Optimal Timing and Outcomes of Minimally Invasive Approach in Acute Biliary Pancreatitis

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Background: We analyzed the outcomes of early biliary decompression by a minimally invasive approach in acute biliary pancreatitis (ABP).

Material/Method: A retrospective study was conducted on 143 patients with ABP who underwent biliary decompression by laparoscopic or endoscopic approach between January 2015 and March 2022. Data from the observation sheets and surgical protocols were analyzed in terms of demographic characteristics, clinical and paraclinical features at admission, comorbidities, therapeutic management, and outcomes.

Results: The mean patient age was 62.3±11.4 years. Mild ABP had a higher frequency in men (75.5%) and urban areas (70.4%). The comorbidities associated with a higher risk of severe forms were diabetes mellitus (odds ratio [OR]: 11.250), chronic bronchopneumopathy (OR: 29.297), and ischemic coronary disease (OR: 2.784). The mean hospital stay was 7.6±3.8 days and was significantly higher in severe forms (10±2.4 days, $P<0.001$). The time from onset to presentation was significantly higher in severe vs mild forms (5.6 vs 1.8 days, $P<0.001$) and was associated with systemic and local complications. Creatinine over 2 mg/dL (OR: 4.821) and leukocytes >15 000/mmc at admission (OR: 3.533) were risk factors for systemic complications, while obesity was associated with increased local complications (OR: 5.179). None of the patients with an early presentation developed severe ABP.

Conclusions: Early biliary decompression, as soon as possible after onset, either by an endoscopic or minimally invasive approach, is a safe and effective procedure in ABP. The type of procedure and optimal timing should be individualized, according to the patient's local and general features.

Keywords: **Biliary Tract Surgical Procedures • Laparoscopy • Pancreatitis**

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Background

Acute pancreatitis is an inflammatory condition of the pancreas and is one of the most common causes of gastrointestinal hospitalization worldwide [1,2]. Although in most cases the disease is mild and self-limited, approximately 20% of patients develop life-threatening complications, leading to multiple organ failure and death. A recent multicentric study by Matta et al [1] showed that the causes of acute pancreatitis are most frequently related to biliary obstruction (42%), followed by alcohol abuse (25%). Less common causes are related to disturbances in lipid metabolism, trauma, and toxicity or are idiopathic.

The current guideline for the diagnosis of acute pancreatitis is the revised Atlanta classification, with diagnosis requiring at least the first 2 out of 3 of the following findings: (1) characteristic upper abdominal pain, (2) elevated levels of serum amylases of more than 3 times above the normal value, and (3) features on ultrasound or computed tomography (CT) examination suggesting acute pancreatitis [3,4].

According to the revised Atlanta classification, the severity of the disease is based on the presence and persistence of organ insufficiency or the onset of pancreatic and peripancreatic collections. The patients are categorized as having mild acute pancreatitis if no organ failure was present at admission; moderate-severe pancreatitis if transient organ dysfunction was present initially but resolved within <48 h or a sterile peripancreatic collection is documented; and severe acute pancreatitis if it is associated with persistent single or multiple organ failure or an infected pancreatic collection [4].

The revised Atlanta classification discriminates the evolution of acute pancreatitis, with an early phase (during the first week from the onset of symptoms) characterized by local pancreatic and peripancreatic inflammation with systemic involvement, in which the diagnosis and monitoring should be based on biochemical and laboratory data more than on imaging data [3]. The late phase is characterized by organic changes at the level of the pancreas that can be documented on CT and magnetic resonance imaging examinations.

Acute biliary pancreatitis occurs most frequently as a result of increased pressure in the main and intracanalicular bile ducts, resulting in the reflux of enzymes from the Wirsung canal. This hypertension occurs through the following mechanisms of production: papillary obstruction due to the inclusion of a stone or papillary edema caused by lesions provoked by the passage of a stone through the papilla, a pathogenic mechanism that occurs in biliary pancreatitis, and reflux of duodenal contents due to the relaxation of the Oddi sphincter or bile reflux through a spasm of the Oddi sphincter in the pancreatic canalicular system, a mechanism found in alcoholic pancreatitis.

The evolution toward severe acute pancreatitis is the result of maintaining hypertension in the main and intracanalicular bile ducts and is influenced by the duration of its persistence. Early decompression of the bile-pancreatic tree is necessary to prevent progression to severe acute pancreatitis.

