

Endoscopic Retrograde Cholangiopancreatography in Acute Biliary Pancreatitis: Urgent vs. Delayed and the Outcome of Same-Admission Cholecystectomy

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Abbreviations:
AP: Acute pancreatitis;
ERCP: endoscopic retrograde
cholangiopancreatography.

Rezumat

Colangiopancreatografia retrogradă endoscopică în pancreatita acută biliară (urgentă vs. amânată) și colecistectomia în cadrul aceleiași internări

Introducere: Pancreatita acută reprezintă o provocare pentru sistemul medical, având rate importante de morbiditate și mortalitate. Această lucrare se concentrează pe teme de actualitate în managementul pancreatitei acute biliare - indicațiile, momentul optim și rezultatele ERCP-ului pe de o parte, iar pe de altă, ale colecistectomiei în cadrul aceleiași internări, ca măsură de prevenție a episoadelor recurente de boală.

Material și metodă: A fost realizat un studiu retrospectiv incluzând 108 pacienți cu pancreatită acută biliară, la care s-a efectuat ERCP, tratați în Spitalul Clinic de Urgență București în perioada 2016-2020. În ceea ce privește gradul de urgență al procedurii, pacienții au fost împărțiți în 2 grupuri: ERCP de urgență și ERCP amânat.

Rezultate: ERCP de urgență a fost realizat la 52 de pacienți, în timp ce ERCP amânat s-a efectuat la 56 dintre ei, cu o durată de spitalizare crescută la grupul de urgență (10 versus 8 zile), fără diferențe semnificative în ceea ce privește morbiditatea. Durata medie de așteptare între ERCP și intervenția chirurgicală a fost de 5 zile, fără diferențe semnificative între cele 2 grupuri. Abordul laparoscopic a fost de elecție, cu o rată de conversie de aproximativ 7%.

Concluzii: ERCP cu extragere de calcul biliar urmat de colecistec-

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tomie în aceeași internare rămâne o opțiune sigură, ce previne pancreatita recurentă. Momentul optim al ERCP reprezintă subiect de dezbatere, fiind necesare studii prospective pentru a obține rezultate semnificative statistice.

Cuvinte cheie: ERCP, pancreatita acută biliară, colecistectomia în aceeași internare

Abstract

Introduction: Acute pancreatitis (AP) represents a major burden for the medical system, associating important morbidity and mortality rates. This paper is focused on debatable aspects of the management of biliary AP, namely indications, timing and outcomes of endoscopic retrograde cholangiopancreatography (ERCP) on the hand and, on the other hand, same-admission cholecystectomy as a preventive measure for recurrent disease.

Material and methods: This is a retrospective study including 108 patients with biliary AP in whom ERCP was performed, treated in the Clinical Emergency Hospital of Bucharest between 2016 and 2020. According to the urgency of the ERCP, we divided the patients into two groups: urgent versus delayed ERCP.

Results: Urgent ERCP was performed in 52 patients, while delayed ERCP was performed in 56 patients; the hospital stay was higher in the urgent group than in the delayed group (10 days vs 8 days, $p = 0.299$) with no difference in morbidity rates. The mean time between ERCP and surgery was 5 days, without significant difference between the groups. The laparoscopic approach was the preferred method, with a conversion rate of 7%.

Conclusion: ERCP with stone extraction followed by same-admission laparoscopic cholecystectomy is a safe therapeutic option, that prevents recurrent pancreatitis. The timing of the procedures remains debatable, further prospective studies being needed to achieve statistical significance.

Key words: ERCP, acute biliary pancreatitis, same-admission cholecystectomy

Introduction

Acute pancreatitis (AP) is a well-known gastrointestinal condition characterized by inflammation of the pancreas, requiring hospitalisation. It represents a major clinical and financial burden for the medical system in Western countries, which involves a multidisciplinary effort with distinctive roles for gastroenterologists, radiologists, and surgeons. Currently, the incidence of AP is increasing worldwide, gallstones and excessive alcohol intake being the two most common causes. Despite the latest medical progress in diagnosis and treatment, AP is still an important cause for high morbidity and mortality rates (1,2). The literature is abundant on the topic which is of great interest. However, most reports focus on

severe AP. There are also clinical guidelines providing evidence-based recommendations for the management of AP, using a multidisciplinary approach. This paper is focused on two aspects which are still debatable in the management of biliary AP: delayed versus urgent ERCP procedure (endoscopic retrograde cholangiopancreatography), as it aimed to evaluate the indications, timing and outcomes of ERCP and, in addition, the outcomes of same-admission cholecystectomy as a preventive measure for recurrent disease.

