

The Effect of Tourniquet Application on the Morphology and Function of Quadriceps in Patients Undergoing Total Knee Arthroplasty: A Study Protocol for a Single Blind Randomized Controlled Trial

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Abstract

Background:

Tourniquet is currently widely used in total knee arthroplasty to reduce intraoperative blood loss. Academic view of tourniquet application in TKA is now in dispute. Some scholars argue that tourniquet may cause quadriceps injury and bring extra side effects so they oppose the application of tourniquet. Others find that tourniquet application has no significant adverse impact on TKA patients. Regarding its advantages in reducing intraoperative blood loss, they advocate regular application of tourniquet in TKA. Quadriceps injury is considered the main cause of tourniquet side effects. There are now many high-quality trials about tourniquet application in TKA but few of them concentrate on quadriceps morphology and function.

Methods:

A prospective, single blind, randomized controlled trial will be adopted. The target sample is 130. Patients who meet the eligibility criteria will be randomly allocated to tourniquet group and non-tourniquet group. Primary outcomes are thickness, stiffness and function of quadriceps, which will be evaluated by ultrasound and rehabilitation tests. Secondary outcomes consist of circumference of thigh, VAS score, opioid consumption, knee function score, postoperative satisfaction score, operation time, intraoperative blood loss, perioperative blood loss, blood transfusion rate, D-Dimer, C-reactive protein, and complications.

Discussion:

This proposed study will contribute to improve evidence of tourniquet application in total knee arthroplasty. This will be a high-quality single blind randomized controlled trial with sufficient sample size and strict study design. It will investigate the effects of tourniquet application especially on the morphology and function of quadriceps in patients undergoing total knee arthroplasty and offer advice for tourniquet application in clinical practice.

Trial registration:

Chinese clinical trial registry, ChiCTR2000035097. Registered 31 July 2020,
<http://www.chictr.org.cn/showproj.aspx?proj=57093>

1. Background

Total Knee Arthroplasty (TKA) is currently considered the optimal treatment of severe knee osteoarthritis^[1, 2]. Intraoperative and perioperative blood loss is quite considerable in TKA because a lot of osteotomy and soft tissue release is required. In order to decrease intraoperative blood loss and create a bloodless surgical field, tourniquet is now widely used in TKA^[3, 4]. Its hemostasis function is accomplished by squeezing quadriceps to close lower limb vessels.

However, some scholars argue that tourniquet may have ischemia reperfusion damage to quadriceps^[5, 6]. They find that tourniquet have no significant impact on decreasing perioperative blood loss but bring certain side effects such as pain, swelling and deep vein thrombosis for TKA patients^[5, 7], so they advocate to reduce or even avoid tourniquet application in TKA. Rames et al^[8] recently published results from their retrospective study, which showed that patients without tourniquet had less narcotic consumption and increased distance ambulated prior to discharge. Dong et al^[9] showed less pain and larger range of motion in patients without tourniquet. A meta-analysis conducted by Liu et al^[10] also found that the absence of tourniquet could significantly reduce postoperative pain and complication rate, and therefore, beneficial to Enhanced Recovery after Surgery (ERAS).

To contrast, other scholars hold an opposite idea. Their studies find that tourniquet have no significant impact on postoperative outcomes in TKA patients^[4, 11, 12]. Considering the bloodless surgical field and shorter operation time, they propose regular application of tourniquet in TKA. Nicolaiciuc et al^[11] found in a retrospective study that there was no significant difference in pain, narcotic consumption and range of motion caused by tourniquet application. Furthermore, Jawhar et al^[13] conducted a randomized controlled trial. They introduced the method of a rope pulley isokinetic system and showed that tourniquet had little influence on quadriceps strength and function, patient satisfaction as well as physical condition. McCarthy et al^[4] also found there was no significant difference in pain, range of motion, and average length of stay for TKA patients with or without tourniquet.

Above all, there is no consensus on tourniquet application in TKA and tourniquet related side effects are considered relevant to quadriceps injury^[14]. Therefore, we design this perspective single blind randomized controlled trial to focus on tourniquet impact on quadriceps. With the assistance of ultrasonic and rehabilitation tests, we aim to evaluate tourniquet impact of quadriceps morphology and function, pain, morphine equivalence, blood loss, limb swelling, operation time, knee function and complications for TKA patients and offer advice for clinical practice.

