Acute biliary pancreatitis in the era of minimally invasive surgery

Panek J, Rembiasz K, Karcz D, Winiarski M, Zasada J*

2nd Surgical Department, Jagiellonian University, Collegium Medicum, Kraków, Poland

Abstract

Purpose: Opinions about early endoscopic sphincterotomy and time of laparoscopic cholecystectomy in acute biliary pancreatitis are still controversial. Some authors reserved this procedure only for cases in which the stones were visualized during ERCP or patients had clinical symptoms of acute cholangitis. The aim was the assessment of the dynamic of changes of proinflammatory cytokines and white blood cells in time in patients with acute biliary pancreatitis after performed endoscopic sphincterotomy and laparoscopic cholecystectomy.

Material and methods: We enrolled 43 consecutive patients with clinically diagnosed mild forms of acute biliary pancreatitis. All were treated by early endoscopic sphincterotomy and laparoscopic cholecystectomy performed during the first 48 hours after admission.

The course of the disease was monitored by measurement of the level of proinflammatory cytokines.

Results: Marked decrease of the level of proinflammatory interleukins within 24 hours after endoscopic sphincterotomy was observed. Mean values of IL-6 and IL-8 were statistically lower immidiately after this procedure ($p<0.001$). Subsequent decrease was achieved after laparoscopic cholecystectomy. The mean values of TNF-α and IL-12p40 were relatively constant throughout the study period.

Conclusion: All patients suffering from mild acute biliary pancreatitis should be treated by using minimally invasive procedures. However, such a only treatment should be reserved for experienced centers.

* CORRESPONDING AUTHOR:

2nd Surgical Department, Jagiellonian University, Collegium Medicum
ul. Kopernika 21, 31-501 Kraków, Poland
Tel: +48 12 4248209; Fax: +48 12 4213456
email: mspanek@cyf-kr.edu.pl (Józefa Panek)

Received 06.04.2006 Accepted 30.06.2006

Key words: pancreatitis, surgical procedures, minimally invasive, endoscopy, interleukins, TNF-α, leukocytes.

Introduction

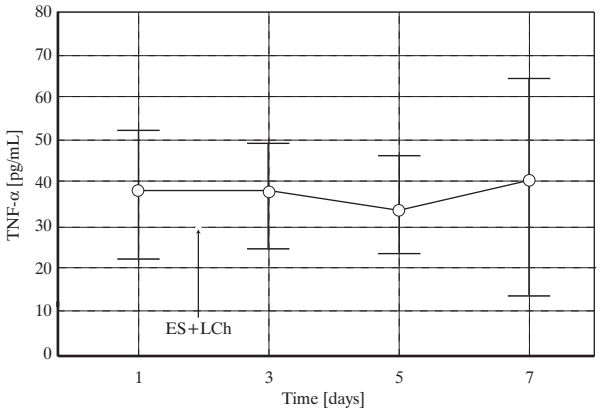
Biliary stones are one of the most important etiological factors of acute pancreatitis. Impairment of bile flow by concrements is the most important mechanism in the development of this disease. The most dangerous stones, called microlithiasis, are 2-3 mm in diameter. Such small particles can easily migrate from the gallbladder to the biliary ducts and also along the biliary tree, consequently blocking the bile flow at the level of the papilla of Vater [1-5]. It was proved that these small stones spontaneously migrate to the duodenum during 48 h and in this period the risk of blockade of the papilla is the highest [4,6]. This migration results in oedema of the papilla of Vater, which is also an important factor in the blockade of bile flow [7]. The "two phases theory" proposes that in the first phase small migrating stones initiate the mild form of acute pancreatitis. In the second phase, persisting stones or repeated passage of small stones effected intermitted or continuous obstruction of the main bile duct and pancreatic duct and developed severe form of the disease [8,9]. It is known, from the experimental and clinical studies, that the time of impediment of bile flow and the possibility of recurrent blockade of the papilla play fundamental roles in the progression of changes in the pancreas [10]. From these reasons is rationale perform early biliary decompression in patients with acute gallstone pancreatitis.