Material and Methods

This is a retrospective study performed in patients with biliary acute pancreatitis, who were admitted to and treated in the Clinical Emergency Hospital of Bucharest between

2016 and 2020. The following inclusion criteria were applied: patients with acute pancreatitis as defined by the revised Atlanta Classification, presenting biliary gallstones, elevated serum total bilirubin and dilated common bile duct (CBD) with suspected choledocholithiasis on ultrasonography (US), computer tomography (CT), magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS), in whom ERCP was necessary. With respect to these criteria, of the 263 patients with acute biliary pancreatitis, 108 patients that required ERCP were selected and included in our study. Tokyo Guidelines were used to establish the urgency of ERCP. According to the urgency of the ERCP procedure, we divided the patients into two groups: urgent versus delayed ERCP.

The following parameters were evaluated: age, gender, symptomatology, length of hospital stay, the diagnostic imaging techniques used, the timing of ERCP, post-ERCP complications, the type of cholecystitis (acute or chronic), the mean time between ERCP and surgery, intra-operative difficulties, postoperative morbidity evaluated using Clavien-Dindo classification. The biomarkers assessed were leukocyte count, total and direct bilirubin, alkaline phosphatase, ALT (alanine aminotransferase), AST (aspartate aminotransferase), GGT (gamma-glutamyl transferase), amylase, lipase, glucose, urea, creatinine, total protein, and albumin.

The primary outcomes of the study were: the total length of hospital stay compared between the two groups (urgent vs. delayed ERCP), the morbidity and mortality rates of the procedure. The secondary outcomes included cholecystectomy timing and post-operative complications using Clavien-Dindo classification.

Informed consent was obtained from all patients who underwent ERCP and surgery. Moreover, the study received approval from the Ethics Board for using the patients' data.

The statistical analysis was performed with IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp and Microsoft Corporation Microsoft Excel. Categorical variables were

described in percentages and frequencies while continuous variables were represented as median and range or mean $\pm$ SD, after checking for normality. Chi-square test was used when comparing categorical variables. Continuous variables with quasi-normal distributions were compared using ANOVA and Student's T-test while if severe deviation from normality, appropriate nonparametric tests were applied. Differences were considered significant at a p-value of < 0.05 .

Results

Using the revised Atlanta classification, of the total of 108 patients with biliary AP who required ERCP, 3 were classified as severe, while 8 were classified as moderate, and 97 as mild. The mean age was 59 years old, ranging from 20 to 91 and over half of the patients (55%) were women.

All patients experienced moderate to intense epigastric pain as the dominant symptom, while 63% presented nausea and vomiting and only 51% had jaundice when admitted.

All the patients included in this study had elevated serum amylase and/ or lipase. Serum bilirubin and liver enzymes were elevated in the entire study group.

At ultrasound examination, all the patients had gallstones or biliary sludge and in 82% a dilated CBD could be visualized, with a mean calibre of 11 mm, ranging from 7 to 23 mm. Choledocholithiasis was found in 63% of the patients through this method. In 24 patients (22%), US showed increased pancreatic volume with decreased echogenicity secondary to fluid exudation. In 23 cases (21%), acute cholecystitis was diagnosed, with positive sonographic Murphy sign, gallbladder wall thickening (>3 mm) and pericholecystic fluid. The remaining cases had an ultrasonographic aspect of chronic cholecystitis; 32 patients had a single gallstone, whereas 48 had multiple infra-centimetric gallstones and 28 had biliary sludge or microlithiasis. One patient with hepatitis C virus (HCV) infection had a cirrhotic configuration of the liver at ultrasound imag-

istic, as well as abnormal liver function tests, being classified as Child-Pugh C.

On CT scan, all patients had diffused parenchymal enlargement with surrounding retroperitoneal fat stranding. In addition, 41 patients (40%) had peripancreatic fluid.

MRCP and EUS were also performed in selected cases in which US and CT scan were inconclusive to certify the diagnosis of choledocholithiasis. Therefore, 8 patients underwent MRCP, while 4 of them underwent EUS.

The mean time from admission to ERCP was 48 hours.

Of the total of 108 patients, urgent ERCP (within 24 hours from admission) was performed in 52 patients, while delayed ERCP (after 24 hours from admission) was performed in 56 patients. Tokyo Guidelines were used to establish the urgency of the procedure. Their characteristics are detailed in *Table 1*.

The total length of hospital stay was higher in the urgent ERCP group than in the delayed ERCP group (10 days vs 8 days, $p=0.299$), without significant difference between the groups. 41% of the delayed ERCP group (23 out of 56 patients) were admitted during the weekend and had to wait for at least 24 hours for the ERCP procedure, which increased the length of hospital stay.

