

RESEARCH ARTICLE

Acute recurrent pancreatitis: Relative risk factor, etiology, diagnosis procedure and treatment in the pancreatic disease institute of Wuhan union hospital of china

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This study describes the relative risk factors, etiology and treatment option of recurrent acute pancreatitis. The data of 71 patients with acute recurrent pancreatitis were retrospectively studied from January 2010 to December 2014. Of 71 patients, 41 were male and 30 were female with a sex ratio of 1.4:1 with a mean age of 49 years. Their age ranged from 14 to 85 years. After reviewing the clinical data, the risk factors were analyzed using univariate and multivariate analysis. The etiology was investigated in each case using specialized laboratory analysis, ERCP, EUS and MRCP. Their pain was labeled severe, moderate and mild by using the Analgesic Ladder by World Health Organization. Subsequent to the investigation reports, therapeutic ERCP and endoscopic sphincterotomy were performed. Of the 71 patients, 52 cases were biliary pancreatitis, 13 were idiopathic pancreatitis, 3 were alcohol induced pancreatitis and 3 were hyperlipidemia pancreatitis. The univariate analysis showed easy recurrence with obstructive jaundice, hepatic function injury and local complication of pancreas ($P=0.016 < 0.05$, $P=0.003 < 0.05$ and $P=0.024 < 0.05$ correspondingly). Multivariate analysis showed no single factor related to recurrence. Upon definition of etiology, there were 33 cases of common bile duct stones, 14 cases of pancreatic duct stones, 5 cases of gallbladder stones, 3 cases of pancreas divisum, 2 cases of ampullary tumor, 4 cases of sphincter of Oddi dysfunction, 6 cases of chronic pancreatitis, 1 case of post liver transplant complication and 3 cases of duodenal diverticulum. The 71 patients performed ERCP followed by either endoscopic sphincterotomy in 69 cases or endoscopic resection in 2 cases. The procedure was curative and successfully performed. A complication rate of 2.8% with no mortality was observed. Post-therapy, a decline in pain intensity was observed in 56 cases of the patients. ERCP and endoscopic sphincterotomy has a curative effect in diverse etiology of acute recurrent pancreatitis.

Keywords: Acute pancreatitis; Acute recurrent pancreatitis; Etiology; relative risk factor; Endoscopic treatment; ERCP

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Introduction

Acute Pancreatitis (AP) is described as an acute inflammatory process of the pancreas with the involvement of peripancreatic tissues or remote organ systems; it may be associated with severe upper abdomen pain and a 2-3 fold rise in both amylase and lipase, according to the Atlanta Symposium [1]. It is found to be the first cause of hospitalization in pancreatic center of Wuhan union hospital [2]. It may cause mild discomfort and may become severe or a life-threatening illness. Most people with acute pancreatitis recover completely after getting the right treatment. Acute pancreatitis is classified as mild when the APACHE-II scores and Ransom's signs are low and there are no systemic complication, and the CT scan rules out necrotizing pancreatitis. Severe cases of AP can result in bleeding, serious tissue damage, infection, and cyst formation in pancreas. The criteria for severity of AP include organ failure that include shock, pulmonary insufficiency, renal failure and/or local complications which include pancreatic necrosis, abscess and pseudo cyst which may result in substantial morbidity and mortality^[1,3]. Approximately 300,000 cases occur in the United States each year, 10 to 20% of which are severe and leading to over 3000 deaths.

Studies have shown that after the first episode of pancreatitis, 30% of the patients may experience a relapse [4]. Atlanta Symposium defined acute recurrent pancreatitis (ARP) as at least 2 episodes of acute pancreatitis with complete or near complete resolution of symptoms and signs of pancreatitis between episodes^[1,3]. Therefore, it's important in clinical diagnosis to differentiate between the initial and recurrent episodes of AP, fortunately, only a limited workup (history, routine laboratory evaluation, transcutaneous ultrasonography and/or computed tomography) for an initial attack is needed to conclude the etiology compared to ARP patients which requires more extensive workup to discover the causative factor^[5,7]. Usually either alcoholism or gallstone disease results in ARP. When the cause of ARP is undetectable, then the diagnosis is assumed to be idiopathic acute recurrent pancreatitis (IARP). Thereafter, an extensive evaluation would be performed including specialized laboratory investigations, such as endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), or magnetic resonance cholangiopancreatography (MRCP). These typically leads to a diagnosis of microlithiasis, sphincter of Oddi dysfunction (SOD), or pancreas divisum. Consequently, if no etiology has been established then the diagnosis of "true" IARP is assigned.

