



Kinetics of C-reactive protein, interleukin-6 and -10, and phospholipase A₂-II in severely traumatized septic patients

Kinetika C-reaktivnog proteina, interleukina 6 i 10 i fosfolipaze A₂II kod bolesnika sa teškim povredama i sepsom

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Abstract

Background/Aim. Injury-induced energy is one of the key factors contributing to trauma victims' high susceptibility to sepsis. This group of patients is mostly of young age and it is therefore essential to be able to predict as accurately as possible the development of septic complications, so appropriate treatment could be provided. The aim of this study was to assess kinetics of interleukin (IL) -6 and -10, phospholipase A₂-II and C-reactive protein (CRP) in severely traumatized patients and explore the possibilities for early detection of potentially septic patients. **Methods.** This prospective study included 65 traumatized patients with injury severity score (ISS) > 18, requiring treatment at surgical intensive care units, divided into two groups: 24 patients without sepsis and 41 patients with sepsis. C-reactive protein, IL-6 and -10 and phospholipase A₂ group II, were determined within the first 24 hours, and on the second, third and seventh day of hospitalization. **Results.** Mean values of IL-6 and phospholipase A₂-II in the patients with and without sepsis did not show a statistically significant difference on any assessed time points. In the septic patients with ISS 29–35 and > 35 on the days two and seven a statistically significantly lower level of IL-10 was found, compared with those without sepsis and with the same ISS. C-reactive protein levels were significantly higher in septic patients with ISS 18–28 on the first day. On the second, third and seventh day CRP levels were significantly lower in the groups of septic patients with ISS 29–35 and > 35, than in those with the same ISS but without sepsis. **Conclusion.** Mean levels of CRP on the first day after the injury may be useful predictor of sepsis development in traumatized patients with ISS score 18–28. Mean levels of CRP on the days two, three and seven after the injury may be a useful predictor of sepsis development in traumatized patients with ISS score more than 28. Mean levels of IL-10 on the second and seventh day after the injury may be a useful predictor of sepsis development in traumatized patients with ISS score > 28.

Key words:

wounds and injuries; trauma severity indices; C-reactive protein; interleukin-6; interleukin-10; group II phospholipases A₂; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Anergija izazvana povredom jedan je od najvažnijih faktora koji uslovljavaju predispoziciju bolesnika sa teškim povredama za nastanak sepse. Grupa povređenih bolesnika najčešće je mlađeg životnog doba, pa je izuzetno važno što ranije predvideti nastanak sepse, kako bi se pravovremeno sprovelo odgovarajuće lečenje. Cilj ove studije bio je da se ispita kinetika interleukina-6 i -10, fosfolipaze A₂-II i C-reaktivnog proteina (CRP) kod teško povređenih bolesnika i mogućnosti ranog otkrivanja bolesnika sa rizikom od nastanka sepse. **Metode.** Sprovedena je prospektivna studija koja je obuhvatila 65 povređenih sa skorom težine povrede > 18 koji su lečeni u hiruškoj jedinici Intenzivne nege Urgentnog centra Kliničkog centra Srbije, podeljenih u dve grupe: 24 povređena kod kojih se tokom hospitalizacije nije razvila sepsa i 41 povređeni kod kojih se razvila sepsa. Koncentracije IL-6 i -10, fosfolipaze A₂-II i CRP u serumu bolesnika određivani su tokom prvih 24 h, sa ponavljanjem merenijama drugog, trećeg i sedmog dana hospitalizacije. **Rezultati.** Prosečna koncentracija IL-6 i fosfolipaze A₂-II u grupama bolesnika sa i bez sepse nisu se statistički značajno razlikovale na dan prijema, kao ni drugog, trećeg i sedmog dana hospitalizacije. Kod bolesnika sa sepsom i skorom težine povrede 29–35 i > 35, u odnosu na bolesnike bez sepse sa istim skorom težine povrede, drugog, trećeg i sedmog dana registrovana je statistički značajno niža prosečna koncentracija CRP, a drugog i sedmog dana niža prosečna koncentracija IL-10. Prosečne koncentracije CRP bile su značajno više na dan prijema kod bolesnika sa sepsom i sa skorom težine povrede 18–28. **Zaključak.** Koncentracija CRP prvog dana povrede mogući je prediktor razvoja sepse kod povređenih sa skorom težine povrede 18–28. Ukoliko je skor težine povrede veći od 28, koncentracija CRP drugog, trećeg i sedmog dana posle povrede, kao i koncentracija IL-10 drugog i sedmog dana korisna je za identifikovanje bolesnika koji će razviti sepsu.