Another significant difference observed between the groups was the dimension of the

CBD stone diagnosed by means of ultrasound. In the urgent ERCP group, the mean dimension of stone was 14.5 mm compared with 7.25 mm in the delayed ERCP group ($p = 0,026$). However, when extracted during ERCP, there was actually no significant difference of the stone diameters between the two groups.

Regarding pancreatitis severity, the patients with moderate or severe pancreatitis are more likely to be included in the delayed group, due to initial equilibration (*Table 2*).

According to ERCP, 88% of the patients had dilated main bile duct. A filling defect during ERCP was discovered in 93 patients (86%), of whom 92 had calculi or microlithiasis extracted and sphincterotomy performed (in only one patient the stone could not be extracted due to the dimensions of the calculus - 5/2 cm). In 15 cases (14%) only biliary sludge was found, without any filling defect. However, sphincterotomy was also performed in these patients in order to avoid complications if another stone passed. In two cases the papilla could not be cannulated during the first attempt due to papillary edema, but ERCP was repeated successfully three days later. Regarding intraprocedural events, 17 patients experienced minimal bleeding on sphincterotomy (with no significant difference between the groups), which was successfully managed with local adrenaline injection. The mortality of the

Table 1. Urgent ERCP group vs delayed ERCP group

Variable	Total ERCP patients (n=108)	Urgent ERCP (n=52)	Delayed ERCP (n=56)	p
Age	59.01±17.57	60.92±17.27	57.23±17.81	0.277
US CBD diameter	8.63±2.83	8.69±3.08	8.58±2.65	0.882
US stone diameter	9.67±4.32	14.50±3.53	7.25±1.89	0.026
ERCP CBD diameter	10.86±3.69	10.96±3.53	10.76±3.85	0.784
ERCP stone diameter	7.89±2.93	7.79±3.10	8.00±2.82	0.833
Total hospital stay*	9 (1-28)	10 (2-28)	8 (1-26)	0,299

*For this variable the Mann-Whitney Test was used due to data not being normally distributed

Table 2. Distribution of patients within the two groups based on pancreatitis severity

Pancreatitis classification	Group		
	Urgent ERCP	Delayed ERCP	Total
Mild, n (%)	49 (51%)	48 (49%)	97
Moderate, n (%)	2 (25%)	6 (75%)	8
Severe, n (%)	1 (33%)	2 (67%)	3

procedure was nil.

In 63 patients, same-admission cholecystectomy was performed; 28 of them were delayed after the remission of moderate AP or due to severe associated conditions that required proper preoperative management (cardiovascular disease, cirrhosis, renal failure); 2 of the 3 patients with severe AP died before surgery; the remaining 15 underwent cholecystectomy in another medical centre. The mean time between ERCP and surgery was 5 days, without significant difference within the early and delayed ERCP groups. The laparoscopic approach was chosen in 59 cases, with a conversion rate of 7% (4 patients) for following reasons: perichole-cystic adhesions (2 patients), impossibility to identify the elements of Calot's triangle because of inflammation (1 patient), and pericholecystic abscess (1 patient). The open approach was chosen in 4 patients due to: failure of calculus extraction during ERCP in which choledocholithotomy was performed with the extraction of a 5/2 cm gallstone (1 case); moderate/ severe AP with acute cholecystitis where necrosectomy was also necessary (2 cases); associated voluminous incisional hernia that could not be approached laparoscopically (1 case).

Postoperative complications were evaluated using Clavien-Dindo classification. Four patients were classified as Clavien-Dindo II, with conditions that were treated conservatively (wound infection in 2 cases, postoperative ileus in 1 case, pulmonary edema in 1 case). Two patients were classified as Clavien-Dindo V (death), namely: postoperative hemorrhage where reintervention was necessary in 1 patient with important cardiac comorbid conditions, sepsis in an elderly patient with acute cholecystitis and pericholecystic abscess).

All 3 patients with severe AP had persistent organ failure that led to death. There were no cases of recurrent pancreatitis or other late complications.

Discussions

Elevated serum lipase and/ or amylase more

than 3 times the normal range, abdominal pain and characteristic imaging findings are used for the diagnosis of AP. The sensitivity of serum lipase is higher for the diagnosis because the elevation occurs earlier and lasts longer than in serum amylase (2). From symptom onset, the serum lipase rises within 4-8 h, decreasing within 8-14 days, while the serum amylase activity increases within 5-8 h, returning to normal after 3-4 days (3). This is the reason why serum lipase level is especially useful in patients who present themselves late to the hospital. All the patients included in this study had elevated serum amylase and/or lipase.

