



Soluble Selectin Profiles Associated with Severe Trauma

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Abstract. Severe trauma acts as a trigger for the complex cascade of postinjury events leading to the release of different mediators and the development of generalized inflammation. Selectins are a family of adhesion proteins that are responsible for the adherence of polymorphonuclear neutrophils to the endothelium. This interaction plays an important role in the development of severe complications after multiple trauma. The aim of the present study is to follow the sequential alterations in circulating selectin levels after severe injury and to evaluate the clinical significance of these mediators in monitoring prognosis and outcome. Thirty four severely traumatized patients were entered into the study. Serum sE-selectin, plasma sP-selectin and sL-selectin concentrations were measured and an APACHE II score was calculated on admission to the intensive care unit and during the subsequent 5 days. The patients were divided into survivors and nonsurvivors. Initial soluble P- and E-selectin concentrations were significantly elevated in all trauma patients. The highest values of these adhesion molecules were measured in all the observed days in patients with poor prognosis and outcome. In survivors we found a systematic decrease in the sP-selectin concentrations. On admission, the sL-selectin concentrations in all trauma patients were decreased. There were stable, very low values in nonsurvivors and a slow increase in circulating L-selectin in patients who survived. The pattern of soluble selectins in patients with severe trauma is characterized by increased levels of P- and E-selectin and a decreased concentration of L-selectin. These findings suggest a widespread microvascular endothelial activation on injury in the early posttraumatic period, which may be associated with increased neutrophil – endothelial adhesion, neutrophil extravasation and migration. We suppose that these parameters of endothelial cell activation/injury may be useful as another early prognostic factor in severe trauma.

Key words: severe trauma; endothelium; selectins; prognosis.

Introduction

Patients after severe trauma are at risk of developing of many serious complications, such as acute respir-

atory distress syndrome (ARDS), sepsis and multiple organ dysfunction syndrome (MODS) resulting in delayed morbidity and mortality^{8, 14, 33}. Multiple alterations in inflammatory and immunological functions

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have been demonstrated in clinical situations within several hours of trauma. The secretion of proinflammatory mediators, endothelial cell activation and leukocyte-endothelial interactions are fundamental stages in the development of systemic inflammatory response syndrome (SIRS) and the pathogenesis of numerous complications in injured patients^{1, 7, 12, 31}. The selective recruitment of subpopulations of circulating leukocytes to the sites of injury or inflammation is a complex process involving the coordinated interaction of various primary (selectin) and activation-dependent (integrin) adhesion receptors with different proinflammatory stimuli (cytokines, chemokines and chemoattractants) that activate leukocyte subtypes and endothelial cells. The selectin family includes E-, P- and L-selectin, which are expressed on the surface of stimulated endothelial cells, activated platelets and leukocytes. After activation, selectin receptors are shed from the surface and are measurable in the circulation^{5, 25}.

The aim of the present study is to follow the sequential alterations in soluble circulating selectin levels in previously healthy patients after severe injury, and evaluate the clinical significance of these mediators in the monitoring of prognosis and outcome.

Materials and Methods

This study was conducted in the medical Intensive Care Unit (ICU) of the Anesthesiology and Intensive Therapy Department, Medical Academy of Białystok, Poland. Our procedures were reviewed and approved by the Medical Ethics Committee of the Medical Academy of Białystok. Thirty four severely traumatized patients were enrolled in the study (10 women and 24 men, 38.1 ± 15.7 years of age). The entry criteria required adult patients with severe multiple injuries and acute respiratory failure as a result of road traffic accident or blunt trauma; only those patients admitted to the ICU within 1 h after trauma were considered. Patients were assigned an injury severity score (ISS) using the method of BAKER et al.², and had severe lesions of vital organs with serious clinical consequences (ISS>25). All patients were sedated, treated with appropriate antibiotics, infusions of crystalloid and colloid solutions, packed red cells, inotropic support and muscle relaxants when necessary, and received analgesics and low subcutaneous doses of low-molecular-weight heparin to prevent thromboembolism. Mechanical ventilation was instituted with a Bennett 7200 AE respirator. All patients requiring surgical intervention re-

ceived standard surgical care and postoperative intensive treatment.

