Perioperative inflammatory response in patients with rheumatoid arthritis undergoing orthopaedic surgery

Barbara Lisowska[1], Włodzimierz Maśliński[2], Paweł Małdyk[1]

[1]Department of Rheumoorthopaedic Surgery, Institute of Rheumatology, Warsaw, Poland
[2]Department of Pathomorphology, Institute of Rheumatology, Warsaw, Poland

Submitted: 6 April 2008
Accepted: 28 April 2008

Arch Med Sci 2009; 5, 2: 248-254

Corresponding author:
Assoc. Prof. Barbara Lisowska, MD, PhD
Department of Rheumoorthopaedic Surgery
Institute of Rheumatology
Spartanska 1
02-637 Warsaw, Poland
Phone: +48 22 844 42 41
Fax: +48 22 844 77 97
E-mail: aleksander_lisowski@sggw.pl

Abstract

Introduction: This study investigates the course of blood cytokine levels and CRP in patients with rheumatoid arthritis (RA) undergoing total knee replacement (TKR). Additionally, we set out to examine the relationship between cytokines IL-6, TGF-β1 and CRP and parameters such as body temperature, tourniquet time and blood loss.

Material and methods: The study concerns 40 patients with RA undergoing total knee replacement (TKR). Operative and postoperative details were recorded, including circulation, ventilation, body temperature, tourniquet time under operation and postoperative blood loss. Peripheral vein blood was serially sampled; the first was obtained before anaesthesia and next at 6, 12, 24, 36 h after the end of surgery. IL-6, TGF-β1 and CRP were evaluated in blood and at the same time body temperature (°C) was measured.

Results: In patients with RA undergoing TKR under regional anaesthesia, the levels of IL-6 and TGF-β1 in the peripheral blood were not significantly changed compared with the levels before operation. The rise of CRP protein concentration was achieved at first 36 h postoperatively. No significant changes in serum IL-6, TGF-β1 and CRP levels with regard to tourniquet time were found. The volume of blood loss was not associated with changes in cytokine and CRP blood concentrations either. A correlation between postoperative CPR levels and temperature was found. The body temperature remained elevated up to 36 h postoperatively.

Conclusions: Our data indicate that high production of cytokines (IL-6, TGF-β1) present in chronic inflammation prevents further enhancement of cytokine synthesis triggered by surgery. The rise of CRP concentrations postoperatively and the significant correlation between CRP and temperature were addressed. The postoperative rise of temperature in the first 3 days following TKR may be a normal physiological response.

Key words: inflammatory response, orthopaedic surgery, rheumatoid arthritis.

Introduction

Surgical stress is accompanied by changes in blood levels of certain cytokines including interleukin-6 (IL-6) and transforming growth factor β (TGF-β), an immunomodulatory cytokine. Surgical stress and ischaemia-reperfusion injury are pathophysiological mechanisms that may result in activation of inflammatory cells and mediators. However, the magnitude of the inflammatory response is roughly proportional to the severity of surgery and the patient's condition [1-3].

The major circulating cytokine is interleukin-6, which is synthesized by many cells, but particularly those of the macrophage/monocyte series.

The functions of IL-6 are well known and include stimulation of T and B lymphocytes, acute phase protein synthesis in the liver and induction of fever after trauma.

Transforming growth factor β1 (TGF-β1) is a multifunctional peptide which controls proliferation and functions of cells specific to bone such as chondrocytes, osteoblasts, osteoclasts and mesenchymal precursor cells [4]. Although TGF-β1 is known for its immune-suppressive and anti-inflammatory properties, it is also capable of promoting inflammation. Transforming growth factor β1 is also known to be a powerful chemoattractant for neutrophils, lymphocytes and monocytes in the earlier stages participating in effective wound healing. Its activity in an anti-inflammatory manner in the later steps and chronic inflammation may be harmful to the host [5-7].

C-reactive protein (CRP) is one of the acute phase proteins that increase during systemic inflammation. C-reactive protein is a well-known screening parameter for monitoring postoperative infectious complications.

