**RESEARCH ARTICLE**

# Use of tourniquet does not increase serum concentration of inflammatory markers following total knee arthroplasty during the first 24 postoperative hours

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**Abstract**

**Background:** The literature on the systemic inflammatory reaction following tourniquet-induced ischemia and reperfusion in elective orthopedic surgery is limited.

**Methods**: This prospective comparative study compared the levels of clinically relevant cytokines and peripheral blood counts and major complications in patients undergoing total knee arthroplasty (TKA) with or without a tourniquet during the first postoperative day. Forty-three patients undergoing primary TKA for degenerative osteoarthritis were divided into two groups; 21 patients were operated on using (TG group) and 22 (NTG group) without using a tourniquet. Proinflammatory cytokines interleukin-1b, interleukin-6, anti-inflammatory cytokine interleukin-10, intercellular and vascular adhesion molecules, C-reactive protein, and full blood count were evaluated preoperatively and at one, three, six, and 24 hours postoperatively in both groups.

**Results:** Demographics, American Society of Anesthesiologists score, surgery duration, osteoarthritis grade, and other preoperative variable values were comparable between groups. The average tourniquet time was 67.8 minutes. The majority of testing variables did not demonstrate significant postoperative differences between groups. However, the mean IL-6 value was non-significantly higher for the TG than the NTG group during the first six postoperative hours. It demonstrated a trend to significance at the end of the first postoperative day. The mean hemoglobin and hematocrit levels were significantly higher for the NTG group at the sixth postoperative hour.

**Conclusions:** The tourniquet use may affect the systemic inflammatory response. Patients undergoing TKA with or without a tourniquet demonstrated a similar systemic inflammatory response. However, reperfusion following approximately 70 minutes of tourniquet ischemia is a safe practice. HIPPOKRATIA 2021, 25 (1):31-37.

**Keywords:** Ischemia-reperfusion, tourniquet, total knee arthroplasty, interleukins, TKA

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## Introduction

The tourniquet is now routinely used in elective orthopedic and trauma surgery[1]. It provides a bloodless field improving visualization and bone-cement integration[2] while reducing operating time and blood loss[3]. On the other hand, tourniquet use has been implicated with several postoperative complications, such as thigh pain, muscle and nerve injury, skin burn, hematoma and wound healing problems, and deep vein thrombosis (DVT)[3,4].

After tourniquet application, ischemia and reperfusion trigger a complex cascade of metabolic and inflammatory responses caused by numerous local and systemic inflammatory mediators[4,5]. These substances induce microvascular permeability and changes in acid-base balance and potentially pulmonary and cardiovascular dysfunction[4,6].

The ischemia-reperfusion (I/R) syndrome has been studied *in vivo* preclinical studies in animal models[7] and limited clinical studies evaluating patients undergoing arthroscopic knee surgery with or without tourniquet[8,9]. Wakai et al demonstrated transient neutrophil and monocyte activation in patients undergoing knee arthroscopy with a tourniquet in a randomized controlled trial than those undergoing surgery without ischaemia[9]. This acti-

vation was considered the potential for tissue injury. The inflammatory response is considered higher following reconstructive compared to arthroscopic knee surgery. However, studies measuring the systematic inflammatory response following reconstructive surgery are missing[4,10].

Our study primarily aimed to compare for the first time the most clinically relevant cytokines' peripheral blood levels implicated in systematic inflammatory immune response and full blood counts in patients undergoing unilateral total knee arthroplasty (TKA) with or without tourniquet during the first postoperative day. The secondary aim was to compare major complications as postoperative infection and DVT between the two groups and correlate the course of the markers with them. We hypothesized that tourniquet application affects the inflammatory response significantly during the first postoperative day.

**Materials and Methods**

The Institution's Scientific Research Board approved this prospective clinical study in a tertiary hospital unit (KAT Hospital, decision No 7692, date: 13/06/19). The study was organized according to the World Medical Association, Declaration of Helsinki of 1964, and its later amendments. All patients provided informed consent following preoperative provision of information regarding the study.

