Prospective randomized controlled trial of functionally aligned robotically assisted total knee arthroplasty vs patient specific custom made total knee arthroplasty

Short title: Knieathlon

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Background and rationale:

Total knee arthroplasty (TKA) is an established treatment for patients with symptomatic endstage osteoarthritis. The aim of TKA is to provide pain relief and restore function; however, published literature identifies a consistent subset of patients who are not satisfied post-operatively[1]. There is a strong push away from what used to be the golden standard of TKA, mechanical alignment (MA)[2]. In brief, MA is a strategy of implant positioning that completely disregards any patient specific anatomy and orients the femoral and the tibial component parallel to the ground or perpendicular to the mechanical axis of the femur and the tibia, respectively[2]. In the sagittal plane, a similar approach is performed – the femoral component should be the smallest possible and the tibial component is always put at 3 degrees to the floor. Finally, in the axial plane, the tibial component is oriented according to the axis between the attachment of the posterior cruciate ligament and the medial/mid third junction of the tibial tuberosity. As one can expect, a very recent paper lists 10 flaws of this approach[2]. This approach, due to its predictability and safety, remains the golden standard[1].
A strong and a safe transition towards more personalized alignment is advised[3]. This is achieved safely and effectively using robotic assisted surgery (RAS), such as the MAKO Surgical System (Stryker). The system is intraoperatively used to adjust the implant position according to the patient anatomy and the soft tissue structure for every given knee. This approach, labelled functional alignment (FA) is still very new and complicated as it requires excellent understanding of the anatomy and the surgical software, forcing the surgeon to perform significantly more decisions. For this procedure, the surgeon still uses a uniform design, off the shelf-implant that has been demonstrated to force the surgeon to compromise on the trochlear position due to the fixed rotation of the posterior femoral component and the trochlea orientation[4]. The results of this approach, however, do seem to bring improvements at 1 year compared to MA[5]. Currently, one study comparing this approach (FA) and the traditional approach (MA) is being compared in a blinded fashion, using RAS in both instances, in New Zealand [6].
The huge downside of RAS for the healthcare providers are very high upfront costs and significant costs of disposables making the cost-effectiveness of RAS always a topic of debate with ongoing trials [7–9]. One potential alternative that has no upfront costs and marginal increase in manufacturer costs is a custom-made, patient specific implant (CM-PSI). The tools

to deliver the implant, patient-specific instruments (PSI), are less precise than RAS, but the implant itself is completely customized to the patient's anatomy and soft tissue envelope, without any compromise, even in the design of the trochlea. This results in a reported patient satisfaction of 94% at 2 years[10].

Currently there is no ongoing trial or a published planned trial comparing these two techniques in the world. To the authors' best knowledge and information, such a study is also not planned due to a number of high preconditions that are needed for such a study.

Objectives and hypothesis

The primary objective of this study is to compare the Forgotten Joint Score (FJS) in RAS-FA TKA versus CM-PSI TKA at 2 years post-operatively. The FJS is a score that measures the restoration of 'normal joint feeling', and the hypothesis is that patients undergoing RAS-FA TKA will have a superior score.

Secondary objectives include:

- Clinical outcomes using the Kujala anterior knee pain Score. This questionnaire is designed to assess the anterior knee compartment. This has been included due to the difference in implant design that cannot be compensated for using robotics
- Satisfaction after surgery (very dissatisfied-somewhat dissatisfied-neutral-satisfied-very satisfied)
- Pain scale using VAS
- Surgical efficiency by comparing operative times and total theatre time
- Comparison of opioid use
- Number of physiotherapy sessions during hospital stay
- Range of motion measurements
- Radiographic data including radiolucent lines

Methods

The study will be conducted across the 2 sites of the AUVA UKH Steiermark Hospitals. All patients will have surgery, inpatient stays and follow-up at the sites.

