International Journal of Medicine and Medical Sciences Vol. 2(10), pp. 295-307, October 2010
Available online http://www.academicjournals.org/ijmms
ISSN 2006-9723 ©2010 Academic Journals

Full Length Research paper

Impact of patient- and intervention-related factors on the outcome of acute biliary pancreatitis treated by urgent ERCP and biliary sphincterotomy

József Pozsár[1]*, Ferenc László[2], Ildikó Brandhuber[3], Péter Sahin[1] and Lajos Topa[1]

[1]Department of Gastroenterology, Szent Imre Hospital, Budapest, Hungary.
[2]Department of Comparative Physiology, University of Szeged, Szeged, Hungary.
[3]Medical Faculty, Semmelweis University, Budapest, Hungary.

Accepted 29 June, 2010

Risk factors of post- ERCP pancreatitis are well characterized in various clinical settings. These factors may worsen the outcome of acute biliary pancreatitis treated by endoscopic sphincterotomy. Our aim was to investigate the effect of patient- and intervention- related factors on the outcome of acute biliary pancreatitis treated by endoscopic sphincterotomy. The data of 69 retrospectively analyzed using multiple logistic regression method to explore factors significantly associated with the outcome of pancreatitis. We found that multi-system organ failure was associated with predicted severe pancreatitis (odds ratio [OR] 24.24; 95% confidence interval [CI]: 1.35 – 434.76; p = 0.030), condition of previous cholecystectomy (OR 23.94; 95% CI: 1.58 – 361.03; p = 0.022) and the performance of access precut sphincterotomy (OR 21.34; 95% CI: 1.32 – 344.92; p = 0.031). Predictors of development of necrosis were post-sphincterotomy bleeding (OR 52.01; 95% CI: 1.67 – 1617.54; p = 0.024), the predicted severe pancreatitis at admission (OR 20.30; 95% CI: 2.92 – 141.19; p = 0.002) and female gender (OR 6.70; 95% CI: 1.00 – 44.73; p = 0.049). The single variable post-cholecystectomy state proved to be a predictor of mortality (OR 13.40; 95% CI: 1.5-∞; p = 0.026). We concluded that the outcome of acute biliary pancreatitis treated by ERCP and biliary sphincterotomy of acute biliary pancreatitis is influenced by certain patient- and intervention-related factors.

Key words: Acute biliary pancreatitis, sphincterotomy, risk- factors, outcome.

INTRODUCTION

Gallstones are thought to be etiologic factors in at least 40% of all cases of acute pancreatitis. Migrating gallstone downward through the common bile duct impacts into the ampulla of the main duodenal papilla leading to temporary occlusion of pancreatic outflow (Opie, 1901; Acosta and Ledesma, 1974; Rünzi et al., 1993; Acosta et al., 1978). These processes result in elevation intraductal pressure and launch intracellular activation of pancreatic enzymes that initiate the various inflammatory pathways leading to pancreatitis (Acosta et al., 1974; Rünzi et al., 1993). Endoscopic retrograde cholangiopancreatography and biliary sphincterotomy has been applied to decompress the ampullary region. The majority of studies investigating the effect of sphincterotomy on the course of biliary pancreatitis focused primarily on the timing of the intervention and postulated that more earlier decompression of the ampullary region might result in better outcome (Neoptolemos et al., 1988; Fan et al., 1993; Fölsch et al., 1997; Nowak et al., 1995; Nowak et al., 1996; Kohut et al., 2001; Kohut et al., 2002; Acosta et al., 2006; Oría et al., 2007). Some studies showed beneficial effect (Neoptolemos et al., 1988; Fan et al, 1993; Nowak et al., 1995; Nowak et al., 1996; Kohut et

*Corresponding author. E-mail: jozsefpozsar@yahoo.co.uk. Tel: 36-1-464-8600. Fax: 36-1-464-8717.

al., 2001; Kohut et al., 2002; Acosta et al., 2006) and others evidenced no improvement (Fölsch et al., 1997; Oría et al., 2007), even worse (Fölsch et al., 1997) outcome due to early endoscopic sphincterotomy on the course of the disease. One of the potential cause of the inconsistent results of these studies may be explained by the fact that they did not take account the potential negative impact of biliary intervention on the course of the pancreatitis. Post-ERCP pancreatitis is the most common complication of ERCP and sphincterotomy with well-known patient- and intervention related risk factors (Cheng et al., 2006; Freeman et al., 2001; Freeman et al., 1996). These factors may be operational in cases of acute biliary pancreatitis treated by sphincterotomy. However, the impact of patient- and endoscopy-related factors that are proved to be associated to post ERCP pancreatitis have never been investigated in the setting of ABP treated by ERCP and endoscopic sphincterotomy. To address these issues we conducted a retrospective observational study in a cohort of patients with ABP.

PATIENTS AND METHODS

Patients

Between the period of 2006 December and 2008 January, all patients presented primarily or transferred from outside institution to our department for evaluation of ABP were evaluated for eligibility of the study. All data of eligible patients were entered into a database for further analyses. Acute pancreatitis was diagnosed in the presence of acute onset of upper abdominal pain, elevation of serum amylase concentration of at least three times of normal and/or characteristic signs or acute pancreatitis on trans-abdominal ultrasonography or CT-scan. Biliary origin of pancreatitis was assumed if biliary stone disease was revealed by abdominal imaging or the presence at least two of the following laboratory parameters: Elevated serum alkaline-phosphatase (> 275 U/l), serum alanine transaminase (> 75 U/l) and serum total bilirubin (> 39 µmol/l) (Goodman et al., 1985; Wang et al., 1988). Inclusion criteria were the followings: Verified biliary origin of acute pancreatitis, patients older than 18 years, intact gastro-duodenal anatomy, no coagulopathy or other bleeding diathesis, endoscopic intervention performed less or equal to 72 h from the onset of symptoms. Patients with surgically altered gastro-duodenal anatomy, uncorrectable coagulopathy, and possible alcoholic or metabolic cause of pancreatitis were excluded from the study. Cases with failed ERCP were also excluded, since our decision whether common bile duct stone was present or not, was based solely on cholangiographic findings as a gold standard. Patients presented with signs suggestive for acute cholangitis were not excluded.