Between September 2005 and May 2006, 43 consecutive patients who underwent primary, unilateral TKA were sequentially allocated in two groups. The tourniquet group (TG) consisted of the first 21 consecutive patients and the non-tourniquet group (NTG) with the following 22 patients. We included in the study patients above 18 years of age, scheduled for primary unilateral TKA for end-stage knee osteoarthritis. The exclusion criteria were a systemic inflammatory disease, revision, bilateral knee arthroplasty, history of trauma, neoplasia, drug hypersensitivity, prior corticosteroid, or cancer treatment.

All patients received spinal anesthesia. An experienced surgeon in knee arthroplasty performed all TKAs through a medial parapatellar approach, using fully cemented, posteriorly stabilized prostheses. These techniques are still valid and appropriate for the surgical treatment of end-stage knee osteoarthritis. The tourniquet pressure was twice the systolic blood pressure in the TG group before skin incision until skin closure. We used a deep drain routinely for the first postop day. All patients received anti-embolic stockings and low-molecular-weight heparin beginning 6-8 hours postoperatively and continued once daily for a month. All patients received intravenous vancomycin 500 mg twice and cefuroxime 750 mg three times a day. Chemoprophylaxis started preoperatively and continued 24 hours postoperatively. Postoperative pain was controlled with intravenous paracetamol, 1g three times daily and tramadol 50 mg twice a day. All patients were mobilized during the first postoperative day and ambulated with partial weight-bearing for 20 postoperative days. All patients were followed up clinically for the first postoperative year concerning severe complications as postoperative infection, pneumonic embolism, and DVT.

The primary outcome was comparing the groups regarding the mean difference of postoperative cytokines and adhesion molecules' values, and peripheral venous blood counts several postoperative times. Venous blood samples were collected preoperatively and at one, two, three, six, and 24 hours postoperatively. Cytokines, namely Interleukins 1b (IL-1b), 6 (IL-6), and 10 (IL-10), measured in pg/ml, and adhesion molecules as the intercellular adhesion molecule (ICAM) and vascular adhesion molecule (VCAM) measured in ng/ml were evaluated. They were measured using commercially available ELISA kits (R&D Systems, Europe). Peripheral venous blood samples measured white blood cells count (WBC), hematocrit (Hct), hemoglobin (Hb), and C-reactive protein (CRP).

*Statistical analysis*

There are no similar studies concerning the course of inflammatory markers after TKA. For this reason, the adequate sample size was determined based on the reported drop of Hb following TKA in previous studies[11]. Using Lehr's formula, we evaluated that with sufficient power of 0.8 and the α value of 0.05 to see a Hb difference of 1 g/dl between groups with a standard deviation of 1 g/dl, at least 16 patients had to be enrolled in each group.

We utilized standard statistical methods for descriptive statistics and evaluated the normality of data distribution based on the Kolmogorov-Smirnov and Shapiro-Wilk tests. We compared continuous variables using Student's t-test and Mann-Whitney tests, and tested categorical data with Pearson chi-square and Fisher's exact test between groups. We utilized paired-samples t-test and Wilcoxon's signed-rank test to compare variables on different time points within the same group. Pearson's (r) and Spearman's rho (ρ) correlation coefficients were used for measuring the relationship between age, surgery duration, and the testing variable value at the first postoperative day. The hypothesis of equality of means was discarded when the probability of a Type-I error was <5 %. All statistics were two-tailed. IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) was used to perform the analyses.

**Results**

A senior surgeon examined seventy-seven patients for elective primary unilateral TKA during the screening period. Thirty-four patients did not meet the inclusion criteria, 12 patients due to revision surgery, six for posttraumatic, and nine for inflammatory arthritis. Seven patients did not consent to participate.

Forty-three patients (nine males, 34 females) with a mean age of 70.67 years were finally enrolled in the study. Table 1 shows comparative demographic and preoperative data between groups. The two groups were comparable as far as gender, age, body mass index

**Table 1:** Comparative demographic and preoperative data of the study groups: 21 patients who underwent total knee arthroplasty with and 22 patients without using a tourniquet.

| | | Tourniquet group | Non-Tourniquet group | p-value |
|---|---|---|---|---|
| Age (years)* | | 71.29 (8.7) | 70.09 (6) | 0.60[@] |
| Gender** | Male | 4 | 5 | 1.00[%] |
| | Female | 17 | 17 | |
| Body Mass Index (kgr/m$^2$) * | | 28.3 (1.4) | 29 (1.8) | 0.136[@] |
| ExtremityOperated** | Right | 10 | 8 | 0.45[&] |
| | Left | 11 | 14 | |
| Duration of surgery (minutes)* | | 67.86 (6.4) | 70.86 (9.5) | 0.32[$] |
| ASA score * | I | 8 | 9 | 0.814[&] |
| | II | 12 | 11 | |
| | III | 1 | 2 | |
| Kellgren-Lawrence classification* | III | 11 | 9 | 0.451[&] |
| | IV | 10 | 13 | |

