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Inflammatory response in patients undergoing hip surgery due to osteoarthrosis or different types of hip fractures[1]

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Summary

Objective: Hip surgery represents a major intervention associated with significant inflammatory response. The objective of our study was to compare markers of systemic inflammation and soluble adhesive molecules in patients undergoing elective hip replacement to those with hip fracture either intracapsular (IC) or extracapsular (EC).

Design: We included 65 consecutive patients undergoing hip surgery – 17 patients with elective hip replacement (EL group), 29 patients with EC fracture (EC group) and 11 patients with IC fracture (IC group). Fibrinogen (FBG), orosomucoid (ORM), C-reactive protein (CRP), transferrin (TRF) and white blood cells count (WBC), sP-selectin, sE-selectin, and soluble intercellular adhesion molecule-1 (sICAM-1) were measured before surgery 4 h, 48 h, and 7 days after surgery.

Results: IC patients had preoperatively highest values of inflammatory markers including FBG, CRP, ORM, WBC and lowest values of TRF, as compared to intermediate values found in EC and lowest values in EL groups. The surgery has led in all three subgroups to significant elevation in CRP, ORM and decrease in TRF. In IC group, the subsequent recovery of inflammatory markers was very slow. We noted a significant suppression of sP-selectin and sE-selectin values in all subgroups after surgery. The decrease of sE-selectin but not of sP-selectin correlated with changes in hemoglobin and blood transfusions' administration.

Conclusions: Hip surgery is associated with significant inflammatory reaction. In patients with hip fractures, inflammatory markers are elevated already preoperatively, more so in IC than in EC fractures. The unexpected observation of a significant postoperative decrease in sE-selectin and sP-selectin will require further research for elucidation.

Key words: Hip surgery, Hip fracture, Inflammatory response, Soluble adhesion molecules.

Introduction

Hip fractures represent major source of morbidity in elderly patients. The long-term survival of patients is jeopardized by potential peri- and postoperative complications and high rate of lethality for cardiovascular diseases. Recent advances have been made in surgical procedures, anesthesia techniques and thromboprophylaxis. It was shown that hip fractures' surgery is associated with significantly higher morbidity and mortality as compared to elective hip surgery for osteoarthrosis[1]. Factors causing the high morbidity burden in hip fractures' surgery are typically older age and cardiorespiratory comorbidities. In the ESCORTE study analyzing the outcomes after hip fracture surgery in a large cohort of French patients, the 6 months' mortality was 14.7% and almost one-third of deaths were due to cardiovascular disease[2]. There appears to be a close bidirectional link between inflammation and thrombosis and the activation of the two processes may also contribute to the subsequent destabilization of atherosclerosis[3].

Hip surgery represents a major traumatic event regardless the indication. Trauma and surgery are associated with a significant activation of prothrombotic mechanisms and systemic inflammatory response of the organism depending on the trauma extent and surgery invasiveness[4,5]. As shown by Larsson and co-workers, this inflammatory reaction may persist more than 6 weeks after the surgical procedure[6]. Recent study by Neumaier and co-workers demonstrated significant differences in CRP values between patients undergoing hemiarthroplasty or total arthroplasty and those treated by percutaneous screws[4].

The aim of our study was to analyze the inflammatory response to the trauma and surgery in patients suffering from

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different types of hip fractures and to compare it to patients undergoing elective hip surgery for osteoarthrosis. To avoid additional confounding factors only patients operated within first 24 h after the trauma were included. For this purpose we assessed the dynamics of traditional acute phase proteins and soluble adhesion molecules. These were studied as they were shown to play important roles in white blood cells' recruitment, adhesion, homing, and activation and to serve as a major connecting bridge between thrombosis and inflammation. Their role was confirmed in many diseases, namely in atherosclerosis, autoimmune diseases (lupus erythematodes, glomerulonephritis), postischemic, and infectious inflammatory reactions[7].

Methods

We included 65 consecutive patients undergoing hip surgery in General Teaching Hospital of Prague who fulfilled the following inclusion criteria: hip surgery indication for traumatic fracture or for osteoarthrosis, no other traumatic event than hip fracture, and time trauma to surgery less than 24 h in patients with hip fracture. The study was approved by the local ethical committee and all patients gave their informed written consent. Patients were divided into three groups according to the surgery indications: elective surgery (EL), extracapsular fractures (EC), and intracapsular fractures (IC).