Eligibility criteria

Inclusion criteria:

- The patient is a male or non-pregnant female between the ages of 40 and 90 years
- The patient requires a primary total knee replacement
- Patient is deemed appropriate for a cruciate retaining knee replacement
- The patient has a primary diagnosis of osteoarthritis (OA)
- The patient has intact collateral ligaments
- The patient is able to undergo CT scanning of the affected limb
- The patient has signed the study specific, ethics-approved, informed consent document
- The patient is willing and able to comply with the specified pre-operative and post-operative clinical and radiographic evaluations

Exclusion criteria:

- The patient has a history of total, unicompartmental reconstruction or fusion of the affected joint
- Patient has had a previous osteotomy around the knee
- The patient is morbidly obese (BMI > 41)
- The patient has a deformity which will require the use of stems, wedges or augments
- The patient has a varus deformity ≥ 15°
- The patient has a valgus deformity >3°
- The patient has a neuromuscular or neurosensory deficiency, which would limit the ability to assess the performance of the device
- The patient is unable to speak German
- The patient is pregnant

For recruitment purposes, a special Knee arthroplasty clinic will be organized at the hospitals. All patients will be screened by the orthopaedic surgeon and research coordinator based on the criteria. Patients that meet these criteria and express an interest in participating will be provided an ethics approved patient information sheet following initial consultation with their treating doctor. This sheet provides more detail about the study, potential risks and

requirements for follow-up. Pre-operative visits include the collection of consent, CT scan, x-rays and completion of patient reported outcomes.

Interventions

Both techniques have a demonstrated safety track record comparable to MA, and have data supporting increased outcomes when compared to MA. Their direct comparison is yet to be performed in an RCT.

All patients will receive a CT scan of the leg, either the MAKO protocol[11] or the Symbios protocol[12].

In case of RAS TKA, the CT is loaded onto the MAKO planning software, calibrated by a technician and the plan is approved by the surgeon prior to the study. The initial position of the implant is kinematic alignment (KA), aiming to restore the lost bone+cartilage using the implant. The position is then intraoperatively, prior to the cuts, modified by the surgeon to accommodate any differences caused by the soft tissue envelope. Research has demonstrated that an adjustment is performed in more than 90% of cases[13]. The primary goal of FA is to maintain the native joint line while achieving even soft tissue gaps in extension and medial flexion, while preserving the femoral orientation as much as possible (femoral preserving FA).

In case of CM-PSI TKA, the CT scan is uploaded to the Symbios online Planning platform where a technician performs a “pre-plan”, adjusting the implant position to similar principles as for RAS TKA. However, the perfect balancing and positioning can be achieved by modifying the implant design. The design and the position is approved by the surgeon digitally, and the implant with the instruments in manufactured and shipped to the healthcare facility. This process requires 6 weeks.

Both interventions are made via a central incision and medial parapatellar approach, patients receive a CT scan in both cases and the waiting list is longer than 6 weeks irrespective of the study, making the procedure blinded for the participant.

As the intervention relates to surgical technique, all strategies are focused on patient management intraoperatively. All participants will continue standard post-operative care with their surgeon at their conclusion of the trial. All participants will undergo assessment by the research team pre-operatively, and at 6 weeks, 6 months, 12 months and 24 months post-

operatively. The research team will assist in the randomisation process and cannot be blinded to the allocation. Physiotherapists will also record functional measures of recovery during in-patient stay and will be blinded to the allocated alignment. Participants will be recruited from AUVA UKH Hospitals in Graz, Austria. The trial aims to recruit 10 patients per month, with the recruitment process estimated to take 12 months.

Sample size

This trial seeks to determine if robotic arm-assisted TKA following FA principles provides superior clinical outcomes to patient specific custom made TKA. Ingelsrud et al. reported that the minimal clinically important change in FJS for TKA patients was 14 points[14] which has been used as the effect size for this study. Mean forgotten joint score in clinical trials at 2 years has been reported at 66 with a standard deviation of 26[15]. Using a power of 80% (β=0.2), significance level of 5% (α=0.05) and accounting for 10% loss to follow-up yields a sample size of 60 participants per arm.

