ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2019 Apr 30; 7(8):1282-1286.
https://doi.org/10.3889/oamjms.2019.292
eISSN: 1857-9655
Clinical Science

The Role of Presepsin in Patients with Acute Surgical Diseases

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Citation: Mugazov M, Turgunov Y, Kaliyeva D, Matyushko D, Koishibayev Zh, Omertayeva D, Nurbekov A, Koishibayeva L, Alibekov A. The Role of Presepsin in Patients with Acute Surgical Diseases. Open Access Maced J Med Sci. 2019 Apr 30; 7(8):1282-1286. https://doi.org/10.3889/oamjms.2019.292

Keywords: Intra-abdominal hypertension; Compartment syndrome; Presepsin; sCD14: D-dimer

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Received: 27-Feb-2019; **Revised:** 14-Apr-2019; **Accepted:** 15-Apr-2019; **Online first:** 25-Apr-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

AIM: The purpose of this study was to determine the level of significance of markers in the development of intra-abdominal hypertension in patients with acute surgical diseases of the abdominal cavity.

METHODS: The authors surveyed 100 patients who were monitored at the Regional Clinical Hospital, Karaganda. The criterion for inclusion in the study was the informed consent of patients to participate in the study, the presence of acute surgical pathology, and the monitoring of intra-abdominal pressure over time. The exclusion criteria for patients from the study is the presence of sub and decompensation of associated diseases: trauma (hematoma of the bladder), bladder tumour and impaired integrity of the pelvic ring. The design of the study was by the legislation of the Republic of Kazakhstan, international ethical norms and normative documents of research organizations, approved by the ethics committee of the Karaganda State Medical University.

RESULTS: According to the world scientific literature, there are 4 indicators that change their value in response to increases in pressure in the abdominal cavity: fibrinogen and prothrombin index (the main indicators of the coagulogram); marker of blood clots D-dimer; early marker of translocation of bacterial flora into the bloodstream sCD14 (presepsin).

CONCLUSION: The authors concluded that the obtained data indicate that an increase in intra-abdominal pressure in acute surgical diseases of the abdominal cavity causes hypercoagulation and an increase in presepsin. Monitoring IAP with simultaneous measurement of the level of presepsin significantly improves the stratification of critical patients in need of emergency surgery.

Introduction

Intraabdominal hypertension (IAH, intraabdominal pressure, IAP) is one of the most dangerous complications of the abdominal catastrophe in patients with acute surgical diseases. The main reason for the lethality from abdominal compartment syndrome is the translocation of microorganisms with the development of abdominal sepsis. Surgical abdominal sepsis takes 30% from all it cases [1] and is the principal cause of the death rate in the surgical departments of intensive therapy (IT) [2], [3]. The multivariable character of development of acute surgical pathology of abdominal organs, a complication of pathogenesis, creates problems for determination of diagnostics criteria and an adequate surgical correction. The traditional biomarkers of systemic inflammatory response syndrome (SIRS) or abdominal sepsis are not always sufficiently informative for early diagnosis and monitoring of systemic infection.

Currently focuses on the study of presepsin and D-Dimer for an in-depth understanding of SIRS, abdominal sepsis and severe sepsis.

Presepsin is the circulating concentration of protein in the blood increases rapidly with the

development of systemic infections, sepsis, severe sepsis and septic shock, it was first described in 2005 by a group of researchers from the Medical University, Iwate, Japan [4].

Presepsin is a membrane glycoprotein with a molecular weight of 55 kDa. The mCD14 is expressed on the surface of monocytes/macrophages, neutrophils, chondrocytes, the cells, dendritic cells and other mature myeloid cells [5], [6].

The mCD14 is a receptor, which "learns" the signal of the infecting bacteria presence and turns the nonspecific immunity system and inflammatory process on [7], [8].

The mCD14 may independently communicate with LPS and turns activation signal of macrophages, a special lipopolysaccharide-binding protein on (LSB, LBP lipopolysaccharide-binding protein), improves the effectiveness of such a binding in the 100-1000 times.