The values are given as the mean with the standard deviation in parentheses (*) or as raw numbers (**). Tests performed using [@]: Independent Sample t-test, [$]: Mann-Whitney test, [&]: Chi-square (x2) test, [%]: Fisher Exact test.

(BMI), American Society of Anesthesiologists (ASA) score, duration of surgery, and Kellgren and Lawrence's grade of osteoarthritis were concerned (Table 1). The average tourniquet time was 67.86 minutes in the TG group, which coincides with surgery duration since the tourniquet was released after skin closure. The NTG group demonstrated a non-significantly longer mean surgery duration than the TG group (Table 1).

None of the patients in both groups had a major complication during the postoperative period. During the first three postoperative months, no prosthetic joint infection cases, periprosthetic fracture, DVT, or pneumonic embolism were recorded.

The mean preoperative variable values did not differ between the groups (Table 2). No significant difference was also found between groups postoperatively for most testing variables (Table 2). However, the mean IL-6 value was non-significantly higher for the TG than the NTG group during the first six postoperative hours. Il-6 demonstrated a trend to significance at the end of the first postoperative day. At the sixth postoperative hour, the mean Hct level was significantly lower (p =0.02) for the TG than the NTG group (Table 2).

The flowcharts of Figure 1(a-i) depict the fluctuation of variables between groups during the first postoperative day. The time when the mean postoperative value of each variable differed significantly from the mean preoperative one is also depicted in these charts. At the end of the first postoperative day, no testing variable significantly correlated with patients' age or surgery duration.

## Discussion

Tourniquet use is a common practice in trauma and elective orthopedic surgery. However, tourniquet-induced ischemia followed by reperfusion may trigger a cascade of potentially harmful to the patient reactions. This study evaluated the systematic inflammatory response by comparing the most clinically relevant cytokines and full blood counts between two groups of patients undergoing TKA with or without a tourniquet[12]. We found no significant differences concerning most testing variables between groups during the first postoperative day. The variables demonstrated the greater difference between groups following the sixth postoperative hour. The IL-6 level was non-significantly higher for TG than the NTG group during the first six postoperative hours and showed a trend towards significance at the end of the first postoperative day.

IL-1b and tumor necrosis factor-a (TNF-a) are central proinflammatory cytokines produced by activated macrophages and monocytes following tissue damage[12,13]. They stimulate other cytokines release, such as IL-6 and adhesion molecules causing vascular injury and increased vessels' permeability[12,13]. Anti-IL-1b treatment in animal models lessens tissue injury by decreasing vascular permeability, leukocyte accumulation, and mRNA expression of early response cytokines[14]. It is supported that the rise of IL-1b levels can only be detected using intraoperative sampling[15]. In our study, IL-1b levels were substantially decreased during the first postoperative hour and then more slowly during the first postoperative day in the TG group; no significant change of the mean IL-1b value was observed for the NTG group at the early postoperative hours followed by a progressive decrease (Figure 1a). The IL-1b levels did not reach statistical significance compared to preoperative values for both groups at any follow-up time. A similar kinematic was detected in young patients who underwent elective knee surgery under a two-hour tourniquet application[8].

IL-6 is a central cytokine of the acute phase response produced by stimulated proinflammatory cytokines as IL-1b and TNF-a[12,13,16]. IL-6 levels increased gradually postoperatively in our study, reaching peak values at the sixth postoperative hour for both groups (Figure 1b). TG group demonstrated a not significantly higher IL-6 value at the sixth postoperative hour than the NTG group. This difference showed a trend towards significance for the TG at the end of the first postoperative

**Table 2:** Comparison of the mean levels of cytokines, adhesion molecules, and peripheral venous blood counts between groups preoperatively and at different postoperative times.