All patients were monitored for surgery and anesthesia type, blood transfusion requirements, intravenously administered fluid volume resuscitation, mobilization time and all adverse clinical events, symptomatic deep venous thrombosis in particular. The follow-up was terminated with the discharge from the hospital.

Blood samples for laboratory analysis were drawn 1–2 h before surgery and 4, 48 h and 7 days after surgery.

LABORATORY METHODS

Peripheral blood samples for laboratory investigations were collected from a cubital vein into Vacutainer™ vacuum test tubes (Becton Dickinson, Vacutainer Systems, Rutherford, New Jersey, USA). Whole blood was used to determine the hemogram using analyzer Coulter HmX (Beckman Coulter, Fullerton, USA).

For all analytical methods as follows normal values are those assessed by our own laboratory. For soluble adhesion molecules, serum samples were stored for a maximum of 60 days at −80°C until assay. Enzyme-linked immunosorbent assay (ELISA) methods were performed using Human soluble ICAM-1™, Human soluble P-selectin™ and Human soluble E-selectin™ kits (R&D Systems Europe, R&D Systems, Minneapolis, USA) with the analyzer MRX Microplate Reader™ (Dynatech Laboratories, Chantilly, USA). We assessed soluble adhesion molecule-1 – sICAM-1 [normal values ($n = 98$) are 214 ± 41 ng/ml, coefficient of variation – CV (intraassay 6.8%, interassay 3.4%)], sP-selectin [normal values ($n = 69$) are 133 ± 38 pg/l, CV (intraassay) 4.9%, CV (interassay) 5.3%] and sE-selectin [normal values ($n = 100$) are 34.2 ± 12.7 pg/l, CV (intraassay) 3.6%, CV (interassay) 3.9%].

In addition we analyzed the "positive" acute phase reactants C-reactive protein (CRP) [normal values ($n = 30$) are 1.5 ± 0.8 mg/l, CV (intraassay) 3.1%, CV (interassay) 2.5%] and orosomucoid or α-1-acid glycoprotein (ORM), [normal values ($n = 59$) are 0.72 ± 0.18 g/l, CV (intraassay) 3.1%, CV (interassay) 1.9%] and the "negative" acute phase reactant transferrin (TRF) [normal values ($n = 59$) are 2.43 ± 0.45 g/l, CV (intraassay) 2.7%, CV (interassay) 2.3%]. The concentrations of the above reactants were determined by nephelometry method with CardioPhase hsCRP Reagent™ and N Antiserum™ to Human a1-acid Glycoprotein and to Human Transferrin kits using analyzer Behring Nephelometer II (BN II), all from Dade Behring Comp., Marburg, Germany.

Citrate plasma was used to determine the levels of fibrinogen (FBG) (Fibrinogen reagent, Technoclone GmbH, Wien, Austria) using analyzer Behring coagulation system (BCS) (Dade Behring, Marburg, Germany) [clotting assay by Clauss, normal values ($n = 20$) are 2.0–4.0 g/l, mean ± SD 3.0 ± 0.5 g/l, CV (intraassay) 2.9%, CV (interassay) 1.6%].

STATISTICAL ANALYSIS

Data were analyzed using SAS JMP 5.1 statistical package. Data are expressed as mean ± standard deviations or as percentage of subjects. The changes of variables within groups were compared using repeated measures analysis of variance (RANOVA) and paired t tests, the differences between groups using analysis of variance (ANOVA) and unpaired t tests for continuous variables with normal distribution or using the Mann–Whitney U test analysis of nonparametric variables. χ^2 test was applied for dichotomous variables. The linear relationship between continuous variables was analyzed with linear regression, and the corresponding Pearson correlation coefficient (r) values were calculated. Statistical significance was defined as a P value < 0.05.

Results

We included 17 patients undergoing surgery on elective basis (EL group), 29 patients with EC fractures (EC group), and 11 patients with IC fractures (IC group). Table I summarizes baseline patients' characteristics, types of anesthesia, transfusion needs, intravenously resuscitated fluid volume, and the duration of in-hospital stay. Patients with EC fractures were significantly older as compared to similar age of IC and EL patients ($P < 0.0001$ vs IC and EL group). There were no significant differences in preoperative history of coronary heart disease between the three study groups. Although mean serum creatinine values were higher in patients from both fracture subgroups, the differences were not statistically significant. Equally the differences in preoperative non-steroid anti-inflammatory drugs (NSA) and corticoid use were not significant. There was only a non-significant trend towards a more frequent use of spinal and epidural anesthesia in patients with fractures.