The chronic inflammatory state is thought to play a key role in stress response to surgery. There is no evidence that chronic inflammatory state can decrease the inflammatory response to surgery, although further confirmatory studies are needed. Recent developments in immunology and surgery may help explain these disappointing findings.

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic, autoimmune disease characterized by sustained overproduction of cytokines. Inflammatory diseases such as arthritis share some clinical characteristics including degradation of connective tissue and bone. Interleukin 6 together with tumour necrosis factor (TNF) and IL-1 have been shown to play pathological roles in RA. Overproduction of IL-6 has been reported to be pathologically involved in the rheumatic diseases and, therefore, blockade of IL-6 actions may improve the disease [8, 9]. Postoperative fever after surgery is a normal inflammatory response but its source and importance are unclear. Temperature in the febrile range is a frequent occurrence in patients after surgery. Characterization of the typical febrile response after operation serves two purposes. First, it may be part of the body's response to surgery mediated by inflammatory cytokines. Second, it may be due to other sources, which are triggered by an inflammatory process such as pneumonia, atelectasis, wound infection, or urinary tract infection. However, some studies have shown that the presence of atelectasis does not correlate with fever or wound infection [10, 11].

This study investigates the course of blood cytokine levels and CRP in patients with RA undergoing total knee replacement (TKR). Additionally, we set out to examine the relationship between cytokines IL-6, TGF-β1 and CRP and parameters such as body temperature, tourniquet time and blood loss.

Material and methods

The study population consisted of 40 patients (35 women, 5 men) with a mean age of 58.9 ±8.5 years and with a primary diagnosis of RA undergoing total knee replacement (TKR).

All patients were operated under spinal anaesthesia. Standard monitoring including continuous electrocardiogram, noninvasive automated blood pressure and pulse oximetry was applied. Cardiovascular and respiratory monitoring was continued in the first 24 h following surgery in the postoperative care unit where patients were transferred after the operation. Postoperative analgesia was achieved using IV or SC opioids. Perioperative fluid therapy used crystalloids and colloids. All patients required transfusion and received homologous blood. No cell saver and reperfusion drain blood was given.

Patients on long-term steroids received additional steroid doses during the postoperative period in a predefined regimen. Thromboprophylaxis was given as SC low-molecular weight heparin. All patients were treated with an antibiotic during observation. Exclusion criteria included an ASA physical status greater than III, allergy to local anaesthetics, contraindications to spinal anaesthesia, and weight > 100 kg. A tourniquet was used in all patients. The mean duration of tourniquet time was 85 ±20 min. Tourniquet pressure was 350 mm Hg. The blood loss and transfusion were calculated after operation. The blood loss was 674 ±152 ml. The blood transfusion was 405 ml.

The duration of RA and Disease Activity Score 28 (DAS 28) was evaluated in all patients. The duration of rheumatoid arthritis was 18.6 ±1.6 years. Disease activity was assessed by the number of swollen and tender joints, erythrocyte sedimentation rate (ESR, mm/h) and VAS general health. Disease Activity Score 28 (DAS 28) was calculated – mean 5.1 ±1.1. No significant differences in cardiac and respiratory values were found in the groups of patients with regard to blood loss and tourniquet time.

During observations the normal physical examination of the respiratory system was performed in all patients. No patient had significant tachycardia, tachypnoea or other symptoms of atelectasis. Moreover, none of the patients

complained of a sharp pain or burning sensation in the urinary tract that might be a sign of infection and no patient had documented wound complications during observations.

Peripheral vein blood was serially sampled; the first was obtained before anaesthesia and next at 6, 12, 24, 36 h after the end of surgery. Vein blood was collected in a 5 ml tube and it was stored at –70°C after centrifugation of samples until further analysis. The serum of IL-6, TGF-β1 and CRP was determined. Serum CRP was determined rapidly after obtaining samples. Patients' axillary temperature was obtained preoperatively and at 6, 12, 24, 36 h after surgery. Peripheral vein blood was serially sampled; the first was obtained before anaesthesia and next at 6, 12, 24, 36 h after the end of surgery. Concentrations of IL-6 and TGF-β1 in the samples then were determined using commercially available enzyme-linked immunosorbent assays (ELISA) (R & D System). All assays were carried out according to the manufacturer's instructions. The results of cytokine concentrations are expressed in pg/ml. Serum C-reactive protein (CRP) was identified on the following day using the Vitros 250 Clinical Chemistry analyzer (Johnson & Johnson) and it is expressed in mg/l.

