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Full Length Research paper

Evaluating Inflammatory Responses in Total Hip and Knee Arthroplasties: Insights from Blood Transfusion and Ischemic Extremity

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This study aims to clarify the difference between surgical stress of total hip arthroplasty (THA) and total knee arthroplasty (TKA) under the same conditions through blood transfusion and ischemic extremity. Body temperature, white blood cell (WBC) count, the level of C- reactive protein (CRP), and interleukin-6 (IL-6) were measured for eleven patients undergoing THA and eight patients undergoing TKA. All the patients who underwent THA and TKA received a transfusion of 2 units of autologous blood but no transfusion with homologous blood, and the TKA surgery was performed without an air tourniquet. The first day after the surgery, there was no significant difference between the THA and TKA with respect to body temperature and CRP. However, there was a significant difference between the THA and TKA in WBC count ($p < 0.05$) and IL- 6 ($p < 0.01$) on the first day after the surgery. In addition, there was a significant difference between the THA and TKA in IL-6 ($p < 0.05$) and CRP level ($p < 0.05$) on the seventh day after the surgery. The surgical stress of TKA was significantly larger than the surgical stress of THA. There may be more potential complications in the patients who underwent TKA than those who underwent THA.

Key words: Cytokine, surgical stress, total hip arthroplasty, total knee arthroplasty.

INTRODUCTION

Many articles have so far reported that total joint arthroplasties were extremely effective for treating the destroyed joints in the patients afflicted with such diseases as rheumatoid arthritis, osteoarthritis, or osteonecrosis (Keisu et al., 2001; Ritter et al., 2007). Total joint arthroplasty is the major treatment option for pain and physical disabilities, and it can improve the patient's quality of life (Fujita et al., 2006; Bourne, 2008). However, the surgical stress of total joint arthroplasty may be too great for the patients. The surgical stress can elicit a characteristic response involving the increased circulating concentrations of stress hormones (such as cortisol and catecholamines), the synthesis and release of various humoral mediators (such as proinflammatory cytokines), the induction of synthesis and the release of acute-phase proteins such as C-reactive protein (CRP), and the possible induction of various metabolic changes (such as lipolysis or hyperglycemia) (Heinrich et al., 1990). The surgical stress was evaluated using the body temperature, the white blood cells (WBC) count, the CRP, and interleukin-6 (IL-6), as a stress marker (Guinn et al., 1999; Eriksson et al., 1997; Larsson et al., 1992; Grande et al., 2002). Interleukin-1 , inerleukin-8, interleukin-10, tumor necrosis factor, and cortisol were also measured to investigate the surgical stress (Matsumoto ED et al., 2005; Nesher N et al., 2006). Furthermore, the pain after the operation was assessed to evaluate the minimally invasive surgery (Dorr et al., 2007) . Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are major joint arthroplasties, and some studies have compared the surgical stress of THA to TKA (White et al., 1998; Shaw and Chung, 1999; Hall et al., 2000; Wirtz et al., 2000). There are a few reports in which the use of multi-factors, including IL-6, were used to compare THA and TKA (Hall et al., 2000; Wirtz et al., 2000). However, the markers, especially IL-6, for surgical stress were affected by blood transfusion or ischemia (Guinn et al., 1999; Larsson et al.,

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Abbreviations: CRP, C-reactive protein; **WBC,** white blood cells; **IL-6,** interleukin-6; **THA,** total hip arthroplasty; **TKA,** total knee arthroplasty; **ELISA,** enzyme-linked immunosorbent assay; **JOA,** Japanese Orthopedic Association.

1992; Shaw and Chung, 1999; Ydy et al., 2007; Seekamp et al., 1998; Krohn et al., 1999; Bottner et al., 2003; Kennedy et al., 1997). Nearly all TKA cases need blood transfusions whether or not a tourniquet is used, and some types of THA also require a blood transfusion (Smith and Hing, 2009).

Therefore, in this study, all the subjects were tailored to the condition of the blood transfusion and ischemia. The aim of this study was therefore to investigate the surgical stress differences between THA and TKA using the plural factors.

