Unloading the osteoarthritic knee: osteotomy and joint distraction

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Mechanische ontlasting van de arthrotische knie:
standbeencorrectie en distractie
(met een samenvatting in het Nederlands)

Proefschrift
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Chapter 1

General introduction and aims

KNEE OSTEOARTHRITIS

Osteoarthritis of the knee is in general a slowly progressive joint disorder, causing pain, function limitations, and tissue structure changes. These include peri-articular bone changes, cartilage degeneration, and low-grade synovial inflammation. Also changes in ligament and muscles strength and proprioception may be involved. Ultimately these changes lead to debilitating pain, functional limitations, and inability to perform activities of daily living.[1-3] It is a multi-factorial disease and governed by a complex interplay of biological and mechanical factors. Pre-disposing factors for development and progression are of importance as well. Among these factors are gender, mechanics (such as trauma), bone morphology (leg alignment), obesity (consisting of mechanical and metabolic parameters), genetics (e.g. collagen polymorphisms) and age.[4] The most important mechanical factor is considered leg alignment. It is generally accepted that in people with natural varus alignment the cartilage of the medial compartment of the knee is predominantly loaded.[5] Varus malalignment is associated with both development and progression of knee osteoarthritis; once the medial compartment starts to lose cartilage thickness, a perpetuating circle of increasing medial compartment pressure and decrease in medial joint space is setup.[6,7] One of the major biological factors playing a role in the increasing risk of knee osteoarthritis is obesity, with a five-fold increased risk of developing knee osteoarthritis in obese individuals.[8,9] The interaction between obesity and alignment is also described, with the association between malalignment and joint loading being the highest in patients with the highest mass.[10,11] However, metabolic factors related to inflammation (orchestrated by adipokines) are important as well.[12] Another important, if not the major risk factor for knee osteoarthritis, is older age.[13,14] Prevalence increases steeply with age, starting at around age 50 to 55 years. Many age related changes contribute to this increase, amongst them cartilage (chondrocyte) senescence, muscle weakness, diminished proprioception leading to altered (impact) mechanics, and ligamentous laxity.[13,15] Considering that the populations of developed countries are ageing and the rates of obesity specifically in younger patients are rising, an increase in incidence and prevalence, and progression to end stage disease of knee osteoarthritis is inevitable.[16,17] Recent data show that 13.8% of the population >45 years is diagnosed with symptomatic knee osteoarthritis, and this number is predicted to increase to 15.7% in 2032.[18]

The initial treatment of knee osteoarthritis is conservative, consisting of restricted activity, decreasing weight, patient education, and physical therapy.[19-21] To modify symptoms pharmacological treatment is started (e.g. analgesics, anti-inflammatory drugs). When all conservative therapy fails, surgical treatment is the next step.[22] Joint preserving treatments are scarce. Arthroscopic debridement is not recommended any more, because studies showed that the improvement in symptoms could easily be attributable to a placebo effect[23], osteotomies are mainly considered in unicompartmental knee osteoarthritis[24], and unicompartmental knee arthroplasty (UKA) is not advised in younger patients, since significant higher rates of revision have been reported.[25,26] Novel treatments for medial compartmental osteoarthritis, like the KineSpring, need further proof of efficacy. Generally, in severe knee osteoarthritis affecting the medial and the lateral tibiofemoral compartment with persistent severe pain, a total knee arthroplasty (TKA) is often indicated. The first TKA was done in the 1970s and is now generally regarded as the gold standard for end-stage knee osteoarthritis, being an (cost)-effective treatment.[27] Nevertheless, joint replacement also has its drawbacks. Especially in the young and active population results after knee replacement are less satisfactory with lower implant survival rates.[28-31] Therefore, in case of persisting, painful, conservative treatment-resistant knee osteoarthritis at relative young age, alternative, joint preserving, treatments strategies are a necessity. In this population the surgical treatment should include alteration of the mechanical factors associated with the development and progression of knee osteoarthritis. This is, amongst others, possible by unloading the knee joint. Depending on the severity of the osteoarthritis (unicompartmental or bicompartmental) and malalignment, unloading of the knee joint is possible by performing an osteotomy (partial unloading) in case of clear malalignment or by knee joint distraction (temporarily unloading) in case bi-compartmental knee osteoarthritis is involved.

OSTEOTOMIES

Before being almost entirely replaced because of the success of TKA and later UKA, osteotomies around the knee were a well-established technique in the treatment of unicompartmental knee osteoarthritis.[32] Compared to TKA and UKA, osteotomies were considered to be technically demanding, make subsequent revisions more complex and to have potentially higher complication rates.[33,34] Nevertheless, the formulation of better guidelines for the selection of candidates for osteotomy[35], the newly published planning techniques by Paley in 2003[36] and newly available operation techniques and fixation methods all contributed to the resurgence of osteotomies. Where in the past the surgical techniques were difficult and dependent on unstable methods of fixation (e.g. staples), with the introduction of specific adapted plates for use in osteotomy surgery[37], based on the locking-compression-plate concept, and with new opening-wedge tibia and femur osteotomy techniques, the predictability of outcome was significantly increased.[38]

The main indication for osteotomies is the correction of malalignment in case of unicompartmental tibiofemoral osteoarthritis of the knee. The aim of osteotomies is to shift the load from the 'diseased' compartment toward the less affected compartment of the knee and thus achieving a more even distribution of the load of the knee joint. With that it is aimed to accomplish pain relief and to postpone joint replacement surgery.[39] Besides that, osteotomies may be indicated to decrease a joint axis deformity to normal leg alignment or to obtain a leg alignment symmetrical to the contralateral side. Considered as ideal candidate are younger (40 to 60 years of age) patients, with greater activity demands.[35] Depending on the location of the deformity an osteotomy can either be performed in the proximal tibia (High Tibial Osteotomy; HTO) or in the distal femur (Distal Femoral Osteotomy; DFO). Traditionally HTO is used to correct varus deformity and DFO to correct a valgus deformity. However, the source of a varus deformity can be localized in the tibia, in the femur or in both. The same is true for a valgus deformity. Generally, the deformity should be treated at its source[36], in order to prevent excessive joint-line obliquity, which is not well tolerated (increased shear stresses)[40] and leads to technical difficulties in case of TKA.[41]

High tibial osteotomy

A valgus producing HTO in order to correct varus malalignment in medial compartment osteoarthritis is most commonly performed using a medial opening-wedge or lateral closing-wedge technique. For both techniques good clinical mid-term follow-up results are demonstrated by many studies.[42] The medial opening-wedge being the preferable technique, since no fibula osteotomy is needed and it avoids the peroneal nerve. Additionally, closing-wedge techniques change the posterior tibial slope[43], which could lead to more technical concerns in TKA conversion[44], and are associated with more early conversions to TKA.[45] Moreover, with the bi-plane medial based opening-wedge technique[46] there is more room for proximal fixation and due to the ventrally located buttress there is stability in the sagittal and transverse planes. Combined with the locking compression plates (internal fixation) there is no need for additional bone grafting and even early full weight bearing four weeks after surgery without loss of correction is possible.[47] Survival rates of HTO differ between 87-99% at five years and 66–84% at ten years.[48-53] A recent published cost-effectiveness study even showed that HTO is the most cost-effective strategy in younger patients (<60 years) with isolated medial knee osteoarthritis when compared with UKA or TKA.[54]

In literature evidence can be found for intrinsic cartilaginous tissue repair and regeneration after opening-wedge HTO, however it is sparse.[55-58] Spahn et al.[57] reported restoration of deep cartilage lesions in 60% one and a half years after the surgery, and Koh et al.[58] found partial or even fibrocartilage coverage in 50% of the patients with additional mesenchymal stem cell therapy. To date, no studies are conducted comparing HTO on clinical outcome and on cartilage regeneration with other knee joint preserving treatments.

