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A randomized controlled trial comparing functional outcomes for navigated kinematically aligned total knee arthroplasty versus navigated mechanically aligned total knee arthroplasty

THE MAKKRO TRIAL

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Aims

Nearly 99,000 total knee arthroplasties (TKAs) are performed in UK annually. Despite plenty of research, the satisfaction rate of this surgery is around 80%. One of the important intraoperative factors affecting the outcome is alignment. The relationship between joint obliquity and functional outcomes is not well understood. Therefore, a study is required to investigate and compare the effects of two types of alignment (mechanical and kinematic) on functional outcomes and range of motion.

Methods

The aim of the study is to compare navigated kinematically aligned TKAs (KA TKAs) with navigated mechanically aligned TKA (MA TKA) in terms of function and ROM. We aim to recruit a total of 96 patients in the trial. The patients will be recruited from clinics of various consultants working in the trust after screening them for eligibility criteria and obtaining their informed consent to participate in this study. Randomization will be done prior to surgery by a software. The primary outcome measure will be the Knee injury and Osteoarthritis Outcome Score The secondary outcome measures include Oxford Knee Score, ROM, EuroQol five-dimension questionnaire, EuroQol visual analogue scale, 12-Item Short-Form Health Survey (SF-12), and Forgotten Joint Score. The scores will be calculated preoperatively and then at six weeks, six months, and one year after surgery. The scores will undergo a statistical analysis.

Discussion

There is no clear evidence on the best alignment for a knee arthroplasty. This randomized controlled trial will test the null hypothesis that navigated KA TKAs do not perform better than navigated MA TKAs.

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Introduction

National Joint Registry data for England, Wales, Northern Ireland and Isle of Man has shown that nearly 99,000 total knee arthroplasties (TKAs) are performed in UK annually.[1] Despite advances in total knee arthroplasties, satisfaction rates have been reported to be around 60% to 80%.[2,3] There is enough evidence to suggest that the satisfaction rate after TKA cannot be predicted from preoperative variables alone.[4] The intraoperative variables which determine long-term

outcomes include alignment, cementing techniques, implant selection, balancing of knee, patella resurfacing, and deformity correction.[2,5] Alignment is still one of the most important intraoperative factors.[5] To improve alignment, various techniques have been used, such as navigation- and patient-specific instrumentation.[6] There is some evidence to suggest that low satisfaction rates could be due to change in natural joint line obliquity.[7]

Hirschmann et al[8] have suggested that research should focus on more individualized alignment strategies in TKAs. Alignment has a significant role to play in loading variability and knee arthroplasty mechanics.[5] Mechanical alignment (MA) is the widest-used method used in TKA, probably mainly due to high reproducibility and ease.[9] This was originally described by Insall et al.[9] The distal femoral cut and the proximal tibial cut are made perpendicular to mechanical axis of the femur and tibia, respectively. The alignment thus obtained is in 3° to 5° valgus in general but could be variable.[10] This aims to create alignment with even load distribution on the new joint line. It also limits the femoral component positioning in external rotation (approximately 3°) in order to balance flexion gap. Most surgeries and clinical studies are based on mechanical alignment and hence for practical purposes we can consider it as the 'gold standard'.

Eckhoff et al[11] gave a detailed description of the 3D mechanics, kinematics, and morphology of the knee in the year 2005. They demonstrated in this paper that the mechanical axis of the lower limb is not always neutral. It has also been proven that the transepicondylar axis varies significantly from the cylindrical axis of the distal femur and hence cannot be used as a reference for the flexion-extension axis of the knee.[12]

Most of the knee arthroplasties done today are mechanically aligned (MA TKA).[13] Kinematically aligned (KA) TKA is relatively a new technique, described by Howell et al[14] in 2008 using conventional and mechanical jigs, and can be performed by using conventional jigs, patient-specific jigs, or using a navigation-based technique. There is no clear evidence on which technique is better, or should be preferred. Therefore, a study is required to investigate and compare the effects of two types of alignment (mechanical and kinematic) on functional outcomes and range of motion (ROM).

We propose a null hypothesis that KA TKAs performed using navigation do not perform better than MA TKAs performed using the navigation technique in terms of function and ROM.

Methods

Objectives. The trial proposes to compare the functional outcomes of KA TKA versus MA TKA performed using navigation technique, and to compare ROM and alignment of knee in the two groups.

