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Correlation of Procalcitonin and C-Reactive Protein with Intra-Abdominal Hypertension in Intra-Abdominal Infections: Their Predictive Role in the Progress of the Disease

Bedri Braha[1], Dafina Mahmutaj[1], Mehmet Maxhuni[1], Burim Neziri[2], Shaip Krasniqi[2*]

[1]Clinic of Surgery, University Clinical Center of Kosovo, Prishtina, Kosovo; [2]Faculty of Medicine, University of Prishtina "Hasan Prishtina", Prishtina, Kosovo

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***Correspondence:** Shaip Krasniqi. Faculty of Medicine, University of Prishtina "Hasan Prishtina", Prishtina, Kosovo. E-mail: shaip.krasniqi@uni-pr.edu

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Abstract

AIM: To analyse the correlation of procalcitonin (PCT) and C-reactive protein (CRP) values with increased intra-abdominal pressure and to evaluate their predictive role in the progression of Intra-abdominal infections.

MATERIALS AND METHODS: A non-randomized prospective study conducted in the group of 80 patients. We have measured the PCT, CRP and intra-abdominal pressure (IAP).

RESULTS: According to IAH grades (G), there was a significant difference of PCT values: G I 3.6 ± 5.1 ng/ml, G II 10.9 ± 22.6 ng/ml, G III 15.2 ± 30.2 ng/ml ($p = 0.045$) until CRP values were increased in all IAH groups but without distinction between the groups: GI 183 ± 64.5, GII 196 ± 90.2, GIII 224 ± 96.3 ($p = 0.17$). According to the severity of the infection, we yielded increased values of PCT, IAP and CRP in septic shock, severe sepsis and SIRS/sepsis resulting in significant differences of PCT and IAP.

CONCLUSION: Based on the results of our research, we conclude that the correlation of PCT values with IAH grades is quite significant while the CRP results remain high in IAH but without significant difference between the different grades of IAH.

Introduction

Intraabdominal infections are defined as peritoneal inflammation in response to microorganisms [1]. Despite the achievements in the diagnosis, management, and proper treatment of patients with intra-abdominal infections the presence of secondary peritonitis reflects the critical prognosis, which has a high mortality rate of up to 30% [2] [3] [4] [5] [6]. Early prognosis estimation of complicatediIntra-abdominal infections is important in evaluating the severity of the disease sinceiIntra-abdominal infections might advance to severe sepsis and septic shock [4]. It is often associated with hypoperfusion followed by tissue damage and organ dysfunction following increased severity of systemic response to infection [7] [8] [9]. There are some promising biomarkers for sepsis that are currently used for relatively few diagnostic purposes [10]. Studies are aimed to find a single marker at low cost, that can be measured quickly, to repeat measurement easy, and that measurement does not cause disturbances in patients [11]. From this group of biomarkers, CRP and PCT are most commonly used in clinical practice [10]. CRP is the acute phase protein synthesised in the liver and is released after inflammation and tissue damage [12] [13].

In many studies, the role of PCT in the diagnosis and treatment of systemic and local infections was investigated, includingiIntra-abdominal infections [14]. PCT in secondary peritonitis has improved diagnostic value for identification of patients with severe sepsis endangered by septic shock [15]. Bacterial infection is a strong PCT stimulus, while viral systemic inflammation results in PCT values to be low [14][16]. In recent years, there was expressed interest iniIntra-abdominal hypertension (IAH) that is defined as a pathological increase ofiIntra-abdominal pressure above 12 mmHg [17]. IAH is determined by the elasticity of the abdominal wall/diaphragm, the volume

of internal organs and the presence of ascites, blood, and intestinal contents. Some abdominal clinical conditions (peritonitis, ileus, volvulus, pancreatitis, complications after abdominal surgery) and systemic conditions (sepsis, mechanical ventilation, pneumonia, and burns) found to be related with IAH [17].

The purpose of this prospective study is to compare the values of PCT and CRP with IAP grades toiIntra-abdominal infections and determination of the correlation between them, and correlation of these parameters about the severity of the infection, which points to their predictive role in evaluating the prognosis of the disease.

