


# Effects of Tourniquet Application on Faster Recovery after Surgery and Ischemia-Reperfusion Post–Total Knee Arthroplasty, Cementation through Closure versus Full-Course and Nontourniquet Group

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J Knee Surg 2022;35:1577–1586.

## Abstract

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 faster recovery post-TKA. Our hypothesis was that inflammation and limb function would be similar with different tourniquet applications. A prospective randomized double-blinded trial assessed tourniquets effects on postoperative pain, swelling, and early outcome in TKA. In present study, 50 TKAs were enrolled in each group as follows: full course (FC), cementation through closure (CTC), and no tourniquet (NT), CTC as treatment group while FC and NT as control groups. Topical blood samples of 3 mL from the joint cavity and drainage bags were obtained at special time point. At last, all samples such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), C-C motif chemokine ligand 2 (CCL2), pentraxin 3 (PTX3), prostaglandin E2 (PGE2), superoxide dismutase 1 (SOD1), and myoglobin (Mb) were detected by ELISA. Active and passive range of motion (ROM) values, pain score by the visual analog scale (VAS), change of thigh circumference were recorded at special time point as well. In topical blood, the change of inflammatory factors, such as TNF- $\alpha$ , PTX3, CCL2, PGE2, SOD1, and Mb, was lower in CTC and NT groups than in FC group ( $p < 0.01$  and  $0.05$ ). Although VAS and ROM were comparable preoperatively in three groups ( $p > 0.05$ ), the perimeter growth rate was lower, pain scores (VAS) were reduced, and ROM values were improved in CTC and NT groups compared with FC group at T4, T5, and T6 postoperatively ( $p < 0.01$  and  $0.05$ ). Improved therapeutic outcome was observed in the CTC group, indicating patients should routinely undergo TKA with cementation through closure tourniquet application.

## Keywords

- ▶ tourniquet
- ▶ total knee arthroplasty
- ▶ swelling
- ▶ pain

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received  
August 10, 2018  
accepted after revision  
March 12, 2021  
article published online  
May 5, 2021

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Thieme Medical Publishers, Inc.,  
333 Seventh Avenue, 18th Floor,  
New York, NY 10001, USA

DOI <https://doi.org/10.1055/s-0041-1728814>.  
ISSN 1538-8506.

With advances in technology and instruments, total knee arthroplasty (TKA) is currently considered one of the most effective orthopaedic surgeries.<sup>1</sup> A tourniquet can provide a bloodless field of view for surgery, may help reduce intraoperative blood loss and improve cement penetration, and could also shorten the operation time. However, tourniquet use can be associated with postoperative swelling, joint stiffness, muscle injury or nerve dysfunction, and infrequent major nerve or vascular injury. Moreover, some studies found that the use of a tourniquet may increase postoperative hidden blood loss.<sup>2-9</sup>

The most common complications related to the use of tourniquet are seen in early postoperative period and therefore these may have short-term effects on the patient.<sup>10,11</sup> It was believed that tourniquet duration is a very important determinant of faster recovery after operation. There is still no consensus regarding the duration of its use during TKA. Our prospective randomized controlled trial (RCT) was aimed to evaluate the outcomes of short duration versus long duration and no tourniquet (NT) during TKA. We hypothesized that inflammation and limb function would be similar with different tourniquet applications. Others will take the information and decide if this will change how they use tourniquets.

## Patients and Methods

After obtaining institutional ethics committee approval and patient consent, 150 patients with unilateral knee osteoarthritis were randomized into three groups for TKA (50/group), CTC as treatment group while full course (FC) and NT as control 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 flow chart (►Fig. 1). The patient demographics showed no significant differences.

All patients underwent TKA by a single surgeon using a medial parapatellar approach and standardized technique using a cemented, fixed bearing, posterior cruciate-retaining prosthesis with patellar resurfacing and underwent general

anesthesia without regional blocks or local anesthesia in an effort to rule out confounding factors that may influence pain scores.

In present study, an above knee tourniquet (width, 10.5 cm; length, 65.5 cm; VBM Medizintechnik GmbH, Sulz, Germany) was used for patients in CTC or FC group and NT group during surgery. The tourniquet was inflated to 280 mm Hg just prior to initial skin incision in FC group and to 280 mm Hg immediately prior to mounting the cemented prosthesis in the CTC group. The tourniquet was deflated following wound closure and application of dressings, while NT applied throughout entire surgery for patients in the NT group. The average tourniquet duration and operation time were 37.5/70.2 minutes in CTC group, 66.4/66.4 minutes in FC group and 0/78.4 minutes in NT group.

