

How to Cite:

Omaia, A., Khalil, K. A., Omar, S. A., & Abdo, M. M. (2023). A randomized controlled trial for comparing the results of early endoscopic retrograde cholangiopancreatography and conservative treatment in patients with acute gallstone pancreatitis. *International Journal of Health Sciences*, 7(S1), 3031–3042. <https://doi.org/10.53730/ijhs.v7nS1.14679>

A randomized controlled trial for comparing the results of early endoscopic retrograde cholangiopancreatography and conservative treatment in patients with acute gallstone pancreatitis

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Abstract---Introduction: Gallstone pancreatitis is one of the most dangerous complications of gallstone disease with a high risk of complications and death. Therefore, accurate diagnosis and timely management of acute gallstone pancreatitis are very important. Most guidelines recommend urgent ERCP in cases of biliary obstruction with cholangitis. However, the best time to perform an ERCP in patients suffering from acute gallstone pancreatitis without cholangitis is not universally agreed upon. Aim: The purpose of this study was to compare the outcomes of early ERCP versus conservative management in patients with acute gallstone pancreatitis in terms of complications, mortality, and length of hospital stays. Materials and Methods: A randomized controlled trial was carried out at the Suez Canal University Hospitals between January 2020 and January 2022. After meeting the inclusion criteria, forty patients were enrolled in this study and were allocated randomly into ERCP and Conservative groups. A written informed consent form was taken from all patients.

Patient demographics, symptoms, and a detailed history were all collected. Laboratory tests were performed and reported. ERCP's findings were reported. Results: A total of 40 patients were included in the study. The average age was 42 years in the ERCP group and 39 in the conservative group. The most frequent symptom at presentation was epigastric pain. The study showed that the Conservative group had a 20% complication rate, whereas the ERCP group had a five percent complication rate. The average hospital stay was about 6 days in the conservative group, while the ERCP group's average hospital stay was about 4 days. No deaths were observed in both study groups. Conclusion: In comparison to conservative therapy, early ERCP was safe and reduced complications and hospital stay for mild-moderated acute gallstone pancreatitis. Furthermore, it demonstrated that ERCP had no significant influence on mortality as compared to conservative therapy.

Keywords---acute gallstone pancreatitis, ERCP, pancreatitis, results ERCP.

Introduction

Acute pancreatitis (AP) is one of the most overwhelming gastrointestinal disorders, causing enormous emotional, physical, and financial burdens [1]. Acute pancreatitis has become more common in many parts of the world in recent decades [2,3]. The frequency of AP per 100,000 people worldwide varies between 4.9 and 73.4 cases, according to several studies [4,5]. Acute pancreatitis is most frequently caused by gallstones (40-70%) and alcohol (25-35%), but other factors can also contribute to AP, including drugs (such as azathioprine, 6-mercaptopurine, and thiazide diuretics), infectious diseases, and metabolic disorders [such as hypercalcemia, hyperparathyroidism, and hypertriglyceridemia >1000 mg/dl] [1].

Acute gallstone pancreatitis, the most common type of pancreatitis, arises from a brief obstruction of the bile duct and pancreatic duct, which causes bile reflux or increased hydrostatic pressure in the pancreatic duct [6]. The clinical course of acute gallstone pancreatitis is like pancreatitis due to other causes: about 80% of patients have a benign and self-limiting course, while 20% of patients will develop a severe form with mortality up to 30% [7]. Spontaneous passage of common bile duct (CBD) stones into the duodenum occurs in about 50% of cases of acute gallstone pancreatitis. Acute gallstone pancreatitis responds well to conservative therapy, but a biliary complication rate of up to 20% is present with conservative care of these individuals. ERCP is deferred in these conditions and may be performed in more difficult cases, increasing the failure rate [8]. According to Omar and Marwa, after the initial attack of acute gallstone pancreatitis has been treated, patients frequently experience a second attack of the condition (40-60%) within two weeks, as well as other gallstone-related complications like biliary colic, acute cholecystitis, acute cholangitis, or CBD obstruction [9].