The results of these studies have important clinical implications. The opinions about early endoscopic papillotomy are still controversial. Some authors reserved this procedure only for cases in which the stones were visualized during endoscopic retrograde cholangiopancreatography (ERCP) or when patients had clinical symptoms of acute cholangitis [7,11-13]. However, there were reports suggesting that early improvement of bile flow could reduce the mortality and improve the prognosis in patients with acute pancreatitis [14-20].

Today, the standard of practice requires the removal of the gallbladder during the same hospitalization, but even in the leading centers the time of cholecystectomy is delayed [21].

Taking into consideration the controversy regarding the treatment of patients with biliary pancreatitis and the unpredictable clinical course of the disease, we introduced, as a standard, the early endoscopic sphincterotomy and laparoscopic cholecystectomy. These procedures were performed during the first 48 hours. In this way, we removed the reservoir of biliary stones. These procedures were used in all patients with mild form of acute pancreatitis. To evaluate this model of management of patients with biliary pancreatitis we measured the level of cytokines and absolute account of white blood system during the first seven days of hospitalization.

Figure 1. **TNF-α dynamic changes in time in study group. ES – endoscopic sphincterotomy, LCh – laparoscopic cholecystectomy**



Material and methods

The study was performed on 43 consecutive patients with clinically diagnosed mild form of acute biliary pancreatitis. The diagnosis was based on the clinical picture, ultrasound examination and the increase of the level of amylase in the serum and urine (at least three times above the upper normal limit). The aetiology of pancreatitis was based on the history and ultrasonografic examination which revealed the presence of stones in the gallbladder and/or in the biliary tree. The degree of involvement of pancreas was based on Becker's scale [22]. The increase in size of whole or part of the pancreas with unchanged borders and with diffuse or focal decrease of its echogenicity was classified as 1st degree according to Backer's scale (21 patients). The changes which were characterised by significant increase in the size of the pancreas with the foci of hypoechogenicity in the pancreas and the surrounding fat but with the unchanged border of the pancreas and with the presence of fluid around its nearest neighbourhood were classified as 2nd degree according to Backer scale (22 patients). The clinical severity of the disease was measured using the Apache II scale [23], Ranson criteria [24] and Atlanta criteria [25].

Every patient had endoscopic sphincterotomy with removal of the stones or biliary sludge from the main biliary duct (spontaneously or using the Dormia basket) during the first 24 h after admission. In this way the bile flow was improved. Considering the fact that stones can migrate during the next day, the early cholecystectomy was performed (during the first 48 hours after admission).

During the 1st, 3rd, 5th and 7th day of hospitalization the following biochemical measures were performed: hematocrit, WBC with blood smear, and the level of cytokines such as: TNF-α, IL-1β, IL-6, IL-8 and IL-12p40. The cytokines level was measured using ELISA method (Bio Source Europe SA).

The aim of this study was assessment of the role of endoscopic sphincterotomy on the clinical course of mild form of acute biliary pancreatitis. To achieve this goal we checked the dynamic of changes of proinflammatory interleukins and white blood cells in time in patients with biliary pancreatitis after performed endoscopic sphincterotomy. Also the correlation between the level of interleukins and leukocytes in the 1st day of hospitalization was checked.

Before the statistical analysis was done we assumed that the result "zero" of the concentration of interleukins is caused by the limitation of the used measurement method and not by the real absence of these proteins in the blood. The "zero" were replaced with the minimal results achieved in the whole group of the patients. The results were as follows: IL-1β – 0.59, TNF-α – 0.31, IL-6 – 3.28, IL-8 – 1.88, IL-12p40 – 0.41. Such data were analysed used the model of one factorial analysis of variances for repeated measurements. The impact of endoscopic papillotomy was checked using so-called planned comparison of the contrast method. The mean level of interleukins and leucocytes before the endoscopic sphincterotomy and in the next three measurements after the procedure was compared (contrast: –3, 1, 1, 1). The study of the dynamic of suspected results was based on the analysis of the linear trends (contrast: -3, -1, 1, 3) or if the dynamic of changes had a curvilinear shape based on the square trends (-1, 1, 1, -1). The statistical analysis was done using module GLM of the STATISTICA 6.0 program (company Stat Soft).

