Robotic assisted surgery comparing personalized alignment versus mechanical alignment of total knee arthroplasty – A randomized controlled trial

the personalKNEE Trial

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Introduction

Mechanical alignment (MA) has for many years been the most used surgical alignment technique in total knee arthroplasty (TKA). This means that regardless of constitutional native anatomy (i.e. valgus or varus), one strives to achieve a neutral coronal knee axis on postoperative x-rays (Hip-Knee-Ankle angle, HKA). To achieve MA, the cuts are made perpendicular to the mechanical axes, and subsequent soft tissue balancing is performed if necessary. However, many patients do not have a neutral knee alignment before they develop osteoarthritis (1). Several authors therefore advocate the personalized alignment (kinematic, KA or functional alignment, FA), where the aim is to restore the patient's original pre-arthritis anatomy and joint line (2). This means that tibial component placement in varus or valgus is accepted, despite the possible result of a postoperative non-neutral HKA axis (3, 4). Studies indicate that good clinical results can be achieved in terms of range of motion (ROM) and patient reported outcome measures (PROMs) with these techniques, but it has not been tested properly in terms of activity measurements, strength testing or migration of implants (5). There is diversity in the literature regarding whether tibial component with too much deviation from a neutral axis can lead to increased migration and eventually aseptic solution (6, 7). To date, only a few trials, with diverging results, have assessed migration of the implants implanted with KA or FA. The methods are so far perceived as controversial, despite the widespread use (6-8).

KA or FA can be performed by manual conventional surgery; however, the newly introduced robotic assisted surgery probably yields higher accuracy and precision of the cuts during surgery (9). This makes robotic assisted surgery well suited for personalized surgery. Yet, it is claimed that because of diversity of the different features for planning and executing the surgery, each system should be evaluated separately, and not as a group (10). We therefore planned this study to assess the efficacy of robotic assisted surgery comparing MA and personalized alignment (PA) techniques.

Aims of the trial

1. Evaluate the clinical outcomes of patients who have had TKA with PA and compare it with conventional MA.

2. Analyse and compare the in vivo stability over time of TKA operated with PA vs. MA using CT- based radiostereometric analysis (CT-RSA).

3. Evaluate the postoperative position of the implants using two different alignment philosophies.

Objective

Perform TKAs on patients using ROSA® Knee System (Zimmer Biomet, Warsaw, Indiana USA, Figure 2) robotic assisted surgery and randomize the patients to either PA *or* MA.

Material and methods

A multiple blinded randomized controlled parallel superiority trial will be performed, where the patients, study nurse, statistician and physiotherapists are blinded to the surgical method (PA or MA). The study will include 152 patients (Figure 1). The study adheres to the consort statement (11).

Inclusion criteria

Patients aged 18-80 years with femoro-tibial or patello-femoral osteoarthritis (Kellgren-Lawrence, K-L) grade 2-4 with persistent pain, referred to Kristiansund Hospital for primary TKA will be included in the study.

Exclusion criteria

Patients with serious psychiatric disorders, dementia, drug abuse or patients not able to speak and read Norwegian language making them noncompliant or unable to perform an informed consent. Patients with ongoing cancer therapy and or ASA classification >3 (12).

Knee implant

Medial Pivot (MP) and Medial Congruent (MC) prostheses seek to render the patient's constitutional kinematics (13, 14). Because of this, they are believed to be particularly well suited to PA, whom which also seeks to achieve natural knee axes for the patient. We therefore aspire to perform the study with the Persona ® MC (Zimmer Biomet, Warsaw, Indiana USA) prosthesis. The Persona MC TKA is a well-documented implant through both clinical and RSA studies (15-17). In addition, the implant is well known previously for several of the study surgeons. All TKAs will be performed with patella resurfacing.

Robot assisted surgery

The interventions will be carried out with the ROSA Knee robot-assisted surgery (Figure 2), with high accuracy and precision in the cuts (18). This is important because we want great agreement between the planned procedure and the achieved result in terms of alignment of the extremity and placement of the implant. The interventions will be performed at Kristiansund Hospital. A special protocol for the robotic MA and PA surgery will be made, whom to all the surgeons are obliged to adhere to.

