	0.0824†						
	(23-68)	(17-72)							
Gender (F:M)	58:16	140:31	0.524*						
Ranson's score 1	28	68	0.777*						
Ranson's score 2	46	103							
ALT (7-55 U/L)	129.43±35.09	130.33±12.38	0.7674†						
	(50-173)	(54-165)							
AST (8-48 U/L)	125.45±29.08	127.54±9.67	0.4035†						
	(48-146)	(51-107)							
ALP (45-115 U/L)	191.67±32.61	192.32±31.09	0.8824†						
	(163-212)	(147-206)							
TB (5.1-17 mmol/L)	44.12±4.54	42.59±4.73	0.0194†						
	(25-49)	(26-49)							
DB (1.7-5.1 mmol/L)	26.32±5.78	26.93±7.58	0.5368†						
	(22-33)	(20-32)							
*Chi-square test, ALT - alanine aminot	†student t-test fo	r independent grou							
ALP- alkaline phospha									

was controlled endoscopically and one patient sustained perforation at the junction of first and second part of duodenum, which was treated by laparotomy, primary repair of duodenal injury, and cholecystectomy. Overall within group A, 65 patients (88%) had unnecessary ERCP, and 6 patients (8%) developed ERCP related complications (Figure 1A).

In group B with 171 patients, the decision whether to perform ERCP or not was deferred until repeat LFTs results were available (Figure 1). Significant improvement in the level of LFTs was evident in 163 patients on repeat study (Table 2). Endoscopic retrograde cholangiopancreatography was not performed on these patients. They were discharged after laparoscopic cholecystectomy for OPD follow up. Eight patients who persisted to have deranged LFT on repeat study (Table 3) underwent ERCP 4-6 days after admission. Five patients were found to have CBD stones; all underwent sphincterotomy, stone extraction, and biliary duct clearance (Figure 1). None of them had any ERCP related complications. They were discharged after laparoscopic cholecystectomy and remained asymptomatic during the OPD follow up. Three patients (2%) from this group who did not have preoperative ERCP presented to ED, 6, 14 and 21 months after laparoscopic cholecystectomy with bilio-pancreatic events. Two of them with obstructive jaundice, underwent ERCP and CBD stone extraction whereas one patient who presented with acute pancreatitis was only found to have biliary sludge with mildly dilated biliary tree on ERCP. Three patients improved and remained asymptomatic during the follow up. There was no mortality in this series.

**Discussion.** Gallstone has been reported as the underlying cause in 68.5% of acute pancreatitis in a study from Saudi Arabia,6 whereas in USA, the incidence of pancreatitis is approximately 40% of all cases.7 Treatment of gallstone pancreatitis has traditionally included clearance of any CBD stones followed by cholecystectomy to prevent further attacks of acute gallstone pancreatitis. Patients recovering from the first attack of gallstone pancreatitis have a 30-fold higher risk of subsequent attacks than in the general population if the surgery is delayed.<sup>1</sup> Therefore, the performance of cholecystectomy during the index admission to the hospital become the accepted standard of care.8 In this study, cholecystectomy has been performed in all patients within 7 days of hospital admission. Methods of assessment and clearance of biliary duct before performing cholecystectomy has remained a subject of discussion among clinicians. Serial

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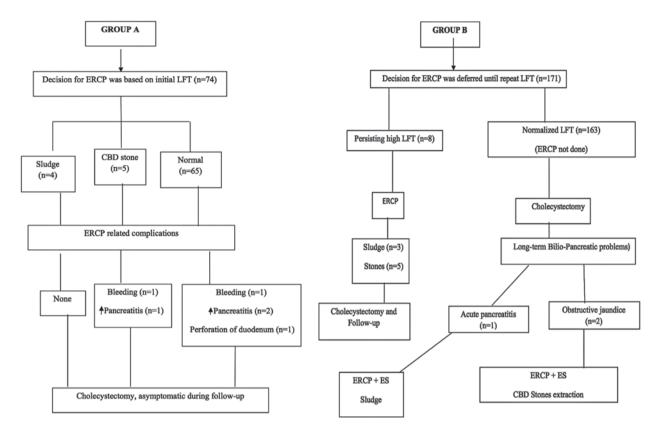


