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Endoscopic Retrograde Cholangiopancreatography in Acute Biliary Pancreatitis

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Abstract

Acute pancreatitis (AP) is the most serious emergent disease in the gastroenterology field. The most common cause of AP is naturally gallstones. The most cases have mild disease and the illness limits itself in a short time period. In 15–20% of cases, the severe form of acute biliary pancreatitis (ABP) develops. Some patients have concomitant cholangitis. In these patients, relieving biliary obstruction with endoscopic retrograde cholangiography (ERCP) and endoscopic sphincterotomy (ES) is essential. However, correct timing of ERCP is a debate. While some authors and guidelines suggested that ERCP can be performed in first 24 hours, the others suggested its use during the first 72 hours. In the first 24 hours, ERCP is difficult to apply due to ampullary edema and general ill situation of the patient. Rather than ERCP, aggressive fluid replacement and supportive therapy are very much important in the first 72 hours of admission. Moreover, there is no consensus on timing of ERCP in patients with severe pancreatitis without cholangitis. But all international guidelines suggested that ERCP should be performed in all patients with mild or severe pancreatitis together with concomitant cholangitis during the first 72 hours. After resolution of ABP, cholecystectomy should be performed to prevent recurrent pancreatitis during the same hospitalization period (index cholecystectomy). If the patient is not suitable for cholecystectomy, ERCP and ES should be done to prevent further attacks of acute pancreatitis.

Keywords: acute biliary pancreatitis, urgent ERCP, early ERCP, endoscopic sphincterotomy, biliary duct stone

1. Introduction

Acute pancreatitis (AP) is the most serious emergent disease in the gastroenterology field. The most common cause of AP is naturally gallstones. The most cases have mild disease and the illness limits itself in a short time period. In 15–20% of cases, the severe form of AP develops. The triage of patients with AP in accordance with the severity of illness is the single most important factor affecting monitoring and treatment protocol of these patients. Acute biliary pancreatitis (ABP) develops due to gall stones and or sludge mostly coming from gall bladder, impacted in ampulla Vateri (AV) leading to increased pancreatic ductal pressure, pancreatic edema, inflammation and possibly necrosis. A lot of human and animal studies displayed that biliary obstruction lasting more than 48 hours creates pancreatic necrosis. Therefore, before the endoscopic retrograde cholangiography (ERCP)

area, surgery was used to induce biliary decompression and impede progression into pancreatic necrosis, however, new quests started after facing high rate of morbidities and mortalities associated with surgery.

Introduction of ERCP and endoscopic sphincterotomy into the daily practice, endoscopic relieving of biliary obstruction has come into reality. Nevertheless, occurrence of complications even mortality in association with ERCP initiated new debate about its indications and timing in patients with ABP. Although for the last 30 years, there has been many ongoing studies about to whom and when ERCP will be performed in ABP, a certain conclusion has not been encountered yet. There has been 2 main strategies on debate [1].

1. Early routine ERCP strategy: If acute gallstone pancreatitis is triggered by duct obstruction caused by a stone, it would be reasonable to suggest that early ERCP with removal of any residual stones might reduce the severity of pancreatitis. The strategy of early ERCP is strongly supported by results from experimental studies and human studies, which show that the duration of biliary obstruction is a major factor in determining the severity of pancreatitis and that decompression of the biliary system can prevent progression of the disease. In addition, patients with severe pancreatitis tended to have stones impacted in the ampulla, and early (within 48 hours) surgical decompression of the obstruction has been shown to decrease mortality rates. These observations lend support to the theory of using early ERCP to remove obstructing stones in acute gallstone pancreatitis.
2. Early conservative management with or without delayed or selective use of ERCP strategy: Proponents of early conservative management with selective use of ERCP argue that early routine ERCP may lead to many unnecessary ERCPs in the majority of patients as the offending gallstone has often passed before the diagnosis of pancreatitis is made. Also, it remains unclear whether early ERCP improves the prognosis of acute gallstone pancreatitis. The severity of the pancreatitis may be determined at its inception and may not be dependent on the duration of duct obstruction. Furthermore, performing ERCP in the setting of acute pancreatitis can be technically difficult because of swollen ampulla and duodenal wall. Thus, it may be prudent to identify patients with persistent duct obstruction who would benefit from ERCP after a period of conservative medical management in order to avoid unnecessary negative ERCPs.