Results

In each patient the presence of stones in the biliary tree was confirmed. In 5 patients the stones were not visualized during ERCP, but after sphincterotomy their spontaneous removal was observed. There were no complications observed in any of the patients related to using therapeutic procedures (endoscopic sphincterotomy and laparoscopic cholecystectomy).

The cytokines level

There were no differences between the mean concentration of TNF-α in the following days of the study (*Fig. 1*), ($F_{1,10}$= 0.09; p=0.9610). Also the endoscopic sphincterotomy has no influence on the concentration of TNF-α in the patients' serum ($F_{1,10}$=0.09; p=0.9169).

There were changes of mean concentration of IL-6 after endoscopic sphincterotomy. The level of this interleukin decreased, although this drop was on the border of statistical significance (*Fig. 2*), ($F_{1,18}$=4.37; p=0.0509). The test of the

Figure 2. **IL-6 dynamic changes in time in study group. ES – endoscopic sphincterotomy, LCh – laparoscopic cholecystectomy**

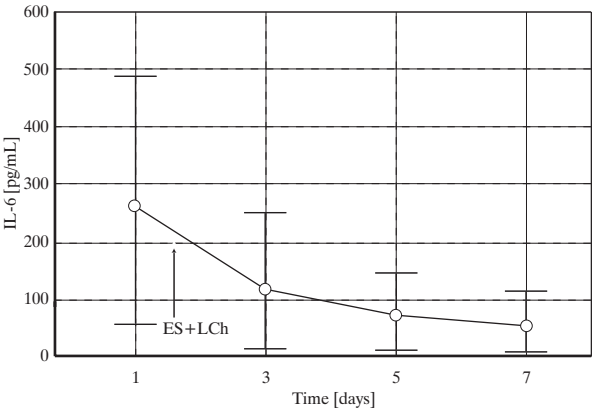


Figure 3. **IL-8 dynamic change in time in study group. ES – endoscopic sphincterotomy, LCh – laparoscopic cholecystectomy**

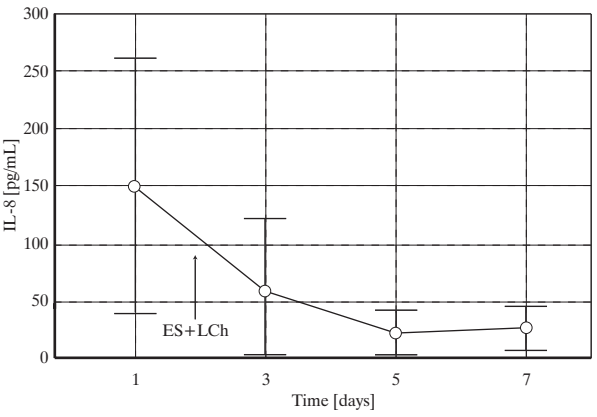


Figure 4. **IL-12p40 dynamic changes in time in study group. ES – endoscopic sphincterotomy, LCh – laparoscopic cholecystectomy**

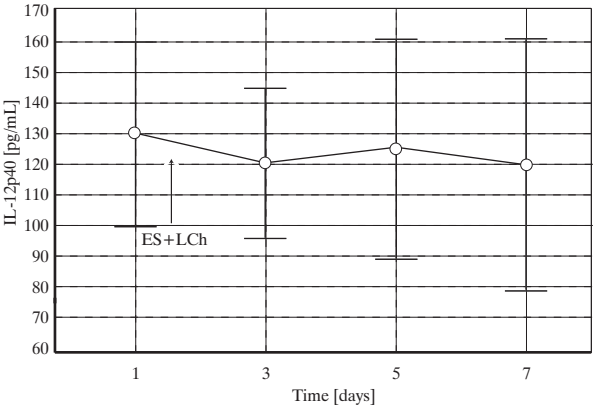


Figure 5. **White blood cells (WBC) dynamic changes in time in study group. ES – endoscopic sphincterotomy, LCh – laparoscopic cholecystectomy**