Comparisons of mean cytokine, CRP and temperature levels at the five different times were done using a one- and a multi-way analysis of variance (ANOVA). All statistical analyses were done with Statgraphics and SPSS 14.0. A *p*-value less than 0.05 was considered as representing a statistically significant relationship between the variables at 99% confidence level. Data are expressed as mean ± SEM (standard error of the mean).

The study was approved by the Institute Ethical Committee and informed consent was obtained from the patients.

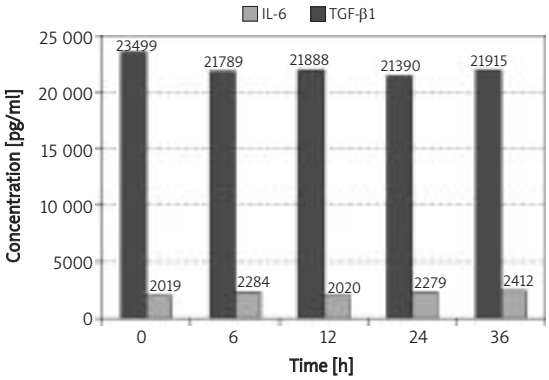

Figure 1. Mean blood levels of cytokines at predefined times

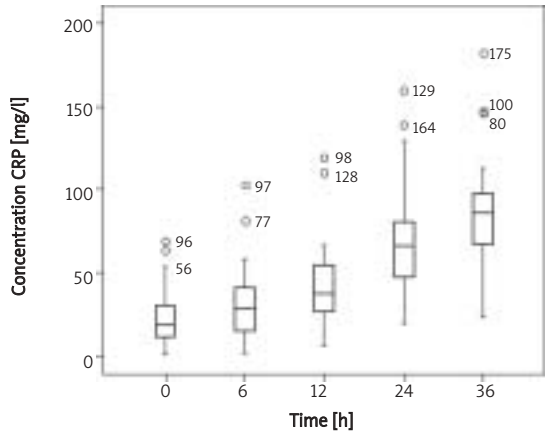

Figure 2. Box and whisker plot showing rise in blood CRP concentration perioperatively. The boxes illustrate the mean (horizontal bar), the 25th and 75th centiles (box). The whiskers indicate the 5th and 95th centiles. The numerals indicate the number of the test

Table I. ANOVA analysis for IL-6, TGF-β1 and CRP depends on time

Parameter	Factor	D.f.	F-ratio	*P*-value
IL-6	time	4	0.15	0.9629
TGF-β1	time	4	0.16	0.9587
CRP	time	4	43.87	< 0.0001

F-ratios are presented from ANOVA analysis between the blood concentrations of immunological parameters and time. Degrees of freedom (D.f.)

Results

An analysis of perioperative changes in cytokine concentrations and CRP in blood was done. The increase in IL-6 blood levels 36 h postoperatively was not statistically significant, in comparison to the preoperative value (Figure 1). Taking into consideration the range of IL-6 values, we may conclude that the concentrations of IL-6 were kept at similar levels after operation.

After operation blood TGF-β1 was lower compared to the preoperative value, but the concentrations did not decline significantly (Figure 1). The postoperative concentrations of TGF-β1 remained at similar levels. Before operation, particularly high levels of blood cytokines were detected in all patients. The data suggest that surgical procedures did not have a major effect on cytokine response.

The blood concentrations of CRP were found to be significantly elevated during the course of the study (Figure 2). The peak CRP value was achieved at 36 h. The median perioperative CRP was 51 ±4 and the peak median value was 87 ±4. The rise of CRP from the preoperative concentration to 36 h after operation was significant ($p < 0.0001$).

The analysis of changes in cytokines and CRP at predefined time is presented in Table I. ANOVA analysis between the blood cytokine concentrations and time demonstrated that the variables did not change significantly with time ($p > 0.05$). The

variables characterizing CRP levels changed significantly with time ($p < 0.0001$).