Intra-articular drainage on low suction was performed prior to wound closure and removed on day 2 postoperatively. Topical blood samples of 3 mL from the joint cavity (T1) and drainage bags at T2, T3, and T5 in all cases were obtained. Plasma was separated by centrifugation at 3,000 rpm and 4°C for 10 minutes. Then, the supernatant was stored at -80°C for further analysis. Serum concentrations of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), C-C motif chemokine ligand 2 (CCL2), pentraxin 3 (PTX3), and prostaglandin E2 (PGE2) were measured with a specific human ELISA kit (Fcmacs, Nanjing, China). Superoxide dismutase 1 (SOD1) and myoglobin (Mb) were determined with another human ELISA kit (Jiangsu KeyGEN BioTECH Corp. Ltd.). All operations were performed according to the manufacturers' instructions.

The same standardized physiotherapy protocol was used in all patients postoperatively. Active and passive range of motion (ROM) values were evaluated. Pain score was measured by the visual analog scale (VAS). Change of thigh circumference was recorded using a measuring tape at 10 cm above the superior pole of the patella. VAS, ROM, and the change of thigh circumference were recorded before operation (T0) and at 12 hours (T4), 24 hours (T5), and 48 hours (T6) after tourniquet removal, respectively.

Electrocautery was used for hemostasis. Intraoperative blood loss was measured (volume in suction container amount of saline wash used) + (total weight of wet sponges used - total weight of dry sponges used) in all cases. Postoperative blood loss was determined from closed suction drain output. On the second postoperative day, hemoglobin assessment and of the knees were performed. The patients were mobilized on day 1 postoperatively and discharged when they were safe for independent ambulation. The primary outcome measures included inflammatory factors such as TNF- $\alpha$ , CCL2, PTX3, PGE2, SOD1, and Mb, as well as clinical function indicators such as VAS, ROM, and change of thigh circumference. Secondary outcome measures included blood loss, transfusion requirements, and hospitalization days. There were no complications directly related to tourniquet application in this study.