Patients with EC fractures were treated by dynamic hip screw osteosynthesis in two cases, Ender osteosynthesis in eight cases and proximal femoral nailing in the remaining 19 cases. Patients with IC fractures received total hip arthroplasty and hemiarthroplasty in four and seven cases, respectively. All elective hip replacements were performed using total hip endoprosthesis (cemented in five out of the 17 patients – 31%). The mean time between trauma and surgery was slightly longer in IC fractures as compared to EC. The mean in-hospital stay was significantly shorter in EL patients ($P < 0.0001$) as compared to that in EC and in IC patients.

All patients were properly anticoagulated using LMW heparins or fondaparinux in doses adapted for patient's weight and renal function. During follow-up, only one patient

Table I
Baseline and procedural characteristics of the subgroups

	EL ($n=17$)	EC ($n=29$)	IC ($n=11$)	*P* value (ANOVA or χ^2)
Male gender, *n* (%)	9 (53%)	11 (38%)	2 (18%)	0.17
Age (years)	68 ± 7	83 ± 9	71 ± 9	<0.0001
Coronary heart disease	9 (53%)	19 (66%)	8 (73%)	0.58
Preoperative serum creatinine (μmol/l)	76 ± 17	112 ± 80	120 ± 103	0.20
Chronic NSA use	5 (29%)	7 (24%)	5 (45%)	0.37
Chronic corticoid use	1 (6%)	1 (3%)	1 (9%)	0.82
Time trauma to surgery	–	5 ± 2 range 2–24 h	7 ± 3 range 2–24 h	0.02
Anesthesia				
Total (endotracheal)	9 (53%)	9 (31%)	4 (36%)	0.33
Spinal or epidural	8 (47%)	20 (69%)	7 (64%)	
Blood transfusions needs (units)	2.76 ± 1.75	1.4 ± 0.3	0.5 ± 0.5	$P<0.001$
Total fluid volume resuscitation (ml)	3176 ± 1911	5094 ± 1960	4500 ± 1900	$P<0.01$
Mean in-hospital stay (days)	8 ± 3	16 ± 3	12 ± 4	<0.0001

with IC fracture developed a symptomatic deep venous thrombosis. All patients received a prophylactic antibiotic treatment by amoxycillin–clavulanic acid combination or by cephalosporines of the second generation.

TRANSFUSION NEEDS, FLUID VOLUME RESUSCITATION, AND HEMOGLOBIN CHANGES

All patients were monitored for blood transfusion needs. Overall, blood transfusion was required in 68% of patients. The average need for transfusion units was highest in EL subgroup as compared to EC subgroup and IC subgroup (Table I). In contrast, the total intravenously administered fluid volume (excluding transfusion volumes) was highest in EC subgroup, intermediate in IC subgroup and lowest in EL subgroup (EC vs EL $P<0.001$, NS for other comparisons). As shown in Fig. 1 the time distribution of volume resuscitation was skewed towards early postoperative period, while blood transfusion administration had this pattern only in EL subgroup and was more spread in time for fracture subgroups. Neither baseline values nor the changes of hemoglobin and hematocrit were different between the three study groups.

PLATELET COUNT, FBG, AND D-DIMERS

Platelet count had similar evolution in all subgroups (Fig. 1). After surgery we observed a significant decrease, which was early followed by an increase up to the levels exceeding the baseline values.

Before surgery D-dimers were higher in EC and IC groups as compared to EL group. Immediately after surgery the level increased very high in IC group ($P<0.01$ vs EL and EC). This increase was in part driven by the single patient developing manifest venous thrombosis. However, even excluding this subject from the analysis, IC subgroup's values remained higher than in other subgroups. Subsequently a decrease was noted in all three subgroups and by the end of follow-up the values did not differ significantly (Fig. 1).

At baseline FBG levels were highest in IC patients as compared to intermediate values of EC patients and lowest in EL patients. In the blood sample drawn 4 h after surgery FBG decreased in EL and EC patients. A subsequent steep increase was observed in EL and EC patients reaching similar levels as in IC subgroup 48 h after surgery and remaining similar and stable 7 days after surgery (Fig. 1).

WBC AND ACUTE PHASE PROTEINS

At baseline, WBC was lowest in EL patients as compared to similar WBC elevation observed both in EC and IC patients. After surgery, WBC slightly decreased both in EC and IC groups while there was a steep WBC rise in EL patients. These initial changes were followed by subsequent stabilization in all three groups at comparable levels corresponding in most patients to mild WBC elevation (Fig. 2).