The study protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki, and the study was approved by the institutional review board of the Faculty of Medicine, Saga University at Saga.

MATERIALS AND METHODS

Between August 2006 and July 2007, 558 patients underwent THA and 233 patients underwent TKA in our institution. We selected the patients that were taking 2 units of autologous blood transfusion for the THA and the TKA groups, and the TKA surgery was performed without an air tourniquet. Furthermore, we excluded any patients who had inflammatory arthritis, a systemic inflammatory or auto-immune disorder, trauma at the surgical site, or a history of any type of cancer or chronic illness, or any type of surgery within 6 months. In addition, we selected the patients who possessed all the necessary data for the current study. We enlisted the remaining 11 patients (all females) in THA and 8 patients (4 males and 4 females) in the TKA group for this study. The indication for each patient was osteoarthritis of the hip or the knee. The strict inclusion criteria for TKA included clinically significant osteoarthritic changes in the knee, symptomatic at the time of surgery, and failure of conser-vative treatment for osteoarthritis of the knee. The clinical findings at the time of surgery were evaluated using the Japanese Ortho-pedic Association hip rating score (JOA hip score) or Japanese Orthopedic Association knee rating score (JOA knee score). The JOA hip score consisted of four categories and 100 points as full marks: pain (40 points), range of motion (20 points), walking (20 points), and activity of daily life (20 points). In addition, the JOA knee score consisted of four categories and 100 points as full marks: pain and walking (30 points), pain and ascending or descending stairs (25 points), range of motion (35 points), and joint effusion (10 points). In addition, all the patients in both groups were classified according to the American Society of Anesthesiologists (ASA) physical status as grade 1 or grade 2.

The anesthesia team was not involved in this study: however, all patients were administered either spinal and/or an epidural anes-thesia as determined by the anesthesia team. The patients who received an epidural anesthesia were provided with a continuous epidural anesthesia on the first postoperative day. The THA was done via a conventional postero-lateral approach and used all cementless components (PerFix, AMS Series; JMM Inc., Kyoto, Japan) . The TKA procedure was performed via a conventional medial parapatellar approach and used cementless components (Scorpio; Stryker Orthopaedics, Mahwah, NJ). All the patellae were not replaced by the implant. In both groups, flurbiprofen axetil, diclofenac sodium and loxoprofen sodium were used as directed by the physician in charge of the post-operative analgesia.

The venous blood samples were obtained before the surgery, and also on the first- and the seventh-day after the surgery, as a routine inspection in accordance with the critical path in our institution. The blood samples were spun in a centrifuge for 7 min at 3500 rpm to separate the serum. The supernatant was stored at -25°C until the sample analysis could be performed. An enzyme-linked immuno-sorbent assay (ELISA) was used for the IL-6 of the serum and drainage fluid determination (Bio Source Human IL-6 ELISA kit, Camarillo, Calfornia, USA). The ELISA was conducted according to the manufacturer's instructions. The assay had a sensitivity of 2 - 500 pg/ml for IL- 6. The CRP concentration was measured by immunonephelotomy (Hitachi 7600 modular system, Hitachi, Tokyo, Japan). The detection limit of the CRP assay was 0.01 mg/dl. All the samples were also tested for the total WBC count. We recorded the body temperature three times per day, and the maximum daily temperature was also detected and recorded. The body temperature was measured at the axilla in each patient.

All numerical data were expressed as the mean and standard deviation. The mean variables in the THA and TKA were compared using Student's *t*-test. The comparison of the maximum daily temperatures, the WBC counts, the CRP levels, and the mean IL-6 levels were done using a one-way analysis of variance (ANOVA) with the Bonferroni adjustment. The mean variables in the JOA scores were compared using Paired *t*-test. Statistical significance was set at a value of $p < 0.05$ for each test.