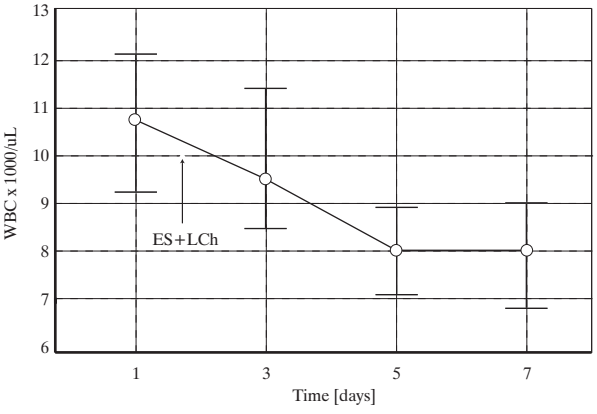
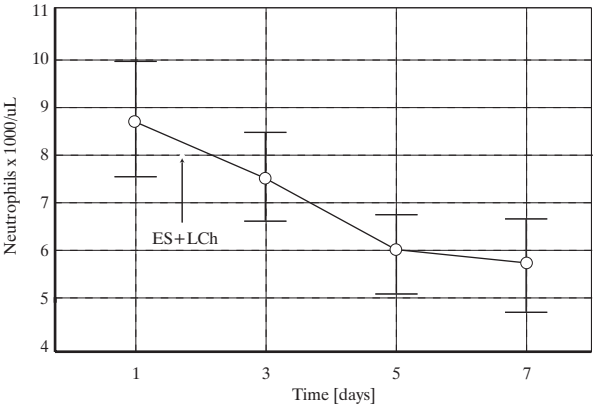


Figure 6. **Neutrophils dynamics changes in time in study group. ES – endoscopic sphincterotomy, LCh – laparoscopic cholecystectomy**



characteristic of trends does not confirm linear other square nature of this process (linear trend – $F_{1,18}$=3.04; p=0.0983, square trend – $F_{1,18}$=2.96; p=0.1021).

The differences of the mean concentrations of IL-8 were statistically significant (*Fig. 3*), ($F_{1,25}$=4.40; p=0.0065). The decrease of IL-8 after endoscopic sphincterotomy was observed ($F_{1,25}$=6.14; p=0.0203). This trend had an asymptomatic character (square trend, $F_{1,25}$=5.04; p=0.0338).

There was no influence of endoscopic sphincterotomy on the concentration of IL-12p40. The mean concentration was on this same level during 7 days of observation (*Fig. 4*), ($F_{1,37}$=0.22; p=0.8806).

The white blood cells system

After endoscopic sphincterotomy the decrease of mean values of leucocytes was observed. This decrease was statistically significant (*Fig. 5*), ($F_{1,38}$=14.42; p=0.0001). The test of the significance of trends showed the linear character of this process ($F_{1,38}$=25.21; p<0.0001).

The mean level of neutrophils also decreased after endoscopic sphincterotomy. This drop was also statistically significant (*Fig. 6*), ($F_{1,38}$=19.94; p<0.0001). The drop had also linear character ($F_{1,38}$=36.32; p<0.0001). No statistically significant changes were observed in the levels of monocytes and lymphocytes after performed endoscopic sphincterotomy (*Fig. 7* and *8* respectively), (lymphocytes – $F_{1,38}$=0.10; p=0.7518, monocytes – $F_{1,38}$=0.6; p=0.1591).