Due to 2 different approaches, how an imminent ERCP will affect the existing clinical situation in patients with ABP holds its uncertainty. There has been also no agreement on the preference of an urgent ERCP (U-ERCP) within 24 hours of patients' admission or an emergent ERCP (E-ERCP) within 48–72 hours [2]. These terms; U-ERCP and E-ERCP have been used in recent reports and the first paper published by Neoptolemos and et al. defined U-ERCP and E-ERCP differently than the other papers; the first one within 72 hours and the later within 35 days after admission [3]. Later on, ERCP within first 72 hours was labeled as U-ERCP [4] and after the year of 2000, U-ERCP has been defined as ERCP within 24 hours and E-ERCP as ERCP within 24–72 hours [2]. In severe ABP, there are some risks such as patient's bad general situation, technical difficulties due to pancreatic edema and potential interruption of aggressive fluid resuscitation during and after the ERCP procedure. Therefore, valid only for patients having persisting indication for biliary decompression, several authors and our clinical experience favor E-ERCP together with immense supportive treatment of these patients rather than U-ERCP in the absence of life threatening cholangitis.

In severe cases with AP, there can be pain, fever, cholestasis, mental confusion and hypotension due to ongoing pancreatic inflammation and necrosis and under this circumstances, an imminent ERCP can make the situation even worse [5]. Although, if we scrutinize the real life data, we will see that there is some kind of pressure on ERCP physicians to perform ERCP at night and or at weekends by the physicians seeing these patients with ABP in the emergency room [6]. However, in severe ABP, it would be impossible to guarantee the co-existence of cholangitis only by looking at some clinical and biochemical parameters, the use of harmless non-invasive methods such as magnetic resonance cholangiography (MRCP) and or endoscopic ultrasonography (EUS) seems to be more reasonable. Hence, endoscopist who will perform ERCP should estimate the clinical situation of patient with ABP correctly and know very well to whom and when ERCP should be done. Thirty four years after the first report by Neoptolemus [3] suggesting wider application of ERCP with ES during AP, Schepers NJ [4] reported a multicentric article (APEC study) which underlined the fact that U-ERCP with ES does not reduce AP associated complications and mortality compared with conservative approaches. These authors supported a conservative strategy in severe ABP with ERCP indicated only in patients with cholangitis or persistent cholestasis.

In this chapter, we will mention about the role of ERCP during ABP in accordance with the clinical studies and meta-analysis published on this subject and we will add our self clinical experience and practice in this area. The order of titles will be as such,

- The pathogenesis and natural history of ABP
- The estimation of cholangitis and cholestasis
- The treatment steps in the first 72 hours in reference to International Guidelines
- To whom and when ERCP should be done during ABP?

2. The pathogenesis and natural history of ABP

In the setting of ABP, biliary stones or sludge material impacted in ampulla Vateri induce transient obstruction in the biliary tree and pancreatic ductus, followed by reflux of bile into the pancreatic channel. Consequently, undraining pancreatic channel develops increased ductal pressure leading to backflow of activated pancreatic enzymes into the parenchyma. This starts a cascade of tissue injury with a spectrum of events starting with mild parenchymal inflammation ending with loss of pancreatic parenchyma due to severe necrosis [7]. For sure, cholestasis and or cholangitis due to biliary obstruction in addition to pancreatic inflammation can add into the clinical scenario. There are several evidences indicating the duration of obstruction correlates with the severity of pathology in the pancreas. These evidences reveal that persisting obstruction after 48 hours leads to different degrees of necrosis and if the ductal decompression is obtained before that time period, disease associated morbidity and mortality decreases significantly [8–16]. Runzi et al. [8] used an animal model of AP by balloon obstructed biliopancreatic ductal system and they relieved the obstruction at 1th, 3rd and 5th days. The authors documented that the severity of parenchymal inflammation, fat necrosis, hemorrhage, acinar cell vacuolisation and necrosis were most prominent in animals with obstructed ductal system at 5th days of the experiment. On contrary, animals

having decompressed ductal system at 1st and 3rd day of experiment, pancreatic injury was able to be avoided. Another report by Acosta et al. [11] investigating the same subject on a clinical study put forth that severe pancreatitis develops significantly more in patients with the obstruction lasting more than 48 hours compared to those having less than 48 hours of obstruction. These authors suggested to wait for 48 hours to implement an ERCP as the impacted stone may fall down spontaneously and if the signs of obstruction persists after 48 hours, then we should think about ERCP. On the grounds that at least half of the cases, the impacted stone in Ampulla Vateri will fall down spontaneously within 24–48 hours after ampullary and duodenal edema diminishes, we know that the pancreatitis in these patients will limit itself and recover within a few days. Acosta et al. [12] investigated the effects of early ductal decompression in a report and they compared 30 patients who underwent ERCP within first 48 hours with 31 patients who got only conservative treatment. Within the first group, 16 had passed the stone into the duodenum during 48 hours and only 14 patients underwent ERCP in whom 11 were shown to have impacted stones. In the second group of patients, 22 patients had got rid of obstruction spontaneously and 9 patients who had persistent signs of obstruction underwent ERCP and only 3 of them had impacted stone. As a result, 78% of patients passed stones spontaneously into the duodenum and E-ERCP was performed on the others within 48 hours without an uneventful clinical course and mortality. Another report by Cavdar et al. [13] indicated that 74% of patients with ABP passed stones into the duodenum within 72 hours of admission.