Distal femoral osteotomy

Opposite to HTO a distal femoral osteotomy (DFO) is mainly used to correct a valgus malalignment in lateral compartment osteoarthritis. Techniques that can be used are the lateral opening-wedge and medial closing-wedge.[59,60] The lateral opening-wedge appears to be technically easier, since it includes a single bone cut, however disadvantages include delayed union or even non-union and irritation of the iliotibial band by the implant.[61] The medial closing-wedge technique has as its most important limitation that the osteotomy disrupts the soft-tissue gliding mechanism, often causing a haematoma, and subsequently slowing of the rehabilitation process.[62] In the past, in both techniques for fixation often an angled blade plate was used. However, the correct insertion of the blade plate is considered technically demanding and the blade location itself dictates the final correction.[62]

In the past years DFO technique and fixation methods as treatment for lateral OA in patients with femoral deformities have evolved. In concordance with HTO, the locking compression plate concept was also specifically designed for the fixation of DFO[63] and a new biplane technique was developed.[64] The biplane technique allows a more distal positioning of the lateral hinge, it avoids the trochlea and does not disrupt the soft tissue gliding mechanism. The specifically designed angle stable plate was found to be more stable in biplanar technique than in the uniplanar technique[65] and, has the best bone healing potential in the biplane closing-wedge technique compared to other DFO techniques.[66] All these improvements resulted in more accurate corrections, decreased bone healing problems and improved clinical scores.[64,67-69] Nowadays, even a less invasive approach to the distal medial aspect of the femur in biplanar medial closed-wedge distal femoral osteotomy is described and proved to be feasible and safe.[70]

However, where literature on varus-producing DFO's is increasing, specific reports on valgus-producing DFO's (in case of varus deformity at the femur) is absent. Furthermore, specific literature on the vascular supply of the medial and lateral femoral condyle, and the relationship to height of the osteotomy cuts in distal femoral osteotomies is absent.

KNEE JOINT DISTRACTION

Knee joint distraction (KJD) is a surgical technique in which the femur and tibia are gradually separated for a period of time and to a certain extent. This is achieved by using an external fixation frame/device. It is a more recently developed joint preserving treatment for persisting, painful, conservative treatment-resistant osteoarthritis at a relatively young age, with the goal to postpone a TKA and thereby avoid revision surgery.

The precise mechanism by which joint distraction causes the improvements is not exactly known yet. The aim in joint distraction is to reduce mechanical stresses on the cartilage and by that initiating a regenerative response. By using the external fixation frame/device further wear and tear of the articular cartilage is prevented and allows chondrocytes to initiate regeneration. Coiled springs in the distraction tubes combined with stiffness of the joint capsule cause changes in the synovial fluid pressure during loading and unloading of the knee joint, improving the nutrition of the cartilage supporting regenerative activity.[71-73] Additionally, the presence of these intermittent hydrostatic compressive forces in the joint is reported to attract and retain mesenchymal stem cells into the joint and can stimulate the mesenchymal stem cells in co-culture with chondrocytes, leading to cartilage matrix synthesis.[72,74,75] Distraction also relieves mechanical loading of the peri-articular bone, leading to temporary osteopenia. Bone turnover is known to be involved in cartilage growth because it is considered as a rich store of cartilage growth factors. After distraction the subchondral bone is less dense, supporting the chondrocytes in the cartilage regeneration and absorbing greater stress.[76,77] Also changes in synovial fluid composition as a result of distraction have been related to the potency of resident stem cells in cartilage regeneration.[74]

In the past, four clinical studies[78-82] have been performed using distraction treatment for knee osteoarthritis. All studies showed significantly improvement on clinical outcome (pain and function) and also a clear increase in radiographic joint space width (JSW). Two studies evaluated the cartilage regeneration in the knee arthroscopically[78,80,81] and two others did so by MRI.[78,80] The most convincing study, the only one based on prospective evaluation, was by Intema et al.[78] In this, prospective open uncontrolled study twenty patients aged <60 years and originally considered for TKA, were included and treated with distraction between 2006 and 2008 in the University Medical Center Utrecht. Already at three months follow-up a clinical improvement, based on the total WOMAC index, was observed. This improvement reached a plateau within six months, and was sustained at least until two-year post-treatment.[83] The results of the clinical improvement were corroborated with actual cartilage regeneration, analyzed by use of weight-bearing radiographs and MRI quantitative cartilage measurements.[78,83] Even after two years the cartilage regeneration was still present and the newly formed tissue showed to be mechanically resilient, as under weight-bearing the JSW was significantly increased on radiographs.[83]

Comparative data with other treatments (such as HTO for unicompartmental osteoarthritis and TKA for bicompartmental osteoarthritis) is lacking. So, it is not known which patient would benefit best from which joint preserving treatment. Furthermore, since KJD is a relatively new treatment, the long-term health effects, the cost-effectiveness compared to the gold-standard treatment, specific parameters predicting outcome, and the optimal duration of the distraction treatment are also not described.

AIMS OF THIS THESIS

As mentioned in the previous introduction, regarding knee joint preserving treatment a lot is not clarified yet. HTO is never compared on clinical outcome and on cartilage regeneration with other knee joint preserving treatments. Specific literature describing valgus-producing DFO's and relating the vascular supply of the femoral condyle to the osteotomy cuts in DFO's is absent. In the field of KJD, comparative date with other treatments (such as HTO for unicompartmental osteoarthritis and TKA for bicompartmental osteoarthritis) is lacking, leaving unknown what the optimal treatment will be in relatively young patients with knee osteoarthritis.

The aim of this thesis therefore is to improve the knowledge regarding these knee joint preserving treatments.

The following specific aims were defined:

Part I: Osteotomies

Aim I: To evaluate the outcome in a cohort of patients that received a valgus-producing DFO and find out whether there is a difference in bone healing time between the uniplanar and biplanar technique.

Aim II: To investigate the vascular supply of the medial and lateral side of the distal femur and the relationship to the height of distal femoral osteotomies.

Aim III: To compare HTO with KJD in a RCT to determine the clinical outcome and the cartilaginous tissue repair one-year after treatment.

Part II: Knee joint distraction

Aim IV: To evaluate the long-term effect of KJD (five years after treatment) and how the changes in cartilaginous tissue repair compares to the natural course of joint degeneration.

Aim V: To predict the health economic value of KJD potentially followed later in life by TKA as compared to performing TKA directly.

Aim VI: To determine whether shorter (6 weeks continuous) duration of distraction treatment influences the outcome as compared to the original (intermittent) 8 weeks distraction.

Aim VII: To compare KJD with TKA in a RCT to determine the clinical outcome one-year after treatment.

Aim VIII: To identify parameters that can predict cartilaginous tissue repair after KJD.

OUTLINE OF THIS THESIS

In **chapter 2** we present a consecutive case series of lateral uniplanar and biplanar closed-wedge valgus osteotomies of the distal femur in patients with a symptomatic femoral varus deformity. Specifically, we focused on the influence of the uniplanar and biplanar technique on the bone healing time.
DFO specific literature on the vascular supply of the femoral condyle and the relationship to the height of distal femoral osteotomies was absent. Therefore a human cadaver dissection study (presented in **chapter 3**) was conducted to provide evidence regarding this subject.
Regarding HTO, no studies were conducted comparing this treatment on clinical outcome and on cartilage regeneration with other knee joint preserving treatments. To determine what the optimal joint-preserving treatment would be in case of unilateral knee osteoarthritis in relatively young patients, we performed a RCT comparing HTO with KJD on clinical outcome and cartilaginous tissue repair and regeneration. In **chapter 4** we describe the one-year results.

To evaluate the long-term health effect of KJD and the observed cartilaginous tissue repair we followed the patients treated in the original study of Intema et al.[78] In **chapter 5** we present the five-year follow-up data. Additionally, the five-year changes after KJD were compared with the natural progression of osteoarthritis.
To guide optimal implementation of KJD for patients and society, in **chapter 6** a model is created to predict the cost-effectiveness compared to TKA.
In the RCT's comparing KJD with HTO and TKA the duration of distraction was, based on empirical knowledge, shortened to six weeks and performed continuously. To determine whether this adjustment in distraction treatment influences the outcome one-year after treatment, in the study described in **chapter 7** the twenty patients treated in the original study of Intema et al.[78] (with intermittent eight weeks of distraction) were compared with the first twenty patients, treated with KJD, that were included in one of the two RCT's.
Since the original study of Intema et al. [78] was a prospective, uncontrolled study lacking a control group, no comparative data on efficacy between KJD and TKA was available. Therefore a RCT was performed to evaluate whether there is a clinical relevant difference in clinical outcome between KJD and TKA. In **chapter 8** we describe the one year results.
To improve patient selection for KJD, in **chapter 9** an attempt to identify baseline characteristics, which can predict the degree of cartilaginous tissue repair after KJD is decribed.
Finally, in **chapter 10** all evidence from this thesis is summarized, put it into a general perspective and some general recommendations for further research are made.

