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Does presence of common bile duct stones in patients with acute biliary pancreatitis affect the severity of illness or laboratory findings?

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Background/aims: *To determine the effect of stone within the common bile duct, on the severity of acute biliary pancreatitis.* **Material and Methods:** *This is a prospective and cross sectional study which was conducted at a tertiary care hospital including 103 patients. Serum biochemical values and white blood cell counts at the first 12th and 72nd hours of presentation were evaluated. The patients were grouped according to the presence or absence of common bile duct stones which were diagnosed by endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography. Besides, the patients were classified as mild and severe acute pancreatitis according to the data provided by computed tomography (Balthazar scoring) and clinical assessment and blood samples.* **Results:** *Among the 103 patients with acute biliary patients, radial endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography revealed stones and/or sludge within the common bile duct or ampulla in 41 (39.8%) patients. There was not any persistent common bile duct stone in 62 (60.2%) patients. Severe pancreatitis developed in 9 (22%) of 41 patients who were determined to have stones by endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography, and in 13 (21%) of 62 patients who were not. There was no difference in the incidence of progressing to severe acute biliary patients between patients with and without common bile duct stones (p=0.45).* **Conclusion:** *Presence of common bile duct stones do not correlate with the severity of acute biliary pancreatitis.*

Key words: Pancreatitis severity, common bile duct stones, ERCP, endosonography

Akut biliyer pankreatitli hastalarda ana safra kanalı taşları varlığı hastalığın şiddetini ve laboratuvar bulgularını etkiler mi?

Amaç: *Akut biliyer pankreatitin şiddeti ile ilgili olarak ana safra kanalındaki taşların etkisini tanımlamak.* **Yöntem:** *Bu tersiyer bir hastanede 103 hastalık, prospektif ve cross sectional olarak yapılmış bir çalışmadır. Başvurunun ilk 12 ve 72. saatlerindeki serum biyokimyasal ve beyaz küre sayımları değerlendirildi. Hastalar, endoskopik ultrasonografi ve endoskopik retrograd kolanjiopankreatografide tanımlanan ana safra kanalı taşlarının varlığına göre gruplandırıldı. Bunun yanında hastalar bilgisayarlı tomografi ve kan örneklerinden derlenen verilerle (Baltazar skorlamasına göre) hafif ve ciddi akut pankreatit olarak sınıflandı.* **Bulgular:** *Akut biliyer pankreatitli 103 hasta arasında, 41 (%39,8) hastada endoskopik ultrasonografi ve endoskopik retrograd kolanjiopankreatografi ile ana safra kanalı veya ampullada taş ve/veya çamur saptandı. Altmışiki (%60,2) hastada ana safra kanalında taş yoktu. Endoskopik ultrasonografi ve endoskopik retrograd kolanjiopankreatografide taş saptanan 41 hastanın 9'unda (%22), saptanmayan 62 hastanın 13'ünde (%21) şiddetli pankreatit gelişti. Ana safra kanalında taş olan ve olmayan hastalar arasında şiddetli akut biliyer pankreatite gidiş insidansında fark saptanmadı (p=0.45).* **Sonuç:** *Ana safra kanalı taşları varlığı akut biliyer pankreatit şiddeti ile ilişkili değildir.*

Anahtar kelimeler: Pankreatit, ana safra kanalı taşları, ERCP, endosonografi

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INTRODUCTION

Gallstones are a common cause of acute pancreatitis and determined in 40-60% of pancreatitis patients (1). Gallstone pancreatitis, in most cases, is caused by gallstones passing into the bile duct (2). Screening methods often fail to detect the presence of common bile duct (CBD) stones in patients with acute biliary pancreatitis (ABP). Generally, CBD stones causing pancreatitis spontaneously pass into the duodenum via the ampulla of Vater (3,4). On the other hand, the frequency of persistent CBD stones in patients with ABP was reported to range between 10%-72% depending on the timing of cholangiography (5,6,7,9). The presence of CBD stones also affects the treatment method (2-4). Although there remains some controversy, persistence of stones in the bile duct or ampulla was claimed to be associated with more severe pancreatitis (8-10).