Based on all this data and our clinical experience about the natural progression of ABP, we suggest conservative approach during the first 24 to 48 hours to limitate the severity of pancreatitis by aggressive fluid resuscitation correction hypovolemia and organ hypoperfusion. This approach also allows us to evaluate the patients with regard to the presence of cholestasis and cholangitis and to find out which patients need ductal decompression.

APACHE II, Ranson, Glasgow veya Atlanta criteria are used to evaluate the severity of AP. Cholangitis and or cholestasis are assessed according to the presence or absence of severe pain, mental confusion, hypotension, jaundice, elevated serum bilirubin ve liver enzymes and absence of bile in the aspirated gastric juice. Acosta and et al. [14] clearly demonstrated that absence of bile in the aspirated gastric juice hyperbilirubinemia and severe pain are the parameters most sensitive and specific for the ongoing obstruction of AV. The authors concluded to apply ERCP to this subgroup of patients. However, these findings may also occur in patients with severe pancreatitis and do not indicate the existence of cholangitis. Thus, ERCP performed based only on these findings may worsen pancreatitis, even end up with death. Therefore, we need better methods to show the stone in the biliary tree. Before the area of MRCP and endoscopic ultrasonography (EUS), we would do diagnostic ERCP and endoscopic sphincterotomy in every patient with a diagnosis of ABP even if we did not detect gall stones in the bile duct. This policy has changed to 'never do diagnostic ERCP in ABP' and do first MRCP or if possible more sensitive EUS to decide if ERCP will be done or not.

3. The estimation of cholangitis and cholestasis

On clinical practice, the presence of cholangitis and or cholestasis in a patient with ABP is estimated by clinical and biochemical parameters together with abdominal ultrasonography (USG) [15–19]. Severe abdominal pain, fever, mental confusion, hypotension and jaundice can be seen in severe acute pancreatitis even in the absence of cholangitis. In 20% of patients, the liver enzymes can be persistently

normal. The sensitivity of abdominal USG is very low around 27–50% in the diagnosis of cholestasis and cholangitis. The bile duct diameter can persist several days after spontaneously passing stones. Thus, we need more sensitive methods to detect cholangitis and or cholestasis. Nearly 20 years ago, ERCP has been widely used for a diagnostic purpose. However, there have been important developments with the administration of MRCP and EUS into the gastroenterology practice [20–29]. EUS is better than MRCP to detect gall stones smaller than 5 mm and after detecting the stone by EUS and as an advantage of this procedure, ERCP can be used to extract the stone from the bile duct at the same session after EUS procedure [21–27]. Moon and his colleagues [28] reported the accuracy rates of USG, computed tomography, MRCP, ERCP and intraductal USG to detect bile duct stones are 20%, 40%, 80%, 90%, 95%, respectively. The authors underlined IDUS and ERCP as the most sensitive methods to detect a CBD stone and suggested to use MRCP to choose the suitable patient for ERCP. They also notified that the rate of agreement between ERCP and MRCP is 90.6% and the large common bile duct has been mentioned as a factor for MRCP to overlook the bile duct stones.

MRCP has a low diagnostic value compared to EUS in a patient with dilated CBD having small sized stones. Scheiman and his colleagues [29] investigated and compared the cost and clinical efficacy of EUS and MRCP done 24 hours before the ERCP procedure. The authors identified EUS as the best cost-effective modality to prevent unnecessary ERCP. Thus, this will protect patients from potential complications of ERCP. Furthermore, 20% of bile duct stones smaller than 8 mm and detected by MRCP were found to pass spontaneously into the duodenum until the time comes for an ERCP procedure. Thus, EUS will reliably help us to give final decision to do ERCP or not. Another advantage of EUS is its applicability on bed side for patients warded in intensive care units. Additionally, in patients with normal gall bladder evaluation on percutaneous USG, EUS can detect sludge in the gall bladder in the setting of ABP. We can also use a quick EUS examination performed within 72 hours of hospitalization to decide if patients can be discharged early from the hospital. This strategy can decrease the health expenses as well. Thus, it seems very rational to increase cost effectivity of caring for ABP patients by provoking the motivation of ERCP physicians to get learn how to do EUS and vice versa [25–27].