In a retrospective study, Nguyen et al. [10] discovered that ERCP (5.1% vs. 13.1%) or cholecystectomy (5.6% vs. 14%) significantly reduced hospital readmission rates for acute gallstone pancreatitis within 12 months. A study in Turkey reported about 15% of stones detected during an initial episode of acute gallstone pancreatitis pass naturally. Persistent bile duct stones, on the other hand, may cause continuous pancreatic duct or bile duct blockages, leading to severe acute pancreatitis or cholangitis in a few people [11].

It is controversial whether performing ERCP within 24 hours in patients with acute gallstone pancreatitis and biliary obstruction despite the existence of multiple research studies on ERCP in patients with acute gallstone pancreatitis and clinical practice recommendations [6]. In patients with acute gallstone pancreatitis and choledochal obstruction, early ERCP within 72 hours is needed, and ERCP within 24 hours in cases of cholangitis. It is questionable if ERCP is necessary for patients with acute gallstone pancreatitis who don't exhibit cholangitis [12,13].

Material and Methods

Study design

This is a randomized controlled study that was conducted during the period between January 2020 and January 2022. Randomization was done by using a computer random number generator. The sealed numbered envelopes method was used for allocation concealment. The Institutional Ethics and Research Committee at Suez Canal University Faculty of Medicine obtained the study's written approval (IRB approval number 1260). Written informed consent was obtained from all participants.

Inclusion and exclusion criteria

A total of 40 patients with acute gallstone pancreatitis were recruited from Suez Canal University Hospitals and were randomly allocated into two groups; the ERCP group (who underwent early ERCP within 72 hours from admission) and the conservative group. The inclusion criteria were Adults from 18-70 years old and mild-moderate acute gallstone pancreatitis.

Exclusion criteria included those who were pregnant; those who reported alcohol consumption; those who had concomitant cholangitis or chronic pancreatitis or pancreatic cancer and those who had severe medical conditions contraindicating ERCP including bleeding disorders (severe thrombocytopenia $PLT < 50000$ cell/ml, decompensated liver disease, and prolonged INR > 1.5).

Data collection

Demographic data of the patients including age, sex, occupation, alcohol consumption, drug history, and residence were reported. Symptoms of presentation and signs were reported. Laboratory investigations were done, including a complete blood count, serum amylase or lipase, renal profile, liver function tests, and serum electrolytes, and data was recorded. Further

radiological evaluation was done with abdominal U/S for all patients, while contrast-enhanced abdominal CT was used for 3 patients who could not be properly assessed by U/S due to gases (which obscure the biliary tree and pancreas).

ERCP procedure

The ERCP procedure was performed under general anesthesia in the Suez Canal University endoscopy unit, and monitoring was done by an anesthesiologist and endoscopist. All ERCPs were performed under fluorescence guidance to diagnose and manage obstruction using a large accessory channel (4.2 mm) duodenoscope (Pentax ED-3490 TK, Tokyo, Japan). Common bile duct (CBD) catheterization was done by a sphincterotome and guidewire.

Definitions

Acute Pancreatitis was diagnosed by the presence of at least two of the three following criteria:

1. Epigastric pain radiates to the back and is relieved by bending forward.
2. S. amylase and/or S. lipase elevations above three times the upper limit of normal.
3. Characteristic findings from abdominal imaging (U/S or CT).

Gallstone pancreatitis was diagnosed by:

1. Imaging confirmation of gallstones, sludge, and/or
2. CBD dilatation; and
3. Elevated ALT, AST with elevated GGT, and alkaline phosphatase.

Patients were stratified according to the severity of disease by Ranson's score for Gallstone pancreatitis. The onset of Acute Pancreatitis was defined as the time of onset of abdominal pain not the time of admission to the hospital. The total length of the hospital stay was defined as the time between admission to the hospital and discharge from the hospital.

Conservative management was defined as follows: IV fluids, analgesics, and proton pump inhibitors. Selective ERCP within 3 weeks after discharge from the hospital if indicated (fever, persistent biliary colic, persistent jaundice, or persistent CBD dilatation).

Results

Demographic data of the studied patients is displayed in Table 1. The majority of studied patients were females in both groups. The conservative group's mean age was around 39 years old, whereas the ERCP group's mean age was around 42 years old. The age and gender differences between study groups were statistically negligible.