A history of biliary colic is suggestive at the time of admission for the diagnosis of biliary pancreatitis, but other etiologies must be considered, such as alcohol abuse, medication or infectious agents. Several biomarkers like AST, ALT, alkaline phosphatase, and serum bilirubin are useful in differentiating biliary pancreatitis from other causes of pancreatitis (4). Each patient from the study group had abdominal pain as the dominant symptom; 63% presented nausea and vomiting, and only 51% had jaundice on admission. Serum bilirubin and liver enzymes were elevated in the entire study group.

Female gender is considered to be a risk factor for gallstone pancreatitis, since they have a higher frequency of gallstones (4); in this study 55% of the patients were women.

Ultrasound examination is the first imaging exploration that should be performed in cases where acute biliary pancreatitis is suspected, due to its availability, low cost and no radiation exposure, having also high sensitivity and specificity in detecting gallstones (5). However, the sensitivity is lower for choledocholithiasis in the context of ileus with distended bowels that occurs in AP (6-9). US also has a positive predictive value greater than 90% in the diagnosis of acute cholecystitis, identifying signs like gallbladder wall thickening and edema, gallbladder sludge, pericholecystic fluid, and sonographic Murphy sign (10). Regarding this study, ultrasonography identified gallstones or biliary sludge in all patients, acute cholecystitis

in 21%, and increased pancreatic volume with decreased echogenicity secondary to fluid exudation in 22%, while among the rest of the patients the pancreas could not be assessed due to certain difficulties (abdominal distension, overweight patients). It also revealed dilated CBD in 82% of the cases. One patient with HCV infection and abnormal liver function tests had cirrhotic configuration of the liver on ultrasonography, being classified as Child-Pugh C. This condition is associated with increased perioperative risks in case of an eventual cholecystectomy. Therefore the patient could be delayed considering the absence of acute cholecystitis that would have imposed the intervention (11). Computer tomography is useful mostly to distinguish between interstitial acute pancreatitis and necrotizing acute pancreatitis and to rule out local complications. It can also reveal indirect signs of choledocholithiasis and only sometimes can it visualize the actual stones in the CBD (12). However, the best timing for CT is after 48-72 hours from the onset of symptoms and if the patient experiences no improvement after initial care. Therefore, CT has limited use on admission, except for the situations when it is necessary to rule out differential diagnosis (12-13). Magnetic resonance cholangiopancreatography (MRCP) is useful in identifying common bile duct stones, being capable of identifying choledocholithiasis as small as 3 mm, as well as pancreatic duct disruption and having an overall sensitivity and specificity to diagnose biliary obstruction of 95-97%, according to a systematic review that included 67 studies (14). Thereby, it is useful in avoiding a diagnostic ERCP. However, the use of MRCP should be limited due to its cost in the diagnosis of gallstones or acute cholecystitis, especially with the availability and utility of ultrasonography for the same purpose (15). Clinical applications of endoscopic ultrasound (EUS) and ERCP have evolved for the evaluation of patients with suspected acute biliary pancreatitis. ERCP is not recommended as a pure diagnostic tool, having an important complication rate of 5-10% with risks involving cholangitis, perforation, and haemorrhage (16). A review by De Lisi S et

al. evaluating EUS and ERCP in acute biliary pancreatitis on 545 patients included in seven studies, showed that EUS had a lower failure rate without complications. Moreover, ERCP was avoided in 71.2% of cases by the use of EUS (17).

In this study, all patients who underwent a CT scan had diffuse parenchymal enlargement with surrounding retroperitoneal fat stranding on computer tomography, whereas 40% had peripancreatic fluid. EUS and MRCP were performed when US and CT scans were inconclusive for establishing the indication for ERCP.

However, current literature is conflicting on the role and timing of ERCP in the setting of biliary obstruction. There is a universal agreement for performing urgent ERCP (within 24 hours) when biliary AP is complicated by cholangitis (2,18-20). Otherwise, the indications and timing are less clear (2,18,19). Prior guidelines do not recommend routine use of urgent ERCP for biliary AP (2,18-21). The 2018 AGA (American Gastroenterological Association) technical review concludes that urgent ERCP, when compared with conservative management, had no significant impact on major outcomes (mortality, organ failure, infected pancreatic necrosis, and total necrotizing pancreatitis) (21). A single randomized clinical trial (RCT) suggested that urgent ERCP for persistent biliary obstruction impacted positive secondary outcomes; it shortened hospital length of stay (9.5 days versus 17.0 days) (21-22). The AGA technical review offered a conditional recommendation against urgent ERCP in patients with biliary AP and no cholangitis (21).