In this study, we aimed to determine the frequency of persisting CBD stones in patients with biliary pancreatitis and whether the presence of CBD stones affects the severity of pancreatitis or laboratory values in these patients.

MATERIALS AND METHODS

This study was designed as a cross-sectional prospective study, which was conducted between January and October 2009 in the Gastroenterology Clinic of a tertiary care hospital.

The diagnosis of ABP was based on consistent clinical presentation (severe upper abdominal pain) that started before hospitalization and consistent laboratory findings. According to biochemical analysis 12 hours following the onset of pain, those with a serum lipase >500 U/L, amylase >400 U/L, total bilirubin >2.0 mg/dl, alanine aminotransferase (ALT) >60 U/L, aspartate aminotransferase (AST) >60 U/L, and alkaline phosphatase (ALP) more than twice the upper normal limit were accepted as ABP (3,11,12), and 103 patients were enrolled into the study.

Patients with a history of pancreatic, biliary or gastrointestinal tract malignancies or those with malignancies determined during hospitalization; cirrhosis and renal failure; gastrectomy or gastroenterostomy operations impeding endosonography; age younger than 18 years; regular ethanol consumption or consumption of any dose within the last week; and pregnant patients were excluded from the study.

Serum values of all patients were evaluated for AST, ALT, ALP, gamma-glutamyl transpeptidase (GGT), C-reactive protein (CRP), amylase, lipase, bilirubin, and white blood cell (WBC) counts within the first 12th and 72nd hours after presenting to the emergency service. In the first 24 hours of admission, the gallbladder and CBD were examined by transabdominal ultrasonography (US) using Hitachi EUB 500 3.5 MHz convex ultrasound probe. On the fifth day of admission, upper abdominal contrasted multislice pancreas tomography scans were taken for the patients who were suspected of having severe pancreatitis by clinical assessment (persistent pain, decreased PaO2, increased creatinine, decreased thrombocyte count, worsening laboratory findings). We determined computerized tomography (CT) severity index according to the Balthazar scoring system. Based on clinical, laboratory and CT findings, the patients were classified as mild or severe pancreatitis (13).

Between 3-5 days regardless of the patient's pain, the CBD and intrahepatic biliary tract were examined by radial endosonography (using Hitachi EUB 6000 ultrasonography, combined with Pentax EG 3630 UR 270 5-10 MHz Doppler radial endoscopic ultrasonography [EUS] probe). After 12 hours of fasting, an intravenous route was provided, and while being monitored, patients were sedated with midazolam, 1 mg at the beginning, followed by 1 mg additional doses every 30 seconds, up to a total of 4 mg, accompanied with nasal oxygenation. The distal part of the CBD and ampulla of Vater were examined from the 1st and 2nd parts of the duodenum at 6.0 and 7.5 MHz frequency, while the proximal part of the CBD, intrahepatic biliary tract and gallbladder were examined from the gastric antrum and corpus at 6.0 and 7.5 MHz frequency. The shape of the ampulla (edematous, normal), the width of the CBD (CBD >8 mm is dilated, distal intrahepatic biliary tract >3 mm is dilated) and intrahepatic biliary tract, existence of any calculi or sludge inside the lumen or benign or malignant narrowing (compression of pancreatic edema), and any calculi (calcific hyperechogenicity >3 mm was accepted as gallstone) or sludge in the gallbladder were determined (14). In addition, the pancreatic tissue was examined to determine the likelihood of the lesions to be malignant.

Patients who had CBD stones and/or sludge diagnosed by EUS (either mild or severe) and all patients with severe pancreatitis (regardless of EUS findings) were treated by endoscopic retrograde

cholangiopancreatography (ERCP). ERCP was performed with the goal of selective cannulation of the CBD and endoscopic sphincterotomy (ES) procedure. Early ERCP was performed in patients with severe pancreatitis and elective ERCP in the others. Stones were extracted by balloon sweeping or mechanical lithotripsy; in cases of non-extraction, plastic stents were applied.