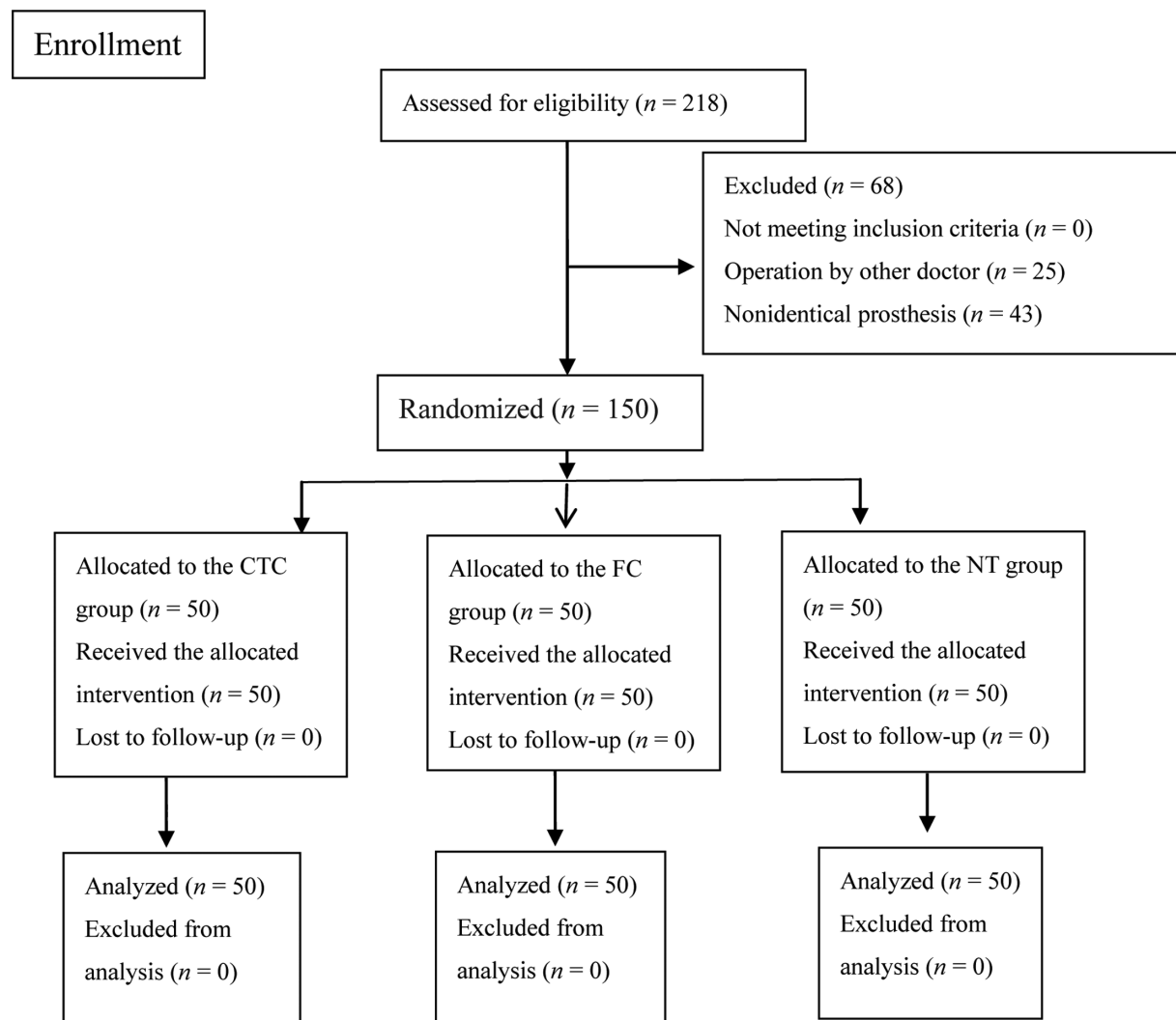
## Randomization

A surgeon not involved in the study removed slips from nontransparent sealed envelopes. The knees selected for surgery were randomly allocated to the CTC or FC or NT

**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 immunosuppression
50 years $\leq$ age $\leq$ 80 years	Any peripheral neurovascular disease
	Inflammatory arthritis, like rheumatoid arthritis

Abbreviations: IV, intravenous; OA, osteoarthritis; TKA, total knee arthroplasty.



**Fig. 1** Consolidated standards of reporting trials (CONSORT) flow diagram for the study. CTC, cementation through closure; FC, full course; NT, no tourniquet.

group (50/group). All eligibility criteria (► **Table 1**) were assessed and all patients were evaluated for 2 weeks, with no patients lost to follow-up.

### Blinding

Patients and the investigator collecting data were blinded during the procedure and postoperative follow-up.

### Statistical Analysis

Analysis of variance (ANOVA) and  $\chi^2$ -test were used for statistical analysis, and  $p < 0.05$  was considered statistically significant. The SPSS Statistics 21.0 software (SPSS, Chicago, IL) was used for data analysis.

### Results

Change in distal thigh circumference was compared in three groups. Between groups: CTC and FC ( $p = 0.026$  at T4,  $p < 0.01$  at T5, and  $p = 0.003$  at T6), NT, and FC ( $p = 0.014$  at T4,  $p < 0.01$  at T5, and  $p = 0.021$  at T6), while between CTC and

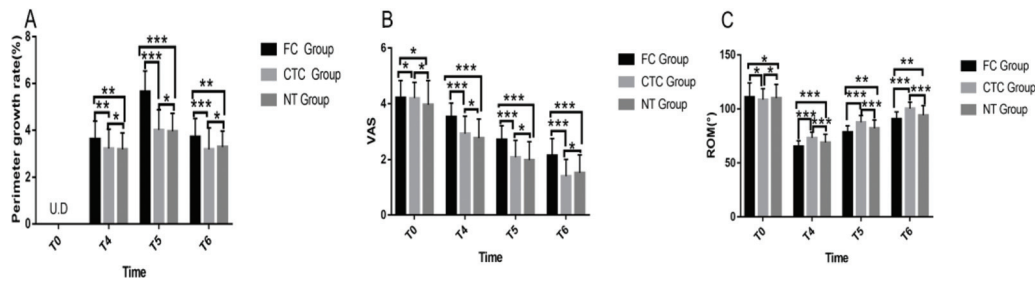
NT groups, there was no statistical difference ( $p > 0.05$  at T2, T3, and T4; ► **Fig. 2A**; ► **Table 2**).

Pain scores (VAS) were compared in three groups. Between groups: CTC and FC ( $p < 0.01$  at T4, T5, and T6), NT and FC ( $p < 0.01$  at T4, T5, and T6), CTC and NT ( $p > 0.05$  at T4, T5, and T6), while between groups: CTC and FC, NT and FC, NT and CTC ( $p > 0.05$  at T0; ► **Fig. 2B**; ► **Table 3**).

ROM values were compared in three groups. Between groups: CTC and FC ( $p < 0.01$  at T4, T5, and T6), NT and FC ( $p = 0.008$  at T4,  $p = 0.019$  at T5, and  $p = 0.03$  at T6), and CTC and NT ( $p = 0.002$  at T4,  $p < 0.01$  at T5 and T6), while there were no differences compared between the three groups at T0 ( $p > 0.05$ ; ► **Fig. 2C**; ► **Table 4**).

In topical blood, there were no significant differences statistically in TNF- $\alpha$ , PTX3, CCL2, SOD1, PGE2, and Mb amounts between the three groups at T1, respectively ( $p > 0.05$ , ► **Fig. 3**). However, there were statistically significant differences in the three groups at T2, T3, and T5.