Ključne reči:

povrede; povrede, indeksi težine; sepsa; C-reaktivni protein; interleukin-6; interleukin-10; fosfolipaze A₂; osetljivost i specifičnost.

Introduction

A cytokine cascade activated in response to injury consists of a complex biochemical network with diverse effects on an injured host. Traumatic injury leads to the systemic inflammatory response syndrome (SIRS) followed by a period of recovery mediated by compensatory anti-inflammatory response (CARS), which may induce a prolonged immunosuppressed state^{1, 2}. Injury-induced energy is one of the key factors contributing to trauma victims' high susceptibility to sepsis^{3, 4}.

Unlike other patients' groups with sepsis, trauma patients are mostly young and with unremarkable past medical history. Studies demonstrate that the degree of an initial injury is important in determining patient's susceptibility to post-traumatic complications, but the issue of secondary surgical procedures acting as additional inflammatory insults (second hit) and a genetic predisposition are suspected to be responsible for different outcomes¹. These factors can explain why some patients develop serious post-traumatic complications and others do not, despite the same injury severity scores.

Numerous studies indicate that development of sepsis begins before clinical manifestations^{1, 5}. In a great number of patients clinically full-blown sepsis is a stage with not much left to be done. It is therefore essential to be able to predict as accurately as possible the development of sepsis and determine early indicators of sepsis, so appropriate treatment could be provided. The aim of this study was to determine kinetics of interleukin (IL)-6, IL-10, phospholipase (PL) A₂-II and C-reactive protein (CRP) in traumatized septic patients and assess the possibility of early detection of patients who will develop sepsis following severe trauma.

Methods

This prospective study included 65 patients with severe trauma treated surgically or conservatively at surgical intensive care units of the Clinical Center of Serbia. Patients with primary neurosurgical injury were not included in the study. The entry criteria were: injury severity score (ISS) > 18 (severe injury), age range 16 to 65, admission to the hospital within the first 24 hours following the injury, survival longer than 48 h. The patients with severe trauma were divided into two groups: 24 patients without sepsis and 41 patients with sepsis.

Markers and mediators of inflammation were determined in all patients within the first 24 hours after the trauma, immediately after admittance to the hospital, and on the second, third and seventh day of hospitalization. Phospholipase A₂-II (PLA₂-II) concentration was determined using enzyme-linked immunoadsorbent assay (ELISA; Boehringer Mannheim GmbH, Germany). Reference range was 0–6 ng/mL. The reference range for PLA₂-II, which is not a routine test, was determined from the samples of 120 healthy control group subjects⁶. C-reactive protein concentration was determined by immunonephelometry (the Behring laser nephelometer; normal value < 9mg/mL). Using immunotech

test based on "sandwich" enzyme immunodetermination, concentration of interleukins was determined. The reference range for IL-6 was 0–8 pg/mL, and for IL-10 was 0–10 pg/mL.

Sepsis was diagnosed according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee⁷.

One-way analysis of variance was applied to compare group mean values. The χ^2 test for contingency tables was used to compare frequencies of injured patients with ISS score above and below 29 (median value) in different groups. Values $p < 0.05$ or $p < 0.01$ were considered significant. Kaplan-Meier diagram was used to illustrate mortality and survival of septic and non-septic patients per hospital days.