Serum samples were collected in nonheparinized tubes for measurement of sE-selectin, and in EDTA tubes for that of sP-selectin and sL-selectin. All samples were kept at 4°C, centrifuged (2500×g for 15 min at 4°C) within 30 min of collection, aliquoted and stored at -70°C until the time of assay. Blood specimens were obtained from arterial catheters. Concentrations of all circulating selectins were measured by sandwich-type enzyme-linked immunosorbent assay (ELISA) – commercial kits supplied by R&D Systems Products, Abington, UK.

For each patient, the data collection was performed on hospital admission and then daily during the first 5 consecutive days of ICU stay. Severity of illness was estimated using the APACHE II severity of illness classification system¹⁷.

The patients were divided into two groups:

group I – survivors (n = 23),

group II – nonsurvivors (n = 11).

Healthy control subjects (n = 14) were recruited from hospital staff (10 women and 4 men, 41.3 ± 7.1 years of age).

Statistical analysis. The results were reported as a median value and 5 and 95% quartiles. A Mann-Whitney U test was used to determine the differences in concentrations of each mediator between survivors and nonsurvivors. Spearman's rank order correlation was used to analyze relationships between different variables. A value of $p < 0.05$ was considered to be significant.

Results

The clinical and laboratory characteristics of patients on admission to the ICU are presented in Table 1. Of the 34 patients who had severe multiple trauma and early signs of acute lung injury, 23 (67.6%) recovered (group I) and 11 (32.4%) died (group II). The main causes of death were severe head injury and sepsis with multiple organ failure. Three patients died in the ICU within the first week after severe injury, 3 within the second, 3 patients within the third week, and the last 2 after 30 days. Time of ICU stay and artificial respiratory supplementation were 17.8 ± 8.6 days (5–37) and 12.7 ± 7.6 days (3–29) in survivors and 17.5 ± 19.8 days (6–73) in nonsurvivors, respectively. Thirty patients (88.2%) underwent surgical procedures within the first hour after hospitalization. Frequency, type and extension of surgical intervention as well as blood transfusion volumes were similar in both analyzed groups.

Table 1. Clinical characteristics of trauma patients

	Group I (survivors)	Group II (nonsurvivors)	p
Number of patients	23	11	
Age: mean $\pm$ SD (years)	33.0 $\pm$ 11.2	48.7 $\pm$ 18.4	0.012
Sex (male/female)	17/6	7/4	
Data on admission: mean $\pm$ SD			
systolic blood pressure (mmHg)	102.2 $\pm$ 16.4	90.3 $\pm$ 21.6	NS
diastolic blood pressure (mmHg)	72.8 $\pm$ 8.1	69.2 $\pm$ 11.7	NS
heart rate (beats/min)	99.0 $\pm$ 10.2	124 $\pm$ 16.8	0.017
injury severity score	34.5 $\pm$ 7.3	42.7 $\pm$ 6.1	0.001
APACHE II score	14.7 $\pm$ 5.4	24.2 $\pm$ 7.3	0.001
Injury:			
head	6 (26.1%)	6 (54.5%)	
chest	17 (73.9%)	8 (72.7%)	
abdomen	15 (65.2%)	9 (81.8%)	
extremity	18 (78.3%)	10 (90.9%)	
Initial selectins concentration: median value and range (ng/ml)			
sE-selectin	57.7 (34.3–82.6)	134.3 (31.0–228.2)	0.039
sP-selectin	122.8 (62.3–173.5)	126.8 (46.1–168.4)	NS
sL-selectin	509.3 (258.0–1046)	339.0 (148.8–672.0)	NS

The initial APACHE II score was significantly higher in patients with a poor prognosis and outcome compared with survivors. In group I we found a significant decrease of the APACHE II score during the course of the 5 days postinjury. Of the patients who died, the APACHE II scores remained at a high initial level and were significantly greater than those calculated for patients who survived during all days studied ($p < 0.001$).