2. Methods

2.1 Study Design

This study is a clinical randomized controlled trial of estimated 130 patients with knee osteoarthritis undergoing TKA in Peking University Third Hospital. All patients are divided into tourniquet group and non-tourniquet group (65 patients each). Tourniquet is applied throughout the surgery in tourniquet group while in non-tourniquet group, tourniquet is tied up but won't be inflated. The trial compares outcomes of TKA with or without tourniquet. Single binding is performed in this trial which means that the patient doesn't know whether the tourniquet is used in their surgery.

We assume three primary hypotheses of this trial. First, intraoperative blood loss in tourniquet group is less than that in non-tourniquet group (superiority study). Second, quadriceps thickness in tourniquet

group is not less than that in non-tourniquet group (non-inferiority study). Third, centrifugal force of knee extending in tourniquet group is not less than that in non-tourniquet group (non-inferiority study).

2.2 Eligibility Criteria and Recruitment

The inclusion criteria for this trial are as follows:

(1) patients with primary knee osteoarthritis; (2) planning to operate unilateral primary total knee arthroplasty.

The exclusion criteria are as follows:

(1) severe varus or valgus deformity of the knee; (2) Previous long-term consumption of anticoagulant drugs or complicated with the following diseases: renal insufficiency ($Cr > 2.5$), liver dysfunction, severe heart disease (or coronary stenting in the late 12 months), severe respiratory system diseases, previous venous thromboembolism history or high-risk of thrombosis (genetic or acquired thrombosis diseases), blood coagulation dysfunction, the acquired thrombotic diseases), blood coagulation dysfunction, stroke or malignant tumor history; (3) patients who refuse to sign the informed consent for any reason.

According to the eligibility criteria, a sample of 130 patients is included in this single-center trial.

2.3 Allocation and Randomization

All participants who met the study inclusion and exclusion criteria are randomly assigned in a 1:1 ratio to the tourniquet and non-tourniquet groups respectively. Random sequence was computer-generated in permuted blocks of 4 participants, which was generated by the SAS software 9.4 (SAS Inc., Cary, N.C., USA). The electronic data capture system automatically generates participant identification numbers in sequence at baseline, which are subsequently linked to tourniquet assignments at randomization.

2.4 Trial registration, Ethics review and informed consent

The trial is registered at Chinese clinical trial registry (Registration number: ChiCTR2000035097).

The trial is also registered in Peking University Third Hospital Medical Science Research Ethics Committee (Registration number: M2020290). All the intended benefits and risks of tourniquet use are explained to every patient. All the patients sign the informed consent before the trial. The trial is conducted with the Declaration of Helsinki.

2.5 Baseline Procedures

All patients are operated by the same surgeon. This surgeon has more than 15 years of TKA experience including non-tourniquet TKA and operates at least 300 TKAs per year. All the surgeries are operated by conventional tools without PSI, CAS or robot. Medial patellar skin incision, medial parapatellar arthrotomy and measured resection are adopted in all patients. Patella is resurfaced and denervated by hand saw instead of patella replacement. Posterior stabilized cementless implants (Legion from Smith and Nephew, Triathlon from Stryker Orthopedics) are selected.

Perioperative treatments are the same in both groups. Patients all receive intraspinal anesthesia or general anesthesia along with controlled hypotension which is defined as a reduction of the systolic blood pressure to less than 90mmHg and a reduction of mean arterial pressure (MAP) to less than 65mmHg or a 30–40% reduction of baseline MAP. Before the surgery, all the patients receive a single time femoral nerve block instead of continuous femoral nerve block to reduce postoperative pain. Tranexamic acid is used before skin cutting (1g ivgtt) and before skin suture (1g ivgtt). Thromboprophylaxis is done with sodium enoxyparin, 4000 IU per day, starting the same day of surgery. After the surgery, no femoral block tube or drainage tube is reserved. Compression of elastic bandage to the surgery limb after suture (removed 24h after surgery), active and passive ankle pump training (start immediately after surgery) are adopted in both groups. No patients use continuous passive motion machine. Patients stay in a rest position with the knee in full extension and 36–48 hours after surgery, they start active and passive rehabilitation training guided by surgeons and nurses (local ice compress for 15min after each training). The standard plan of postoperative analgesia is also the same. Flurbiprofen Axetil (100mg bid ivgtt) is regularly used for all patients for 2days after surgery (patients with sulfonamides allergy use Parecoxib Sodium 40mg bid ivgtt). If pain control is not satisfying, tramadol or oxycodone (1 tablet once, po) will be used.