In vivo, at low LPS (low numbers of bacteria that can grow quickly) LSB in advance "strengthens" signal for activation of the inflammatory response [9].

In addition to endotoxin of gram-negative bacteria, LSB specifically binds to cell wall components: gram-positive bacteria — lipoteichoic acids, peptidoglycans [10]; mycobacteria — lipoproteins, lipomannans [11]; Mycoplasma — lipopeptides [12]; spirochete — glycolipids and lipoproteins [13] and fungi [14]. The spectrum of microorganisms, activating monocytes/macrophages through interaction with mCD14 are very wide. The mCD14 receptor associated with the LSB-LPS complex is activated and transmits a signal to the TLR4 co-receptor located next to the membrane and related to the so-called Toll-like receptors (Toll-like receptor), which activate non-specific immunity. After activation of macrophages mCD14 is disconnected from the membrane, goes into circulation and becomes soluble sCD14 (s-soluble). sCD14 function-is induction of inflammation in endothelial and other cells that do not have mCD14 and do not respond to endotoxins. It is assumed that the circulating sCD14-marker of monocyte response to the action of LPS; increased blood sCD14 levels are associated with the severity of inflammation and septic shock [15].

Presepsin is an early biomarker of sepsis development, which reliability is 100%, confirmed by hemocultures, diagnoses sepsis is defined before manifestation of clinical symptoms and predicts treatment outcomes, with dynamic monitoring, reflects the real severity of sepsis, changes rapidly depending on the effectiveness of therapy, predicts recurrence of sepsis after remission, when clinical characteristics temporarily normalize [16], [17], [18], [19], [20], [21], [22].

The purpose of the study was to assess the relationship of the level of presepine with the development of intraabdominal hypertension in patients with acute surgical deseases.

Material and Methods

The present study is based on clinical observations of 100 patients with various acute surgical diseases who were hospitalised and operated in the regional clinical hospital of Karaganda in 2017. Among them 52 (52%) men and 48 (48%) women. The number of men as a whole exceeded the number of women by an average of 1.08 times.

The design of this study was approved by the ethical Commission at Karaganda state medical University.

The age of patients ranged from 20 to 80 years (mean age — 46.66 years). At the same time, the age composition was dominated by young patients: younger than 25 years – (7.3%), 25-44 years – (38.1%), 45-60 years – (29.3%), older than 60 years – (25.3%) patients. It was found that the prevalence of diseases of the abdominal cavity is high in the groups of patients 25-44 and 45-60 years.

Clinical and laboratory-instrumental examination of patients with acute surgical pathology before surgery allowed to distribute patients according by nosology (the structure of patients):

- acute appendicitis 16 (16%),

- acute intestinal obstruction 37 (37%) patients,

- pancreonecrosis 5 (5%),

- perforated ulcer 22 (22%) patients,

- acute cholecystitis (mechanical jaundice) 15 (15%) patients,

- varicose veins of the lower extremities (control group) 5 (5%) patients.

Criteria for inclusion of patients in the study were the presence of acute surgical pathology: acute intestinal obstruction, acute appendicitis, pancreatic necrosis, perforated ulcer, acute cholecystitis (mechanical jaundice),

Control group is the patients with varicose veins of the lower extremities; the age of patients 20-80 years of age; disease duration more than 24 hours.

Group of patients:

1. group-patients with IAD within normal limits (0-4 mmHg).

2. group-patients with IAD 5-15 mmHg art.

3. group-patients with IAD 16-25 mmHg art.

4. group-patients with IAD 26-35 and more mmHg.

A common criterion for excluding patients from the study (for all groups) is the presence of sub- and decompensation (remission) of comorbidities,

injury (hematoma) and swelling of the bladder. Concomitant pathology in the studied patients was in remission, which was confirmed by anamnesis and clinical and laboratory.

Measurement of IAP was carried out using the device "Triton-electronics", invasive portable electronic meter Autonomous Central venous pressure and other low pressures in various cavities of the human body.