Norman et al introduced the term "therapeutic window" in the treatment of acute pancreatitis to indicate the first 7 days after the onset of the disease [5,6]. Their study focused on cytokines and their role in the pathogenesis of acute pancreatitis, knowing that cytokines are responsible for the systemic complications of acute pancreatitis, up to multisystem organ failure, as evidenced by experimental animal studies [5,6].

The proposed drug therapy of Normal et al includes [6-8] rapid ductal decompression performed by oddian spasmolysis by contact papillary anesthesia (xylin 1%) and general lysis of the oddian spasm (coronary dilator-nitroglycerin patch), blockage of secretion by digestive emptying (gastric tube), and pharmacological therapy through specific antisecretory (Sandostatin) and general (atropine and gastric antisecretory) analgesics (and sometimes epidural analgesia in patients with severe pancreatitis). Antibiotic therapy, by administration of Meronem, has been given to all patients with severe pancreatitis at a dose of 3 g/day for at least 10 days [6,7,9]. A central venous catheter was placed routinely for hydro-electrolytic rebalancing through the administration of crystalloid and colloidal solutions and the administration of parenteral feeding [9,10].

In our department, we applied a new concept regarding the therapeutic window in acute pancreatitis, namely the introduction of minimally invasive surgical therapy in the first 7 days after the onset of pancreatitis, in addition to drug therapy.

The primary objective of the minimally invasive pathogenic therapeutic approach in acute biliary pancreatitis is to interrupt the pathogenic chain through early biliopancreatic decompression through a laparoscopic approach in order to improve the evolution of acute pancreatitis. It also aims to resolve symptoms of pain, dyspeptic syndrome, vomiting, and dynamic ileus and prevent local and systemic complications.

In this study, we analyzed the outcomes of early biliary decompression by a minimally invasive approach in acute biliary pancreatitis in terms of postoperative morbidity and mortality. The preoperative data that correlated best with the surgical decision and postoperative outcomes were analyzed by binary logistic regression.

Material and Methods

Study Design

We conducted a retrospective study on a group of 143 patients who were admitted in an emergency setting with acute biliary pancreatitis between January 2015 and March 2022 to the Surgical Department of Sibiu County Clinical Emergency Hospital, Romania. The data from the observation sheets and the surgical protocols were analyzed in terms of demographic characteristics, time from onset to presentation, clinical and paraclinical data, comorbidities, therapeutic management, and outcomes.

The diagnosis of acute pancreatitis at admission was performed according to the revised Atlanta classification. The biliary etiology was documented based on imagistic findings.

The inclusion criteria were early phase acute pancreatitis, within a maximum of 7 days from the onset of symptoms to admission to the hospital, as defined by the revised Atlanta classification; proven biliary origin by imagistic examinations (CT and/or abdominal ultrasound); and biliary decompression procedure, by laparoscopic or endoscopic approach performed during hospitalization.

The exclusion criteria were the onset of pancreatitis of more than 7 to 10 days, pancreatic abscess, pancreatic pseudocyst, acute pancreatitis of other etiology than biliary, and patients that did not undergo surgery, either because of a personal decision or severe general condition.

The severity of acute pancreatitis was evaluated according to the revised Atlanta classification [3].

Data Comparison and Statistical Analysis

Three categories of patients were defined in the study: those with mild ABP, moderate-severe ABP, and severe ABP, according to the revised Atlanta classification. Descriptive statistics were reported as percentages or means. The nonparametric Kruskal-Wallis test was used to compare the distributions of scale variables (continuous or discrete). Fisher's exact test was used for contingency tables. The odds ratio (OR) was estimated with a binary logistic regression model. A P value less than 0.05 was considered statistically significant. Data analysis was performed with SPSS version 22 (IBM Corp, Armonk, NY, USA).

Results

Of the total 143 patients, 53 patients had mild ABP, 24 patients presented with moderate-severe ABP, and 57 presented with severe ABP (**Table 1**).

The mean age of the patients included in the study was of 62.3±11.4 years. The statistical analysis showed a trend of increasing age with the severity of ABP. However, the differences between the 3 categories were not statistically significant (P=0.175).

There was a slight male predominance (59.7%) in the total study population. The sex distribution according to the severity of the forms of ABP showed significant differences between male and female patients. Mild ABP had a higher frequency in men (75.5% vs 25.5%), while most women that presented with ABP had a severe form of ABP (30 of 54 patients, 55.5%).

