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Prognostic Importance of Interleukins and Computerized Tomography in Assessment of the Outcome and Severity of Acute Pancreatitis

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Published Date: February 10, 2016

ABSTRACT

Background: The discovery of a highly specific and accurate system which could predict the severity of acute pancreatitis would have major significance in the treatment of these patients. The aim of this prospective study was to establish the prognostic importance of cytokines and computerized tomography **(CT)** in the assessment of the *severity* and out- come of acute pancreatitis.

Patients and methods: Sixty patients with the diagnosis of acute pancreatitis were divided into two groups by using the Ranson, Glasgow and APACHE II score systems. The first group consisted of 35 patients with mild acute pancreatitis and the second group of 25 patients with *severe* acute pancreatitis. A CT examination of the pancreas was performed in the first week of the disease and on the basis of the Balthazar score an index of severity of the acute pancreatitis defined. ln all patients the concentrations were found of the pro-inf1ammatory cytokines IL-6, IL-8 and TNF-a and the anti-inf1ammatory cytokines IL-lra and lL-10 in the serum, on Days 1,3 and 5 from the beginning of the disease.

Results: The values of the pro-inf1ammatory interleukins tested IL-6 were statistically significantly different between the groups tested on Days 1, 3 and 5 from the beginning of the disease. The values of the pro-inf1ammatory interleukin TNF-a were statistically significantly higher in the group of patients with severe acute pancreatitis, on Days 1, 3 and 5 from the beginning of the disease. The values of the interleukin IL-8 on Day 1 were statistically significantly higher in the group of patients with severe acute pancreatitis, but no statistically significant difference was found on Days 3 and 5 of measurement between the groups. A statistically significant difference was found regarding the anti-inf1ammatory interleukin IL-1ra on Days 1,3 and 5 from the beginning of the disease between the groups.

Conclusion: The most important predictors of the severity of acute pancreatitis are: pro-in-f1ammatory interleukin IL-6 on Day 1,3,5. On the basis of these predictors of the severity of acute pancreatitis IL-6, IL-8 i IL-l ra in the first week of the disease and definition of a CT point index in the first week of the disease, early prognosis is possible of the severity and outcome of the acute pancreatitis, and thereby early prevention of multi-organ dysfunction, which also reduces the morbidity and mortality rate in patients with acute pancreatitis.

Keywords: acute pancreatitis, cytokines

INTRODUCTION

Most attacks of Acute Pancreatitis **(AP)** are self-limiting and patients recover in a few days or weeks [1]. In some cases, however, the course of the disease is severe, with the development of organ failure (individual or multiple) and local complications. The incidence of the disease by genders is almost equal at 30-50/100,000 per head of the population a year', In 15-20% of cases there is a severe form of acute pancreatitis, with a mortality rate of at least 20%, or significantly higher if secondary pancreatic infections and sepsis develop [2]. The aetiological factors in acute pancreatitis are many [3]. The most common cause in women is cholelithiasis and in men pancreatitis is caused by excessive alcohol consumption [4]. The basic pathophysiological mechanisms of AP have still not been fully explained. In the new pathophysiological concept of severe pancreatitis, early activation of an inflammatory cascade and the development of microcirculatory disorder of the pancreas have a central place [4]. AP is a disease whose course is determined by its complications [5]. The main problems include septic complications, often caused by bacteria primarily originating from the intestines, and Multiple Organ Dysfunction Syndrome **(MODS)**, which is linked with high mortality of 30-50% [6]. Clinical and basic research has shown that massive systemic inflammatory response, and not pancreatitis in itself, leads to a fatal outcome in cases of severe forms of the disease [6], therefore, the "exclusion" of this inf1ammatory response would be a major success. Most patients with AP come to a doctor within 12 to 18 hours of the beginning of the disease, and the production of proinflammatory cytokines does not reach a peak until 36 to 48 hours, with the resulting MODS, which begins after 72 hours [7]. From this point of view it is clear that we have a very short interval during which it is necessary to act, with a speedy and accurate prognosis of the degree of severity of the

AP and specific therapy. The changes in the morphological structure of the pancreas, which lead to necrosis, can be seen on CT imaging within 48 hours, while in that time it is possible to find markers of pancreas infection and individual markers of immunological response of the organism for the sake of early prognosis of the severity and outcome of AP. The aim of this study was to determine the val- ues of pro-inflammatory (IL-8, lL-6, TNF-u) and anti- inflammatory (IL-Ira, IL-la) cytokines in the serum of patients with acute pancreatitis in the first week of the disease, so that by the multiple regression method early prognosis of the severity of the AP would be isolated from these cytokines.

