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Effects of infrapatellar fat pad preservation versus resection on clinical outcomes after total knee arthroplasty in patients with knee osteoarthritis (IPAKA): study protocol for a multicentre, randomised, controlled clinical trial

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ABSTRACT

Introduction The infrapatellar fat pad (IPFP) is commonly resected during total knee arthroplasty (TKA) for better exposure. However, our previous studies have suggested that IPFP size was protective against, while IPFP signal intensity alteration was detrimental on knee symptoms and structural abnormalities. We hypothesise that an IPFP with normal qualities, rather than abnormal qualities, should be preserved during TKA. The aim of this study is to compare, over a 1-year period, the postoperative clinical outcomes of IPFP preservation versus resection after TKA in patients with normal or abnormal IPFP signal intensity alteration on MRI.

Methods and analysis Three hundred and sixty people with end-stage knee osteoarthritis and on the waiting list for TKA will be recruited and identified as normal IPFP quality (signal intensity alteration score ≤1) or abnormal IPFP quality (signal intensity alteration score ≥2). Patients in each hospital will then be randomly allocated to IPFP resection group or preservation group. The primary outcomes are the summed score of self-reported Knee Injury and Osteoarthritis Outcome Score (KOOS), KOOS subscales assessing function in daily activities and function in sport and recreation. Secondary endpoints will be included: KOOS subscales (pain, symptoms and quality of life), Knee Society Score, 100 mm Visual Analogue Scale (VAS) Pain, timed up-and-go test, patellar tendon shortening, 100 mm VAS self-reported efficacy of reduced pain and increased quality of life, and Insall-Salvati index assessed on plain X-ray. Adverse events will be recorded. Intention-to-treat analyses will be used.

Ethics and dissemination The study is approved by the local Medical Ethics Committee (Zhujiang Hospital Ethics Committee, reference number 2017-GJGBK-001) and will be conducted according to the principle of the Declaration of Helsinki (64th, 2013) and the Good Clinical Practice standard, and in compliance with the Medical Research Involving Human Subjects Act . Data will be published in peer-reviewed journals and presented at conferences, both nationally and internationally.

Trial registration number This trial was registered at Clinicaltrial.gov website on 19 October 2018 with identify number NCT03763448.

Strengths and limitations of this study

- The trial stratifies patients with normal infrapatellar fat pad (IPFP) quality and abnormal IPFP quality and emphasises the need of preoperative IPFP quality assessment in order to optimise surgical strategy.
- The results of this multicentre randomised controlled trial would provide evidence-based recommendations on clinical practice to improve patients with osteoarthritis' postoperative outcomes.
- A possible limitation is interoperator or interassessor variations between centres in terms of outcome measurement and operational technique.

INTRODUCTION

Knee osteoarthritis (KOA) is one of the most prevalent chronic diseases that cause pain, loss of function and reduced quality of life in older adults.[1 2] Total knee arthroplasty (TKA) is a well-established surgical intervention with the intended benefits being pain relief and functional improvement. Although current reports estimate that over 80% of patients are satisfied with their TKA, a substantial number of patients' daily life are compromised by persistent postoperative knee pain and impaired functional outcomes after surgery.[3 4]

The infrapatellar fat pad (IPFP) or Hoffa's fat pad is a fatty mass lying beneath the patellar ligament, between the inferior pole of the patellar and tibial tubercle.[5] The function of the fat pad is debated. It is thought to have a role in the blood supply to the anterior cruciate ligament, patella and patella tendon via reticulated genicular arteries.[6 7] Additionally, it fills the gap inside the knee joint during joint motion and sends synovial fluid to the articular surface.[5] In contrast, studies have pointed out that abnormal IPFP could produce various proinflammatory cytokines such as IL-1β, tumour necrosis factor-α, IL-6 and IL-8, as well as adipokines such as leptin and resistin, and thus might play a detrimental role in KOA.[8–11]