The severe forms of ABP were most frequent in patients from rural areas (47 of 90 patients, 52.2%), while patients from urban areas presented most often with mild ABP (31 patients, 70.4%). The difference was statistically significant (P<0.001) and could be explained by a delayed presentation of the patients from the rural area, and possibly by associated neglected comorbidities.

The distribution of the number of comorbidities per patient was different across categories of severity of ABP (P<0.001 for Kruskal-Wallis Test). While the statistical analysis of pairwise comparison did not find a significant difference between the mild and moderate-severe groups, the difference between the mild and severe groups had an adjusted significance of P<0.001.

The univariate logistic regression analysis showed that the comorbidities associated with an increased risk of developing a severe form of ABP in the study group were diabetes mellitus (OR: 11.250; CI: 3.950-32.039), chronic bronchopneumopathy (OR: 29.297; CI: 6.547-131.109), and ischemic coronary disease (OR: 2.784; CI: 1.373-5.646).

The time from onset of symptoms from admission was significantly different among the 3 groups of ABP (P<0.001). A delayed presentation was associated with severe disease. Patients with mild ABP were characterized by early presentation (1.8±1.1 days from the onset), which allowed early therapeutic intervention for biliary decompression.

The paraclinical evaluation showed that there were statistically significant differences in the mean values for amylases, transaminases, leukocytes, neutrophil-to-lymphocyte ratio, and creatinine among the 3 groups of ABP, with a trend of increasing values from the mild to severe forms. However, these clear differences could also be explained by the delayed presentation in severe forms, in which, in the absence of appropriate therapy, the pathologic conditions in and around the pancreas could have progressed to systemic inflammatory response syndrome. Leukocytes >15 000/mmc and creatinine >2 mg/dL were significantly associated with moderate-severe and severe forms of ABP (P<0.001).

Table 1. General data of patients included in the study.

Parameter	Mild ABP (n=53)	Medium-severe ABP (n=24)	Severe ABP (n=57)	Total (n=143)	P value
Age (mean±SD, years)	60.2±13.2	61.7±8.2	64.6±10.4	62.3±11.4	0.175*
Sex (female;	13 (24.5%)	11 (45.8%)	30 (52.6%)	54 (40.3%)	0.008**
male)	40 (75.5%)	13 (54.2%)	27 (47.4%)	80 (59.7%)	
% Urban	31 (58.5%)	3 (12.5%)	10 (17.5%)	44 (32.8%)	<0.001**
% Rural	22 (41.5%)	21 (87.5%)	47 (82.5%)	90 (67.2%)	
No. comorbidities	0.9±0.8	1.6±1	2.4±1.3	1.69±1.3	<0.001*
Comorbidities (no. patients, %)					
• Diabetes	0	5 (20.8%)	25 (43.9%)	30 (22.4%)	<0.001**
• Obesity	0	0	20 (35.1%)	20 (14.9%)	<0.001**
• Chronic broncho pneumopathy	0	2 (8.3%)	25 (43.9%)	27 (20.1%)	<0.001**
• Arterial hypertension	27 (50.9%)	19 (62.5%)	23 (40.4%)	65 (48.5%)	0.191**
• Ischemic coronary disease	19 (35.8%)	9 (37.5%)	35 (61.4%)	63 (47%)	0.02**
Time from onset to hospitalization (days)	1.8±1.1	2.6±0.4	5.6±1.1	3.5±2	<0.001*
Amylase (mean±SD, UI/L)	232.40±43.9	404.8±52.3	2067.8±777.9	1044±1020	<0.001*
Bilirubin (mean±SD, mg/dL)	2±0.7	3.4±0.5	15.1±5	7.8±7.1	<0.001*
ALT (mean±SD, UI/L)	75.4±18.4	275.5±41.6	681±110.8	368.9±288.5	<0.001*
AST (mean±SD, UI/L)	88.7±21.2	323±50.2	646.4±138.6	367.9±270.8	<0.001*
Leukocytes (mean±SD, nr/mmc)	12706±941.3	15422.5±779	22370.7±3947.7	17312.7±5200.4	<0.001*
Leukocytes >15 000/mmc	0	18 (75%)	57 (100%)	75 (52.4%)	<0.001**
NLR (mean±SD)	8.6±2.4	11.6±1.9	19.8±2.8	13.9±5.7	<0.001*
Creatinine (mean±SD)	0.7±0.5	3.3±1	7.6±1.6	4.1±3.3	<0.001*
Creatinine >2 (no. of patients,%)	0	20 (83.3%)	56 (98.2%)	76 (53.1%)	<0.001**
Balthasar CT score at admission:					<0.001**
A	18 (34%)	0	0	18 (13.4%)	
B	33 (62%)	2 (8%)	0	35 (26.1%)	
C	2 (4%)	21 (88%)	1 (2%)	24 (17.9%)	
D	0	1 (4%)	50 (87.5%)	51 (38.1%)	
E	0	0	6 (10.5%)	6 (4.5%)	