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Part I

Femoral and tibial osteotomies

Chapter

2

Distal femoral valgus osteotomy: bone healing time in single plane and biplanar technique

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ABSTRACT

Purpose: Varus deformity can be localized in the tibia, in the femur or in both. If varus deformity is localized within the femur it is mandatory to correct it in the femur. This report presents the technique and results of a consecutive case series of lateral uniplanar and biplanar closed-wedge valgus osteotomy of the distal femur for the treatment of varus deformity of the knee.

Methods: Retrospectively, fifteen patients (sixteen knees) were identified. Indications for surgery varied from unloading an osteoarthritic medial compartment to reduction to symmetrical varus leg aligment. Pre- and post-operative x-rays, including a full leg radiograph, were assessed as well as bone healing time at follow-up intervals. Clinical outcome was assessed using different questionnaires.

Results: There were nine male and six female patients with a median age at surgery of 45 (± 14) years. The mLDFA changed from 95.9° (± 2.7°) preoperatively to 89.3° (± 2.9°) postoperatively. Preoperative planning and the use of angle stable implants resulted in accurate corrections according to preoperative aims in all but one patient. At follow-up (mean, 40 months) the mean VAS score was 2.5 (± 2.4) and the WOMAC score averaged 80 (± 20). The mean bone healing time of biplanar osteotomies (4 ± 3 months) was shorter than in the uniplanar osteotomies (6 ± 3 months).

Conclusions: Distal lateral closed-wedge valgus osteotomy of the femur for the treatment of femoral varus deformities resulted in clinical improvement and accurate corrections in patients with different aims for correction. A biplanar osteotomy technique shortens bone healing time.

INTRODUCTION

A large longitudinal population based study has shown that varus malalignment of the knee is not only associated with progression of knee osteoarthritis, but also with the development of knee osteoarthritis.[1] In a biomechanical loading study it was demonstrated that the cartilage of the medial compartment of the knee is predominantly loaded in a varus knee, a neutral mechanical axis slightly loads the lateral more than the medial compartment and in valgus alignment, the main load runs through the lateral compartment.[2] The rationale for osteotomies around the knee in symptomatic osteoarthritic joints is to decompress the overloaded or affected compartment of the knee by shifting the weight bearing axis to the more normal compartment and thus achieving a more even distribution of the load of the knee joint and accomplish pain relief. Besides that, osteotomies may be indicated to decrease a deformity to normal leg alignment or to obtain a leg alignment symmetrical to the contralateral side. Traditionally high tibial osteotomy (HTO) is used to correct varus deformity and distal femoral osteotomy (DFO) to correct a valgus deformity. However, the source of a varus deformity can be localized in the tibia, in the femur (Figure 1) or in both. The same is true for a valgus deformity. If a varus deformity that is localized in the femur is corrected using a valgus-producing HTO an excessive joint-line obliquity will be the result.[3,4] Joint-line obliquity of the knee is not very well tolerated because of the increased shear stresses.[3] Furthermore, excessive joint-line obliquity may lead to technical difficulties when later performing a total knee arthroplasty.[5] Distal femoral osteotomy technique and fixation methods as treatment for lateral OA in patients with femoral deformities have evolved in recent years resulting in more accurate corrections, decreased bone healing problems and improved clinical scores.[6-9] Whereas literature on varus-producing distal femoral osteotomies is increasing, specific reports on valgus-producing DFO's is absent. The retrospective study described here was set out to present the technique and results of a consecutive case series of distal lateral closed-wedge valgus osteotomy of the femur for the treatment of patients with symptomatic femoral varus deformity.

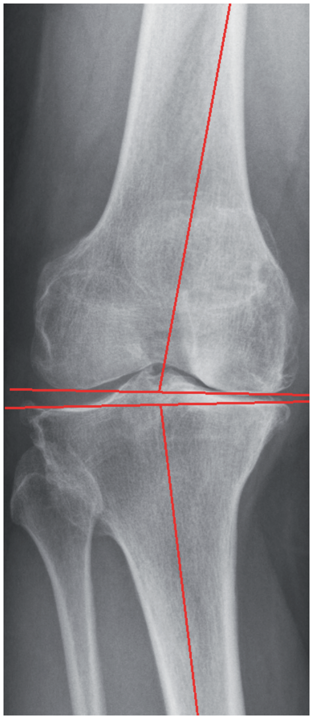

Figure 1. Example of varus deformity in the distal femur (mLDFA 100°, MPTA 86°).

MATERIALS AND METHODS

Patients

Retrospectively, we identified fifteen patients (sixteen knees) who underwent a closed-wedge valgus-producing osteotomy of the femur for the treatment of varus deformity in our department in the past decade. The osteotomies were performed between 2005 and 2012, in two centers in the Netherlands (Maartenskliniek Woerden and Sint Maartenskliniek Nijmegen). Two experienced surgeons (RJvH and SS) performed all osteotomies using the techniques described below. The aims for correction differed from unloading in case of medial osteoarthritis, decrease of varus to normal varus or decrease to leg alignment symmetrical to the contralateral leg.

Measurements

In order to evaluate the degree of knee deformity and degree of osteoarthritis before and after surgery, all patients underwent preoperative and postoperative plain x-rays of the knee in 3 planes (AP-weightbearing view, lateral view, PA 45º weight-bearing tunnel view and patella skyline view) and a full leg standing AP radiograph. The full leg standing anteroposterior radiographs were obtained using a standardised protocol. This means that the patient is standing on both feet with the knees in full extension, and with the X-ray beam centred on the knee. The knee should be positioned in such a way that a true AP view of the knee is obtained with the patella centred.[10] The degree of osteoarthritis was scored with the use of the scale of Kellgren and Lawrence.[11] In addition, the degree of varus deformity was assessed by measuring preoperatively and postoperatively the mechanical tibiofemoral angle, the medial proximal tibia angle (MPTA), the mechanical lateral distal femoral angle (mLDFA) and the knee joint line convergence angle (JLCA).[4] The mechanical axis of the femur is defined as the line between the centre of the femoral head (identified using Mose circles) and the apex of the intercondylar notch of the femur. The mechanical axis of the tibia runs from the midpoint between the tibial spines to the mid-width of the distal tibia. The mechanical tibiofemoral angle is the angle between the mechanical axis of the femur and tibia[4] and was expressed as a deviation from 180º (positive values indicate varus, negative values valgus). The MPTA is the angle measured medially between the mechanical tibial axis and the tibial joint line (defined as a line tangential to the flat or concave aspect of the subchondral line of the two tibial plateaus).[4] The mLDFA is the angle measured laterally between the femoral mechanical axis and the femoral joint line (a line tangential to the most distal points on the convexity of the two femoral condyles).[4] MPTA and mLDFA values between 85º and 90º are considered normal. A MPTA less than 85° indicates that the varus deformity is located in the tibia. When there is a mLDFA higher than 90°, the femur contributes to the varus deformity. The JLCA was defined as the angle between the femoral and tibial knee joint lines in the frontal plane. A medially converging joint line greater than 3º is abnormal and indicates either ligamentous laxity or loss of cartilage thickness as source of varus malalignment.[4] All measurements were performed by two of the authors (SS and JTW)) and not one case had any fixed joint contracture, which could influence radiographic measurements.

Clinical outcome

The range of motion of the knee was measured preoperatively and during the postoperative visits. The function of the knee joint and quality of life (Qol) was evaluated postoperative using the validated Dutch knee injury and osteoarthritis outcome score (KOOS)[12] and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[13], both normalized to a 100% scale, 100 being the maximum score. The VAS pain score (0-100mm; "0" meaning no pain) was used to evaluate pain. The Lysholm knee score provided information on instability and functional limitations[14] and the Tegner knee function score (range 0–10) was used to determine the level of activity in work and sports.[15] Questionnaires were sent by postal mail to all patients.