4. First 72 hours treatment steps according to the International Guideliness

Severe cases with ABP should be hospitalized in specific centers having MRCP, ERCP and preferably EUS facilities under the control of a team of physicians consisted of gastroenterologist, pancreatobiliary surgeon and invasive radiologist [30–35]. First, the severity of AP in accordance with the international scoring models must be determined and the patient's co-morbidities should be recorded. Thereafter, these patients should be vigorously hydrated to prevent the collapse of pancreatic circulation. Indeed, we will especially emphasize aggressive fluid replacement therapy in these patients in the first 3 days of admission with patients with AP. This issue is also very important for the prophylaxis of post-ERCP pancreatitis [36].

A meticulous fluid replacement within this very 24 hours limits pancreatitis by correcting the hypovolemia and organ hypoperfusion, hinders local and systemic complications of AP by decreasing Systemic Inflammatory Response Syndrome (SIRS) and associated multiorgan failure and lowers inhospital mortality. This helps to improve the general status of the patient and decreases the risks of further invasive procedures like ERCP in these circumstance. During the first 24 hours,

iv crystalloid and or colloid solutions can be given [30–35, 37, 38]. Although a retrospective study depicted no difference between ringer lactate (RL) and normal saline (SF) infusion with regard to the severity and complications of pancreatitis [39], there are vast data from the experimental and clinical studies supporting the benefits of RL; such as RL infusion hampers hyperchloremic acidosis and other metabolic complications of AP and by improving intraparenchymal pH status, RL infusion inhibits zymogen activation and worsening of AP [40, 41]. For these reasons, RL has been suggested by many international guidelines as first choice to be used as fluid therapy in these patients with AP [30–36]. In the absence of heart and kidney failure, RL infusion at 5–10 ml/kg/hour dose within the first 24 hours is recommended to these patients as targeted fluid therapy. By this way, we aim to get normal hemodynamic parameters, urine output 0.5–1 ml/kg/hour and hematocrit value as between 35–44%. However, we need to be scrupulous to avoid hypervolemia in elderly patients during fluid resuscitation. Therefore, it is important to limit the dose to 5 to 10 ml/kg/hour as more than 10 ml/kg/hr. infusion rate has been associated with mechanical ventilation, abdominal compartment syndrome and increased mortality [42].

5. ERCP when and to whom in ABP?

Before 1978 when Classen [43] first did ERCP and endoscopic sphincterotomy in acute pancreatitis, ERCP was considered as contraindicated in AP. Thereafter, this dogma has changed by Safrany and his colleagues [44] who did ERCP in 15 cases with ABP in 1980. They detected impacted stone at AV in 8 patients and in 7 of them, they showed choledochal stone and removed the stones in all the patients. None of the patients developed any complications and discharged within a short period after ERCP procedure. After 1980, case series have been reported in this area and first randomized controlled study about this subject was published by Neoptolemos and his colleagues in 1986 [3]. In 1993, Fan and et al. [45] published a report in which they investigated the effects of early ERCP on progression of AP. The authors showed that early ERCP was useful only in patients with biliary sepsis compared to conservative group if there is an existing biliary pathology both in mild and severe cases of AP. However, early ERCP did not introduce declined morbidity and mortality when all other etiologies of AP had been included in the study cohort.

Nonetheless, many complications associated with ERCP have been reported in the following years and when and to whom ERCP questions became subject to many researches. ERCP and endoscopic sphincterotomy can make the situation worse in a patient with AP since therapeutic ERCP had been reported to have 10% morbidity and 0.1% mortality rates [46, 47]. Additionally in patients with AP, there is potential risk of technical failure in ERCP procedure due to edema in the AV and duodenum itself.

For this reason, both the timing of ERCP and determining the correct patient who needs this procedure carry the utmost importance. In 2013, International Pancreas Union and American Pancreas Union published together ‘the management guidelines of AP’ and the suggestions about biliary system problems were written as follows [31]:

1. “ERCP is not indicated in predicted mild biliary pancreatitis without cholangitis. (GRADE 1A, strong agreement). ERCP is probably not indicated in predicted severe biliary pancreatitis without cholangitis (GRADE 1B, strong

agreement). ERCP is probably indicated in biliary pancreatitis with common bile duct obstruction (GRADE 1C, strong agreement) ERCP is indicated in patients with biliary pancreatitis and cholangitis (GRADE 1B, strong agreement)

2. Urgent ERCP (<24 hrs) is required in patients with acute cholangitis. Currently, there is no evidence regarding the optimal timing of ERCP in patients with biliary pancreatitis without cholangitis. (GRADE 2C, strong agreement)
3. MRCP and EUS may prevent a proportion of ERCPs that would otherwise be performed for suspected common bile duct stones in patients with biliary pancreatitis who do not have cholangitis, without influencing the clinical course. EUS is superior to MRCP in excluding the presence of small (<5 mm) gallstones. MRCP is less invasive, less operator-dependent and probably more widely available than EUS. Therefore, in clinical practice there is no clear superiority for either MRCP or EUS. (GRADE 2C, strong agreement)”

Therefore, we will discuss the subject of biliary tree management in patients with AP as subtitles; 1-Mild pancreatitis in the absence of cholangitis and persistent cholestasis. 2- Severe pancreatitis in the absence of cholangitis and persistent cholestasis 3- Acute pancreatitis together with the presence of cholangitis and persistent cholestasis. We will also discuss; 4- U-ERCP versus E-ERCP and 5-the role of elective ERCP 3 days after patient's admission to prevent recurrence of AP.