Materials and Methods

This is a prospective, controlled clinical trial involving hospitalised patients at the University Clinical Center of Kosovo in Pristina, registered in the period from July 2016 to February 2017. The research was conducted at the University Clinical Center of Kosovo, Pristina, where 80 patients were hospitalised as abdominal cases in whichiIntra-abdominal hypertension was present. The research protocol has been approved by the Ethics Committee within the University of Prishtina – Faculty of Medicine and the consent form is completed by all participants or their family members.

Inclusion Criteria: Age over 18 years, the presence of SIRS due toiIntra-abdominal infections, the presence of intra-abdominal hypertension, consent from the patient's relatives.

Exclusion criteria: Urinary trauma, urinary bladder injury, immunosuppression, chronic kidney failure, liver cirrhosis, SIRS is not present, long-term use of corticoids, acute hepatic insufficiency, diabetes.

Protocol and Treatment

The baseline criterion during the research was the measurement of the IAP before the operation every four hours, and it was evaluated as IAH if the average of these measurements was > 12 mmHg. The measurement was performed even after the operation, where the measurement was performed three times in 24h, and the mean was calculated for each day. The duration of the measurement has continued until the normalisation of the IAP. TheiIntra-abdominal pressure measurement was done by the method evaluated by Kron. PCT and CRP measurement were performed before surgery, after the 1st, 4th and 7th days and the following days after the surgery if necessary. The PCT marker level measurement is done with the Elecsys BRAHMS method. Laboratory measurements and analyses that are relevant to the designation of IAH / ACS (Intra - abdominal Hypertension / Abdominal Compartment Syndrome), MODS (Multiple Organ Dysfunction Score), APACHE II (Acute Physiology and Chronic Health Evaluation), SOFA (Sequential Organ Failure Assessment), IMP (Index Mannheim Peritonitis), MAP (Mean Arterial Pressure) were realized. The fluid balance in the body is determined based on the weight, ordinated juices, and diuresis APP (APP = MAP - IAP) before and after surgery, FG (FG = MAP - 2IAP) before and after surgery. Based on the clinical, laboratory and general findings, the severity ofiIntra-abdominal infection has been classified into three groups: SIRS/sepsis, severe sepsis and septic shock. At the same time, based on the values of IAP, patients are grouped into three groups: Grade I: IAP 12 - 15 mmHg, Grade II: IAP 16 - 20 mmHg, Grade III: IAP 21 - 25 mmHg. There are also cases involving ACS in GIII. In the realised measurements, we did not have cases with IAP > 25 mm Hg. The PCT and CRP relationships with IAP grades, APP, FG, diuresis and fluid balance also were analysed in correlation with these parameters according to the severity of the infection.

Statistical Analysis

Statistical data processing was performed with the statistical package SPSS 22.0. The arithmetic average, the standard deviation, the minimum and the maximum values were calculated. Spearman correlation coefficient was used for non - parametric data. Qualitative data testing was done with the Pearson's chi-squared test ($\chi 2$) and the exact Fisher test of quantitative data that had a normal distribution with T-test and One Way ANOVA, while those with non - normal distribution with the Mann - Whitney test or Kruskal Wallis test. The difference is significant if $P < 0.05$.

Results

In the study, procalcitonin and CRP were analysed about IAH of diagnoses of different structures withiIntra-abdominal infections.

In Table 1, we presented the patient's related characteristics and the diagnosis structure of these patients about the three grades of IAH. In the total cohort of patients, male patients were dominant in comparison to females (54 vs 26). The average age of the participants was 49.4 years (SD ± 18.3 years), ranging from 18 to 56 years. The results showed a significant difference ($P < 0.003$) between the age of the patients, the gender and the degree of IAH. First-degree hypertension was registered in 46 or 57.5%,

second degree in 24 or 30.0% and third degree in 10 or 12.5% patients. Regarding the diagnosis structure, acute perforated appendicitis with diffuse peritoneal diffuse has dominated all degrees of IAH In cases with SIRS/sepsis, the presence of GI hypertension was more common in severe sepsis, and septic shock GII and GIII of IAH were more pronounced. Abdominal Compartment Syndrome was present at 4 (5%) cases (Table 1).