Results

Ratio of male to female was 52 : 13, which is common for traumatic injuries. Average age of patients was 47.13 ± 15.03 years. Two thirds of patients ($n = 43$; 66.1%) were surgically treated, while 22 patients (33.9%) were either not operated on or had undergone minor surgical intervention under local anesthesia. Length of stay was 23.85 ± 5.94 days, ranging from 2 days (which was entry criterion) to 131 days. Injury severity score ranged from 18 to 45 in all included patients, mean value being 30.48 ± 6.23 . Ten patients had ISS > 35 defining critical injury, while other 55 patients had severe injury. More than one half of patients ($n = 41$; 63.07%) had sepsis. Overall mortality rate was 50.76% (33 patients died, 32 survived). Mortality rate in the septic patients was 75.6%.

Sepsis was diagnosed between the third and the fourth day of hospitalization. By the day five of hospitalization, it was diagnosed in 56% of patients, reaching 96% by the eleventh day of hospital stay (Figure 1).

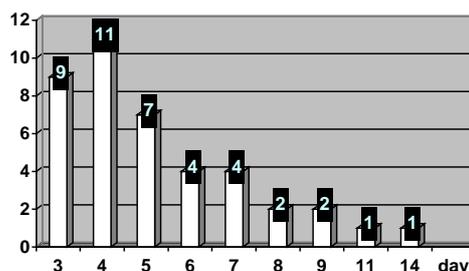


Fig. 1 – Number of patients with development of sepsis per hospital day

Mean values of CRP (mg/L), IL-6, IL-10 and PLA₂ II (ng/L) for both groups per days of hospitalization are shown in Table 1. A statistically significant difference was found in CRP levels between the patients with and without sepsis on the second day (Table 1). A statistically significant difference was found in IL-10 levels in two patient groups on the first and second day (Table 1). Levels of IL-6 and PLA₂-II were not found to be statistically significantly different between the patient groups.

Table 1
C-reactive protein (CRP), interleukin (IL)-6, IL-10 and phospholipase A₂-II (PLA₂-II) daily levels (shown as mean ± SD)

| Hospital day | Presence of sepsis | CRP | IL-10 | IL-6 | PLA ₂ -II |
|--------------|--------------------|-----------------|-----------------|-----------------|----------------------|
| 1 | + | 171.72 ± 13.70 | 182.09 ± 34.17* | 563.70 ± 89.53 | 82.33 ± 15.29 |
| | - | 170.64 ± 24.90 | 293.25 ± 101.68 | 517.33 ± 114.4 | 80.53 ± 18.94 |
| 2 | + | 190.35 ± 16.86* | 115.29 ± 20.69† | 412.58 ± 76.44 | 84.66 ± 13.10 |
| | - | 223.72 ± 27.66 | 247.50 ± 98.91 | 451.33 ± 114.4 | 87.13 ± 26.70 |
| 3 | + | 186.30 ± 14.94 | 115.70 ± 39.12 | 280.00 ± 54.19 | 82.41 ± 11.09 |
| | - | 218.33 ± 28.32 | 77.46 ± 25.66 | 252.92 ± 105.0 | 87.13 ± 26.70 |
| 7 | + | 194.84 ± 15.66 | 78.14 ± 21.23 | 208.28 ± 49.90 | 78.68 ± 14.15 |
| | - | 192.56 ± 36.03 | 185.00 ± 142.74 | 344.60 ± 289.92 | 80.32 ± 37.61 |

**p* < 0.05; †*p* < 0.01; *p* – derived from ANOVA (analysis of variance)

A statistically significant difference was not found in frequencies of injured patients with ISS score above and below 29 (median value) in different groups (Table 2).

