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RESEARCH ARTICLE

Serum kinetics of soluble triggering receptor expressed on myeloid cells-1 differs in relation to the type of arthroplasty

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Abstract

Context: Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) participates in the inflammatory process.

Purpose: To describe changes of sTREM-1 in the serum after hemiarthroplasty (HA) and total hip arthroplasty (THA).

Methods: Serial blood samples were drawn from 122 patients with hip fracture. Interleukin-6 (IL-6), sTREM-1, and C-reactive protein (CRP) were measured.

Results: IL-6 and CRP were similarly increased after both HA and THA. sTREM-1 was increased early in HA and late after THA. The only parameter that was higher among patients who developed systemic inflammatory response syndrome was IL-6.

Conclusions: Kinetics of sTREM-1 differs among patients undergoing HA of the hip and those undergoing THA.

Keywords: sTREM-1, IL-6, hip fracture, arthroplasty, inflammation

Introduction

Hip fracture is one of the most common and potentially devastating injuries in elderly population. The trauma itself and the operation that follows are associated with systemic inflammatory reaction.

The last few years there is increasing interest regarding the inflammatory status of the injured patient. It is proposed by many trauma surgeons that polytrauma patients should not be permanently operated the first hours after the injury, because this worsens the inflammatory status and leads to increased complication rate (Pape et al. 2001). Measurement of serum cytokines has been proposed as a method of prediction of unfavorable outcome and of the advent of the systemic inflammatory response syndrome (SIRS; Bone 1996; Giamarellos-Bourboulis et al. 2008).

Hip fractures are a common cause of surgery, particularly in the elderly. In that patient population, where comorbidities are very often, one major factor affecting the outcome of surgery is the inflammatory response to trauma (Giannoudis 2008). It is highly probable, even though still under investigation that the inflammatory response varies when different procedures are applied to these patients. Limited data are available for the kinetics of proinflammatory cytokines within hip-fracture-operated patients (Beloosesky et al. 2007). It is questionable if complications can be predicted, and if the type of operation affects the inflammatory response.

sTREM-1 (soluble triggering receptor expressed on myeloid cells-1) is a newly described peptide. It is the soluble counterpart of the TREM-1 receptor that is highly expressed on the cell membranes of neutrophils and of monocytes in the event of a bacterial infection. TREM-1 is shed in the systemic circulation in systemic bacterial infections and this soluble counterpart of the receptor is known as sTREM-1 (Bouchon et al. 2001).

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Recent studies propose that TREM-1 and sTREM-1 participate in the SIRS that develops after multiple injuries even in the absence of bacterial complications (Giamarellos-Bourboulis et al. 2008).

Whether sTREM-1 participates in SIRS arising after hip hemiarthroplasty (HA) or after total hip arthroplasty (THA), remains unanswered. In the present study, kinetics of sTREM-1 was investigated in a cohort of elderly hip-fracture-operated patients to determine their relationship with appearance of SIRS and the extent of the inflammatory response following HA and THA. Results were compared with serum levels of C-reactive protein (CRP) and of interleukin-6 (IL-6).

Patients and Methods

One hundred and twenty-two patients were enrolled in this prospective study during the period June 2004 to December 2005. The study protocol was approved by the Ethics Committee of Vostanion General Hospital of Mytilini. All patients provided written informed consent.

Inclusion criterion was the occurrence of a hip fracture necessitating surgical treatment with either HA or THA with the implantation of a sliding nail and a plate.

Exclusion criteria were as follows: (i) the presence of infection by the human immunodeficiency virus; (ii) neutropenia defined as any absolute neutrophil count below 500 per mm^3; and (iii) intake of corticosteroids defined as any equal to or more than oral daily intake of 1mg/kg of equivalent prednisone for more than 30 days.

Four blood samples were taken from each patient after venipuncture of one antecubital vein under sterile conditions; on the day before surgery; on the first postoperative day; on the fourth postoperative day; and on the eighth postoperative day. Blood was centrifuged and serum was kept refrigerated at −70°C until assayed. Concentrations of IL-6 and of sTREM-1 were estimated in sera in duplicate by an enzyme immunoassay (R&D Inc., Minneapolis, USA). The lowest detection limits were as follows: for IL-6 6.25 pg/ml; and for sTREM-1 15.1 pg/ml. Concentrations of CRP were estimated in duplicate by nephelometry (Behring, Berlin, Germany). The lowest detection limit of the assay was 3.2 mg/l.

All patients were followed up daily until their discharge. SIRS was diagnosed in any patient presenting with at least two of the following signs (Levy et al. 2003): (i) core temperature >38°C or <36°C, (ii) respiratory rate >20 breaths/min or P_{co2} < 32 mm Hg, (iii) pulse rate > 90/min, and (iv) white blood cells > 12,000/μL or < 4000/μL, or >10% of band forms.