There is limited data available on the time non-urgent ERCP should be performed. The Cochrane analysis concluded that ERCP when performed within the first 72 hours, it associates a reduction in local and systemic complications related to AP (20). In support of this recommendation, Lee et al. performed a retrospective comparison of outcomes in 73 patients with acute biliary pancreatitis, having biliary obstruction but without cholangitis, treated with either urgent ERCP (< 24 hours)

or early ERCP (24-72 hours). Overall, total length of hospital stay, post-ERCP complications, and complications due to pancreatitis were not influenced by the timing of ERCP (23).

In this study, urgent ERCP (under 24 h) was performed, according to Tokyo Guidelines, in 52 patients, while delayed ERCP (after 24 h) was performed in 56 patients. In the second group (delayed ERCP), initial conservative treatment was attempted, as 41% of them were admitted over the weekend, when the procedure is not technically available in our institution. Therefore, ERCP was performed the following Monday. However, these patients had no cholangitis, in consequence the procedure could be postponed. The total length of hospital stay was higher in the urgent ERCP group. There was no significant difference between the groups concerning morbidity.

Cholecystectomy should be performed after ERCP as secondary prevention for acute biliary pancreatitis (24). Regarding the timing of cholecystectomy as a pathogenic treatment, guidelines recommend that, for mild gallstone AP, it should be performed as early as possible, during the same admission (2,18-19,25). In the technical review accompanying the AGA guideline, Vege et al. (21) identified one RCT that evaluated the effect of same-hospitalization versus delayed (post-discharge) cholecystectomy on outcomes in patients with mild acute gallstone pancreatitis (26). When compared to delayed cholecystectomy, same-admission cholecystectomy significantly reduced gallstone-related complications and readmissions for recurrent pancreatitis and pancreaticobiliary complications without having a notable impact on mortality during the next 6 months of follow-up (26). A controversial subject remained is the timing of surgery during the index hospitalization (21). ERCP with biliary sphincterotomy in patients unfit for surgery appeared to reduce the risk of recurrent acute biliary pancreatitis, but not for other biliary complications (27-28). A systematic review (29) of 8 cohort studies (n=948) and 1 RCT (n=50) revealed that while the readmission rate for gallstone disease in patients admitted for

acute gallstone pancreatitis and discharged without cholecystectomy was 18% within the first 58 days after discharge, it was 0% in the cohort that underwent index admission cholecystectomy. These results are supported by several retrospective studies that also cited significantly higher recurrence rates of gallstone disease (15%–32%) in patients who did not undergo index admission cholecystectomy (30-32). The majority of these recurrent attacks occurred before the time of interval cholecystectomy (31-32). In an RCT that included 50 patients with mild acute gallstone pancreatitis, laparoscopic cholecystectomy performed within 48 hours of admission resulted in a shorter hospital stay (mean 3.5) than one performed after resolution of pain and laboratory abnormalities (mean 5.8) (33). A second study demonstrated similar findings with a significant reduction in the mean total length of stay from 7 to 5 days ($p < 0.001$) (32).

In cases of moderate to severe AP, interval cholecystectomy is recommended, once pancreatic necrosis is controlled, and the patient no longer presents with organ failure, unless acute cholecystitis or the need of necrosectomy impose the intervention (25,34). However, there is a risk of infectious complications when cholecystectomy is imposed earlier than 3 weeks after severe AP, with a consequent higher mortality rate (35). The mortality of patients with infected pancreatic necrosis is higher than 30%, and up to 80% of fatal outcomes in patients with AP are due to septic complications resulting from pancreatic infection (36). Fluid collections, common in patients with moderate to severe AP, are additionally problematic. Cholecystectomy should be delayed until fluid collections or pseudocysts either resolve or persist beyond 6 weeks, at which time pseudocyst drainage can safely be combined with cholecystectomy (35). In this study, same-admission cholecystectomy was performed in only 2 patients with moderate/severe AP that presented with acute cholecystitis and where necrosectomy was also necessary. The one with severe AP died due to MSOF (multiple system organ failure) without a surgery related cause. Regarding the post-

operative mortality registered in this group, both cases presented acute cholecystitis. Moreover, one of them was 82 years old and had pericholecystic abscess and sepsis, which confirms the higher risk of dying from sepsis in patients over 80 years of age (37).

Conclusions

In acute biliary pancreatitis, ERCP with stone extraction followed by same-admission laparoscopic cholecystectomy is a safe therapeutic option, with low morbidity, that prevents recurrent pancreatitis. The timing of the procedures remains controversial, prospective studies being required to achieve statistical significance.

Conflict of Interest

The authors declare no conflicts of interests.

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