On admission to the ICU after severe trauma, median concentrations of circulating P-selectin were significantly elevated in both the surviving (122.8 ng/ml, $p < 0.001$) and nonsurviving patients (126.8 ng/ml, $p < 0.001$) compared with control subjects (33.1 ng/ml). The highest sP-selectin values were measured in multiple trauma patients with poor prognosis (group II) and on the third and fifth days after injury, significant differences between the groups were observed. In patients with good prognosis and outcome, a systematic decrease in the concentrations of this adhesion molecule was found.

On presentation to the ICU, the circulating E-selectin concentrations in all trauma patients were significantly higher than those in the healthy controls (group I: $p < 0.001$, group II: $p = 0.002$) (Fig. 1). The sE-selectin values for nonsurvivors were greater than in patients with good prognosis and outcome ($p = 0.039$). Marked differences in sE-selectin concentration in patients who survived versus those who died were observed on all

the days studied. A significant elevation of circulating E-selectin in nonsurvivors was found.

In the first hours after hospitalization, a significant decrease of soluble L-selectin in both groups of patients was determined (Fig. 1). There were stable, very low values in nonsurvivors, and a slow increase of circulating L-selectin in patients who survived in the following days observed. Significant differences were found between the groups after the second day postinjury.

We observed a close association between APACHE II scores and all the measured selectin levels (Fig. 2). There were significant correlations between all selectin concentrations, with the highest Spearman's correlation coefficient ratio in the case of sL-selectin and sP-selectin ($R_s = -0.380$, $p < 0.001$).

Discussion

Severe trauma is associated with pathophysiological occurrences such as hemorrhagic shock, hypoxia, reperfusion injury, induction of the complement system and activation of leukocytes and endothelial cells. These events are characterized by the involvement of an early humoral mediator response followed by a cellular phase involving intravascular margination and activation of neutrophils (PMN's), activation of the contact system (including the complement fragments), coagulation and fibrinolysis^{9, 11, 13, 22, 30–32}. Within several hours