RESULTS

The details of the patients are shown in Table 1. The age, the operation time, and the total blood loss were significantly greater in the TKA group ($p < 0.05$). All the patients in both groups had 2 units of autologous blood transfusions which were done up to 12 h after the surgery. In the TKA group, all the operations were per-formed without any air tourniquets. All the patients in the THA group received only spinal anesthesia, and all the patients in the TKA group received a spinal as well as an epidural anesthesia. The epidural anesthesia was used as postoperative analgesia on the first day after the surgery; 0.2% ropivacaine hydrochloride hydrate (4 ml/h) was used in 6 cases and 0.2% ropivacaine hydrochloride hydrate (3 ml/h) was used in 2 cases. In the THA and TKA groups, the amount of diclofenac sodium was 27 ± 26 and 44 ± 32 mg ($p = 0.23$), and the amount of penta-zocine was 5.5 ± 7.6 and 11 ± 11 mg ($p = 0.18$) on the operation day, respectively. All cases were given flurbi-profen axetil through the catheter procedure, 250 mg on the operation day, and loxoprofen sodium orally (180 mg per day ($60 \text{ mg} \times 3$) from the first day after the surgery).

Figure 1 displays the perioperative variables data which were compared between the THA and TKA groups. In the maximum daily temperature, there was no significant difference between the preoperative day and the first day after the operation in both groups ($p = 0.65$ in the THA group, $p = 0.92$ in the TKA group). Regarding the WBC count, there were no significant differences between the day before surgery, the first day after the surgery, and the seventh day after the surgery in both groups ($p = 1.0$). However, the WBC count in the TKA group was significantly higher than that in the THA group on the first day after the surgery ($p < 0.05$).

In the THA group, the CRP level significantly increased before the surgery and the first day after the surgery ($p < 0.01$), and it significantly decreased from the first day after the surgery to the seventh day after the surgery ($p <$

Table 1. Details of patients studied

Parameter	THA group	TKA group	P value
No of patients	11	8	
Male/Female	0/11	4/4	
Age(year)	62.3 ±6.3	72.6 ±7.6	<0.01
Weight(kg)	53.8± 8.4	59.3±5.6	0.12
Height(cm)	150.0±7.9	156.5±4.6	0.54
BMI(Kg/m^2)	24.2±5.7	24.2±1.6	0.99
Operation time	36.5±5.1	79.3±13.2	<0.01
Total blood loss	656.6±251.6	1066.0±150.2	<0.01
JOA score(pre-operation)	46.8±11.9	47.0±9.7	

THA, total hip arthroplasty; TKA, total knee arthroplasty; BMI, body mass index; JOA, Japanese Orthopedic Association.