2.6 Intervention

Tourniquet is tied to patients in both groups after anesthesia so that tourniquet application is blind to patients. Tourniquet in tourniquet group is inflated to a pressure of 150 mmHg higher than patient's systolic pressure throughout the surgery (from skin cutting to skin suture). Tourniquet in non-tourniquet group won't be inflated.

2.7 Outcomes and Measures

2.7.1 Preoperative measurements

Demographic information of all the patients are collected, including gender, age, height, weight and BMI. Baseline outcomes including quadriceps thickness and stiffness, thigh circumference, knee function scores, hematocrit and hemoglobin level, D-Dimer and C-reactive protein level in serum are evaluated before surgery but after randomization and allocation.

2.7.2 Primary outcomes

2.7.2.1 Quadriceps thickness and stiffness

Bilateral lower extremity ultrasonography is performed before surgery and 3 days after surgery to detect the occurrence of venous thrombosis. The thickness and stiffness of quadriceps muscle are determined simultaneously.

The inspection is performed by a Canon Apilio I900 ultrasound with L18-5 probe. The probe is placed vertically on the body surface without compressing. The maximum distance from the front to the back of

the quadriceps on the horizontal cross-section is selected as the quadriceps thickness, meanwhile, muscle echo and texture are observed. With the method of shear wave elastography (SWE), the muscle shear wave propagation velocity (m/s) along the long and short axis in the same section is measured 5 times and its median is taken as quadriceps stiffness. All the ultrasound measurements are conducted by the same ultrasound examiner.

2.7.2.2 Quadriceps function

It is difficult for end-osteoarthritis patients to accomplish tests of quadriceps function. Therefore, quadriceps function was assessed at 6 weeks postoperatively. 3 tests including isokinetic muscle strength testing, three-dimensional gait analysis (3DGA), and posture stability testing are selected.

☒ Isokinetic muscle strength test

The quadriceps muscle strength is evaluated using BIODEX's multi-joint isometric training test system. All patients are tested by the same therapist to reduce operator bias in the trial. The instrument shall be systematically calibrated before the test, and the patients shall be informed of the methods and requirements of isometric test, but no warm-up exercises is performed. The non-operative limb is tested first to obtain basic reference data, and then the operative limb. Outcomes include peak torque, peak torque/weight ratio, peak torque angle, total work, average power, etc.

☒ Three-dimensional gait analysis

SMART-D 400 3D gait analysis system is used. Patients are asked to make 6 round trips with a natural gait, and Smart Analyzer software issued to calculate the spatial and temporal parameters and ankle kinematics parameters. Outcomes include stride time, standing time, swinging time, standing phase, swinging phase, leg support phase, stride length, step length, step speed, stride frequency, and angle change of hip, knee and ankle when walking.

☒ Posture stability testing

Active Balancer EAB-100 is used for testing. 4 static postures in different standing conditions are included. T1: Standing on a hard plate with eyes open; T2: Standing on a hard plate with eyes closed; T3: Standing on a sponge pad with eyes open; T4: Standing on the sponge with eyes closed. Test time for each condition is 30s, and there is a rest of 3min (sitting position) in two test intervals. The real-time movement of the center of plantar pressure are recorded, and the parameters related to its movement is analyzed by professional software. Outcomes include the total track length and average velocity of the displacement of plantar pressure center.

2.7.3 Secondary outcomes

We choose several secondary outcomes to evaluate tourniquet effects as supplements, including thigh circumference, VAS score, morphine equivalent, knee function score, postoperative satisfaction score,

operation time, blood loss, transfusion rate, D-Dimer and C-reactive protein level in serum, and complications.

