ORIGINAL PAPER

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Interleukin-6: a potential inflammatory marker after total joint replacement

Accepted: 1 February 2000

Abstract In a prospective study C-reactive protein (CRP) and interleukin-6 (IL-6) measurements were taken serially in 30 patients before and after 20 total hip arthroplasties (THR) and 10 total knee arthroplasties (TKR). There were no peri- and postoperative complications. Postoperatively the IL-6 serum concentration increased rapidly and peaked 6 h postoperatively at maximum levels (399 ± 140 pg/ml). There was a mean half-life of 15 h and thereafter a rapid return to normal concentrations. In comparison, the postoperative CRP concentration rose more slowly and reached maximum levels (138 ± 54 mg/l) on the second postoperative day. There was thereafter a slow descent with a mean half-life of 62 h. There was no significant difference between the patients with THR and those with TKR ($P > 0.05$). IL-6 is therefore a superior marker for the inflammatory phase after THR and TKR.

Résumé Nous avons contrôlé la “C-Reactive Protein” (CRP) et l’“Interleukin-6” (IL-6) chez 30 patients avant et après l’implantation de 20 prothèses totales de la hanche et 10 prothèses totales du genou. L’évolution péri- et post-opératoire chez tous les patients était sans complications. Les valeurs de la CRP étaient déterminées par turbidimétrie immunologique et les valeurs de l’IL-6 étaient déterminées par dosage immunologique des enzymes. La concentration de IL-6 dans le sérum augmentait très vite après l’opération et atteignait, 6 h après, ses valeurs maximales. Par contre les concentrations du CRP augmentaient moins vite et atteignaient leurs valeurs maximales seulement le 2^e jour après l’opération. La détermination de IL-6 s’avère très adaptée pour le contrôle de l’évolution chimique après implantation d’une prothèse totale.

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Introduction

IL-6 is formed from monocytes, macrophages, fibroblasts and T2-lymphocytes when tissue is traumatised. The subsequent inflammatory action induced by IL-6 produces CRP and serum amyloid A-protein in the liver, T and B cellular activation in the peripheral blood and bone marrow and pyrexia via pituitary hormones [3]. The value of IL-6 for monitoring inflammation in trauma, sepsis, shock and after major cardiac and abdominal surgery has been shown in several studies [2, 4]. There has, however, been no prospective study to determine the value of IL-6 concentrations as a marker of inflammation in orthopaedic patients. The measurement of CRP, which is induced by IL-6, has an established place in assessing inflammation, particularly after prosthetic replacement [9]. The aim of this study was therefore to investigate the value of IL-6 measurements, when compared with CRP measurements, after THR and TKR.

Patients and methods

Thirty patients were studied. There were 18 women and 12 men, with a mean age of 64.2 years (55–88 years). There were 20 THRs and 10 TKRs. Serum samples were taken preoperatively and immediately postoperatively after closure of the wound; and thereafter 6, 12 and 24 h postoperatively and on the second, third, fourth, fifth, sixth and seventh postoperative days. All patients received routine antibiotic prophylaxis with cefazolin 2 g preoperatively and 8 h and 16 h postoperatively. Twelve of the patients undergoing THR were given local fractional radiation doses (3×3 Gy) between the first and third postoperative day to avoid periarticular ossification. Four of the patients undergoing THR and six of the patients undergoing TKR were given 3×50 mg diclofenac orally as analgesia for a total of 10 days postoperatively.

IL-6 and CRP measurements were performed on routine venous blood samples stored directly after they were taken at $+2^\circ$ – 6° C for 24 h, then centrifuged at 3,500 rpm for 10 min and deep-frozen at -20° C until determination. The CRP measurements were carried out by immunologic turbidimetry (Tina-quant CRP; Boehringer Mannheim, Germany). The recommended cut-off level for this turbidimetric test is 5 mg/l. The IL-6 concentration was determined using an enzyme link immunosorbent assay (ELISA; Immulite; DPC Biemann, Bad Nauheim, Germany). The recommended cut-off level is 4 pg/ml.

