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ORIGINAL ARTICLE

Knee Joint Distraction as an Alternative Surgical Treatment for Osteoarthritis: Rationale and Design of two Randomized Controlled Trials (*vs* High Tibial Osteotomy and Total Knee Prosthesis)

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ABSTRACT

AIM: In case of refractory knee osteoarthritis at a relatively young age causing persisting pain, treatment options are limited. In case of medial degeneration high tibial osteotomy (HTO) may be considered, or in case of more generalized OA, a total knee prosthesis (TKP). However, these young and active patients have a major risk of revision surgery. Knee joint distraction (KJD) could be an alternative treatment; prolonged clinical benefit and cartilage tissue repair have been demonstrated. Therefore, two RCTs were designed, evaluating clinical efficacy and for HTO additionally comparing cartilage tissue repair.

MATERIALS AND METHODS: Patients<65 years of age considered in regular clinical practice for TKP or HTO were included. TKP and HTO were performed according to usual standard of care. KJD was performed for six continuous weeks by use of an external fixator bridging the joint, fixed at each side to two bone pins.

RESULTS: Inclusion rate was stable over time and took 42 and 22 months for TKP *vs* KJD and HTO *vs* KJD, respectively. At baseline, patient characteristics differed: age was 55.2±0.9 and 50.0±0.7 p<0.000, KOOS-score was 36.6±1.4 and 42.2±1.6 p=0.012, and VAS-pain was 68.7±2.1 and 61.4±2.4 p=0.028, in the KJD-TKP cohort and KJD-HTO cohort, respectively.

CONCLUSIONS: For implementation of KJD a comparison with available surgical alternatives is needed. TKP and HTO were chosen as the most relevant comparators. Inclusion is closed, and all treatments are completed. Data have to be awaited to determine the position of KJD in surgical treatment of refractory knee OA.

Key words: Knee osteoarthritis; Treatment; Joint distraction; Randomized controlled trial; High tibial osteotomy; Total knee prosthesis

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INTRODUCTION

Osteoarthritis (OA) is a slowly progressive joint disorder clinically characterized by pain and functional impairment[1]. Tissue pathology comprises cartilage damage and loss, changes in subchondral

bone, and secondary low-activity synovial inflammation. Although the association between structural tissue changes and clinical characteristics is not clear and depends on the definition of the parameters and population[2], tissue changes seem related to[3], and are considered causal to pain, physical disability, and a poor quality of life[4,5].

OA in general, and specifically knee OA, is the most frequent musculoskeletal disorder (prevalence >10% in Europe), and is a great socioeconomic problem[6], with a significant burden for patient and society[7]. The incidence of OA is increasing, due to a physically active aging population and an increase of obesity as well as high demanding sports[8,9].

Several etiologic and pathophysiologic pathways, including chemical (e.g. inflammatory cytokines and tissue destructive proteases[10]) and mechanical ones (e.g. abnormal joint alignment and traumatic impact[11]), are considered important. After initiation of OA there is an interplay between all intra- (and extra-) articular tissues and processes involved, resulting in a biochemically and mechanically disturbed joint homeostasis, with concomitant progressive joint tissue damage[12].

Different forms of treatment are available however there is no actual cure for OA yet. The current treatment of knee OA (see different guidelines[13-16]) at best slows down progression of tissue damage. In case of failed conservative treatment[17] and failed joint preserving surgery (when indicated), placement of a total knee prosthesis (TKP) is recommended[18].

TKP is a final option, considered effective in relieving pain and regaining function. The total number of TKPs is increasing as is the rate of revisions[19], estimated at approximately 1.5 million and 125 thousand, respectively, in 2020 in the US alone[20]. The revision rate is predominantly determined by the limited life span of TKPs. Especially for relatively young (<65 years) and physically active patients progressive wear and tear of the prosthesis will result in costly and less effective revision surgery[21]. In 2006, over 41% of all knee replacements and up to 44% of all total knee revisions in the NIS cohort (USA) were performed in patients' aged 65 and younger[19,22,23]. Clearly, TKP adds considerably to the socio-economic and healthcare problem of OA.

Therefore, development of alternative joint saving therapies for conservative treatment resistant knee OA at a relatively young age is necessary to enable a final TKP treatment later in life, and with that prevent or at least reduce the chance for revision surgery.