According to the presence of CBD stones in EUS and ERCP, the patients were grouped in two groups as either with or without stones. Furthermore, patients were classified as mild or severe acute pancreatitis.

Statistical Analysis

Statistical analysis was made by using SPSS version 15.0 database. Non-parametric values were evaluated with Fisher exact chi-square test, and parametric values were evaluated with Student-t test. A p value <0.05 was accepted as statistically significant.

RESULTS

A total of 103 patients, 47 (45.7 %) male and 56 (54.3%) female, were enrolled into the study. The mean age was 56±23 years.

Mean lipase 2615 U/L, amylase 1610 U/L, AST 230 U/L, ALT 263 U/L, ALP 313 U/L, GGT 379 U/L, total bilirubin 4.0 mg/dl, WBC count 13.991/mm^3, and CRP 14.7 mg/dl were determined in the blood serum samples taken within 12 hours following the beginning of the pain.

In 57 (55.3%) of the patients, US and/or CT and EUS revealed stone or sludge in the gallbladder. In 39 patients (37.8%), EUS showed CBD stone and/or sludge in the CBD and/or ampulla of Vater. In 7 (6.8%) patients, stone(s) were observed inside the ampulla of Vater.

In 39 patients in whom CBD stone(s) were shown by EUS, ERCP was done, and the CBD stone(s) or sludge were extracted in 35 (89.7%) of the patients. Early ERCP was performed at a mean of 7 days (range: 5-11 days) in 20 patients with severe pancreatitis. Of the patients, 7 were CBD stone (shown by EUS)-positive patients. Elective ERCP was performed at a mean of 16 days (range: 8-21 days) in 32 patients with mild pancreatitis. In 2 patients who were diagnosed as having stone in the ampulla by EUS, there was no stone in ERCP. In another 2 patients, we could not extract the stones and applied biliary stents.

Early ERCP was performed in 13 patients with severe pancreatitis without CBD stones (in EUS), and in 2 of these patients, CBD stones <5 mm were extracted by ERCP.

We added the 2 stone-positive patients in ERCP to the CBD stone-positive patients in the EUS and evaluated laboratory values. Of the 103 ABP patients, 41 had CBD stone and/or sludge and 62 had no stone or sludge in the ampulla, CBD or intrahepatic bile ducts. The evaluation within the first 12 hours determined that 41 CBD stone-positive patients and 62 CBD stone-negative patients showed the following values: serum lipase 2587.6 U/L and 2891.1 U/L, amylase 1480.9 U/L and 1651.4 U/L, AST 245.7 U/L and 225.2 U/L, ALT 255.6 U/L and 262.1 U/L, ALP 333.3 U/L and 281.1 U/L, GGT 265.5 U/L and 273.5 U/L, total bilirubin 4.9 mg/dl and 3.7 mg/dl, WBC count 18535/mm^3 and 12517/mm^3, and CRP 16.9 mg/dl and 14.1 mg/dl, respectively. In the first 12 hours of admission, there were no statistical differences in the blood serum values of the patients determined to have stones in the CBD and of those who did not have stones (p>0.05). Twenty-two patients progressed into severe pancreatitis; 9 of them were from the stone-positive and 13 from the stone-negative patient groups. There was no statistical difference between the two groups in terms of progressing into severe pancreatitis (p>0.05).

By evaluating clinical and laboratory findings and using Balthazar scoring system according to multislice CT findings, 22 (21.3%) of the patients were diagnosed as severe and/or necrotizing pancreatitis.

Abdominal CT scan revealed necrosis in 6 patients, pancreatic abscess in 4, pancreatic cyst >50 mm in 4, and free retroperitoneal fluid and/or ascites in 8 patients. Two of them underwent surgery, and these 2 patients were followed up by the surgery clinic.

