Effects of tourniquet application on enhanced recovery after surgery (ERAS) and ischemia-reperfusion post-total knee arthroplasty: Full- versus second half-course application

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Abstract

Purpose: Pneumatic tourniquets are used in total knee arthroplasty (TKA) for surgical field visualization and improved cementation; however, their use is controversial. This study aimed to assess the effects of tourniquet application on enhanced recovery post-TKA. Methods: A prospective randomized single-blinded trial assessed tourniquet’s effects on postoperative pain, swelling, and early outcome in TKA. One-hundred and two patients with knee osteoarthritis were randomized to full-course (FC) and second half-course (SHC) application (n = 51/group). Tumor necrosis factor-alpha (TNF-α), C-C motif chemokine ligand 2 (CCL-2), pentraxin-3 (PTX-3), prostaglandin E-2 (PGE-2), superoxide dismutase-1 (SOD-1), and myoglobin (Mb) were assessed by enzyme-linked immunosorbent assay, while the visual analog scale (VAS), range of motion (ROM), and thigh circumference growth rate were recorded. Results: Average tourniquet duration significantly differed between the SHC (37.5 ± 5.1 min) and FC (66.4 ± 7.2 min) groups (p < 0.01); VAS and thigh circumference growth rate in the SHC group were much lower compared with the FC group, while ROM was higher within 48 h of tourniquet removal (p < 0.01). Blood TNF-α, PTX3, CCL2, PGE2, SOD-1, and Mb were lower in the SHC group than the FC group (p < 0.01). Additionally, intraoperative blood loss was significantly elevated in the SHC group than the FC group (p < 0.01), with lower postoperative blood loss in the drain (p = 0.001). Postoperative drainage volume was reduced in the SHC group compared with the FC group (p < 0.01); five and two patients in the FC and SHC groups required blood transfusion, respectively (p = 0.025). Hospital stay tended to be shorter in the SHC group (p = 0.023), and no tourniquet-related complications were recorded. Conclusion: Improved therapeutic outcome was observed in the SHC group, indicating patients should routinely undergo TKA with SHC tourniquet application.

Keywords

pain, swelling, total knee arthroplasty, tourniquet

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Introduction

With advances in technology and instruments, total knee arthroplasty (TKA) is currently considered one of the most common performed orthopedic surgeries. A tourniquet can be used during TKA to improve visibility and cementation. The tourniquet’s benefits include decreased amounts of both intraoperative and postoperative blood loss,
intraoperative “bloodless” visual field, cement–bone inter-
digitations, and reduced operation time.²

However, tourniquet application also has an increased risk of nerve palsy, vascular injury, muscle damage, post-
operative swelling, and stiffness.³,⁴ Therefore, its use in
TKA remains controversial. Recent emphasis has been placed in TKA on postoperative pain control and soft tissue trauma during surgery.⁵,⁶ We thus recently performed a ran-
domized controlled trial (RCT) to assess pain and swelling caused by ischemic-reperfusion injury after primary TKA, in an attempt to improve recovery and function, while reducing hospital stay.⁷ The findings of this study would contribute to improve procedural recommendations for TKA.

**Patients and methods**

The current study was a prospective RCT. We randomized 102 patients with osteoarthritis undergoing unilateral TKA into the second half-course (SHC) and full-course (FC) groups (51 knees/group). Inclusion and exclusion criteria were predefined (Table 1). Patients with symptomatic peripheral vascular disease or contraindication to tourniquet use were excluded. The consolidated standards for reporting trials are summarized in the study flowchart (Figure 1).

Institutional ethics committee approval was obtained prior to study commencement, and all patients provided informed consent.

All patients underwent TKA by the same surgeon following the same technique and prosthesis type. Randomization and blinding were carried out. All patients underwent general anesthesia without regional blocks or local anesthesia in an effort to rule out confounding factors that may influence pain scores. A medial parapatellar approach was used with eversion of the patella. A cemented fixed bearing posterior cruciate-retaining prosthesis was used in all patients with the patella everted.