At baseline, CRP was comparable in EL and EC patients and significantly lower as compared to IC (Fig. 2). After surgery CRP increased in all subgroups and decreased afterwards. In IC patients the CRP increase immediately after

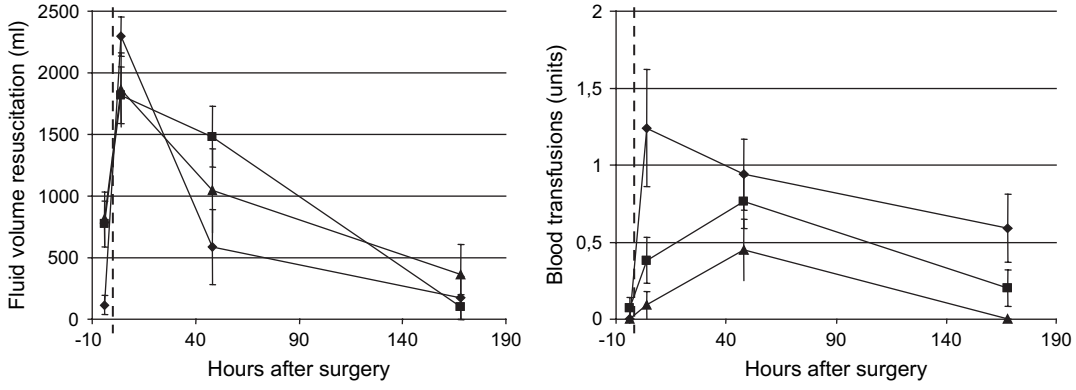

Fig. 1. The diagram showing the time distribution of fluid volume resuscitation and blood transfusions before and after the surgery (dashed line), in EL patients (diamonds), EC fracture patients (squares), and IC fracture patients (triangles).

surgery was steeper. However, already 48 h after surgery, all three groups had similar elevation in CRP levels. Subsequently EL and EC subgroups showed steeper decrease to lower values measured at 7 days as compared to IC subgroup.

The dynamics of ORM are shown in Fig. 2. At baseline ORM levels were higher in IC patients as compared to both EL and EC subgroups. After an initial minor decrease in EL subgroup ORM continued to increase in all subgroups with highest values observed in IC patients.

Baseline TRF levels were highest in EL, and lowest in IC patients (Fig. 2). Subsequently TRF values decreased to similar levels immediately and 48 h after surgery. At the end of follow-up, the levels rose again, more so in EL than in other subgroups.

SOLUBLE ADHESION MOLECULES

In all subgroups sP-selectin values have shown a U-shape evolution with a decrease immediately and 48 h after surgery and a subsequent increase at the end of follow-up (Figs. 3 and 4). Although sP-selectin values appeared highest in EC patients, the only statistically significant difference was that seen 48 h after surgery ($P < 0.05$ vs EL patients, NS vs IC).

As shown in Fig. 4, a similar U-shape with a decrease after surgery was seen in sE-selectin. At any sample, the three groups did not differ significantly (Fig. 4).

sICAM-1 values were highest before, 4 and 48 h after surgery in IC patients (Fig. 4). In this subgroup minimal variation was noted with respect to surgery and values remained more or less stable. At the end of follow-up, the differences between the three subgroups were not statistically significant.

RELATIONSHIPS OF INFLAMMATORY FACTORS DYNAMIC CHANGES WITH OTHER FACTORS

In patients with hip fracture a negative correlation between CRP increase and age was noted ($r = -0.36$, $P < 0.05$).

Relationships between hemoglobin changes, blood transfusion administration, volume resuscitation and changes of all inflammatory markers were tested. Despite similar distribution in time we were not able to demonstrate any significant relationships except for TRF and sE-selectin changes. A weak but significant correlation was observed between TRF decrease after surgery and hemoglobin decrease ($r = 0.42$, $P < 0.01$). Similar correlation was found between sE-selectin and hemoglobin decrease ($r = 0.39$, $P < 0.05$). In addition we found an inverse correlation between sE-selectin decrease and transfusion units administered within first 48 h ($r = -0.30$, $P < 0.05$). In a multivariate model both hemoglobin changes and transfusion amounts showed an independent relationship with sE-selectin changes.

sICAM-1 changes correlated with changes in WBC ($r = 0.35$, $P < 0.05$). In patients with hip fracture, we observed a significant positive correlation between age and sICAM-1 changes induced by the surgery ($r = 0.37$, $P < 0.05$).

sP-selectin decrease vaguely correlated with platelet count decrease ($r = 0.33$, $P < 0.05$).