The analysis of correlations between IL-6, TGF-β1 and CRP and temperature, blood loss and tourniquet time is presented in Table II. There were no significant changes in serum IL-6, TGF-β1 and CRP levels observed with regard to tourniquet time. The volume of blood loss also did not contribute to changes in cytokine and CRP blood concentrations (Table II).

The correlation coefficient < 0.5 indicates a relatively weak relationship between the variables. The results show a correlation between postoperative CRP concentrations and temperature. Correlations between the remaining parameters with temperature, blood loss and tourniquet time were not found. For clarity, only the postoperative values of variables were used for that analysis.

The changes of CRP protein concentrations with time are presented in Figure 3. The form of the perioperative CRP response curve was similar in the temperature range 36-37.5°C, while a significant rise of CRP level was found between temperatures 37.5 and 38°C. The numbers shown in Figure 3 presented.

The mean perioperative temperature in °C profile for all patients is shown in Figure 4. In the postoperative period, a gradual increase of body temperature was observed, which peaked at 36 h at 37.6°C. The mean preoperative temperature of 36.0°C was recorded in 4 (10%) patients.

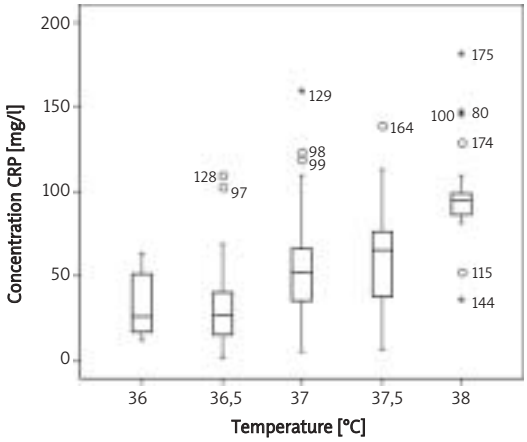

Figure 3. Blood CRP concentration changes with regard to temperature. The boxes illustrate the mean (horizontal bar), and the 25th and 75th centiles (box). The whiskers indicate the 5th and 95th centiles. The numerals indicate the number of the test

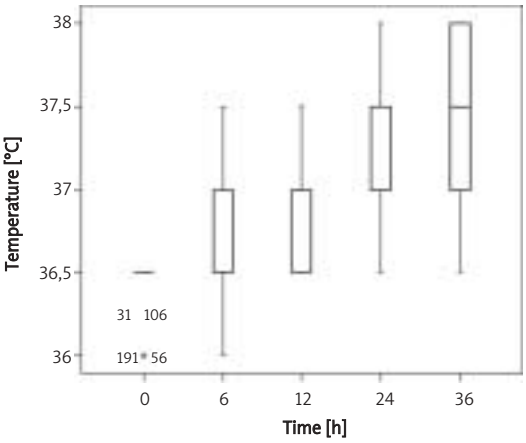

Figure 4. Perioperative body temperature in °C measured in all patients ($n = 40$). The boxes illustrate the mean (horizontal bar), and the 25th and 75th centiles (box). The whiskers indicate the 5th and 95th centiles. The numerals indicate the number of the test

Discussion

In normal conditions the immunological response is characterized by release of cytokines, inflammatory mediators, and synthesis of acute-phase proteins. In contrast, when the immune system is disturbed by a chronic inflammatory process the response to surgery may not be so pronounced.

An increase of postoperative temperature is common after orthopaedic surgery and the source of those changes could be either postoperative infection or inflammatory response to surgery. Postoperative pyrexia was defined as an axillary temperature greater than 37°C on any or all of the 5 days after surgery.