Traditionally, the IPFP has been removed in order to improve surgical exposure and to prevent interposition during baseplate implantation.[12] Despite the significant evolution of TKA technology, which no longer requires the resection of IPFP for better surgical access, IPFP is still partially or totally resected in around 88% of TKAs.[3] Our previous population-based cohort study revealed that IPFP maximal area and volume were associated with reduced knee pain, decreased loss of cartilage volume and reduced risks of cartilage defect progression, indicating a beneficial effect of IPFP size.[13 14] On the other hand, our further investigation demonstrated that IPFP signal intensity alteration was negatively associated with maximum area of IPFP and, moreover, associated with increased knee cartilage defects, subchondral bone marrow lesion and knee pain, suggesting IPFP with abnormal quality may play a detrimental role in KOA.[8] Based on these findings, we proposed that IPFP with normal qualities, rather than abnormal quality, should be preserved or not damaged during TKA, while IPFP with abnormal quality should be resected rather than preserved.[15]

Although a number of studies have reported the beneficial effects of IPFP preservation,[16–18] none of them is of high quality in terms of study design. Moreover, none of these studies has ever considered differentiating IPFP quality before conducting the trials. A recent systematic review concludes that although there is moderate level evidence that IPFP resection increases postoperative knee pan, high-quality clinical trials are required to support the rationale for or against IPFP resection.[19]

Therefore, the purpose of the current multicentre, randomised, controlled clinical trial is to examine the effect of preservation versus resection of IPFP on clinical and functional outcomes, including Knee Injury and Osteoarthritis Outcome Score (KOOS) and subscale assessing function, Knee Society Score (KSS), patellar tendon shortening, 100 mm Visual Analogue Scale (VAS) pain, self-reported efficacy of reduced pain and increased quality of life and timed up-and-go test in patients with normal or abnormal quality of IPFP on MRI.

METHODS

Study design

The design of this study is a multicentre randomised double-blinded clinical trial that will enrol 360 patients with a diagnosis of symptomatic and radiographic KOA considering eligible for TKA from seven hospitals (Zhujiang hospital of Southern Medical University, Peking University People's Hospital, Xiangya Hospital Central South University, The First Affiliated Hospital of Jinan University, The First Affiliated Hospital of Anhui Medical University, Anhui Provincial Hospital and Peking Union Medical College Hospital). MRI will be taken before the trial to evaluate IPFP signal intensity alteration.[8 20]

Patients will be identified as normal IPFP quality or abnormal IPFP quality based on MRI evaluations and will then be randomised to either TKA with complete IPFP excision group or TKA with IPFP preservation group in each hospital. Outcome measurements will be taken at baseline before surgeries and follow-up at 3, 6 and 12 months after surgeries.

The study will conform to Consolidated Standards of Reporting Trial guidelines for reporting parallel group randomised trials.[21] Ethics approval will be received from each institution, and informed written consent will be obtained from all participants. Additional inclusion and exclusion criteria are listed as follows.

Patient and public involvement

Patient and the public were not involved in the design of current trial protocol. The individual results of current study will be informed by research nurses to participants who desire to know. Free lectures of summarised reports will be delivered once the study has accomplished. The resulting publications will be disseminated to participants and public via mass media. Study participants as a whole will be acknowledged in the end of our publications and presentations.

Participant recruitment

Inclusion criteria

- Clinically diagnosed primary OA with radiographically confirmed KOA (Kellgren-Lawrence score of ≥2).
- Referred to an orthopaedic surgeon in one of the selected trial hospitals for evaluation of the need for TKA.
- Considered eligible for a TKA by a surgeon according to standard evaluating procedures.
- Aged 40–80 and able to provide written informed consent.
- Capable of understanding the study requirements and willing to cooperate with the study instructions.

Exclusion criteria

- Medical history of rheumatoid arthritis or psoriatic arthritis, lupus or cancer.
- A need for contralateral knee arthroplasty in 12 months.