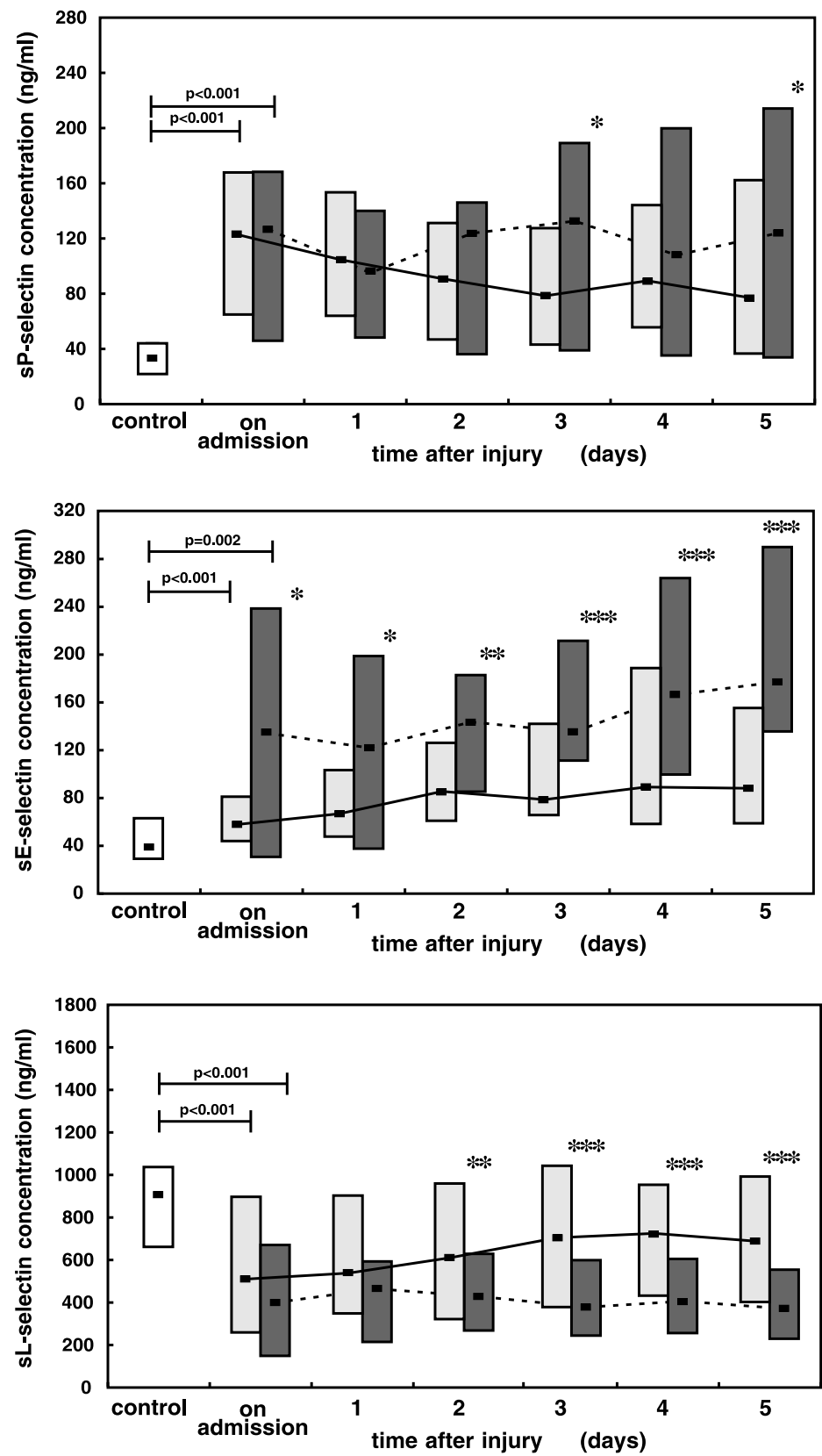


Fig. 1. Time course of plasma P-selectin (ng/ml), L-selectin (ng/ml) and serum E-selectin (ng/ml) concentrations in trauma patients. Values in group I – survivors (hatched box) and group II – nonsurvivors (dark box). Each box indicates the range between the 5th and 95th percentiles of the data. Closed squares indicate the median value. Statistical significance of differences between groups: *p<0.05, **p<0.005, ***p<0.001