Trial summary. We aim to have a sample size of 84 patients (42 in each group) in the trial. To achieve this we will need to recruit 96 patients in total, based on a power calculation and considering an attrition rate of 15%. The patients will be recruited from clinics of various consultants working in the Hull University Teaching Hospitals NHS trust after screening them for eligibility criteria and obtaining their informed consent to participate in this study. Randomization will be done prior to surgery by using www.randomization.com software. The primary outcome measure will be the Knee Osteoarthritis Outcome Score (KOOS).[15] The secondary outcome measures include the Oxford Knee Score,[16] range of motion (measured using a digital goniometer), EuroQol five-dimension questionnaire (EQ-5D),[17,18] EuroQol visual analogue scale (EQ-VAS),[18] 12-Item Short Form Health Survey (SF-12),[17] and Forgotten Joint Score.[19] The scores will be calculated preoperatively and then at six weeks, six months, and one year after surgery. The scores will undergo a statistical analysis. This study has been approved by the regional ethics committee and informed ethical consent will be obtained from the patients.

Study type. This study will be a randomized controlled trial comparing the results of navigated KA TKA and MA TKA.

Participants. Patients who enter the clinics of participating consultants and are suitable for a TKA will be included in the study. These clinics will be run by consultants, registrars, trainees, or fellows working in trauma and orthopaedics in our department.

Treatment details. All surgical procedures will be carried out at our local elective orthopaedic unit. This is a single-centre trial. Randomization will be done by a research nurse. All patients will have a B. Braun Columbus knee implant (Aesculap, Germany) with patellar resurfacing using Orthopilot navigation software V5 (Aescula).

Eligibility

Inclusion criteria are age between 18 and 90 years, and a diagnosis of degenerative osteoarthritis (OA). Exclusion criteria are post-traumatic arthritis; varus/valgus deformity of more than 20°; flexion contracture of more than 20°; a reduced ability to make decisions, such as patients with dementia; any orthopaedic procedure to the lower limbs within the last year; neuromuscular or neurosensory deficiency; inflammatory arthritis of the knee joint; patients who suffered a complication which might influence the final outcome such as a deep infection, fracture, or dysfunction of the extensor mechanism in postoperative period (however, complication rate data will be analyzed and reported); pregnancy; and patients involved in other clinical trials within last six months prior to being recruited in the study.

Recruitment. Patients will be recruited from the outpatient clinic of participating orthopaedic surgeons

working at our trust hospitals. The patients coming to clinic during this period will be given an explanation of the trial and an explanantion of MA TKA and KA TKA. The participants involved in this study will not be paid any remuneration. The procedure involved and the follow-up details will be explained to the patient and information leaflets given to them. The expected number of patients eligible for the trial is 96 (48 in each group). One surgeon will perform all KA TKA and other surgeons will perform MA TKA, which will ensure that there is no change of clinical practice for any surgeons in terms of kinematic or mechanical alignment of the TKA.

Randomization. Patients will be randomized using research randomizer computer software (randomization. com).[20] This programme is a pseudo-random number generator. The numbers are generated by complex algorithm (seeded by computer clock) that gives the appearance of randomness. This will help us randomly assign our study population into the two groups (KA TKA and MA TKA). It is a single-blinded study and patients will be blinded. Envelopes will be opened after the clinic appointment and patients will be booked for surgery. This will be handled by a research nurse working in the department who is not a part of the trial.

Withdrawal of subjects. Patients may be withdrawn at any stage of the follow-up/trial. If any patient develops dementia, deep infection, fracture, failure of extensor mechanism, or any other injury which affects their mobility or ability to make decision, they will be withdrawn. Under such circumstances, randomization codes may have to be broken. Furthermore, if the patients want to seek a second opinion or continue the treatment outside the trust, the codes may have to be broken. The withdrawn subjects will be followed up in the clinics of respective surgeons, until a suitable period when they can be discharged.

Study treatments. The MA TKA proedure will cut the distal femur perpendicular to a line drawn from the centre of the femoral head to the centre of the knee (the mechanical axis of the femur) and cut the proximal tibia perpendicular to a line drawn from the centre of the knee to the centre of the ankle, i.e. the mechanical axis of the tibia. In KA TKA, equal and measured resection of tibia and femoral cut surface is done, while accounting for the amount of cartilage wear of the femoral (distal and posterior) condylar surface and tibial articular surface. The aim is to get the thickness of the femoral (distal and posterior) condylar cuts and proximal tibia cuts to match the thickness of the implant that is replacing it, accounting for the wear. The surgeon aims to restore the joint line obliquity in this particular technique. After recording femoral data on navigation system and gap measurements, femoral resection is planned to achieve equal medial and lateral gaps in full extension but slightly wider gap on lateral side in flexion. Both groups will undergo

patella resurfacing irrespective of condition of the patella to remove potential bias if the patellar resurfacing is performed only in selective cases.