Early ERCP was performed in a total of 20 severe pancreatitis patients. CBD stones were extracted from 9 (36.3%) of the patients who underwent early ERCP. Of the 9 patients, 7 were determined to have CBD stones by EUS, and in 2 patients, stones were diagnosed during ERCP. CBD stones were extracted from 9 (36.3%) of the patients who underwent early ERCP.

Of the 103 patients, a total of 22 patients developed severe ABP. Severe ABP developed in 9 (21.9%) of the 41 patients who had CBD stones

and in 13 (20.9%) of the 62 patients who did not (p=0.45).

Of the 103 patients, 4 (3.8%) with severe pancreatitis (2 from the stone group, 2 from the without-stone group) died due to multiple organ failure (MOF) and infection despite intensive care unit (ICU) therapy.

The CRP value was 28 mg/dl in severe pancreatitis patients and 4.3 mg/dl in mild pancreatitis patients within the first 72 hours, and it was significantly higher in severe pancreatitis patients (p<0.05). WBC was 12,400/mm^3 in severe pancreatitis patients and 7,800/mm^3 in mild pancreatitis patients at 72 hours, and it was statistically significantly higher in the severe group (p<0.05). While the mean length of stay in the hospital for severe pancreatitis patients was 43.3 days, it was 6.2 days for mild pancreatitis patients. Length of stay was markedly longer for severe pancreatitis patients (p<0.05).

DISCUSSION

There are several theories about the mechanisms of ABP. Basically, either transient or persistent bile duct stones are the main reason for the beginning of ABP. However, the role of the persistence of stone in the bile duct in the ongoing damage or in increasing the severity of pancreatitis remains controversial. In several clinical studies, it was reported that persisting biliopancreatic obstruction correlates with the severity of pancreatitis, and early ERCP and ES were offered in the treatment of ABP patients (8-10). In contrast, it was also reported that ERCP did not show any benefit in ABP patients and that ERCP and ES did not show any effect compared to standard medical treatment (7,15). Interestingly, these studies were focused on the effect of early ERCP in decreasing the complications of pancreatitis, with the assumptions that the presence of stone in the CBD or ampulla increases complications of pancreatitis and that their early removal may decrease complications. However, persistence of CBD or ampullary stone, whether causing obstruction or not, is not really shown to cause more severe pancreatitis.

In our study, we found that the presence of CBD stone or sludge did not have any influence on laboratory values or on the severity of pancreatitis. Data interpretation and comparison of our results with the literature present some difficulties. Heterogeneous populations were included in the literature. In studies supporting that early ERCP and ES decrease complications, the patients were predicted severe pancreatitis patients, CT was not performed, and necrosis was not shown. Moreover, even the presence of stone was not shown in those studies. Our study is different from those studies with respect to the homogenicity of the study population, timing of early ERCP and diagnosis of severe pancreatitis (8-10,32,33). Our findings did not support that the presence of stone in the CBD or ampulla has an effect on the severity of pancreatitis. Our findings are consistent with the studies suggesting that the persistence of main bile duct stones does not by itself contribute to the worsening or persistence of pancreatic inflammation (7,15,34).

The aim of our study was to show the effect of persistent stone on the severity of pancreatitis, so we performed early ERCP after the diagnosis of actual severe pancreatitis. CT is very effective for diagnosing severe pancreatitis. However, the problem is the correct timing of CT scans, since very early CT scans do not show necrosis. A CT scan 4-5 days after the onset of pain shows necrosis and truly stratifies the patients. We diagnosed local complications by CT after 5 days of pain, which is the preferred timing of CT for diagnosing local complications (16). However, this led to our waiting for about 6 days for performing ERCP. Our early ERCP is performed after EUS and CT at a median of 6 days after the onset of pain. For these reasons, we could not directly compare our results with the literature supporting that the persistence of CBD stone affects the severity of pancreatitis, but with our approach, we performed ERCP in actual severe pancreatitis patients and prevented unnecessary procedures. We think it is a realistic timing for not performing unnecessary ERCP, which itself has possible serious complications (17,18). We performed ERCP in 54 (52.4%) patients (severe pancreatitis and persisting stone patients). As there was no expected gain from ERCP for the other 49 (47.6%) ABP patients (mild pancreatitis and no CBD stone) in our series, we did not perform ERCP in these patients.