The *t*-test was applied for statistical differences between the groups of patients. The Pearson correlation was used to show correlations between IL-6 and CRP concentrations.

Results

There were no anaesthetic or surgical complications. The mean serum concentrations for the first 7 postoperative days are shown in Fig. 1. There is a fast rise of IL-6 concentration with a peak 6 h postoperatively (399 ± 140 pg/ml) and a rapid fall with a half-life of 15 h postoperatively. The CRP concentrations show a slow rise with a peak 2 days postoperatively (138 ± 54 mg/l) and a slow decrease with a half-life of 62 h. The mean time from the end of the operation to the return of the IL-6 measurements to 50 pg/ml or less was 48 h (24–70 h). The corresponding time for CRP to return to 50 mg/l or less was 157 h (66–168 h). This difference is highly significant ($P < 0.0001$).

Comparison of the two inflammatory parameters shows a significant difference during the first 24 h postoperatively ($P < 0.0001$). After the second postoperative day there was a significant correlation between the se-

Fig. 1 Mean serum concentrations of IL-6 and CRP of all patients included in the study

Fig. 2 Mean serum concentrations of IL-6 and CRP of 20 patients with THR

Fig. 3 Mean serum concentrations of IL-6 and CRP of 10 patients with TKR

Fig. 4 Mean serum concentrations of IL-6 and CRP of 12 patients with THR who received radiation treatment in the hip area postoperatively

rum concentration of the two parameters ($k=0.9905$, $P=0.00006$). The results for the patients after THR compared with those after TKR are shown in Figs. 2 and 3. A slightly prolonged inflammatory course is seen for the patients with TKR, with a peak of IL-6 concentration 12 h postoperatively (399.5 ± 129 pg/ml) and a return to 50 pg/ml after 3 days. There is also a slightly protracted increase in CRP concentration with a slower decline thereafter in the patients with TKR. A statistically significant difference between the maximum concentrations of IL-6 and CRP is not seen when comparing these two groups ($P > 0.05$). The findings were the same in the group of patients who received irradiation to the hip after THR (Fig. 4; $P > 0.05$). The measurements were also similar in the group of patients who received non-steroidal anti-inflammatory agents (Fig. 5). There was a slightly protracted rise of both inflammatory parameters compared with patients who did not take non-steroidal anti-inflammatory medication but the difference was not statistically significant ($P > 0.05$).

Fig. 5 Mean serum concentrations of IL-6 and CRP of 10 patients with THR or TKR who were treated with NSAID postoperatively

Discussion

Macrophages are mainly responsible for the production of IL-6 as the main mediator of the acute inflammatory reaction after surgery [1, 3]. IL-6 is also responsible for inducing the hepatic synthesis of CRP, which has been considered the inflammatory marker of choice in orthopaedic surgery [5, 7]. It has been shown in several studies that the CRP concentrations increase within the first 48–72 h postoperatively and then decrease slowly over several days [7–9]. In the present study the maximum CRP concentrations were seen 48–72 h postoperatively and returned to levels below 50 mg/l at an average time of 157 h postoperatively. This period is considered critical for the initiation of bacterial infection [6, 10]. In contrast, the IL-6 concentration increased rapidly with a peak 6–12 h postoperatively and a descent thereafter returning to levels below 50 pg/ml within 48 h. Kraghsbjerg et al. [4] have suggested that IL-6 levels above 50 pg/ml should be considered as an indication of active infection. Our study was prospective and no infections occurred. We can therefore draw no conclusions about the relative

value of serum IL-6 or CRP concentrations in the early recognition of infection. We can conclude, however, that the IL-6 concentration correlates with a high degree of inflammatory activity with a more rapid increase and a quicker return to normal values than CRP; and this suggests IL-6 measurements give a better indication of postoperative inflammatory response than the CRP measurements after THR and TKR. Niskanen et al. [7] and White et al. [9] have previously reported similar results. Local irradiation or systematic non-steroidal anti-inflammatory medication did not affect the postoperative IL-6 and CRP serum concentrations.

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