* Kruskal-Wallis Test; ** Fisher exact test. ABP – acute biliary pancreatitis; ALT – alanine aminotransferase; AST – aspartate aminotransferase; CT – computed tomography; NLR – neutrophil-to-lymphocyte ratio; SD – standard deviation.

The therapeutic protocol in our department recommends early biliary decompression in all cases of acute pancreatitis in which a biliary origin is suspected. At admission, all patients underwent medical therapy, according to the following protocol: rapid canal decompression performed by oddian spasmolysis by papillary contact anesthesia (xylin 1% administered orally, 2 ampoules every 6 h) and lysis of oddian spasm in general (coronary dilator-nitroglycerin patch, 1 patch every 3 days); blockade of secretion by gastric emptying (gastric tube) and pharmacology by specific antisecretory Sandostatin (3 ampules/day subcutaneously), general antisecretory atropine (1 ampoule/day subcutaneously), and gastric antisecretory medications (Controloc/pantoprazole 2 ampoules/day i.v.). Analgesia was performed by administration of pethidine hydrochloride, with 2 mL diluted every 4 h, Dynastat 3 ampoules/day, and in selected cases,

epidural analgesia in patients with severe pancreatitis with xyline on the injection pump, 5 ampoules of 1% diluted in 50 mL saline, with administration of 4 to 6 mL/h, with external local refrigeration. Antibiotic therapy included the administration of Meronem at a dose of 3 g/day for at least 10 days. Hydroelectrolytic rebalancing was done via a central venous catheter with crystalloid and colloidal solutions, up to 4000 mL of liquids, according to patients' cardiovascular comorbidities, and parenteral nutrition (Kabiven buffered with 8 U insulin, depending on glycemia, administered in 72 h). For the patients admitted during the Covid-19 pandemic, RT-PCR testing at admission and strict adherence to Covid-19 prevention measures were respected, including wearing full protective personal equipment, admission of the patients following special design circuits, and isolation until the results were obtained [11].

Table 2. Types of surgeries and outcomes in the study groups.

Parameter	Mild ABP (n=53)	Medium-severe ABP (n=24)	Severe ABP (n=57)	Total (n=143)	P value
Type of surgery:					<0.001**
• ERCP+LC at 24-48 h	41 (77.4%)	0	0	41 (30.6%)	
• LC	12 (22.6%)	24 (100.0%)	0	36 (26.9%)	
• Laparoscopic biliary drainage (cholecystostomy) +LC at 5-7 days	0	0	57 (100.0%)	57 (42.5%)	
Systemic complications (no.; %)	3 (5.7%)	4 (16.7%)	17 (29.8%)	24 (12.5%)	0.002**
Distribution of systemic complications:					0.089
• Digestive superior hemorrhage (mild)	1 (1.9%)	1 (4.2%)	2 (3.5%)	4 (2.7%)	
• Malign arterial hypertension	0	1 (4.2%)	0	2 (1.4%)	
• Acute coronary event	1 (1.9%)	0	1 (1.8%)	2 (1.4%)	
• MSOF	0	0	1 (1.8%)	1 (0.7%)	
• Pleurisy/pulmonary infiltrates	0	1 (4.2%)	10 (17.5%)	11 (7.6%)	
• Pulmonary embolism	1 (1.9%)	0	1 (1.8%)	2 (1.4%)	
• Respiratory failure	0	1 (4.2%)	0	1 (0.7%)	
• Sepsis	0	0	1 (1.8%)	1 (0.7%)	
Local complications (no.;%)	3 (5.7%)	4 (16.6%)	11 (19.3%)	18 (15.7%)	0.021**
Distribution of local complications:					0.103**
• Intrabdominal abscess	0	1 (4.2%)	1 (1.8%)	2 (1.4%)	
• Pancreatic abscess	0	0	3 (5.2%)	3 (2.1%)	
• Bile leak	1 (1.9%)	1 (4.2%)	2 (3.5%)	5 (3.4%)	
• Hemorrhage	1 (1.9%)	1 (4.2%)	3 (5.2%)	5 (3.4%)	
• Pancreatic pseudocyst	0	1 (4.2%)	2 (3.5%)	3 (2.1%)	
• Seroma	1 (1.9%)	0	0	1 (0.7%)	
HAIs (no., %):	1 (1.9%)	2 (8.3%)	9 (15.7%)	13 (9.7%)	0.095**
• Clostridium	0	0	5 (8.8%)	5 (3.7%)	
• Urinary infections	0	1 (4.2%)	2 (3.5%)	3 (2.2%)	
• Pneumonia	0	0	1 (1.8%)	1 (0.7%)	
• SSI	1 (1.9%)	1 (4.2%)	1 (1.8%)	3 (2.2%)	
• Thrombophlebitis	0	0	1 (1.7%)	1 (0.7%	
Deaths (no., %):	0	1 (4.2%)	3 (5.3%)	4 (3%)	0.235
Causes of deaths:					
• MSOF	0	0	1 (1.8%)	1 (0.7%)	NS
• Respiratory failure	0	1 (4.1%)	0	1 (0.7%)	NS
• Pulmonary embolism	0	0	1 (1.8%)	1 (0.7%)	NS
• Sepsis, pleurisy	0	0	1 (1.8%)	1 (0.7%)	NS
Mean hospital stay±SD (days)	5.1±4.1	7.4±1.8	10±2.4	7.6±3.8	<0.001**

