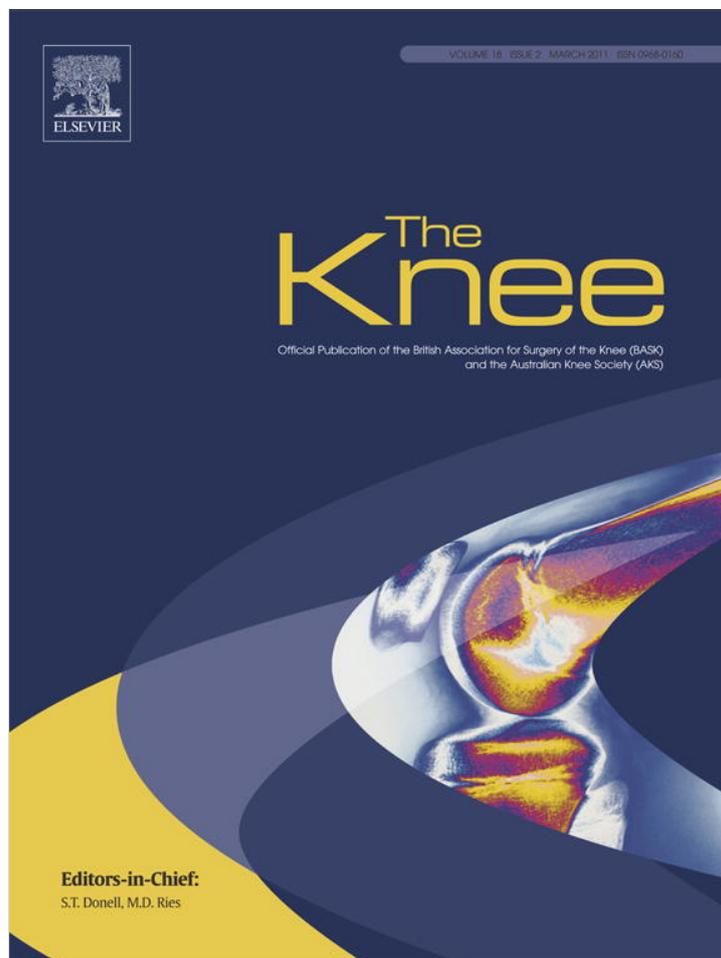


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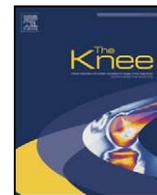
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The Knee



Which is more important after total knee arthroplasty: Local inflammatory response or systemic inflammatory response?

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ARTICLE INFO

Article history:

Received 11 September 2009

Received in revised form 21 March 2010

Accepted 24 March 2010

Keywords:

Interleukin-6

C-reactive protein

Recovery

Arthroplasty

Knee

ABSTRACT

We aimed to determine the relationship between functional recovery after knee arthroplasty and systemic and local inflammatory responses. A prospective, clinical study of thirty patients who had osteoarthritis was conducted. After the total knee arthroplasty (TKA), intraarticular IL-6 levels, serum IL-6 levels and serum CRP levels were measured. The primary outcome measures for functional recovery after TKA were the the Knee Society Score (KSS) and Western Ontario and McMaster Universities Index (WOMAC). All patients were examined preoperatively and at 4, 8 and 24 weeks postoperatively. The mean postoperative intraarticular IL-6 level was 218355.1 pg/ml, the mean postoperative serum CRP level was 109.9 mg/L and the mean postoperative serum IL-6 level was 219.0 pg/ml. Preoperative and 4-, 8- and 24-week postoperative KSS and WOMAC scores were evaluated. Significant correlations were found between intraarticular IL-6 concentrations and KSS and WOMAC scores at the first month according to the Pearson correlation test, but no correlations were found between serum IL-6 and CRP levels and KSS and WOMAC scores. The local inflammatory response is more important than the systemic response for early postoperative functional recovery. After TKA, control of local inflammation is much more important than control of systemic inflammation.

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1. Introduction

Major surgeries can cause physiological, subjective and behavioral changes in patients. The cause of these changes is a stress response to surgery, and many of these responses are physiological. Neuroendocrine, metabolic and inflammatory changes following major surgeries have been reported in the literature [1–4]. Several studies have investigated the relationship between postoperative physiological changes and outcomes. Kehlet reported that the neuroendocrine response to surgery is not essential for survival and may contribute to postoperative complications and delaying recovery [3]. Kennedy et al. have suggested that the inflammatory response is more important than neuroendocrine changes in determining postoperative recovery [5].

We hypothesized that, in terms of functional recovery, the local inflammatory response would be more important than the systemic inflammatory response. We choose total knee arthroplasty patients because knee joints allow us to measure local inflammatory responses. The local inflammatory response was determined with intraarticular IL-6 levels, and the systemic inflammatory response determined with postoperative serum IL-6 and CRP levels. The

relationship between local inflammatory response, systemic inflammatory response and functional recovery was investigated.