5.1 ERCP in patients without cholangitis or persistent cholestasis

The first randomized controlled trial in this field is published by Neoptolemus et al. in 1986 [3]. No relationship was found related to pancreatitis complications and mortality between the conservative treatment group and the ERCP group in mild acute biliary pancreatitis patients in this study and in the meta-analysis which contains 4 randomized controlled studies of Sharma et al. [48]. The patients were stratified by the severity of pancreatitis in the study of Burstow et al. [49] but the patients with or without cholangitis were not analyzed separately and eventually, a strong tendency to decrease pancreatitis complications has been suggested in patients with mild acute biliary pancreatitis, although this is not statistically significant (OR 0.67; 95% CI, 0.43, 1.03; P = 0.06). Another meta-analysis of 5 randomized controlled studies including 702 patients, which compared the conservative treatment and E-ERCP in acute biliary pancreatitis patients by Moriatti et al. [50] showed no effect on pancreatitis complications (1.8% (95% CI -5.6% to 9.3%); p = 0.6). Since there is no mortality in patients with mild pancreatitis, a comparison could not be made in this regard. Petrov et al. [51] did not demonstrate any statistically significant difference between the E-ERCP group and the conservative treatment group in terms of reducing complications of pancreatitis in neither mild nor severe acute pancreatitis in their meta-analysis of 5 randomized controlled studies including 717 patients. A systematic review by Geenen et al. that published in *Pancreatology* in 2013 [52] examined the guidelines and meta-analysis in this field till then, reported that U or E-ERCP±ES had no place in mild acute biliary pancreatitis. As we do in our clinical practice, Elective ERCP (EL-ERCP) might be performed before the cholecystectomy only in case, the stuck stones in AV have escaped back into the choledoc and if this is proved by MRCP or EUS.

As a result, there is consensus that U or E-ERCP±ES is not indicated in mild acute biliary pancreatitis without cholangitis [31, 33–35].

5.2 Emergency ERCP in severe acute biliary patients without cholangitis or persistent cholestasis

ERCP in acute biliary pancreatitis is still a controversial issue, and there is no consensus about it. As mentioned before, clinical and animal studies showed that if the biliary obstruction is not terminated within 48 hours, the pathology progresses to necrosis and then organ failure occurs. Therefore, the first studies demonstrated that U or E-ERCP decreased the mortality and morbidity in severe acute pancreatitis patients compared to the control group [53]. In 1997, Fölsch et al. [54] reported that especially deaths due to respiratory failure were more common in the E-ERCP group than the control group in their randomized controlled trial about the role of E-ERCP in acute biliary pancreatitis. The APEC study [4] that includes 232 patients from 26 centers published in July 2020 compared U-ERCP and conservative treatment, and this study changed the paradigm. Besides, acute biliary pancreatitis patients with cholangitis excluded from the APEC study and no significant difference demonstrated between two groups in regard of local or systemic complications of pancreatitis. Whereas, the cholangitis and recurrent attacks of pancreatitis were more common in the U-ERCP group than the conservative treatment group. This is because the criteria for persistent cholestasis or cholangitis were fever, serum bilirubin levels greater than 2.3 mg / dl, common bile duct width greater than 8 millimeters in patients younger than 75 years and 1 centimeter in patients older than 75 years, and the presence of stones in common bile duct in this study. Another cause of these findings were that it was unclear whether MRCP or EUS, which are the most sensitive methods in detecting stones in choledoc, were performed or not.

Some conflicting results were obtained in the meta-analysis of randomized controlled trials about the role of emergency ERCP in acute biliary pancreatitis, according to the including and excluding criteria of the involved randomized controlled trials and whether subgroup analysis is done or not. Petrov et al. [55] published a meta-analysis in 2008 including 7 randomized controlled trials with 450 patients about the effects of E-ERCP on acute biliary pancreatitis without cholangitis, and they indicated that emergency ERCP has no effect on local complications of pancreatitis in neither mild nor severe pancreatitis. Van Santvoort et al. [56] compared E-ERCP with conservative treatment in patients with and without cholangitis in their randomized controlled trial and demonstrated that in patients without cholestasis, ERCP (29/75 patients: 39%) was not associated with reduced complications (45% vs. 41%, $P = 0.814$, multivariate adjusted OR: 1.36; 95% CI: 0.49–3.76; $P = 0.554$) or mortality (14% vs. 17%, $P = 0.754$, multivariate adjusted OR: 0.78; 95% CI: 0.19–3.12, $P = 0.734$).