* Kruskal-Wallis test; ** Fisher exact test. ERCP – endoscopic retrograde cholangiopancreatography; HAI – hospital-acquired infection; LC – laparoscopic cholecystectomy; MSOF – multisystem organ failure; SSI – surgical site infection.

In mild cases of ABP with an early presentation, less than 48 h from the onset, endoscopic retrograde cholangiopancreatography (ERCP) was performed in the emergency setting, followed the next day by laparoscopic cholecystectomy. When ERCP service was not available, laparoscopic cholecystectomy with exploration and drainage of the main bile duct was performed as soon as possible after admission.

In moderate-severe and severe cases, the laparoscopic approach was preferred for biliary decompression. If dissection of the Calot triangle could be performed safely, laparoscopic cholecystectomy and drainage of the main bile duct were performed. In patients with severe local inflammatory changes, a laparoscopic cholecystostomy was placed initially, followed by laparoscopic cholecystectomy after an interval of 5 to 7 days. The early surgical-laparoscopic treatment performed in the surgical therapeutic window had exploratory, pathogenic, and radical indications. Laparoscopy allowed an exploration of the peritoneal cavity, with the staging of pancreatitis, sampling of pancreatic ascites, evaluation of cytosteatonecrosis,

and continuous capsular analgesia, by administration of contact anesthetics (xyline, lidocaine).

The technical procedure consisted of the celioscopic approach of the upper abdominal region by inserting the trocars after performing the pneumoperitoneum, with the first trocar, the optical one, being inserted in the supraumbilical area, and the following trocars being introduced under optical control.

Peritoneal cavity exploration was performed, with the confirmation of the diagnosis of acute pancreatitis and the establishment of the intra-abdominal lesion balance. Biliary decompression was performed by cholecystostomy and transcystic or Kehr drainage. To allow the approach and exploration of the whole pancreas, the alternative insertion of the working channel telescope could be performed in all three 15-mm trocars (supraumbilical, epigastric, and on the right flank), facilitating the direct access to the necrotic corporeo-caudal areas.

The types of surgical interventions and the outcomes in the study groups are presented in **Table 2**.

Complications were classified as local (pancreatic abscess, pseudocyst, biliary leak, hemorrhage, and sepsis requiring surgical or endoscopic intervention), systemic (renal failure, respiratory failure, shock, coagulopathy, pulmonary embolism, and acute cardiac events), and hospital-acquired infections.

Local postoperative complications were present in 18 patients (15.7%). Most of the complications were managed conservatively, requiring no further intervention. Pancreatic abscesses (3 patients, 2.1%), were resolved by percutaneous drainage under CT guidance. Hemorrhages from the omental bursa in 2 patients (3.3%) were resolved by laparoscopic hemostasis. Pancreatic pseudocysts were documented in 3 patients (2.1%), of which there were 2 patients who had external drainage performed laparoscopically and the other had a favorable outcome by conservative treatment, with no surgical treatment being necessary.