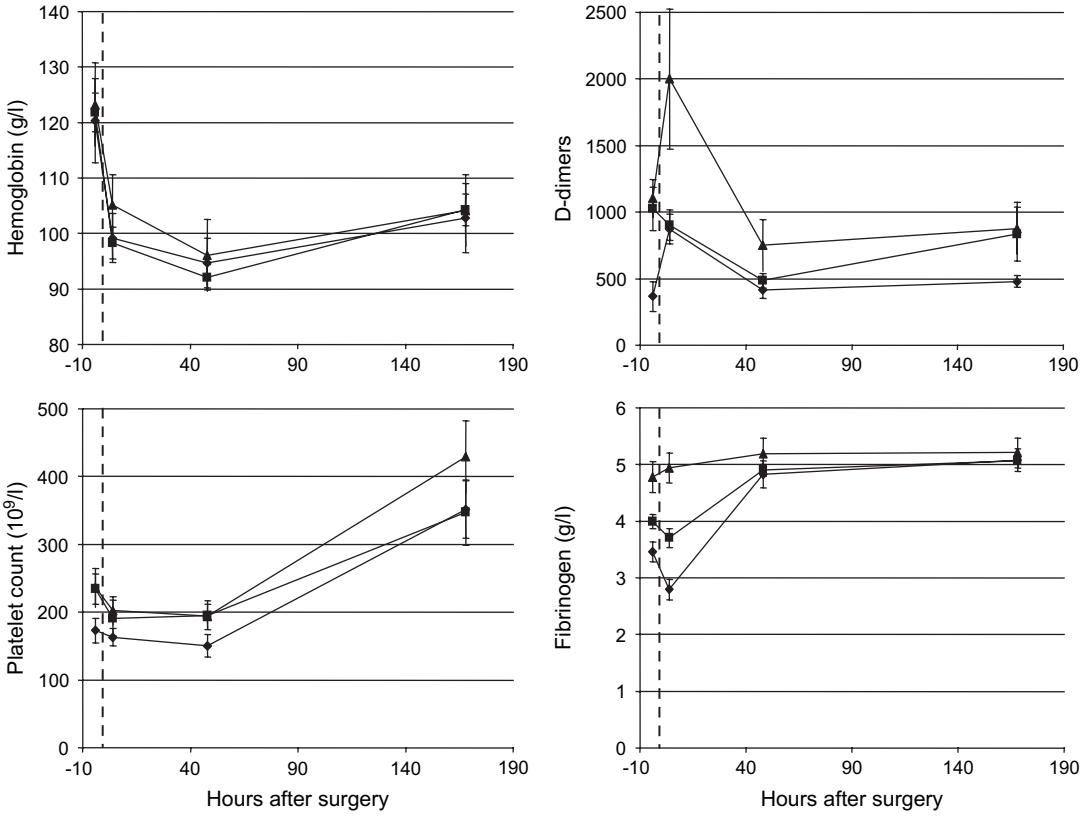

Fig. 2. Changes in hemoglobin, platelet count, D-dimers, and FBG, in EL patients (diamonds), EC fracture patients (squares), and IC fracture patients (triangles).