The circumference of the upper third of the affected thigh is measured with a tape 1 day before surgery as well as 1 day and 3 days after surgery, with an accuracy of 0.1cm. The swelling degree of quadriceps can be reflected by comparing the circumference in two groups preoperatively and postoperatively.

VAS scores of thigh and knee are separately evaluated at 1 day, 3 days, 2 weeks and 6 weeks after surgery. Visual analogue Scale is widely used in clinical practice to assess pain in affected limb^[15-17]. Opioid consumption (in morphine equivalence) in 3 days after surgery is also recorded to further evaluate postoperative pain.

The knee function score KSS (Knee Society Score) and WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) are also evaluated before surgery as well as 3 months and 1 year after surgery. Both of the scores are widely used knee function scores worldwide. Their validity and reliability have been verified many times^[18-23].

Postoperative satisfaction score is recorded 3 months and 1 year after surgery. It ranges from 1 to 5 points to reflect patients' satisfaction rate of surgery and recovery. (1 = very dissatisfied, 2 = not satisfied, 3 = neutral, 4 = satisfied, 5 = very satisfied)

Operation time, which also means tourniquet application time, is evaluated as well. It is defined as the time from skin cutting to the skin suture, and it is accurate to minutes.

Intraoperative blood loss and postoperative blood loss (3 days after surgery) are also evaluated in this trial. Hematocrit level is tested before surgery and 3 days after surgery. Calculating methods are as follows: Intraoperative blood loss = intraoperative fluid intake volume + intraoperative irrigation volume + gauze infiltration volume (ml); Postoperative blood loss = total blood loss - intraoperative blood loss; Total blood loss is calculated by Gross linear equation^[24]: preoperative blood volume (PBV) × (preoperative Hct - postoperative Hct); Preoperative blood volume is calculated by Nadler equation^[25]: $PBV = K1 \times \text{height (m)}^3 + K2 \times \text{weight (kg)} + K3$ (for male: $K1 = 0.3669$, $K2 = 0.03219$, $K3 = 0.6041$; for female, $K1 = 0.3561$, $K2 = 0.03308$, $K3 = 0.1833$).

Blood transfusion and transfusion volume after surgery is recorded, and blood transfusion rate is calculated in 1 day, 3 days, and 2 weeks after surgery. Hemoglobin level is tested before surgery as well as 1 day and 3 days after surgery. Blood transfusion is done only if Hb level is lower than 70g/L, or Hb level is between 70g/L and 90g/L with symptoms of anemia like weakness and palpitations. The standard transfusion solution is 400ml of suspended erythrocyte each time, with a reexamination of blood routine on the second morning.

In addition, D-Dimer and C-reactive protein (CRP) level in serum is tested before surgery as well as 1 day and 3 days after surgery to reflect ischemia reperfusion injury and inflammatory reaction. Complications

of patients in both groups such as deep vein thrombosis, hematoma and anemia are recorded at 2 weeks, 6 weeks, 3 months, and 12 months after surgery.

2.8 Follow-up

Participants are followed up via study questionnaires at 2 weeks, 6 weeks, 3 months, and 12 months after surgery. In 2-week follow-up, the wound recovery, complications, blood transfusion volume and VAS score of the affected limb are recorded. In 6-week follow-up, quadriceps function is evaluated, including isokinetic muscle strength testing, three-dimensional gait analysis, and posture stability testing. In 3 and 12 months after surgery, knee X-ray examination is applied and complications, KSS score, WOMAC scores and postoperative satisfaction score are recorded.

2.9 Data Collection and Management

All the data should be collected timely, correctly and completely in the case report form. The stiffness and thickness of the quadriceps muscle is collected by ultrasound researchers. The isokinetic muscle strength tests, three-dimensional gait test, and balanced postures test are collected by rehabilitation medicine researchers. The rest of the outcomes are collected by Orthopaedics researchers. All the data is stored in the database and processed by Microsoft Excel®.

2.10 Statistical Analysis

The statistician who conducted the analysis is blinded to group allocation. Summary statistics are used to describe the participant characteristics of the trial groups at baseline in the intention-to-treat (ITT) analysis set. The missing data of quadriceps thickness and stiffness is imputed by the multiple imputation method. The results of multiple imputation data are used as a type of sensitivity analysis for comparing primary outcomes between groups.