- Previous metal implants in the knee.
- Possible pregnancy or planning pregnancy.
- Inability to comply with the protocol.
- Patients suffering from any significant concurrent disease, illness, psychiatric disorder, cognitive and/or neurological disorders that could compromise their safety or compliance or interfere with consent, study participation, follow-up or interpretation of the results.
- Patients with severe valgus knee '(anatomic valgus angulation >30°)'.
- Contraindication to receiving operation or MRI.

Randomisation and blinding

Randomisation will be done by an online random number generator (www.randomizer.org) and be stratified by hospitals and IPFP status (normal or abnormal). Participants in each site will be randomly assigned to either IPFP resection arm or IPFP preservation arm in a ratio of 1:1. Allocation concealment will be ensured by the use of a central automated allocation procedure, with security in place to ensure allocation data cannot be accessed or influenced by any person. The outcome assessor will be blinded to group allocation and not involved in operational procedures. The participants, researchers and statistician performing the statistical analyses will be blinded as well. The allocation outcomes will be put into concealed, opaque envelopes prepared by an independent researcher. Following concealment instructions, a randomisation envelope will be opened in the operating room after general anaesthesia is administered. Blinding of surgeons delivering operations to treatment allocation will not be possible but they will not be involved in any assessments.

Intervention

The surgery will be performed by a single surgeon per hospital who had experiences in TKA. All participants will have cruciate-sacrificing TKA using mobile-bearing systems. Each study centre will be restricted to use one type of implant from trial initiation to completion. The same surgical techniques are used throughout the study except for IPFP management (resection or preservation). In the IPFP resection group, the entire IPFP will be removed underneath the patellar tendon before femoral preparation. In the IPFP preservation group, the entire IPFP will be preserved by retracting it out of the operative field.

The patella will be regularly resurfaced in the patients who had intraoperative findings of articular surface erosion to the subchondral bone. All components will be fixed with cement. All patients received the same perioperative management with regards to anaesthesia, multimodal analgesics and wound management.

Primary outcome measure

The primary outcome will be KOOS total score ranging from 0 (worst) to 100 (best)[22 23] and KOOS subscale assessing function of daily activities and KOOS subscale assessing function in sport and recreation (table 1).

Knee Injury and Osteoarthritis Outcome Score

The KOOS is a knee-specific patient-reported questionnaire with 42-items in five separately analysed subscales of pain, other symptoms, function in daily living, function in sport and recreation and knee-related quality of life.[24] Scores are transformed to a 0–100 scale, with 0 representing extreme knee problems and 100 representing no problems. The KOOS has been validated for use in TKA and has been shown to be a valid, reliable and responsive measure.[25]

Secondary outcome measures

A number of secondary outcome measures will be taken (table 1): KOOS subscales including pain, symptoms and quality of life; pain intensity measured on a 100 mm VAS with terminal descriptors of 'no pain' and 'worst pain possible' in the following situations: at rest, after 30 min of walking and on most days of the last month; self-reported efficacy of reduced pain and increased quality of life using a 100 mm VAS with terminal descriptors of 'very unsure' and 'very sure'; the Timed Up and Go walk test[26 27] will be employed to evaluate functional performance of participants. The KSS is a rating system that consists of two scores: knee and patient functional scores. Both scores range from 0 (worst health or functioning) to 100 (best health or functioning). It has been used for tracking and reporting postoperative outcomes of TKA worldwide.[28 29]

The Insall-Salvati ratio (ISR)[30] is used to assess changes in the length of the patellar tendon at baseline and month 12. Lateral radiographs with the knee in about 30°of flexion will be taken by well-experienced X-ray technicians using standardised radiographic techniques. The numerator of the ISR—the length of the patellar tendon—was determined by measuring the distance from inferior aspect of the patella to the superior aspect of the tibial tubercle. The longest dimension of the patella on the lateral radiograph will be obtained as denominator of the ISR.

Adverse events (AEs) including but not limited to falls, infection, gastric ulcer and serious adverse events (SAEs, eg, death, AE that is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability) will be collected and closely monitored to ensure the ongoing safety of participants. AEs and SAEs will be recorded and compared. All SAEs will be notified to the study sponsor and reviewed by the Trial Steering Committee.