| | | Non-Tourniquet group | Tourniquet group | p-value |
|---|---|---|---|---|
| IL-1b (pg/ml) | Preoperatively | 1.01 (0.64) | 2.45 (5.8) | 0.95** |
| | 1st postop hour | 1.29 (0.88) | 1.36 (1.23) | 0.76** |
| | 3rd postop hour | 1.87 (1.94) | 1.31 (1.56) | 0.22** |
| | 6th postop hour | 1.29 (2.05) | 0.81 (0.6) | 0.42** |
| | 1st postop day | 1.05 (1.04) | 0.96 (0.68) | 0.71** |
| IL-6 (pg/ml) | Preoperatively | 12.4 (32.3) | 5.6 (9.8) | 0.28** |
| | 1st postop hour | 49.53 (100.73) | 26.74 (36.92) | 0.24** |
| | 3rd postop hour | 114.9 (102.6) | 96.13 (96.16) | 0.40** |
| | 6th postop hour | 160.8 (184.9) | 278.6 (469.3) | 0.39** |
| | 1st postop day | 102.9 (80.9) | 207.8 (220.6) | 0.055* |
| IL-10 (pg/ml) | Preoperatively | 3.7 (3.7) | 2.1 (2.1) | 0.29** |
| | 1st postop hour | 31.5 (40.4) | 25.7 (38.1) | 0.71** |
| | 3rd postop hour | 40.8 (77.5) | 16.3 (21.2) | 0.22** |
| | 6th postop hour | 10.43 (19.3) | 12.7 (30.8) | 0.14** |
| | 1st postop day | 12.4 (19.3) | 12.7 (30.8) | 0.83** |
| CRP (μg/ml) | Preoperatively | 9.4 (13.7) | 9.3 (11.8) | 0.67** |
| | 1st postop hour | 10.0 (16.2) | 10.2 (14.5) | 0.69** |
| | 3rd postop hour | 12.8 (20.4) | 11.1 (14.1) | 0.68** |
| | 6th postop hour | 19.4 (22.3) | 15.6 (15.2) | 0.97** |
| | 1st postop day | 42.4 (27.8) | 38.8 (22.6) | 0.64* |
| ICAM (ng/ml) | Preoperatively | 400.9 (173,58) | 399.0 (88.1) | 0.96* |
| | 1st postop hour | 331.13 (148.5) | 368.8 (95.9) | 0.33* |
| | 3rd postop hour | 346.4 (148.7) | 351.2 (124.5) | 0.90* |
| | 6th postop hour | 378.3 (155.6) | 365.8 (92.6) | 0.94** |
| | 1st postop day | 387.1 (86.02) | 400.5 (131.12) | 0.69* |
| VCAM (ng/ml) | Preoperatively | 1239.8 (619.7) | 1513.5 (846.0) | 0.24** |
| | 1st postop hour | 1218.4 (542.6) | 1749.3 (1145.9) | 0.24** |
| | 3rd postop hour | 1373.4 (769.6) | 1280.9 (398.7) | 0.80** |
| | 6th postop hour | 1269.7 (355.5) | 1647.9 (747.3) | 0.21* |
| | 1st postop day | 1335.3 (667.2) | 1425.0 (884.3) | 0.59** |
| Hct (%) | Preoperatively | 37.2 (6.1) | 36.3 (5.31) | 0.6* |
| | 1st postop hour | 35.6 (4.8) | 36.1 (4.4) | 0.72* |
| | 3rd postop hour | 35.5 (4.6) | 33.3 (5.5) | 0.16* |
| | 6th postop hour | 35.7 (4.7) | 32.2 (5.2) | 0.02* |
| | 1st postop day | 34.0 (4.4) | 31.9 (5.3) | 0.38** |
| Hb (g/dl) | Preoperatively | 12.59 (2.21) | 12.12 (1.78) | 0.45* |
| | 1st postop hour | 11.99 (1.78) | 11.89 (1.47) | 0.84* |
| | 3rd postop hour | 11.66 (1.61) | 10.93 (1.76) | 0.16* |
| | 6th postop hour | 11.6 (1.71) | 10.6 (1.72) | 0.06* |
| | 1st postop day | 10.7 (2.5) | 10.72 (2.78) | 0.92** |
| WBC ($x10^3$ / μL) | Preoperatively | 7.17 (2.58) | 6.7 (1.58) | 0.84** |
| | 1st postop hour | 7.2 (2.5) | 7 (1.85) | 0.84** |
| | 3rd postop hour | 7.63 (2.57) | 7.49 (2.53) | 0.61** |
| | 6th postop hour | 8.01 (2.65) | 8.02 (2.07) | 0.57** |
| | 1st postop day | 10.1 (3.7) | 10.1 (2.7) | 0.60** |