For primary outcomes comparison, the ITT analysis is performed to evaluate differences between groups, and effective analysis population (EAP) and per-protocol (PP) analyses are also performed for sensitivity assessment. The primary outcomes do not follow the Gaussian distribution and are presented as median (IQR) and tested by the Mann-Whitney U test. Bonferroni correction is used to reduce the significance level. The means (95% CIs) of between-group differences of medians are calculated by the bootstrap method (1000replications). The generalized linear mixed models (GLMM) are also performed for the primary endpoint, including group, gender, age, height and weight as fixed covariates.

For comparing the secondary and exploratory endpoints, continuous data are presented as means (SDs) or medians (IQRs) as appropriate. The secondary endpoints are analyzed by the linear mixed model (LMM), adjusted for gender, age, height, weight and other covariates. The correlation type of different measurement time points is assumed as the first order autocorrelation in the LMM. Exploratory endpoints are compared by the Mann-Whitney U test, and the significance level is submitted to Bonferroni correction.

For safety endpoints, categorical data are presented as counts and percentages, and tested by the Pearson's Chi-square test or Fisher's exact test. The 95% CIs of absolute risk differences between groups are calculated by the Newcombe-Wilson Score method. All statistical analyses are conducted with the statistical package SPSS, V.18.0 (SPSS Inc) and R 3.4.0 software. Besides Bonferroni correction, statistical significance is defined as $p < 0.05$ with two-sided testing.

2.11 Pilot Study

A pilot study has already been conducted. We enrolled 10 knees with primary osteoarthritis undergoing. 5 knees were operated with tourniquet, and the other 5 knees were operated without tourniquet. Postoperative swelling, VAS score, quadriceps morphology and function were recorded. Finally, the pilot study found that there was no significant difference in these outcomes between two sides, indicating that tourniquet might not cause severe quadriceps injury.

2.12 Sample Size Consideration

We assume three primary hypotheses of this trial based on our previous pilot study.

First, intraoperative blood loss in tourniquet group is less than that in non-tourniquet group. Intraoperative blood loss is 64.6 ± 22.5 ml in non-tourniquet group and 6.6 ± 2.8 ml in tourniquet group. Superiority margin (σ) is 6.64ml, which is 10% of the average intraoperative blood loss in non-tourniquet group. We apply superiority test by PASS14 and find that we need at least 14 participants in each group. ($\sigma = 6.46$ ml, $\alpha = 0.0000025$, $\beta = 0.2$)

Second, quadriceps thickness in tourniquet group is not less than that in non-tourniquet group. Quadriceps thickness is 3.1 ± 0.5 cm in non-tourniquet group and 3.1 ± 0.6 cm in tourniquet group. Non-inferiority margin (σ) is 0.31cm, which is 10% of the average quadriceps thickness in non-tourniquet group. We apply non-inferiority test by PASS14 and find that we need at least 58 participants in each group. ($\sigma = 0.31$ cm, $\alpha = 0.0000025$, $\beta = 0.2$)

Third, centrifugal force of knee extending in tourniquet group is not less than that in non-tourniquet group. Centrifugal force of knee extending is 202 ± 9 N in non-tourniquet group and 217 ± 8 N in tourniquet group. Inferiority margin (σ) is 20.2N, which is 10% of the average centrifugal force of knee extending. We apply non-inferiority test by PASS14 and find that we need at least 59 participants in each group. ($\sigma = 20.2$ N, $\alpha = 0.0000025$, $\beta = 0.2$)

Above all, we determine that a total of 59 participants per group would have an 80% statistical power in detecting tourniquet impact between two groups. This will result in a total of 118 participants. Estimating that 10% of participants would drop out, a sample size of 130 participants is considered to be adequate for this study. Details of sample size estimation is shown in Table 1.

3. Discussion

Tourniquet is now widely used in TKA, but its latent adverse effects are problems that we cannot neglect. Some researchers recommend regular tourniquet application in TKA because of its advantage in reducing intraoperative blood loss and operation time. Other researchers hold an opposite idea. They believe that tourniquet application has obvious damage to quadriceps and extra side effects such as pain, swelling and blood loss, which may go against patients' enhanced recovery after surgery (ERAS), so they resist using tourniquet in TKA. After years of studies including meta-analysis and randomized controlled trials, tourniquet application in TKA is still in dispute.