2. Methods

2.1. Patients

After the Ethics Committee of Haseki Training Hospital gave approval, the study was started. Forty one consecutive patients undergoing elective knee replacement surgery were studied. Eight patients with general anesthesia, one patient with myocardial infarction, one patient with acute renal insufficiency, and one patient with Still's disease were excluded from the study. The remaining 30 patients fulfilled the following criteria: age over 18 years, absence of malignant or infectious disease, absence of rheumatoid arthritis, and not on steroid medication. Informed consent was obtained from all patients. None of patients had activated osteoarthritis at the time of operation. All patients used nonsteroidal anti-inflammatory drugs for pain management preoperatively and received 1 g cefazolin for perioperative infection prophylaxis. None of the patients developed infectious complications. Postoperative pain was managed with opioids during the study period.

On the day before surgery, the Knee Society Score (KSS) and Western Ontario and Mac Master Universities Index (WOMAC) were determined [6,7]. Knee replacement surgery was performed under

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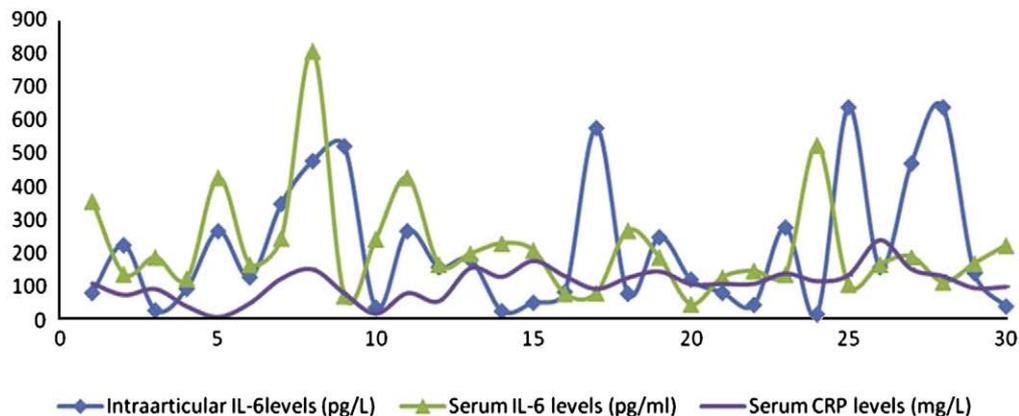


Fig. 1. Intraarticular IL-6, serum IL-6, and serum CRP levels for each case are shown. Note that intraarticular IL-6 levels are shown per liter instead of per milliliter.

tourniquet, which was applied with a pressure of 100 mmHg above the patient's systolic blood pressure. All prostheses were applied with cement, and all were Foundation® Knee systems with rotating platforms (Encore Medical, USA). Preoperatively, two drainage suction tubes were placed, one of which was attached to the drainage suction system and the other of which was not. Intraarticular IL-6 levels peaks at postoperative 24 h [8]. The second tube was used to obtain an intraarticular fluid sample to determine intraarticular IL-6 levels. All intraarticular samples obtained by senior author (A.A.U.) at 24 h postoperatively. The second tube was cut near the exit hole. Generally after a few second there was enough blood to collect. If it was not, a needle inserted into the drain tube and aspirate some blood deeply into the knee. Patients' blood samples were collected 24 h postoperatively for systemic IL-6 and CRP levels.

2.2. Analysis of blood and intraarticular fluid samples

The drain fluid samples were spun in a centrifuge for five minutes at 3000 rpm to separate the serum. The resulting serum was then stored at -70 °C pending analysis [9]. IL-6 concentrations were measured with the Immulite 2500 device (BioDPC, USA). Imm 2500 IL-6 is a solid-phase enzyme-labeled chemiluminescent sequential immunometric assay. Beads were coated with monoclonal murine anti-IL-6. Alkaline phosphatase was conjugated to polyclonal sheep anti-IL-6. Serum CRP concentrations were measured with a BN PROSPEC device (Dade-Behring, USA). Polystyrene particles were coated with a monoclonal antibody to CRP that agglutinates when mixed with samples containing CRP. The intensity of the scattered light in the nephelometer depends on the concentration of CRP in the sample, and as a consequence, the CRP content of the sample can be determined by comparison with dilutions of a standard of known concentration.

2.3. Physiotherapy regimen

All patients were seen by a physiotherapist after surgery. On the first postoperative day, active assisted range of motion exercises and walking practice were started. On the third postoperative day

stepping exercises were started. At one month after surgery, the second level of strengthened exercises began. All patients were followed up at 4, 8 and 24 weeks postoperatively. At each visit, an orthopedic surgeon and a physiotherapist examined the patients and completed score sheets (KSS, WOMAC).