Operation technique

Surgery is performed in supine position with the knee in full extension and a tourniquet is placed at the root of the thigh to create a bloodless field. A single shot of antibiotic is recommended preoperatively. Fluoroscopic visualization of the hip, knee, and ankle joint is possible during surgery. The image intensifier is positioned at the side of the non-affected lower limb.

A 10-15 cm straight lateral incision is made, starting 3 cm proximal from the knee joint line and extending proximally. After the fascia lata is split longitudinally, a lateral subvastus approach is started by palpation of the natural opening under the distal part of the vastus lateralis muscle belly at the level of the supratrochlear area. A Langenbeck's retractor or a blunt Hohmann retractor is used to lift the muscles anteriorly. The dorsal part of the lateral vastus muscle is freed from the intermuscular septum by blunt and sharp dissection. Special care is taken to visualize and ligate the perforating vessels that may be present in this area while creating enough room proximally to allow for plate fixation. A blunt Hohmann retractor is placed posteriorly in contact with the bone protecting the popliteal neurovascular bundle in the area where the osteotomy is planned. The two retractors stay in place throughout the rest of the procedure.

The starting point for the distal osteotomy at the lateral femur is defined by preoperative digital planning and intraoperative fluoroscopy check using temporary plate application to relate osteotomy height to optimal plate position (Figure 2) The desired height of the osteotomy is marked. Under fluoroscopic control two K-wires are inserted for an oblique down sloping wedge with the wedge base length at the lateral cortex

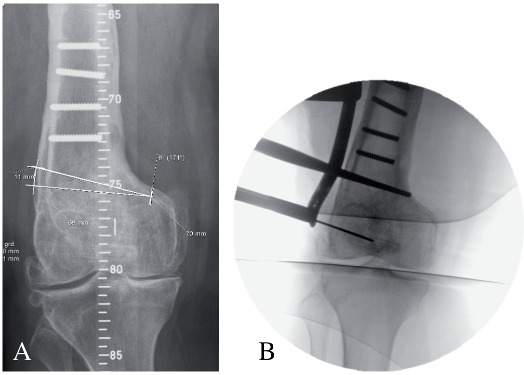

Figure 2. The starting point for the distal osteotomy at the lateral femur is defined by pre-operative digital planning (**a**) and intraoperative fluoroscopy check using temporary plate application (**b**) to relate osteotomy height to optimal plate position.

corresponding to the preoperative planning. The K-wires converge just proximal to the medial femoral condyle, end 0.5–1 cm short of the medial cortex and may be inserted free-hand or using an osteotomy guiding device.

Between 2005 and 2008 a uniplanar closing wedge osteotomy was performed, by making two transverse cuts with an oscillating saw within the two K-wires. Since 2009 we only use the biplanar osteotomy technique.[16] In the biplanar technique the dorsal ¾ is used for the two transverse osteotomy cuts whereas a proximal directed frontal plane saw cut is made in the ventral ¼ of the distal femur. The dorsal cortex can be used as a reference for a parallel cutting direction in the frontal plane cut that should be made with a thinner saw blade (Figure 3).

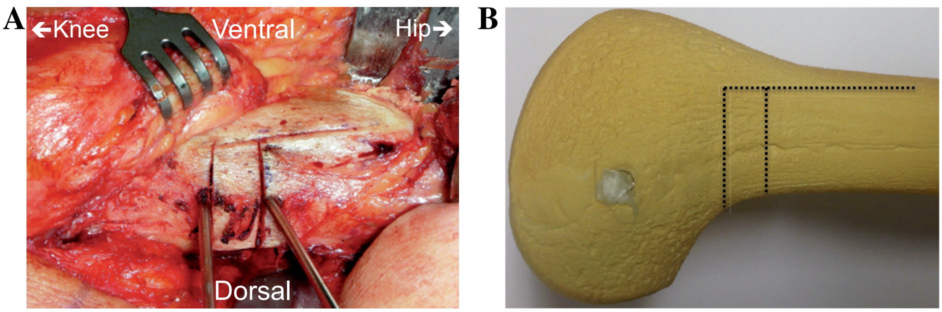

Figure 3. Example of the biplanar technique in a left distal femur intra-operatively (**a**) and in a sawbone **(b)**. The two transverse cuts are made in the dorsal ¾ whereas the proximal directed frontal plane saw cut is made in the ventral ¼ of the distal femur.

After wedge removal it is important to inspect the area of the resected wedge for completeness because remaining bone fragments may cause incomplete closure and fracture of the medial cortical hinge during closure. Additional bone removal and weakening of the hinge with help of a special bone impaction instrument (blunt chisel) is then indicated. Closing the wedge must be performed gradually by gentle valgus force. It may take several minutes to enable plastic deformation of the medial cortex to close the osteotomy gap. It should be noted that the medial cortex of the distal femur in general is weaker and the hinge point of the osteotomy will fracture more often as compared to the lateral cortex hinge point in a medial closing wedge osteotomy. An intact medial cortex after osteotomy closure provides for a higher axial and rotational stability.

Limb alignment is now evaluated fluoroscopically by placing a long rigid alignment rod between the center of the femoral head and the center of the ankle. The rod representing the weight-bearing line should pass the knee joint at the preoperatively defined mechanical axis. If adequate correction is achieved, the osteotomy is stabilized with either a TomoFix (Synthes) Lateral Distal Femur plate (LDF) (ipsilateral version) or with a TomoFix Medial Distal Femur Plate (MDF) (contralateral version). The decision which plate is used is based on personal choice of the surgeon. However, the MDF plate is less pronounced after insertion and therefore more suitable in relatively shorter and smaller femurs.

The plate mounted with drill guides and a distance holder to protect the periosteum is distally placed on the lateral femur condyle and proximally in line with the femur shaft in the frontal and sagittal plane. Temporary fixation distal to the osteotomy is performed with a K-wire drilled through a guiding sleeve. Plate position is checked fluoroscopically. As the TomoFix is an internal fixator precise fit to the femur is not necessary. After drilling, at least four self-tapping locking screws are inserted distally. Next, a bicortical self-tapping lag screw is inserted eccentrically in the dynamic part of the combi hole directly superior to the osteotomy putting the osteotomy under axial compression. Three self-tapping monocortical or bicortical (depending on bone quality and patient's stature) screws are inserted in the remaining holes proximal of the lag screw. Finally, the lag screw is changed for a self-tapping bicortical locking screw inserted in the locking part of the combi hole. After a final check with the image intensifier, the wound is closed over a non-suction drain. Care is taken to meticulously close the fascia lata before subcutaneous closure. The skin is closed intracutaneously.

Post-operative care

A sterile compressive bandage is applied immediately after surgery and radiographs in two (AP view and lateral view) directions are made post-operative. In the first 24 hours during rest the knee is positioned in a 60-90° flexion position to prevent adhesions of the vastus lateralis muscle to the femur.[17,18] Full range of active and passive movement of the knee is started as soon as tolerated by the patient with the help of a physiotherapist. During the first six weeks post-operative partial (no more than 15 kg to 20 kg) weight-bearing is allowed between crutches. After clinical and radiographic prove of bone healing at 6 weeks follow-up progressive weight-to full weight bearing is started.

Comparison of bone healing time

Bone healing at the postoperative follow-up times at 6 weeks, 3, 6, 9 and 12 months was evaluated on standard coronal and sagittal radiographs. Full bone healing was defined as full reformation, though osteotomy recognizable, as earlier described by van Hemert et al.[19] Bone healing time at different follow-up times for biplanar and uniplanar osteotomies was scored and compared using standard T-test for comparison.

RESULTS

Of the fifteen patients (sixteen knees) who underwent an isolated valgus producing closing-wedge distal femoral osteotomy (DFO), one patient had a total knee arthroplasty within two years post-operatively. There were nine male and six female patients with a median age at surgery of 45 (± 14) years, and preoperatively 63% of the cases had a Kellgren and Lawrence grade of III. Table 1 shows the study population characteristics. One patient had a bilateral closed wedge valgus DFO. The varus deformity was caused by femoral malunion in five knees, due to overcorrection of a valgus deformity (previous osteotomy) in four knees, secondary to an (hemi)-epiphysiodesis in two knees, and idiopathic in five knees with osteochondritis dissecans of the medial femoral condyle in two knees. Five osteotomies were preceded by an arthroscopy; one had a partial lateral meniscectomy and four a partial medial meniscectomy.