None of the patients studied had any symptoms of infection from wounds or respiratory and urinary tracts during observation and so the potential cause of the presented temperature could be associated with the inflammatory response. However, another potential cause of fever is the transfusion of blood [12, 13]. No correlations were found between postoperative temperature and volume of blood loss and blood transfusion (correlation coefficient < 0.5) in our study. Our observations are in agreement with the findings of other authors, who demonstrated similar results with regard to sources

Table II. Correlation analysis between blood parameters (IL-6, TGF-β1, CRP) and temperature, blood loss and tourniquet time

	Parameters	Correlation coefficient
IL-6	temperature	0.1000
	blood loss	0.0729
	tourniquet time	0.1267
TGF-β1	temperature	0.0647
	blood loss	0.0017
	tourniquet time	0.0666
CRP	temperature	0.5330
	blood loss	0.2500
	tourniquet time	0.3138

of postoperative fever [14-16]. An interesting finding was a difference in the number of patients who developed pyrexia – in both studies pyrexia developed in all patients. In contrast, 34 (85%) patients in this series developed postoperative pyrexia after knee arthroplasty. This finding might suggest that these observations might also be influenced by the time of evaluation, which was longer (5 days) than in our study. No correlations were found between postoperative temperature and volume of blood loss and blood transfusion (correlation coefficient < 0.5) in our study. In that group of patients mean blood transfusion was 405 ml and blood loss was 674 ml. Therefore, a low volume of blood loss and blood transfusion might result in a lack of correlations between them and temperature. Our finding suggest that a post-operative rise of temperature in the first 3 days following TKR may be a normal physiological response and should not cause undue concern about the presence of infection.

Cytokines including IL-6 and TGF-β1 are involved in the acute stress reaction after surgery. Both ischaemia with reperfusion injury and blood loss following orthopaedic surgery may alter blood concentrations of cytokines. The extent of the operation also may be correlated with IL-6 concentrations, which was demonstrated in patients who underwent a major surgical operation [17, 18].

Both surgery and accidental trauma caused a rise in serum IL-6 [19]. In patients who underwent elective limb surgery with a tourniquet the rise in IL-6 was shown within 8-20 h of reperfusion. Therefore, in patients with multiple organ dysfunction syndrome, the increase in serum IL-6 was demonstrated within 4-5 days after trauma, and these increased serum cytokine levels were correlated with increased levels of circulating adhesion molecules [20].

We could not demonstrate any relevant correlation between cytokines evaluated and other variables such as body temperature, tourniquet time and postoperative blood loss. There is a suggestion that low volume of both blood loss and blood transfusion could influence a lack of correlations between parameters. The next cause could be the short time of observations.

However, it is more difficult to explain how our data relate to those of others who showed an elevated number of cytokines after surgery [21-23]. One possible explanation could be that the studies of other authors were done in patients without disturbance of the immune system [24, 25]. This is a relatively new finding and our study may confirm the concept that although the nature of the cytokine response is determined by surgery, the chronic inflammatory state is capable of modifying its extent. This concept is in agreement with the study which showed that the abnormal production of cytokines might negatively influence immune responses after surgery [26].

Very high concentrations of cytokines should be associated with destructive changes in joints which needed surgery and with long-lasting and severe rheumatoid arthritis in patients studied. In this group of patients the mean time of RA was 18.6 years, and the mean value of DAS was 5.1.

Elevated serum IL-6 levels have been observed and there have been correlations between serum and clinical indices of RA [27, 28]. Serum IL-6 level also correlated with ERS, CRP levels, and the number of swollen joints [29]. Interleukin-6 has a multifactorial role in the body's response to injury and it may also play a part in wound healing. Additionally, IL-6 also might be a useful predictor of postoperative infection and periprosthetic infection in patients who have had a total knee arthroplasty [30-32]. Therefore, the lack of significant changes of IL-6 concentrations after surgery may impede the early manifestation of postoperative infection development.

High blood levels of IL-6 have been linked to risks of several other conditions, too, such as cardiovascular disease, type 2 diabetes, mental health complications, and some cancers [33].

Interleukin-6 is consistently found in septic, trauma and post-operative patients and correlated well with the severity of sepsis or injury. Interleukin-6 is responsible for the fever and metabolic changes in the acute phase. The persistent elevation of IL-6 was responsible for the post-operative unstable clinical condition in the infected patients and it was also related to a poor outcome in patients with adult respiratory distress syndrome (ARDS) [34, 35]. High concentrations of circulating IL-6 were found in patients with septic shock and in trauma patients but much higher concentrations of IL-6 were detected in septic shock patients than in trauma patients. Moreover, IL-6 concentrations were significantly higher in non-survivor septic shock patients than in non-survivor patients with sepsis, septic shock and multiple organ dysfunction syndrome [36-38].