A meta-analysis by Tse et al. [1] which contains 5 randomized controlled studies, indicated that unweighted pooled mortality rates for participants were 9.6% in the early routine ERCP strategy and 4.9% in the early conservative management strategy in patients without cholangitis. Three years after this meta-analysis, Burstow et al. [49] analyzed 11 RCTs consisting of 1314 patients (conservative management = 662, ERCP = 652). There was a near significant decrease in mortality for the ERCP group compared with conservatively managed patients with severe pancreatitis [odds ratio (OR) 0.45; 95% confidence interval (CI), 0.19, 1.09; $P = 0.08$]. In patients with mild pancreatitis, mortality results were comparable for both groups (OR 0.66; 95% CI, 0.02, 28.75; $P = 0.83$). Overall complications were

significantly reduced in the ERCP group in severe pancreatitis patients (OR 0.32; 95% CI, 0.17, 0.61; $P = 0.00$). The authors' comments about this meta-analysis are as follows: this meta-analysis demonstrates a significant decrease in complications in patients with severe ABP managed with early ERCP/ES compared with conservative management. As far as the mortality is concerned, no significant decrease was observed in mortality even in severe ABP patients treated with early ERCP/ES.

The meta-analysis and systematic review about the comparison of E-ERCP and conservative treatment in acute biliary pancreatitis by Coutinho et al. [57] reported that; the pain and fever resolved in a shorter time, the hospitalization time was shorter with reduced complications and hospital costs were lower in the E-ERCP group than the conservative treatment group. Uy et al. [58] performed a meta-analysis including 2 randomized controlled trials that compares the E-ERCP ($n = 177$) and the conservative treatment ($n = 163$) in acute biliary pancreatitis. This meta-analysis revealed low mortality rates for both mild and severe pancreatitis in the ERCP group (RR = 1.92, 95% CI: 0.86–4.32) whereas the morbidity rates were similar in both groups (RR = 0.95, 95% CI: 0.74–1.22). Moretti et al. [50] demonstrated that ERCP had no effect on complications in mild pancreatitis however, ERCP reduced the complications in severe pancreatitis but it did not have any effect on mortality rates in their meta-analysis including 5 prospective randomized trials with 702 patients. Geenen et al. [52] performed a review including 12 international guidelines and 8 meta-analysis. Although 3 meta-analysis and 1 guideline recommended against ERCP in acute biliary pancreatitis, 7 out of 11 guidelines recommended routine E-ERCP in severe acute biliary pancreatitis regardless of the presence of cholangitis, and they agreed on the lack of consensus about routine E-ERCP in severe acute biliary pancreatitis. However, the 4 main international guidelines that we evaluated (2 out of them belonged the same group but published at different times) recommended against the emergency ERCP in acute biliary pancreatitis without cholangitis because it did not significantly reduce mortality and morbidity compared to the conservative treatment group [31, 33–35]. Contrary to these guidelines, another guideline of the United Kingdom published in 2005 [32] has controversial suggestions about E-ERCP in severe acute biliary pancreatitis without cholangitis as; *“Urgent therapeutic endoscopic retrograde cholangiopancreatography (ERCP) should be performed in patients with acute pancreatitis of suspected or proven gall stone etiology who satisfy the criteria for predicted or actual severe pancreatitis, or when there is cholangitis, jaundice, or a dilated common bile duct.”*

Because of the lack of statically significant data about the reduction in local and systemic complications or mortality rates of pancreatitis by emergency ERCP in severe acute biliary pancreatitis from many RCTs and meta-analyses until to date, international guidelines referring to these results indicated that U- or E-ERCP have no benefit in every patient with severe acute biliary pancreatitis unless cholangitis is present. The ESGE guideline published in 2018 [33] explains why ERCP should not be performed in a patient with severe pancreatitis without cholangitis: *“A possible explanation why urgent ERCP with sphincterotomy within 24 h did not show an advantage over conservative treatment could be that the opportunity to positively influence the disease course had already passed at the time of the ERCP despite the fact that it was performed early. Animal models have shown that trypsinogen activation within the pancreas occurs within 10 min after chemically inducing pancreatitis. It is well known that most bile duct stones in patients with gallstone pancreatitis cause only temporary obstruction and pass spontaneously into the duodenum. This temporary obstruction already initiates pancreatitis and data from animal models show that this includes intrapancreatic trypsin activation, rupturing of vacuoles releasing active trypsin, and pancreatic autodigestion. In the current trial, urgent ERCP was done after a median*

29 h after onset of symptoms and common bile duct stones were found in 43% of patients. Even this narrow time window might already be too long to prevent pancreatitis from deteriorating by performing an urgent ERCP with sphincterotomy”.