Other measures

Several other measures will also be assessed (table 1).

All participants will be asked to rate their satisfaction with the operation to date on a 5-point (very dissatisfied, dissatisfied, neutral, satisfied and very satisfied) Likert scale[31] at each follow-up.

Table 1 Timetable and measures to be made

	Screening	Preoperation	Postoperation month(s)		
			3	6	12
Coprimary outcomes					
KOOS total score		√	√	√	√
KOOS daily activity score		√	√	√	√
Secondary outcomes					
Five individual subscales KOOS		√	√	√	√
Knee Society Score		√	√	√	√
VAS pain	√	√	√	√	√
Self-reported efficacy for reducing pain			√	√	√
Self-reported efficacy for improving quality of life			√	√	√
Timed up-and-go test		√			√
The Insall-Salvati ratio		√			√
Adverse events			√	√	√
Other measures					
PHQ-9 (X)		√	√	√	√
Knee radiograph	√				√
Weight		√			√
Height		√			√
Cigarette smoking		√			
Alcohol intake		√			
Number of falls		√			√
Occupation		√			
Previous knee injury	√				
Satisfaction (Likert scale)			√	√	√
Serum inflammatory cytokines		√			√
Pain medication		√	√	√	√
MRI (IPFP)		√			

IPFP, infrapatellar fat pad; KOSS, knee injury and osteoarthritis outcome score; PHQ, patient health questionnaire; VAS, visual analogue scale.

Depression will be evaluated based on the Patient Health Questionnaire-9,[32] which is a valid and reliable instrument for detecting states of depression in patients under treatment in hospital.

Radiographs will be taken at baseline by a standing semi-flexed anterior–posterior, radiograph as per the Altman atlas[33] and assessed simultaneously by trained observer using the Osteoarthritis Research Society International atlas to score osteophytes and joint space narrowing on a 4-point scale (0–3).

Anthropometrics: height will be measured to the nearest 0.1 cm (with shoes removed) using a stadiometer. Weight will be measured to the nearest 0.1 kg (with shoes and bulky clothing removed) using electronic scales.[34]

Occupation, smoking status, alcohol intake, duration of KOA symptoms, previous knee injury, previous arthroplasties, number of falls, comorbidities, education level, employment status will be assessed by questionnaires.

Pain medication usage will be recorded at baseline and during the follow-up period.

Serum inflammatory cytokines including but not limited to high-sensitivity C reactive protein, IL-6, IL-23 will be measured.

Target knees will be imaged in the sagittal plane on a 1.5 T whole body MRI unit using a commercial transmit receive extremity coil before TKA. Fat-saturated T1-weighted spoiled gradient echo and T2-weighted/proton density-weighted fast spin echo sequences will be used. The score of IPFP signal intensity alteration will be assessed by appointed reader before randomisation using the methods described in our previous publications,[8 35] and osteoarthritic abnormalities will be assessed.

Sample size calculation

Sample size and power calculation was based on the primary endpoints of KOOS daily activity function score and total score in the mean change from baseline to 12

months. All sample size calculations assume α=0.05 and β=0.20 and are performed using formulae provided by Cohen.[36]

Based on the data collected in previous study,[37 38] a between-subject SD of 14 on KOOS daily activity function score will be used and at least 15% improvement would be detected.[39 40] To obtain a power of 80% at a significant level of α=0.05, a total of 48 participants per group are needed. Assuming a 10% drop out rate, we will need to enrol approximately 54 participants per group to complete the study.

Sample size calculation is also performed based on another primary outcome total KOOS score with a between-subject SD of 17,[41] and eight points difference between groups would be detected according to the literature.[42] A total of 82 participants per group are needed to obtain 80% power to detect a significant group effect using an α level of 0.05. Assuming a 10% drop out rate, 90 participants are needed in each group.