Therefore, the impairment of immune responses may demonstrate clinical importance; for example it may be predictive of a delay in postoperative recovery, predictive of infection, and may signal a disturbance in wound healing.

The results of our study showed that neither tourniquet time nor blood loss was responsible for changes in concentrations of CRP after operation in patients with RA. However, we found relationships between concentrations of CRP and body temperature and significant rises of CRP protein level after operation.

Our observations of an increase in CRP levels from pre-operation to post-operation are in agreement with the findings of other authors, who demonstrated rises in concentrations of CRP protein postoperatively [39, 40].

Kragsbejerg *et al*. showed that during uncomplicated operations in patients without chronic inflammatory state, high IL-6 concentrations were present which may be responsible for high concentrations of CRP protein [41]. Our data do not confirm these results. That might be related to the shorter time of observations and presence of a chronic inflammatory process.

C-reactive protein is used as an indicator of inflammatory processes. However, its expression is unspecific and will increase after surgery. C-reactive protein synthesis is induced promptly after tissues are injured and elevated serum levels can be detected after 24 to 72 h.

Serum concentrations of routinely used indicators of the inflammatory response such as CRP are often difficult to interpret when measured postoperatively and give little guidance about the difference between infective inflammation and inflammation caused by the operation. However, it is unclear why; we could not find a correlation between levels of CRP and blood loss in these patients. One possible factor could be the short observation period (36 vs. 72 h). Our finding suggests that these changes might also be influenced by the time of measurement, which could be too short to demonstrate the changes in concentrations of CRP protein followed by the blood loss.

However, opioids may also influence cytokine production, but with regard to these patients with RA we do not expect that the used opioids might affect cytokine concentrations. The levels of cytokines in blood were also very high before surgery.

Similarly, for the same reason – very high level of cytokines in patients with RA – we do not think that the present results might also be influenced by regional anaesthesia.

However, our previous studies including other groups of patients (with regard to type of operation and number of observed patients) demonstrated that surgical stress may cause some changes in the inflammatory response [42, 43].

In addition, the studies performed in patients without chronic inflammatory diseases showed a weak relationship between serum IL-6 and type of anaesthesia [44, 45].

In conclusion, data on the dynamic changes of postoperative serum concentration of IL-6 and TGF-β1 revealed the impaired response of the immune system to surgical stress in patients with chronic inflammatory state. The ability of a chronic inflammatory process to modify the cytokines' response to surgery may determine the outcome in the postoperative period. In our study, the pattern of cytokine production was consistent regardless of the chronic inflammatory state. A rise of CRP concentrations postoperatively and a significant correlation between CRP and temperature were observed. The postoperative rise of temperature in the first 3 days following TKR may be a normal physiological response.