Randomization

A master randomisation sequence will be generated prior to the start of the trial using an online random number generator (www.sealedenvelope.com). The master sequence will be maintained by the principal investigator and patients will be allocated a treatment in sequential order following consent.

Blinding

The participants, physiotherapists and assessors will be blinded to the treatment allocation. The participant identification list will be archived at the site on a secure network in a password-protected file, with the research team having access to the file. The investigators and research team are unable to be blinded to the allocation due to their role in the allocation of treatment and execution of surgery. Participants will be unblinded to the intervention at the end of the trial, unless there is a medical reason to do so prior to the end of the study. Due to the minimal requirement of 6 weeks to manufacture the custom-made implant, surgery will be performed not sooner than 6 weeks after booking of the case.

Data collection

Outcomes will be primarily captured on paper, transferred to an excel table manually and stored using a password-protected electronic platform on the internal server of the healthcare facility.

For the purposes of group comparisons, we will collect age, gender, BMI and ASA score. In order to compare radiologic osteoarthritis severity and knee phenotypes, we will classify all knees according to the Kellgren-Lawrence classification[16] and the CPAK classification[17].

Preop	**In-hospital stay**	**6 weeks**	**3 months**	**6 months**	**12 months**	**24 months**
x-ray		x-ray		x-ray	x-ray	x-ray
FJS		FJS	FJS	FJS	FJS	FJS
Kujala		Kujala	Kujala	Kujala	Kujala	Kujala
VAS		VAS	VAS	VAS	VAS	VAS
		Satisfaction	Satisfaction	Satisfaction	Satisfaction	Satisfaction
ROM		ROM	ROM	ROM	ROM	ROM
	Times Opioids Physio					

Table 1 – Overview of timepoints for data collection

Data management

The International Council for Harmonisation guidelines for Good Clinical Practice (ICH GCP) will be followed throughout the study. The sponsor will conduct routine monitoring visits for data verification against source material, as defined by participant entered data or medical records. Data collected by the sponsor will be stored electronically in a password-protected folder with restricted user access. Periodic surgeon investigator meetings will also be held to review participants where treatment has deviated from the protocol. The chief investigator will be responsible for the training and sign- off of all staff working on the study.

Confidentiality

All research staff and investigators will be employed by the AUVA and will comply with its confidentiality practices. All participants will be allocated a unique non-identifiable study number and any information disseminated in journals or conferences will ensure patient anonymity is maintained.

Statistical methods

The primary and secondary outcome data gathered from patients in each study group will be pooled and summarised. The mean, standard deviation and 95% confidence intervals will be calculated for each measure in each group. All outcome measures will be assessed on their distribution and homogeneity to confirm the appropriate statistical model. Adjustments will be made for multiple testing over time. Pairwise comparisons will be examined using a paired t-test if normally distributed or non-parametric test for skewed distribution. Categorical data will be evaluated using frequency and percent distributions, with significance testing performed using Fisher exact test or chi-squared test. Statistical significance is defined as a p-value < 0.05.

Data assessment

Interim analysis will be conducted at milestones of 6-month and 1-year follow-up for dissemination of results. Periodic analysis will also be conducted for patient safety. Sub-group analysis based on patient phenotype will be dependent on sufficient post hoc sample size calculations. A per-protocol and intention to treat analysis will be performed. In the event of randomisation errors, the participant will be converted to the study arm that represents the received treatment. The statistical model will be corrected in the event of missing data and to avoid type I error when performing multiple comparisons.

Oversight and monitoring

The principal investigator will be responsible for execution of GCP, delegation of authority to research staff and will review adverse events and protocol deviations. The principal investigator will review all adverse event forms for safety assessment. Any device or treatment related adverse events will be reviewed regularly by the Investigator team and a midpoint assessment of patient report outcomes will be conducted. An adverse event (AE) is

defined as any undesirable clinical occurrence in a participant, whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device. A serious adverse event (SAE) is an adverse event that results in hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity, life-threatening or death. All will be reported to the principal investigator. All series adverse events will be periodically examined using an alert in the participants electronic medical records and will be reviewed periodically in-line with the evaluation schedule.

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