MATERIALS AND METHODS

Sixty patients, who had been diagnosed with AP, were analysed by a prospective study. All patients were treated at the Surgical Clinic and Intensive care unit of the University Clinical Center **(UCC)** Tuzla, in the period from 2005 to 2007. Patients were divided in to two groups using the Ranson, extended Glasgow and APACHE II score systems: Group 1 were patients with mild pancreatitis (Ranson < 3, Glasgow < 3 and APACHE II < 8) (n=35); group 2 were those with severe pancreatitis (Ranson > 3, Glasgow > 3 and APACHE II > 8) (n=25). The diagnosis of AP was made on the basis of a combination of clinical and biochemical criteria: history and high levels of serum enzymes, and in all cases the diagnosis was confirmed by imaging techniques (ultra-sound and CT of the abdomen). For assessment of the severity of the pancreatitis, the established combined clinical and biochemical indexes were used (Ranson score index, extended Glasgow and the APACHE II score index).

Blood samples were taken for analysis from all patients on Day I, the n on Days 3 and 5 from the beginning of the disease. In all patients we found the values of the following parameters: dernographic data, CBC, blood glucose, potassium, sodium, calcium lactate dehydrogenase, aspartate aminotransferase, arterial p02, Acid- base status, proteinogram, total bilirubin, lipasis, TAP (trypsinogen activation peptide), neutrophil elastasis, urea and creatinins.

In the patients' plasma samples the concentrations of the following cytokines were established: IL-8, IL-6, TNF-u, IL-Ira, IL-10. The concentration of IL-Ira was found by using a commercial ELISA kit, by Qunatikine Systems USA, and the concentrations of IL-8, IL-6, TNF-u and IL-10 were found by the commercial ELI- SA kit by Milenia Biotec Germany, in the Institute for Laboratory Diagnostics, Immunology Department of the UCC Tuzla. All patients underwent CT examination of the pancreas with contrast, in order to establish the index of severity of AP according to the Balthazar score, with in the first week from the beginning of the disease (severity of pancreatitis was scored from 0-4, for the degree of necrosis of the pancreas from 0.6). Following their consent to take part in the research, two groups of subjects were formed (ASA I and ASA II). For data processing SPSS for MS WINDOWS Release 10.0 and Statistica for Windows Release 4.5 were used. The basic statistics were calculated for all variables per group. The differences between the group s were established by t-test and discriminative analysis. The statistical link between the variables examined was tested by.

RESULTS

We us ed at-test in order to test the differences between the subjects with MAP (Mild Acute Pancreatitis) and the subjects with SAP (Severe Acute Pancreatitis) within the group of variables relating to the demographic characteristics and aetiological factors of AP. There was a statistically significant difference regarding the sexes in both group s of subjects ($p<0.05$). The length of hospitalization for the group with MAP was 10.64±7.33 days, and for the group with SAP 26.85±6.56. There was a statistically significant difference regarding the length of hospitalization between the groups. Mortality in the first group was 0%, whilst in the second group it was 6 (24%) which is a statistical1y significant difference ($p=0.049$) (Table 1).

Table 2 shows the results of the t-test for the fol1owing score indexes: CT index of severity, Ranson, Glasgow and APACHE II between the groups. There is a statistically significant difference between mild and severe forms of AP regarding all the score indexes of severity of pancreatitis.

Establishing the difference in values of interleukins examined between subjects with MAP and subjects with SAP. In order to examine the difference between the groups the Pearson coefficient. Regression analysis showed the link between the criteria and other predictive variables on a level of significance of 5%.

of patients with MAP and SAP in terms of the group of variables relating to the value levels of inter1eukins IL-6. TNF-a IL-8. IL-l ra and IL-10 on Days 1,3 and 5 from the beginning of the disease, two test were used: test and discriminative analysis. The results of the t-test for each individual interleukin at three different times (Day 1, 3 and 5) are shown in Tables 3,4,5.