Alternative treatments to diminish pain and improve function start conservatively with analgesics and/or disease modifying osteoarthritis drugs (DMOADs). However currently no pharmacological agent exists that unambiguously promotes the healing of articular cartilage lesions[24]. As tissue structure damage underlies pain and functional limitations, strategies aiming at tissue repair, to be accompanied by clinical benefit, are at present the common focus of research on knee joint degeneration. Despite that multiple joint tissues are involved, there is a focus on cartilage repair therapies[25], generally being most effective for local, relatively fresh isolated cartilage defects however contra-indicated if generalized OA is present. In case of micro-fracturing, areas of denuded bone are stimulated to form fibro-cartilaginous tissue to fill up the defect[26]. The use of more recently propagated platelet (en)rich(ed) plasma (PRP) formulations mimics such effects[27]. Alternatively, various tissue-engineering techniques to extrinsically restore articular surfaces have been attempted, including those that deliver a matrix/gel seeded with chondrogenic cells and/or factors[28,29]. Although promising, these techniques require mostly multiple surgical interventions, frequently with in vitro culture conditions, with or without gene transfection involved, and as such still have limited implementation in clinical practice and are very costly[30]. In case of generalized (advanced) OA, limited to one of both knee joint compartments, placement of a unicompartmental knee prosthesis (UKP) could be considered, with moderate but still improving results[31]. More recently a permanent implant providing partial medial unloading (Kinespring®) has been promoted as an alternative[32], with still limiting results, potential risks[33], and without cartilage repair activity. In case unicompartmental damage exists in combination with a mechanical axis deviation, high tibial osteotomy (HTO) is often the treatment of choice[34]. Although it is not a simple surgical procedure to unload the affected joint compartment, it provides good and prolonged clinical results, with even cartilage repair reported by second-look arthroscopy and qualitative MRI[35,36].

The potential benefit of unloading a degenerated joint surface was described not only to improve pain and function, but to provide a mechanism for structural tissue repair as well[37]. It has been demonstrated that by use of joint distraction using an external device, creating temporarily total absence of contact between the cartilage surfaces, sustained clinical benefit with intrinsic cartilage repair can be observed[38-42]. Although joint distraction in general, including knee joint distraction, is reported on more frequently now (for review see ref 1) only limited prospective data on joint distraction for treatment of knee OA are available. Only one prospective open uncontrolled trial has been performed. Follow-up of the 20 treated patients is reported on at one, two, and five years post-treatment[43,44] (ms under review). Clinical benefit with cartilaginous tissue repair has been demonstrated to sustain for up to five years after treatment in over three-quarter of the patients treated. This observation is supported by several animal in vivo studies, (for overview see[38]). Most recently KJD in a canine model of OA has demonstrated that cartilage tissue repair is accompanied by pain relief[45].

In the abovementioned prospective uncontrolled trial, relatively young (average 50 years, range 32-57) patients with end-stage knee OA, indicated for a TKP, were included. The question is why these patients did not get the TKP earlier (note that in general 44% of TKP is placed under the age of 65 years[19]), and as such whether there has been an inclusion bias. This raises the question how clinical results would have been in relation to the change in clinical features if treated with a TKP in a really randomized approach. Moreover, looking in retrospect, most of the patients included in this study had predominantly medial tibial-femoral OA and some were earlier treated with HTO (n=5). This raises the question how clinical results would have been in relation to the change in clinical features as well as cartilaginous repair activity if treated with HTO in a real randomized approach.

Rationale

The lack of a control group in the previous study, potentially creating an inclusion bias (highly motivated patients), and with that limiting generalizability of the results tempted us to design two separate randomized controlled trials based on patients considered for TKP or HTO in which these treatments were by randomization compared with KJD with respect to clinical outcome and for HTO with respect to cartilage tissue repair as well.

MATERIALS AND METHODS

The KJD *vs* TKP trial is a randomized controlled, multi-center, phase II trial with participation of the Maartensclinic Woerden and the Maastricht University Medical Center registered in the Dutch Trial

Database under number NTR2809.

Successive patients considered for TKP based on persistent knee pain, radiologic features of joint degeneration, and failing conservative therapy, were approached for participation. In case of interest, patients were included following the protocol (Figure 1). The primary outcome is the two years improvement in WOMAC score. The Western Ontario and McMaster Universities Arthritis Index (WOMAC 3.0[46]) is the most used questionnaire for OA clinical research[47] to analyze post-operative and follow-up clinical outcome. The WOMAC-total score is extracted out of the KOOS questionnaire[48] (comprising self-assessment of five instead of three dimensions using a five point Likert scale). The trial accommodates a total of 60 participants.