The incidence of systemic and local complications increased significantly with the severity of ABD, with values of $P=0.002$ and $P=0.021$, respectively. However, the statistical analysis did not show a significant correlation between the distribution of various local and systemic complications and the severity of acute pancreatitis. There was no statistically significant association between local and general complications encountered ($P=1.00$).

In the severe ABP group, the most frequent systemic complications encountered were pleuropulmonary, specifically, pleurisy and pulmonary infiltrates (10 patients, 17.5%), while the most frequent local complications were pancreatic abscess (3 patients, 5.2%), pseudocysts (2 patients, 3.5%), hemorrhage (3 patients, 5.2%), and bile leak (2 patients, 3.5%).

Nosocomial infections were higher in the severe forms of ABP (9 patients, 15.7%) but there was not a statistically significant difference among groups ($P=0.095$). This finding may be correlated with an increased hospital stay and invasive procedures in the patients with severe ABP.

Overall mortality in the study was low (3%, 4 patients). Only 1 patient's case progressed to death, with multisystem organ failure, the patient having had severe pancreatitis since admission.

The mean hospital stay was 5.1±4.1 days in mild cases and increased to 10±2.4 days in patients with severe forms of ABP ($P<0.001$). No patient with early presentation below 48 h that underwent early biliary decompression surgery developed severe ABP.

Binary logistic regression analysis was conducted to investigate the factors associated with adverse outcomes in the 3 groups. The factors associated with increased risk of systemic complications were creatinine >2 mg/dL (OR: 4.821; CI: 1.547-15.026), leukocytes >15 000/mmc (OR: 3.533; CI: 1.232-10.135), and time from onset to presentation (OR: 1.432; CI: 1.137-1.805). For the local complications, the statistically significant risk factors were obesity (OR: 5.179; CI: 1.786-15.022) and the time from onset to presentation (OR: 1.268; CI: 1.007-1.597).

Discussion

The pathophysiological processes in acute pancreatitis are systematized chronologically as the pre-enzymatic, enzymatic, enzymatic and cytotoxic septicemia, and post-enzymatic stages [15].

The *pre-enzymatic stage* also called the "neurocirculatory" stage, is characterized by altered pancreatic microcirculation under the action of various etiological factors: obstruction of the pancreatic ducts, excessive secretory and alimentary stimulation by secretin and pancreozymins, alcohol consumption, glandular trauma, allergic reactions, or ERCP [16-19].

The *enzymatic stage* is the culmination of intracellular, interstitial, and intraductal enzymatic activities, which is the conversion of trypsinogen to trypsin in the presence of various activating factors: lysosomal cathepsin B, enterokinase, bile acids, cell kinases, coagulation, and fibrinolysis systems. The production of a small amount of trypsin is sufficient to trigger the enzyme autodigestion chain cascade [16-22].

The fundamental local manifestations are edema and inflammatory processes, hemorrhage, and necrosis, with anatomical-clinical forms, from mild, edematous to extremely severe, with extensive necrosis. Exocrine secretion of the pancreas is paradoxically reduced or absent in the first 3 to 5 days after the onset of acute pancreatitis [16,23-25].

The *enzymatic and cytotoxic sepsis stage* is represented by activated pancreatic enzymes, toxic substances, biologically active polypeptides, and other substances resulting from the degradation of pancreatic tissue, diffuse in the peripancreatic and retroperitoneal spaces and the peritoneal cavity. Their action in the peritoneal and retroperitoneal cavity produces capillary hyperpermeability with abundant exudate and hemorrhage and proteolysis, resulting in the appearance of an abundant peritoneal, peripancreatic, and retroperitoneal effusion [19,24].

The *post-enzymatic* or *recovery stage* starts at 15 to 20 days after the onset of acute pancreatitis and it is characterized by intense anabolism and the normalization of biological features, including serum and urinary amylases, fluid, electrolyte, and acid-base balance [19,21,22].

Complications of acute pancreatitis are common during and at the end of the enzymatic stage but can also occur in the post-enzymatic stage, characterized by bacterial contamination of areas of pancreatic necrosis, with repercussions, such as several local and systemic secondary complications that cause and maintain toxic-septic shock [25]. Pancreatic aggression in the early stages leads to the release and activation of proteolytic and lipolytic enzymes responsible for glandular and periglandular autodigestion. The damage caused is of an inflammatory type in the early stages (edema, leukocyte infiltrates), followed by the hemorrhagic and necrotic stage (through ischemic vascular disorders and/or thrombosis). To these are added the effects of the systemic response to the products, resulting in the enzymatic-toxic stage and multiple visceral lesions [26,27].