Intra-articular drainage on low suction was performed prior to wound closure and stopped on day 2 postopera-
tively. The patients were mobilized on day 1 postopera-
tively and discharged when moving safely. The same standardized physiotherapy protocol was used in all patients postoperatively. Active and passive range of motion (ROM) values were evaluated.

**Randomization**

A surgeon not involved in the study removed slips from nontransparent sealed envelopes, whose information directed to which knee would receive long- or short-duration tourniquet.

**Blinding**

Subjects and the personnel were blinded until before surgery. Both patients and the staff in the operating theater were blinded as for which patient knee long- or short-duration tourniquet was being used. The investigator collecting data was blinded during the procedure and follow-up. The knees selected for surgery were randomly allocated to the SHC or FC groups. An above knee tourniquet (width 10.5 cm, length 65.5 cm; VBM Medizintechnik GmbH, Sulz, Germany) was used for all patients during surgery. The tourniquet was inflated to 280 mmHg just prior to initial skin incision in the FC group and to 280 mmHg immediately prior to mounting the cemented prosthesis in the SHC group. This was the standard pressure used at our institution at the time of study.

The tourniquet was deflated following wound closure and application of dressings. Electrocautery was used for hemostasis; intraoperative blood loss was measured ((volume in suction container − amount of saline washed) + (total weight of wet mops used − total weight of dry mops used)) in all cases. Postoperative blood loss was determined from the volume of blood in drains. On the second postoperative day, hemoglobin assessment and X-ray of the knees were performed. The threshold of postoperative blood transfusion was hemoglobin < 8 g/dl.

Peripheral blood samples (3 ml) from the elbow vein were collected when opening the joint cavity (T1) and at 3 h (T2), 8 h (T3), and 24 h (T5) after removal of the tourniquet; 3 ml topical blood samples from the joint cavity (T1) and drainage bags at T2, T3, and T5 in all cases were obtained as well. Then, tumor necrosis factor-alpha (TNF-α), PTX3, CCL2, PGE2, SOD-1, and myoglobin (Mb) were detected at T1, T2, T3, and T5 by enzyme-linked immunosorbent assay (ELISA). Plasma was separated by centrifuga-
tion at 3000 r/min and 4°C for 10 min. Then, the supernatant was stored at −80°C for further analysis. Serum concentrations of TNF-α, CCL2, PTX3, and PGE2 were measured with a specific human ELISA kit (Fcmacs, Nanjing, China). SOD-1 and Mb were determined with another human ELISA kit (Jiangsu KeyGEN BioTECH Corp. Ltd, China). All operations were performed according to the manufacturer’s instructions.

**Pain score** was measured by the visual analog scale (VAS), and ROM was recorded as well. Thigh and knee swelling was recorded using a measuring tape at 10 cm

### Table 1. Study inclusion and exclusion criteria.

| Inclusion criteria                                      | Exclusion criteria                                      |
|----------------------------------------------------------|--------------------------------------------------------|
| Symptomatic grade IV knee OA                            | Any hematological disease (e.g. coagulopathy)          |
| Signed informed consent for the procedure               | Any infective foci in the body                         |
| Unilateral TKA for the first time                        | A history of immune suppression                        |
| 50 years ≤ age ≤ 80 years                               | Any peripheral neurovascular disease                   |
|                                                           | Inflammatory arthritis, like rheumatoid arthritis.     |

OA: osteoarthritis; TKA: total knee arthroplasty.
above the superior pole of the patella. VAS, ROM, and thigh’s circumference growth rate were recorded, respectively, before operation (T0) and at 12 h (T4), 24 h (T5), and 48 h (T6) after tourniquet removal. Secondary outcome measures included postoperative drainage, transfusion requirements, and hospitalization days.

There were no complications directly related to tourniquet application in this study. Because many previous reports have reported that tourniquet application has no significant effects on long-term function of the affected limb, this study only assessed early postoperative function.

**Statistical analysis**

No previous studies have evaluated the inflammatory response of ischemia-reperfusion injury caused by tourniquets, so sample size could not be estimated. Data are mean ± standard deviation. Paired t-test and the χ² test were used for statistical analysis, and p < 0.05 was considered statistically significant. The SPSS Statistics 21.0 software (SPSS, Chicago, Illinois, USA) was used for data analysis.