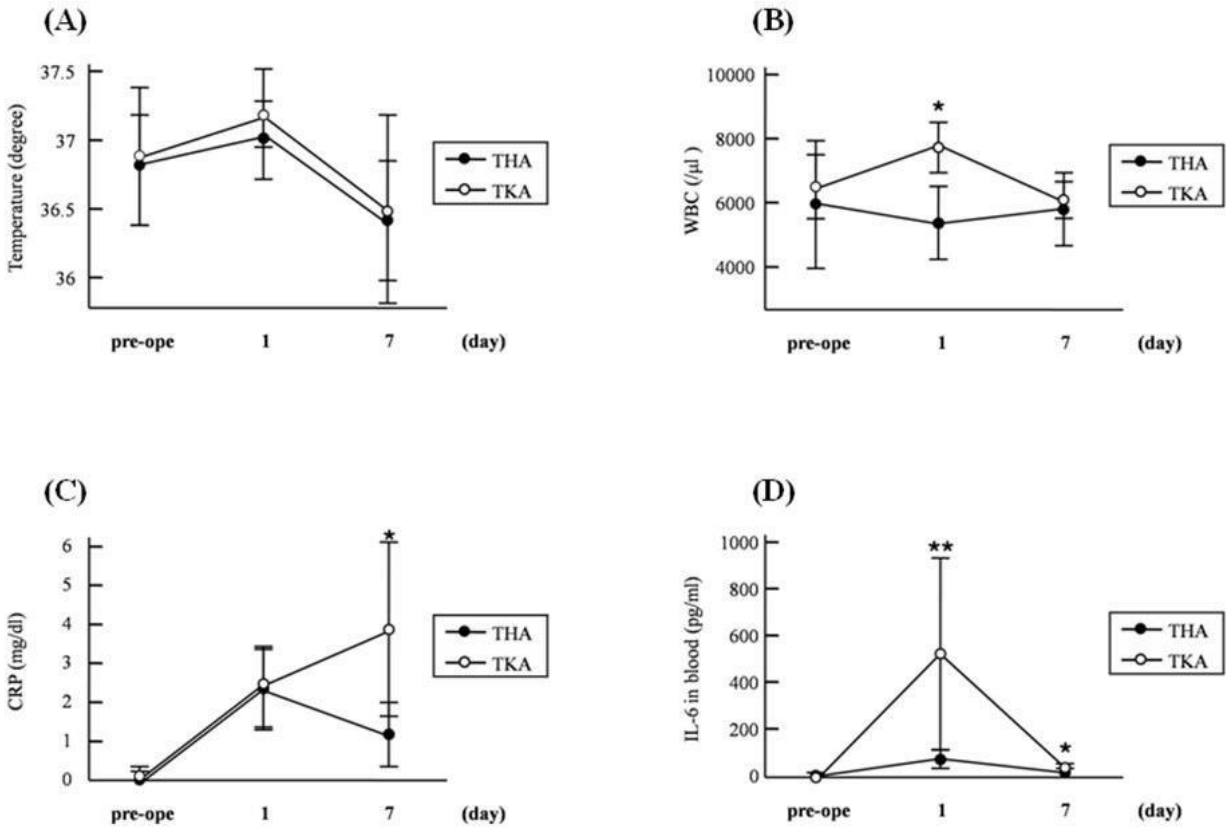

Figure 1. The mean and standard deviation of THA and TKA in (A) temperature, (B) WBC, (C) CRP, and (D) IL-6. ($p < 0.05$, $p < 0.01$, analyzed by one-way analysis of variance (ANOVA) with the Bonferroni adjustment).

0.01). However, the CRP level on the seventh day after the surgery did not completely return to the level observed before the surgery ($p = 0.15$). In the TKA group, the CRP level significantly increased from before surgery to the first day after the surgery ($p < 0.05$), and there was no significant difference between the first day after the surgery and on the seventh day after the surgery ($p = 0.20$). In addition, no significant difference was seen between the THA and TKA group on the first day after the surgery ($p = 0.96$); however, a significant difference was observed between the THA and TKA group on the seventh day after the surgery ($p < 0.05$). The IL-6 level on the first day after surgery was significantly higher in comparison to the period before surgery in both groups ($p < 0.01$), while it significantly decreased on the seventh day after surgery ($p < 0.01$). The IL-6 level on the first day

in the TKA group was around 9 times that of the THA group (61.7 ± 30.6 pg/ml in the THA group and 535.4 ± 411.5 pg/ml in the TKA group). On the first day and the seventh day after surgery, the IL-6 level in the TKA group was higher in comparison to the IL-6 level in the THA group ($p < 0.01$ and $p < 0.05$, respectively).

At the 1-year follow up, no patient in either group demonstrated any wound infection. The JOA hip score increased from 46.8 ± 11.9 to 89.0 ± 3.2 after THA ($p < 0.01$), while JOA knee score increased from 47.0 ± 9.7 to 84.0 ± 5.5 ($p < 0.01$).

DISCUSSION

The surgery was an example of a planned trauma in which an increase in the plasma levels of the acute-phase proteins, as well as the occurrence of fever and the changes in the hematologic, the endocrinologic, the immunologic, and the neurologic parameters, can be observed (Grande et al., 2002). In the present study, we investigated the temperature, the WBC count, the CRP, and the IL-6 in response to the THA and the TKA procedures. This is the first report to compare the response to the surgery of THA and TKA by using patients who were under the same conditions for blood transfusion and ischemic extremity.

In the current study, however, significantly differences were observed regarding the age, operation time, and total blood loss between the two groups. In general, immune response impairment is frequent in the elderly. If the ages had been matched between the two groups, then the results may have demonstrated even larger differences. And the operation time and the blood loss in TKA group was larger than those observed in the THA group, however, the operation time and the blood loss do not necessarily correlate with IL-6 known as most important mediator of short- term response (Grande et al., 2002; Yoshida et al., 2000).