After Kolmogorov-Smirnov's statistics, it was found that IL-6, sTREM-1, and CRP followed linear distribution. As a consequence, results were presented by their median and 95% confidence intervals (CI). For comparisons patients were grouped regarding the type of operation and the development of SIRS. Comparisons between groups within the same day were done by the Mann-Whitney U test. Comparisons between consecutive days were done by the Wilcoxon's signed rank test. Any value of p below 0.05 after adjustment for multiple comparisons was considered significant.

Results

Fifty-nine patients suffered from fracture of the femoral neck and were treated with HA of the hip and 63 suffered from a peritrochanteric fracture and were treated with THA. Eighty-eight of them were women and 34 were men. Mean ± SD age of patients undergoing HA was 81.3 ± 9.4 years and of those undergoing THA 79.5 ± 10.9 years (nonsignificant between them, pNS).

Serum kinetics of IL-6, of sTREM-1, and of CRP in relation with the type of operation is shown in Figure 1. No differences in serum levels of IL-6, of sTREM-1 and of CRP were found between patients undergoing HA and patients undergoing THA on any day of sampling. IL-6 was increased on the first postoperative day compared with baseline in both patients undergoing HA ($p = 0.004$ compared with baseline) and patients undergoing THA ($p = 0.001$ compared with baseline). However IL-6 returned at baseline levels on days 4 and 8 of patients undergoing either type of operation.

sTREM-1 followed different patterns of kinetics than IL-6. It was increased ($p = 0.019$ compared with baseline) on the first postoperative day but not on postoperative days 4 and 8 among patients undergoing HA. It failed to be increased on the first postoperative day and on postoperative day 4 among patients undergoing THA. However, it was increased on postoperative day 8 ($p = 0.031$ compared with baseline).

CRP followed similar pattern of kinetics among patients undergoing either type of operation. Among those subject to HA, CRP was increased on the first postoperative day ($p < 0.0001$ compared with baseline) and on postoperative day 4 ($p < 0.0001$ compared with baseline). Among patients subject to THA, CRP was increased on the first postoperative day ($p < 0.0001$ compared with baseline) and on postoperative day 4 ($p = 0.015$ compared with baseline).

Ten patients undergoing HA (16.9%) developed signs of SIRS and eight patients undergoing THA developed signs of SIRS 12.7% (pNS). As no differences of serum IL-6, sTREM-1, and CRP were found between patients undergoing HA and those undergoing THA, patients undergoing either operation who developed SIRS were compared with patients undergoing either operation who did not develop SIRS. Consecutive concentrations are shown in Figure 2. The only parameter that was higher on postoperative day 1 among patients with SIRS compared with those without SIRS was IL-6 ($p = 0.010$ between patients with SIRS and patients without SIRS on day 1). SIRS was resolved in all patients and all patients were discharged from hospitals. None of the enrolled