**Results**

In this study, a total of 102 patients who underwent unilateral TKA for the first time (Figure 1) and fulfilled all eligibility criteria (Table 1) were assessed. All patients were evaluated for 2 weeks, with none lost to follow-up. The patient demographics showed no significant differences between the two groups (all p > 0.05), as well as mean operative time (p = 0.322). However, average tourniquet duration showed a statistically significant difference between the SHC (37.5 ± 5.1 min) and FC (66.4 ± 7.2 min) groups (p < 0.01) (Table 2).

There were no significant differences in PTX3, CCL2, SOD-1, PGE2, and Mb levels in peripheral blood between the two groups at T1, T2, T3, and T5, respectively (p > 0.05; Figure 2). There were no statistically significant differences
in TNF-α, PTX3, CCL2, SOD-1, PGE2, and Mb amounts in topical blood between the two groups at T1, respectively (p > 0.05; Figure 3). However, they were much higher in the FC group compared with the SHC group, respectively (Figure 3). Pain scores (VAS) were comparable preoperatively in both groups, and were significantly reduced in the SHC group at T4, T5, and T6 postoperatively compared with the FC group (p < 0.01). ROM values were comparable preoperatively in both the groups. However, in the postoperative period, ROM was significantly improved in the SHC group at T4, T5, and T6 postoperatively compared with the FC group (p < 0.01). The perimeter growth rate was higher in the FC group compared with the SHC group at T5 (p < 0.01) as well as at T4 and T6 (p = 0.02) (Figure 4).

In addition, intraoperative blood loss in the SHC group was significantly increased than that of the FC group (p < 0.01). Postoperative blood loss in the drain was increased in the FC group (p = 0.001). However, total blood loss (intraoperative + postoperative) showed no significant difference (p = 0.236) (Table 3). There were no events of thromboembolism and deep vein thrombosis (DVT) in either groups. Postoperative drainage volume in the SHC group was increased compared with that of the FC group (p < 0.01). Five patients in the FC group required blood transfusion versus two in the SHC group (p = 0.025). There was a trend toward shorter hospital stay in the SHC group but statistical significance was not reached (p = 0.213 (Table 4).

**Discussion**

This study showed that the use of FC tourniquet had detrimental effects on inflammation and patient recovery following TKA. There were no statistical differences in TNF-α, PTX3, CCL2, SOD-1, PGE2, and Mb levels in topical blood between the two groups at T1, respectively (p > 0.05; Figure 3). However, values were much higher in the FC group than the SHC group (Figure 3). Pain scores were higher in the FC group with statistical significance for days 1 and 2 postoperatively. ROM values were lower in the FC group with statistical significance for days 1 and 2 postoperatively. The tourniquet, therefore, appears to be a significant source of postoperative pain and swelling. We found no difference in postoperative blood drainage; five patients in the FC group required blood transfusion versus two in the SHC group. We acknowledge many patient factors determine transfusion needs but were not assessed in this study. While the tourniquet controls intraoperative blood loss, it does not stop postoperative blood loss or reduce overall blood loss.

Our initial hypothesis was that topical tissue inflammation and postoperative early decline of limb function associated with tourniquet-induced ischemia are more pronounced in the FC group compared with the SHC group, which was verified in this study. The only tangible detrimental effect of the tourniquet during all operations in this
Table 3. Blood loss amounts (intraoperative, postoperative, and overall).a

| Blood loss (ml)   | FC group (n = 51) | SHC group (n = 51) | p Value |
|-------------------|-------------------|-------------------|---------|
| Intraoperative    | 166.4 ± 7.2       | 259.4 ± 14.5      | 0.001   |
| Postoperative     | 185.3 ± 14.6      | 112.9 ± 10.1      | 0.001   |
| Overall           | 351.7 ± 11.8      | 372.3 ± 10.3      | 0.236   |

aData are mean ± SD.
SD: standard deviation; FC: full-course; SHC: second half-course.