2.4. Statistics

Statistical analyses were performed with the NCCS 2007 pocket program. Results were evaluated with descriptive statistical methods such as mean and standard deviation. The Friedman test was used for repeat measurements of multiple groups. Pearson correlation was used to determine the relationship of variables with each other. The significance level was set at $p < 0.05$.

3. Results

The study sample consisted of 30 patients, six male and 24 female. The mean age was 66 (range 55-79) years. Mean duration of surgery was 90 (range 55-110) minutes. Nine patients required single-unit blood transfusions, two patients required two-unit blood transfusions and the remaining 19 patients needed no blood transfusions. The mean postoperative intraarticular IL-6 concentration was 218355 ± 193094 pg/ml (%95 CI 146252-290458), the mean postoperative serum CRP level was 109.9 ± 47.4 mg/L (%95 CI 92,2-127,6) and the mean postoperative serum IL-6 level was 219.0 ± 156.2 pg/ml (%95CI 160,6-277,3). Drain fluid and serum values for each case are shown in Fig. 1.

Preoperative and 4-, 8- and 24-week postoperative KSS and WOMAC scores are given in Table 1.

Significant correlations were found between IL-6 concentrations in articular fluid and KSS knee and WOMAC stiffness scores at the first month according to Pearson correlation test (Table 2) (Fig. 2a and b). Greater intraarticular IL-6 levels were associated with a slower recovery. No significant correlations were found between intraarticular IL-6 levels with the second and sixth month scores (Table 2).

Table 1
Preoperative and 4-, 8- and 24-week postoperative mean KSS and WOMAC scores (Fr: Friedman test).

Median (IQR)	Preop	4-week	8-week	24-week	Fr	p
KSS knee	38 (17.25-49.25)	68 (46-78.25)	74.5 (58.75-80)	82 (70-90)	30.8	0.0001
KSS function	45 (30-50)	45 (38.75-60)	55 (45-65)	75 (55-80)	48.1	0.0001
Womac pain	11 (8.75-12.25)	4.5 (2.75-7)	3 (1-6)	2 (0-5)	59.5	0.0001
Womac stiffness	4 (3-6)	1 (0.75-2.25)	2 (1-2.25)	0.5 (0-2)	37.7	0.0001
Womac function	35.5 (30.75-43)	18 (9-27)	12 (5.75-15)	4 (0-10.5)	61.8	0.0001

Table 2
Correlations of intraarticular IL-6, serum IL-6 and serum CRP concentrations with KSS and WOMAC scores at the first, second and sixth postoperative month.

Months			KSS		WOMAC		
			Knee	Function	Pain	Stiffness	Function
First	Intraarticular IL-6	r	-0.52	-0.25	0.15	0.56	0.06
		p	0.01*	0.18	0.42	0.01*	0.77
	Serum IL-6	r	0.08	0.05	0.08	-0.20	-0.04
		p	0.66	0.8	0.68	0.28	0.83
	Serum CRP	r	-0.13	-0.31	0.10	0.2	0.12
		p	0.51	0.1	0.59	0.29	0.53
Second	Intraarticular IL-6	r	-0.30	-0.15	-0.01	0.25	0.09
		p	0.10	0.42	0.97	0.19	0.62
	Serum IL-6	r	0.23	0.04	0.03	-0.09	0.08
		p	0.21	0.86	0.89	0.64	0.69
	Serum CRP	r	-0.31	-0.13	0.29	0.16	0.36
		p	0.09	0.51	0.11	0.39	0.06
Sixth	Intraarticular IL-6	r	-0.22	-0.14	0.18	-0.36	0.09
		p	0.25	0.46	0.35	0.05	0.62
	Serum IL-6	r	0.06	-0.18	-0.06	0.29	-0.04
		p	0.74	0.34	0.76	0.12	0.83
	Serum CRP	r	-0.24	-0.39	0.31	0.09	0.2
		p	0.2	0.03*	0.10	0.64	0.29

(* : p<0.05).

There were no statistically significant correlations between KSS and WOMAC scores and serum IL-6 or CRP levels except for sixth month KSS function score and serum CRP level (Table 2).

4. Discussion

How does the host inflammatory response affect the functional outcome after surgical trauma? As an answer to this question, some authors have investigated the relationship between the inflammatory process after surgical trauma and functional outcomes. Kehlet found that IL-6 and CRP levels decrease in laparoscopic surgery, and, due to this result, he suggested that the functional recovery of laparoscopic surgery is better than that of open techniques [3,10]. Hall et al. have studied the relationship of functional recovery after hip arthroplasty to neuroendocrine and inflammatory responses and found that the inflammatory response affects immediate functional recovery after hip arthroplasty [4]. In our study, we observed that elevated intraarticular IL-6 levels correlated with slower recovery in the first month. However, we did not observe the same correlation for systemic inflammatory markers. In other words, early recovery after surgery is affected primarily by the local inflammatory response rather than the systemic response.