Tourniquet effects on quadriceps morphology and function is controversial. It is generally considered that tourniquet does have certain damage to quadriceps but how bad it can be and what effects it will have on patients are confusing. Leurcharusmee et al^[6] hold the point that tourniquet application can cause ischemia reperfusion injury to quadriceps, which leads to the release of both oxygen free radicals and inflammatory cytokines. Dennis et al^[26] found in a prospective trial that tourniquet application can reduce quadriceps strength in 3 months after surgery. Guler et al^[27] found that tourniquet use in TKA can decrease the thigh and quadriceps muscle volumes. However, Jawhar et al^[13] reported that tourniquet has no significant effects on quadriceps strength and function. Ayik et al^[28] also reported that avoiding tourniquet cannot improve quadriceps strength after TKA. It is obvious that more studies about quadriceps morphology and function are needed.

It is generally considered that tourniquet application can significantly reduce intraoperative blood loss, but its effects on total blood loss is not explicit. Zhao et al^[29] found out in a randomized controlled trial that tourniquet application may increase hidden blood loss and total blood loss. However, Liu et al^[10] conducted a meta-analysis and found that tourniquet has no significant effects on total blood loss. Herndon et al^[3] hold another idea that tourniquet may reduce total blood loss but has no effects on postoperative blood transfusion rate.

Postoperative pain is an important outcome for TKA patients. It can be evaluated by VAS score as well as opioid consumption. Tourniquet effects on postoperative pain is also controversial. Liu et al^[7] hold the point that tourniquet application can increase postoperative pain, which may be caused by ischemia reperfusion injury and the release of cytokines. Ajnin et al^[30] and Dong et al^[9] both reported that not using tourniquet in TKA can reduce patient's postoperative pain and beneficial to their recovery. While a randomized controlled trial conducted by McCarthy et al^[4] reported that tourniquet application had no significant effect on thigh pain. Palanne et al^[31] also reported that tourniquet application could not affect pain management and postoperative opioid consumption.

Lower limb swelling is also related to postoperative recovery. It can be measured by circumference of thigh. Tourniquet effects is still disputable in respect of swelling. Ajnin et al^[30] and Wang et al^[32] both reported that patients without tourniquet application showed less lower limb swelling. However, Alexandersson et al^[33] reported that tourniquet application had no significant effects on limb swelling.

Postoperative inflammation process is also in association with tourniquet application. It can be reflected by CRP level in blood. A randomized controlled trial conducted by Cao^[34] reported an increase in inflammatory mediators in tourniquet application such as TNF- α , PTX3, CCL2, PGE-2 and SOD-1 and its degree of elevation is positively correlated with the tourniquet time, which is considered relative to ischemia reperfusion injury caused by tourniquet. Zhao et al^[29] also reported that the absence of tourniquet application could reduce postoperative inflammation process.

Above all, there is still no consensus on tourniquet effects on quadriceps morphology and function, blood loss, postoperative pain, lower limb swelling and other outcomes for patients undergoing TKA. Tourniquet-related side effects are mainly about quadriceps injuries, so we decide to concentrate ourselves on tourniquet effects on quadriceps morphology and function and design this single blind randomized controlled trial to offer advice for tourniquet application in clinical practice.

In this study, quadriceps thickness and stiffness are essential primary outcomes. These indicators can effectively reflect quadriceps morphology after tourniquet application. Quadriceps thickness is measured by ultrasound test. Innovatively, we use shear wave elastography (SWE) to evaluate quadriceps stiffness. SWE is an evolving ultrasound technique which is progressively used in musculoskeletal system to evaluate tissue elasticity^[35-37]. It is reported to evaluate the stiffness of soft tissues such as quadriceps tendon or medial collateral ligament in healthy people^[38, 39], but it has never been used to assess quadriceps stiffness of patients undergoing TKA. Shear waves propagate faster through stiffer tissue so we decide to measure shear wave velocity along the long and short axis of quadriceps to represent quadriceps stiffness^[40, 41]. Additionally, we include three tests of rehabilitation department. Isokinetic muscle strength proved to be valid in assessment of muscle function in TKA^[42, 43]. Three-dimensional gait analysis is a useful clinical test to evaluate gait abnormality which can be captured by cameras placed around a walkway^[44]. Posture stability testing is also used in our study to monitor displacement of plantar pressure center^[45]. These tests can provide important indicators to evaluate quadriceps function for TKA patients.