Table 4. Inpatient outcomes for the SHC and FC groups.

| Parameter               | FC group (n = 51) | SHC group (n = 51) | p Value |
|-------------------------|-------------------|-------------------|---------|
| Total drainage          | 185.3 ± 14.6      | 112.9 ± 10.1      | 0.001   |
| Postoperatively         |                   |                   |         |
| Transfusion requirements | 5                 | 2                 | 0.025   |
| Days to discharge       | 6.9 ± 2.4         | 4.7 ± 1.6         | 0.023   |

FC: full-course; SHC: second half-course.
study was the bloodless surgical field. A significant finding of the present study was that inflammation of the topical tissue and postoperative early function were related to tourniquet duration. We specifically analyzed data by a blinded observer.

We believe tourniquet duration is a very important determinant of rapid recovery after operation. The lower statistical power of the study may be one of the reasons why inflammatory markers in peripheral blood were not significantly different between the two groups on postoperative 2 days.

We elected not to use any form of regional anesthesia in this study that may confound pain scores. We believe the present findings are relevant and valid. The strengths of this study include a randomized controlled design in a nonselected population, and few exclusion criteria. In addition, we assessed several highly objective inflammatory factors such as TNF-α, PTX3, CCL2, SOD-1, Mb, and PGE2, and outcome measures including VAS, ROM, and thigh perimeter growth rate.

Surgeons have recently used low tourniquet pressures to reduce the risk of postoperative pain and complications. Setting the tourniquet cuff pressure based on systolic blood pressure plus a margin of 100 mmHg has been reported to reduce cuff pressure and early postoperative pain.8 Olivecrona et al.9 in a randomized study demonstrated that the limb-occlusion pressure method reduces the tourniquet’s cuff pressure without altering the quality of the bloodless field. No advantages were found with lower cuff pressure in postoperative pain, knee ROM, and complications. Therefore, to reduce errors between individuals and groups, we set the tourniquet pressure to 280 mmHg.

Many studies have shown that the potential complications outweigh the benefits of tourniquet application in TKA, but the safe limits of time for the tourniquet remain controversial.

Because TNF-α, CCL2, interleukin 6 (IL-6), PTX3, SOD-1, PGE2, and Mb as test indicators can reflect oxidative stress, inflammatory response, and tissue necrosis,10–14 they are related to quadriceps muscle injury, wound complications, neurovascular injury, swelling and bruising, hidden blood loss, and DVT. No previous studies have assessed the effects of tourniquet application on inflammatory factors such as TNF-α, PTX3, CCL2, SOD-1, Mb, and PGE2. Therefore, the present study assessed peripheral and topical blood samples simultaneously, which can sensitively reflect the degree of local inflammatory reactions and tissue damage to provide insights into pain diagnosis, and serve as indicators to reflect the severity of muscle injury, providing references for clinical treatment.

The most important finding of the current study was that tourniquets could result in aggravated swelling and pain, and were associated with inflammatory factors such as TNF-α, PTX3, CCL2, PGE2, SOD-1, and Mb, with positive correlation with tourniquet duration.

Rasmussen et al.15 demonstrated that at a tourniquet duration of less than 15 min, no metabolic changes or inflammatory reactions in the ischemic tissue occur. However, inflammatory factors increased in levels after reperfusion at longer tourniquet durations; large amounts of inflammatory factors are released after reperfusion at a tourniquet duration of more than 45 min. Meanwhile, inflammatory markers in the ischemic tissue underneath the tourniquet showed a more pronounced increase compared with the ischemic tissue distal to the tourniquet, as demonstrated in the present study. In the current study, average tourniquet duration was 37.5 min in the SHC group and 74.4 min in the FC group (Table 2). Inflammatory factors such as TNF-α, PTX3, CCL2, PGE2, SOD-1, and Mb were increased significantly in both peripheral and topical blood samples after 3 h and 8 h of reperfusion. However, inflammatory factors in peripheral blood showed no statistical differences between the two groups (Figure 2), as long and short tourniquet durations had similar effects on the whole body. In topical blood, the change was greater in the FC group than the SHC group (Figure 3), confirming that longer tourniquet duration causes much greater injury to the local tissue than shorter tourniquet duration. After 24 h of reperfusion, all inflammatory factors decreased in topical and peripheral blood samples (Figures 2 and 3). However, these amounts were closer to preoperative levels in the SHC group than those of the FC group, suggesting that inflammatory reactions and cell damage are reversible; the shorter the tourniquet duration, the faster the recovery.