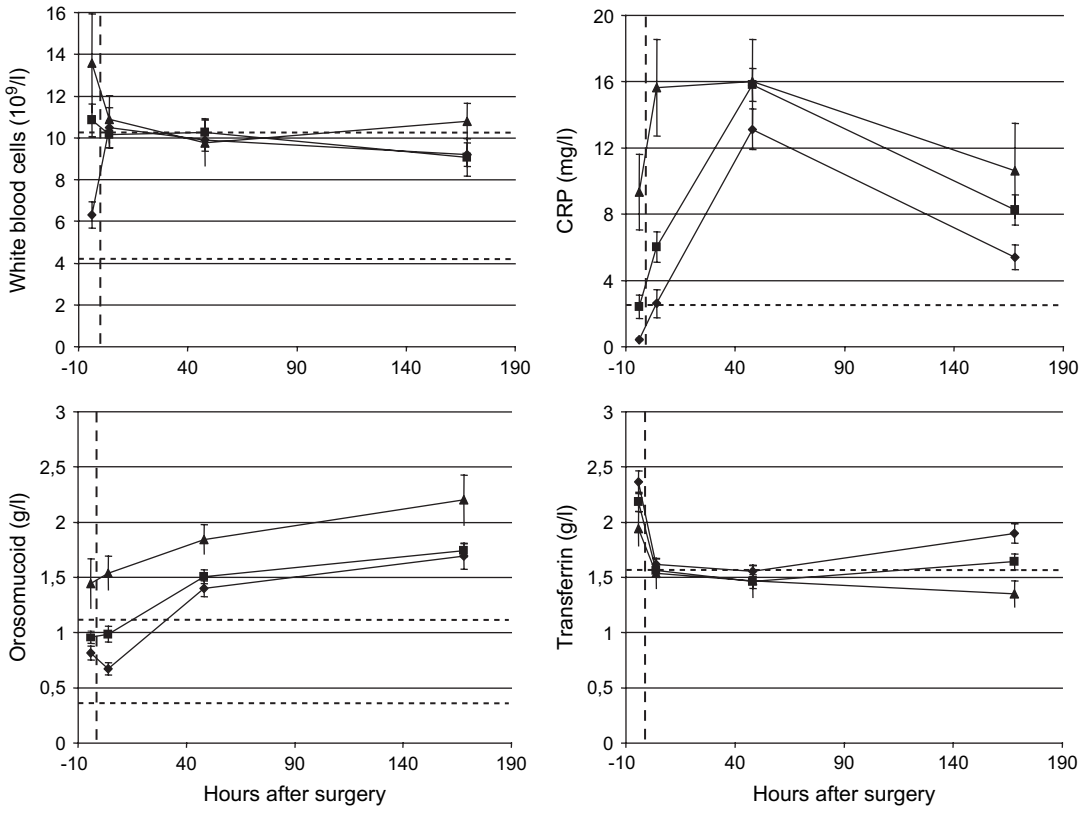

Fig. 3. Changes in WBC, plasma CRP, ORM, and TRF in EL patients (diamonds), EC fracture patients (squares), and IC fracture patients (triangles). Dotted lines stand for normal ranges (for CRP only the upper limit is shown, for TRF only lower limit is shown – upper limit is at 3.33 g/l).

In addition the influence of type of anesthesia was analyzed. The only difference found was less pronounced early CRP increase in patients undergoing elective hip replacement in whom total anesthesia was used (CRP increase 0.02 ± 0.31) as compared to those in whom spinal anesthesia was used (CRP increase 4.6 ± 4.1, $P < 0.01$). The analysis of other factors such as time trauma to surgery, baseline serum creatinine values and history of coronary artery disease did not reveal any significant relationships.

Discussion

Our study is analyzing responses of inflammation and thrombosis markers after major hip surgery. We confirmed the high burden imposed to patients by both elective and urgent hip surgery. Major changes associated with the formation of blood clots during the acute trauma and surgery and subsequent coagulation were characterized by dynamics in platelet count, D-dimers, and FBG decrease immediately after surgery and staying low 48 h after it. Platelet count and FBG elevation observed in the sample drawn 7 days after surgery suggested an important reactive procoagulant reaction occurring at this stage of postoperative disease. As compared to other two subgroups FBG and D-dimers overreacted in IC group and this result persisted even when the only one patient suffering of deep vein thrombosis was excluded. Although D-dimers tended to return to only mildly elevated values after 48 h, in all subgroups a subsequent trend for another elevation in the last sample was noted. Similar observation was previously reported for patients undergoing elective hip surgery[8]. The explanation of this elevation, which was perhaps even better seen in those parameters where an initial fall was noted (e.g., platelets or sP-selectin), remains unclear. One possible mechanism would be a compensatory response provoked by the postoperative abrupt decrease.

The surgery was associated with expected inflammatory response characterized in all subgroups by mild leukocytosis accompanied by the elevation of traditional inflammatory markers. An abrupt increase was seen in CRP values, while ORM responded more slowly. As expected, TRF levels decreased abruptly after surgery in all three subgroups. Similarly as in coagulation markers, CRP and ORM were significantly elevated in IC patients already before surgery and showed more important increase after it.