The correlation coefficient of mean concentration of interleukins and the particular cells of white blood cell system

Figure 7. **Lymphocytes dynamic changes in time in study group. ES – endoscopic sphincterotomy, LCh – laparoscopic cholecystectomy**

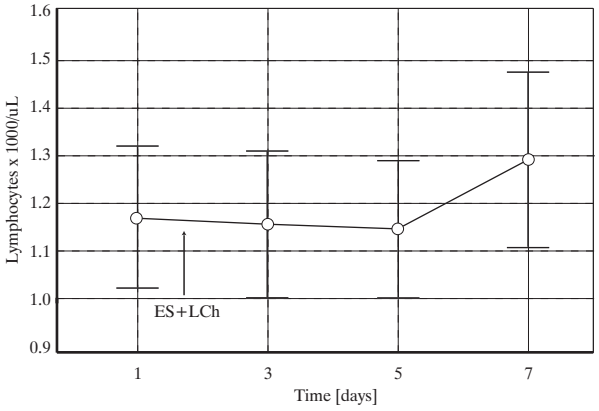
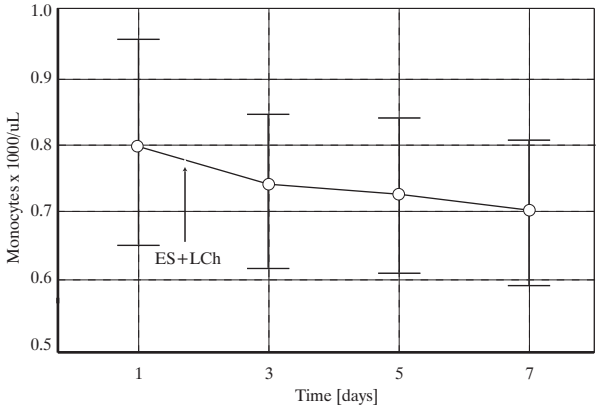


Figure 8. **Monocytes dynamic changes in time in study group. ES – endoscopic sphincterotomy, LCh – laparoscopic cholecystectomy**



in the 1st day of study was significant between IL-6 and neutrophils (correlation =0.5564; p=0.011) and between IL-6 and lymphocytes (correlation =0.4446; p=0.050). This coefficient was on the border of significance between IL-6 and the total number of leucocytes (correlation =0.4309; p=0.058). Among the particular cells of the white blood cells system the strong correlation between neutrophils, monocytes and total number of leucocytes has been shown (respectively: correlation =0.9729; correlation =0.7492 in both cases p<0.001) and between monocytes and neutrophils (correlation =0.7165; p<0.001). The rest of the correlation coefficients showed no statistical significance.

Discussion

The decrease of proinflammatory cytokines was very important, considering the therapeutic procedures which were implemented. This decrease was significantly lower for IL-6 and IL-8 after endoscopic sphincterotomy. IL-6 is a key one for inflammatory process [26]. The same behaviour was observed for IL-8, which is important for chemotactic activity of neutrophils. The positive correlation between the level of IL-6 and monocytes in the 1st day of study indirectly points to the crucial role of macrophages in the production of proinflammatory cytokines [27-29]. The observed decrease of the level of neutrophils may be connected to the implemented procedures, which definitively remove the etiological factor.

The level of TNF-α and IL-12p40 were relatively stable throughout the study. IL-12p40 probably plays a role in the development of necrotic changes in the pancreas, whereas TNF-α plays a role in the regeneration process [30]. For IL-1β we obtained only a few results which cannot be verified by statistical analysis. This is consistent with the observations of other investigators, and can be explained by the fact that this interleukin is produced by the involved organ, its half-life is very short and the tests used for its measurement are not very sensitive.

We believe that in the mild forms of acute biliary pancreatitis the improvement of bile flow is important. There are no clinical measurements which can guarantee that the stones which partially obstruct the biliary duct would not block its flow later. We observed an increase of bilirubin levels in 37 patients. We do not agree that increase of its level above 90 μmol/L is an indication for endoscopic sphincterotomy only [7]. In our patients, the lower levels were also associated with the presence of stones in the bile ducts, and its sphincterotomy produced normalisation. Many authorities in pancreatology reserve the early endoscopic sphincterotomy only for severe cases of biliary pancreatitis [7,11]. But the fact that this disease has an unpredictable clinical course makes such practice controversial. The initial clinical evaluation of the disease severity can change during the next few days. It is also known that even short but recurrent blockade of bile flow constitutes a fundamental risk factor for a severe course of pancreatitis [7]. Stone impaction may lead to severe pancreatitis or death [31,32]. The severe forms of acute biliary pancreatitis treated in our clinic will be presented in the next paper.