Our findings are consistent with the findings of Oria and Fölsch (7,15), that persistence of CBD stone has no impact on the severity of pancreatitis, and there is no good reason for early ERCP in these patients.

In these selected patients, our standard approach is the relief of biliary obstruction in the patients

with shown obstruction or in severe ABP patients. Results of EUS played a key role in deciding the patients in whom we should perform ERCP. No persistent biliary stone was left in any of the patients beyond a maximum of 3 weeks. EUS proved to be sensitive for detection of CBD stone in patients with ABP (17-22). Therefore, we used EUS as the first-line procedure in patients with ABP for deciding therapeutic ERCP.

The frequency of the presence of CBD stones in ABP was reported to range between 10-72% (5-7,9). We found a frequency of 39.8% persistent CBD stone in ABP patients. We think that we diagnosed almost every patient with CBD stone because we combined EUS with ERCP for diagnosis of stone. The timing of the EUS could be criticized in our study, since it is possible that some stones had already fallen into the duodenum before EUS was performed. However, all of the EUS is performed by the same single experienced endoscopist (EA), and 3 days after the onset of pain is a realistic, applicable timing after diagnosis and stabilization of the patient. Moreover, it was reported that prolonged obstruction can be more important than transient obstruction for the development of complications (23,24). We think that EUS performed on the third day is a good timing for categorizing patients.

In two cases, we did not see any stone in ERCP, but they were shown by EUS. ERCP was performed on days 14 and 17 in these two patients. Both of them were mild pancreatitis patients and the stones were in the ampulla. We think that these stones fell into the duodenum while awaiting ERCP. In contrast, we found stones in two severe ABP cases in ERCP, which could not be visualized in the bile duct by EUS. The probable explanations were that the stones were too small for detection in EUS, or that the stones fell into the bile duct from the gallbladder after the EUS session.

Persistent biliary stones did not increase progression to severe pancreatitis in our series. We examined serum values of ALT, GGT, ALP, bilirubin, WBC, and CRP at the 12th and 72nd hours and compared the laboratory values of the patients with and without gallstone in the CBD. All laboratory values, which were evaluated in both groups, were similarly high at the first 12 hours ($p< 0.05$), and these values proportionally regressed in both groups within 72nd hours ($p<0.05$). However, CRP and WBC counts were higher at 72 hours in the patients who progressed to severe pancreatitis than in the mild pancreatitis patients. CRP was reported to be a practical predictor of severe pancreatitis in some studies and not in others (13,25-29). CRP and WBC count are nonspecific markers of infection, and were higher in patients who progressed to severe pancreatitis. We think that presence of infection is probably more important than presence of stone, as presence of infection is associated with morbidity and mortality. There were 22 (21.3%) severe acute pancreatitis patients in our series, and 4 (3.8%) died because of MOF and infection in the ICU. Our mortality was similar to reports from Turkey and other European countries (30,31). Since timing of antibiotic usage was decided individually and presence of cholangitis was not shown, we could not use our data for showing the effect of infection on morbidity and mortality.

Presence of severe pancreatitis is associated with prolonged hospitalization as expected (2,3,35). In our study, the mean length of stay was 6.2 days for mildly ill patients and 43.3 days for seriously ill ABP patients.

In this study, we found that there was no relationship between the existence of CBD stone and the severity of illness in ABP patients. Other factors and most probably presence of infection may play a role in patients who progress to severe pancreatitis. More trials are needed to support our study results.

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