Randomization

Prior to surgery, the patients will be randomized to either MA or PA using stratification on surgeon and gender. The randomization will be performed using the eFORSK Web Clinical Report Form (CRF, HEMIT, Norway).

Analytical methods

<u>Work package 1 (WP1) - Patient reported outcome measures (PROMs) and clinical scores</u>

All patients will be examined with PROMs and clinical score preoperatively and 3, 12, 24 and 60 months postoperatively. PROMs used are the Forgotten Joint Score (FJS) (19), Knee injury and Osteoarthritis Outcome Score (KOOS) (20), Visual Analogue Scale (VAS) (21) and the

generic Eq-5D (EuroQol Research Foundation) (22). Clinical testing will be performed including flexion, extension, range of motion (ROM) and clinical stability.

WP2 - Daily physical activity

ActivePal™ (activePal Technology, UK), an accelerometer-based activity monitor preoperatively, after 3, 12, 24 and 60 months postoperatively will be used. Of interest are the number of steps per day, the number of hours of activity per day, sit-to-stand transitions etc.

WP 3 – Clinical testing and strength testing

Maximum strength knee extension will be tested using a knee extension device preoperatively and after 3, 12 and 24 months postoperatively. Voluntary activation with interpolated twitch will also be used (23). Other clinical tests such as 6 minutes walk test (6MWT), treadmill test, stair climbing and descent test, balance test and sit-to –stand test (24, 25).

WP4 - CT-RSA for implant stability

CT-RSA (Figure 3) has high precision of evaluating tibial implants (26) and will be used to assess implant stability. We will also perform migration analysis of femoral and patellar implants. Bone models of the femur, tibia and patella and implant models (femur and tibia) will be created in the CT based micromotion analysis software (CTMA, Sectra, Linköping, Sweden). A total of 8-9 tantalum markers of size 0.8-1 mm will be implanted in the polyethylene patella and the surrounding patella bone, and will be used to analyse implant migration (27, 28). CT-RSA will be performed postoperatively and after 3 , 12, 24 and 60 months, with double acquisitions of at least 25 % of the patients (29).

WP5 - Body composition

CT images taken of the thigh and calf of the patient with soft tissue reconstruction will be analysed using artificial intelligence (AI) technology to assess the muscle and fat distribution in the relevant part of the thigh (30). This is to contribute to an alternative method for clinical endpoints. The change of muscle volume postoperatively at 3, 12 and 24 months will be correlated to other clinical data including muscle strength, PROMs and activity measures.

WP 6 - Implant position

Postoperative CT images from hip to ankle are used to calculate the coronal, axial and sagittal position of the femoral and tibial implants (31).

WP 7 - Conventional radiology

Preoperative conventional images of the knee for inclusion, postoperatively and after 2 years. Preoperative HKA images, and after 3 months and 2 years for assessment of knee axes.

WP 8 - Miscellaneous

All blood loss during surgery will be estimated and registered.

WP 9 - Knee kinematics

Fluoroscopic footage during step up, step down or lunging of up to 60 patients will be performed with a flat panel fluoroscope, in order to assess the difference of the kinematics of the 2 groups (32).

Statistical analysis

Baseline data

Baseline data such as gender, age, body mass index (BMI), American Society of Anaesthesiologists (ASA) classification, operation side, operation time (knife-to-skin time), total time spent in operating room (OR), type of anaesthesiology (i.e. general, or regional and femoral blocks) performing surgeon, implants used (including size), length of stay or day care surgery will be registered. During surgery, stability will be tested in 90 degrees flexion and full extension with by the robot. Normally distributed baseline data will be presented as means with 95 % confidence intervals (CI) unless otherwise stated. Non-normally distributed data will be presented with medians and interquartile ranges.

Sample size

All sample size calculations uses an alpha level of 5 % and a power of 80 %.

WP1 - Patient reported outcome measures (PROMs) and clinical scores

If we assume a standard deviation of KOOS of 20, and a clinical meaningful difference to be 10, we need at least 126 patients. To account for potential dropouts, we add 10-20% therefore include 150 patients, 75 in each group.

