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The importance of selected immunological indices in risk assessment of severe septic complications in patients after major trauma.

Summary

Introduction

According to the World Health Organization, post-traumatic mortality rates are still very high and show an increasing tendency. Disorders of innate immune response that may increase the risk of serious complications play a key role in the immune response to trauma and infection. The mechanism of these disorders is multifactorial and is still poorly understood. Changing concepts of the early systemic inflammatory response syndrome (SIRS) and compensatory anti-inflammatory response syndrome (CARS), broadened by genetic studies, indicate that excessive gene expression and increased production of mediators of immune response are one of the primary causes of post-traumatic multiple organ dysfunction syndrome (MODS) and increased mortality. The depletion of energy resources accompanying the increased production of cytokines leads to immunosuppression and the persistent inflammation and immune suppression catabolism syndrome (PICS). Early diagnostics of immune disorders and better understanding of the early immune response to injury can significantly reduce the incidence of complications, hospitalization time and mortality.

Aim

The research was conducted to better understand the mechanisms of early immune response to trauma, including the determination of the course of pro- and anti-inflammatory reactions and the distinction between physiological and

pathological responses that increase the risk of complications. On the basis of parameters tested (assessment of the concentration of selected pro- and anti-inflammatory cytokines in the peripheral blood: IL-6, IL1Ra, TNF-α and sTNFR1), an attempt was made to determine immunological indices that may be of practical importance in assessing the risk of serious post-traumatic complications.

Materials and Methods

The study group comprised 51 patients, including 39 men and 12 women, aged 18-80 years, an average of 41.40 ± 16.53, admitted to the Emergency Department (ED) of the Bielański and Praga hospitals due to trauma. The whole group of patients, depending on the severity of the condition and extent of the injury, was divided into two subgroups. Group A (n=23) included patients with ISS≥20 points, and group B (n=28) with ISS<20 points. Inclusion criteria for immunological tests were met by 32 patients among the examined group of patients, i.e., group A n=20 (ISS≥20) and group B n=12 (ISS<20), in whom pro- and anti-inflammatory cytokine (IL-6, IL-1Ra, TNF-α and sTNFR-1) determinations were performed using ELISA tests at the time of admission to the ED, and subsequently after 3, 6, 12 and 24 hours of hospitalization. The control group for immunological analyses consisted of 20 healthy volunteers of similar age range and gender. Clinical monitoring involved the following parameters: type of injury and treatment, including the number of operations/reoperations, type and number of complications, length of hospital stay and duration of respiratory treatment and mortality. Routine laboratory tests were performed in all patients. The results were statistically analyzed based on the following tests: U Mann-Whitney, Wilcoxon, rho-Spearman correlation and receiver operating characteristic (ROC) curve analysis. The analyses were performed using SPSS 13.0 for Windows.

Results

The main cause of multiple organ injury in the presented material was traffic accidents and falls from height, recorded in 53% of patients. Of 51 patients, 33 (64.70%) required hospitalization for more than 24 hours, including 6 patients treated in the intensive care unit (ICU). However, of 32 patients with immunological examinations, 22 (68.75%) required hospitalization longer than 24 hours. In group A (ISS≥20), 13 patients developed severe complications, of whom 5 died. In group B (ISS<20), complications occurred only in 3 patients. Respiratory failure and infectious complications were reported most frequently. Patients with complications had a significantly higher ISS score (C^+ vs. C^-, $p<0.001$) than those who had no complications. Significant differences in cytokine concentrations and disturbances in the dynamics of early immune response to trauma and complications in the studied time intervals were found in comparable patient groups (A vs. B, C^+ vs. C^-). The initial IL-6, sTNFR1 and IL-1Ra concentrations were significantly elevated in group A, in patients with severe injuries, at the time of admission to the ED compared to the standard, and retained at a significantly elevated level up to the 6th hour of observation. In contrast, the initial concentrations of these cytokines were not significantly increased in group B compared to the standard. Observation of the dynamics of changes of the response to trauma and concomitant infection and complications showed that the highest level of IL-6 in group A were recorded in the 3rd hour of hospitalization and were considerably higher compared to the concentration of this cytokine in group B measured at the same time point. The highest values of sTNFR1 in group A occurred during the first test after admission to the ED. However, sTNFR1 concentration in group B patients with minor trauma did not significantly differ from the standard at all time points, and the highest concentration in this group was recorded in the 3rd hour of hospitalization. Further observation of the dynamics of response to injury and complications demonstrated that the highest concentrations of this cytokine in both groups of patients were recorded at 3 hours

of hospitalization. Evaluation of TNF-α concentrations in comparable groups of patients (A vs. B) demonstrated that the baseline values of this cytokine in both patient groups were not significantly elevated compared to the standard. The highest TNF-α concentrations occurred in the 3rd hour of hospitalization for group A and slightly later for group B, in the 6th hour of hospitalization. Statistical analysis showed that IL-6 concentration was significantly higher in patients with post-traumatic complications (C^+), compared to those without complications (C^-) in the 3rd hour of observation ($p=0.001$), while the baseline values did not differ significantly. The concentrations of sTNFR1 and IL-1Ra in patients with complications (C^+) were significantly higher compared to those without complications (C^-) at 0 and 3 hours of observation. The concentration of TNF-α in patients with complications did not differ significantly compared to the group without complications. A rapid increase in all parameters tested was observed after 3 hours of observation in patients who died.

The rho-Spearman correlation showed a statistically significant positive relationship between the initial concentrations of the parameters studied and the ISS scale values: IL-6 ($r=0.64$, $p<0.001$), STNFR1 ($r=0.59$, $p=0.001$) and IL-1Ra ($r=0.37$, $p=0.042$) and TNF-α ($r=0.38$, $p=0.043$). High diagnostic sensitivity calculated from ROC curves was found for the concentrations of the cytokines tested: IL-6 (AUC=0.83, $p=0.024$), IL-1Ra (AUC=0.83, $p=0.021$), TNF-α (AUC=0,91, $p=0.004$) and sTNFR1 (AUC=0.86, $p=0.011$). There were no statistically significant differences regarding age and gender in comparable patient groups with immunological tests (A vs. B and C^+ vs. C^-). The level of ISS significantly correlated with selected results of laboratory tests only in the group of the most critically ill patients (group A): hematocrit (HCT), hemoglobin (HGB), erythrocyte count (RBC), blood glucose level and blood pH value, but only in the first hours of hospitalization ($p<0.05$). Changes in selected parameters were at similar levels in different time intervals, regardless of the study group.

Conclusions

The results of the present research indicate that:

- The highest concentrations of pro- and anti-inflammatory cytokines in the group of patients after major trauma with complications and pathological inflammatory response occurred during the first 3 hours of hospitalization. Pro- and anti-inflammatory reactions proceeded in parallel.
- Monitoring the concentration of selected cytokines after trauma at short time intervals is helpful in distinguishing the systemic pathological SIRS response from the physiological response. The “golden diagnostic window” is short and in the current study “closes” as early as within 6 hours of admission to the ED.
- The assessment of the concentration of selected pro- and anti-inflammatory cytokines in serum in post-traumatic patients can be a useful indicator facilitating the identification of patients with an increased risk of complications.
- Correlations of cytokine concentrations with ISS values and the results of ROC curve analyses indicate a high prognostic value of the parameters tested in the first hours of hospitalization.
- The potential target of therapeutic intervention in patients treated in the ED and at the highest risk of death should be an early cytokine response measured during the first 3 hours of hospitalization. However, the evaluation of the effectiveness of such a procedure requires further research.