In today's world, endoscopic therapy is overshadowing surgical procedures. Endoscopic retrograde

cholangiopancreatography (ERCP) which was mainly used as a diagnostic tool has evolved as a therapeutic modality. ERCP and endoscopic sphincterotomy are being selectively used for patients identified to have a problem which can be solved with a less invasive therapy. We reviewed the data of patients with ARP in our hospital for 5 years and evaluated the relative risk factors, the etiology, diagnosis procedure, and ERCP combined with endoscopic sphincterotomy as treatment.

Materials and methods

Patients and demographic data

Among the acute pancreatitis patients that were treated, from January 2010 to December 2014, in Pancreatic Disease Institute of Wuhan Union hospital of China, 71 patients were diagnosed with acute recurrent pancreatitis from clinical observations and history. Of the 71 patients, 41 were male and 30 were female with a sex ratio of 1.4:1 and a mean age of 49 years. Their age ranged from 14 to 85 years.

Diagnosis standard of ARP

The diagnosis of ARP requires two of the following three features: (1) *abdominal pain* of AP such as acute onset of a persistent, severe, epigastric pain often radiating to the back; (2) serum *lipase with at least three times greater than the upper limit of normal*; and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly MRI or transabdominal ultrasonography. After receiving conservative or operative treatment, these signs and symptoms disappeared, serum and urine amylase returned to normal along with other laboratory test such as liver functions, renal functions, blood leukocyte, glucose and so on were normal(etc)^[1,9]. They could refeed without complaint. Thereafter, if the signs and symptoms recurred in conjunction with elevating serum and urine amylase, the patients were diagnosed as having ARP

Relative Risk Factors

According to recorded clinical data, the possible related risk factors of acute recurrent pancreatitis were observed to be; age more than or equal to 60 years; Male; 3 times more than normal values of serum amylase; biliary pancreatitis; bile duct obstruction; liver injury revealed through high levels of serum glutamic-pyruvic or serum glutamic oxalacetic transaminase with or without elevated serum bilirubin and local complications (acute fluid accumulation, necrosis, pseudo cyst, abscess formation). The risk factors were analyzed using univariate and multivariate analysis (Table 2).

Table 1(a). Classification of biliary SOD

Biliary Type I	<ul style="list-style-type: none"> • Biliary-type pain • Abnormal liver enzymes(ALT/AST twice their normal value) • Dilated common bile duct(12mm diameter) • Delayed drainage of ERCP contrast beyond 45 mins
Biliary Type II	Biliary type pain with one or two of the above criteria
Biliary Type III	Biliary type pain with no other abnormality

Table 1(b) Classification of pancreatic SOD

Pancreatic type I	<ul style="list-style-type: none"> • Pancreatic-type pain • Twice normal amylase or lipase • Pancreatic duct > 6mm in the head or 5mm in the body
Pancreatic type II	Pancreatic-type pain with only one of the above criteria
Pancreatic type III	Pancreatic-type pain with no other abnormalities

Table 2: Relative Risk factors among the ARP patients

Relative factors	No. of cases	Percentage (%)	Univariate analysis P	Multivariate analysis P
Age>60	36	50.7	0.158	0.432
Male	41	57.7	0.542	0.238
Biliary pancreatitis	45	63.4	0.422	0.132
Obstructive jaundice	35	49.3	0.016	0.212
Amylase elevation	59	83.1	0.234	0.246
Liver injury	38	53.5	0.003	0.124
Local complication	26	36.6	0.024	0.931

The factors causing ARP correlated with local complication, obstructive jaundice and liver injury (P=0.024< 0.05, P=0.016< 0.05 and P= 0.003<0.05 respectively) according to the univariate analysis. According to the multivariate analysis, no single factor was shown to be related to ARP.