TNF- $\alpha$ : between groups: CTC and FC ( $p < 0.01$  at T2, T3,  $p = 0.01$  at T5), NT and FC ( $p < 0.01$  at T2, T3, and T5), and CTC



**Fig. 2** (A) Perimeter growth rate, (B) VAS, and (C) ROM in FC group, CTC group, and NT group. Data are mean ± standard deviation (SD).  $> 0.05$   $0.01 \leq ** \leq 0.05$ ,  $*** < 0.01$ . CTC, cementation through closure; FC, full course; NT, no tourniquet; ROM, range of motion; VAS, visual analog scale.

**Table 2** Comparison of changes in distal thigh circumference

Group	Cases	T4	T5	T6
CTC group	50	3.22 ± 0.82	4.08 ± 0.86	3.19 ± 0.9
FC group	50	3.62 ± 0.77	5.65 ± 0.89	3.72 ± 0.31
NT group	50	3.19 ± 0.69	3.95 ± 0.77	3.28 ± 0.68
CTC vs. FC		$p = 0.026$	$p < 0.01$	$p = 0.003$
CTC vs. NT		$p = 0.633$	$p = 0.214$	$p = 0.351$
NT vs. FC		$p = 0.014$	$p < 0.01$	$p = 0.021$

Abbreviations: CTC, cementation through closure; FC, full course; NT, no tourniquet.

**Table 3** Comparison of pain scores (VAS)

Group	Cases	T4	T5	T6
CTC group	50	2.92 ± 0.63	2.08 ± 0.61	1.4 ± 0.61
FC group	50	3.52 ± 0.53	2.7 ± 0.51	2.14 ± 0.6
NT group	50	2.76 ± 0.69	1.98 ± 0.65	1.52 ± 0.65
CTC vs. FC		$p < 0.01$	$p < 0.01$	$p < 0.01$
CTC vs. NT		$p = 0.272$	$p = 0.146$	$p = 0.211$
NT vs. FC		$p < 0.01$	$p < 0.01$	$p < 0.01$

Abbreviations: CTC, cementation through closure; FC, full course; NT, no tourniquet; VAS, visual analog scale.

**Table 4** Comparison of ROM values

Group	Cases	T4	T5	T6
CTC group	50	73.26 ± 5.45	87.62 ± 6.19	100.32 ± 5.88
FC group	50	65.42 ± 5.25	78.44 ± 5.87	90.5 ± 6.31
NT group	50	68.78 ± 7.69	82.06 ± 7.71	94.22 ± 8.68
CTC vs. FC		$p < 0.01$	$p < 0.01$	$p < 0.01$
CTC vs. NT		$p = 0.002$	$p < 0.01$	$p < 0.01$
NT vs. FC		$p = 0.008$	$p = 0.019$	$p = 0.03$

Abbreviations: CTC, cementation through closure; FC, full course; NT, no tourniquet; ROM, range of motion.

and NT ( $p < 0.01$  at T2, T5,  $p = 0.311$  at T3; **►Fig. 3A**; **►Table 5**).

PTX3: between groups: CTC and FC ( $p = 0.021$  at T2,  $p < 0.01$  at T3, T5), NT and FC ( $p = 0.012$  at T2,  $p < 0.01$  at T3, T5), and CTC and NT ( $p > 0.05$  at T2, T3, and T5; **►Fig. 3B**; **►Table 6**).

CCL2: between groups: CTC and FC ( $p < 0.01$  at T2, T3, and T5), NT and FC ( $p < 0.01$  at T2, T3, and T5), and CTC and NT ( $p < 0.05$  at T2, T3, and T5; **►Fig. 3C**; **►Table 7**).

SOD1: between groups: CTC and FC ( $p < 0.01$  at T2, T3, and T5), NT and FC ( $p = 0.02$  at T2,  $p < 0.01$  at T3 and T5), and CTC and NT ( $p < 0.05$  at T2, T3, and T5; **►Fig. 3D**; **►Table 8**).

PGE2: between groups CTC and FC ( $p < 0.01$  at T2, T3, and T5), NT and FC ( $p < 0.01$  at T2, T3, and T5), and CTC and NT ( $p < 0.05$  at T2, T3, and T5; **►Fig. 3E**; **►Table 9**).

Myoglobin: between groups CTC and FC ( $p < 0.01$  at T2, T3, and T5), NT and FC ( $p < 0.01$  at T2, T3, and T5), and CTC and NT ( $p < 0.05$  at T2, T3, and T5; **►Fig. 3F**; **►Table 10**).