ERCP procedures were performed by each of the three expert endoscopists (J.P., L.T, and P.S), each with more than 10 years experience in the field of endoscopic pancreato-biliary interventions and with a workload of more than 300 ERCPs annually.

Intervention

According to our basic purpose, we intended to perform ERCP and EBS in all patients with ABP as soon as possible regardless of the actual presence of common bile duct stone. Successful urgent and late endoscopic intervention were defined as an intended deep common bile duct cannulation and EBS carried out less or equal to 24 h and more than 24 h but not later than 72 h from the onset of pancreatitis. The actual presence or absence of common bile duct stone was judged solely on cholangiographic findings perceived during ERCP. Presence of ampullary-impacted stone was defined if a part of the stone was visible in the orifice of the main duodenal papilla or spontaneous dislodgment of a stone after needle knife papillotomy.

Common bile duct was accessed with a triple lumen papillotome preloaded with 0.035-inch hydrophilic guide-wire. This wire-guided cannulation technique was preferred at all ERCPs because it has been shown that this approach could facilitate selective cannulation of common bile duct, decrease the trauma of pancreatic orifice and virtually eliminate inadvertent contrast filling of the main pancreatic duct, thus theoretically might preclude worsening the preexisting pancreatitis (Artifon et al., 2007; Lella et al., 2004)). After deep common bile duct cannulation has achieved, EBS was performed with a standard fashion using triple lumen pull type sphincterotome. Attempts of filling of contrast material were avoided until selective common bile duct cannulation was achieved. Diathermy was applied with the ERBE system, using endocut mode, 120 W cut and 50 W coagulation current, level 2. When deep common bile duct cannulation failed, precut procedure was performed with a needle knife using freehand technique. Before institution of precut-sphincterotomy, 10 min for biliary cannulation or up to 5 attempts of inadvertent pancreatic duct cannulation were allowed (Kaffes et al., 2005). When needle-knife sphincterotomy became successful, deep biliary access and standard sphincterotomy were performed. In cases of ampullary impacted stone, needle-knife papillotomy was carried out first, followed by standard sphincterotomy. Common bile duct stones, if present, were attempted to remove baskets or retrieval balloons as appropriate. If stone clearance failed, a plastic endoprosthesis was inserted, and stone removal postponed to a later session. Complication of ERCP and sphincterotomy, except of post-ERCP pancreatitis, were classified according to consensus criteria (Cotton et al., 1991).

Definition of outcome measures and the severity of pancreatitis

As outcome measures, we investigated the impact of various patient and endoscopy- related factors on the rates of multi-system organ failure (MOF) and necrosis in patients treated with urgent endoscopic intervention. Systemic complications as cardiovascular, respiratory and renal failures were defined according to the Marshall's system. MOF was defined as two or more organ failing simultaneously at least for 2 or 3 days (Mofidi et al., 2006). Parenchymal and peripancreatic necrosis was defined according to the proposal of Atlanta Classification of Acute Pancreatitis (2008' Revision) (Sarr, 2009). Parenchymal and peripancreatic necrosis were not evaluated as separate entities, rather the term of necrosis was used for either or combined localizations of necrotic process. The investigated patient-related factors were the age, gender, presence of common bile duct stone, presence of ampullary impacted stone, gallbladder status (cholecystectomized or not) and the predicted severity of pancreatitis. The intervention-related factors were the inadvertent pancreatic duct cannulation and the performance of pre-cutting (except for cases of ampullary impacted stone). The selection of patient- and procedure-related factors that have potential impact on the outcome of pancreatitis was based on those that had been proved for risk factor of post-ERCP pancreatitis (Cotton et al., 2009). Severity of pancreatitis was determined by Ranson's score. Patients classified as having severe attack if three

or more points of the Ranson's scoring system were met (Ranson et al., 1974). Since we performed EBS urgently (less than 24 h of onset of pancreatitis), Ranson's criteria were calculated only at admission to the hospital. For patients who were transferred from an outside facility for evaluation and treatment of pancreatitis, we classified the severity of pancreatitis according the data of the initial admission. Patients, who had predicted severe course of the disease, were treated in intensive care unit. Enteral nutritional support was applied in virtually all patients. Ciprofloxacin or imipenem supplemented with metronidazole were given in cases of pancreatic necrosis.

Data presentation and statistical analysis

Baseline data with continuous distribution were expressed as mean (SD) or median (interquartile range [IQR]) as appropriate. The continuous variables with normal distribution were compared using the two-sample t-test; for variables which did not meet the criteria of normality, the Wilcoxon rank-sum test was applied. For each patient, rates for MOF and peripancreatic and parenchymal necroses, as well as the corresponding 95% confidence intervals (95% CI) were calculated and compared between potentially important patient- and endoscopy-related variables. To explore the association of these variables with the development of MOF, necrosis and mortality, age, gender, severity of pancreatitis, presence of common bile duct stone, presence of ampullary impacted stone, presence of gallbladder, application of pre-cutting, inadvertent main pancreatic duct cannulation, timing of endoscopic intervention, complication of ERCP were entered univariate binary regression analysis as independent variables. In cases when zero cell counts were observed exact logistic regression analysis was applied to obtain univariate ORs and 95% CI.

After univariate analysis, multivariable logistic regression analysis was performed to determine independent predictors of development of MOF and necrosis and mortality. Choice of variables entered into the multivariable models was not based on predetermined criteria of significance (that is, $p < 0.2$) having been obtained using univariate analysis. Rather, independent variables for the best fitting models for each outcome variables were derived from the full models by comparing nested models using likelihood ratio tests and Akaike's information criteria (Long and Freese, 2006). Independent categorical factors were dichotomized according the followings: Age (< 60 year, ≥ 60 year), gender (female, male), severity of pancreatitis (severe, slight), the presence of common bile duct stone, impacted ampullary stone, previous cholecystectomy (yes/no), time of ERCP from onset of pancreatitis (≤ 24 h, > 24 h), applications of pre-cutting (yes/no), inadvertent main pancreatic duct cannulation (yes/no) and occurrence of complications of ERCP (yes/no). All statistical test were performed using Stata version 10.1 (StataCorp, College Station, Texas, USA) software with two-sided tests, with a P-value of < 0.05 considered statistically significant.