Take into consideration of these two calculations, 90 participants in each arm will be sufficient to detect the differences of primary outcomes between groups. Because stratified analyses will be performed to compare clinical outcomes after IPFP preservation versus resection in patients with normal as well as abnormal IPFP qualities, in total 360 participants are needed.

Analysis plan

The primary comparisons for KOOS scores and KOOS subscale assessing function in daily activities and function in sport and recreation scores will be made using repeated measures mixed effect model with terms of treatment, time, trial centre and corresponding baseline values as covariates (age, gender, body mass index). Stratified analyses will be performed in participants with normal and abnormal IPFP quality. We will first examine the intervention by time interaction and then proceed to a main effects model with only group and time.

The independent t test will be used to compare changes between IPFP preservation and resection groups from baseline to the end of follow-up when data are normally distributed, and the Mann-Whitney U test will be used when data are not normally distributed. A X^2 test will be used for dichotomous variables.

In secondary analyses, repeated measures mixed model will also be used to examine the associations between treatments and repeated outcome measures. Additionally, linear regression and/or logistic regression analyses will be employed to assess the associations between treatments and changes or increases in outcomes from baseline to 12 months in univariate and multivariate modelling adjusted for relevant covariates.

All data will be analysed using intention-to-treat principles. Multiple imputation by chained equations will be used to address missing data caused by loss to follow-up and non-responses if these missing data are judged to be random. Sensitivity and post hoc analyses will be performed to investigate the intervention effect in different subgroups. Per-protocol analyses will also be performed in the participants who complete the 1-year follow-up. Statistical analysis will be performed using Stata software (V.15.0) and the significant level set at p<0.05.

Quality assurance/monitoring/management

In order to ensure that this trial will be of a high standard and delivered in accordance with the trial protocol, all research staff will be provided with a Manual of Operations and Procedures (MOP) and case report form, and will be trained to competently administer items as per protocol. The investigators, research assistants, clinicians and outcome assessors are different people. Protocols will not be altered during the study time frame. The trial will be consistently monitored by a trained project manager who will visit each site to examine trial procedures to ensure data quality and compliance with trial protocol. The MOP will also describe the monitoring plans to assure patient protection and data integrity, thus facilitating consistency in protocol implementation and data collection. All research staff should receive Good Clinical Practice training.

All data obtained will be kept strict and will be stored electronically on a database with secured and restricted access. Data transfer will be encrypted and any information able to identify individuals will be removed. At the completion of the study, outcome data will be deidentified for analysis by a statistician.

Withdrawal

All participants will be free to withdraw from the study at any time. If a participant withdraws or is removed from the study, the reason and date of discontinuation will be recorded.

Study duration

Recruitment of the trial was began in end of 2018 and 12-month follow-up for all participants is anticipated to be completed by December 2020. See figure 1 for time points and recruitment progress.

Ethics and dissemination

The study has been approved by five of the seven local Medical Ethics Committees (Zhujiang Hospital Ethics Committee, reference number 2017-GJGBK-001; Ethics Committee of Peking University People's Hospital, reference number 2019-PHB062-02; Medical Ethics Committee of Xiangya Hospital, Central South University, reference number KE2019010019; Ethics Committee of the First Affiliated Hospital of Jinan University, reference number 2019-LSPK-002 and Ethics Committee of The First Affiliated Hospital of Anhui Medical University, reference number PJ2018-10-15(1)) and will be conducted according to the principle of the Declaration of Helsinki (64th, 2013). All requirements regarding the welfare, rights and privacy of participants were fulfilled. The potential risks of these clinical trials are considered to be minimal and are addressed in the protocol and consent forms. A written consent will be obtained