Use of treatment within the trial. MA and KA TKA has been used in patients with symptomatic osteoarthritis who have not benefitted from nonarthroplasty options. The efficacy has been validated in various studies. It is an invasive procedure carried out in operating theatres under anaesthesia.[9,21,22] The leg alignment views and the preoperative scores will be completed in a clinic prior to randomization. All follow-up scores will be done by a third person (trust registrars/specialist registrars/trainees/research nurse). The radiation involved in this study will be in form of radiographs which will be taken immediately preoperatively (full leg alignment view), postoperatively (standard anteroposterior/lateral view), and at one-year follow-up (full leg alignment view). After the completion of trial, the patients will be followed up in the clinic of the operative surgeon until a period where they can be discharged to the care of respective general practitioners.

Subject and compliance of study treatment. The compliance will be assessed by the visits at follow-up. If there is any missed follow-up appointment, postal and telephone reminders will be sent. If the patient does not attend follow-up visit on the consecutive appointment, they will be considered as lost to follow-up. Patients lost to follow-ups will be withdrawn from the study.

Assessment of outcomes

The primary outcome measure is KOOS at 12 months.[15] Secondary outcomes include knee ROM and stability (preoperatively and at one year postoperatively); Oxford Knee Society score (preoperatively and at six weeks, six months, and one year postoperatively);[16] SF-12 (preoperatively and at six weeks, six months, and one year postoperatively);[17] EQ-5D (preoperatively and at six weeks, six months, and one year postoperatively);[18] VAS (preoperatively and at six weeks, six months, and one year postoperatively);[18] time taken for operation (tourniquet time); preoperative and one-year postoperative lateral distal femoral angle;[23] proximal tibial slopes on radiographs; Forgotten Joint Score at one year postoperatively;[19] and radiological analysis of joint line obliquity.

Statistical analysis

Sample size. Waterson et al[24] found that at 12 months the mean KOOS score was 77.7 (SD 20.0) in their KA TKA group. The study was powered to demonstrate a 19-point difference in the KOOS score between groups at 12 months which has been defined as the minimal clinical important difference (MCID) in scores by the research team. Further literature review confirmed that the MCID for KOOS after TKA ranges from 11 to 19 for various subcategories of KOOS.[25] As our study involves TKA as the

main intervention, it was agreed with the statistician to use the above MCID figures, which are more relevant to our study, hence the sample size was calculated for detecting a difference of 11 points for KOOS between two groups to ensure that study is sufficiently powered. A sample size of 42 in each group is taken, assuming same standard deviation of 20 points in KOOS, using a one tailed analysis and an α of 0.05 with a power of 0.80. A total of 96 patients will be enrolled, assuming an attrition rate of 15%, which should result in at least 84 patients (42 in each group for analysis).

Analysis. This trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials.[26] Analyses will be conducted following the principles of intention-to-treat with patient's outcomes analyzed according to their original, randomized group, irrespective of deviations based on non-compliance.

Analyses will be undertaken in Stata v. 14 (StataCorp, USA) or later (to be confirmed in the final report). Significance tests will be two-sided at the 5% significance levels unless otherwise stated. The statistician will remain blind to allocation until after the trial is complete and the results have been finalized.

The number of patients screened, found to be eligible, and randomized will be reported. The flow of participants through the trial will be presented in a CONSORT diagram. Questionnaire response rates will be summarized from each timepoint by treatment group. All participant baseline data will be summarized descriptively overall and by trial arm both as randomized and as analyzed in the primary analysis. No formal statistical comparisons will be undertaken. Continuous measures will be reported as means and standard deviations, while the categorical data will be reported as counts and percentages.

The primary analysis will compare the KOOS at 12 months among the patients randomly allocated to KA TKA and MA TKA. This result will be extracted from a covariance pattern model in which KOOS at each timepoint   will be nested within patients and the effect of treatment according to trial arm will be assessed. KOOS at baseline, trial arm, each timepoint of follow-up, each timepoint of follow-up by trial arm interaction, any stratification factors (fixed effects), and KOOS at each timepoint nested within patient (random effects) will be included in the model. This will allow efficient use of the data collected, and account for potential correlation of repeated measures and within patient correlation.[18]

Different covariance structures for the repeated measurements, available as part of Stata, will be explored and the most appropriate pattern will be used for the final model. Diagnostics including Akaike's information criterion[27] will be compared for each model (smaller values are preferred).