Table 1: Characteristics of the patients involved in the study

	Intra-abdominal Hypertension			
	G I	G II	G III	P
Age	43.3 ± 17.5	57.3 ± 17.5	58.2 ± 14.2	0.003[a]
Female	15 (57.7%)	6 (23.1%)	5 (19.2%)	0.366[b]
Male	31 (57.4%)	18 (33.3%)	5 (9.3%)	0.366[b]
Appendicitis acuta gangrenosa perforativa. Peritonitis diffusa fibro purulenta	21	6	4	
Cholecystitis gangrenosa	2	2	-	
Dehiscencio suttura duodeni ,peritonitis diffusa fibropurulenta	1	-	-	
Duodenopancreatectomia cefalica,dehiscencio anastomosis pancreato-jejunalis	-	-	1	
Hernia ventralis per magna.Incarceratio intestine ilei et perforation ilei	-	-	1	
Dehiscencio entero - entero anastomosis	4	5	2	
Perforatio diverticulum Meckeli,Peritonitis seropurulenta	-	1	-	
Perforatio in loci GEA.Peritonitis diffusa	1	-	-	
Perforation liberal	4	2	-	
Perforatio sigmae,Colitis ulcerosa,peritonitis diffusa stercoralis	1	-	-	
St post histerectomiam.Peritonitis fibropurulenta	-	1	-	
Tu perforans colonies colonies	-	1	1	
Ulcus bulbi duodeni perforans. Peritonitis fibropurulenta	10	3	1	
Ulcus ventriculi perforans abscessus multiplices intestini	-	1	-	
Vulnus sclopetarium abdominis.Laesio intestine .peritonitis difusa	2	2	-	
SIRS/Sepsis	41 (70.69%)	14 (24.14%)	3 (5.17%)-ACS(n=1)	
Severe Sepsis	4 (25%)	6 (37.5%)	6 (37.5%)-ACS(n=2)	
Septic Shock	1 (16.7%)	4 (66.6%)	1 (16.7%)-ACS(n=1)	

a - Kruskal Wallis test, b- X^2 – test.

The PCT and mortality rates determined by the scales: APACHE, SOFA, IMP, MODS before surgery, which have been observed in higher results for IAH patients. All these parameters were statistically significant by IAH grades. CRP results to be increased at all levels of IAH but without statistical significance among groups. MODS was 0 % in 19 patients out of which 3 were with GII and 16 were with GI of IAH, at the same time, PCT in these cases was < 2 ng / ml except for only one case with PCT values of 10 ng/ml. SOFA mortality was < 10 % in 18 patients, 14 with GI and 4 with GII of IAH, and PCT > 2 ng/ml in one patient. The GII, GIII / ACS, values of FG, APP, diuresis and fluid balance were significantly reduced, and we have distinguished significant statistical significance of these parameters by IAH grades (Table 2).

Table 2: Predictive parameters in admission in accordance with intra - abdominal pressure degrees

	Abdominal Urgencies n = 80			
	GI (n = 46)	GII (n = 24)	GIII (n = 6)/CSA (n = 4)	P
PCT	3.6 ± 5.1	10.9 ± 22.6	15.2 ± 30.2	0.045[a]
CRP	183.7 ± 64.5	196.3 ± 90.2	224.4 ± 96.3	0.17[a]
FG	56.0 ± 10.8	48.7 ± 25	37.1 ± 16.2	0.005[b]
APP	69.1 ± 10.8	66.1 ± 24.2	56.3 ± 17.3	0.096[b]
Diuretics and fluid balance	1.0 ± 0.5	0.6 ± 0.4	0.4 ± 0.5	<0.0001[a]
SOFA-mortality	11.1 ± 14.2	28.8 ± 27.0	39.6 ± 24.9	0.0001[a]
APACHE II- mortality	12.3 ± 14.7	31.8 ± 26.9	40.4 ± 22.8	<0.0001[a]
IMP- mortality	15.0 ± 12.7	29.3 ± 24.2	38.6 ± 22.4	0.003[a]
MODS- mortality	7.3 ± 12.3	19.3 ± 22.5	26.2 ± 29.8	0.0004[a]

A - Kruskal Wallis test; b - One Way ANOVA. PCT - procalcitonin, CRP - C reactive protein, FG - Filtration gradient, APP - abdominal perfusion pressure, SOFA - Sequential Organ Failure Assessment, APACHE - Acute Physiology and Chronic Health Evaluation IMP - Index Mannheim peritonitis, MODS - Multiple Organ Dysfunction Score.