Inclusion criteria were: patients considered for TKP according to regular clinical practice; age<65 years; radiological joint damage: Kellgren & Lawrence grade (KLG) above 2; intact knee ligaments; normal range-of-motion (min. of 120° flexion; max flexion limitation of 15°); normal stability; Body Mass Index (BMI) <35.

Exclusion criteria were: psychological inabilities or difficult to instruct; not able to undergo MRI examination (standard protocol); inflammatory or rheumatoid arthritis present or in history; post traumatic fibrosis due to fracture of the tibial plateau; bone-to-bone contact in the joint (absence of any joint space on radiography); surgical treatment of the involved knee <6 months ago; an infectious susceptible prosthesis (joint replacement) in situ; primary patello-femoral OA.

The KJD *vs* HTO trial is a randomized controlled, multi-center, phase II trial with participation of the Maartensclinic Woerden and the University Medical Centre Utrecht, registered in the Dutch Trial Database under number NTR2900.

Successive patients with medial tibio-femoral compartmental OA considered for medial opening wedge HTO according to regular clinical practice were approached for participation. The primary outcome parameter was based on cartilaginous repair activity estimated by the percentage of denuded bone areas (dABp) evaluated by quantitative MRI[49]. This trial accommodates a total of 69 participants.

Inclusion criteria were: patients with medial tibio-femoral compartmental OA considered for HTO according to regular clinical practice; age<65 years; radiological joint damage: KLG above 2; intact knee ligaments; normal range-of-motion (min. of 120° flexion); normal stability; BMI <35.

Exclusion criteria were: mechanic axis-deviation (varus) of more than 10 degrees; psychological inabilities or difficult to instruct; not able to undergo MRI examination (standard daily clinical practice protocol); inflammatory or rheumatoid arthritis present or in history; post traumatic fibrosis due to fracture of the tibial plateau; bone-to-bone contact in the joint (absence of any joint space on radiography); surgical treatment of the involved knee<6 months ago; contra-lateral knee OA that needs treatment; primary patello-femoral OA.

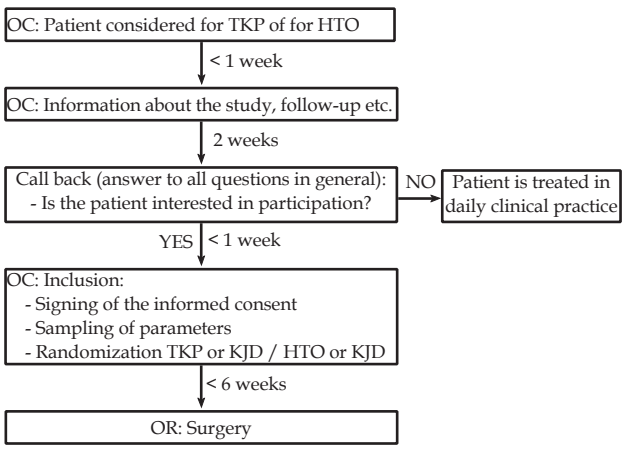

Figure 1 Flow-chart. Description of patient selection for both trials. OC: outpatient clinic. OR: operation room.

Patients were selected and informed at the outpatient clinics. After an obligatory consideration time of two weeks, all patients (n=129) signed the informed consent at time of inclusion (see flow-chart; figure 1). Both study protocols and related documents were reviewed and approved by the independent medical ethics committee of the UMC Utrecht, and approved by the local comities of the Maartensclinic Woerden and Maastricht UMC. The study is being performed in accordance with the ethical principles laid out in the Declaration of Helsinki.