25 or 50 ml of warm sterile isotonic sodium chloride solution was injected into the emptied bladder with a syringe without a needle. The urinary catheter was connected to the device "Triton-electronics". The zero value was set at the level of the pubic junction.

Currently, this method is the "gold standard" for indirect measurement of intraabdominal pressure. All patients underwent 3 measurements of intraabdominal pressure-before surgery, as well as 6 and 24 hours after surgery.

As a result of the IAP measurement of all patients before surgery were divided into 4 groups depending on the degree of IPG:

0 group-IAP 0-11 mm Hg, 6 patients (6%),

group 1-IAP 12-15 mm Hg, 9 patients (9%),

group 2-IAP 16-20 mm Hg, 26 patients (26%),

group 3-IAP 21-25 mm Hg, 23 patients (23%),

group 4-IAP more than 25 mm Hg, 36 patients (24%).

Results

According to the world scientific literature, there are 4 indicators that change their value in response to increased abdominal pressure: fibrinogen and prothrombin index (PTI) (the main indicators of coagulation); a marker of thrombosis D-dimer; an early marker of bacterial flora translocation into blood flow sCD14 (presepsin).

Statistical processing of the results of the study was carried out by methods of variation statistics with the calculation of each indicator of the median and standard deviation (sd). The significance of differences in the groups was determined using nonparametric methods of statistical evaluation: peer-to-peer analysis of variance (ANOVA). Differences were considered statistically significant at $p < 0.05$.

Table 1 shows the median and standard deviation (SD) of these markers by groups.

Table 1: Average and spread of markers value by groups

IAP до	Count	Prothrombin index		Fibrinogen		sCD14		D-dimer	
		Median	SD	Median	SD	Median	SD	Median	SD
< 12	6	90.9	30.1	3.5	0.782	246	162	5.88	13.5
12-15	9	90.1	9.41	4.68	1.15	570	186	24.6	11.2
16-20	26	87.9	18.1	4.65	2.22	651	384	35.3	33.2
21-25	23	78.6	24.3	5.1	1.65	656	336	36.5	35
> 25	36	78.7	26.4	5.94	2.82	800	572	28.2	18.1

The median of the prothrombin index in the blood plasma decreased with an increase in intra-abdominal pressure (IAP). Although the spread of this indicator in each group is quite large, it is larger than the difference of averages between any groups. This difference is not statistically significant. The figure below clearly shows that the values of this indicator are the same in all groups.

The median of the prothrombin index in the control group is 90.9%, which is within the known norm of PTI 80-110%.

IAP 12-20 mmHg (group 1 and 2)-normal values.

IAP 21-25 and more mmHg (group 3 and 4) leads to decrease of PTI compared to normal values (there are statistically significant differences compared to the control group and group 1 and 2, in the direction of hypercoagulation, which possibly associated with a massive flow of tissue thromboplastin into the bloodstream (Figure 1).