Table 1. Characteristics of the study population

Characteristics	DFO group
Number of patients, n	15
Number of osteotomies, n	16
Mean age at surgery, yr (±SD)	45 ± 14
Gender ratio, M:F	9:6
Mean body length at surgery, cm (±SD)	180 ± 11
Mean weight at surgery, kg (±SD)	86 ± 20
Mean Body Mass Index at surgery, kg/m^2 (±SD)	26 ± 4
Side, Left:Right	6:10
Kellgren & Lawrence	
Grade 1 (n)	2 (12.5%)
Grade 2 (n)	3 (18.8%)
Grade 3 (n)	10 (62.5%)
Grade 4 (n)	1 (6.3%)
Mean follow-up, months (±SD)	40 ± 30

Operative data

There were no intraoperative complications. The mean duration of the surgery was 89 minutes (range 50 to 135 minutes). In six knees the DFO was uniplanar and in ten biplanar. An angular stable LDF plate was used in twelve knees, an angular stable MDF plate (contralateral) in three and in one knee, because of non-availability of other plates at time of surgery, a LISS plate. In two knees additional fixation was used: in one knee a staple at the fractured medial hinge in one other knee an antero-posterior lag screw through the anterior flange of the biplane osteotomy. A fracture of the hinge without dislocation was observed in eight knees.

No systemic complications, wound infections, or nerve palsies occurred. Due to tenderness seven patients required plate removal. In one patient an ACL-reconstruction as well as opening wedge valgus producing HTO was performed several years after the index surgery for progressive symptomatic medial osteoarthritis causing tibial varus deformity and instability. In two patients an arthroscopy was necessary (amongst them the patient who underwent the total knee arthroplasty).

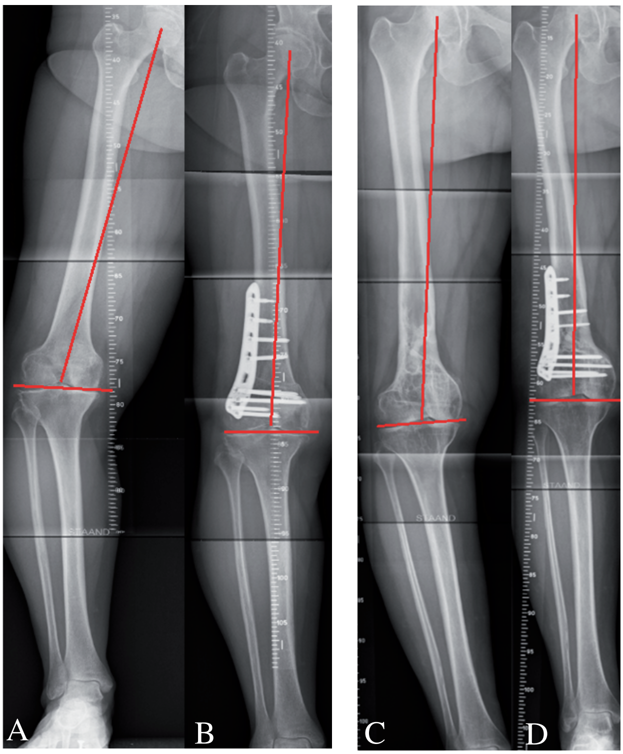

Figure 4. Leg alignment preoperative (**a-c**) and three months postoperative in two cases (**b-d**).

Table 2. Preoperative and postoperative radiographic measurements

Case	Preoperative					Postoperative					
	K&L	TFA	MPTA	mLDFA	JLCA	K&L	TFA	mLDFA	JLCA	HF	BHT
1	3	10	90	99	2	4	2.5	90.7	1.4	Yes	9
2	4	5.5	92	95	3.5	4	4.0	89	2.5	No	3.8
3	3	14	86	95	5	3	3.5	85	5.5	Yes	4.8
4	1	10.5	86.5	95	3	1	1.5	85.5	3.5	No	3.5
5	2	10	87.5	96.5	2	2	2.5	88	2	Yes	3
6	3	8.5	93	102	0.5	3	1.5	95.5	2 Lat	Yes	3
7	2	8.5	89	95.5	3	2	0.2	90.5	0.5 Lat	No	5.5
8	3	10.5	88	95	4	3	6	91	5	Yes	10
9	3	7	88	93	2	3	-1	87	1.5	No	2.3
10	3	16	86	100	2.5	3	5.5	91	1 Lat	Yes	2.3
11	2	13	86	98	0.5	2	7.1	93.9	1.4	Yes	7
12	3	9	88.5	95	3	3	4.5	90	3	No	1.5
13	3	9	86	93	2	3	3	86	3	Yes	8
14	3	9.5	87	91	5	3	7	88	5	No	7
15	3	11	85	95	1.5	3	3.5	90	0	No	4
16	1	8.5	86	95.5	0.5 Lat	1	-1.3	87.5	1 Lat	No	1.5

K&L = scale of Kellgren and Lawrence. Grade 0 = normal, grade 1 = minute osteophytes, grade 2 = definite osteophyte, grade 3 = moderate joint-space reduction, grade 4 = severe joint-space narrowing with sclerosis and osteophytes. TFA = mechanical TibioFemoral Angle (degree, positive values indicate varus alignment, negative values indicate valgus alignment). MPTA = Medial Proximal Tibial Angle (degree). mLDFA = mechanical Lateral Distal Femoral Angle (degree). JLCA = Joint Line Convergence Angle (degree). Lat= Lateral convergence. HF = Hinge Fracture. BHT = Bone Healing Time (months).

Radiographic measurement results

The mean mechanical tibiofemoral axis was preoperatively 10.0° (± 2.6°) of varus and postoperatively 3.1° (± 2.6°) of varus. The mLDFA changed from 95.9° (± 2.7°) preoperatively to 89.3° (± 2.9°) postoperatively. The mean MPTA did not substantially contribute to varus in this group of patients, being 87.8° (± 2.3°) preoperatively. Figure 4 shows pre- and post-operative leg alignment in two cases. All pre- and postoperative radiographically assessed measurements are displayed in Table 2 and Figure 5. The pre-operative indication and aim of correction of each case is displayed in Table 3.

Clinical results

Because one patient had a total knee arthroplasty, in fourteen (fifteen knees) of the included fifteen patients (sixteen knees) the clinical results could be evaluated (see also Table 3). The clinical results were assessed at a mean of 40 months (± 30) postoperatively. At follow-up the mean VAS score was 2.5 (± 2.4). The subjective result according to the Lysholm score was excellent in one patient, good in three patients, fair in six patients

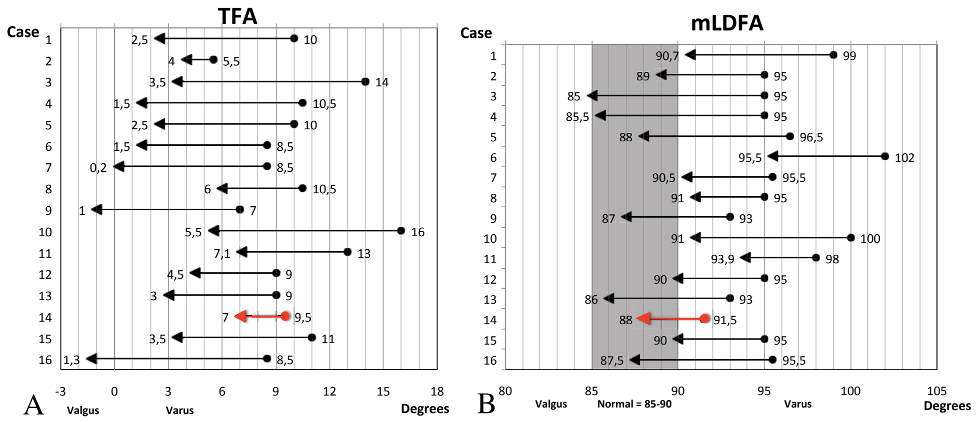

Figure 5. Change of mechanical tibiofemoral angle (TFA) per patient (**a**) and the change of mechanical lateral distal femoral angle (mLDFA) per patient (**b**). The preoperative deformities are represented by the circles and the postoperative values are represented by the arrowheads. The red line represents the failure (i.e. total knee arthroplasty).