Classification of Recurrent pancreatitis

Biliary pancreatitis:

Elevated serum bilirubin (direct bilirubin/total bilirubin>50%) with clinical jaundice

Dilation of intra- and extra- hepatic bile duct with a diameter of more than 1cm which may be observed with a B-ultrasound, CT or ERCP

Alcohol-induced pancreatitis:

A daily intake of 80g of alcohol for more than 5 years or an excessive intake of alcohol just before an attack.

Hyperlipidemia pancreatitis:

Serum lipid elevation, especially triglyceride with levels usually greater than 1000 mg/Dl

Idiopathic pancreatitis:

No apparent cause can be ascribed.

Pain Assessment

In our study, one of the indications of therapy was pain. The severity of pain in the patient was assessed by Analgesic

ladder (Pain Ladder) originated by the World Health Organization (WHO) [10]. It follows the rule of starting with the first step drugs and then climbs the ladder if pain is still present.

According to WHO patients with pain were initially given non-opioid drugs (paracetamol (acetaminophen), dipyron, non-steroidal anti-inflammatory drugs (NSAIDS) or COX-2 inhibitors). Thereafter, if pain were not relieved, mild opioids (codeine phosphate, dextropropoxyphene, dihydrocodeine or tramadol) were added to the existing non opioid regime. If this became insufficient, the mild opioid were replaced by stronger opioid (morphine, diamorphine (heroin), fentanyl, buprenorphine, oxymorphone, oxycodone, hydromorphone). While continuing the non-opioid therapy, the dosage was increased until the patients were either free of pain or had reach the maximum possible relief with tolerable side effects. Nevertheless, if the case presented with severe pain, strong opioid coupled with non-opioids analgesic should be administered directly.

Etiology

ARP is common among ERCP endoscopists in Western world, 70 -80% are due to alcoholism and gallstones [7]. Other include, autoimmune disorders, intraductal papillary mucinous neoplasm, chronic pancreatitis, drugs, hereditary, metabolic syndrome, sphincter of Oddi dysfunction, congenital abnormalities (pancreas divisum, intra-duodenal