The important inflammatory reaction associated with IC fracture as compared to EC fracture before surgery (suggested by WBC, CRP, and ORM levels) is the first rather surprising finding of our study. This seems to be in contradiction with expected larger trauma and more extensive bleeding associated with EC fracture. One possible explanation would be the higher age of EC fracture patients blunting their inflammatory reactions. This would be supported by the documented weak negative correlations of WBC and CRP changes with age. However, several studies did not suggest any important age-dependence in CRP response[6]. Another explanation would be that intraarticular

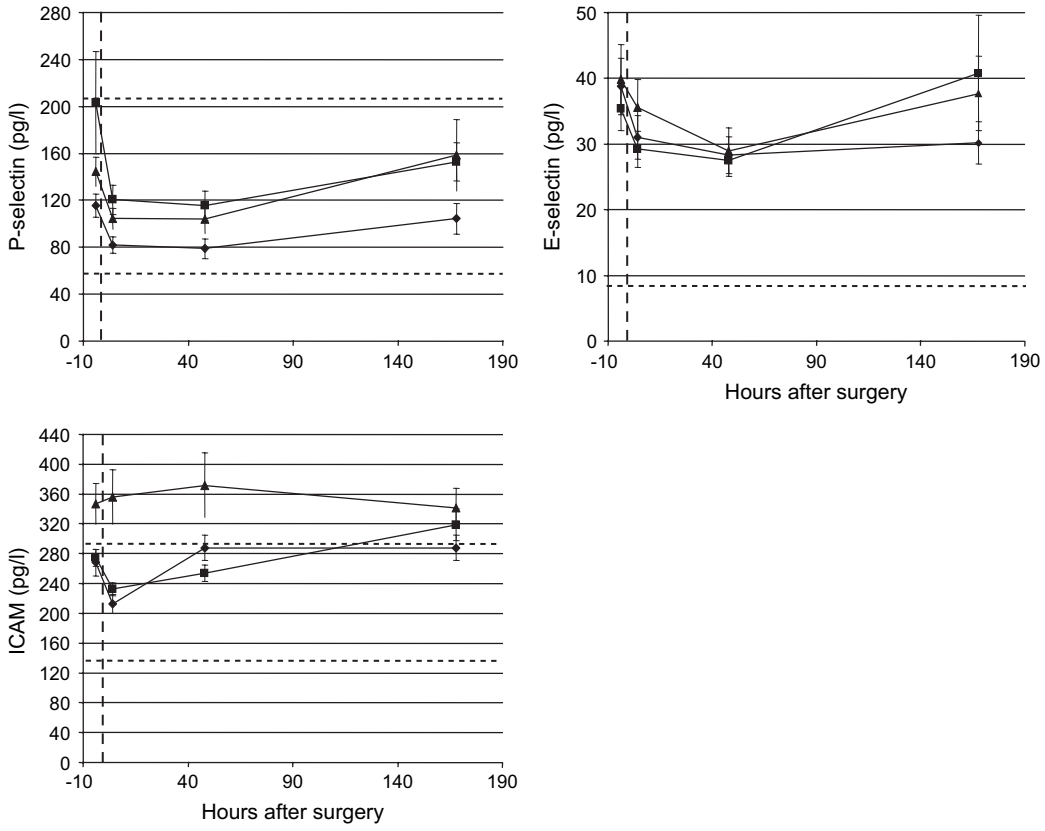

Fig. 4. Changes in plasma and sP-selectin, sE-selectin, and sICAM in EL patients (diamonds), EC fracture patients (squares), and IC fracture patients (triangles). Dotted lines stand for normal ranges (for sE-selectin only the lower limit is shown, the upper limit is at 59.6 pg/l).

character of the IC fracture leads to larger inflammatory response due to the trauma imposed to synovial structures of the joint.

The postoperative evolution of inflammatory markers fits well with results published by Neumeier and co-workers showing highest elevations in CRP values in patients receiving hemiarthroplasty and total hip replacement as compared to slightly less elevated values in patients with proximal femur nails and lowest with hip screws[4]. This is in agreement with the most marked inflammatory reaction of our IC patients treated by total hip arthroplasty and hemiarthroplasty in four and seven cases, respectively. This also might explain why after the surgery EL patients reach inflammatory marker values similar to those observed in EC patients. Due to the advanced age of our patients hip screws were not used.

The second important observation of our study is an important biphasic response in sP-selectin and sE-selectin values, decreasing immediately after surgery and reaching their minimal values 48 h after the procedure. As soluble sP-selectin is produced by activated platelets and endothelial cells, we would expect rather an elevation after surgery and trauma, as these are undeniably associated with an important vascular injury, platelet activation and inflammatory reaction. Our observation is also in contradiction with the observed activation of adhesion molecules induced by acute pain[9]. Possible explanations of this paradoxical reaction have many points of view. Some of the sP-selectin molecules could be increasingly bound by its primary connecting factor sP-selectin glycoprotein connecting factor-1 (PSGL-1) expressed on activated leukocytes. Similarly consumption might occur due to the platelet aggregation where sP-selectin allows a formation of large stable aggregates[10]. This hypothesis would be in part supported by the observed vague correlation between platelet count decrease and sP-selectin changes after surgery. In addition, also the sP-selectin production could be decreased by administered anticoagulants inhibiting thrombin production, which belongs together with interleukin 1 and tumor necrosis factor α to cytokines stimulating its expression. By the end of 7 days' follow-up sP-selectin increased again. This might be a similar phenomenon as seen in patients after deep venous thrombosis as observed by Blann *et al.*[11].