The small stones called microlithiasis are most dangerous. They cannot be visualized by any of the radiological methods. In addition, the oedema caused by passage of stones through the papilla of Vater can block bile flow [7]. From our experience this procedure is safe. We did not observe any complications connected with it. Moreover, the level of proinflammatory cytokines was significantly reduced after endoscopic sphincterotomy.

The following laparoscopic cholecystectomy did not influence the levels of measured interleukin, which gradually decreased. This procedure, except the removal of the reservoir of stones, allowed the objective evaluation of the pancreatitis severity. This management allowed also for a decrease of the interleukins.

This early surgical intervention enabled us to perform a laparoscopic procedure without the necessity of conversion to classical open cholecystectomy. This is in contrast to other investigators who perform cholecystectomy in the 5-7 day of hospitalization and report more than 10% conversions [21]. Also in our opinion early abdominal computed tomography in mild cases of patients with acute pancreatitis is unnecessary.

In our opinion in every patients with biliary acute pancreatitis, the endoscopic sphincterotomy should be done as early as possible and laparoscopic cholecystectomy should be performed early, because it allows the evaluation of morfological changes within the pancreas and around. The decrease of proinflammatory interleukin levels proves a benefit of the early implementation of minimally invasive techniques in management of these patients.

Acknowledgments

The authors thank Assistant Clinical Professor VA Hospital in Los Angeles Richard Pieton for his help in preparing the manuscript.