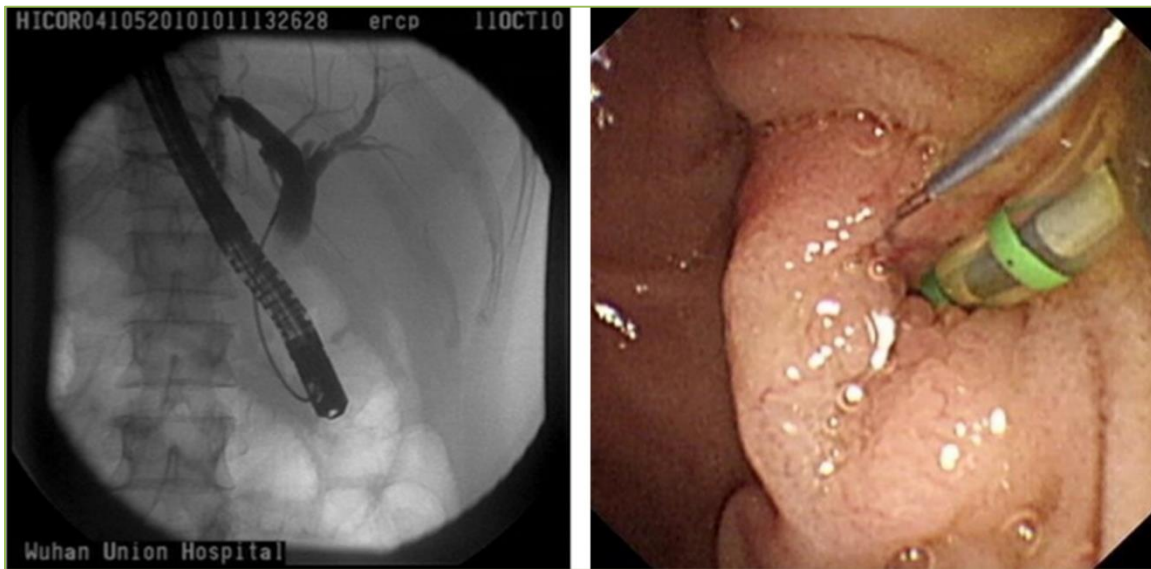


Figure 1. This image captured via endoscopic retrograde cholangiopancreatography, shows cannulation of the ampulla. A guide-wire is inserted into the pancreatic duct via a cannulation device and the guide wire was left inside with cannulation device withdrawn. The cannulation device is then loaded with a second guide-wire and reinserted through the working channel of the endoscope alongside the previously placed pancreatic guide-wire. The tip of the cannulation device is positioned in the papilla, bending the pancreatic wire and targeting the direction of the CBD for cannulation with the second guide-wire.

diverticulum), trauma, etc. Almost any cause of acute pancreatitis may lead to ARP if not corrected. However, the causes that can be managed by endoscopists through ERCP and endoscopic sphincterotomy are: (1) Gallstones disease (biliary Microlithiasis or sludge) whether the patients have gall bladder or not. (2) Sphincter of Oddi dysfunction (biliary and pancreatic). (3) Obstruction to the flow of pancreatic juice. (4) Pancreas divisum, duodenal diverticulitis. (5) Chronic pancreatitis.

ERCP is the technology that has improved our diagnostic accuracy with visualization of biliary-pancreatic system in detail and can detect tiny gallstones that can be ignored by ultrasound. Furthermore, ERCP allows ancillary procedures such as collection of bile for bile crystal testing and manometry of biliary and pancreatic segments of sphincter of Oddi which may be followed by a biliary sphincterotomy.

The treatment and diagnosis vary according to the types:

Type I SOD; delayed drainage is observed in the dilated biliary and pancreatic duct, therefore investigation using manometry is not required for confirmation. Hereafter, patient can proceed to biliary/pancreatic sphincterotomy directly, thereafter they are found to have better result.

Type II SOD; when the dilated ductal system or delayed drainage are documented, sphincter dysfunction may be present. Hence, a manometry is performed first, showing an abnormally elevated basal pressure, thereafter proceed to endoscopic sphincterotomy. A biliary sphincterotomy may

suffice since pancreatic sphincter pressure is also reduced but a dual and complete sphincterotomy (biliary and pancreatic) yields better result. During the procedure, prophylactic stent placement reduces the rate and severity of pancreatitis and it is advocated. Besides, the stent usually migrates spontaneously or is removed after 2 weeks.

Type III SOD; The diagnosis rely on the manometry recording of biliary and pancreatic segment of SOD. The type III is a heterogeneous group with possible hyperalgesia and motility disorders. Treatment is therefore individualized [11, 14, 19].

The gold standard for diagnosing SOD dysfunction is manometry. It helps in the direct measurement of basal sphincter pressure via a thin catheter placed inside the pancreatic or biliary sphincter during ERCP. When a hypertensive SOD pressure (>40mmHg) is measured then the diagnosis is established [12, 25].

Nonetheless, complications related to manometry are significantly more frequent and less acceptable than those after therapeutic ERCP [5]. Therefore manometry is usually reserved for patients with clinically significant symptoms in whom sphincter ablation is planned while confirming the diagnosis. There are indirect methods aimed to diagnose SOD such as detecting a delay in pancreatic juice drainage, which is evident following contrast injection during ERCP or with persistent dilation of pancreatic duct after secretin stimulation on imaging studies.