A significant difference was observed in the usage of epidural anesthesia between the two groups. Regrettably, there have so far been few reports about the stress response to the anesthesia procedure itself, and the magnitude of the procedure in regard to epidural anesthesia is unknown. We believe that the stress of the procedure of epidural tubing and anesthesia may therefore reduce the amount of surgical stress.

There are many reports regarding the effect of the blood transfusion on the immune-inflammatory response. Ydy et al. (2007) described that the blood transfusion enhances the inflammatory systemic response in the IL-6, but in the CRP and the WBC count at the first day after the surgery. Krohn et al. (1999) reported that the blood transfusion induced the production of the cytokines and cortisol; however, the cytokines returned to the preinfusion levels after the blood transfusion. Furthermore, the WBC count also increased due to the blood transfusion, and the development of the WBCs due to blood transfusion was not a transient reaction (Krohn et al., 1999). And, one of the potential causes of fever is the blood transfusion (Kennedy et al., 1997).

In the animal experiments, ischemic and reperfusion contribute to the production of IL-6 (Nezu et al., 2008). Seekamp et al. (1998) reported that in the clinic, a limb tourniquet in the surgery caused an increase in the cytokine following reperfusion. In addition, Larsson et al. (1992) reported that the CRP peak level did not correlate with the quantity of the transfused blood and the ischemic period caused by the tourniquet.

The development of a postoperative fever is common after a surgical procedure (Guinn et al., 1999; Pepys, 1981). Andres et al. (2003) reported that the elevated IL-6 levels in the serum after total joint arthroplasty caused the fever after TKA was performed. In the current study, the temperatures did not increase in both groups, and there was no significant difference between the two groups. Therefore, the fever may not be a suitable factor in the comparative analysis of the surgical stress between THA and TKA.

The WBC count is well known to increase and maintain this level after a surgical stress (Eriksson et al., 1997). The WBC count also increases by blood transfusion, and the development of WBCs due to the blood transfusion is not a transient reaction (Krohn et al., 1999).

In the present study, the WBC count did not increase in both groups. Therefore, the WBC count could not be increased by the surgical stress of THA and TKA.

The measurement of CRP for monitoring surgical stress is generally used, and the CRP is used to compare the different surgical procedures in many studies (Grande et al., 2002; White et al., 1998; Yoshida et al., 2000). Elevated CRP levels are seen in a number of different ailments including infection, inflammation, and malignancy as a response to tissue injury (Pepys, 1981). In the present study, the patients did not have these factors. In both groups, CRP levels were significantly elevated on the first day after the surgery, and there was no significant difference between both groups. However, there was a significant difference on the seventh day after the surgery between both groups. Wirtz et al. (2000) reported that a slightly prolonged inflammatory course is seen for the patients with TKA in comparison to the patients with THA. Kragsbjerg et al. (1995) showed that the peak IL- 6 level differed among surgical procedures and the peak serum IL-6 concentrations occurred 6 - 24 h after surgery for joint replacement surgery. IL-6 was produced locally and through the circulation in the blood, it transmits local information to the whole system. Hall et al. (2000) described a significant difference to exist between the THA and TKA in the serum concentration of IL-6. On the other hand, Wirtz et al. (2000) described that there was no significant difference between the THA and TKA in the serum concentration of IL-6. The conditions for blood transfusion and ischemic extremity were not equalized in either of the studies.

In conclusion, the surgical stress of TKA was signifi-

cantly greater than that of THA. Orthopaedic surgeons should recognize that there may be potential complica-tions in cases of TKA with high risk. All over the world, the number of THA and TKA cases is increasing. Accordingly, the number of such extremely elderly patients with high risk diseases is also expected to increase. However, the number of cases in this study was very small, and as such the small sample size may negatively influence the results of the statistical analysis. The current study is considered to be a preliminary report; the study of a larger number of cases may therefore be required for a more precise analysis in the future.

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