Currently, there is no clinical or paraclinical variable that can predict the severity of acute pancreatitis in individuals. C-reactive protein, inerleukin-1, interleukin-6, serum tumor necrosis factor alpha, and procalcitonin were evaluated for the possible prognostic utility in acute pancreatitis; however, the results still need to be validated by further analysis [28-30]. Arabul et al found that hepcidin, a circulating peptide hormone that regulates the entry of iron into plasma, which increases during inflammation, may be a better prognostic tool than C-reactive protein for the severity of acute pancreatitis [30]. In a recent study, Silva-Vaz et al [31] found that the neutrophil-to-lymphocyte ratio and systemic inflammation response index, defined as neutrophil count×monocyte/lymphocyte count, has a good predictive value for the severity of inflammation in acute pancreatitis [31,32].

In the present study, we found significant differences among the groups of mild, moderate-severe, and severe ABP in the mean value of amylases, transaminases, creatinine, bilirubin, and leukocytes.

However, one of the limitations of this study was related to the relatively wide differences from onset to presentation (1-7 days) in the patients. The increase of these biomarkers in patients with severe forms must be interpreted as a dynamic process of increasing intensity of inflammatory changes during ABP. Binary logistic regression showed correlations only with creatine >2 mg/mL and leukocytes >15 000/mmc at admission and the risk of systemic complications. Although only up to 20% of the patients developed severe ABP, in these cases the mortality rate was high due to a systemic inflammatory response and multisystem organ failure [33].

Any patient with acute pancreatitis should be hospitalized [34,35]. Given the possibility of progression to general or local complications, the patient should be referred to a unit with multidisciplinary care possibilities: gastroenterology with the possibility of biliopancreatic endoscopy, endoscopic ultrasound, intensive care, imaging radiology (CT) and interventional radiology, and surgery. Patients should be monitored clinically, with repeated examinations for identifying any possible worsening. Repeating the dosage of pancreatic enzymes is worthless. Also, in the absence of signs of aggravation, it is not advisable to repeat the CT examination if it has already been performed [36,37].

The minimally invasive pathogenic therapeutic approach in ABP is based on laparoscopic decompression of the bile tree by cholecystostomy, transcystic drainage, and case-appropriate Kehr drainage. According to a recent metanalysis of Zhong et al [38], early laparoscopic cholecystectomy within 48 to 72 h from onset can be performed safely and effectively in patients with mild ABP. The comparative results between early and delayed laparoscopic cholecystectomy in these cases show the benefit of early surgical intervention in terms of decreased hospital stay, number of complications, and need for subsequent ERCP, taking into account that up to 60% of patients with acute gallstone pancreatitis will have recurrent episodes [38]. Similar findings were reported in a randomized clinical study of acute moderate biliary pancreatitis by Davoodabadi et al [39], who compared early to delayed laparoscopic cholecystectomy. In the present study, we also showed the efficiency of early laparoscopic cholecystectomy in mild and moderate cases of ABP. If cholecystectomy cannot be performed safely due to local inflammation, a cholecystostomy is an efficient drainage method, and laparoscopic cholecystectomy may be performed in a second step.

The proposed objectives are disrupting the links of the pathogenic chain from acute pancreatitis through early biliopancreatic decompression by the laparoscopic approach, aiming to improve the evolution of acute pancreatitis and relieving pain, dyspeptic syndrome, vomiting, and dynamic ileus and preventing local and systemic complications.

The minimally invasive approach to acute pancreatitis has multiple benefits. By laparoscopy, we can explore, irrigate, and

perform decompression of the biliopancreatic tree and drain the pancreatic lodge; we can also perform postoperative lavage through drainage tubes. The extrahepatic biliary decompression in ABP allows for the elimination of biliary stasis, avoids the development of acute enzymatic cholecystitis or secondary angiocholitis, reduces pancreatic edema, especially the cephalic type, and prevents the evolution of pancreatitis to a severe form [13]. The laparoscopic approach creates less trauma in the early stages of acute pancreatitis, and postoperative lavage and drainage eliminate the harmful, irritating autodigestive effect of pancreatic ascites and prevent the absorption of toxic products into the systemic circulation. Drainage tubes are also used for continuous peritoneal lavage, which allows for the removal of sphaceli and necrotic debris or for the introduction of lactic acid to cut off the harmful effect of intraperitoneal extravasated pancreatic juice. The pancreatic abscess can be drained by the transcutaneous approach under ultrasound control or CT, which was also performed by us in 2 patients, with subsequent favorable evolution.