WP2 - Daily physical activity

The activity level will be calculated by the use of the primary outcome measure mean steps per day preoperatively and 3, 12 and 24 months postoperatively. Linear mixed model analysis will be performed for calculation of group differences using a fixed (MA vs. PA) and random (patient id) factor (33). Secondary outcome measures are time spent lying, sitting, standing, and transitions between sitting and standing. Assuming a clinical meaningful difference in number of steps is a 1000 steps per day, with an anticipated SD of 2200, at least 76 patients in each group will be needed, using a 2-sided Student T-test (34).

WP 3 - Strength testing

A difference in strength of 15 kg is considered clinically relevant. With an anticipated SD of 20, we need at least 28 patients in each group (35). To account for dropouts, we therefore include 70 patients.

WP4 – CT-RSA for implant stability

In migration studies of the knee, the maximal total point motion (MTPM) of the tibial implant is usually the main outcome variable (36). Suppose a difference in continuous migration of 0.1 mm in order to be clinically relevant. A standard deviation of 0.2 and with a significance level of 95% and a power of 80% would require 16 cases in each group. In clinical studies, it is generally advised to include at least 50 patients in order to achieve balanced groups (37). To account for potential dropouts, we will include 60 patients in the migration study. The statistical analysis of the MTPM will include a linear mixed model analysis with a fixed (MA vs. PA) and random factor (patient id).

Ethics

No patients will be included unless they have signed an informed consent. The trial is approved by the Regional Ethical Committee of Norway (REK, id 738578), but will not commence until approval of the local data access committee (DAC) and data protection officer (PVO) of Møre and Romsdal Hospital Trust. The protocol follows the Helsinki declaration and will be registered in Clinicaltrials.gov. The trial adheres to the Consort statement (11).

Funding

The trial is funded through Møre and Romsdal Hospital Trust, an we will apply for regional and national research and innovation grants.

Adverse events

Complications of TKA are rather rare. All potential complications like readmissions, wound problems, infections, fractures, vessel and nerve damages, cerebral and cardiac incidents, thromboembolism, pneumonia or respiratory complications etc., will be accounted for.

Collaborators

Norwegian collaborating institutions include the Center for Implant Related Research Oslo (CIRRO, Oslo, Norway), Norwegian University of Science and Technology (NTNU, Trondheim, Norway) and Molde University College (Molde, Norway). We also aspire to collaborate with several universities in the EU.

Risks and measures for safety precaution

Surgery

All surgeons involved in the trial are experienced knee surgeons. The surgeons have received thorough tutoring in the use of the ROSA Knee System and the Persona TKA, and both alignment techiques have now been adopted in our standard treatment of end stage OA (38). The learning curve of robotic assisted surgery is probably very small, and more related to time spent on the procedure rather than placement of the implants (39, 40). The placement of the tibial implant will be restricted in the coronal plane to maximum 5 degrees of varus and 2 degrees of valgus. In sagittal plane, the slope will be limited to between 0-10 degrees.

The Persona TKA implant although contemporary, is a well-documented implant with very low migration (15, 16).

The MA and PA techniques are well known and already used in a widespread fashion all around the world. Several clinics in Norway have also adopted the methods.

Implantation of tantalum markers in bone and polyethylene has been performed for more than 40 years in numerous studies without any known complications (27, 41, 42).

Known but rare complications to robotic surgery are fractures at the site of insertion of the bone pins, and pin site infections. In elderly or osteoporotic patients, we will consider using unicortical engagement of the pins. Concerning infections, all the default precautions in the OR will be taken, such as preoperative and postoperative administration of antibiotics, strict sterile procedures etc.

Radiation

CT-RSA utilizes low dose CT protocols. Previous studies show that this method uses less than 0.08 mSv of effective doses per acquisition (26, 43). A special CT protocol will be created in order for as low as possible ED, still with sufficient precision to perform CT-RSA analyses. For the patients in the CT-RSA group of the patients, the total ED of the whole study will not exceed 3mSv. The patients not in the CT-RSA group will all receive well below 1 mSv.