References

1. Ueda K, Turner P, Gagner M. Stress response to laparoscopic liver resection. HPB (Oxford). 2004; 6: 247-52.
2. Shibasaki H, Furukawa K, Yamamori H, Kimura F, Tashiro T, Miyazaki M. The post-operative level of serum monocyte chemoattractant protein-1 and its correlation with the severity of surgical stress. J Surg Res 2006; 136: 314-9.
3. Schietroma M, Carlei F, Franchi L, et al. A comparison of serum interleukin-6 concentrations in patients treated by cholecystectomy via laparotomy or laparoscopy. Hepatogastroenterology 2004; 51: 1595-9.
4. Ozkan K, Eralp L, Kocaoglu M, et al. The effect of transforming growth factor beta1 (TGF-beta1) on the regenerate bone in distraction osteogenesis. Growth Factors 2007; 25: 101-7.
5. Lúdvíksson BR, Gunnlaugsdóttir B. Transforming growth factor-beta as regulator of site-specific T-cell inflammatory response. Scan J Immunol 2003; 58: 129-38.
6. Wahl SM, Hunt DA, Wakefield LM, et al. Transforming growth factor type beta induces monocyte chemotaxis and growth factor production. Proc Natl Acad Sci U S A 1987; 84: 5788-92.
7. Brandes ME, Mai UE, Ohura K, Wahl SM. Type I transforming growth factor-beta receptors on neutrophils mediate chemotaxis to transforming growth factor-beta. J Immunol 1991; 147: 1600-6.
8. Nakahara H, Nishimoto N. Anti-interleukin-6 receptor antibody therapy in rheumatic diseases. Endocr Metab Immune Disord Drug Targets 2006; 6: 373-81.
9. Paul-Pletzer K. Tocilizumab: blockade of interleukin-6 signaling pathway as a therapeutic strategy for inflammatory disorders. Drugs Today (Barc) 2006; 42: 559-76.
10. Engoren M. Lack of association between atelectasis and fever. Chest 1995; 107: 81-4.
11. Pérez-Aispuro I, Pérez-Castro J, Avelar-Garnica F, Wacher-Rodarte N, Lifshitz-Guinzberg A. A reconsideration of postoperative fever due to pulmonary atelectasis [Spanish]. Gac Med Mex 1991; 127: 27-30.
12. Janatpour K, Holland PV. Noninfectious serious hazards of transfusion. Curr Hematol Rep 2002; 1: 149-55.
13. Gloe D. Common reactions to transfusions. Heart Lung 1991; 20: 506-12.
14. Ghosh S, Charity RM, Haidar SG, Singh BK. Pyrexia following total knee replacement. Knee 2006; 13: 324-7.
15. Kennedy JG, Rodgers WB, Zurakowski D, et al. Pyrexia after total knee replacement. A cause for concern? Am J Orthop 1997; 26: 549-52, 554.
16. Andres BM, Taub DD, Gurkan I, Wenz JF. Postoperative fever after total knee arthroplasty: the role of cytokines. Clin Orthop Relat Res 2003; 415: 221-31.
17. Miyawaki T, Maeda S, Shimada M. Elevation of plasma interleukin-6 level in patients undergoing oral and maxillofacial surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996; 81: 15-20.
18. Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. Br J Surg 1992; 79: 757-60.