Table 1: Demographic data of patients

Variables	ERCP [n= 20]	Conservative [n= 20]	P- value
Sex			
Male	4 [20%]	2 [10%]	1.000
Female	16 [80%]	18 [90%]	
Age			
Mean± SD	42.55 ± 14.31	39.74 ± 14.97	0.507
Median [min-max]	41 [19-62]	38 [18-70]	

ERCP: Endoscopic Retrograde Cholangio-Pancreatography

ERCP's findings are displayed in the following Table 2. CBD dilatation was seen in all patients, while IHBRD was seen in 60% of them. After endoscopic sphincterotomy, stones were retrieved by balloon in 30% of patients, and biliary sludge or gravel was extracted in 10% of cases. Lower CBD stricture and stone with failed stone extraction were found in 10% of cases and handled by implantation of the plastic stent. In 50% of cases, nothing was removed by ERCP (slipped stone).

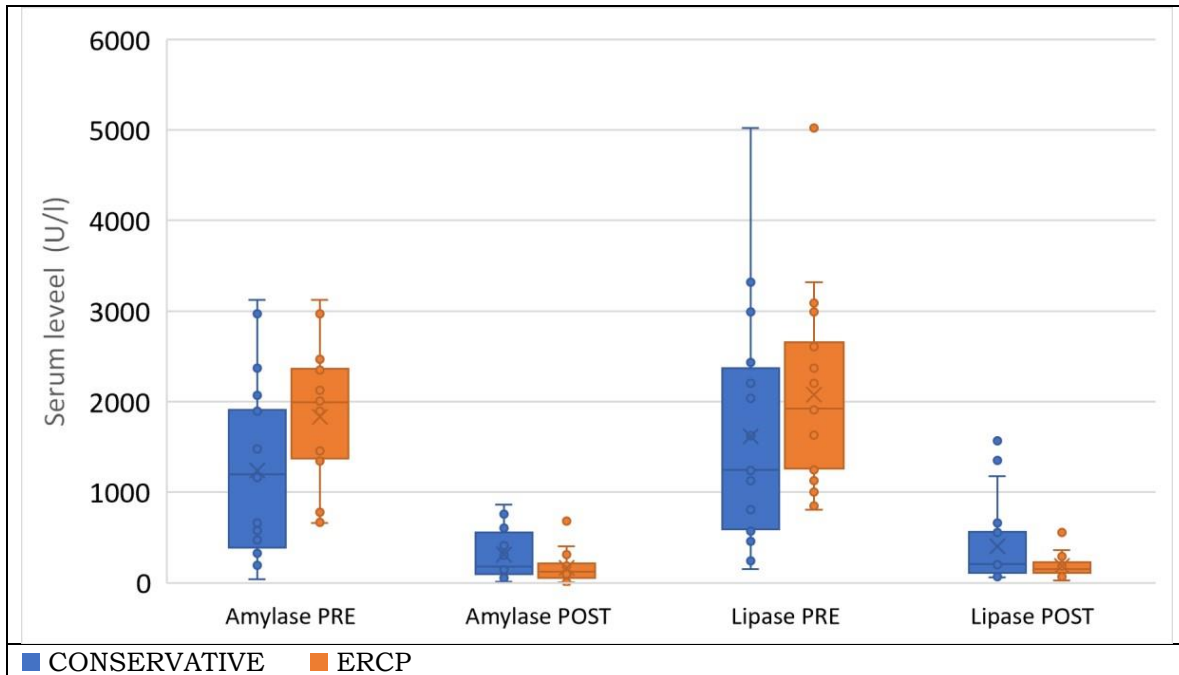
Table 2: Findings of ERCP

ERCP's findings	No. (%)
Dilated CBD	20 (100 %)
Successful Sludge or Gravel/s extraction	2 (10 %)
Intrahepatic biliary radicle dilatation	12 (60 %)
Lower third CBD stricture and stone with failed stone extraction	2 (10 %)
Successful CBD stone/s extraction	6 (30 %)
No stone (slipped stone)	10 (50 %)
Successful biliary cannulation	20 (100 %)
Total	20 (100 %)

ERCP: Endoscopic Retrograde Cholangio-Pancreatography, CBD: Common Bile Duct

Levels of s. amylase and lipases were reduced in both groups with statistical significance after ERCP and after 48 hours of admission in the conservative group, but the level of reduction was markedly observed in the post-ERCP group than in the conservative group (Figure 1).