As for secondary outcomes, thigh circumference, VAS score, opioid consumption in morphine equivalent, knee function score, postoperative satisfaction score, operation time, blood loss, blood transfusion rate, D-Dimer, CRP and complications in tourniquet group and non-tourniquet group will be evaluated. These outcomes work as effective supplements to our study to further evaluate tourniquet effects on TKA patients.

What's more, tourniquet time is also a meaningful indicator. As tourniquet is used throughout the whole operation period, it can be represented by operation time. Quadriceps injury and many other side effects may be time-related, so we hope to further investigate the relationship between tourniquet time and tourniquet effects in this study.

Indeed, there are several limitations in our study. First, ultrasound test is examiner dependent. Though all the patients are tested by the same ultrasound examiner, it may still affect the validity of the assessment

to some degree. Second, tourniquet effects on patients maybe too subtle to be reflected by chosen outcomes like VAS score or knee function score. More sensitive outcomes for patients after TKA are needed. Third, this study mainly focuses on clinical outcomes of tourniquet effects. There is a lack of deeper study of mechanism of ischemia reperfusion and inflammation.

This study is precisely designed to clarify the effect of tourniquet application on the morphology and function of quadriceps in patients undergoing total knee arthroplasty and offer advice for tourniquet use in clinical practice. Indeed, tourniquet application cannot be determined by one single trial, but we believe that more high-quality studies will be conducted and tourniquet impact will be clarified in the foreseeable future.

4. Trial Status

Recruitment commencing July 2020. 80 participants have already been recruited. Important protocol amendments will be communicated to relevant bodies. Recruitment will be finished at the end of 2021.

Abbreviations

TKA: Total Knee Arthroplasty

VAS: Visual Analogue Scale

SWE: Shear Wave Elastography

CRP: C-reactive Protein

KSS: Knee Society Score

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013) as well as local, national or international guidelines and legislation. All participants will sign the informed consent. The study was approved by Peking University Third Hospital Medical Science Research Ethics Committee (NO.: M2020290) and informed consent was taken from all individual participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to declare.

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2. Contributions

Ziyang Dong and Yang Li were both major contributors in designing and writing this protocol. Liyuan Tao offered epidemiology and statistical support. Hua Tian offered administrative support and guidance. All authors read and approved the final manuscript.

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Tables

Table.1 Results of pilot study and sample size consideration

Outcomes	Non-tourniquet group	Tourniquet group	σ	Sample size
Intraoperative blood loss (ml)	64.6±22.5	6.6±2.8	6.46	28
Quadriceps thickness (cm)	3.1±0.5	3.1±0.6	0.31	116
Centrifugal force of knee extending (N)	202±9	217±8	20.2	118

Figures

Time Point		Study Period											
		Enrollment	Allocation	Post-allocation									
				t1	t2	t3	t4	t5	t6	t7	t8		
Enrollment	Eligibility screen	X											
	Informed consent	X											
	Randomization		X										
Interventions	Tourniquet group			X									
	Non-tourniquet group			X									
Assessments	Demographic data			X									
	Quadriceps thickness			X		X							
	Quadriceps stiffness			X		X							
	Isokinetic muscle strength test								X				
	3D gait analysis								X				
	Posture stability testing								X				
	Circumference of thigh			X	X	X							
	VAS score				X	X	X	X					
	Opioid consumption					X							
	Knee function score			X							X	X	
	Postoperative satisfaction score										X	X	
	Operation time				X								
	Intraoperative blood loss				X								
	Perioperative blood loss					X							
	Blood transfusion rate				X	X	X						
	D-Dimer			X	X	X							
	C-reactive protein			X	X	X							
	Complications				X	X	X	X	X	X	X	X	