Table 3,4,5 shows that there is a statistically significant difference regarding the value of the interleukin IL-6 measured on Days 1, 3 and 5 in the serum of patients with mild and severe forms of acute pancreatitis. In the group of patients with MAP on the first day after the beginning of the disease, the mean lL-6 value in the patients' serum was 10.34±3.75, on Day 3 it was 8.82±3.39, and on Day 5 it was 5.85±2.63.

TNF-a values are extremely high in the first week of the disease in the group of patients with severe forms of AP and are an important predictor of the severity of AP. However although its values are as much as 6.5 times higher in the group of patients with severe forms of acute pancreatitis, high values of this interleukin were not found in patients with fatal outcome.

Mean values of the interleukin IL-8 were not statistically significantly different on Day 3 ($p=0.07$) and Day 5 ($p=0.103$). Values of the interleukin Il-8 in both groups of subjects rose during the first week of the disease, in that IL-8 was on the borderline of statistical significance on Day 1 ($p=0.049$).

IL-Ira was statistically significantly higher in the group of subjects with SAP on Days 1,3 and 5 in comparison with the group with MAP.

The values of interleukin IL-10 by group on the first day were not statistically significantly different (p=0.291) but on Days 3 and 5 they were statistically significantly higher in the group of subjects with SAP.

The results of the prognostic validity of anti-inflammatory interleukins IL-10 and ILI ra on Days 1, 3 and 5 obtained by regression of the entire sample with the eritrea variable C'I' is shown on Table 6. The multiple of R is 0.72 and is statistically significant, showing the good prediction of the predictor variable with the criteria variable. The multiple R2 explains the percentage variance between the predictor and the criteria, amounting to 52%. Of the individual predictor values or partial correlation coefficients, the best predictors for the criteria variable C'I' is the variable IL-l ra on Day 5 (p=0.002) then the variable IL-l ra on Day 1 (p=0.048) which is n the borderline of statistical significance.

It may be concluded that the other variables for the total sample of subjects were not good predictors for assessment of the severity of the acute pancreatitis using the criteria variable C'I. Beta represents the severity indicator which is given to a specific predictor. Multivariate analysis of all interleukins, which showed a statistically significant difference between the groups (p<0.05) even after re-grouping on the basis of the regression model, showed that only three interleukins were independent in relation to the severity of the acute pancreatitis according to the C'I' score index, that is: 1L-6 on Days I, 3 and S, IL-8 on Day S, and IL-Ira on Days 5 and I, which means a statistically significant difference in relation to the other interleukins, which makes them important predictors of the severity of the acute pancreatitis.

Table 1: Demographic data on subjects and aetiological factors of acute pancreatitis.

	MAP	SAP	p
	(n=35)	(n=25)	
Male	10 (28.57%)	8 (32%)	p=0.049
Female	25 (71.43%)	17 (68%)	p=0.027
Age	56.01 ±6.66*	60.94±8.87*	p=O.34**
Aetiological factors			
Cholelitiasis	29 (82.88%)	17 (68%)	p=0.021
alcohol	0%	4(16%)	p=0.018
idiopathic	1 (2.85%)	0%	p=O.7**
medical procedures (ERCP)	2 (5.71%)	2 (8%)	p=0.055
trauma	2 (5.71%)	2 (8%)	p=0.055
Metabolic diseases	1 (2.85%)	0%	p=0.7**
(hypertriglyceridemia)			
Hospitalization (days)	10.64±7.33*	26.85±6.56*	p<0.05
Mortality	O	6(24%)	p=0.049

Key: * (X±SD); ** (p>0.05).

Table 2: Distribution of the severity of acute pancreatitis according to the score indexes.

	MAP	SAP	p
	(n=35)	(n=25)	
CT index of severity of AP (week I)	1.28±0.78*	5.32±2.56	p=O.OOO
Ranson index (48 hours)	1.51±0.61	6.72±1.10	p=O.OOl
Glasgow index (48 hours)	1.71±0.75	6.16±1.49	p=O.OOO
APACHE II index (48 hours)	3.48±1.56	8.24±1.39	p=0.010

Key: * (X±SD).

Table 3: Values of interleukin's in serum on Days 1.

	IL-6	TNF-a	IL-8	IL-lra	IL-lO
MAP (n=35)	10.34±3.78*	6.94±2.41 *	280,08±100,32*	107.77±62.37*	4S.74±lS.97*
SAP (n=25)	13.88±2.S2	23.76±10.52	787,28±163,3	232.84±91.66	71.68±13.12
p	p=0.038	P<0.00l	p=0,049	P=0.0ll	P=0.219

Key: * (X±SD).