The analysis of the values of IAP and PCT in all cases involved in the research results with a significant positive correlation of a medium scale (r = 0.42, P < 0.0001) (Fig. 1).

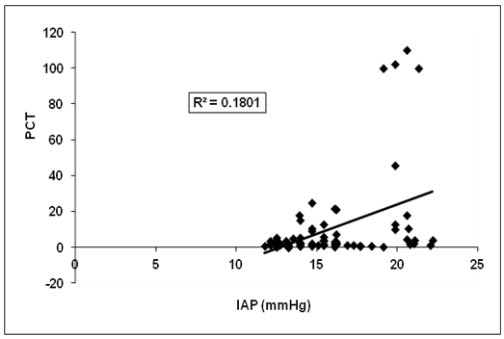

Figure 1: Correlation between intra-abdominal pressure and PCT values

A significant positive correlation of a middle degree was observed with the correlation of Sperman (r = 0.44, P < 0.0001) between IAP and CRP values (Fig. 2).

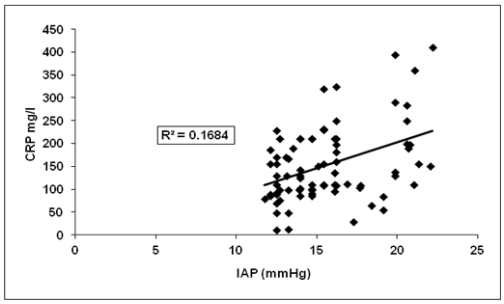

Figure 2: Correlation between intra-abdominal pressure and CRP values

Intra-abdominal pressures, analysed according to the severity of the infection, resulting in higher values for all groups. However, the statistical difference lies within the category of the infection before surgery and the following 4 - day post-surgery period. Even in PCT, we gained statistical significance by infection category before surgery, in day 1 and 4 post - surgery. CRP values were increased in all groups, but there was no significant difference according to the severity of the infection (Table 3).

Table 3: Correlation of PCT and CRP with IAH according to the severity of the infection

	Abdominal IUrgencies			
	Septic Shock	Severe Sepsis	SIRS/sepsis	P
IAP before Surgery	18.4 ± 2.8	18.3 ± 3.2	14.7 ± 2.3	0.0002[a]
IAP after surgery – day 1	16.4 ± 4.0	16.4 ± 3.2	11.8 ± 2.1	<0.0001[b]
IAP after surgery – day 2	16.5 ± 4.1	14.76 ± 3.6	10.1 ± 2.3	<0.0001[a]
IAP after surgery – day 3	15.8 ± 0.97	12.2 ± 3.71	9.8 ± 2.06	0.0031[a]
IAP after surgery – day 4	17.62 ± 8.37	11.31 ± 6.25	9.45 ± 0.72	0.0500[a]
PCT before surgery	49.2 ± 46.6	9.3 ± 12.1	3.1 ± 4.6	0.0002[a]
PCT after surgery – day 1	42.4 ± 48.2	6.5 ± 7.6	2.1 ± 2.6	0.0024[a]
PCT after surgery – day 4	43.3 ± 37.3	3.3 ± 3.4	0.8 ± 0.8	<0.0001[a]
CRP before surgery	189.9 ± 114.4	187.0 ± 90.2	140.6 ± 73.5	0.1447[a]
CRP after surgery – day 1	210.3 ± 117.1	124.7 ± 80.2	115.1 ± 64.7	0.894[a]
CRP after surgery – day 4	124.2 ± 98.2	101.2 ± 48.1	97.1 ± 51.8	0.264 [a]

a - Kruskal Wallis test; One Way ANOVA test.

Discussion

In this clinical study, PCT and CRP correlation with IAH and their predictive role in evaluatingiIntra-abdominal infections with peritonitis were evaluated. Our findings indicate a significant positive correlation of a middle degree ($r = 0.44$, $P < 0.0001$) between IAH and PCT values ofiIntra-abdominal infections. Medium - scale correlation was also found between CRP and IAH iniIntra-abdominal infections ($r = 0.42$,$P < 0.0001$).