Protection and storage of data

The randomization key will be stored in a locked cupboard in a closed envelope in the research room at Kristiansund Hospital. Only the surgeons and the scrub nurses will know the code. The data will otherwise be stored in the eFORSK system requiring safe log-in procedures via BankID (BankID BankAxept AS, Norway). Any export of data from this will be in Excel or SPPS sheets pseudo anonymized. Pseudo anonymized images for CT-RSA analyses will be exported to the server of Sectra located in Sweden. A data protection agreement (DAP) that follows the GDPR regulations will be signed prior to export of the images. A risk and vulnerability analysis (ROS analyse) was executed for this purpose by the safety officer of Møre and Romsdal Hospital Trust (Risikovurdering SECTRA).The CT images for BodyComposition analysis will also be exported to Ullevaal Hospital in Oslo via a safe tele-radiology line in the same manner as clinical images are exported (with full name and person

id). A special data transport agreement (DTA) will be signed for this purpose. These images will be stored in a safe research server at Oslo University Hospital, Oslo. CT images and fluoroscopic footage may also be exported too international collaborators in the EU/EEC after pseudo-anonymization. The latter will not be performed without special application to the REK, Data Access Committee (DAC) of Møre and Romsdal Hospital Trust and PVO (Data protection officer) in advance.

User involvement

The trial has been discussed with the user group of Møre and Romsdal Hospital Trust, and by Kristiansund Revmatikerforening, a regional user group of osteoarthritis. A local user representative will eventually be appointed to the trial.

Articles planned from the trial

1. Maximum strength of thigh after TKA assessing personalized versus mechanical alignment-1 yr. results
    a. Primary outcome variable: Strength of leg extension
    b. Secondary outcome variables: PROMs, sit-to –stand test, balance test, stair climbing and descent test, 6MWT
2. Change of muscular volume up to 1 year after TKA in a study comparing personalized versus mechanical alignment-1 year
    a. Primary outcome variable
    b. Secondary outcome variables
3. Walking distance 1 year after TKA in a study assessing personalized versus mechanical alignment-1 yr. results
    a. Primary outcome variable: Mean steps per day
    b. Secondary outcome variables: Time spent standing, sitting, laying. Number of sit-to stand transitions etc.
4. Kinematics of personalized versus mechanical alignment evaluated using fluoroscopy
5. Stability of tibial implant using personalized versus mechanical alignment-2 yrs.results
    a. MTPM
    b. Secondary outcome variables: Migration and rotation in 6 degrees of freedom (in mms and degrees)
6. Clinical results of personalized versus mechanical alignment-2 yrs. results
    a. Primary outcome variables: $KOOS_5$
    b. Secondary outcome variables: FJS, Eq-5d, steps/day, muscle strength
7. Stability of a patella polyethylene implant-2 yrs. Results
8. Clinical results of personalized versus mechanical alignment-5 yrs. Results
    a. Primary outcome variable: $KOOS_5$
    b. Secondary outcome variables: FJS, Eq-5d, steps/day, muscle strength

9. Stability of tibial implant using personalized versus mechanical alignment-5 yrs. Results
    a. Primary outcome variable MTPM
    b. Secondary outcome variables: Migration and rotation in 6 degrees of freedom (in mms and degrees)

Articles arising from this project will be published in highly ranked orthopaedic journals. Clinical data are to be published after 1 year, 2 years, 5 years and 10 years, and CT-RSA data after 2, 5 years and 10 years.