Table 4: Values of interleukin's in serum on Days 3.

	IL-6	TNF-a	IL-8	IL-l ra	IL-lO
MAP (n=35)	8.82±3.39	S.45±1.88	531,68±143,09	201.68±81.59	77.48±16.33
SAP (n=25)	17.80±2.70	34.12±10.17	917,4±135,6	525.92±151.75	148.44±35.88
p	p=0.030	P<0.00l	p=0,710	P=0.00l	P=0.00l

Key: * (X±SD).

Table 5: Values of interleukin's in serum on Days 5.

	IL-6	TNF-a	IL-8	IL-1ra	IL-lO
MAP (n=35)	5.85±2.63	4.48±1.57	792,88±143,7	345.31±151.12	163.91 ±43.91
SAP (n=25)	22.04±3.31	37.16±8.84	1285,56± 189,7	134.1 2±281. 99	295.44±80.77
p	p=0.026	P<0,00l	p=0,103	p=0.005	P=0.005

Key: * (X±SD).

Table 6: Multiple regression analysis of the C'I' variable in relation to pro-inflammatory cytokines.

Variable	B	Beta	T	SigT
IL-6 Day 1	-0.30	-0.44	-3.64	0.001
IL-6 Day 3	0.27	0.55	2.86	0.006
IL-6 Day 5	0.16	0.54	3.07	0.003
TNF-a Day 1	0.06	0.013	0.05	0.96
TNF-a Day 3	0.12	-0.024	-0.03	0.97
TNF-a Day 5	0.09	0.07	1.22	0.23
IL-8 first	0.42	0.51	1.69	0.096
IL-8 Day 3	-0.43	-0.38	-1.18	0.241
IL-8 Day 5	0.05	0.58	2.64	0.010

Multiple R	R Square	F	Signif F
.79	.62	6.55	.00

Table7: Multiple regression analysis of CT variable in relation of anti-inflammatory cytokine.

Variable	B	Beta	T	SigT
IL 1 ra Day 1	8.44	-.324	-1.49	.048
IL 1 ra Day 3	1.80	.140	.745	.460
IL 1raDay5	4.19	.737	3.28	.002
IL 10 Day 1	2.83	.218	1.39	.168
IL 10 Day 3	-3.03	-.052	-.211	.834
IL 10 Day 5	-8.68	-.031	-.164	.871

Multiple R	R Square	F	Signif F
.72	.52	9.40	.00

DISCUSSION

Early prognosis of Acute Pancreatitis (AP) is a key factor in the treatment of this disease. Amylase and lipase are generally accepted as diagnostic markets of AP, but they are not prognostic markers of the severity of the AP [8]. Many authors have tried to establish the best prognostic markers for AP, with the aim of an early therapy approach, and reduced morbidity and mortality rates. SAP occurs in 20-30% of cases and is characterised by a severe clinical course, multiple organ failure and pancreatic necrosis [1,8]. SAP is a disease whose course is determined by septic complications, often caused by bacteria, primarily of intestinal origin, and MODS, which is linked with a high mortality rate of 30-50% [9]. MAP or interstitial form mainly passes without complications, and with complete restitution of the gland within two weeks. However, SAP based on necrosis of the gland, have a high degree of morbidity and mortality which in some studies amounts to as much as 80% [10]. In our study, the mortality rate was 24% over the entire sample of subjects.

A true assessment of the severity of acute pancreatitis is based on clinical and laboratory evaluation, mainly numerical systems and imaging methods such as ultrasonography and contrast enhanced CT. The numerical systems (APACHE II, Ranson and Glasgow) indirectly indicate the severity of the disease with sensitivity of 70% [11]. The use of individual risk factors defined by laboratory tests, such as markers of pancreas infection and markers of inflammatory responses, are important in the prognosis of the severity of the disease. The CT index of severity of AP shows a positive correlation with the development of local complications and the mortality rate in patients with acute pancreatitis [9,11]. In our study, we showed a statistically significant difference between mild and severe forms of AP regarding the score indexes of the severity of AP. In the group of subjects with MAP, the mean value of the CT score index measured in the first week of the disease was 1.28±0.78, whilst for the same score index in the group of subjects with SAP it was 5,32±2.S6 (p< 0,001).