Figure 1: Pancreatic enzymes among the study groups



ERCP: Endoscopic Retrograde Cholangio-Pancreatography

Amylase or Lipase pre: pre-ERCP in ERCP group / at admission in the conservative group

Amylase or Lipase post: Post ERCP in ERCP group / > 48hrs post admission in conservative group

The duration of hospital stay is displayed in Table 3. The duration of hospital stay in the ERCP group was shorter than the conservative group with a statistically significant difference between study groups.

Table 3: Hospital stay among the studied groups

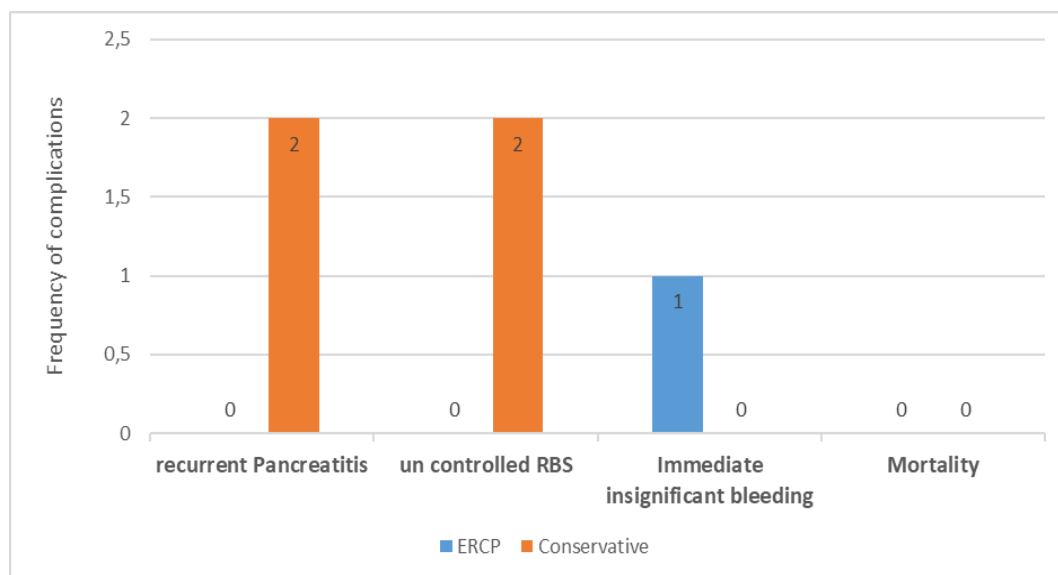
Group	Conservative	ERCP	p-value
Variable	Mean $\pm$ SD	Mean $\pm$ SD	
Hospital-stay length (days)	6.46 $\pm$ 2.63	3.84 $\pm$ 0.64	<0.001
p-value significant if less than 0.05 Mann-Whitney U test.			

ERCP: Endoscopic Retrograde Cholangio-Pancreatography

The following Figure 2 shows that the complications in the conservative group were more common than in ERCP; 10% (two /20) of conservative cases developed uncontrolled RBS while pancreatitis reoccurred in 10% of cases (two /20) one of them during the same admission while another patient was three months after hospital discharge. One patient in the ERCP group had immediate bleeding during the procedure. There were statistically significant differences between

conservative and ERCP groups regarding uncontrolled RBS and recurrent pancreatitis (P-value was < 0.001). No mortality was observed in either study group.

Figure 2: Complications among the studied groups



ERCP: Endoscopic Retrograde Cholangio-Pancreatography, RBS: Random Blood Sugar

Discussion

The effectiveness of ERCP in patients with acute gallstone pancreatitis has long been debatable. Multiple studies evaluated the effectiveness of early ERCP in comparison with conservative management. Inclusion criteria, exclusion criteria, diagnosis of gallstone pancreatitis, timing, and evaluation of severity of acute pancreatitis differ between studies [14]. This study was concerned with comparing the results of early ERCP with conservative management in patients with mild-moderate acute gallstone pancreatitis, attempting to determine whether early ERCP would provide a benefit to such patients. In this study, cases with cholangitis were excluded from the study, while other studies included febrile patients or patients with cholangitis such as Acosta, et al. and Fan, et al. whereas others defined cholangitis as an exclusion criterion such as Oria, et al. & and Fölsch, et al. [15,16].