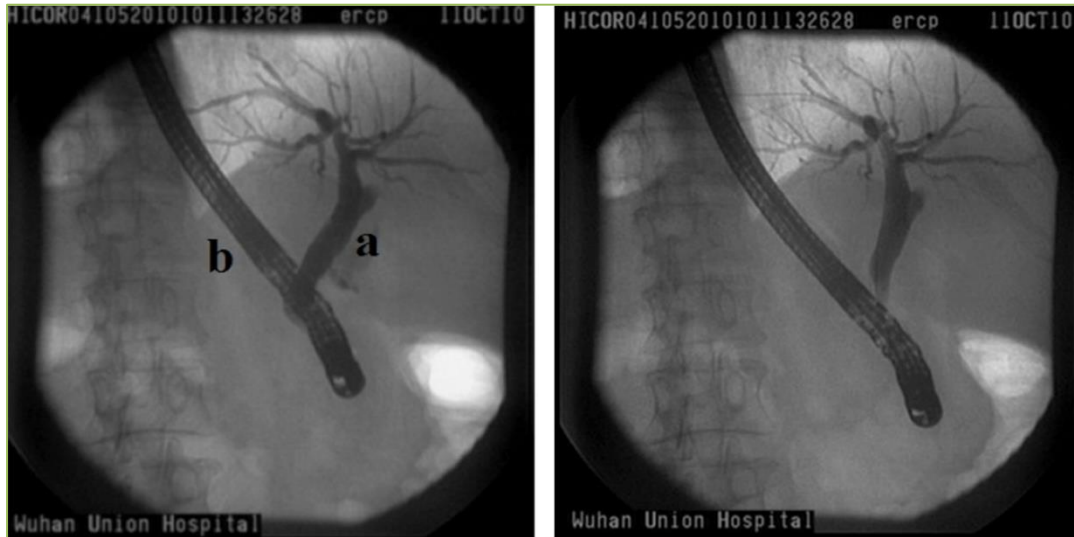


Figure 2. Cholangiogram showing (a) moderately dilated bile duct and (b) duodenoscope positioned in duodenum.

The standard treatment of SOD is considered to be endoscopic sphincterotomy which involves cutting of sphincter with electro-cautery, while performing the ERCP. Tzovaras G. *et al* shows clinical evidence that endoscopic biliary sphincterotomy causes a significant relief of symptoms or complete disappearance of the disease in majority of cases [13]. Therefore, the first therapeutic step in approach to ARP is sphincterotomy instead of cholecystectomy [14, 21]. Biliary sphincterotomy has proved to be effective even in pancreatic duct abnormalities due to the low basal sphincter pressure there is a reduced basal pancreatic duct pressure; basal pancreatic duct pressure is found to be greater than the common bile duct in only 20% patients [15, 23]. Persistently high pancreatic duct pressure may be the cause of slow amelioration of patients after sphincterotomy or sphincteroplasty [16, 17]. Therefore in these situations, pancreatic sphincterotomy is considered.

Results

Classification and Etiology of ARP

Among 71 acute recurrent pancreatitis patients, 52 had biliary pancreatitis, 13 had idiopathic pancreatitis, 3 had alcohol-induced pancreatitis, and 3 had hyperlipidemic pancreatitis. With clinical diagnosis and endoscopic tools, 33 patients had common bile duct stones, 14 had pancreatic duct stones and 5 had gallbladder stones. Furthermore, 3 had pancreas divisum, 3 had duodenal diverticulum, 2 had ampullary tumor, 4 had SOD, 6 had chronic pancreatitis, and 1 had liver transplant complications.

Laboratory tests of Acute Recurrent Pancreatitis

Of the 71 patients, 58 had their serum amylase thrice the upper limit of normal values. Twenty-one had the leucocytes counting more than 10.0×10^9 , 13 with glycaemia more than 6.1mmol/L, 38 with hepatic function injury, and 30 with serum calculi less than 2.2mmol/L.

Pain and Complications analysis

According to the Pain Ladder by WHO, initially all the patients suffered from chronic pain but subsequent to therapy, 21 patients experienced mild pain, 35 experienced moderate pain and 15 had severe pain. A complication rate of 2.8% was noted, comprising of only bleeding, excluding perforations, post-ERCP sepsis, and pancreatitis.

Analysis of Relative Risk factors of ARP

The factors causing ARP correlated with local complication (Fig. 5), obstructive jaundice and liver injury ($P=0.024$, $P=0.016$, and $P=0.003$ respectively) according to the univariate analysis results. According to the multivariate analysis, no single factor was shown to be related to ARP (Table 2).