The patients were then divided into three groups, according to the severity of injury and ISS level: the group I (ISS 18–28), group II (ISS 29–35) and group III (ISS > 35). Interleukine-6 levels did not differ statistically in the patients with and without sepsis, regardless of the ISS score group. Interleu-

kine-10 levels did not differ statistically in the ISS group 18–28. A statistically significant lower IL-10 was found in the septic patients with ISS 29–35 and > 35, compared with those without sepsis on the days two and seven (Table 3).

No statistical difference was found in PLA₂-II levels among the septic and non septic patients (Table 4). On the first day CRP levels were significantly higher in the septic patients with ISS 18–28. It should be noted that on the sec-

Table 2
Frequencies of injured patients with injury severity score (ISS) above and below 29 (median value) in the groups with and without sepsis

| Presence of sepsis | ISS > 29 | ISS ≤ 29 | Total |
|--------------------|-----------|-----------|-----------|
| + | 23 | 18 | 41 |
| - | 14 | 10 | 24 |
| Total | 37 | 28 | 65 |

χ² = 0.1893, *p* = ns

Table 3
Interleukin(IL)-6 and IL-10 daily levels (shown as mean ± SE) range in patients with different injury severity score (ISS) values range in the groups with and without sepsis

| Interleukins | Hospital day | ISS 18–28 | | ISS 29–35 | | ISS 36–45 | |
|--------------|--------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | | Sepsis | | Sepsis | | Sepsis | |
| | | Yes (n = 14) | No (n = 9) | Yes (n = 19) | No (n = 12) | Yes (n = 8) | No (n = 3) |
| IL-6 | 1 | 325.80 ± 113.46 | 180.00 ± 80.71 | 607.21 ± 142.86 | 619.28 ± 194.83 | 816.57 ± 191.62 | 975.33 ± 261.87 |
| | 2 | 238.90 ± 98.25 | 222.83 ± 125.25 | 442.00 ± 123.03 | 541.86 ± 194.68 | 650.57 ± 162.17 | 678.33 ± 165.44 |
| | 3 | 218.60 ± 87.28 | 65.17 ± 20.21 | 234.07 ± 75.86 | 373.83 ± 203.94 | 459.57 ± 129.59 | 528.50 ± 125.50 |
| | 7 | 128.25 ± 74.43 | 24.50 ± 4.50 | 152.54 ± 38.70 | 558.00 ± 472.49 | 363.63 ± 142.58 | 381.00 ± |
| IL-10 | 1 | 109.20 ± 35.17 | 120.00 ± 56.05 | 217.00 ± 67.28 | 326.37 ± 163.23 | 216.43 ± 41.55 | 584.00 ± 286.88 |
| | 2 | 79.40 ± 25.56 | 63.33 ± 24.16 | 125.64 ± 36.27* | 325.37 ± 174.65 | 145.86 ± 43.30* | 326.00 ± 262.24 |
| | 3 | 52.40 ± 17.81 | 29.67 ± 12.14 | 148.93 ± 84.85 | 125.67 ± 48.54 | 139.71 ± 24.67 | 116.00 ± 41.00 |
| | 7 | 20.25 ± 6.50 | 18.00 ± 13.00 | 75.00 ± 26.82* | 296.33 ± 228.85 | 122.50 ± 53.04* | 143.00 ± |

**p* < 0.05

Table 4
C-reactive protein (CRP) and phospholipase A₂II (PLA₂-II) daily levels (shown as mean ± SE) in patients with different injury severity score (ISS) values shown as range in groups with and without sepsis