Figure 1 - Flowchart showing patients (n=245) distribution and endoscopic retrograde cholangiopancreatography (ERCP) results in groups A & B. LFTs - liver function tests, ES - endoscopic sphincterotomy, CBD - common bile duct

Laboratory values	Mean admission±SD	Mean immediate pre-ERCP±SD	P-value*	Laboratory values	Mean admission±SD	Mean immediate pre-ERCP±SD	P-value*	
(Normal range)	(Range)			(Range)				
ALT (7-55 U/L)	107.78±24.85 (46-166)	47.8±9.39 (25-69)	< 0.0001	ALT (7-55 U/L)	127.78±27.97 (49-176)	131.8±8.39 (54-168)	0.7029	
AST (8-48 U/L)	107.56±23.78 (42-132)	34.67±9.67 (18-119)	< 0.0001	AST (8-48 U/L)	123.34±27.98 (50-142)	103.39±8.37 (47-104)	0.0738	
ALP (45-115 U/L)	164.34±21.54 (151-192)	102.22±18.54 (8-145)	< 0.0001	ALP (45-115 U/L)	184.26±24.54 (161-206)	190.73±22.54 (145-211)	0.5915	
TB (5.1-17 mmol/L)	29.22±7.55 (19-37)	11.45±4.33 (3-18)	< 0.0001	TB (5.1-17 mmol/L)	43.09±4.18 (24-48)	41.09±3.93 (28-47)	0.3409	
DB (1.7-5.1 mmol/L)	17.02±4.55 (8-19)	3.44±1.35 (1-7)	< 0.0001	DB (1.7-5.1 mmol/L)	25.02±5.44 (21-32)	24.44±7.27 (19-33)	0.8592	
ALT - alanine aminotransferase, AST - aspartate aminotransferase, ALP- alkaline phosphatase, TB - total bilirubin, DB - direct bilirubin, ERCP - endoscopic retrograde cholangiopancreatography *student t-test (paired t-test)			ALT - alanine aminotransferase, AST - aspartate aminotransferase, ALP- alkaline phosphatase, TB - total bilirubin, DB - direct bilirubin, ERCP - endoscopic retrograde cholangiopancreatography *student t-test (paired t-test)					

 
 Table 2 - Admission day and repeat liver function tests (LFTs) values, which showed improvement in Group B patients (n=163).

 Table 3 - Admission day and repeat liver function tests (LFTs) values, which did not improve in group B patients (n=8).

LFT, MRCP, EUS, routine or selective preoperative ERCP and intraoperative cholangiogram (IOC) have been suggested and practiced as a tool for bile duct evaluation and clearance before cholecystectomy.<sup>7,9</sup> Endoscopic ultrasound, MRCP, and IOC was not used for bile duct assessment in our unit during the study

period. With the advent of laparoscopic surgery, IOC as an assessment tool has lost popularity as it leads to increased operative time and unnecessary conversion to open surgery.<sup>10</sup>

In the natural history of gallstone pancreatitis, the bile duct stones passed spontaneously in most of the

patients.<sup>11,12</sup> It has been reported that the bile duct stones decrease from 70% on admission day to less than 20% by day 4 after admission.13 This would suggest that delaying preoperative ERCP in patients with mild pancreatitis for bile duct evaluation and clearance would naturally allow more stones to pass spontaneously from the biliary tree. By adopting a policy of delaying preoperative ERCP by few days would reduce the number of unnecessary ERCP and its associated morbidity. This has been the focal point of this study. Abnormal LFT or imaging to ensure pre-operative biliary tract clearance is the most common practice.<sup>7</sup> In this study, the LFT has been used as an assessment tool for selecting patients for preoperative ERCP. During this study, some surgical teams considered initial deranged LFTs as an adequate indication for ERCP intervention prior to laparoscopic cholecystectomy. Group A patients were submitted to ERCP based on their admission day deranged LFTs. Endoscopic retrograde cholangiopancreatography was therapeutic in only 8 patients (stone n=5, sludge n=3,) whereas 6 patients (5%) had ERCP related complications. In group B patients where ERCP was deferred until repeat LFTs results were available, only 8 patients (5%) who persisted to have deranged LFTs were submitted to ERCP and it was therapeutic in all (stone n=5, sludge n=3). There was no ERCP related complications in these patients. However, 3 patients who did not have preoperative ERCP presented later with retained stone related complications within 2 years. This study has demonstrated that using LFT as a mean in selecting preoperative ERCP significantly reduced the number of unnecessary ERCP and complications. Moreover, the study further demonstrates that by omitting ERCP in patients whose LFT rapidly improved towards normal, the risk of long term complication due missed stone is minimal. The indication for preoperative ERCP based on initial deranged LFTs is no longer in practice in our surgical department.