The main advantage of the APACHE II score index is the possibility of comparing it with other systems, and in that way it makes possible better supervision of patients as well as monitoring their response to the therapy used. The APACHE II is useful as an early prognosie indicator of the severity of pancreatitis, and after 48 hours the APACHE II score index is comparable with Ranson's score index in the assessment of the severity of pancreatitis, with confidence of 70% to 80% [12].

Despite the many different experimental and clinical studies on AP, no single accurate predictor of the outcome has yet been found. This study had the task of finding precisely that indicator. An ideal predictor of the severity and outcome of AP should be usable, simple, non-invasive, make early detection possible and certainly be a reliable predictor of the outcome of the disease [13]. It should also be possible to use in the early phases of the disease, so that when the possibility exists that complications of the disease could develop, those patients can be monitored more intensively and receive correct therapy. An understanding of a dinical study, in which the CT score index is used in combination with a numerical system of one ar more laboratory markers of the severity of pancreatitis, could give results in the prognosis of the severity of AP [9,12]. In this study we used a comparison of the CT score index of the severity of AP with specific interleukins in both groups of patients, in order to establish an early prognosis of the severity and outcome of the AP. The values of the proinflammatory interleukin Il-6 tested were statistically significantly different between the groups on Days 1,3 and 5 from the beginning of the disease. In the group of subjects with MAP the values of the IL-6 tested were statistically significantly lower and had a tendency to fall, whilst in the group with SAP the IL-6 values were statistically significantly higher and had a tendency to rise. The peak in the serum came after 72 hours and somewhat later than the other interleukins, which was understandable sinee its values in the serum of the patients tested was slightly lower. Our study dealt with examining the values of the interleukin IL-6 in patients with mild and severe forms of pancreatitis. Mayer found significantly higher values of IL-6 in the serum of patients with remate organ failure". The mean values of this interleukin in

their study were 22 pg/ml in MAP and in severe AP 68 pg/ml (p=0.006). In our study the mean value of IL-6 for MAP on Day 1 was 10.34 pg/rnl, on Day 3 8.82 pg/ml and on Day 5 5.84 pg/ml. For SAP on Day 1 it was 13.88 pg/rnl, on Day 3 17.8 pg/rnl, and on Day 5 22.04 pg/ml (p=0.038, p=0.030, p=0.026). The other pro-inflammatory interleukin we analysed in this study was TNF-a. The values of TNF-a were extremely high in the first week of the disease in patients with a severe form of AP and this is an important predictor of the se-verity of AP. However, although its values were as mu eh as 6.5 times higher in the group of patients with the severe form of AP, a high value of this interleukin was not found in patients with a fatal outcomes [14]. Higher levels of TNF-a are an indicator of a better prognosis in the sense of survival. All the patients with values above 200 pg/ml survival [14,15]. Proinflammatory interleukin IL-8 appears earliest in the serum of patients with AP, and in contrast to IL-6, its concentration remains increased for a long period of time. For this reason it may be used as a predictor of the severity of AP for days after the disease begins [11,14] n our study the mean values of interleukin IL-8 were not statistically significantly different on Days 3 and 5, whilst on Day 1 they were on the borderline of statistical significance between the groups. In research by a group of authors, the values of IL-8 for the group of subjects with MAP were 780 pg/rnl, and in the group of subjects with SAP they were 790 pg/ml (p>0.05) [9]. However, in research by other authors, the interleukin IL-8 was the best predictor of all the pro-inflammatory cytokines, indicating a more severe dinical picture and fatal outcome in AP [14]. In our study we only found a positive correlation with the severity of the pancreatitis on the first day measurements were taken. The antiinflammatory interleukin lL-1 ra is a natural inhibitor of IL-I. It acts as an inhibitor by competing with IL-la and IL-l ~ to bind with type I receptor IL-I. In our study the patients with SAP had significantly higher values of this cytokine on all three measurement Days. In the group with MAP its Day 1 value was 107.7 pg/rnl, Day 3 201.6 pg/ml and Day 5 345.3 pg/ml. In the group of subjects with SAP the mean value on Day 1 was 232.8 pg/rnl, Day 3525.9 pg/rnl, and on Days 1134.1 pg/ml. In the research study by a group of authors the mean values of IL-Ira showed a statistically highly significant difference in the groups examined (p< 0.01) [11]. Its values in this research were 2.7 times higher in the group of those who died [7]. In our study IL-l ra proved to be a good predictor of the severity of AP on the fifth day. Interleukin IL-I0 inhibits the synthesis and release of pro-inflammatory cytokines and is seen as a patent anti-inflammatory cytokine. Research by Simović found that concentrations of IL- 10 in the plasma of patients with severe forms of acute pancreatitis were extremely raised, especially in the group of patients who died [7]. The latest research shows how complicated the system is of cytokine signalization in acute pancreatitis and the resulting sepsis, and that there is overlap in the regulatory mechanisms [16]. For this reason individual application of antagonists of any cytokine does not ensure with certainty a better survival rate in patients with a severe form of AP. In our study the mean values of interleukin lL-10 in the groups were not statistically significantly different on Day 1, but on Days 3 and 5 they were statistically significantly higher in the group of subjects with AP. It is evident that there was a statistically significant difference between the groups on Days 3 and 5 (p<0.05). Our results are also confirmed by the results of a