Treatment

Knee Joint Distraction: KJD was performed by use of a proof of concept external distraction device. Two dynamic mono-tubes (Triax®, Stryker®, 45 kg spring with 2.5 mm displacement) were fixed in a standard fashion to bone pins, two for each of the four locations (lateral and medial for femur and tibia; see figure 2), bridging the knee joint lateral and medial. Intra-operatively the tubes were distracted for two millimeters. Postoperatively, every day the tubes were gradually further distracted (1 mm/day), until 5mm distraction is reached. At day four, distraction was checked by weight bearing radiographs and adapted if needed to 5mm distraction compared to pre-operative conditions. After approximately four days of hospitalization, patients were discharged from the hospital and allowed full weight bearing with crutches. At three weeks postoperative the patients visited the outpatient department for clinical examination (control of pin tract wounds) and radiographic evaluation of the distraction distance. At six weeks radiographic control was performed again as final check of distraction distance, before the frame and pins were removed under anesthesia followed by a forced flexion of the knee (stretching of fibrotic scare tissue around the pin holes). Patients were discharged and advised to gradually regain normal full loading according to the physiotherapy protocol as described hereunder. Patients received prophylactic low molecular weight heparine for a total of nine weeks; during the six weeks frame period and the first three weeks after removal because of impaired mobility of the lower extremities.

At three months from baseline the first study related clinical follow-up was performed.

In comparison with the earlier open uncontrolled trial[43] the duration of distraction was shortened with two weeks (from eight to six weeks) to limit treatment burden. The rationale for this shortening to six weeks was founded by the fact that biomarker-turnover of cartilage and bone tissue increases within the first four to six weeks of KJD, and thereafter stabilizes as observed in the prospective uncontrolled trial. With shortening of the distraction period the concern about post-treatment stiffness decreased. In order to further diminish the burden of the patients, a continuous distraction was performed instead of a two weekly interruption for continuous passive motion (CPM) therapy upon temporarily removal of the mono-tubes[43].

In both trials a specified KJD-physiotherapy protocol (based on guidelines for TKP and HTO) was developed to make the whole post-surgical procedure similar for all KJD patients and comparable to HTO and TKP. In the phase direct after KJD removal, weight bearing was gradually regained in about six weeks, for newly formed cartilage to acclimatize to load, with 10-15kg added per week.

Figure 2 Total knee prosthesis (TKP; permanent until revision surgery is indicated), knee joint distraction (KJD; 6 weeks external device), and medial opening wedge high tibial osteotomy (HTO; 18 months until removal of the plate).

Table 1 Post-operative rehabilitation phases per treatment. Every phase represents (according to expectations) six weeks. Every phase is characterized by several goals, and only when those are all reached the patient can start the next phase.

	Phase I	Phase II	Phase III
KJD	Fixateur externe, no physiotherapy.	Fixateur externe is removed. 10-15kg/week increase of weight bearing with two crutches. Start passive flexion exercises.	When 100% weight bearing, finishing crutches and start isometric exercise and active flexion.
HTO	Max 15kg weight bearing with two crutches.	Increase to 100% weight bearing with two crutches, start isometric exercise.	Finishing crutches, isometric exercise.
TKP	Full weight bearing with two crutches, start isometric exercise.	Full weight bearing without crutches, isometric exercise.	Isometric exercise.

Moreover the flexion-range was gradually restored (Table 1). Regain of isometric muscle strength is started up in a later phase, all to prevent joint tissues from over-loading[50,51].

Furthermore, guidelines were developed for nursing of the pins and skin around the pinholes, to mini mize pin-tract infections[52,53]. During hospitalization pinholes were showered daily from day two postoperative and daily cleansed with chlorhexidine. At discharge, it was advised to shower pinholes daily, with additional cleaning of the surrounding skin with chlorhexidine twice a week.

Total Knee Prosthesis, posterior stabilized: The whole joint was replaced with a posterior stabilized femur and tibia component of the Genesis II® model (Smith and Nephew®, figure 2). After fixation with GentaPalacos® cement the definite insert was placed in between the components. After an average hospitalization of four days, with two postoperative days of CPM exercise, patients were discharged and advised to regain gradually full weight bearing guided by a physiotherapist. Patients received prophylactic low molecular weight heparin until six weeks post-operative. After six weeks the stability of the knee was examined, clinically and radiographically. Three months post-operative the first study related follow-up was performed.