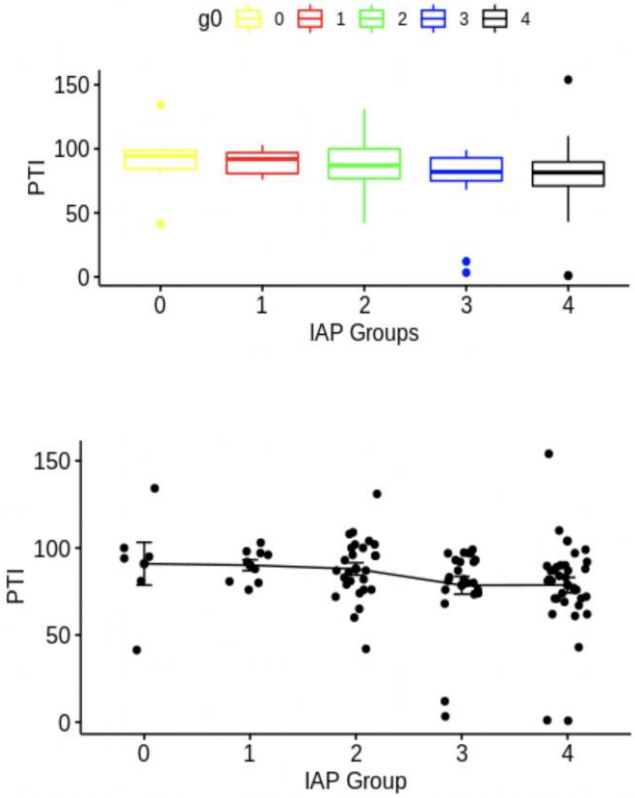

Figure 1: Dependence of the content of PTI in plasma on the level of IAP

The values of fibrinogen, CD14 and D-dimer

in the control group are less than in other groups.

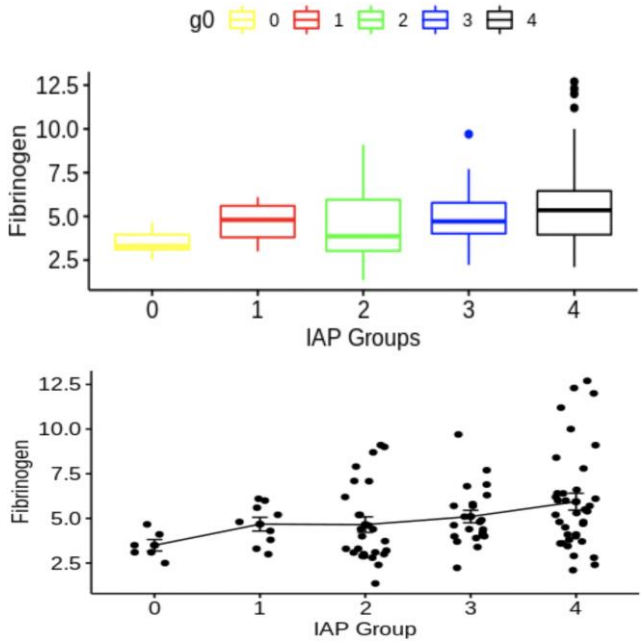

Figure 2: Dependence of the content of fibrinogen in plasma on the level of IAP

The content of fibrinogen in the blood plasma increases in proportion to the increase in pressure in the abdominal cavity. There is a statistically significant difference in the groups with IAH and control group (0 groups). Thus, the average concentration of fibrinogen in the control group is 3.5 g/l, which is within the known norm of fibrinogen 2.0 – 4.0 g/l (Figure 2).

IAP 12-20 mmHg (group 1 and 2) causes a slight increase in the concentration of fibrinogen compared to normal values (also lies within normal values).

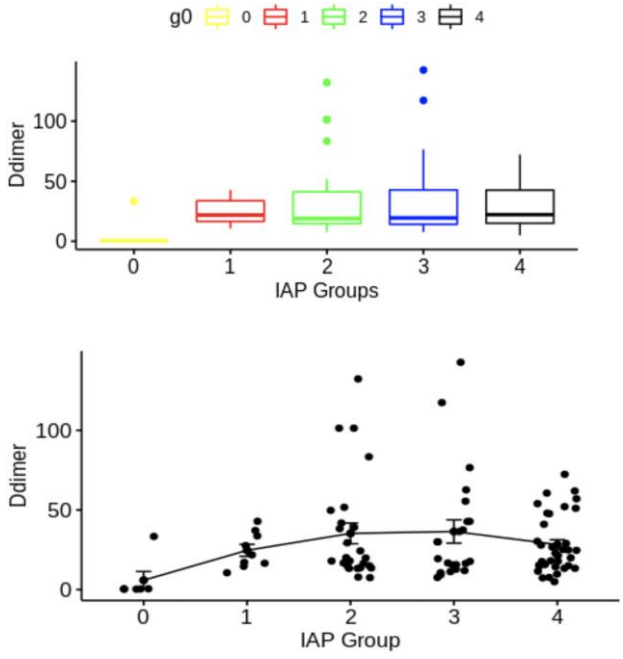

Figure 3: Dependence of the content of D-dimer in plasma on the level of IAP

IAP 21-25 mmHg (group 3) causes an increase in fibrinogen concentration compared to normal values (there are statistically significant differences compared to the control group and group 1 and 2.