RESULTS

Patient characteristics, technical details of intervention and overall complication rate

During the two years period, 95 patients were evaluated for the inclusion into the study. 26 patients were excluded for further analyses either because of failed ERCP and EBS (n = 11) or endoscopic intervention was carried out beyond 72 h from the onset of symptoms (n = 15), thus, total of 69 patients remained for the final analysis.

In six cases, ERCP failed because of the edematous duodenal folds prevented to locate the main duodenal papilla. In the other five patients, selective cannulation of the common bile duct was unsuccessful, despite precut sphincterotomy. On intention-to-treat basis, the overall success rate of endoscopic intervention was 86.2%. Success of ERCP and sphincterotomy was significantly reduced in patients who are equal or over 60 years old (OR 0.12, 95% CI: 0.02 – 0.8; p = 0.028) and in cases where access precut sphincterotomy needed to be used after primarily failed attempt of cannulation of the common bile duct (OR 0.14, 95% CI: 0.02 – 0.9; p = 0.044). We did not exclude though that there were not any patients with the signs suggestive for acute cholangitis in the final study cohort. Demographics, baseline clinical characteristics and the timing of ERCP are summarized in Table 1.

Common bile duct stone and ampullary impacted stone were present at the time of intervention in 16 patients (23.1% 95% CI: 12.9 – 33.4) and 8 patients (11.5%; 95% CI: 3.8 – 19.3), respectively. The combined rate of common bile duct stone and ampullary impacted stone was 33% in patients treated by urgent ERCP. In the subgroup of later intervention, the rate of bile duct stone was 37%. Urgent ERCP and sphincterotomy was performed at a median of 18.0 h (IQR 12.5, range: 4.0 – 24.0), but in those cases where endoscopic intervention was carried out more than 24 h this time was 43.0 h (IQR 28.0; range: 26.0 – 72.0) from the onset of pancreatitis. Access precut sphincterotomy and inadvertent main pancreatic duct cannulation; each were encountered in 8 patients (11.5%; 95%CI: 38.4–19.3). Complication of endoscopic intervention included exclusively bleeding following endoscopic sphincterotomy detected in 4 patients (5.7%; 95% CI: 0.1 – 11.4). All bleeding episodes were mild and responded to endoscopic treatment without the need of red blood cell transfusion or surgery.

The overall complication rate including MOF and necrosis was 21% (95% CI: 68.2 – 88.2) for the entire cohort of patients. Among patients with predicted severe and slight pancreatitis, these proportions were 44% (95% CI: 23.7 – 64.2) and 11% (95% CI: 0.00 – 21.1), respectively (p = 0.005, Fischer's exact test).

Rates of MOF and its associations with patient- and intervention-related factors

As expected, there was more than ten-fold difference in the rates of MOF in cases with pancreatitis classified severe at admission as compared those having mild form of pancreatitis: 24% vs. 2.7% (p = 0.029). Among patients with the history of previous cholecystectomy, three episode of MOF occurred in seven patients, while this rate was only 4/62 in the cohort of patient with gallbladder

Table 1. Clinical characteristics of patients with acute biliary pancreatitis (n = 69).

Variables	N (%)
Age	
Mean (SD)	53.9 (18.2)
≥ 60 years, n (%)	39 (46.5)
< 60 years, n (%)	30 (43.5)
Gender	
Male, n (%)	33 (52.2)
Female, n (%)	36 (47.8)
Predicted severity of AP	
Severe, n (%)	25 (59.7)
Slight, n (%)	37 (40.3)
Previous cholecystectomy	
Yes, n (%)	7 (10.1)
No, n (%)	62 (89.8)
Time of ERCP from the onset of symptomes,	
Median [IQR, range (26.0 – 72.0)]	24 [24, (24.0 – 72.0)]
≤ 24 h, n (%)	42 (39.1)
> 24 h, n (%)	27 (60.4)
Serum total bilirubin [µmol/l, mean (SD)]	53.1 (39.5)

AP = Acute pancreatitis.

*in situ (*42.9% vs. 6.4%, p = 0.01*).* The other variables did not show evidence of meaningful association with MOF (Table 2).

Multivariate logistic regression analysis showed that severe pancreatitis predicted at admission (OR 24.24; 95% I: 1.35 – 434.76; p = 0.030), condition of previous cholecystectomy (OR 23.94; 95% CI: 1.58 – 361.03; p = 0.022) and the performance of access precut sphincterotomy (OR 21.34; 95% CI: 1.32 – 344.92, p = 0.031) carried out in cases of failed common bile duct cannulation were significantly independent predictors of development of MOF during the course of ABP treated by EBS (Table 3).

Rates of necrosis and its associations with patients and intervention related factors

There was a five-fold increase in the frequency of necrosis in patients with predicted severe pancreatitis at admission as compared to those with predicted slight disease (40% vs. 8.1%, p = 0.005). The remaining variables did not showed significant association with the occurrence of necrosis (Table 4.)

By multivariate analysis, complication of endoscopic intervention (that is post- sphincterotomy bleeding) (OR 52.01; 95% CI: 1.67 – 1617.54; p = 0.024), the predicted severe pancreatitis at admission (OR 20.30; 95% CI: 2.92 – 141.19; p = 0.002) and female gender (OR 6.70; 95% CI: 1.00 – 44.73; p = 0.049) were significant predictors of development of necrosis (Table 5).

Mortality

There was an overall of three deaths (4.3%) in this cohort of patients with ABP treated by urgent ERCP and EBS. Previous cholecystectomy with the single variable showed significant difference in mortality by univariate analysis (28.6% vs. 1.6%, p = 0.015). Death, related to pancreatitis was observed in 25% of patients with post-sphincterotomy bleeding, while in patients without post-sphincterotomy complications mortality occurred in 3% of patients showing marginal significance (p = 0.085).

Presence of common bile duct or ampullary impacted stone, inadvertent main pancreatic duct cannulation, timing of intervention and gender of patients, did not showed meaningful association with mortality (Table 6).