The values are given as mean with standard deviations in parentheses. *: tests performed using Student's t-test, **: tests performed using Mann-Whitney U test, IL-1b: Interleukin 1b, IL-6/ IL-10: Interleukin 6 and 10, CRP: C-reactive protein, ICAM: intercellular adhesion molecule, VCAM: vascular adhesion molecule, Hct: hematocrit, Hb: hemoglobin, WBC: white blood cell count.

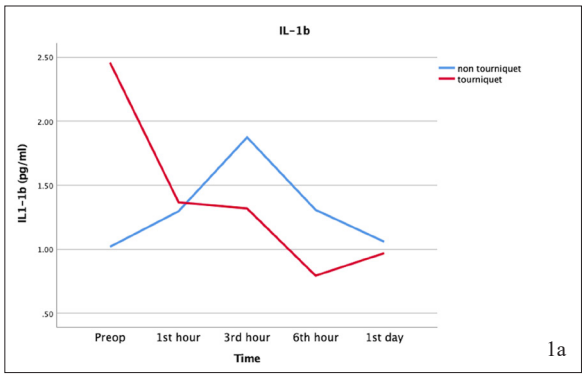
day. The IL-6 level was significantly different from the preoperative values for both groups throughout the first postoperative day. The postoperative rise of IL-6 levels has been well documented for 4-48 hours after tourniquet application[8,17]. It is attributed to additional tissue damage induced by I/R injury[12,13]. The greater tissue injury, the higher documented postoperative increase of IL-6 level[12]. The duration of ischemia is critical on the extent of tissue

damage and the stimulated response. Probably, the short period of tourniquet application in our study affected the IL-6 postoperative course. No testing variable was significantly related to the duration of surgery in our study. Halladin et al did not note any significant release of reactive oxygen species or cytokines following 20 minutes of lower limb ischaemia[18].

CRP is another acute-phase protein that follows the IL-6 increase[12]. A sharper CRP rise at 15 minutes after reperfusion following short periods of forearm ischemia has been reported[19,20]. There was a significant rise in CRP levels for both study groups, mainly following the first six postoperative hours (Figure 1d). However, the differences between groups did not reach significance.

IL-10 is the most crucial anti-inflammatory cytokine inhibiting the synthesis of proinflammatory cytokines, such as IL-1b, IL-6[21]. Low levels of IL-10 after systemic injury are related to poor outcomes[21]. IL-10 levels were increased for both groups. The rise was higher and earlier, followed by an abrupt decline for the TG group during the first six postoperative hours (Figure 1c). The IL-10 levels were reduced until the end of the first postoperative day for both groups. Clemmensen et al showed that IL-10 was not influenced four hours after reperfusion following 100 minutes of ischemia for knee arthroscopy[17]. Another well-designed study demonstrated that IL-10 increased significantly during ischemia in patients undergoing anterior cruciate ligament reconstruction surgery but returned to baseline levels within four hours postoperatively[22].

The release of soluble adhesion molecules in blood circulation is related to the trauma extent and the I/R time[22]. ICAM and VCAM serum levels are inversely related to their concentration on the endothelial membrane[23]. Huda et al recorded a significant decrease in serum levels of ICAM at 50 minutes postoperatively[8]. In our study, the postoperative ICAM and VCAM levels showed similar kinematic without significant altera-



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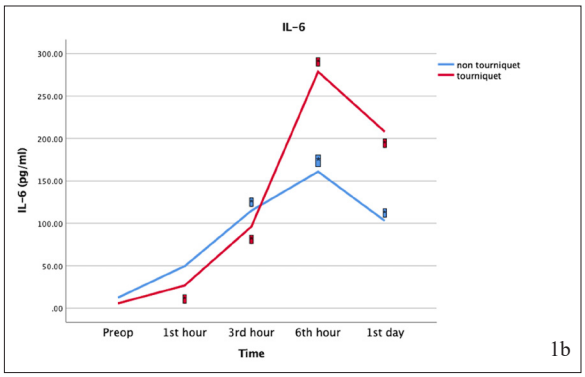