5.3 Emergency ERCP in acute biliary patients with cholangitis or persistent cholestasis

Certainly, biliopancreatic obstruction should be resolved immediately in patients with cholangitis or persistent cholestasis. The most effective method of this is undoubtedly the removal of stone or sludge that caused the obstruction by performing ERCP and ES [59]. The first study in this area was performed by Neoptolemos et al. and it demonstrated that E-ERCP and ES was the most useful method in acute biliary pancreatitis with cholangitis and cholangitis without pancreatitis [60]. Van Santvoort et al. [56] performed a study about the efficiency of ERCP in acute pancreatitis patient with or without cholestasis and findings as follows: In patients with cholestasis, ERCP (52/78 patients: 67%), as compared with conservative treatment, was associated with fewer complications (25% vs. 54%, $P = 0.020$, multivariate adjusted odds ratio [OR]: 0.35, 95% confidence interval [CI]: 0.13–0.99, $P = 0.049$). This included fewer patients with >30% pancreatic necrosis (8% vs. 31%, $P = 0.010$). Mortality was nonsignificantly lower after ERCP (6% vs. 15%, $P = 0.213$, multivariate adjusted OR: 0.44, 95% CI: 0.08–2.28, $P = 0.330$).

Tse et al. [1] performed a meta-analysis which included 5 randomized controlled trials with 644 participants with cholangitis and reported mortality rates, comprising a total of 200 participants in the early routine ERCP strategy and 215 in the early conservative management strategy. Unweighted pooled mortality rates for participants were 1.0% for the early routine ERCP strategy and 6.9% in the early conservative management strategy. In the trials that included participants with cholangitis, the early routine ERCP strategy significantly reduced mortality compared to the early conservative management strategy (RR 0.20, 95% CI 0.06 to 0.68; $P = 0.010$).

5.4 U-ERCP or E-ERCP in acute biliary pancreatitis with cholangitis or persistent cholestasis?

There is no consensus on timing of ERCP in the literature. In most publications, the ERCP performed within 72 hours after the symptom onset is called emergency ERCP, but the emergency ERCP timing could be defined as within 48 hours in some other publications. Additionally, the ERCP which is performed within 72 hours named as U-ERCP in some publications. The only trial that compares the timing of ERCP (within 24 hours versus within 24–72 hours) in acute biliary pancreatitis is performed by Lee et al. [2]. Patients with acute biliary pancreatitis but without cholangitis was excluded retrospectively in this study, and they compared U-ERCP and E-ERCP in acute biliary pancreatitis. No significant difference was found in the total length of hospitalization or procedural-related complications, in patients with biliary pancreatitis and a bile duct obstruction without cholangitis, according to the timing of ERCP (< 24 h vs. 24–72 h). Although the definition is not U-ERCP, in one of Fan et al.'s studies [45] the ERCP which is performed within 24 hours is defined as E-ERCP and there was no significant difference between the ERCP group and the conservative treatment group in terms of local and systemic complications of pancreatitis whereas hospitalization time was a little shorter in the E-ERCP group. With these results, it was demonstrated that performing U-ERCP within 24 hours did not change the pancreatitis course, supporting the study of Lee et al. [2]. When considering the course of acute biliary pancreatitis, naming the ERCP performed within 24 hours as “URGENT” and the ERCP within 24–72 hours as “EARLY” by

Lee et al. is the most appropriate definition [2]. When the literature and international guidelines are reviewed, ERCP is recommended to the acute biliary pancreatitis within 24 hours if the cholangitis is present and within 72 hours if the biliary obstruction is present, instead of this definition.

Although the naming does not resemble, recommendation of ESGE in this respect is as follows: *“ESGE recommends urgent (≤ 24 hours) ERCP and biliary drainage in patients with acute biliary pancreatitis combined with cholangitis. Strong recommendation, high quality of evidence. ERCP should be performed within 72 hours in patients with ongoing biliary obstruction. Weak recommendation, moderate quality evidence. It should not be performed in patients with acute biliary pancreatitis and neither cholangitis or ongoing bile duct obstruction. Weak recommendation, moderate quality evidence”* [33]. According to our clinical experience; although there is a need for randomized prospective trials on this subject, the absence of difference between performing the ERCP within 24 hours or within 24–72 hours leads to escape gastroenterologist or endoscopists from the regression of performing ERCP within 24 hours in a rush and off-duty, which is believed to be the reason of high rates of complications such as aggravation of pancreatitis, possible biliportal reflux in patients with cholangitis during ERCP, bacteriemia or systemic complications (i.e., organ failure) by depriving the patient’s opportunity to receive extensive fluid therapy and broad-spectrum antibiotics within the most important 24 hours for the complications.