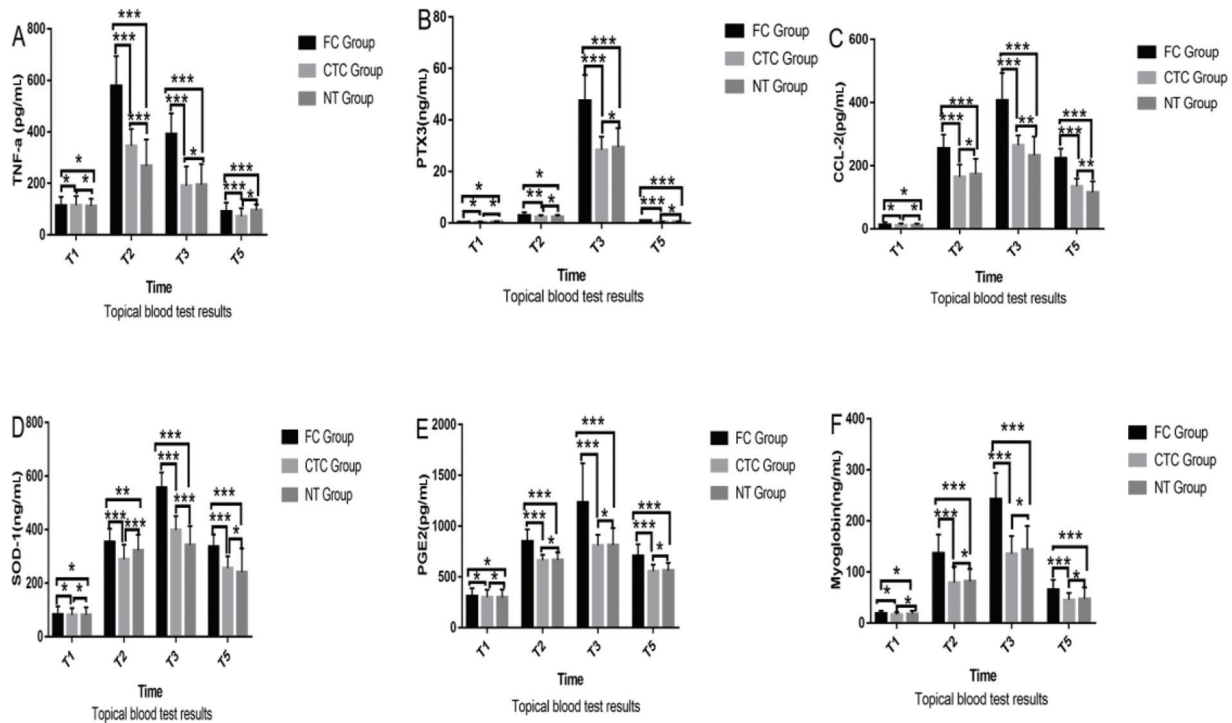
In addition, intraoperative blood loss between groups CTC and FC ( $p < 0.01$ ), CTC and NT ( $p < 0.01$ ), NT and FC ( $p < 0.01$ ). Postoperative blood loss between groups CTC and FC ( $p < 0.01$ ), CTC and NT ( $p < 0.01$ ). Total blood loss (intraoperative + postoperative) between groups CTC and NT ( $p < 0.01$ ) and NT and FC ( $p < 0.01$ ; **►Table 11**).

Blood transfusion, the threshold of postoperative blood transfusion was hemoglobin  $< 8$  g/dL. Five of 50 patients in FC group, 2 of 50 in CTC group, and 14 of 50 in NT group. Days to discharge between groups CTC and FC ( $p < 0.05$ ), CTC and NT ( $p < 0.05$ ), and NT and FC ( $p > 0.05$ ). There were no events of thromboembolism and deep vein thrombosis in every group (**►Table 12**).

## Discussion

It was believed that tourniquet duration is a very important determinant of faster recovery after operation. The most common complications related to the use of tourniquet are seen in early postoperative period and therefore these may have short-term effects on the patient.<sup>10,11</sup> There is still no consensus regarding the duration of its use during TKA.

Studies showed that patients who have had tourniquets applied have lower functional scores due to quadriceps weakness after surgery, as well as residual pain in the thigh.<sup>12-17</sup> Huang et al<sup>18</sup> demonstrated that using tourniquet full-time causes more excessive inflammation and muscle damage. Zhang et al<sup>19</sup> reported that the tourniquet use negatively affects the early postoperative rehabilitation as well. Therefore, in recent years, orthopaedic surgeons tend to perform operations without a tourniquet or only use one with a cement application.



**Fig. 3** (A–F) Topical blood data for FC group, CTC group, and NT group. Data are mean ± standard deviation (SD).  $p > 0.05$ ,  $0.01 \leq p \leq 0.05$ ,  $*** < 0.01$ . CCL1, C-C motif chemokine ligand 2; CTC, cementation through closure; FC, full course; NT, no tourniquet; PGE2, prostaglandin E-2; PTX3, pentraxin 3; SOD1, superoxide dismutase 1; TNF-a, tumor necrosis factor.