Statistically significant changes in fibrinogen level are observed at IAH 25 mmHg and more (group 4) in the direction of hypercoagulation, which possibly associated with organ dysfunction and consumption coagulopathy.

The average concentration of D-dimer in the control group is 5.8 ng/ml.

IAP 12-15 mmHg (group 1) causes a significant increase in the concentration of D-dimer compared with the control group in the direction of hypercoagulation 4 times compared with normal values (Figure 3).

IAP 16-25 and above mmHg (group 2, 3 and 4) causes a pronounced statistically significant increase in the concentration of D-dimer in the direction of hypercoagulation by 5-6 times compared to normal values, which confirms the experimental data; thus, the determination of the d-dimer level is relevant in the development of IAH, since even with IAP 12-15 mmHg, there is a clear statistically significant dynamics to increase this indicator.

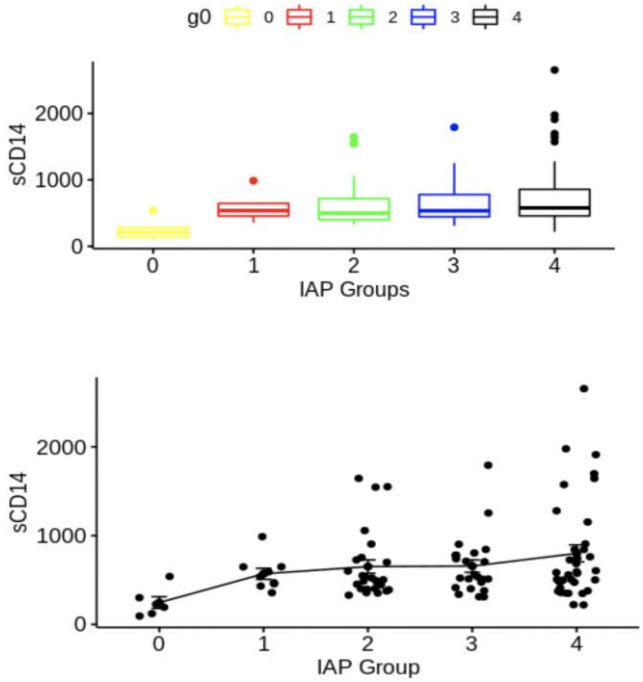

Figure 4: Dependence of the content of sCD14 in plasma on the level of IAP

The average concentration of the sCD14 biomarker of the control group is 246 ng/ml (Figure 4).

IAH 12-15 mmHg (group 1) causes statistically significant changes in the concentration of

sCD14 compared with the control group.

IAH 16-25 mmHg (group 2 and 3) causes an increase of the concentration of the biomarker sCD14 compared with normal values by 30% (there are statistically significant differences compared with the control group and group 1), which confirms the previously conducted experimental studies on the beginning of the enterogenous translocation of the bacterial flora into the bloodstream IAP level;

With IAH 25 or more mm Hg (group 4) there is acute increasing of the concentration of sCD14 almost 4 times, which probably indicates the development of a “preseptic” state.

In conclusion, the literature data and our results are allowed us to formulate a working hypothesis about the change in the level of presepsin, fibrinogen, d-dimer, which increase sharply in response to an increase in IAP, which leads, respectively, to hypercoagulation with further organ dysfunction, consumption coagulopathy.

Having estimated the level of presepsin with the development of intraabdominal hypertension, there is a clear positive correlation with the high sensitivity, specificity (a high level of statistical significance $p < 0.01$ is determined).

Thus, it can be proposed to use the determination of presepsin level in patients with acute surgical pathology of the abdominal cavity as a routine method along with the determination of fibrinogen, PTI, D-dimer to assess the stratification of the risk of abdominal sepsis, prognosis of the course and outcome of the disease, as well as timely surgical treatment.

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