Recently, Feng et al. have shown that preoperative administration of rofecoxib can greatly ameliorate the pain associated with total knee joint replacement surgery and reduce general and local inflammatory reactions [11]. In light of this study, we should consider local administration of anti-inflammatory drugs rather than systemic administration. In this way, we can avoid the systemic effects of anti-inflammatory drugs and obtain early functional recovery after TKA.

Pearle et al. showed a relationship among elevated plasma levels of high-sensitivity CRP, elevated synovial fluid levels of IL-6 and the presence of chronic synovial inflammation in patients with idiopathic osteoarthritis [12]. It is possible that arthritic patients with chronic synovial inflammation show more reaction to surgical trauma, and this predisposition may result in poor recovery. In the present study, we did not determine preoperative IL-6 levels in synovial fluid. Therefore, we did not evaluate any relationship between the local inflammatory state and the postoperative immune response. We are planning another study using local anti-inflammatory drugs.

Several limitations of this model should be acknowledged. The study group is relatively small and there is a predominance of women. Recently, gender-specific aspects of inflammatory response have

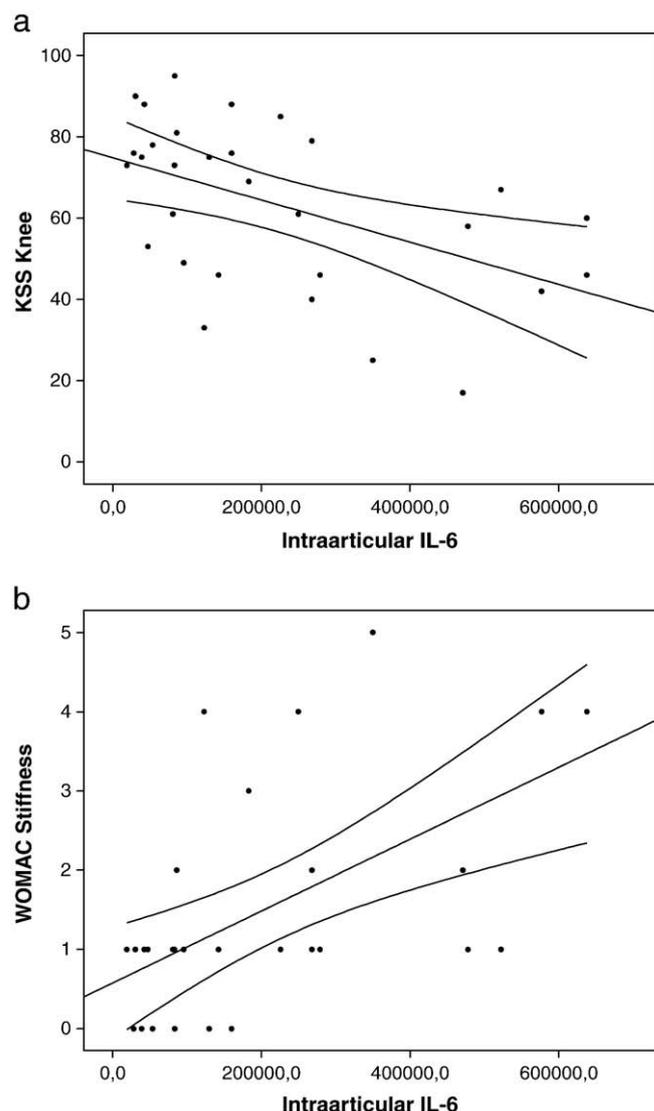


Fig. 2. a and b: Scatterplots of significance correlations. (a) Scatterplot of 4-week KSS Knee score and intraarticular IL-6 levels and (b) Scatterplot of 4-week WOMAC Stiffness score and intrarticular IL-6 levels.

growing attention [13–15]. Prather and colleagues observed that men and women showed different response in cytokine production following acute psychological stress [15]. Also menopausal status partially accounted for these gender differences, with post-menopausal women displaying greater increases in IL-6 production when compared to men [15]. Finally, we found significance correlation between KSS function scores and serum CRP levels at sixth month. But we could not established any relationship between systemic inflammatory markers and late functional recovery.

In conclusion, early functional recovery after total knee replacement surgery is affected by the local inflammatory response. The local inflammatory response is more important than the systemic response for early postoperative functional recovery. After surgical trauma, control of local inflammation may help us to attain better functional results.

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