The best fitting exact multivariable binary logistic modeling for mortality, showed that previous

Table 2. Results of univariate analysis on the association of occurence between MOF and patients and procedure related factors (n = 69).

Variables	N (%)	OR (95% CI)	P-value
Age (y)			
≥ 60 (n = 30)	5 (16.7)	3.70 (0.66 - 20.59)	0.135
<60 (n = 39)	2 (5.1)	1	
Gender			
Female (n = 36)	4 (11)	1.25 (0.25 – 6.05)	0.782
Male (n = 33)	3 (9)	1	
Severity of AP			
Severe (n = 25)	6 (24)	11.36 (1.27 – 101.4)	0.029
Slight (n = 37)	1 (2.7)	1	
Common bile duct stone			
Yes (n = 16)	2 (12.5)	1.37 (0.23 – 7.84)	0.723
No (n = 53)	5 (9.4)	1	
Ampullary impacted stone			
Yes (n = 8)	0 (0)	0.74 (0.0 – 5.74)*	0.808
No (n = 61)	7 (11.5)	1	
Previous cholecystectomy			
Yes (n = 7)	3 (42.9)	10.87 (1.78 – 66.29)	0.010
No (n = 62)	4 (6.4)	1	
Urgent ERCP-EBS			
Yes (n = 42)	3 (7.1)	0.44 (0.09 – 2.15)	0.313
No (n = 27)	4 (14.8)	1	
Access precutting			
Yes (n = 8)	2 (25)	3.51 (0.59 – 23.58)	0.161
No (n = 61)	5 (8.2)	1	
Inadvertent MPD cannulation			
Yes (n = 8)	1 (12.5)	1.30 (0.13 – 12.52)	0.815
No (n = 61)	6 (9.8)	1	
Complication of ERCP-EBS			
Yes (n = 4)	1 (25)	3.27 (0.29 – 36.64)	0.335
No (n = 65)	6 (9.23)	1	

AP = Acute pancreatitis, EBS = Endoscopic biliary sphincterotomy, MPD = Main pancreatic duct, * = Computed by exact univariate logistic regression. Complication of ERCP-EBS denotes post- sphincterotomy bleeding.

cholecystectomy was the only independent predictor of mortality in this cohort of patients (OR 13.40; 95%CI: 1.5-∞; p = 0.026) (Table 7).

DISCUSSION

We found in this observational cohort study that the outcome of ABP treated by EBS performed as early as possible from the onset of the disease was influenced by either patient- and procedure-related factors. In the present study, the success rate of ERCP and sphincterotomy as well as the complication and mortality rates were comparable to those of previous studies (Neoptolemos et al., 1988; Fan et al., 1993; Fölsch et al., 1997; Nowak et al., 1995).

Table 3. Results of logistic regression analysis on the association between MOF and patients and procedure related factors (n = 69).

Variables	OR (95% CI)	P-value
Severity of AP		
Severe	24.24 (1.35 – 434.76)	0.030
Slight	1	
Previous cholecystectomy		
Yes	23.94 (1.58 – 361.03)	0.022
No	1	
Urgent ERCP-EBS		
Yes	0.16 (0.01 – 1.79)	0.138
No	1	
Access precutting		
Yes	21.34 (1.32 – 344.92)	0.031
No	1	

AP = acute pancreatitis, EBS = endoscopic biliary sphincterotomy.

Earlier studies having investigated the role of early ERCP and EBS in the setting of ABP, focused primarily on the timing of endoscopic intervention (Neoptolemos et al., 1988; Fan et al., 1993; Fölsch et al., 1997; Nowak et al., 1995; Nowak et al., 1996; Oría et al., 2007). Moreover, in majority of these studies, EBS was performed only in cases with actual presence of common bile duct stone. Only two studies had a design having been allowed to perform EBS in cases of ABP and without the evidence of common bile duct stone (Nowak et al., 1995; Nowak et al., 1996). In these two studies, it has been shown that in patients treated by ERCP and EBS performed within 24 h from the onset of the symptoms evidenced better outcome of pancreatitis as compared to those for whom the intervention carried out at later time. However, further studies investigating the effect of urgent intervention on the outcome of ABP has not yet been carried out. ERCP and EBS have well characterized complication profiles, which have been investigated in various clinical situations. Specific patient- and intervention-related factors have been identified to be independent risk factors for post-ERCP complications, primarily post-ERCP pancreatitis (Cotton et al., 2009; Wang et al., 2009). These patient- and intervention-related factors proved to be risk factors of post-ERCP pancreatitis which theoretically may have the similar potential to worsen the outcome of ABP treated by ERCP and EBS, but this effect was not investigated in this setting. In the present study, we did not perform analyses stratified by severity of pancreatitis, rather severity of pancreatitis determined by Ranson's criteria included as a covariate in multivariate regression analysis to predict the occurrence of outcome variables. This statistical approach seemed to be more reasonable and more realistic to model the clinical situations than the severity-stratified analysis, since we intended to perform endoscopic intervention in all patients presented with ABP.

Our goal was to perform ERCP and EBS in all cases presented with acute gallstone pancreatitis regardless of the presence of common bile duct stone or ampullary-impacted stone. This approach was based on the results of previous studies that showed that microlithiasis was present in more than 88% of patients with ABP in whom ERCP and sphincterotomy was carried out less than 24 h from the onset of pancreatitis and this rate was still over 60% in cases when endoscopic intervention was performed beyond 48 h (Kohut et al., 2001; Kohut et al., 2002). Early endoscopic intervention was proved as effective as in cases with ABP and microlithiasis as observed in those cases with ABP and common bile duct stone or ampullary-impacted stone (Nowak et al., 1995; Nowak et al., 1996). In the current study, we found that 34% of patients have common bile duct stone or ampullary-impacted stone. This figure is comparable to those rates found in the majority of pervious studies, except the study of Oria et al. (2007), in which they found that the incidence of common bile duct stone was 72% in patients who underwent ERCP within 48 h from the onset of pancreatitis. In the present study there was no difference in the rate of actual presence of bile duct stone between the groups of patients treated by urgent ERCP at a median of 18 h from the onset of symptoms and those treated by intervention carried out later, at a

Table 4. Results of univariate analysis on the association between necrosis and patients and procedure related factors (n = 69).