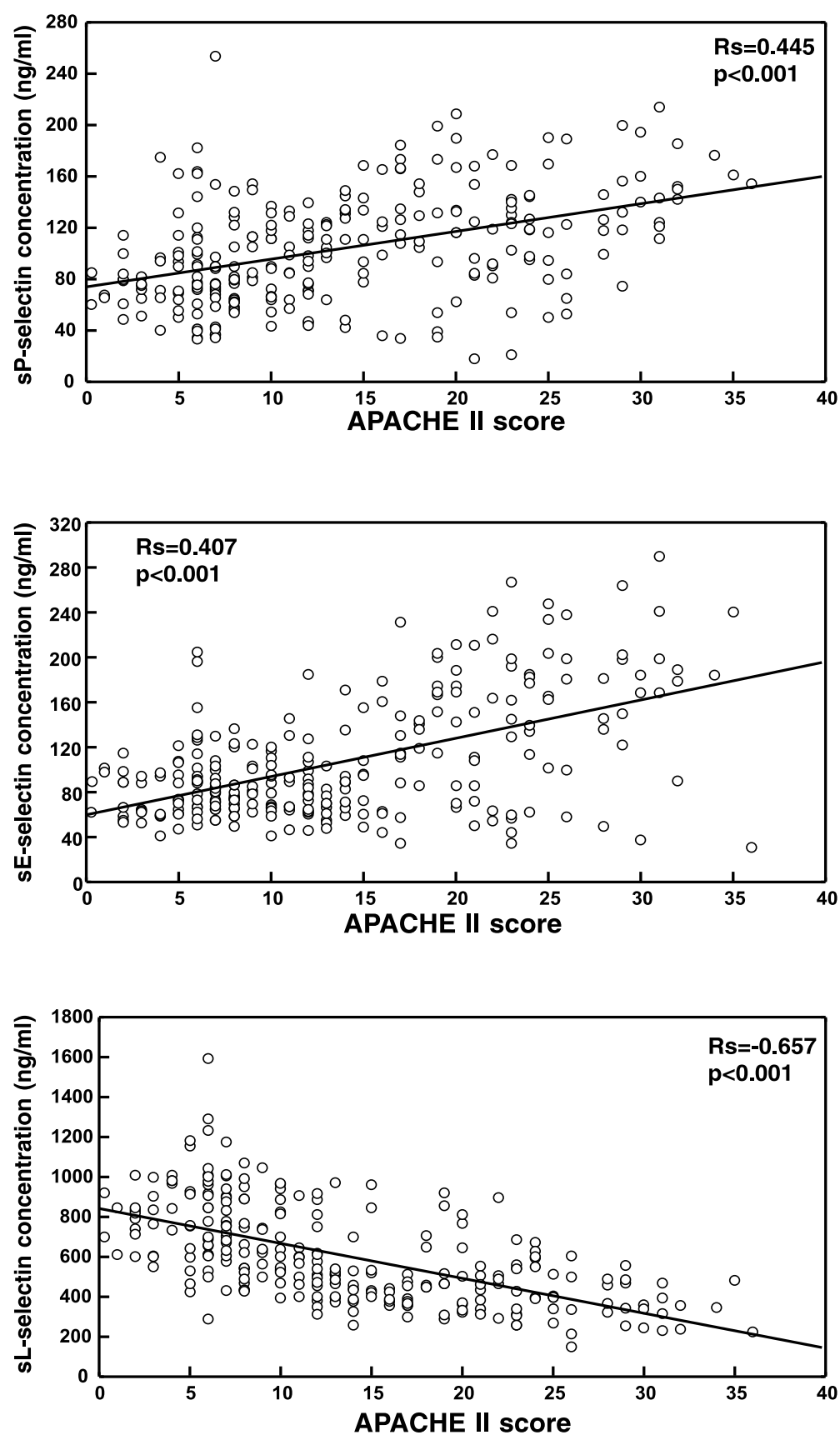


Fig. 2. Correlations of P-selectin, E-selectin and L-selectin concentrations with APACHE II score. Spearman rank coefficient (Rs) values are reported with their respective p values

of trauma, activation of multiple humoral and cellular cascades and activation of proinflammatory cytokine host defense mechanisms were found to occur²². The secretion of numerous mediators results in inadequately regulated inflammation, and may lead to the pathophysiological manifestations of body inflammation, i.e. SIRS^{7, 32}. Severe injury produces rapid, large increases in circulating concentrations of interleukin 1 β (IL-1 β), interleukin 6 (IL-6), interleukin 8 (IL-8), and TNF- α , that may contribute to the subsequent release of other mediators (as well as adhesion molecules) and the development of serious complications^{3, 8, 9, 13, 22, 29, 30}.

Adhesion molecules appear to play a central role in tissue damage secondary to the inflammatory response after severe trauma. Soluble forms of the endothelial-derived adhesion molecules have been detected in the circulating blood, but their importance in the critically ill has not yet been definitely elucidated. Adhesion molecules (particularly selectins) are involved in leukocyte rolling, adhesion, diapedesis, and migration, and as such play a role in inflammatory disorders as well as numerous other pathophysiological processes^{4, 5, 10, 26, 27}.