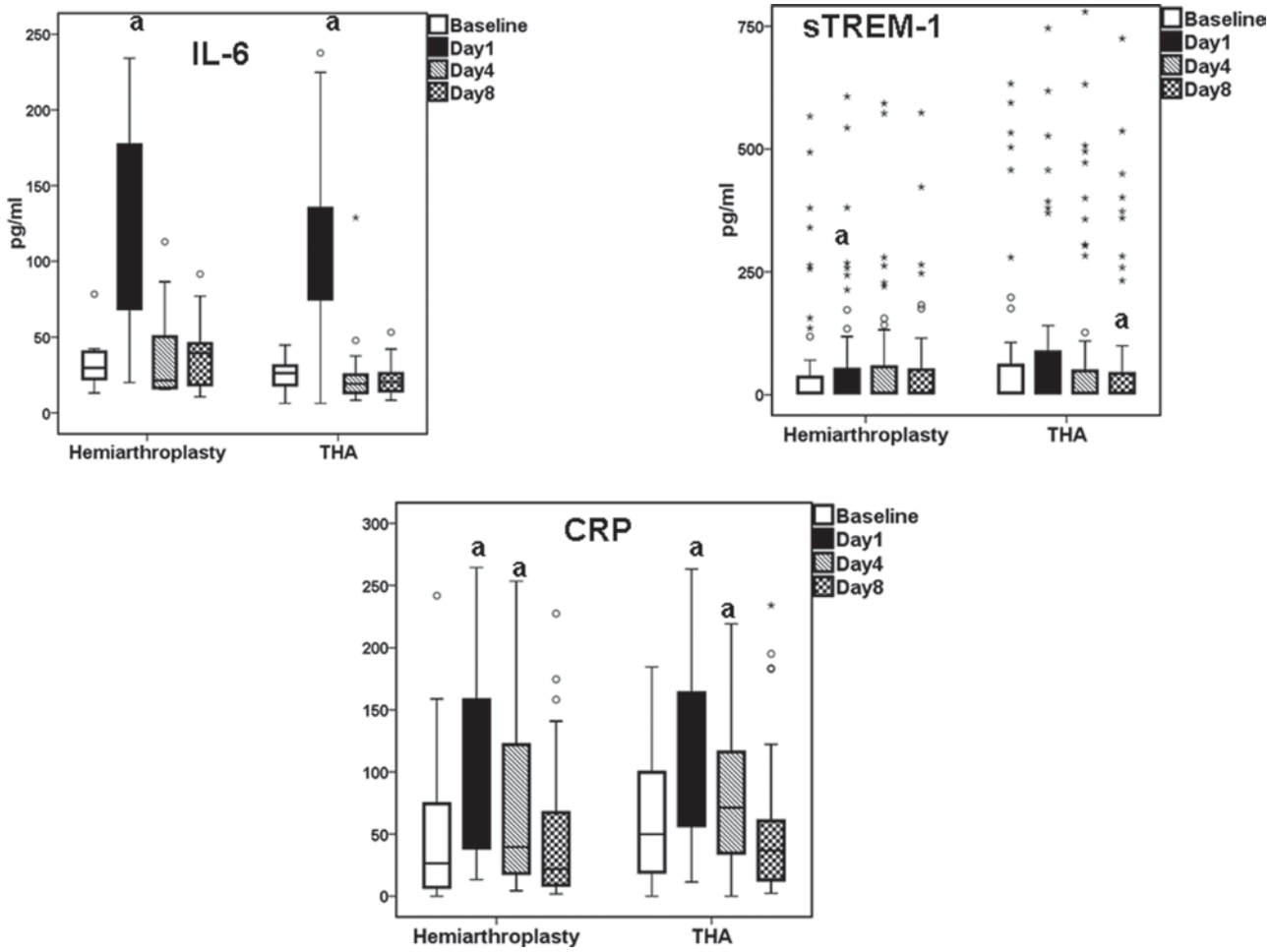

Figure 1. Daily follow-up concentrations of interleukin-6 (IL-6), of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), and of C-reactive protein (CRP) of 59 patients undergoing hemiarthroplasty (HA) of the hip and 63 patients undergoing total hip arthroplasty (THA). Circles denote outliers and asterisks denote extremes. The letter "a" indicates statistically significant differences compared with the respective values before operation.

patients was diagnosed with surgical-site infection after 1 year of follow-up.

Discussion

Hip screw and HA are two importantly different operations often used for treating fractures in elderly people. These fractures are considered common among surgeons, in everyday practice. They are often called "hip fractures" and no attention is paid to the type of operation, regarding patients' inflammatory response. According to presented results, when both types of operation are compared, they seem to differ in kinetics of serum inflammatory mediators.

TREM-1 is a receptor engaged on cell membranes of neutrophils, monocytes, and macrophages taking part in the inflammatory process, when stimulated by invading pathogens. TREM-1 is not considered to be a major player in sterile inflammatory processes (Gibot & Cravoisy 2004). However, more recent studies provide evidence that sTREM-1 participates in posttraumatic SIRS of patients bearing multiple traumas without bacterial complications (Giamarellos-Bourboulis et al. 2008). Its participation in the inflammatory response after operation for hip fractures is currently unknown. The presented findings suggest that serum kinetics of sTREM-1 seems to be affected for a longer postoperative period after THA than after HA. However, in both operations, the changes of sTREM-1 compared with baseline are not dramatic. It may be assumed that the extent of tissue damage produced during the operative process may be responsible for the observed differences which mainly involve sTREM-1. More precisely, more soft tissue damage happens after a pertrochanteric fracture and hip screw insertion, than after a femoral neck fracture and HA. However, it should be underscored that increase of serum levels of sTREM-1 are a main characteristic of SIRS developing in the field of a systemic bacterial infection and not of postoperative SIRS (Gibot & Cravoisy 2004).

Although serum IL-6 levels do not differ in relation with the type of operation, they may be used as an indicator of postoperative SIRS. Similar findings are described by others in both nonorthopedic surgery (Dimopoulou et al. 2007) as well as after total hip replacement and