sE-selectin is an endothelial adhesion molecule which mediates the tethering and rolling of leukocytes on vascular endothelium. As sE-selectin is entirely produced by activated endothelium, its decrease instead of expected elevation due to vascular trauma is difficult to explain. In our study, sE-selectin changes were independently associated with hemoglobin decrease after the surgery and negatively with transfusion administration. They could therefore be to some extent attributed to hemodilution. Moreover, hemodilution may be even more important explanatory mechanism of the observed biphasic responses than would be expected from these weak correlations. Hemoglobin or hematocrit values do not necessarily reflect the real blood losses as they are in part counterbalanced by blood transfusions and hemoconcentration on one hand and enhanced by fluid volume resuscitation. In our study the latter was assessed only by the means of monitoring of intravenously

administered fluids, which in most patients do not reflect the total water balance. To further elucidate the biphasic response of the selectins we examined in detail the possible influences of surgery associated factors including the trauma to surgery time, type of anesthesia, preoperative history of coronary artery disease, and renal function. We did not find any other significant relationships which, however, might be in part attributable to the limited number of patients in the subgroups.

Intercellular adhesion molecule-1 (sICAM-1) is an adhesion factor present on the surfaces of endothelial cells and leukocytes. This protein mediates adhesion and transmigration of leukocytes through the endothelium[7]. We observed a transient decrease in sICAM-1 values in EC and EL patients paralleling to some extent WBC dynamics. The exact mechanism of this reaction is unclear and remains purely speculative.

Of note are the discordant sP-selectin and D-dimer changes after surgery. sP-selectin is rapidly upregulated after a minor trauma to the venous vessel wall and likely influences the development of venous thrombosis in which inflammatory responses play major roles[12]. Therefore, it was suggested to be a promising and sensitive marker of thrombosis[13]. However, we observed a decrease in sP-selectin even in the only patient with symptomatic venous thrombosis, where D-dimers were significantly elevated. This finding is in agreement of lower sensitivity of soluble sP-selectin in detecting clinical deep venous thrombosis as described by Božič *et al.*[14].

The main limitation of our study was the different age of subjects in the three study groups. However, we included consecutive patients undergoing hip surgery. Therefore our study reflects the real clinical practice. In addition, the weak character of negative correlations between inflammatory responses with age in the fracture subgroups is probably unable to explain the observed exaggerated inflammatory reaction of patients with IC fractures as compared to EC patients. The second limitation of our study comprises the relatively small number of patients in the study subgroups. Nevertheless, observed differences were consistent within the subgroups and during the follow-up. In addition we attempted to reduce the number of confounding factors. This was the main reason why we limited our study to patients who received the surgery within 24 h after the trauma as the delayed surgery was shown to aggravate the postoperative outcome[15]. Moreover, in patients with delayed surgery it is difficult to distinguish between the effect of the delay by itself, causing immobilization and increasing the risk of thrombotic complications, from impacts of comorbidities, which are mostly representing the main cause of surgery delay. In contrast, the impact of the surgery timing is probably less important within first 24 h after the trauma[16,17].

In conclusion, our study demonstrated significant inflammatory preoperative burden in patients with hip fractures and important reaction associated with both elective and urgent procedures. Preoperative inflammatory markers and their postoperative reaction were most pronounced in patients with IC hip fractures. After surgery we observed a paradoxical decrease namely in sP-selectin and sE-selectin. This could be in part explained by blood losses and subsequent hemodilution induced by the surgery. This paradoxical decrease is of potential clinical significance showing the incapacity of sP-selectin to reveal potential venous thrombosis associated with hip surgery.

There is large evidence to show that inflammation and coagulation are closely related processes. They may considerably affect each other at the levels of platelet activation, fibrin formation, and resolution as well as physiological anticoagulant pathways. Our findings underline the complex interplay and cross-talk between the two pathways activated by the surgical trauma. Our observations also indicate that many of those factors are markedly modified by blood losses and hemodilution. The definite explanation of several observed changes, namely in soluble selectin levels will require further studies.

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