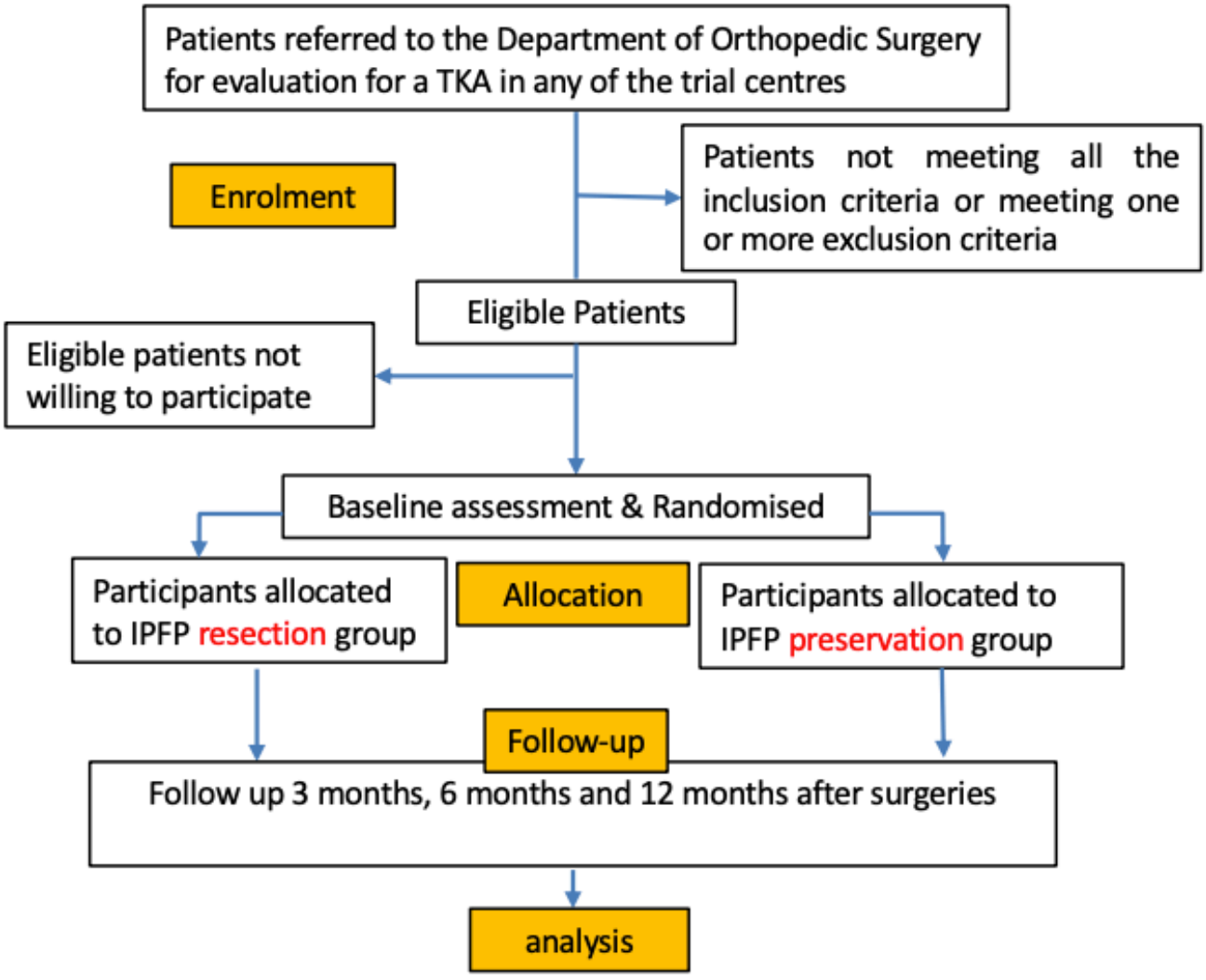

Figure 1 Flowchart of trial participation. IPFP, infrapatellar fat pad; TKA, total knee arthroplasty.

by clinical practitioners from each participant. The trial was registered on ClinicalTrial.gov website. Data will be published in peer-reviewed journals and presented at conferences, both nationally and internationally.