Variables	N (%)	OR (95% CI)	P-value
Age (y)			
≥ 60 (n = 30)	6 (20)	1.14 (0.34 – 3.84)	0.829
<60 (n = 39)	7 (17.9)	1	
Gender			
Female (n = 36)	7 (19.4)	1.08 (0.32 - 3.64)	0.893
Male(n = 33)	6 (18.2)	1	
Severity of AP			
Severe (n = 25)	10 (40)	*7.55 (1.81 - 31.44)	0.005
Slight (n = 37)	3 (8.1)	1	
Common bile duct stone			
Yes (n =16)	2 (12.5)	0.54 (0.10 - 2.76)	0.464
No (n = 53)	11 (20.7)	1	
Ampullary impacted stone			
Yes (n = 8)	0 (0)	0.35 (0.0 - 0.250)	0.339
No (n = 61)	13 (21.3)	1	
Previous cholecystectomy			
Yes (n =7)	1 (14.3)	0.69 (0.07 - 6.32)	0.746
No (n = 62)	12 (12.3)	1	
Urgent ERCP-EBS			
Yes (n = 42)	9 (21.4)	1.56 (0.43 - 5.71)	0.495
No (n = 27)	4 (14.8)	1	
Access precutting			
Yes (n = 8)	3 (37.5)	3.06 (0.67 - 14.91)	0.166
No (n = 61)	10 (16.4)	1	
Inadvertent MPD cannulation			
Yes (n = 8)	2 (25)	1.51 (0.26 - 8.53)	0.637
No (n = 61)	11(18)	1	
Complication of ERCP-EBS			
Yes (n = 4)	2 (50)	4.90 (0.62 - 38.68)	0.131
No (n = 65)	11 (16.9)	1	

AP = Acute pancreatitis; EBS = Endoscopic biliary sphincterotomy; MPD = Main pancreatic duct; *computed by exact univariate logistic regression. Complication of ERCP-EBS denotes post-sphincterotomy bleeding.

median of 43 h from the beginning of pancreatitis (33 and 37%, respectively). Our results and the data of previous studies suggest that the incidence of common bile duct stone during the early period of the pancreatitis do not show a time-dependent decrease; rather it seems to be stabilized around 30 - 40% between the intervals less than 24 h up to 72 h from the onset of the disease.

Indeed, in the present study, we showed that presence of common bile duct or ampullary impacted stone had no significant impact on the occurrence of MOF, necrosis or

Table 5. Results of logistic regression analysis on the association between necrosis and patients and procedure related factors (n = 69).

Variables	OR (95% CI)	P-value
Gender		
Female	6.70 (1.00 – 44.73)	0.049
Male	1	
Severity of AP		
Severe	20.30 (2.92 – 141.19)	0.002
Slight	1	
Previous cholecystectomy		
Yes	0.06 (0.00 – 1.52)	0.090
No	1	
Complication of ERCP-EBS		
Yes	52.01 (1.67 – 1617.54)	0.024
No	1	

AP = acute pancreatitis, EBS = endoscopic biliary sphincterotomy. Complication of ERCP-EBS denotes post-sphincterotomy bleeding.

mortality rate.

This study failed to show any statistically significant advantage of ERCP and EBS performed on urgent basis (< 24 h form the beginning of symptoms) compared to intervention carried out over 24 h from onset of pancreatitis. However, to build the best fitting multivariate model for prediction of occurrence of MOF, the variable of timing of endoscopic intervention was required to be included as a covariate. However, the multivariate model constructed to predict development of necrosis did not required the inclusion of this variable. Endoscopic intervention performed equal or less than 24 h from the onset of pancreatitis seemed to have some protective effect against development of MOF, although this effect was not statistically significant (OR 0.16; 95% CI: 0.01 – 1.79; p = 0.138). Development of necrosis and the mortality were not affected by the timing of ERCP. Nowak et al found in a prospective randomized study that ERCP and sphincterotomy performed within 24 h from the onset of symptoms had significantly lowered complication rate as compared to intervention performed for more than 24 hours (Nowak et al., 1996).

In this study, the highest incidence of complications occurred in the subgroup of patients in which ERCP and sphincterotomy was carried out more than 72 h from admission. These differences remained significant either in subgroups of slight and severe pancreatitis. Neoptolemos et al randomized 121 patients with acute biliary pancreatitis according to early ERCP and sphincterotomy (in presence of common bile duct stone) and conservative treatment and selective ERCP (Neoptolemos et al., 1984). In his study, early intervention was defined as an ERCP carried out within 72 h from admission. They showed significantly improved complication rate and mortality in the subgroup of patients of predicted severe pancreatitis. Fan et al conducted a randomized study having investigated the role of emergency ERCP and sphincterotomy (defined as less than 24 h from admission to the hospital) for the treatment of acute biliary pancreatitis. They found that emergency ERCP and sphincterotomy decreased only the incidence of episodes of cholangitis but not the local and systemic complication and mortality attributable directly to pancreatitis (Fan et al., 1993). Fölsch at al conducted a multicenter randomized study of 238 patients with acute biliary pancreatitis (Fölsch et al., 1997). Patients were randomly assigned to early ERCP and sphincterotomy (in the presence of common bile duct stone) and conservative treatment and selective late endoscopic intervention. The results of this study failed to support the beneficial effect of early endoscopic intervention, moreover some increase in mortality and complication rates was observed in the early intervention group. In a more recent study, Oria et al randomized 103 patients with acute biliary pancreatitis for early ERCP and sphincterotomy that was intended to be performed within 48 h from the onset of symptoms and for conservative treatment and selective ERCP (Oría et al., 2007). Based on the results of this prospective study, there were no differences in the rate of complications and mortality between group of patients with endoscopic intervention performed on time (that is less than 48 h from the onset

Table 6. Results of univariate analysis on the association between mortality and patients and procedure related factors (n = 69).