The severity of AP was assessed by many scores in each study. We used Ranson's score as a parameter of severity, Also Fan, et al. and Acosta, et al. used Ranson's score too. While, Zhou, et al., Oria, et al., and Chen, et al. used the APACHE II score. Neoptolemos, et al. and Fölsch, et al. employed the Glasgow score [15]. This study showed that the majority of studied patients were females in both groups (80% in the ERCP group and 90% in the conservative group). Also, Acosta, et al., reported that female was the predominant gender in the study (81% in the conservative group and 70% in the study group) [17]. Uy, et al. and Pécsi,

et al. reported the same finding [18,19]. Halász, et al. described that females constituted 57% of patients [20]. In this study, about 30% of the patients who underwent ERCP were found to have CBD stones while gravel/sludge was found in 10% in this study. This finding is consistent with those from the RCT meta-analysis by Moretti, et al. and Petrove, et al. In addition, Acosta, et al. reported that 62% of cases undergoing ERCP had CBD stones [7,16,17]. Halász et al. described that CBD stones were found in 36% of patients in ERCP and CBD mud was found in 34% of patients (20).

The incidence of complications in patients treated conservatively was about 20%, but it was 5% in the ERCP group in this study. Meta-analysis of RCTs showed that the incidence of complications in patients treated conservatively varied from 19% to 51%; this difference was due to different definitions of early ERCP, and outcomes used in each trial [16]. This study showed that ERCP significantly reduced complications in mild-moderate acute gallstone pancreatitis while there was no effect of ERCP on mortality compared with the conservative group. The same finding was observed by Acosta, et al. but Acosta, et al. did not exclude cholangitis [17]. Petrov, et al. reported that early ERCP reduced the overall risk of complications, but increased the risk of mortality in acute gallstone pancreatitis and these results did not reach statistical significance. Petrov, et al. demonstrated no advantageous effect of early ERCP with or without ES in both patients with mild and severe acute gallstone pancreatitis without cholangitis [16]. Moretti, et al. reported that ERCP reduced complications in severe gallstone pancreatitis and no advantage for ERCP over conservative management in reducing complications in mild pancreatitis [7].

Coutinho, et al. noticed no statistical difference between early ERCP and conservative management in patients with acute gallstone pancreatitis, in terms of the incidence of systemic adverse events, the development of acute cholangitis, and evolution to death. However, Coutinho, et al. showed that the performance of ERCP early in the management of acute gallstone pancreatitis reduces the occurrence of local adverse events, as well as reducing the time to pain relief and reducing body temperature [15]. Fogel and Sherman reported that ERCP with sphincterotomy must be done within 72 hours of admission in patients with severe acute pancreatitis irrespective of biliary obstruction. However, ERCP may not be needed in patients with mild pancreatitis [21]. Cochrane meta-analysis showed no differences in mortality rate between ERCP and conservative management in mild pancreatitis [22].

Uy, et al. found no significant difference between ERCP & and conservative management of acute gallstone pancreatitis without cholangitis and suggested higher mortality in patients with mild and severe acute gallstone pancreatitis managed by early ERCP. Uy, et al. included RCTs which excluded patients with obstructive jaundice while this study included patients with obstructive jaundice [18]. A multicentric RCT in the Netherlands demonstrated that early ERCP (< 24 hours) did not decrease the incidence of complications or mortality in patients with severe gallstone pancreatitis [23]. Pécsi et al. reported that immediate insignificant bleeding in the ERCP group was 9% while immediate insignificant bleeding was 5% in this study [19].

This study described that the duration of hospital stay in the ERCP group was shorter than the conservative group with statistically significant difference between study groups. Halász, et al. reported that the duration of hospital stay was extended when ERCP was delayed [20]. This result was against Moretti, et al. who reported that length of hospital stay in patients with predicted mild pancreatitis was not different between study groups. While a significantly shorter duration of hospitalization was observed in patients with predicted severe AP who underwent early ERCP group [7]. Also, Coutinho, et al. showed that hospital stay was shorter among patients undergoing ERCP than among those undergoing conservative management alone [15]. The limitations of this study were its small sample size and the COVID-19 crisis. Further studies are required to validate our findings and suggestions.