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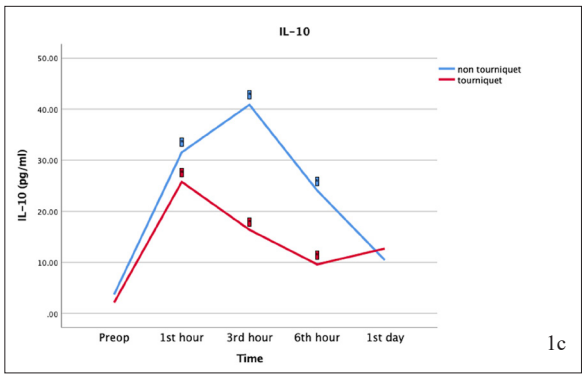

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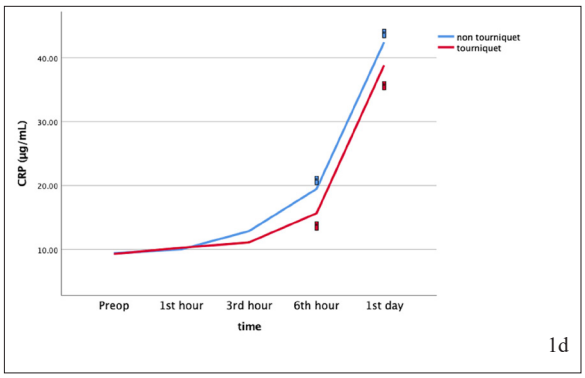

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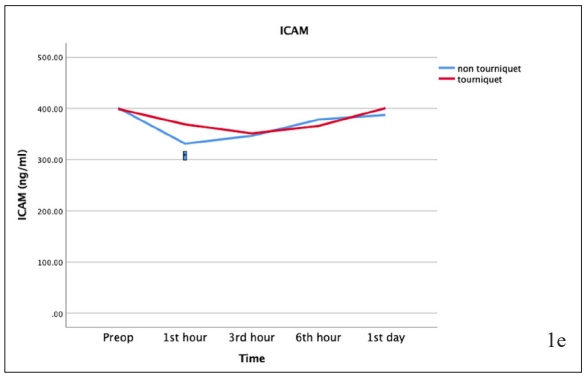

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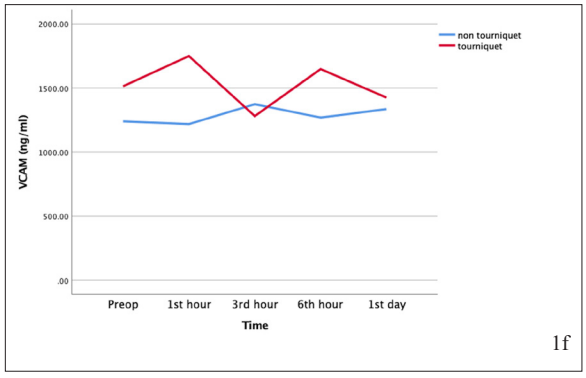

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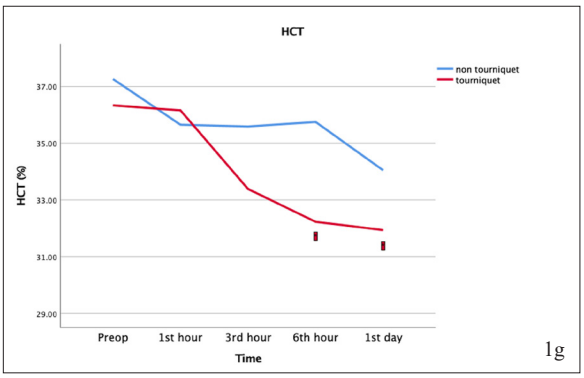