High Tibial Osteotomy, medial opening wedge: Aim of the surgery is to correct load distribution within the knee, however the procedure is accomplished extra-articular. Pre-operative measurements (method of Miniaci[54]) define the size of the osteotomy-opening. With support of radiography the osteotomy direction is identified. Then the osteotomy is accomplished leaving the lateral cortex intact. The "osteotomy-gap" is fixed with a Tomofix® plate or a locking compression plate (LCP) both by Synthes®, see figure 2. In general the gap was left open, however in three cases the gap was filled with an autologous bone-graft from the iliac crest. After an average hospitalization of three days, patients were discharged from the hospital and max 15kg weight bearing was allowed with crutches for the first six weeks. Patients received prophylactic low molecular weight heparin until six weeks post-operative. At six weeks, stability was evaluated based on physical examination and first consolidation was evaluated on a standardized radiographic control. Subsequently, full weight bearing was allowed without crutches, guided by a physiotherapist. Three months post-operative the first study related follow-up was performed. At 18 months postoperative removal of the plate is protocolled to allow proper MRI evaluation at two years post-surgery.

Follow-Up

Clinical outcome: In both trials patient related outcome measures (PROMs) were evaluated by questionnaires: the Knee Injury and Osteoarthritis Outcome Score (KOOS; normalized to a 100-point scale for total and subscales; 100 being the best score)[48], the Intermittent and Continuous OsteoArthritis Pain Score (ICOAP; normalized to a 100-point scale for total and subscales; 100 being the worst score)[55], and the Visual Analogue Pain Score (VAS Pain; 0-100mm; zero meaning no pain).

Additionally quality of life measures were evaluated with the EuroQol-5D questionnaire (EQ-5D)[56] and the Short Form-36 (SF-36)[57], both normalized to a 100-point scale for all subscales; 100 being the worst score). For the SF-36, subscores were converted into a physical and mental component summary (PCS and MCS[58]) whereas a score of 50 is the average score relative to a Dutch reference population, <50 is a worse outcome and >50 a better outcome. For

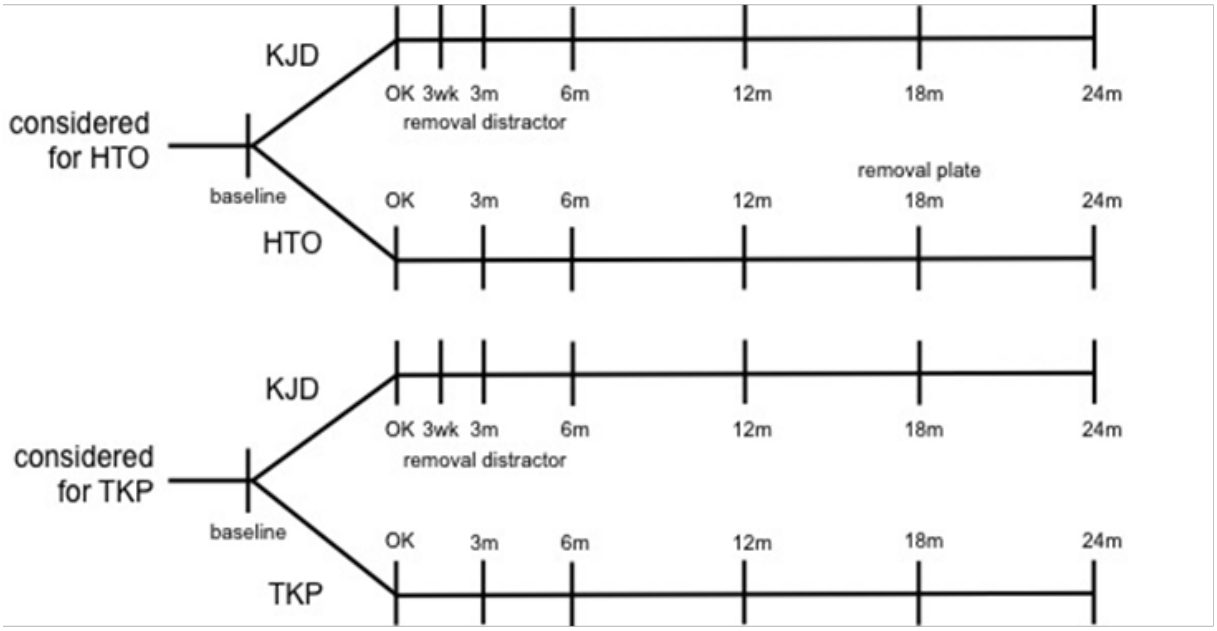

Figure 3 Follow-up moments for both randomized clinical trials.