| Parameters | Hospital day | ISS 18–28 | | ISS 29–35 | | ISS 36–45 | |
|----------------------|--------------|-----------------|----------------|-----------------|----------------|-----------------|----------------|
| | | Sepsis | | Sepsis | | Sepsis | |
| | | yes (n = 14) | no (n = 9) | yes (n = 19) | no (n = 12) | yes (n = 8) | no (n = 3) |
| CRP | 1 | 172.96 ± 19.28* | 97.81 ± 24.30 | 160.23 ± 24.40 | 218.62 ± 38.12 | 196.87 ± 22.80 | 205.33 ± 12.91 |
| | 2 | 178.63 ± 24.90 | 134.30 ± 15.81 | 184.15 ± 29.06* | 282.75 ± 42.74 | 225.62 ± 30.59* | 249.00 ± 46.50 |
| | 3 | 172.11 ± 25.55 | 146.19 ± 29.27 | 174.17 ± 19.94* | 267.70 ± 40.51 | 239.97 ± 38.46* | 316.00 ± 58.00 |
| | 7 | 166.34 ± 28.95 | 105.80 ± 21.42 | 190.92 ± 21.84* | 291.71 ± 52.99 | 250.50 ± 30.86* | 302.00 ± |
| PLA ₂ -II | 1 | 61.96 ± 18.60 | 33.20 ± 17.59 | 70.11 ± 24.35 | 105.05 ± 30.00 | 147.02 ± 36.80 | 128.40 ± 33.34 |
| | 2 | 53.71 ± 18.04 | 41.34 ± 15.08 | 85.53 ± 20.81 | 139.58 ± 37.57 | 136.80 ± 26.39 | 155.63 ± 24.14 |
| | 3 | 54.50 ± 15.89 | 40.39 ± 16.39 | 79.43 ± 16.13 | 127.82 ± 48.91 | 140.75 ± 22.55 | 110.00 ± 9.00 |
| | 7 | 49.54 ± 16.03 | 21.55 ± 8.54 | 82.60 ± 26.00 | 147.50 ± 74.61 | 113.09 ± 14.58 | 104.50 ± |

**p* < 0.05

ond, third and seventh day CRP levels were significantly lower in the groups of septic patients with ISS 29–35 and > 35, than in those without sepsis.

Discussion

Traumatized patients typically show increased inflammatory mediators levels early on admission. These levels then gradually normalize within days. If a second rise occurs, this is usually an indicator of complications development (may include systemic infections). Inflammatory mediator level increase or decrease is always present earlier than the clinical symptoms of sepsis⁵.

Mortality rate of the septic patients in our study was rather high (75.6%). Other authors reported mortality rate in such patients ranging from 24% to 80%⁸. The patients included in our study, however, had significantly higher ISS mean value (30.48 ± 6.23). Bearing in mind severity of injuries, high percentage of surgically treated patients, significant number of patients on prolonged mechanical ventilation, it is not surprising. Recently, studies have reported a gender difference in a host defence after trauma, hemorrhage and sepsis⁹. The imbalance in pro- and anti-inflammatory cytokines due to secondary operation after trauma promotes immunological dysfunction that results in a significant morbidity¹⁰.

A group II phospholipase A₂ belongs to a family of acute phase proteins and participates in the host response to inflammation *via* the production of proinflammatory arachidonic acid metabolites. Several authors investigated the role of PLA₂-II in patophysiology of sepsis and multiple trauma^{11–13}. In these studies it was reported that PLA₂-II concentration and kinetics correlate reasonably well with progression and outcome of sepsis. Furthermore, studies report no significant rise in serum concentration of this enzyme 24 hours after trauma or surgery¹¹. This is somewhat different from our results, although mean levels of PLA₂-II in our study are lower on day one of hospitalization than on the following days. It should be emphasized, however, that some patients included in our study (particularly those from remote areas of the country), were admitted to hospital after a longer period of time than in studies done by other authors (always within 24 hours from the injury). This may be the reason for somewhat higher PLA₂-II levels in our patients compared with subjects in other studies. No significant difference in PLA₂-II serum concentration was found between patients with and without sepsis. It may be a result of later development of infectious complications in severely traumatized patients due to immunosuppression (the second hit theory).