Moreover, we have investigated the correlation of PCT, CRP, APACHE II, MODS, SOFA, IMP, APP, FG, diuresis and fluid balance about IAH grades. The results showed a statistical significance of these parameters, and exposure of IAH yielded a predictive role of PCT and IAH in the course of the disease. There is relevant evidence that proves the PCT correlation with IAH, involving only acute pancreatitis. Berenau et al., analysed the correlation between maximum IAP values and mean PCT values in acute pancreatic patients, which was highly significant [18]. Bettina M. Rau et al., [19] has established conclusion that pancreatic patients with acute pancreatitis, with infected pancreatic necrosis and MODS or those who have died have significant association with PCT's high values compared to complications, while Bezmarevic concludes that in the first 24 hours acceptance of acute pancreatitis to determine the severity of the disease PCT has higher sensitivity and similarity to APACHE II while CRP has low sensitivity in this regard, at the same time the growth of IAP is followed by increased PCT, so there is a correlation between these parameters and have a predictive role of disease progression [20].

In our study, the PCT values were high in severe sepsis and septic shock patients. High PCT values in septic shock were also found in other studies [21] [22] [23]. Despite that CRP values are high in all IAH groups of our study; there is no significant difference between groups. Many authors conclude that patients with a severe degree of IAH manifest, evident clinical changes in cardiovascular function [24] [25] [26], splanchnic hypoperfusion [27] and acute renal failure [28] [29]. The high values of the IAP result in organ dysfunction, which results in high values of the MODS escalation [30] [31]. The development of purulent peritonitis increases the IMP degrees that correspond to the growth of the IAP [32]. In other studies, results showed that the IAH presence was associated with significant increases in the SOFA scaling indicating that the IAH has negative effects not only on the abdomen but also on the function of other organs [33] at the same time the high values ofiIntra-abdominal pressure are in correlation with high APACHE II values [33] and complied to the data from our study. Studies conducted to confirm that patients with IAH and high scores of SOFA and APACHE II have a worse clinical prognosis for hospital treatment and intensive care [33] [34] [35] [37]. Taking into account the correlation of APACHE II with PCT it has been concluded that the increase in values of this marker is related to the severity of the disease and is the early marker of sepsis [29] APACHE II shows significant PCT correlation in dysfunctional and non - dysfunctional patients, whereas CRP correlation with APACH II was not significant [28]. Similar data are also provided by Lopez et al. [34].

In our study of GII, GIII/ACS we had a decrease in the GF, APP, diuretic and fluid balance values and we have gained a distinction of statistical significance of these parameters by the IAH grades. Even in other studies, patients who did not survive had high levels of IAP and low values of APP, diuresis and fluid balance and FG [33] [37] [38]. In the research work of Kovac, it turns out that APP has a significant correlation with MODS, APACHE II and SIRS until the IAP shows no correlation with these parameters [32].

PCT and IAP transmitted before and after the operation resulted in higher values of probability of septic shock and severe sepsis have a significant difference in these parameters according to the severity of the infection, indicating that the deterioration of the overall state of the average of these parameters grows. CRP values are increased, but there is no significant difference according to the severity of the infection. Nargis findings show that PCT is more predictive than CRP in identifying and assessing the severity of sepsis even though both markers cannot differentiate infectious and non - infectious clinical syndromes [39]. In our study, we also found that PCT is more reliable in assessing the severity of the disease. PCT remains elevated in patients with severe sepsis and septic shock; this increases the risk of mortality regardless of the level [15] [39] [40].

The study performed by Sameh in 25 patients diagnosed as SIRS, sepsis, severe sepsis and septic shock with aetiology from all organs, analysed the PCT and CRP valued and its data resulted that CRP does not show any degree of differentiation of severity of sepsis [41]. Similar data was also given in the study conducted by Castelli [42] that corresponds to the data from our research.

In conclusion, the increase in IAP is followed by increased PCT and CRP values. In this study, we have identified the correlation in the values of PCT and CRP toiIntra-abdominal infections where IAH is present. PCT results are high in all cases with IAH, and there is a significant statistical significance by IAH grades in the first 24 hours. However, CRP results are high but without a significant difference to IAH grades. High PCT and IAP values are evident in severe sepsis and septic shocks that are correlated with low FG, APP, diuresis and fluid balance and high mortality rate scores. The role of PCT iniIntra-abdominal infections is of greater diagnostic and predictive value compared

to CRP values; however, the role of CRP remains important for the identification of other clinical circumstances.

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