Discussion

ARP has a high recurrent rate which represents a challenging clinical problem. During the past few years, ERCP was the main diagnostic and therapeutic tool. However this diagnostic algorithm of ARP has changed with the introduction of EUS and MRCP. Therefore diagnosis of ARP with non-invasive procedures has been promoted, limiting ERCP to its therapeutic role combined with endoscopic sphincterotomy.

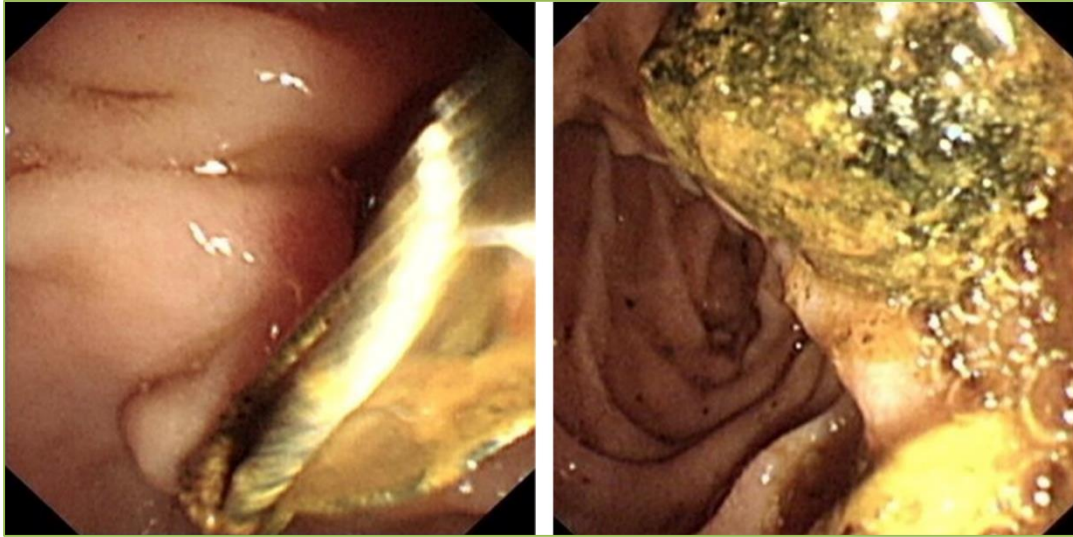


Figure 3. The therapy (stone removal from CBD through sphincterotomy).

Out of the 71 ARP patients in this study, 52 (73.2%) had biliary pancreatitis, 13 (18.3%) had idiopathic pancreatitis, 3 (4.2%) had alcohol induced pancreatitis and 3 (4.2%) had hyperlipidemic pancreatitis. Alcohol induced pancreatitis was fewer in our hospital. Although a lot of drugs could induce acute pancreatitis, it was mainly limited in case reports. The recent years, hyperlipidemia pancreatitis had been emphasized [27]. A high level blood viscosity in hyperlipidemic pancreatitis patients would make the pancreas microcirculation abnormal, eventually acute pancreatitis would relapse. Hence, patients were suggested to do serum lipid test routinely. Biliary pancreatitis was easily diagnosed using B-ultrasound, CT, ERCP and MRCP but for idiopathic pancreatitis the causes were difficult to analyze. After an initial negative evaluation, patients were labeled as idiopathic pancreatitis but later with meticulous investigation the etiology was revealed and specific therapy was directed. Nonetheless, the detailed analysis was carried out only in severe patients or those having 2 or more episodes. If ERCP was conducted, concurrently bile was aspirated for microcrystal's analysis, manometry was performed if SOD was suspected, and minor papilla was cannulated when pancreas divisum was suspected.