References

1. Acosta JM, Pellegrini CA, Skinner DB. Etiology and pathogenesis of acute pancreatitis. Surgery, 1980; 88: 118-25.
2. Acosta JM, Ledesma CL. Gallstone migration as a cause of acute pancreatitis. New Engl J Med, 1974; 290: 484-8.
3. Kelly TR. Gallstone pancreatitis: pathophysiology. Surgery, 1976; 80: 488-92.
4. Kelly TR, Swaney PE. Gallstone pancreatitis: the second time around. Surgery, 1982; 92: 571-5.
5. Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. New Engl J Med, 1992; 326: 589-93.
6. Kelly TR, Wagner DS. Gallstone pancreatitis; a prospective randomized trial of the timing of surgery. Surgery, 1988; 104: 424-8.
7. Steinberg WM, Chair, Barkin JS, Bradley EL, DiMagno E, Layer P. Controversies in Clinical Pancreatology. Steinberg WM, Neoptolemos JP, Folsch UR, Layer P (editors). The management of severe gallstone pancreatitis. Pancreas, 2001; 22: 221-9.
8. Uomo G, Slavin J. Endoscopic sphincterotomy for acute pancreatitis: arguments in favour. Ital J Gastroenterol Hepatol, 1998; 30: 557-61.
9. Imada R, Ayub K, Slavin J. Endoscopic retrograde cholangiopancreatography in gallstone acute pancreatitis. Cochran Library, 2003, 1: 1-7.
10. Kueppers PM, Russell DH, Moody FG. Reversibility of pancreatitis after temporary pancreaticobiliary duct obstruction in rats. Pancreas, 1993; 8: 632-7.
11. Neoptolemos JP, Carr-Locke DL, London N, Bailey IA, James D, Fossard DP. Controlled trial of urgent endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet, 1988; II: 979-83.
12. Fan ST, Lai ECS, Mok FTP, Lo CM, Zheng SS, Wong J. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. New Engl J Med, 1993; 328: 228-32.
13. Folsch UR, Nitsche R, Ludtke R, Hilgers RA, Creutzfeld W. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. New Engl J Med, 1997; 336: 237-42.
14. Nowak A, Nowakowska-Dulawa E, Maret TA, Rybicka J. Final results of prospective, randomised, controlled study on endoscopic sphincterotomy versus conventional management in acute biliary pancreatitis. Gastroenterology, 1995; 108: A380.
15. Zając A, Karcz D, Łukasiewicz J. Endoskopowa papillotomia w ostrym zapaleniu trzustki. Acta Endosc Pol, 1998; 8: 15-20.
16. Acosta JM, Katkhouda N, Nebian K, Groshen SG, Tsao-Wei D, Berne T. Early ductal decompression versus conservative management for gallstone pancreatitis with ampullary obstruction: a prospective randomised clinical trial. Ann Surg, 2006; 243: 33-40.
17. Acosta JM, Rossi R, Rubio Galli OM. Early surgery for acute gallstone pancreatitis: evaluation of a systemic approach. Surgery, 1978; 83: 367-70.
18. Acosta JM, Pellegrini CA, Skinner DB. Etiology and pathogenesis of acute biliary pancreatitis. Surgery, 1980; 88: 118-25.
19. Acosta JM, Rubio Galli OM, Rossi R. Effect of duration of ampullary gallstone obstruction on severity of lesions of acute pancreatitis. J Am Coll Surg, 1997; 184: 499-505.
20. Acosta JM, Ronzano GD, Pellegrini CA. Ampullary obstruction monitoring in acute gallstone pancreatitis: a safe, accurate, and reliable method to detect pancreatic ductal obstruction. Am J Gastroenterol, 2000; 95: 122-7.
21. Mai G, Baer HU, Uhl W, Muller Ch, Buchler MW. Timing of laparoscopic cholecyestectomy in acute biliary pancreatitis. Acute Pancreatitis. Novel concepts in biology and therapy. (ed.) Buchler MW, Uhl W, Friess H, Malfertheiner P. Blackwell Wissenschafts-Verlag-Berlin-Viena 1999, 377-86.
22. Becker V. Pathological anatomy and pathogenesis of acute pancreatitis. World J Surg, 1981; 5: 303-13.
23. Knaus W, Draper E, Wagner DP. APACHE II: a severity of disease classification system. Crit Care Med, 1985; 77: 633-8.
24. Ranson JHC, Rifkind KM, Roses DF. Prognostic sings and the role of operative management in acute pancreatitis. Surg Gynecol Obstet, 1974; 139: 69-81.
25. Bradley EL. A clinically based classification system for acute pancreatitis. Arch Surg, 1993; 128: 586-90.
26. Berney T, Gasche Y, Robert J, Jenny A. Serum profile of interleukin-6, interleukin-8, and interleukin-10 in patients with severe and mild acute pancreatitis. Pancreas, 1999; 18: 371-7.
27. Chen Ch-Ch, Wang S-S, Lee F-Y, Chang F-Y, Lee S-D. Proinflammatory cytokines in early assessment of the prognosis of acute pancreatitis. Am J Gastroenterol, 1999; 94: 213-7.
28. De Beaux A, Ross JA, Maingay JP, Fearon KCH. Proinflammatory cytokine release by peripheral blood mononuclear cells from patients with acute pancreatitis. Br J Surg, 1996; 83: 1071-8.
29. McKay CJ, Gallagher G, Brooks B, Imrie CW, Baxter JN. Increased monocyte cytokine production in association with systemic complications in acute pancreatitis. Br J Surg, 1996; 83: 919-23.
30. Pezzilli R, Minierro R, Cappelletti O, Barakat B. Behavior of serum interleukin 12 in human acute pancreatitis. Pancreas, 1999; 18: 247-51.
31. Wilson C, Imrie CW, Carter DC. Fatal acute pancreatitis. Gut, 1988; 29: 782-8.
32. Corfield AP, Cooper MJ, Wiliamson RCN. Acute pancreatitis: a lethal disease of increasing incidence. Gut, 1985; 26: 724-9.