Variables	N (%)	OR (95% CI)	P-value
Age (y)			
≥ 60 (n = 30)	3 (10)	*5.29 (0.55-∞)	0.155
< 60 (n = 39)	0 (0)	1	
Gender			
Female (n = 36)	2(5.5)	1.88 (0.16 – 21.78)	0.613
Male (n = 33)	1 (3)	1	
Severity of AP			
Severe (n = 25)	3 (12)	*6.10 (0.89-∞)	0.121
Slight (n = 37)	0 (0)	1	
Common bile duct stone			
Yes (n = 16)	0 (0)	*0.84 (0 – 8.18)	0.894
No (n = 53)	3 (5.6)	1	
Ampullary impacted stone			
Yes (n = 8)	0 (0)	*1.97 (0.00 – 19.86)	1.000
No (n = 61)	3 (4.9)	1	
Previous cholecystectomy			
No (n = 7)	2 (28.6)	24.40 (1.87 – 318.1)	0.015
Yes (n = 62)	1 (1.6)	1	
Urgent ERCP-EBS			
Yes (n = 42)	2 (4.7)	1.30 (0.11 – 15.07)	0.834
No (n = 27)	1 (3.7)	1	
Access precutting			
Yes (n = 8)	1 (12.5)	4.21 (0.33 – 52.64)	0.264
No (n = 61)	2 (3.3)	1	
Inadvertent MPD cannulation			
Yes (n = 8)	0 (0)	*1.97 (0.00 – 19.86)	1.000
No (n = 61)	3 (4.9)	1	
Complication of ERCP-EBS			
Yes (n = 4)	1 (25)	10.50 (0.73 – 150.9)	0.084
No (n = 65)	2 (3)	1	

AP = Acute pancreatitis, EBS = Endoscopic biliary sphincterotomy, MPD = Main pancreatic duct, * = Computed by exact univariate logistic regression. Complication of ERCP-EBS denotes post- sphincterotomy bleeding.

of the disease) as compared to patients with early conservative management. Another recent study of acute biliary pancreatitis showed that there was significantly more immediate complication in patients with biliary obstruction lasting more than 48 h from the onset of pancreatitis, suggesting a therapeutic window lasting not more than this time interval (Acosta et al., 2006). In totality three studies have shown that early endoscopic intervention can significantly decrease the occurrence of pancreas-specific complications of acute biliary

Table 7. Results of logistic regression analysis on the association between mortality and patients and procedure related factors (n = 69).

Variables	OR (95% CI)	P-value
Previous cholecystectomy		
Yes (n = 7)	13.40 (1.5-∞)	0.026
No (n = 62)	1	
Access precutting		
Yes (n = 8)	7.31 (0.38-∞)	0.123
No (n = 61)	1	
Complication of ERCP-EBS		
Yes (n = 4)	2.50 (0.131-∞)	0.287
No (n = 65)	1	

AP = Acute pancreatitis, EBS = Endoscopic biliary sphincterotomy. All ORs and p-values are computed by exact logistic regression analysis. Complication of ERCP-EBS denotes post-sphincterotomy bleeding.

pancreatitis (Neoptolemos et al., 1984; Nowak et al.,1995; Nowak et al., 1996). The design of our study shared some features with the studies of Nowak et al. (1996) in that endoscopic intervention was carried out as early as possible and either in the presence and absence of common bile duct stone. Both study showed decreased complication rate when ERCP and sphincterotomy were done on urgent basis (that is ≤ 24 h from the beginning of pancreatitis) as compared to later interventions, although in the present study this difference was not significant probably due to the small sample size. According to the study of Acosta et al, the time interval of ampullary obstruction regardless whether this obstruction is caused by stone, sludge or ampullary edema due to previous stone passage is an important factor for the development of complications. This observation and the high incidence of microlithiasis at the early period of pancreatitis and the rapid sequence of pathophysiologic events described by experimental studies, may justify the performormance of sphincterotomy as early as possible from the onset of abdominal pain associated with acute biliary pancreatitis (Kohut et al., 2001; Kohut et al., 2002; Lerch et al., 1995).

Among the patient-related factors, the previous cholecystectomy proved to be a significant risk factor of development of MOF by both univariate and multivariate analyses. There was a higher, but not significant, incidence of mortality by univariate analysis, but multivariate analysis showed a significant predictive effect of cholecystectomized state on the mortality. There are some possible explanations of this interesting finding. Several studies had shown a high incidence of Oddi sphincter dysfunction among cholecystectomized patients (Neoptolemos et al., 1988; Ciacala et al., 2002). It is a well-known fact, that ERCP and sphincterotomy is associated with a considerably high incidence of post-ERCP pancreatitis with a relative high rate of severe pancreatitis or even death (Cotton et al., 1991; Wang et al., 2009). It is possible that the same association between Oddi sphincter dysfunction and more severe course of ABP exist in cases when pancreatitis is treated by sphincterotomy. Alongside with this, the state of previous cholecystectomy is significantly associated with mortality. Interestingly, development of necrosis was related inversely to the state of previous cholecystectomy, although this association was not statistically significant. It is hard to explain this finding, and it may reflect the different pathomechanism.

According to the majority of studies been addressed, the issue of post-ERCP pancreatitis, the female gender had been proved to be an independent risk factor associated to post-ERCP pancreatitis (Cotton et al., 2009; Wang et al., 2009; Freeman et al., 2001). However, there are studies which questioned that female gender as an independent predictor of post-ERCP pancreatitis (Freeman et al., 2001). In the present cohort of patients with ABP treated by EBS, it had been shown that female gender tended to be associated with higher incidence of MOF, necrosis and mortality. However, except for necrosis where female gender was a significant predictor, for the two other variables the associations were only marginal.

Precut sphincterotomy is a useful technique to access common bile duct in cases when primary cannulation attempts failed, but harbors a significant risk of pancreatitis as a complication of the procedure (Cotton et al., 2009; Wang et al., 2009; Freeman et al., 1996). One may speculate that in ABP, as like in cases of other bilio-pancreatic pathologies, precut sphincterotomy can worsen the severity and the course of the preexisting

pancreatitis. Despite this possibility, no study had been conducted to address this question specifically in the setting of acute biliary pancreatitis. In the present study, we showed that application of precut sphincterotomy to gain access to common bile duct is a significant predictor of development of MOF in patients with ABP. Application of precut sphincterotomy resulted in an increased rate of necrosis by univariate analysis, but this difference was not significant. The building of multivariate model did not require the inclusion of precut sphincterotomy as a variable into the final model. This suggested that precut sphincterotomy exerted a little impact on development of necrosis. Performance of precut sphincterotomy increased the rate of mortality without reaching significance. Multivariable model showed positive association between precut sphincterotomy and mortality, but this association was not significant. The pathomechanism of precut sphincterotomy associated pancreatitis had not been fully elucidated, but pancreatic duct obstruction due to periorificial edema resulted from local heat-induced damage may be an important causative factor (Pezzilli et al., 2002). Consequently, the obstructed outflow and the increased pressure in the pancreatic ductal system may further worsen the inflammatory process of the pancreas during the course of ABP.