Table 3. Indication, aim of correction, clinical scores and plate complaints

Preoperative			Postoperative				
Case	Ind.	Aim	VAS	WOMAC	Lys	Teg	PC
1	PO	B	1	81	73	2	No
2	ID	A	5	74	63	5	No
3	PE	C	1	93	82	2	No
4	PT	B	2	99	92	7	Yes
5	PT	B	0	100	85	3	Yes
6	PO	B	0	92	80	2	No
7	ID	A	7	21	32	0	Yes
8	OCD/ID	A	2	75	58	3	Yes
9	OCD/ID	A	2	75	58	3	Yes
10	PE	C	3	57	78	2	No
11	PT	B	1	98	97	5	No
12	PO	B	7	76	67	2	No
13	ID	A	-----	84	60	2	No
14	PT	A	-----	------	-----	-----	Yes
15	PT	B	4	81	75	3	Yes
16	PO	A	2	94	90	3	No

Ind. = indication. PT = Posttraumatic (femoral malunion). PE = Previous epifysiodesis. ID = idiopathic, PO = Previous osteotomy. OCD = osteochondritis dissecans. Aim: A = unloading, B = correction to normal varus, C = correction to symmetrical leg alignment. Lys = Lysholm. Teg = Tegner. PC = Plate complaints resulting in plate removal. Case 14 represents the failure (i.e. total knee arthroplasty).

and poor in four patients. All the patients who scored good or excellent on the Lysholm scale had grade I or II of osteoarthritis according to the scale of Kellgren and Lawrence. On the Tegner activity scale the mean level was 3 (± 1.7). At follow-up the WOMAC score averaged 80 (± 20). The mean score at follow-up of the individual components of the WOMAC index (pain, stiffness and function) were: 80 (± 18), 75 (± 26) and 81 (± 21). The range of flexion and extension showed not a great difference between the preoperative and the postoperative measurements (118° (± 14°) pre-operative versus 117° (± 15°) postoperative). The mean length of hospital stay was 3 (± 1) days.

Bone healing time results

All but 3 patients in the biplane DFO group showed full consolidation at the three months follow-up radiographs. The remaining patients showed full consolidation at respectively six months, seven months and nine months of follow-up. In the single plane DFO group two patients showed full consolidation at the three months follow-up radiographs, one at five months, one at seven months, one at eight months and one at ten months. Comparison of the mean time to full consolidation between the biplane osteotomy group (3.9 ± 2.5 months) and the single plane group (6.1 ± 2.7 months) did not show a significant difference (p=0.118).

DISCUSSION

A distal lateral closed-wedge valgus osteotomy of the femur is an uncommon procedure. While such a procedure has been referred to in previous publications, this retrospective cohort study as yet represents the first short to mid-term description of treatment results. Carefully preplanned single plane and biplane osteotomies meeting the aim of correction resulted in significant symptoms relief in most patients although clinical scores in two patients indicated persistent functional impairments. Moreover, this is the first literature available comparing the bone healing time between single plane and biplanar osteotomies, showing the better bone healing potential of the biplanar osteotomies.

In our opinion each deformity around the knee should be subjected to a systemic deformity analysis according to Paley, using standardized full leg standing radiographs.[20] In the patient cohort of the present study this analysis revealed a femoral varus deformity in all patients causing the varus deformity of the leg. Each deformity should be corrected at its source; otherwise joint-line obliquity will be the result.[5,21] Accordingly, in our clinic valgus producing osteotomies will be performed at the tibial level, femoral level or both levels simultaneously depending on the source of the deformity (i.e. tailored approach) and because of that the patients in this study were indicated for a femoral valgus osteotomy.[3] Joint-line obliquity is not desirable for two reasons. Firstly, it results in increased shear stresses at the cartilage joint surface and even tibiofemoral subluxation. Second, it may hamper subsequent joint replacement surgery.

The influence of joint line obliquity, as well as varus orientation of the distal femur on the results of osteotomies around the knee has been discussed before. Terauchi et al.[22] found that the presence of a preoperative varus deformity of the distal femur was associated with recurrence of varus deformity and poor results after HTO. Van Raaij et al.[23], however, did not find a significant correlation between distal femur joint line orientation and failure of HTO. This can be explained by the fact that the mean preoperative distal femur alignment in their patients was mild valgus (mean mLDFA 89.1 ± 2.1°), whereas our patients had a clear varus malalignment of the distal femur with a mean mLDFA of 95.9° (± 2.7°). Moreover, Babis et al.[5] looked at obliquity of the joint line as a prognostic factor. In a series of patients with large varus deformities and medial compartment osteoarthritis, treated with a double level osteotomy, normal knee joint line orientation was preserved and they showed in a computer model that the tension of stabilizing ligaments (i.e. collateral ligaments) remained normal after correction.

The leg alignment after correction of deformity ranged from 1.3° valgus to 7.1° varus because of aims for correction differed from unloading in case of medial compartment osteoarthritis, decrease of varus to normal varus or decrease to leg alignment symmetrical to the contralateral leg (see also Table 3). Moreover, in four of the performed distal femoral valgus osteotomies there was an overcorrected previous valgus deformity (previous distal femoral varus osteotomy). In most of these cases a neutral mechanical axis was intended. Only one osteotomy had resulted in an under correction. Performing a closed wedge osteotomy is known to be technically difficult, because the surgeon has to rely on the accuracy of the bony resection. Careful preoperative planning and the use of oblique downsloped osteotomy cuts of equal length in an isoscale triangle prevents cortical overlap after gap closure.[6,16] Our final range of tibiofemoral angles achieved is certainly within range when compared with the broad range of tibiofemoral angles achieved with closing-wedge distal femoral varus osteotomy (6° varus to 10° valgus).[24]

Our rate of hinge fractures (50%) (Table 2) is high compared with the 10-20% reported after closing-wedge HTO.[25] One of the main reasons for this difference could be the performed correction. For example, in six of the sixteen osteotomies the correction angle was greater than eight degrees and it is described in the literature that the risk of a hinge fracture gets higher when the correction angle increases, due to the limited plasticity of the cortical (supracondylar) bone.[26] Of the fractured hinges not one dislocated and by using a temporary bicortical lag screw compression over the osteotomy, including the hinge, is created. When a hinge fracture occurs, this can cause instability. In particular patients with more developed leg muscles are subjected to more axial and torsional loading, which can lead to increased instability. In those cases a medially placed staple can be used or, as was used in another case, an antero-posterior lag screw through the anterior flange of the biplane osteotomy.

The highest clinical scores were found in patients with posttraumatic deformities that according to aim had been corrected to normal varus alignment (Tables 2 and 3). Patients with a failed previous femoral osteotomy also scored high clinical scores whereas lower scores were found in patients presenting with grade III osteoarthritis following osteochondritis dissecans (cases 8 and 9) aimed to correct the femoral deformity into remaining varus unloading the lateral OA. To our knowledge there is no literature available to compare our clinical results with. In our series eleven osteotomies were performed in patients with moderate and severe (stage III and IV) osteoarthritis according to the scale of Kellgren and Lawrence. As observed by other authors a significant association exists between preoperative Kellgren & Lawrence grade and HTO failure.[27] Nevertheless we present moderate to good results in these patients, with an average WOMAC score of 80 and only one patient requiring a total knee arthroplasty. When performing a femoral osteotomy pain relief in the extended knee (i.e. walking) is accomplished. In 90 degrees of flexion the contact point of the loaded posterior condyles on the tibia remains unchanged.[6]

Only one case (6.3%) required a total knee arthroplasty and was classified as a failure. This is in line with failure rates of HTO (3.4% before 24 months to 7.8% between 24 and 47 months[25]) and double level osteotomy (3.7%).[5] In hindsight, this patient might not have been the ideal candidate for a closed wedge valgus DFO. In this case the aim was to correct the femoral deformity with unloading the OA. The pre-operative Kellgren and Lawrence grade was III, the mLDFA was pre-operatively not that distinct (91.5°) and the post-operative mechanical tibiofemoral axis was 7° of varus. This could have contributed to the persistent disabling pain and functional impairment resulting in a total knee arthroplasty. In seven cases (44%) the osteosynthesis material was removed. Jacobi[28] already reported that fixation of an osteotomy on the lateral side of the distal femur leads to irritation of the iliotibial band. Nevertheless, our rate of 44% is lower than the 86% of Jacobi et al[28], who described patients following a distal lateral opening-wedge varus osteotomy of the femur fixated with a lateral distal femur Tomofix plate. Probably the lower rate of plate irritation related symptoms in our study is caused by the use of the less prominent MDF plate for fixation. None of the three patients that received a MDF plate had their plate removed. As mentioned before, a MDF plate can be chosen in patients with a relatively shorter and smaller femur.