Among the several relative risk factors of ARP, the univariate analysis indicated that patients with local complication such as acute fluid accumulation, necrosis, pseudo cyst, abscess formation, had a tendency to recur which would be responsible for the alteration in the pancreas structure. Furthermore, it indicated that acute pancreatitis patients with obstructive jaundice and hepatic function injury are easy to recur. According to multivariate analysis, there was no single factor related to the relapse during treatment, hence pointing to the fact that ARP is probably a result of multiple factors acting together.

The signs and symptoms along with the laboratory results such as amylase, blood glucose, blood calculi, local and systemic complications of ARP and liver function tests corresponded to those patients with primary acute pancreatitis [28].

Defining the etiology of ARP has often been the greatest challenge for clinicians. Nevertheless, diagnostic tool and specialized laboratory test has proved of great help in establishing the correct etiology. Subsequently, guiding the therapy and improving patients' long-term prognosis.

Five (7.0%) ARP patients having an intact gallbladder were shown to have gallstones. Therefore, they underwent bile microscopy through ERCP followed by biliary sphincterotomy which helped to prevent recurring of episodes. This procedure was opted due to unshakable common bile duct stone, cholangitis, evidence of biliary obstruction shown by the elevated liver test and patients were poor candidate for cholecystectomy.

Forty-seven post-cholecystectomy patients with microlithiasis and sludge were observed to show progressive increase in serum bilirubin and other liver functions test and a persistent dilatation of common bile duct are strongly suggestive of common bile duct obstruction by gallstones. Hence, patients were preceded to ERCP and biliary sphincterotomy which is the perfect choice in this situation and was successfully performed in all the 47(66.2%) patients by our endoscopists.

Endoscopic sphincterotomy is the current standard therapy for SOD patients and the 4 (5.6%) patients preferred this procedure compared to drug treatment which does not help to improve the stenosis and is a lifelong therapy that responds in

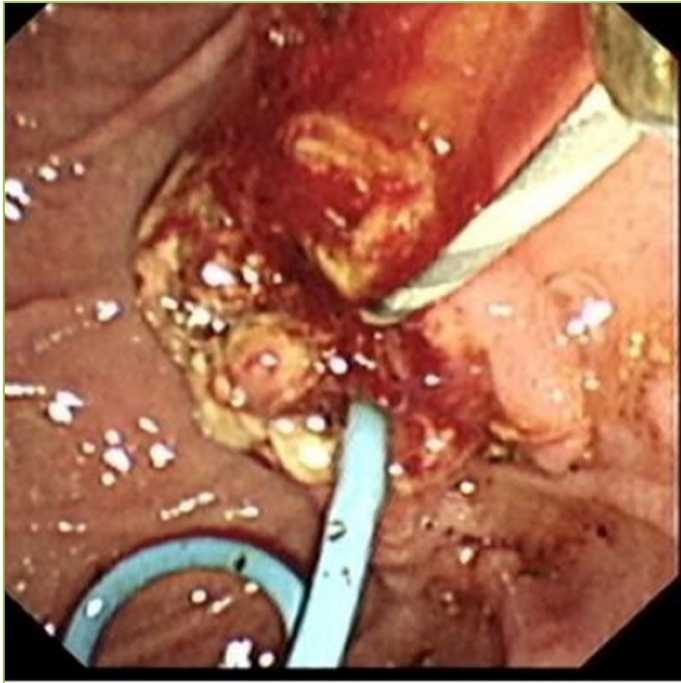


Figure 4. Endoscopic retrograde pancreatic drainage (ERPD) is performed and endoscopic nasal biliary drainage (ENBD) is placed after the therapy.