**Table 5** Comparison of TNF-a

Group	Cases	T2	T3	T5
CTC group	50	345.43 ± 65.59	190.95 ± 77.44	72.5 ± 31.2
FC group	50	578.63 ± 115.77	399.6 ± 80.71	90.12 ± 34.91
NT group	50	268.17 ± 63.31	195.5 ± 80.62	96.53 ± 21.68
CTC vs. FC		$p < 0.01$	$p < 0.01$	$p = 0.01$
CTC vs. NT		$p < 0.01$	$p = 0.311$	$p < 0.01$
NT vs. FC		$p < 0.01$	$p < 0.01$	$p < 0.01$

Abbreviations: CTC, cementation through closure; FC, full course; NT, no tourniquet; TNF-a, tumor necrosis factor-a.

**Table 6** Comparison of PTX3

Group	Cases	T2	T3	T5
CTC group	50	4.33 ± 0.51	28.42 ± 5.14	0.53 ± 0.12
FC group	50	5.87 ± 1.37	47.6 ± 9.71	0.94 ± 0.19
NT group	50	4.46 ± 0.73	29.45 ± 7.62	0.57 ± 0.17
CTC vs. FC		$p = 0.021$	$p < 0.01$	$p < 0.01$
CTC vs. NT		$p = 0.252$	$p = 0.263$	$p = 0.515$
NT vs. FC		$p = 0.012$	$p < 0.01$	$p < 0.01$

Abbreviations: CTC, cementation through closure; FC, full course; NT, no tourniquet; PTX3, pentraxin 3.

Stroh et al<sup>20</sup> found excellent clinical outcomes in TKA performed without a tourniquet and commented that the use of tourniquet negatively impacts patient outcome. Zhang et al<sup>21</sup> showed small benefits in the early postoperative period in their study in surgery done without tourniquet. Li et al<sup>22</sup> found that increased pain and swelling were found

in long duration tourniquet groups during the first postoperative week and the patients undergoing TKA without tourniquet achieved earlier straight-leg raising (SLR) and knee flexion. In our RCT, at T4, T5, and T6, change in distal thigh circumference was less in NT group than in FC group, the pain control was better in NT group than in FC

**Table 7** Comparison of CCL2

Group	Cases	T2	T3	T5
CTC group	50	164.9 ± 38.62	268.42 ± 31.43	135.33 ± 23.84
FC group	50	254.67 ± 44.14	406.92 ± 86.61	223.7 ± 30.48
NT group	50	176.32 ± 0.73	232.61 ± 60.11	115.52 ± 34.99
CTC vs. FC		$p < 0.01$	$p < 0.01$	$p < 0.01$
CTC vs. NT		$p = 0.048$	$p = 0.034$	$p = 0.004$
NT vs. FC		$p < 0.01$	$p < 0.01$	$p < 0.01$

Abbreviations: CCL2, G-C motif chemokine ligand 2; CTC, cementation through closure; FC, full course; NT, no tourniquet.

**Table 8** Comparison of SOD1

Group	Cases	T2	T3	T5
CTC group	50	288.72 ± 55.38	398.43 ± 52.87	256.27 ± 44.99
FC group	50	352.74 ± 50.75	556.42 ± 57.06	336.27 ± 46.08
NT group	50	322.91 ± 58.45	343.31 ± 70.23	240.9 ± 54.56
CTC vs. FC		$p < 0.01$	$p < 0.01$	$p < 0.01$
CTC vs. NT		$p = 0.006$	$p < 0.01$	$p = 0.044$
NT vs. FC		$p = 0.02$	$p < 0.01$	$p < 0.01$

Abbreviations: CTC, cementation through closure; FC, full course; NT, no tourniquet; SOD1, superoxide dismutase 1.

**Table 9** Comparison of PGE2

Group	Cases	T2	T3	T5
CTC group	50	662.43 ± 58.12	809.95 ± 105.78	555.9 ± 65.6
FC group	50	849.51 ± 118.84	1,234.98 ± 281.25	706.09 ± 116.48
NT group	50	666.42 ± 74.93	814.18 ± 168.91	562.06 ± 77.97
CTC vs. FC		$p < 0.01$	$p < 0.01$	$p < 0.01$
CTC vs. NT		$p = 0.731$	$p = 0.762$	$p = 0.644$
NT vs. FC		$p = 0.02$	$p < 0.01$	$p < 0.01$

Abbreviations: CTC, cementation through closure; FC, full course; NT, no tourniquet; PGE2, prostaglandin E2.

**Table 10** Comparison of myoglobin

Group	Cases	T2	T3	T5
CTC group	50	79.11 ± 31.52	135.93 ± 34.55	43.35 ± 13.79
FC group	50	136.37 ± 37.27	242.52 ± 51.64	65.35 ± 19.4
NT group	50	81.82 ± 24.27	144.15 ± 46.29	47.56 ± 22.14
CTC vs. FC		$p < 0.01$	$p < 0.01$	$p < 0.01$
CTC vs. NT		$p = 0.706$	$p = 0.362$	$p = 0.44$
NT vs. FC		$p = 0.02$	$p < 0.01$	$p < 0.01$

Abbreviations: CTC, cementation through closure; FC, full course; NT, no tourniquet.

group, the ROM values were better in NT group than in FC group. The result is consistent with the original conclusion (→ Fig. 2; → Tables 2,3,4).