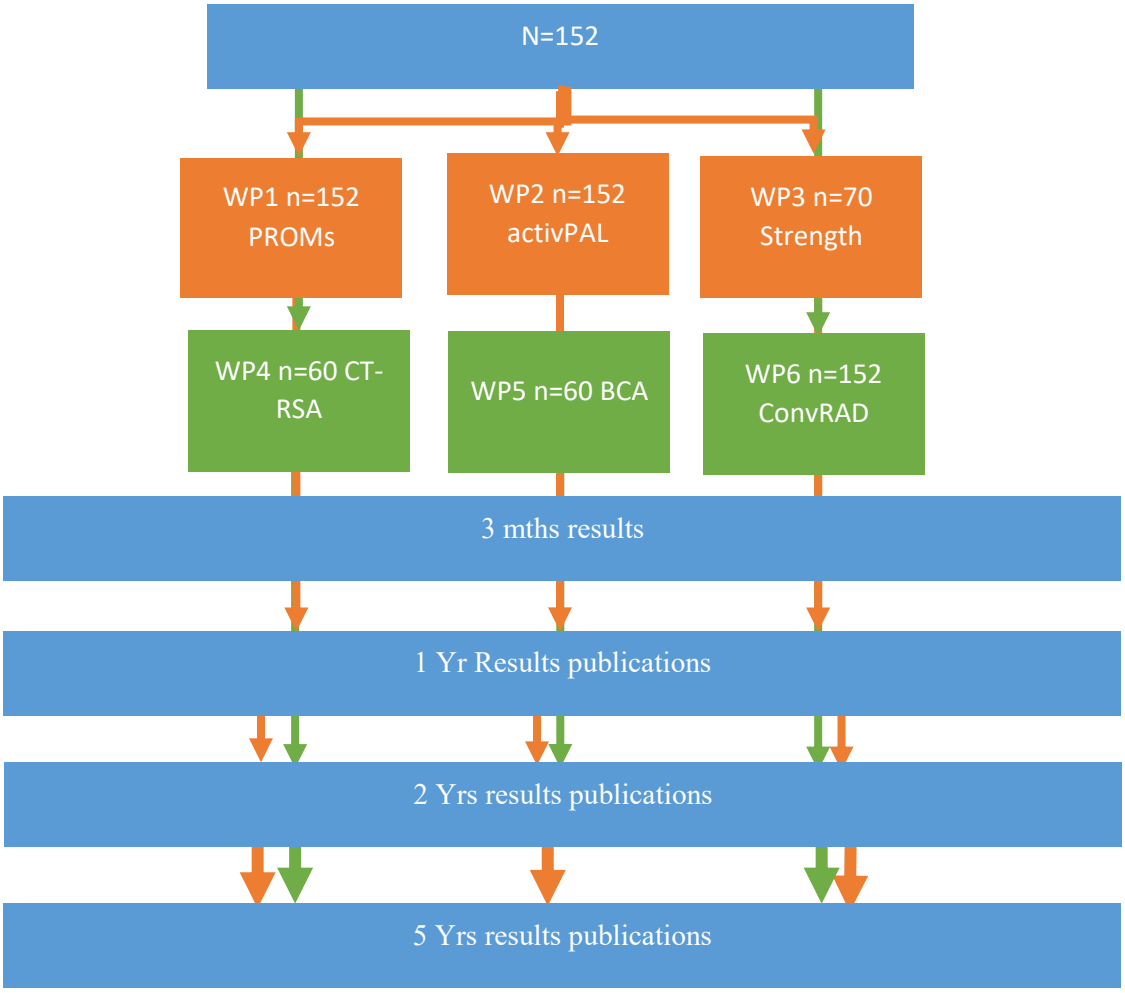

Figure 1 Flowchart of the study

Modality	Preoperative	Postoperative	3 mths	12 mths	2 yr.	5 yr.	10 yr.
CT scan (incl CT-RSA)		xx	x	x	x	x	x
BodyComposition		x	x	x	x	x	x
HKA	x		x		x	x	
X-ray knee	x	x			x	x	x
PROMs	x		x	x	x	x	x
activePAL	x		x	x	x	x	x
VAS	x	x	x	x	x	x	x
Strength testing	x		x	x	x	x	x
Walk and stairs	x		x	x	x	x	x
Gait	x		x	x	x	x	x
ROM	x		x	x	x	x	x
Kinematics				x			

Table 1 Table indicating time schedule for the patients. PROMs includes KOOS, FJS, EQ-5D and Knee Score.

Figure 2 ROSA® Knee System already located in Kristiansund Hospital

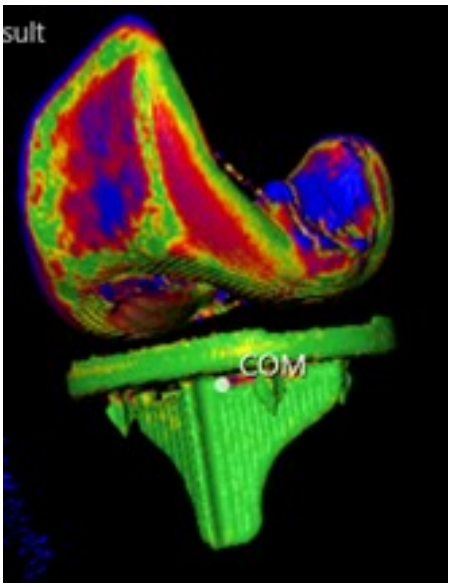

Figure 3 CT-RSA model of tibial and femoral implants in a T

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