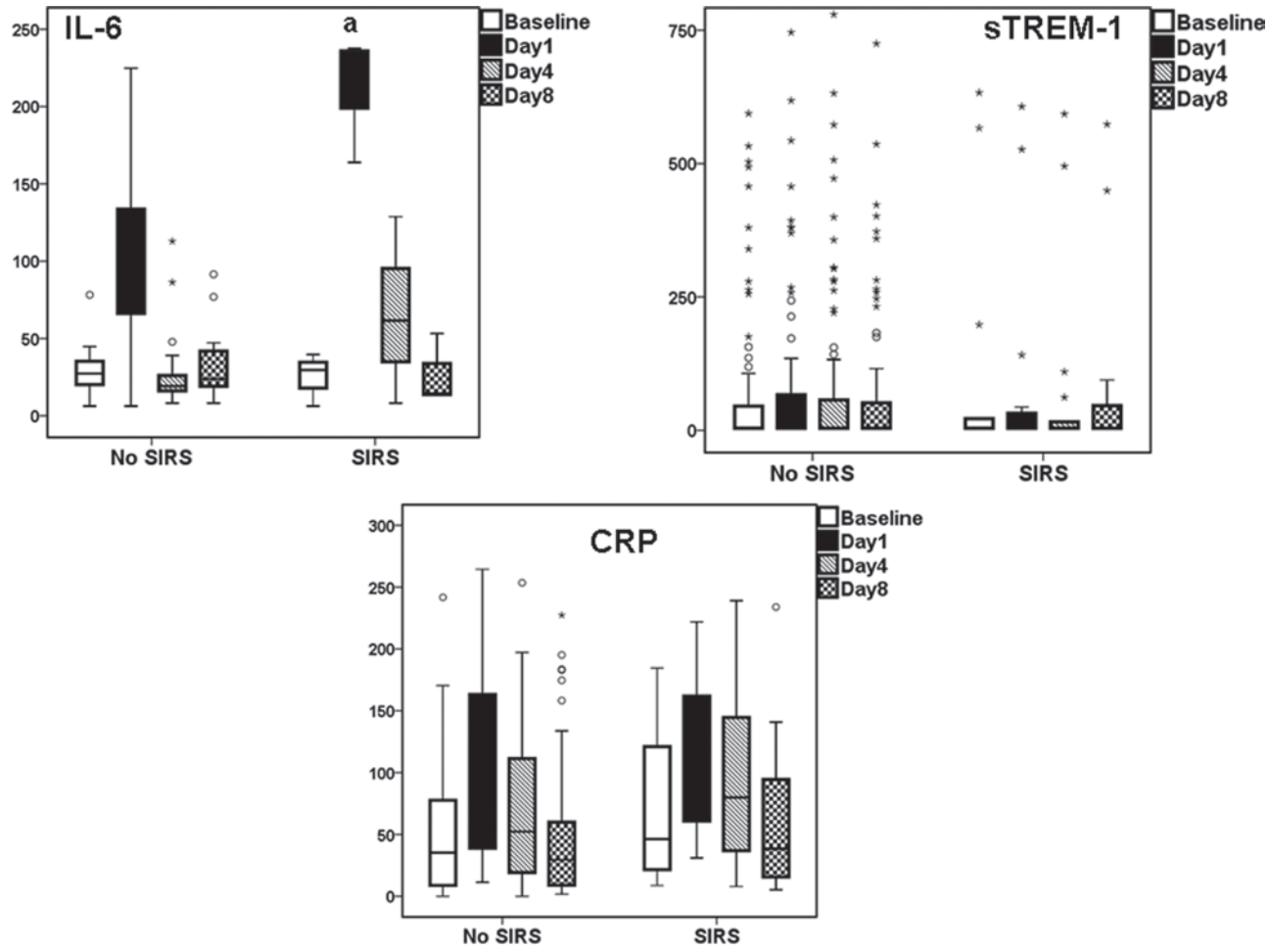

Figure 2. Follow-up serum concentrations of interleukin-6 (IL-6), of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), and of C-reactive protein (CRP) of patients undergoing either hemiarthroplasty (HA) or total hip arthroplasty (THA) for fracture of the hip. Patients are divided into those who developed postoperative systemic inflammatory response sysndrome (SIRS) ($n=18$) or not ($n=104$). Circles denote outliers and asterisks denote extremes. The letter "a" indicates statistically significant differences compared with the respective values before operation.

other types of operation of the hip (Beloosesky et al. 2007; Neurmaier et al. 2006).

It should be underscored that the presented results signify that one destructive sterile process in the human host like an operative procedure is highly probable to stimulate an inflammatory reaction per se. This observation is consistent with the hypothesis that once cellular constituents of the human body are released after tissue destruction, they stimulate innate immune responses. These constituents are known as alarmins (Rittirsch et al. 2008). In consistence with that it has recently been described that mitochondrial DNA released from patients suffering multiple injuries may stimulate the innate immune response yielding proinflammatory phenomena (Zhang et al. 2010).

Conclusions

The results revealed that kinetics of sTREM-1 differ among patients undergoing HA of the hip and those undergoing THA. Although kinetics of IL-6 does not differ in relation with the type of operation, they are significantly elevated within the first postoperative day among patients complicated with SIRS.

Declaration of interest

None of the authors has any conflict of interest to declare in relation with this submission.

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