19. Maruna P, Gürlich R, Frasko R, et al. Cytokines and soluble cytokine receptors in the perioperative period [Czech]. Sb Lek 2002; 103: 273-82.
20. Seekamp A, Jochum M, Ziegler M, van Griensven M, Martin M, Regel G. Cytokines and adhesion molecules in elective and accidental trauma-related ischemia/reperfusion. J Trauma 1998; 44: 874-82.
21. Bastian D, Sun J, Danckert Krohn C, ReikerÍs O. Immune modulation after total hip surgery. A prospective ex vivo study. Eur Surg Res 2007; 39: 296-302.
22. Wirtz DC, Heller KD, Miltner O, Zilkens KW, Wolff JM. Interleukin-6: a potential inflammatory marker after total joint replacement. Int Orthop 2000; 24: 194-6.
23. Hall GM, Peerbhoy D, Shenkin A, Parker CJ, Salmon P. Relationship of the functional recovery after hip arthroplasty to the neuroendocrine and inflammatory responses. Br J Anaesth 2001; 87: 537-42.
24. Gilliland HE, Armstrong MA, Carabine U, McMurray TJ. The choice of anesthetic maintenance technique influences the antiinflammatory cytokine response to abdominal surgery. Anesth Analg 1997; 85: 1394-8.
25. Ruzic B, Tomaskovic I, Trnski D, Kraus O, Bekavac-Beslin M, Vrkic N. Systemic stress responses in patients undergoing surgery for benign prostatic hyperplasia. BJU Int 2005; 95: 77-80.
26. Baxevanis CN, Papilas K, Dedoussis GV, Pavlis T, Papamichail M. Abnormal cytokine serum level correlate with impaired cellular immune responses after surgery. Clin Immunol Immunopathology 1994; 71: 82-8.
27. Madhok R, Crilly A, Watson J, Capell HA. Serum interleukin 6 levels in rheumatoid arthritis: correlations with clinical and laboratory indices of disease activity. Ann Rheum Dis 1993; 52: 232-4.
28. Nishimoto N. Interleukin-6 in rheumatoid arthritis. Curr Opin Rheumatol 2006; 18: 277-81.
29. Klimiuk PA, Sierakowski S, Latosiewicz R, et al. Interleukin-6, soluble interleukin-2 receptor and soluble interleukin-6 receptor in the sera of patients with different histological patterns of rheumatoid synovitis. Clin Exp Rheumatol 2003; 21: 63-9.
30. Sander M, von Heymann C, von Dossow V, et al. Increased interleukin-6 after cardiac surgery predicts infection. Anesth Analg 2006; 102: 1623-9.
31. Aguilar-Nascimento JE, Marra JG, Slhessarenko N, Fontes CJ. Efficacy of National Nosocomial Infection Surveillance score, acute-phase proteins, and interleukin-6 for predicting postoperative infections following major gastrointestinal surgery. Sao Paulo Med J 2007; 125: 34-41.
32. Di Cesare PE, Chang E, Preston CF, Liu CJ. Serum interleukin-6 as a marker of periprosthetic infection following total hip and knee arthroplasty. J Bone Joint Surg Am 2005; 87: 1921-7.
33. Godbout JP, Glaser R. Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. J Neuroimmune Pharmacol 2006; 1: 421-7.
34. Tang GJ. Similarity and synergy of trauma and sepsis: role of tumor necrosis factor-alpha and interleukin-6 [Chinese]. Acta Anaesthesiol Sin 1996; 34: 141-9.
35. Meduri GU, Headley S, Kohler G, et al. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. Chest 1995; 107: 1062-73.
36. Martin C, Boisson C, Haccoun M, Thomachot L, Mege JL. Patterns of cytokine evolution (tumor necrosis factor-alpha and interleukin-6) after septic shock, hemorrhagic shock, and severe trauma. Crit Care Med 1997; 25: 1813-9.
37. Adamik B, Zimecki M, Właszczyk A, Kübler A. Immunological status of septic and trauma patients. I. High tumor necrosis factor alpha serum levels in septic and trauma patients are not responsible for increased mortality; a prognostic value of serum interleukin 6. Arch Immunol Ther Exp (Warsz) 1997; 45: 169-75.
38. Riché FC, Cholley BP, Panis YH, et al. Inflammatory cytokine response in patients with septic shock secondary to generalized peritonitis. Crit Care Med 2000; 28: 433-7.
39. Mehra A, Langkamer VG, Day A, Harris S, Spencer RF. C reactive protein and skin temperature post total knee replacement. Knee 2005; 12: 297-300.
40. Laiho K, Mäenpää H, Kautiainen H, et al. Rise in serum C reactive protein after hip and knee arthroplasties in patients with rheumatoid arthritis. Ann Rheum Dis 2001; 60: 275-7.
41. Kragsbjerg P, Holmberg H, Vikerfors T. Serum concentrations of interleukin-6, tumour necrosis factor-alpha, and C-reactive protein in patients undergoing major operations. Eur J Surg 1995; 161: 17-22.
42. Lisowska B, Małdyk P, Kontny E, Michalak C, Jung L, Cwiek R. Postoperative evaluation of plasma interleukin-6 concentration in patients after total hip arthroplasty. Ortop Traumatol Rehabil 2006; 8: 547-54.
43. Lisowska B, Maśliński W, Małdyk P, Ząbek J, Baranowska E. The role of cytokines in inflammatory response after total knee arthroplasty in patients with rheumatoid arthritis. Rheumatol Int 2008; 28: 667-71.
44. Schneemilch CE, Bank U. Release of pro- and anti-inflammatory cytokines during different anesthesia procedures. Anaesthesiol Reanim 2001; 26: 4-10.
45. Høgevold HE, Lyberg T, Kähler H, Haug E, Reikerå O. Changes in plasma IL-1beta, TNF-alpha and IL-6 after total hip replacement surgery in general or regional anaesthesia. Cytokine 2000; 12: 1156-9.