The possible reason is the direct damage of the tourniquet and reperfusion injury that might increase pain that would hamper patients' postoperative rehabilitation.<sup>23</sup> And addi-

tional limb swelling in the long-duration tourniquet group after TKA might cause an increased weight in the affected limb that is sufficient to require more muscle strength for performing SLR. Furthermore, Dennis et al<sup>12</sup> indicated that patients who underwent TKA using a tourniquet had diminished quadriceps strength during the first 3 months after

**Table 11** Blood loss amounts (intraoperative, postoperative, and overall)

Blood loss (mL)	FC group (n = 50)	CTC group (n = 50)	NT group (n = 50)	p-Value
Intraoperative	266.4 ± 7.2	359.4 ± 14.5	429.4 ± 21.6	<0.01
Postoperative	285.3 ± 14.6	112.9 ± 10.1	209.5 ± 13.3	<0.01
Overall	551.7 ± 11.8	472.3 ± 10.3	638.9 ± 12.7	<0.01

Abbreviations: CTC, cementation through closure; FC, full course; NT, no tourniquet.

Note: Data are mean ± standard deviation.

**Table 12** Inpatient outcomes in CTC, FC, and NT groups

Parameter	FC group (n = 50)	CTC group (n = 50)	NT group (n = 50)	p-Value
Transfusion requirements	5	2	14	
Days to discharge	5.9 ± 2.4	3.7 ± 1.6	6.2 ± 2.3	FC vs. CTC (p = 0.043)
				CTC vs. NT (p = 0.03)
				FC vs. NT (p = 0.32)

Abbreviations: CTC, cementation through closure; FC, full course; NT, no tourniquet.

TKA. Early mobilization after TKA may be delayed in the patients with quadriceps weakness.

Interestingly, the current study showed better outcome following TKA in CTC group than in FC group, even better in terms of ROM than in NT group, although VAS and change in distal thigh circumference were comparable in CTC group and in NT group ( $p > 0.05$ ). Fan et al<sup>24</sup> also discovered the limited use of a tourniquet in TKA that provides the benefit of decreased limb swelling and better active knee flexion while not compromising the operation time or blood loss and recovery. It therefore seems to be highly desirable to keep the duration of tourniquet to a minimum.<sup>25–28</sup> The tourniquet application only during cementation may be considered superior, since it hardly influences the functional recovery after TKA.

Some researchers wanted to gather reliable evidence by integrating high-quality clinical trial data. However, their results were not convincing, because the reported influence of the use of tourniquet on the functional outcomes after TKA is variable. Therefore, we assessed several highly objective inflammatory factors such as TNF- $\alpha$ , PTX3, CCL2, SOD1, Mb, and PGE2. Because TNF- $\alpha$ , CCL2, interleukin (IL)-6, PTX3, SOD1, PGE2, and Mb, as test indicators, can reflect oxidative stress, inflammatory response, and tissue necrosis<sup>12,29–31</sup>; they are related to quadriceps muscle injury, wound complications, neurovascular injury, swelling and bruising, hidden blood loss, and deep venous thrombosis. No previous studies have assessed the effects of tourniquet application on these inflammatory factors, so the present study not only assessed functional outcomes, but also 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.

In topical blood, there were no significant differences statistically in TNF- $\alpha$ , PTX3, CCL2, SOD1, PGE2, and Mb amounts in the three groups at T1, respectively ( $p > 0.05$ ,

► **Fig. 3**). However, the change was lower in CTC and NT groups than in FC group at T2, T3, and T5 (► **Fig. 3**; ► **Table 3**), confirming that longer tourniquet duration causes much greater inflammation than shorter tourniquet duration and NT in local tissue. A significant finding of the present study was that inflammatory factors in topical tissue, such as TNF- $\alpha$ , PTX3, CCL2, PGE2, SOD1, and Mb, were in positive correlation with tourniquet duration, postoperative early function was related to tourniquet duration as well. The tourniquet, therefore, appears to be a significant source of postoperative pain, swelling, and reduction of ROM. After 24 hours of reperfusion, all inflammatory factors decreased in topical samples. these amounts were closer to preoperative levels in CTC and NT group than those in FC group, suggesting that inflammatory reactions and cell damage are reversible; the shorter the tourniquet duration, the faster the recovery.