Epidemiological data show evidence of a correlation between increased IL-6 levels after trauma and the ISS, the incidence of complications and mortality^{14,15}. Interleukin-6 can be seen as marker for the severity of trauma and a resource in triage, diagnosis and prognosis¹⁵. Most authors agree that an early increased IL-6 level can be marker for a high risk of complications and organ failure^{14,15}. According to previous studies a threshold level of

800 pg/mL on admission might be a good indicator of differentiating between patients with or without organ failure¹⁵. There is a lot of evidence that IL-6 concentration is in a good correlation with severity and outcome of sepsis in humans¹⁵. It was reported that septic patients admitted in intensive care unit had high levels of IL-6, which correlated well with severity of the disease (septic shock) and mortality¹⁵. Several studies reported that IL-6 concentrations correlated well with late development of sepsis and resulting mortality rate in patients urgently admitted to intensive care units^{14,15}.

Mean levels of IL-6 in our patients were very high, especially on the first and second day of hospitalization. Some authors always include cytokine status when stratifying injured patients based on severity of the injury and expected outcome¹⁶. According to these models, cytokine concentrations are classified in four groups with an adequate prognostic significance (number of points)¹⁴. Almost half the patients in our study (45%) fell into the third (IL-6 > 250 pg/L) and fourth (IL-6 > 500 pg/L) group, predicting adverse outcome. Although some authors describe significant IL-6 increase on the first, or even second day after trauma, most report that the window closes after three days, implying that levels of IL-6 have no prognostic value after that point¹⁵. We came to the same conclusions in our study. We found a significant decrease of IL-6 after the second day of hospitalization. Unfortunately, IL-6 level was not particularly useful in early identification of patients who will develop sepsis. Daily values of IL-6 did not differ significantly between the patients with and without sepsis.

Interleukin-10 plays an important role in the anti-inflammatory response. This protein is produced simultaneously with the pro-inflammatory cytokines, but peaks hours later. One of the functions of IL-10 is the negative feedback on the production of TNF- α , IL-6 and IL-8.

Increased levels of IL-10 have been shown to correlate with the development of sepsis or adverse outcome during sepsis. However, IL-10 is unable to discern outcome or severity of illness on an individual level¹⁶. In addition, the biological activity of IL-10 is dependent on the pH and temperature, which is often altered in severely injured or septic patients.

In vitro experiments show that human monocytes produce IL-10 following lipopolysaccharide stimulation, but later than tumor necrosis factor (TNF)- α , IL-1, IL-6, or IL-8. The presence of anti IL-10 antibodies in culture results in an increased production of these cytokines, especially TNF α and IFN- γ , thus implying the regulatory role of IL-10¹⁷.

Our study confirms its protective role. In patients without sepsis mean values of IL-10 are higher on all days except the third one. Statistically significant difference was found in IL-10 levels between two patient groups on the first ($p < 0.05$) and second day ($p < 0.01$). Interleukin-10 has kinetics similar to IL-6.

We did not analyze the ratio between interleukins in question, which was suggested as a predictive factor in some studies¹⁸.

Amongst biomarkers, CRP proved to be useful in the infection diagnosis, infection prediction and monitoring response to antibiotics¹⁹. However, there is still some debate concerning a correlation between its serum concentrations and sepsis severity¹⁹. In our study, all investigated patients had CRP levels higher than normal. The septic patients with less severe trauma (ISS 18–28) had higher CRP levels than those without sepsis. This is an expected finding. The septic patients with ISS over 28 had lower CRP levels than the patients with the same ISS without sepsis. We speculate that these critically injured patients developed anergy, hepatic malfunction, and consequently relatively lower levels of CRP for sepsis.

Conclusion

Mean levels of CRP on the first day after the injury may be useful predictor of sepsis development in traumatized patients with ISS score 18–28. Mean levels of CRP on day two, three and seven after the injury may be useful predictors of sepsis development in traumatized patients with ISS score more than 28.

Mean levels of IL-10 on the second and seventh day after the injury may be a useful predictor of sepsis development in traumatized patients with ISS score > 28.

Interleukin-6 and PLA₂ II kinetics in the first seven days after trauma does not differentiate patients with and without sepsis.

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