Table 2 Frequency of data collection by questionnaires, imaging and biomarker samples. The first row contains patients of the KJD *vs* TKP trial, the second row patients of the KJD *vs* HTO trial. KJD: knee joint distraction. HTO: high tibial osteotomy. TKP: total knee prosthesis. Baseline I at inclusion, max 3 months before surgery; Baseline II at the day before/at surgery.

	Baseline I	Baseline II	3 m	6 m	12 m	18 m	24 m
Q clinical	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD
Q QOL + costs	TKP/KJD HTO/KJD		TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD
MRI	KJD HTO/KJD				KJD KJD		KJD HTO/KJD
X-ray	KJD HTO/KJD		KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD
Serum/urine	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD

the EQ-5D an EQ-5D total score was calculated[59] ranging from 0-1; 1 being the best possible score. Costs were evaluated by a custom made questionnaire; evaluating costs related to the disease and treatment of the patient. For a schedule of measurement time-points, see figure 3 and table 2.

Structural outcome: For patients treated with KJD and HTO (within both trials), structural outcome parameters are evaluated. For imaging markers standardized semi-flexed radiographs according to the KIDA protocol[60], and coronal 3-Tesla MRI images 3D spoiled gradient recalled (SPGR) with fat suppression according to a protocol in cooperation with Eckstein *et al*[49], were made. The primary outcome parameters are defined as minimal and mean medial joint space width (JSW) by KIDA measurements on radiographs and percentage denuded bone (dBAp) and average cartilage thickness (ThCtAB) by use of custom made software (Chondrometics GmbH, Ainring, Germany) on MRI. For a schedule of measurement time-points, see table 2.

Additionally, for biochemical markers blood and urine samples (non-fastened, not taking care of diurnal changes, because of practical feasibility) were taken at regular time points to evaluate cartilage and bone turnover[61].

In a subgroup of 20 KJD and 20 HTO patients the standard MRI measurements were extended to specifically measure cartilage proteoglycan content/distribution (dGEMRIC), cartilage collagen content/distribution (T2-relaxation) and bone marrow lesions (T2-fat suppressed). Additionally a CT-scan was performed to analyze bone density.

Statistical Methods

In both trials group size calculation was based on a non-inferiority hypothesis, implying that KJD will lead to a similar result in comparison with the conventional therapy. Sample sizes of both trials were estimated based on the primary outcome parameter, with a 5% type one error, and with a power of 80% (as calculated using PS Power and Sample size calculations version 3.0 by an epidemiologist from the Julius Centre, UMC Utrecht). Both sample sizes were increased with 15% to account for possible dropout and/or insufficient data quality. A randomization rate of 2:1 was used (special demand by the ethical committee), with KJD being considered as experimental and therefore the potential risk and limited capacity to perform this treatment.

For the KJD *vs* TKP trial a change in WOMAC score of more than 15 points (SD±16.7) compared to baseline was considered clinically relevant[62], leading to a total of 60 patients that could participate; 40 treated with TKP and 20 with KJD.

For the KJD *vs* HTO trial based on the previous study results, for dABp an average decrease of 14% (SD±20%) in two years could be expected for KJD. For HTO it seems sensible that changes in cartilage quality can occur but actual quantified cartilage growth has never been reported[35]. Based on the available literature we expect

none to limited decrease in denuded bone areas after HTO, leading to a total of 69 patients that could participate; 46 treated with HTO and 23 with KJD.

Baseline patient characteristics are described for both trials and were compared by use of a non-parametric independent t-test (Mann-Whitney U). In case double baseline measurements were available these were averaged. A p-value <0.05 was considered statistically significant. IBM SPSS Statistics Version 20 was used for all analyses.

RESULTS

In the KJD *vs* TKP trial, after randomization and before treatment, three patients (all TKP) withdrawn from further participation. These three patients were excluded from further follow-up. One patient was pre-operatively excluded because of development of severe complaints of the contra-lateral knee after inclusion. In the KJD *vs* HTO trial one patient withdrew before treatment (HTO) and one patient (KJD) was not able to undergo surgery, based on cardiac status analyzed by the pre-operative screening. These two patients were excluded from further follow-up (summarized in figure 4).

Patient characteristics of the two trials are summarized in table 3. As anticipated, characteristics differed between both trial populations, for both demographic as well as clinical features. Patients indicated for TKP are older and mainly females, whereas patients indicated for HTO are mainly males. In both groups patients were somewhat overweight (BMI >25kg/m^2), statistically significant increased for TKP indicated patients. The right knee was, in both groups similarly, the most affected joint and Kellgren and Lawrence grades were equally distributed within both groups.