group of Japanese authors, which state that values of IL-10 in the serum of patients suffering from a severe form of AP were significantly higher than the values of the same interleukin in the serum of patients with a mild form of AP [16]. Therefore, it is a significant early predictor of the severity of AP.

CONCLUSION

On the basis of the established predictors of the severity of acute pancreatitis (IL-6, IL-8 and IL-Ira.) and by using the CT score index in the first week of the disease, early prognosis is possible of the severity and outcome of acute pancreatitis, and thereby also early prevention of multiple organ dysfunction and a reduction in the morbidity and mortality rates in patients with severe forms of the disease.

References

1. Mešić D, Hasukić Š, Prašo M, Odobašić A, Kadrić N, et al. Operativno liječenje akutnog pankreatitisa. Acta Med Sal. 2004; 33: 139-146.
2. Romero- Ughart G, Phillips J. Pancreatitis acuta Am J Gastroenterol. 2007; 34: 234-245.
3. Beger HG, Rau B, Mayer J. Natural course of acute pancreatitis. World J Surg. 2002; 21: 130-135.
4. Saluja AK, Steer ML. Pathophysiology of pancreatitis: role of citokines and other mediators of inflammation. Digestion. 1999; 60: 27 -33.
5. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med. 1994; 330: 1198-1210.
6. Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. Am J Surg. 1998; 175: 76-83.
7. Simović MO, Bonham MJD, Abu-Zidari FM, Wind-sor JA. Antiinflamammatory cytokine response and clinical outcome in acute pancreatitis. Crit Care Med. 1999; 27: 2661-2665.
8. Mayer J, Rau B, Gansauge F, Beger HG. Intlammatory mediators in human acute pancreatitis: dinical and pathophysiological implications. Gut. 2000; 47: 546-552.
9. Mortele KJ, Wiesner W, Intriere L, Shankar S, Silverman SG. A modified CT severity index for evalu- ating acute pancreatitis: Improved correlation with patient outcome. AJR. 2004; 183: 1261-1265.
10. Mirković D, Šurbatović M, Filipović N, Radaković S. Prognostički značaj pro i anti-inflamatornih citoki- na u procijeni težine i ishoda akutnog pankreatitisa. Jugoslav Med Biohem. 2005; 24: 253-257.
11. Balthazar EJ. Staging of acute pancreatitis. Radiai Clin North Am. 2002; 40: 1199-1209.
12. Bradley EL. A dinically Based Classification System for Acute Pancreatitis. Arch Surg. 1993; 128: 586- 590.
13. Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. Am J Surg. 1998; 175: 76-83.
14. Pooran N, Indaram A, Singh P, Bank S. Cytokines (IL-6, IL-8, TNF): early and reliable predictors of severe acute pancreatitis. J Clin Gastroenterol. 2003; 37: 263-266.
15. Frossare JL, Pastor CM. Experimental acute pancre- atitis: new insights in to patho-physiology. Frontiers in Bioscince. 2002; 7: 275-287.
16. Crozier TA, Muller JE, Quittkat D, Sydow M, Wuttake W, et al. Effect of anesthesia on the cytokine responses to abdominal surgery. Br J Aneesth. 1994; 72: 280-285.