After introduction of the biplanar technique in medial closing wedge distal femur osteotomies[8] in our group, since 2009 a biplanar osteotomy technique was also used for lateral closing wedge osteotomies. Following clinical observations it was recently demonstrated in saw bone models that a biplane medial closing-wedge osteotomy has better bone healing potential compared with the uniplanar technique.[29] In clinical studies rapid and uncomplicated bone healing has been found using biplanar osteotomies in medial closing wedge osteotomies[9] as well as lateral opening wedge[30] osteotomies correcting femoral varus deformities. To our knowledge there are no publications on bone healing in femoral varus correcting lateral closing wedge distal femoral osteotomies whether uniplanar or biplanar techniques have been used. Bone healing time of the uniplanar osteotomies in the present study was 6.1 ± 2.7 months, whereas the bone healing time of the patients operated with a biplanar technique averaged 3.9 ± 2.5 months. Bone healing was complete in 7 of 10 patients operated on with the biplanar technique at the 3 months follow-up which is comparable to the bone healing times reported for single planar[7,8] and biplanar medial closing wedge distal femoral techniques[9] as well as recently reported lateral open wedge biplanar osteotomy results of Bagherifard et al.[30] Of the remaining 3 patients with longer bone healing times in the biplanar osteotomy group, 2 had medial hinge fractures. Increased bone healing time because of hinge fractures causing instability in closing wedge osteotomies has been reported for DFO and HTO.[31,32] In our population the mean bone healing time in patients with hinge fractures was 5.8 ± 2.8 months.

Our study has limitations. It was a retrospective study with a small study population. Due to this limited number of patients the correlation of different variables was not possible. The next step would be a prospective study comparing patients preoperatively and postoperatively after a distal lateral closed-wedge valgus osteotomy of the femur. Nevertheless, the results in our series are encouraging for selected knees. Regarding bone healing time evaluation, the intervals of follow up hampers an accurate registration of bone healing time. A monthly follow-up would have given us more accurate information on bone healing time.

Based on the results of this study a biplane distal lateral closed-wedge valgus osteotomy of the femur for the treatment of varus deformity of the knee is a valuable procedure when the deformity is localized in the femur with clinical benefit in most of the patients.

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Chapter 3

Periosteal vascularization of the distal femur in relation to distal femoral osteotomies: a cadaveric study

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ABSTRACT

Background: The purpose of this study was to investigate periosteal vessels location as intra-operative landmarks in distal femoral osteotomies and focused on the branching pattern of the vascular supply of the medial and lateral femoral condyle, its constancy, and the relationship to the height of distal femoral osteotomies. Anastomoses of relevant vessels were studied to analyze the risk of vascular insufficiency after transection of landmark vessels.

Methods: A human cadaver dissection study on the vascular supply of the medial and lateral side of the distal femur was conducted. Surgical dissection was performed in eight knees in total. Distances between the vascular supply and bony landmarks were calculated. Relation of the vascular structures to the transverse bone cuts of distal femoral osteotomies was described, as well as anastomoses of relevant vessels.

Results: On the medial side of the distal femur the periosteum was primarily supplied by the descending genicular artery (DGA) in 87.5 % of the specimens. In the absence of the DGA, the superior medial genicular artery was the supplier. Vascularization took place through two constant branches, the upper transverse artery (UTA) and the central longitudinal artery. The UTA originated at a mean distance of 6.9 cm (range 5.9–7.9 cm) above the knee joint line. On the lateral side of the distal femur the superior lateral genicular artery was the main vessel. In all dissected knees it gave off the lateral transverse artery (LTA). The LTA originated at a mean distance of 6.9 cm (range 5.8–7.6 cm) above the knee joint line. Anastomoses between the UTA, LTA and the longitudinal arch of the femoral shaft were found that could prevent vascular insufficiencies after transection of the UTA and LTA.

Conclusions: The vascular supply of the medial and lateral aspects of the femoral condyle is highly constant. Both the UTA, on the medial side, and the LTA, on the lateral side, can serve as a landmark for orthopedic surgeons in determining the height of the osteotomy cuts in distal femoral osteotomies. Transection of these landmark vessels during the osteotomy will not result in vascular insufficiency because of a collateral supply.

BACKGROUND

Osteotomies of the distal femur, for realigning a varus or valgus leg alignment in mono-compartment osteoarthritis and thereby unloading the degenerated part of the knee, are a well-established treatment.[1] In new, improved osteotomy techniques bone cuts are made in the most distal metaphysical area of the femur, which is known for good bone healing capacity.[2,3] In distal femoral open-wedge osteotomies the starting point of transverse osteotomy cuts lies approximately six and a halve cm above the knee joint line, medially as well as laterally, and approximately one cm proximal of the femoral condyles (Figure 1).[2,4-5] In distal femoral closed-wedge osteotomies the second transverse bone cuts are positioned in the area proximal to the open-wedge osteotomy (Figure 1). In this area periosteal vessels have been observed medially as well as laterally that often need to be coagulated to prevent bleeding complications.

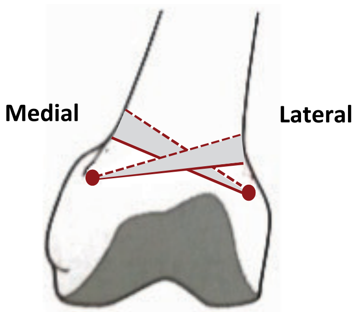

Figure 1. Schematic overview of the transverse osteotomy cuts in medial and lateral open- and closed-wedge osteotomies. The solid line represents the first transverse cut in open- and closed-wedge osteotomies. The dotted line represents the second transverse cut in closed-wedge osteotomies (height depending of pre-planned distance).

Osteotomies may cause bleeding complications not only as periosteal vessels are cut in the trajectory of the osteotomy bone cuts, but also when larger vessels near to the bone are not protected. Previous conducted cadaveric studies mainly have focused on high tibial osteotomy and the associated risk to the larger vessels.[6-11] With respect to the medial side of the distal femur, the vascular anatomy has been studied in the midvastus approach in total knee replacement surgery.[12,13] In contrast, discontinuing vascularity by cutting, suturing or coagulating vessels may cause vascular insufficiency. This has been studied with regard to the use of vascular bone grafts of the medial femoral condyle.[14-17] In addition, for both the medial and lateral side of the distal femur, the arterial supply was analyzed to find out if there are any differences in blood supply of the medial and lateral femoral condyles to explain the preponderance of osteonecrosis on the medial side.[18,19] Furthermore, damage to small- and mediums-size vessels may be important to consider as a predisposing factor for delayed union and non-union of femoral osteotomies and therefore it is important to know whether anastomoses are present preserving blood supply to the condylar area.[20] Specific literature on the vascular anatomy related to distal femoral osteotomies is scarce.[4,8] Visser et al.[4] described a less invasive approach to the distal medial aspect of the femur in biplanar medial closed-wedge distal femoral osteotomy, which proved to be feasible and safe. Bisicchia et al.[8] performed a cadaver study to assess the risk of vascular injury in realignment osteotomies, amongst them a medial closed-wedge osteotomy and a lateral open-wedge distal femoral osteotomy. However, the pattern of ramifications of the blood vessels which supply the femoral condyles, its variability and the topographical relation of these branches with the osteotomy height in distal femoral osteotomies have never been described. This study focused on the branching pattern of the vascular supply of the medial and lateral femoral condyle, its constancy, and the relationship to the height of the transverse osteotomy cuts in distal femoral osteotomies.