P-selectin (PS) is produced and stored for rapid release in the Weibel-Palade bodies of the endothelium and in the α granules of platelets²³. After appropriate activation by histamine, thrombin, complement and reactive oxygen species, the molecule is rapidly mobilized to the external plasma membrane. Cytokines such as IL-1 and TNF- α do not induce the expression of this adhesion molecule. Elevations in sP-selectin expression coincide with an increase in the number of leukocytes "rolling" along the endothelium, a response that is inhibited by treatment with a PS specific monoclonal antibody²⁷. In addition, functionally active plasma-soluble PS may modulate leukocyte adhesion to the P-selectin expressed on endothelial cells. SAKAMAKI et al.²⁸ indicated that the soluble form of P-selectin is elevated in acute lung injury. We demonstrated that soluble PS concentrations after severe trauma exceeded those observed in healthy volunteers and were the highest in nonsurvivors in all periods. Our data suggest that these patients demonstrated evidence of permanent endothelial activation and sustained SIRS.

E-selectin (ES) is found only on activated endothelium and its production and expression are rapidly induced after stimulation by a variety of inflammatory mediators, including TNF- α , IL-1 β and IFN- γ . Many findings indicate the role of ES in mediating leukocyte-endothelial cell interaction, but numerous studies have been unable to show the definitive role for E-selectin as a mediator of leukocyte rolling^{4, 20}. A finding of shed, circulating ES in the blood would, therefore, be

taken as evidence of endothelial activation, and this mediator is reckoned to be a quantitative marker of endothelial activation^{7, 18}. There appears to be no storage form of E-selectin. Raised levels of circulating ES have been found in diabetes, hypertension, ischemic heart disease, systemic lupus erythematosus, burns and septic shock^{4, 10, 15, 19, 31}. Higher concentrations or persistently raised values of sE-selectin in septic patients were associated with greater mortality. SCHINKEL et al.²⁹ could find no correlation between ES kinetics and the development of infective complications, but an opposite point of view was presented by SIMONS et al.³¹. These authors concluded that major trauma patients with increased levels of circulating ES were at increased risk of death and, possibly, at risk for infectious complications and organ failure. Soluble E-selectin was present at very low concentrations in healthy humans, but our study has demonstrated increased levels of circulating E-selectin in trauma patients. These concentrations were elevated as early on as admission to the ICU and continued to increase during 5 days investigated. Soluble E-selectin levels were the highest in patients who did not survive, suggesting that the endothelium could have been more intensively activated or injured in these patients.

L-selectin (LS) is a lectin adhesion molecule that is constitutively expressed on all human leukocytes except for a subpopulation of memory lymphocytes. A soluble form of L-selectin is cleaved or shed from the cell surface by proteases and is active and present at measurable levels in human plasma. Release of LS from the cell surface appears to result from activation-induced changes in the conformation of L-selectin protein. Widespread binding to activated endothelium reduces soluble L-selectin concentration and may represent a marker of endothelial activation. Elevated levels of circulating LS are observed in patients with AIDS, leukemia and SIRS, whereas decreased concentrations can be noted in patients with ARDS, brain injury and severe organ failure^{6, 8, 16, 21, 24, 26}. We have found decreased values of LS concentrations after trauma, the lowest in critically ill and nonsurviving patients, which suggests that shed molecules were rapidly bound to endothelial receptors. Reduced sL-selectin levels may then represent a peripheral blood marker of pan-endothelial activation/injury. Sustained low concentrations of this adhesion molecule indicate a severe form of disease and poor prognosis. The close correlation between all measured selectin levels and APACHE II score indicates the influence of illness severity on endothelial activation/injury magnitude.

Surgical management in our patients set out to re-

strict and repair traumatic damage, decreasing the inflow and intensity of injurious stimuli. These treatment procedures in severe trauma patients were similar in both studied groups and, therefore, did not significantly affect the levels of circulating selectins.

In summary, the results of the present study indicate that increased levels of E- and P-selectin and a decreased concentration of L-selectin characterize the soluble selectin pattern of patients with severe trauma. Our data demonstrate that patients with elevated and sustained high values of circulating E- and P-selectins or a decreased L-selectin level after injury may be at increased risk of subsequent death. We suppose that these parameters of endothelial cell activation/injury may be useful as another early prognostic factor in severe trauma.

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