It is known that short-duration tourniquet use would result in faster recovery and less pain during the early rehabilitation period following TKA.16–18 In the present trial, the short-duration tourniquet group was associated with better clinical outcomes, less pain, and reduced limb swelling during the early stage of rehabilitation (Figure 4). Similar results were reported by Zhang et al.19 and Ejaz et al.20 A possible explanation is that longer tourniquet use results in more pronounced oxidative stress, inflammatory response, and tissue necrosis. TNF-α, CCL2, IL-6, PTX3, SOD-1, PGE2, Mb, and other pro-inflammatory cytokines are increased, contributing to enhanced telangiectasia and capillary permeability while promoting inflammatory cell infiltration and exudation, followed by severe congestion and acute inflammatory edema.21–28 Enhanced swelling also increases soft tissue tension; additional swelling may hinder the patient’s early postoperative rehabilitation exercises. Furthermore, as Dennis et al.10 reported, patients submitted to TKA using a tourniquet have diminished quadriceps strength. Loss of lower quadriceps strength may result in reduced recovery of the active ROM of the knee. Postoperative pain might be caused by physical damage, reperfusion injury, and even fibrotic events in the muscle tissue.29 Due to nerve injury, inflammatory reactions and necrotic tissue infection induce various immune and glial cells in the peripheral nerve to produce a variety of pro-inflammatory cytokines and chemokines, which break the balance between pro-
inflammatory and anti-inflammatory cytokines in the microenvironment, decrease the thresholds of excitability in peripheral and central neurons, increase excitability of neurons and hyperalgesia, and cause pain.10,21–28

Multiple studies have compared clinical manifestations, such as thigh pain, limb swelling, nerve palsy, muscle injury, postoperative stiffness, and DVT, and drew different conclusions because of large variability of these indicators. However, the present study, through a combination of inflammatory marker changes in blood and clinical manifestations, drew a reliable conclusion: shortening the tourniquet time can effectively reduce ischemia-reperfusion injury and the amounts of inflammatory factors, significantly decrease swelling and pain, promote functional exercise in the early stage, and speed up recovery. We acknowledge the detrimental effect of the tourniquet is time-dependent.30 Future research into optimal cuff pressure and optimal tourniquet time would determine the ideal individualized strategy for tourniquet use in TKA.

The main limitation of this study is that it failed to carry out long-term detection of inflammatory markers and postoperative rehabilitation process.

Currently, instead of discussing whether or not to use a tourniquet in TKA, we suggest refining the debate to focus on the acceptable duration of ischemia. Understanding the time-dependent influence of the tourniquet in TKA patients would improve the overall therapeutic outcome and safety.

Conclusion

This study suggests that reduced amounts of inflammatory factors, decreased limb swelling, less pain, and faster recovery during the early rehabilitation period are achieved with short-duration tourniquet use in the initial postoperative period. We believe that short-duration tourniquet use in TKA may be advantageous to patient recovery, without overt detrimental effects. However, optimal tourniquet time is required to clarify for tourniquet use in TKA.

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Author contributions

QC, NB, ZH, and JZ carried out the experiments. QC and YF analyzed the data and drafted the manuscript. TY collected the specimens. JZ, NB, and JM revised the manuscript critically for important intellectual content. QC, ZH, and YF are the first authors. All authors read and approved the final manuscript.

Availability of data and materials

The authors declare that the materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for noncommercial purposes, without breaching participant confidentiality.

Consent for publication

Written informed consent for publication of clinical details and images was obtained from all patients.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

Ethics approval was obtained from the Ethics Committee of Jinling Hospital Affiliated to the Medical College of Nanjing University (Clinical Trial Registration no. 2018NZKY-004-02, registered on March 13, 2018). All procedures involving human participants were in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki declaration and its amendments or comparable ethical standards. Written informed consent was obtained from all participants.

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