A decline in the level of LFT toward normal level within 3-4 days of the attack of acute pancreatitis as seen in our patients is probably evidence of spontaneous passage of stones. Intraoperative cholangiogram has demonstrated that the incidence of unsuspected CBD stones varies between 2.8-5.8% in patients with normal preoperative LFT and imaging.<sup>14</sup> Shayan et al<sup>7</sup> concluded in their study that the incidence of bile duct stones among patients recovering from mild to moderate acute gallstone pancreatitis with normal preoperative LFT and imaging is not significantly (7.6%) higher than patients undergoing elective laparoscopic cholecystectomy for symptomatic cholelithiasis. A very similar bile duct stone rate in patients undergoing cholecystectomy for

symptomatic cholelithiasis or gallstone pancreatitis has also been reported.<sup>15</sup> In the present study, the incidence of missed stone among patients with normalized preoperative LFTs was low (2%). In Ito et al's<sup>16</sup> study, the incidence of recurrent acute pancreatitis due to retained CBD stones in patients who did not undergo preoperative ERCP or IOC during surgery was 8%. They recommended to omit the routine biliary tract evaluation in low risk patients. In the present study, only 3 patients (2%) without preoperative ERCP developed bilio-pancreatic events due to missed CBD stones. Such a low rate of bilio-pancreatic complications due to missed choledocholithiasis cannot justify the routine use of ERCP in low risk patients recovering from mild acute gallstone pancreatitis. In fact, the complication rate of routine ERCP among these low risk group patients as observed in this study was 8%, which is higher than the risk of omitting routine preoperative ERCP. In another study,<sup>17</sup> the complication rate of ERCP with ES was reported to be 4.95% with a mortality of 0.12%. However, there was no mortality in the present study. Thus, a routine preoperative ERCP can be safely omitted in patients recovering from biliary pancreatitis if their initial deranged liver functions return to normal or near normal within 3-4 days from the onset of illness. However, the retrospective nature of the present study limits its strength, which needs controlled trials to support this recommendation. The persistence of CBD stones in acute gallstone pancreatitis does not contribute to persisting or worsening of pancreatic inflammation.<sup>18</sup> In this study, all patients with continued high LFT after 72 hours that underwent ERCP were found to have either stones or sludge. None of them developed local or systemic complications. Use of more advance tools can further help define the indications of pre-operative ERCP in these patients. Endoscopic ultrasound is highly accurate in showing even tiny stones that can be easily masked by contrast medium during the ERCP.<sup>19-21</sup> Magnetic resonance cholangiopancreatography is a noninvasive imaging tool to evaluate for bile duct stone in gallstone pancreatitis, and to guide for therapeutic ERCP. However, it is known to miss small CBD stones (<6mm).<sup>22</sup> During the study period, facilities and expertise for EUS and MRCP were not available in our institute. Performance of IOC in patients undergoing cholecystectomy results in a prolonged operative time and a longer postoperative course with no effect on the incidence of retained stones in the CBD.<sup>23</sup>

Due to limited experience in laparoscopic CBD exploration, we believe that routine IOC will increase the rate of conversion to open surgery. Furthermore, false

positive IOC will lead to unnecessary CBD exploration. Patients who later develop bilio-pancreatic symptoms even after a normal IOC will need re-evaluation by either MRCP or ERCP. Thus, cholecystectomy without IOC can be performed safely in patients recovering from mild gallstone pancreatitis with normal preoperative LFT and imaging.<sup>10</sup>

In conclusion, in patients with predicted mild acute gallstone pancreatitis with admission day deranged LFTs and no evidence of cholangitis, the preoperative ERCP should be deferred until a repeat LFT in 3-4 days is available. Those with persistently deranged LFTs can undergo preoperative ERCP. It is safe to omit preoperative ERCP if repeat LFTs return to normal. This will reduce the unnecessary ERCP and its complications.

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