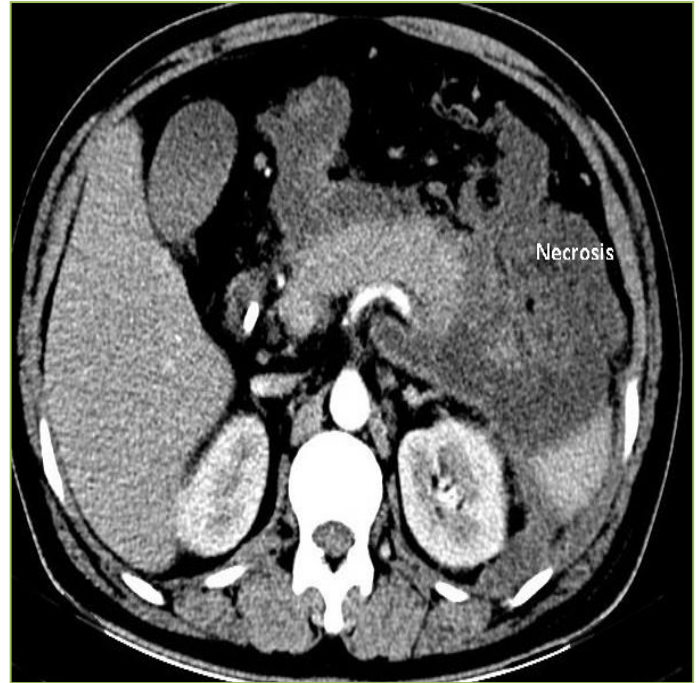


Figure 5. The figure shows necrosis on the tail of pancreas.

minimal cases. At present the only way to measure biliary and pancreatic sphincter pressures is to perform ERCP using manometry catheter followed by placement of a prophylactic stent to reduce the risk of post-ERCP pancreatitis. All 4 SOD cases performed an ERCP and biliary sphincterotomy that proved to be effective even if patient had pancreatic duct abnormality with reduced basal pancreatic duct pressure. However, ERCP is associated with 3-5 % complication rate which may rise in SOD, thus it is carried for SOD manometry followed by immediate biliary sphincterotomy.

Pancreas divisum, the congenital abnormality was treated using ERCP and minor papillary sphincterotomy combined with short terms stents. This therapeutic procedure which is less invasive and cost effective; relieved the symptoms. It has proved to be efficient by Lans *et al.* clinical trial. After ERCP and endoscopic sphincterotomy the 3 (4.2%) patients showed great improvement with no further episode.

Three (4.2%) ARP patients' having an intact gallbladder was diagnosed with periampullary duodenal diverticulum and was chosen to be managed by ERCP and endoscopic sphincterotomy. The procedure prevented the recurrent episodes of pancreatitis. However, bleeding complication occurred in 1 case during the procedure and was managed efficiently by the endoscopists [29].

Of 71 patients, 1 (1.4%) suffered from post-liver transplant biliary anastomotic strictures, whom underwent

endoscopic therapy with stent placement. Moreover, 6 (8.5%) patients with ARP were discovered to have chronic pancreatitis through ERCP. Treatment opted for them was endoscopic pancreatic sphincterotomy. This procedure has shown a success rate of 97.7% in the study, bleeding occurred in 1 case but was medically managed well.

ARP patients with ampullary tumor were confirmed with ERCP thereafter endoscopic resection was carried out under same anesthesia. It relieved the obstruction and solved the ARP.

The immediate efficacy of the endoscopic treatment was evaluated with the intensity of pain according to the Pain Ladder originated by WHO. All the 71 cases presented with severe pain thus they were on strong opioid along with non-opioid therapy before the endoscopic treatment. However, post-endoscopic treatment, a decline in pain intensity was observed in 78.9% of the patients. The improved laboratory results confirmed the success in all the cases. Bleeding as a complication did occurred in 2.8% of the cases but was medically controlled with no mortality.

Conclusions

In our series, 100% performed ERCP with either endoscopic sphincterotomy (97.2%) or endoscopic resection (2.8%). These procedures appeared to be a curative method in all these patients. ERCP has already evolved as a therapeutic tool and now along with it, endoscopic

sphincterotomy has proven its benefits in the clinical field among the patients in preventing ARP attacks. Although endoscopic procedures are less invasive than surgery, they are not completely safe. They can cause bleeding, perforation, pancreatitis and anxiety. Thus before resorting to invasive procedures such as ERCP, sphincter of Oddimanometry, major or minor papilla sphincterotomy and biliary sphincterotomy the endoscopists must review the patients' history and individualize the therapy having in mind that "first he must do no harm".

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Conflicting interests

The authors declare that they have no Conflicting interests.

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