Table 3 Baseline table. Means of both cohorts are presented ± SEM for demographic characteristics and clinical outcome parameters.

	TKP *vs* KJD	HTO *vs* KJD	*P-values*
Age	55.2±0.9	50.0±0.7	0.000
Gender (M)	38%	64%	0.005
BMI	28.1±0.8	27.3±0.4	0.032
Affected joint (Right)	59%	55%	0.681
MAC (medial)	79%	100%	0.000
KLG (2/3/4)	35%/38%/27%	40%/52%/8%	0.205
WOMAC	47.7±1.8	53.8±2.0	0.017
KOOS	36.6±1.4	42.2±1.6	0.005
ICOAP	53.5±2.6	49.8±2.5	0.243
VAS	68.7±2.1	61.4±2.4	0.051
SF-36 PCS	38.8±1.3	42.5±1.3	0.031
SF-36 MCS	42.1±0.8	39.5±0.8	0.029
EQ-5D total	0.54±0.03	0.64±0.02	0.024
EQ-5D VAS	69.0±1.9	71.6±2.0	0.206

MAC: most affected compartment; KLG: Kellgren and Lawrence grade.

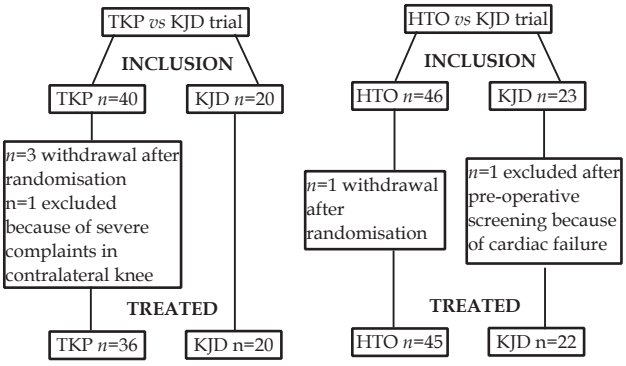

Figure 4 Flow-chart. Patients included and eventually treated per trial.

Pain seems more explicit for patients indicated for a TKP (lower WOMAC/KOOS scores and higher VAS pain score). All patients of both trials have worse SF-PCS and SF-MCS outcomes compared to the Dutch reference population, and whereas TKP indicated patients have most physical problems, the HTO indicated patients suffer more mentally, both statistically significant different compared to the other trial population. Quality of life at baseline is statistically significant better for HTO indicated patients, whereas the self reported EQ-5D VAS showed no differences between both groups. Between the arms of both trials each, there are no statistical significant differences suspected as anticipated based on randomization.

CONCLUSION

KJD is a novel surgical treatment, with the potential to postpone a TKP and with that decreasing the chance for knee prosthesis revision surgery later in life significantly. Despite earlier promising results, it is often questioned whether an inclusion bias would have favored the outcome of knee joint distraction. The outcome of both these randomized controlled trials will address this question and will provide predicting parameters to indicate which patients (profile) may benefit best from joint distraction.

Inclusions for both clinical trials are closed. For the KJD *vs* IInTKP trial the last patient was included in August 2014, and for the KJD *vs* HTO trial the last patient was included in March 2013. The two years data are anticipated to be published at the end of 2016.

DISCUSSION

For further comparison and future implementation of KJD, randomized controlled trials are prerequisite. Moreover, extending the number of patients treated with KJD under controlled research conditions would add to implementation in clinical practice of this promising joint sparing treatment as well. Surgical intervention is the next step after failure of conservative treatment, as is the case with the patients included in this study. As such HTO and TKP are considered as the most relevant competitors in this randomized study.

An additional step could be to see how the outcome of KJD relates to conservative treatment. A first comparison was already made earlier for structural parameters, five years after KJD (ms submitted for publication[63]) with patients from the OsteoArthritis Initiative (OAI; http://www.oai.ucsf.edu). This showed that the cartilage repair and growth gained within the first two years in KJD treated patients, sustained until five years follow-up even though in most cases the natural progression of OA proceeded again. This might be also interesting for clinical outcome although it must be taken into account to which extent these patient-groups are comparable in case of disease progression and disablement, despite similar baseline WOMAC scores.

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CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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