We used wire-guided cannulation technique for all ERCP, because it had been shown that this cannulation approach could decrease the trauma of the main duodenal papilla and virtually exclude possibility of inadvertent filling with contrast material of the main pancreatic duct (Artifon et al., 2007; Lella et al., 2004; Pezzilli et al., 2002). Indeed, using this technique, we were capable to avoid entirely from inadvertent contrast filling of the pancreatic ductal system at all ERCP procedures, but inadvertent cannulation of the main pancreatic duct with a guide-wire occurred in 11.5% in this cohort of patients. We have found that inadvertent cannulation of the main pancreatic duct has only a little impact on the occurrence of MOF, necrosis and mortality according to the results of univariate analyses. Because of the highly insignificant associations in univariate analyses, inadvertent pancreatic duct cannulation has no contributions to the multivariate models predicting the development of MOF, necrosis and mortality. Although, at this time, only one study had shown repeated deep main pancreatic duct cannulation association with post-ERCP pancreatitis(Wang et al., 2009), the results of our study suggested that guide-wire cannulation of pancreatic duct did not worsen the outcome of ABP by EBS.

The post-sphincterotomy bleeding was the single complication encountered in the present study cohort. All bleeding episodes were mild in its nature and could be controlled with local epinephrine injection, if required. There was no need of packed red blood cell transfusion. In cases, where post-sphincterotomy bleeding occurred there was a higher incidence of MOF as compared those without this complication, however this difference was not significant. Development of necrosis was observed also more frequently in patients in whom post-sphincterotomy bleeding occurred. By multivariate analysis post–sphincterotomy bleeding proved to be an independent predictor of development of necrosis ($p = 0.024$). Mortality rate was increased in patients with post-sphincterotomy bleeding with univariate analysis, but with multivariate analysis, this association was only marginal. The post- sphincterotomy bleeding and the endoscopic injection hemostasis may induce trauma and edema formation of the pancreatic orifice and adjacent tissue leading to obstructed outflow of main pancreatic duct. This mechanism can provide one possible explanation of how post-sphincterotomy hemorrhage and associated local treatment of bleeding can worsen the outcome of ABP treated endoscopically.

The strength of this study was that it tries to provide a more realistic and more detailed insight into the course of acute biliary pancreatitis treated by endoscopic biliary sphincterotomy, since we included patient and endoscopy-related factors that had potential impact on the outcome of pancreatitis. The study showed that these factors had more influence on the outcome of ABP than the timing of intervention, which was basically the sole variable applied to the majority of the previous studies. The lack of this multifaceted approach may be the explanation, at least in part, of the inconsistent results published in the previous studies.

However, there are limitations of the present study as well. The present study has a retrospective design, although our basic intention was to perform ERCP and sphincterotomy as soon as possible from the onset of symptoms suggesting the beginning of pancreatitis. The definition of urgent ERCP (that is ≤ 24 h from the onset of symptoms) was arbitrary and it was possible that application of other time ranges might modify our results. However, the median time for intervention, performed not urgently was more than twice as compared to that carried out on urgent basis (43 vs. 18 h, respectively). According to our opinion, this difference of timing of ERCP was reasonably large to make meaningful conclusion about the effect of urgent intervention on the outcome of pancreatitis as compared to those performed at later time. Our sample size was relatively small as compared to that of previous randomized trials. It also should be mentioned that we did not use non-invasive imaging modalities as MRCP or EUS to identify patients with common bile duct stone for selection for ERCP and sphincterotomy. Previous studies have shown that EUS had the same accuracy as ERCP for detection of common bile duct stones in patients with acute biliary pancreatitis (Karakan et al., 2009; Stabuc et al. 2008).

However, these diagnostic modalities have not validated, so far for their diagnostic capabilities for detection of microlithiasis or biliary sludge, despite the

fact that microlithiasis is considered as a significant causative factor in the pathogenesis of biliary pancreatitis.

Based on the results of our present study, we can conclude that the outcome of ABP treated by ERCP and EBS was influenced primarily by certain patient- and procedure-related factors other than the timing of endoscopic intervention. Such factors are: Post-cholecystectomy state, female gender, application of precut sphincterotomy and bleeding complication of sphincterotomy proved risk factors for unfavorable outcome of biliary pancreatitis treated by ERCP and sphincterotomy. Further studies aiming to investigate the role of ERCP and EBS on the outcome of ABP should include patient- and procedure-related factors as controlling variables to model clinical situations more precisely.

REFERENCES

Acosta JM, Katkhouda N, Debian KA, Groshen SG, Tsao-Wei DD, Berne TV (2006). Early ductal decompression versus conservative management for gallstone pancreatitis with ampullary obstruction: a prospective randomized trial. Ann. Surg., 243: 33-40.

Acosta JM, Ledesma CL (1974). Gallstone migration as a cause of acute pancreatitis. N. Engl. J. Med., 290: 484-487.

Acosta JM, Rossi R, Rubio Galli OM, Rossi R, Chinellato AV, Pellegrini CA (1978). Early surgery of acute gallstone acute pancreatitis: evaluation of a systematic approach. Surgery, 83: 367-370.

Artifon EL, Sakai P, Cunha JE, Halwan B, Ishioka S, Kumar A (2007). Guide-wire cannulation reduces the risk of post- ERCP pancreatitis and facilitates bile duct cannulation. Am. J. Gastroenterol., 102: 2147-2153

Cheng CL, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Lazzell-Pannell L, Rashdan A, Temkit M, Lehman GA (2006). Risk factors for post-ERCP pancreatitis: a prospective multicenter study. Am. J. Gastroenterol., 101: 139-147.