Currently, less invasive alternatives to laparoscopic biliary decompression are considered the endoscopic approach by ERCP or, in selected cases, abdominal external drainage. In severe forms, with increased local inflammation and high anesthetico-surgical risk, cholecystostomy under local anesthesia can be performed by abdominal external drainage, either by CT or echocardiogram guidance [40].

The 2019, the World Society of Emergency Surgery guidelines for the management of severe acute pancreatitis [4] recommend ERCP in patients with ABP with proven biliary obstruction and cholangitis. In these patients, early routine ERCP was documented to significantly decrease mortality and complications. However, the routine use of ERCP in patients with gallstone pancreatitis is still a subject of controversy. A systematic review and metanalysis of Tse et al [41] showed no proven benefits of routine ERCP in decreasing the severity of acute pancreatitis. Moreover, according to the current guidelines, in severe ABP with no signs of biliary obstruction or angiocholitis, ERCP cannot be recommended, based on the previously published evidence [4,42]. Similar results were confirmed by the recently published APEC study, which showed that in patients with predicted severe gallstone pancreatitis but without cholangitis, urgent ERCP with sphincterotomy did not reduce the composite endpoint of major complications or mortality, compared with conservative treatment [43].

The present study had some limitations. The relatively small number of patients and the differences in the time from onset to presentations between the mild and severe ABP groups could not allow the assessment of predictive factors of biological data upon severity. Although the differences found between study groups were statistically significant for most paraclinical

data, they could be strongly influenced by the time factor from the onset of symptoms. We found good results of early surgery in ABP, with a therapeutic approach depending upon the severity and local conditions. However, owing to the protocol of practice in our surgical department, a comparative group treated only medically was not available for statistical analysis. ABP is still a topic for future research, as consensus was not reached on several issues. A future study direction could include the identification of biomarkers with a more accurate prediction of severity and the role of early ERCP in patients expected to develop severe forms. Another question still to be answered is whether ERCP alone may be sufficient in preventing recurrences of ABP, especially in patients with high anesthetic-surgical risk.

The therapeutic management of ABP is complex through medical and surgical conduct, both having the same common denominator of biliopancreatic decompression through the administration of antisecretory medicine, spasmolytic medicine, and nasogastric tube assembly associated with cholecystostomy. In addition to surgical treatment, medical therapy is equally important in the patient's recovery and consists of hydro-electrolytic rebalancing to compensate for the loss of space III, gastric decompression by mounting a nasogastric tube, introduction of anti-enzymatic therapy, treatment of organ failure if it occurs, antibiotic therapy, and parenteral nutrition, following as much as possible the proposed medical protocol.

Laparoscopic treatment in acute pancreatitis has multiple advantages that allow exploration of the peritoneal cavity, biliopancreatic decompression, drainage of harmful secretions from the abdominal cavity, and continuous postoperative washing with betadine solution or lactic acid, eliminating the enzymatic toxic effect in the abdominal cavity and preventing the occurrence of systemic inflammatory response syndrome and multiple organ dysfunction syndrome.

Conclusions

The surgical therapeutic window protocol in ABP consists of pathogenic medication administration of oddian spasmolytics, inhibitors of gastric and pancreatic secretion, antibiotic therapy, and hydro-electrolytic rebalancing and a minimally invasive procedure for the decompression of the biliary tree (cholecystostomy, transcystic drainage, or Kehr drainage, adapted to the patient). It showed a favorable evolution of the cases, with minimum mortality (3%) and reduced morbidity and hospital stay. Creatinine >2 mg/dL and leukocytes >15 000/mmc at admission were associated with an increased risk for systemic complications. The delayed presentation was associated with increased risk both for systemic and local complications.

Early biliary decompression, either by an endoscopic or minimally invasive approach is a safe and effective procedure in ABP. It allows disrupting the pathogenic chain that leads to systemic inflammation and multisystem organ failure. The type of procedure and optimal timing (either 1-step or 2-step surgery) should be individualized, according to the patient's local and general features.

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