t1= before operation

t2= in operation

t3= 1 day after operation

t4= 3 days after operation

t5= 2 weeks after operation

t6= 6 weeks after operation

t7= 3 months after operation

t8= 1 year after operation

Figure 1

Schedule of enrollment, interventions and assessments

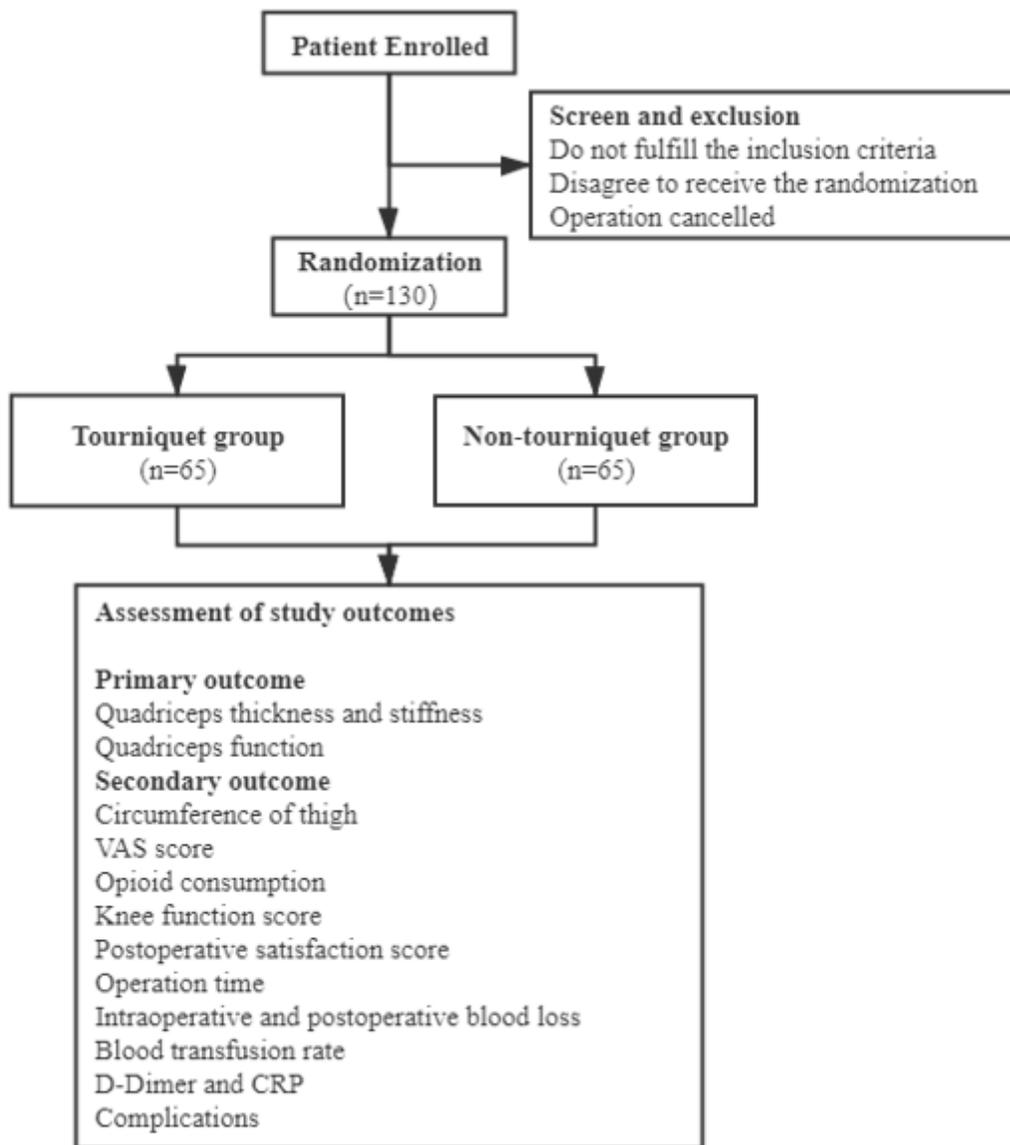


Figure 2

Flowchart of the study process

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