Ciacala M, Habib FI, Vavassori P, Pallotta N, Schillachi O, Costamagna G, Guarino MP, Scopinaro F, Fiaocca F, Torsoli A, Corazziari E (2002). Outcome of endoscopic sphincterotomy in post cholecystectomized patients with sphincter of Oddi dysfunction as predicted by manometry and quantitative choledochoscintigraphy. Gut, 50: 665-668.

Cotton PB, Garrow DA, Gallagher J, Romagnuolo J (2009). Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. Gastrointestinal. Endosc., 70: 80-88.

Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N (1991). Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest. Endosc., 37: 383-393.

Fan ST, Lai EC, Mok FP, Lo CM, Zheng SS, Wong J (1993). Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N. Engl. J. Med., 328: 228-232.

Fölsch UR, Nitsche R, Luedke R, Hilgers RA, Creutzfeldt W (1997). Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. N. Engl. J. Med., 336: 237-242.

Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP (2001). Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest. Endosc., 54: 425-434.

Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM (1996). Complications of endoscopic biliary sphincterotomy. N. Engl. J. Med., 335: 909-918.

Goodman AJ, Neoptolemos JP, Carr-Locke DL, Finlay DB, Fossard DP (1985). Detection of gall stones after acute pancreatitis. Gut, 26: 125-132.

Kaffes AJ, Sriram PV, Rao GV, Santosh D, Reddy DN (2005). Early institution of pre- cutting for difficult biliary cannulation: a prospective study comparing conventional vs. a modified technique. Gastrointest. Endosc., 62: 669-674.

Karakan T, Cindoruk M, Alagozlu H, Ergun M, Dumlu S, Unal S (2009). EUS versus endoscopic retrograde cholangiography for patients with intermediate probability of bile duct stones: a prospective randomized trial. Gastrointest. Endosc., 69: 244-252.

Kohut M, Nowak A, Nowakowska-Duława E, Marek T (2002). Presence and density of common bile duct microlithiasis in acute biliary pancreatitis. World J. Gastroenterol., 8: 558-561.

Kohut M, Nowak A, Nowakowska-Duława E, Kaczor R, Marek T (2001). The frequency of bile duct crystals in patients with presumed biliary crystals. Gastrointest. Endosc., 54: 37-41.

Lee TH, Park do H, Park JY, Kim EO, Lee YS, Park JH, Lee SH, Chung IK, Kim HS, Park SH, Kim SJ (2009). Can wire-guided cannulation prevent post- ERCP pancreatitis? A prospective randomized trial. Gastrointest. Endosc., 63: 444-449.

Lella F, Bagnolo F, Colombo E, Bonassi U (2004). A simple way of avoiding post-ERCP pancreatitis. Gastrointest. Endosc., 59: 830-834.

Lerch MM, Saluja AK, Rünzi M, Dawra R, Steer ML (1995). Luminal endocytosis and intracellular targeting by acinar cells during early biliary pancreatitis in the opossum. J. Clin. Invest., 95: 2222-2231.

Long JS, Freese J (2006).Regression models for categorical dependent variables using Stata. 2nd. ed. College Station, TX: Stata Press

Mofidi R, Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW (2006). Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. Br. J. Surg., 93: 738-744

Neoptolemos JP, Bailey IS, Carr-Locke DL (1988). Sphincter of Oddi dysfunction: results of treatment by endoscopic sphincterotomy. Br. J. Surg., 75: 454-459.

Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP (1988). Controlled trial of urgent retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet, 2: 979-983.

Nowak A, Nowakowska-Dulawa E**,** Marek TA**,** Rybicka J (1995). Final results of the prospective, randomized, controlled study on endoscopic sphincterotomy versus conventional management in acute biliary pancreatitis. Gastroenterology, 108(suppl A): 380.

Nowak A, Nowakowska-Dulawa E, Marek TA, Rybicka J (1996). Timing of endoscopic sphincterotomy for acute biliary pancreatitis- a prospective study. Gastrointest. Endosc., 43: 391.

Opie EL (1901). The etiology of acute hemorrhagic pancreatitis. Bull Johns Hopkins Hosp., 12: 182-188.

Oría A, Cimmino D, Ocampo C, Silva W, Kohan G, Zandalazini H, Szelagowski C, Chiappetta L (2007). Early endoscopic intervention versus early conservative management in patients with acute gallstone pancreatitis and biliopancreatic obstruction. Ann. Surg., 245: 10-17.

Pezzilli R, Romboli E, Campana D, Corinaldesi R (2002). Mechanism involved in the onset of post-ERCP pancreatitis. JOP, 3: 162-168.

Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC (1974). Prognostic signs and the role of operative management in acute pancreatitis. Surg. Gyneco. Obstet., 139: 69-81.

Runzi M, Saluja A, Lerch MM, Dawra R, Nishino H, Steer ML (1993). Early ductal decompression prevents the progression of biliary acute pancreatitis: an experimental study in the opossum. Gastroenterology. 105:157-164.

Sarr MG (2009). Revision of the Atlanta classification of acute pancreatitis. Http:

//www.pancreasclub.com/resources/AtlantaClassification.pdf.
Stabuc B, Drobne D, Ferkolj I, Gruden A, Jereb J, Kolar G, Mlinaric V, Mervic M, Repse A, Stepec S, Markovic S (2008). Acute biliary pancreatitis: detection of common bile duct stones with endoscopic ultrasound. Eur. J. Gastroenterol. Hepatol., 20: 1171-1175.
Wang P, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, Huang Q, Zhang X, He LP, Sun WS, Zhao Q, Shi RH, Tian ZB, Li YQ, Li W, Zhi FC (2009). Risk factors for ERCP- related complications: a prospective multicenter study. Am. J. Gastroenterol., 104: 31-40.
Wang SS, Lin XZ, Tsai YT, Lee SD, Pan HB, Chou YH, Su CH, Lee CH, Shiesh SC, Lin CY (1988). Clinical significance of ultrasonography, computed tomography, and biochemical test in the rapid diagnosis of gallstone- related pancreatitis: a prospective study. Pancreas, 3: 153-158.