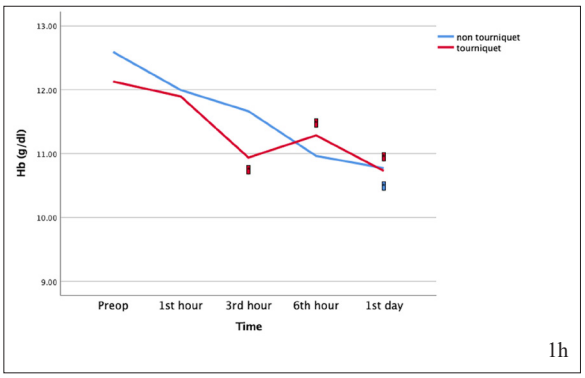


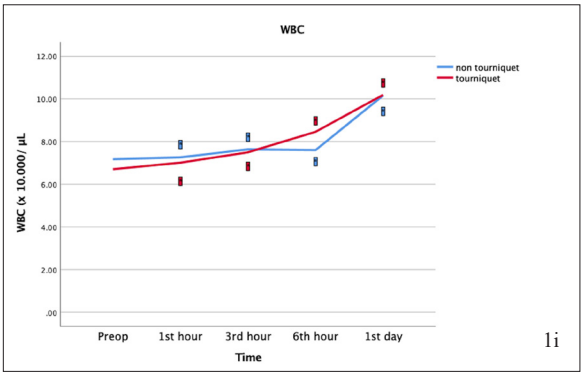


**Figure 1(a-i):** Schematic diagrams showing the mean change of cytokines, adhesion molecules, hematocrit, hemoglobin, and white blood cell count for both patients' groups.

*: Statistically significant different value ($p < 0.05$) compared to baseline (preoperative) value. IL-1b: Interleukin 1b, IL-6/ IL-10: Interleukin 6 and 10, CRP: C-reactive protein, ICAM: intercellular adhesion molecule, VCAM: vascular adhesion molecule, Hct: hematocrit, Hb: hemoglobin, WBC: white blood cell count

tions in both groups (Figure 1e,f). Except for the ICAM level at the first postoperative hour for the NTG group, no other significant difference was recorded for both groups than the preoperative values. The latter may be attributed to the limited trauma of this elective surgery[22].

Whether the tourniquet use reduces blood loss following TKA remains controversial[2,6,24]. There was a significant difference in Hct and Hb levels between the two groups on the sixth postoperative hour (Figure 1g,h). However, the transfusion needs during hospitalization were similar between groups. Although blood transfusion may also trigger inflammatory reactions[25], most blood units were transfused following the first postoperative day in our study. Consequently, they cannot be related to the estimated inflammatory response.

Our study has some limitations. First, it is not randomized; however, most recently published papers are animal or clinical studies without a control group[8,13,17-19]. Our two groups were matched and comparable in various parameters, and appropriate sample sizing was done. Another limitation of our study is that measurements are limited to the first postoperative day and do not necessarily reflect the whole inflammatory response spectrum. However, almost all values were declined at the end of the first day. Besides, we did not correlate the course of markers with other clinical findings as clinical scores.

## Conclusion

Our study evaluated cytokines, acute-phase proteins, and adhesion molecules for the first time between patients undergoing TKA with or without a tourniquet. No significant differences between groups were found for the majority of testing variables. IL-6 demonstrated a potentially higher systematic inflammatory response. There was no clinical evidence of a higher systemic inflammatory response in the TG group, as no significant complication was recorded. A 70-minute tourniquet application was considered a safe practice. Higher-level studies are needed to clarify the pathways of systemic response following I/R injury.

## Conflict of Interest

The authors declare no conflict of interest.

## References

1. Berry DJ, Bozic KJ. Current practice patterns in primary hip and knee arthroplasty among members of the American Association of Hip and Knee Surgeons. J Arthroplasty. 2010; 25: 2-4.
2. Li X, Yin L, Chen ZY, Zhu L, Wang HL, Chen W, et al. The effect of tourniquet use in total knee arthroplasty: grading the evidence through an updated meta-analysis of randomised, controlled trials. Eur J Orthop Surg Traumatol. 2014; 24: 973-986.
3. Zhang W, Li N, Chen S, Tan Y, Al-Aidaros M, Chen L. The effects of a tourniquet used in total knee arthroplasty: a meta-analysis. J Orthop Surg Res. 2014; 9: 13.
4. Estebe JP, Davies JM, Richebe P. The pneumatic tourniquet: mechanical, ischemia-reperfusion and systemic effects. Eur J Anaesthesiol. 2011; 28: 404-411.
5. Muyskens JB, Hocker AD, Turnbull DW, Shah SN, Lantz BA, Jewett BA, et al. Transcriptional profiling and muscle cross-section analysis reveal signs of ischemia-reperfusion injury following total knee arthroplasty with tourniquet. Physiol Rep. 2016; 4: e12671.
6. Kageyama K, Nakajima Y, Shibasaki M, Hashimoto S, Mizobe T. Increased platelet, leukocyte, and endothelial cell activity are associated with increased coagulability in patients after total knee arthroplasty. J Thromb Haemost. 2007; 5: 738-745.
7. Grace PA. Ischaemia-reperfusion injury. Br J Surg. 1994; 81: 637-647.
8. Huda R, Solanki DR, Mathru M. Inflammatory and redox responses to ischaemia/reperfusion in human skeletal muscle. Clin