Participants are included in the model if they have full data for the baseline covariates and outcome data for at least one post-randomization timepoint. A comparison of baseline data for patients as analyzed in the primary analysis will allow assessment of whether attrition has introduced selection bias.

This linear mixed model will also provide an estimate of the comparable effect of KA TKA and MA TKA in terms of a change in KOOS at every timepoint for secondary investigations aimed at determining any potential pattern of improvement. Treatment effect sizes will be reported with 95% confidence intervals for each timepoint. The assumptions of the linear model will be checked visually. The normality of the standardized residuals will be assessed via a histogram and QQ-plot, and the homoscedasticity of the errors will be checked by plotting the residuals against the fitted values. If model assumptions are in doubt, transformations will be considered.

Secondary outcome data will be summarized descriptively at each timepoint, overall, and by trial arm, and will be analyzed in exactly the same way as the primary outcome.

Blinding. The scoring will be done by independent assessors like research nurses, senior consultants, trainees, or clinical fellows who are not part of the trial. Randomization will be done by a research nurse who is not a part of the trial.

Data collection. Data will be collected from patient questionnaires, patient notes, electronic data (patient clinic letters), and radiographs. Data will be collected preoperatively (baseline score), six weeks postoperatively, six months postoperatively, and at one-year follow-up. Data-handling and record-keeping will be in accordance to the hospital and the research and development (R&D) guidelines, in line with data protection laws.

Protocol deviations. All deviations from the protocol or good clinical practice will be recorded by investigators on the Protocol Deviation Form for the trial. A serious breach is likely to affect, to a significant degree, either the safety or physical or mental integrity of a trial subject or the scientific value of the trial. Major deviations or serious breaches will be reported by investigators to the R&D team of the trust by telephone or in person within 24 hours of the deviation or breach being identified. R&D will notify the Regional Ethics Committee within seven days of becoming aware of a serious breach. Investigators will take into account all protocol deviations and any serious breaches in the final study analysis and publication.

Informed consent. All the patients who meet the inclusion criteria and who agree to participate will sign an informed consent form. They will confirm that their participation is voluntary, they have been given the information that they require, and that the study has been explained to them. The consent will be obtained in the clinic, in the presence of a nurse and / or family members of the

patient. In case of non-English-speaking patients, an interpreter will be called to do the translation of the communication between doctor and the patient. The interpreter in such scenarios will have to sign on the consent form in addition to the patients. Patients will be given sufficient time to arrive at a decision. In case they want to think over this study, they will be given one month, after which a telephonic conversation will be conducted to reach a decision. On the day of surgery, reconfirmation of the consent to participate in the trial will be undertaken. Patient will be free to come out of trial at any stage of the trial if they wish to do so. Patients with special needs (mentally ill, those suffering from dementia) will be excluded from the study.

Confidentiality. Only trial organisers and R&D team of the trust will have access to patients notes and questionnaires. All recorded data will be securely saved separately from patient identifier details.

Monitoring. The study may be monitored in accordance with R&D department standard operating procedures to ensure compliance with Good clinical Practice and the Research Governance Framework 2005. All trial-related documents will be made available upon request for monitoring by R&D monitors.

End of trial. The trial will end when the last patient participating in the trial will complete one-year follow-up. In case of discontinuation of trial, an interim analysis will take place with the help of clinical director for orthopaedics for the hospital. An end-of-study declaration form will be submitted to the ethics committee and trust R&D within 90 days from completion of the trial and within 15 days if the trial is discontinued prematurely. A summary of the trial report/publication will be submitted to the ethics committee and trust R&D within one year of the end of trial.

Ethics. The trial has been given ethics permission by our local Ethics Committee and is registered on clinicaltrials.gov with registration number NCT04246138, ENDURA CT registration number is 2020-000398-26, and EDGE database registration number is 106178.

Indemnity. This is an NHS-sponsored research study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff and medical academic staff with honorary contracts only when the trial has been approved by the trust R&D department. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Where the chief/principal investigator is employed by our trust, it has an insurance policy that includes cover for no-fault compensation in respect of accidental injury to a research subject.

Sponsorship. This study is sponsored by our hospital R&D team.

Take home message

- Kinematically aligned total knee arthroplasty (KA TKA) is being recognized as a possible alternative to mechanically aligned TKA (MA TKA).
- Navigation allows the surgeon to implant the prosthesis with a more accurate alignment.
- This study aims to find out if the clinical outcomes are different when these two techniques (navigated MA TKA vs navigated KA TKA) using a randomized controlled trial.

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