DISCUSSION

This project is a fully powered randomised controlled trial (RCT) to compare 1-year postoperative clinical outcomes of IPFP preservation versus resection after TKA in patients with or without significant IPFP signal intensity alteration on MRI. The trial stratifies patients with normal IPFP quality (IPFP signal intensity alteration ≤1 on MRI) and abnormal IPFP quality (IPFP signal intensity alteration ≥2 on MRI) and emphasises the need of preoperative IPFP quality assessment in order to optimise surgical strategy. The trial intends to prove the hypothesis that IPFP with normal quality should be persevered or not damaged; while IPFP with abnormal quality should be resected rather than reserved during TKA.

Although a number of clinical studies have been conducted, there are currently no guidelines regarding IPFP resection or preservation as part of TKA procedure. One small (90 patients) RCT by Pinsornsak *et al*[17] reported that patients with their IPFP excised had more anterior knee pain at the end of 1-year follow-up. Another retrospective designed trial demonstrated that although IPFP preservation delayed operation time, it decreased wound complications after minimal invasive TKA.[43] In contrast to these studies favouring IPFP preservation, a prospective randomised study of 68 patients by Macule *et al*[44] reported a significant relationship between Hoffa's fat pad fibrosis and anterior knee pain in TKA during the first six postoperative months and recommended systematic resection of Hoffa's fat pad during TKA. The two most recent systematic reviews concluded contradictory findings. One showed that IPFP preservation improved post-TKA knee pain,[19] whereas the other suggested that there were no differences in function, range of motion and anterior knee pain between preservation and

resection groups after TKA in KOA.[12] Nevertheless, both reviews concluded that high-quality well-designed RCTs investigating whether IPFP should be preserved or not during TKA are required.

This comparative study is unique as we are not aware of any previous or ongoing multicentre RCTs designed with consideration of the biphasic role that IPFP may play in KOA. According to previous observational studies, IPFP size (maximal area or volume) may have protective roles for knee symptoms and structural changes in KOA,[13 14 45] while IPFP with abnormal quality may play a detrimental role in KOA.[8 35 46] The rationale of differentiating IPFP quality before conducting the trial is based on these previous findings. We hypothesise that IPFP preservation could improve patients' postoperative outcomes if the IPFP quality is not abnormal. Furthermore, we hypothesise that IPFP resection could improve patients' postoperative outcomes if the IPFP quality is abnormal.

It is essential to evaluate postoperative improvement with appropriate outcome measures. This trial has included outcome measures from different domains of physical functional performances, patient-reported measures, objective measures and even psychological assessments, which will ensure a comprehensive comparison of postoperative improvement between IPFP resection and preservation groups. We recognise that some outcome measures (such as timed up-and-go test) are not normally used in the clinics/hospitals; however, these measures are widely used in clinical research. A possible limitation is interoperator or interassessor variations between centres in terms of outcome measurement and operational technique. In order to minimise these variations, only one experienced surgeon from each centre will be required to perform TKA, and assessors will be trained to competently administer assessments in accordance to the protocol. Furthermore, intention-to-treat analysis strategy will be used with all available data included.

The participants have been recruited to the present trial prior to protocol submission. According to the reviewers' pertinent recommendations, we deleted previous inclusion criteria of 'knee pain ≥20 mm' and exclusion criteria of 'knee pain <20 mm', which tended to be repetitive, and modified 'radiographically confirmed KOA' to 'clinically diagnosed primary OA with radiographically confirmed KOA'. Actually, we have used the surgeon-defined criteria of KOA to recruit patients with TKA from the start of this trial. Therefore, the authors are confident to state that the amendments of inclusion and exclusion criteria had not affected the recruitment and will only improve the feasibility and readability of the protocol.

In summary, there are currently no evidence-based guidelines regarding appropriate management of IPFP during TKA procedure. IPFP may have a beneficial role physiologically through increased size but could be detrimental when pathological changes are observed as signal intensity alteration on MRI. This multicenter randomised controlled clinical trial has been designed to determine postoperative clinical outcomes of IPFP preservation versus resection after TKA in patients with KOA. The knowledge gains from this study will provide evidence for a possible future guideline on IPFP management to optimise benefits of TKA.

Trial status

On submission, the study is in the process of patient recruitment.

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