In the present trial, the short-duration tourniquet and NT groups were associated with better clinical outcomes, less pain, and reduced limb swelling during the early stage of rehabilitation (► **Fig. 2**; ► **Table 2**). Similar results were reported by Zhang et al<sup>19</sup> and Ejaz et al.<sup>32</sup> A possible explanation is that longer tourniquet use results in more pronounced oxidative stress, inflammatory response, and tissue necrosis. TNF- $\alpha$ , CCL2, IL-6, PTX3, SOD1, PGE2, Mb, and other proinflammatory 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.<sup>33–40</sup> Enhanced swelling also increases soft-tissue tension; additional swelling may hinder the patient's early postoperative rehabilitation exercises. Furthermore, as Dennis et al<sup>12</sup> 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.<sup>23</sup> 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 proinflammatory cytokines and chemokines which can break the balance between proinflammatory 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.<sup>12,33–40</sup>

However, between CTC and NT groups, in term of PTX3, PGE2, and Mb, there was no statistical difference. Surprisingly, in term of TNF- $\alpha$ , CCL2, SOD1, better results were observed in CTC group compared with NT group. The results showed that it is not the best without tourniquets, but reasonable application of tourniquet can achieve the best results in TKA.

Besides, in our RCT, intraoperative blood loss was CTC versus FC versus NT ( $p < 0.01$ ), postoperative blood loss was CTC versus FC versus NT ( $p < 0.01$ ), and total blood loss was CTC versus FC versus NT ( $p < 0.01$ ; ► **Table 11**). Blood transfusion was as follows: 5 of 50 patients in FC group, 2 of 50 patients in CTC group, and 14 of 50 patients in NT group. Days to discharge were as follows: CTC versus FC ( $p < 0.05$ ), CTC versus NT ( $p < 0.05$ ), and NT versus FC ( $p > 0.05$ ; ► **Table 12**).

Compared with the other two groups, FC group has the least intraoperative blood loss and the most postoperative blood loss (► **Table 11**). This finding is in line with the findings of many other previous authors. Due to compression of vessels of lower limb by tourniquet, the blood flow distal to tourniquet is reduced, and therefore the blood loss is lesser. It was believed that with the use of tourniquet, a bloodless operating field is created which helps in better visualization and requires less operative time. However, once the tourniquet is deflated at the end of the procedure, there is a reactionary increase in the blood flow to that limb, due to which there is comparatively more blood loss in the drain in long-duration tourniquet group, as compared with short-duration and NT group.

CTC group has the least postoperative and total blood loss, with the use of tourniquet, a bloodless operating field is created which helps in better visualization and requires less operative time, while not increasing the number of transfusion and operation time. In addition, compared with long-duration tourniquet application, the limited use of a tourniquet results in less knee pain, less time needed to achieve SLR, and less minor complications following TKA. Correspondingly, the functional recovery seems to be faster during the early rehabilitation period and the hospital stay period was significantly reduced.

NT group has the most intraoperative and total blood loss, a bloodless operating field made worse visualization and requires more operative time, besides increasing the number of transfusion and extending hospital stay.

By comparing with each other group, the present study, through a combination of inflammatory marker changes in blood and clinical manifestations drew a reliable conclusion: patients in CTC group have more advantages than in FC group and in NT group for faster recovery postoperatively. Reasonable application of tourniquet can effectively reduce ischemia-reperfusion injury and the amounts of inflammatory factors, can significantly decrease swelling and pain, can promote functional exercise in the early stage, and can speed up recovery.

We acknowledge that the detrimental effect of the tourniquet is time dependent,<sup>6</sup> there are still controversies on the optimal timing of tourniquet application. 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 tourniquet. Future research into optimal tourniquet time would determine the ideal individualized strategy for tourniquet use in TKA, understanding the time-dependent influence of the tourniquet in TKA patients would improve the overall therapeutic outcome and safety.

## Limitations

The main limitation of this study is that it failed to carry out long-term detection of inflammatory markers and postoperative rehabilitation process. Further, large well-designed RCTs with extensive follow-up are still needed to validate this research.

## Conclusion

Reduced amounts of inflammatory factors, decreased limb swelling, less pain, and faster recovery were achieved with short-duration tourniquet use in the initial postoperative rehabilitation period which have showed that short-duration tourniquet use in TKA may be advantageous to patient recovery, without overt detrimental effects. However, optimal tourniquet time are required to clarify for tourniquet use in TKA.

### Availability of Data and Materials

We 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 non-commercial purposes, without breaching participant confidentiality.

### Authors' Contributions

Q.C., N.B., Z.H., and J.Z. performed the experiments. Q.C. and Y.L. analyzed the data and drafted the manuscript. Q.W. collected the specimens. J.Z., N.B., and J.M. revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

### Ethical Approval

Ethics Committee of Jinling Hospital Affiliated to the Medical College of Nanjing University; Clinical Trial Registration number 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.

### Funding

This work was supported by the Natural Science Foundation of Jiangsu Province of China (no.: BK20161385), and Social Development-General Program of Science and



Technology Department of Jiangsu Province (no.: BE2015686).

#### Conflict of Interest

None declared.

#### Acknowledgments

The authors would like to thank all the participants in this study.

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