5.5 Elective ERCP to prevent pancreatitis recurrence

Early laparoscopic or open cholecystectomy as soon as AP recovers completely is the only proven treatment modality to prevent recurrence of ABP. Index cholecystectomy is defined as cholecystectomy applied during the same hospitalization period of ABP and interval cholecystectomy is cholecystectomy performed 6 weeks after patient’s recovery from AP [61].

Sinha and colleagues [61] reported that index cholecystectomy in a case suitable for surgery has similar results with elective cholecystectomy in a patient without AP and they also reported significant difficulty to do dissection during interval cholecystectomy. In 2019, Fu-ping Zhung and colleagues [62] published a meta-analysis of 19 studies enrolling 2639 who underwent index or interval cholecystectomy. They noted that there was no differences with regard to intraoperative and postoperative complications, duration of operation and the rates of open cholecystectomy. However, index cholecystectomy cases had lesser hospitalization period, lower biliary complications due to surgery and lesser rates of ERCP.

In cases with severe pancreatitis, most of the time it is impracticable to perform index cholecystectomy. Therefore, interval cholecystectomy is obligatory in these cases. Unfortunately, these patients reamit with AP attacks and ot biliary complications during this 6 weeks period. Thus some authors offer ERCP and endoscopic sphincterotomy to prevent AP recurrences and or biliary complications to occur during this time period [63, 64].

In a retrospective study comparing index cholecystectomy and post ERCP/ES plus interval cholecystectomy, both group of patients did not reveal mortality. Only 2 patients (%5) developed AP recurrences and acute cholecystitis and hospitalized. The authors suggested that ERCP/ES is highly successful to prevent recurrences in patients with severe ABP who can not undergo index cholecystectomy. ES and interval cholecystectomy in severe ABP is considered a reasonable alternative to an index cholecystectomy in patients with severe ABP [64].

Another report by Dedemadi and his colleagues [65] published in 2016 noted that ERCP and ES in cases with AP who can not undergo cholecystectomy

developed biliary events 0%–28.6%, recurrent pancreatitis 0%–8.2%, mortality 3%–4.7%. Other cases under conservative treatment had biliary events 9.4%–14.3%, recurrent pancreatitis 12%–23%, mortality 3.9%. Statistical evaluation showed that ERCP and ES group had significantly less biliary complications and less recurrent pancreatitis with no difference in mortality compared to conservative treatment group. The conservative group consisted of patients who were elderly persons with multiple comorbidities and complications of AP. These conditions may be responsible for similar mortality rates in both groups. Nevertheless, because of high rates of biliary events and pancreatitis in the ERCP/ES group, this approach should be reserved only for patients not suitable for cholecystectomy.

The advice of IAP/APA about timing of cholecystectomy in a case with ABP is as follows [31]:

5.5.1 “Timing of cholecystectomy (or endoscopic sphincterotomy)”

1. *Cholecystectomy during index admission for mild biliary pancreatitis appears safe and is recommended. Interval cholecystectomy after mild biliary pancreatitis is associated with a substantial risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis. (GRADE 1C, strong agreement).*
2. *Cholecystectomy should be delayed in patients with peripancreatic collections until the collections either resolve or if they persist beyond 6 weeks, at which time cholecystectomy can be performed safely. (GRADE 2C, strong agreement).*
3. *In patients with biliary pancreatitis who have undergone sphincterotomy and are fit for surgery, cholecystectomy is advised, because ERCP and sphincterotomy prevent recurrence of biliary pancreatitis but not gallstone related gallbladder disease, i.e. biliary colic and cholecystitis. (GRADE 2B, strong agreement).”*

Moreover, If we consider surgery for pancreatic cystic collections, pseudocyst and or walled off necrosis, it should be performed at the same time with cholecystectomy [65].

6. Conclusion

We want to finish with the conclusive statement made by ESGE [35]; “*In conclusion, urgent ERCP with sphincterotomy did not reduce the composite endpoint of major complications or mortality in patients with predicted severe gallstone pancreatitis, compared with conservative treatment. These findings support a conservative strategy with an ERCP indicated only in patients with cholangitis or persistent cholestasis. With this conservative strategy, about two-thirds of patients did not need to undergo ERCP*”. In the presence of cholangitis, ERCP as E-ERCP should be done only after hemodynamic stabilisation and relieved organ hypoperfusion with aggressive fluid replacement and antibiotic treatment within the first 24 hours, Elective ERCP to prevent ABP attacks is suggested only for patients unsuitable for a cholecystectomy procedure.

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