Sci (Lond). 2004; 107: 497-503.
9. Wakai A, Wang JH, Winter DC, Street JT, O'Sullivan RG, Redmond HP. Tourniquet-induced systemic inflammatory response in extremity surgery. J Trauma. 2001; 51: 922-926.
10. 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.
11. Stamatopoulos A, Stamatopoulos T, Kenanidis E, Potoupnis M, Sayegh F, Tsiridis E. Intravenous and intraarticular tranexamic acid plus epinephrine for the management of blood loss after cemented total knee arthroplasty: a case-control study. Hippokratia. 2018; 22: 86-90.
12. Desborough JP. The stress response to trauma and surgery. Br J Anaesth. 2000; 85: 109-117.
13. Conrad MF, Stone DH, Albadawi H, Hua HT, Entabi F, Stoner MC, et al. Local inflammatory and thrombotic responses differ in a murine model of partial and complete hindlimb ischemia/reperfusion. Surgery 2005; 138: 375-381.
14. Krishnadasan B, Naidu BV, Byrne K, Fraga C, Verrier ED, Mulligan MS. The role of proinflammatory cytokines in lung ischemia-reperfusion injury. J Thorac Cardiovasc Surg. 2003; 125: 261-272.
15. Baigrie RJ, Lamont PM, Dallman M, Morris PJ. The release of interleukin-1 beta (IL-1) precedes that of interleukin 6 (IL-6) in patients undergoing major surgery. Lymphokine Cytokine Res. 1991; 10: 253-256.
16. Sheeran P, Hall GM. Cytokines in anaesthesia. Br J Anaesth. 1997; 78: 201-219.
17. Clementsen T, Reikerås O. Cytokine patterns after tourniquet-induced skeletal muscle ischaemia reperfusion in total knee replacement. Scand J Clin Lab Invest. 2008; 68: 154-159.
18. Halladin NL, Ekeløf S, Alamili M, Bendtzen K, Lykkesfeldt J, Rosenberg J, et al. Lower limb ischaemia and reperfusion injury in healthy volunteers measured by oxidative and inflammatory biomarkers. Perfusion. 2015; 30: 64-70.
19. Hughes SF, Hendricks BD, Edwards DR, Bastawrous SS, Roberts GE, Middleton JF. Mild episodes of tourniquet-induced forearm ischemia-reperfusion injury result in leukocyte activation and changes in inflammatory and coagulation markers. J Inflamm (Lond). 2007; 4: 12.
20. Hughes SF, Hendricks BD, Edwards DR, Middleton JF. Tourniquet-applied upper limb orthopaedic surgery results in increased inflammation and changes to leukocyte, coagulation and endothelial markers. PloS One. 2010; 5: e11846.
21. Opal SM, DePalo VA. Anti-inflammatory cytokines. Chest. 2000; 117: 1162-1172.
22. 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: 874-882.
23. Kusterer K, Bojunga J, Enghofer M, Heidenthal E, Usadel KH, Kolb H, et al. Soluble ICAM-1 reduces leukocyte adhesion to vascular endothelium in ischemia-reperfusion injury in mice. Am J Physiol. 1998; 275: G377-380.
24. Parvizi J, Diaz-Ledezma C. Total knee replacement with the use of a tourniquet: more pros than cons. Bone Joint J. 2013; 95-B: 133-134.
25. L'Acqua C, Bandyopadhyay S, Francis RO, McMahon DJ, Nellis M, Sheth S, et al. Red blood cell transfusion is associated with increased hemolysis and an acute phase response in a subset of critically ill children. Am J Hematol. 2015; 90: 915-920.