Conclusion

In comparison to conservative therapy, early ERCP was safe and reduced complications and hospital stay for mild-moderate acute gallstone pancreatitis. Furthermore, it demonstrated that ERCP had no significant influence on mortality as compared to conservative therapy.

Illustrated Cases

Case 1

A 34-year-old female patient presented with acute epigastric pain referred to the back, jaundice, elevated liver enzymes, amylase, and lipase levels. Abdominal U/S showed dilated CBD with a stone inside it, dilated intrahepatic biliary radicles, and a few stones inside the gallbladder. Findings of ERCP were dilated CBD with two stones inside the distal part of CBD and retrieval of the stones by an extractor balloon after sphincterotomy (Figure 3).

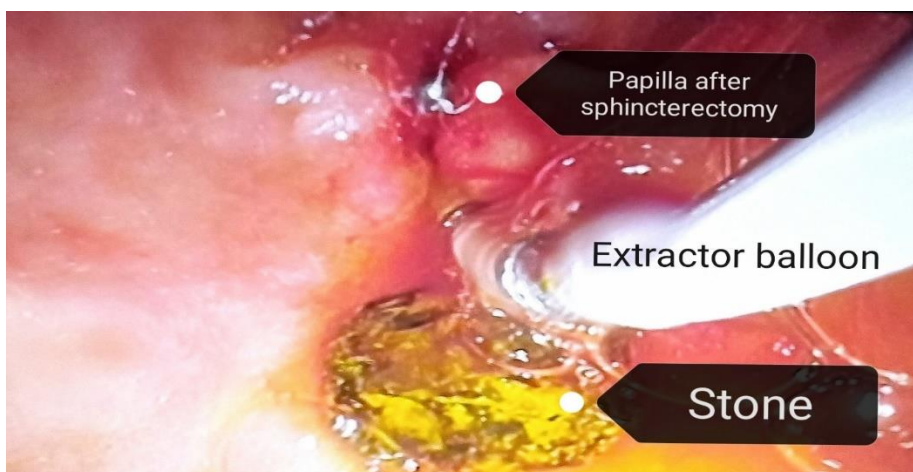


Figure 3: Endoscopic picture showing retrieval of stone by a balloon from CBD after sphincterotomy.

Case 2

A 39-year-old female patient presented with acute epigastric pain, vomiting, elevated liver enzymes, amylase, and lipase levels. Abdominal U/S showed dilated CBD, mildly dilated intrahepatic biliary radicles, a few small stones inside the gallbladder, and peripancreatic fluid collection with a bulky pancreas. Findings of ERCP were dilated CBD with multiple small filling defects (stones) at the distal part of CBD (Figure 4).

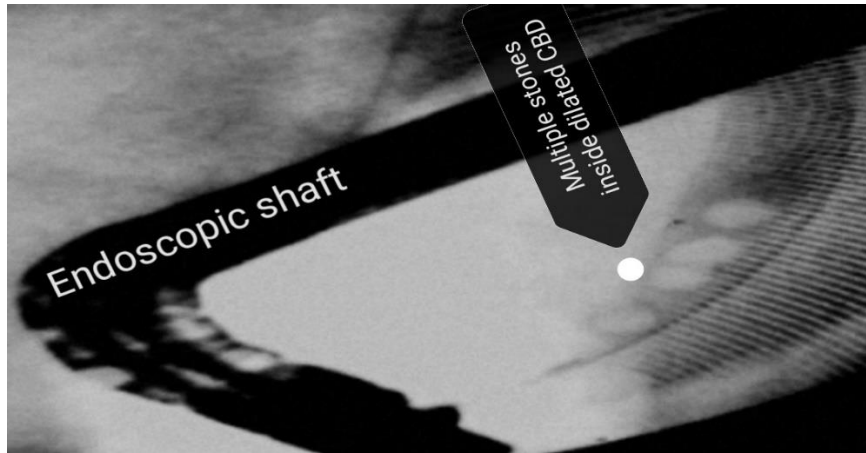


Figure 4: Cholangiogram showing dilated CBD with multiple small filling defects inside the distal part of the CBD (CBD: Common Bile Duct)

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