METHODS

Five left and three right fresh frozen lower limbs were obtained from eight human bodies. The specimens were derived from bodies who entered the Department of Anatomy of the University Center Utrecht through a donation program. From these persons written informed consent was obtained during life that allowed the use of their entire bodies for educational and research purposes. Each leg was amputated from the trunk about 10–15 cm below the hip joint, and the foot was amputated at the level of the conjoint fascia of the soleus and gastrocnemius muscle. The common femoral artery or superficial femoral artery was identified, cannulated, and flushed with normal saline until the venous outflow was clear.

Dissection and sectioning

In all legs both the medial and the lateral structures covering the distal femur were dissected manually using regular sharp dissection techniques. The arteries could easily be recognized and dissected free from the surrounding structures. This resulted in an overview of the arterial branching pattern. All patterns and anatomic relationships to the surrounding soft tissues were photographed. Using ImageJ software (Image J 1.48, National Institutes of Health, USA) distances between the vascular supply of the medial and lateral femur condyle and bony landmarks were calculated. The chosen landmarks were: the knee joint line, the insertion of the adductor magnus tendon at the adductor tubercle (medial), the origin of the lateral collateral ligament (lateral), and the punctum maximum (most pronounced part) of both femoral condyles. Finally the relation of the vascular structures to the standardized heights of the medially and laterally started transverse bone cuts of distal femoral osteotomies was observed and described.

Statistical methods

Descriptive statistics were used to report the distances. Measurements have been reported in centimeters (rounded to the first decimal); mean and ranges are provided. Statistical analysis was not performed due to the limited number of legs used.

RESULTS

Dissection findings medial femoral condyle

In seven of the eight dissected knees (87.5 %) the medial femoral condyle's periosteum was primarily supplied by the descending genicular artery (DGA). The DGA originates from the superficial femoral artery, at a mean distance of 13.3 cm (range 10.8–15.1 cm) from the medial knee joint line. Hereafter it courses down to the adductor tubercle where it divides into two terminal branches: the upper transverse artery (UTA) and the central longitudinal artery (CLA) (Figure 2). The UTA and the CLA were always present. The UTA originates at a mean distance of 6.9 cm (range 5.9–7.9 cm) above the medial knee joint line and descends anteriorly in an oblique manner. In Table 1 the distances between all landmarks and the UTA are given for each dissected knee. The CLA proceeds downwards in front of the adductor tubercle and of the medial collateral ligament. The superior medial genicular artery (SMGA) was present in all dissected knees and supplied the medial femoral condyle as the dominant vessel in one knee (12.5%). The SMGA origi-

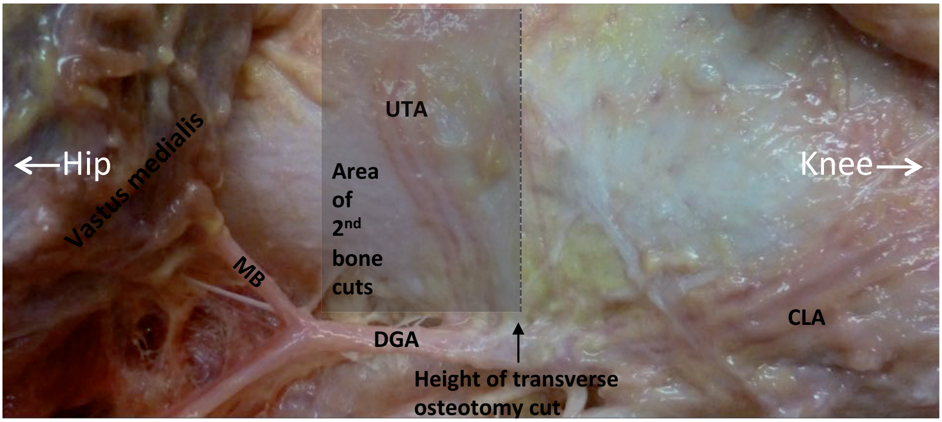

Figure 2. Medial side of a left distal femur with the typical branching of the descending genicular artery (DGA). Along its course the DGA gives off an anteriorly directed muscular branch (MB) to the vastus medialis, before the terminal branching in the upper transverse artery (UTA) and the central longitudinal artery (CLA). Each of the arteries is accompanied by two venae comitantes. The dotted line represents the height of the first transverse osteotomy cut (medial open- and closed-wedge distal femoral osteotomies) and the proximal grey zone is an example of the area were the second transverse bone cuts are positioned in medial closed-wedge distal femoral osteotomies (depending of pre-planned distance).

Table 1. Distance between the UTA and LTA and the landmarks*

Knee number	UTA			LTA		
	Knee joint line	Insertion adductor Magnus tendon	Punctum maximum medial condyle	Knee joint line	Origin lateral collateral ligament	Punctum maximum lateral condyle
1	7.5	1.3	4.7	7.6	2.0	4.5
2	5.9	1.0	3.8	6.2	1.7	3.7
3	7.0	1.6	3.5	5.8	1.0	4.3
4	7.6	1.0	4.6	6.8	1.8	4.6
5	6.0	1.1	4.9	7.4	1.8	5.0
6	7.9	1.8	4.5	7.3	1.8	4.7
7	6.8	1.6	3.6	6.9	1.8	4.7
8	6.7	1.2	3.9	7.2	1.8	4.0
Mean (range)	6.9 (5.9-7.9)	1.3 (1.0-1.8)	4.2 (3.5-4.9)	6.9 (5.8-7.6)	1.8 (1.0-2.0)	4.5 (3.7-5.0)

*In centimeters

nated from the popliteal artery, at a mean distance of 6.0 cm (range 4.1–8.8 cm) above the knee joint line. After crossing from behind the adductor magnus tendon, it coursed anteriorly along the upper ridge of the medial femoral condyle.

The terminal ramifications of the UTA and CLA anastomose with the longitudinal arch of the femoral shaft (Figure 3). The terminal branches of the SMGA anastomose with those of the DGA. In the case where the DGA was absent, the upper transverse and the central longitudinal artery originated from the SMGA. The longitudinal arch of the femoral shaft was identified in each dissected knee. This longitudinal arch originates from the superficial femoral artery, at a distance of 13.4 cm (range 7.7– 16.9 cm) above the knee joint line, proximal to the DGA branch takeoff.

Dissection findings lateral femoral condyle

The periosteum of the lateral femoral condyle was supplied by the superior lateral genicular artery (SLGA) in all dissected knees. The SLGA originates from the popliteal artery, at a mean distance of 6.2 cm (range 3.9– 8.7 cm) above the lateral knee joint line. Conversely with the SMGA, it courses along the upper ridge of the lateral femoral condyle, where it forms terminal branches. One of them travels transversely, being the lateral transverse artery (LTA) (see Figure 4). The LTA was in all dissected knees present. The LTA originates at a mean distance of 6.9 cm (range 5.8–7.6 cm) above the lateral knee joint line and descends anteriorly in an oblique manner. In Table 1 the distances between all landmarks and the LTA are given for each dissected knee. The terminal ramifications of the LTA anastomose with the longitudinal arch of the femoral shaft and with the UTA (Figure 3).

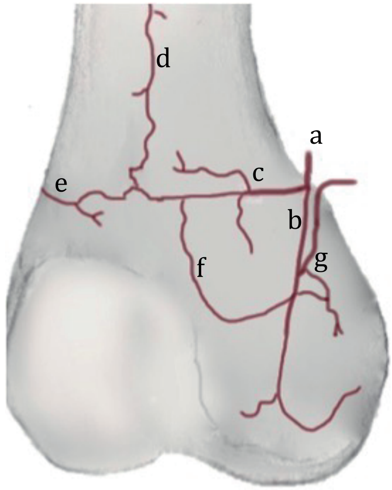

Figure 3. Anastomoses of the arterial vascularization of the femoral condyle (anteromedial view of a right knee). **a** Descending branch of the descending genicular artery (DGA). **b** Central longitudinal artery (CLA). **c** Upper transverse artery (UTA). **d** Longitudinal arch of the femoral shaft. **e** Lateral transverse artery (LTA). **f** Anastomotic arch of the medial condyle. **g** Branch of the superomedial genicular artery.

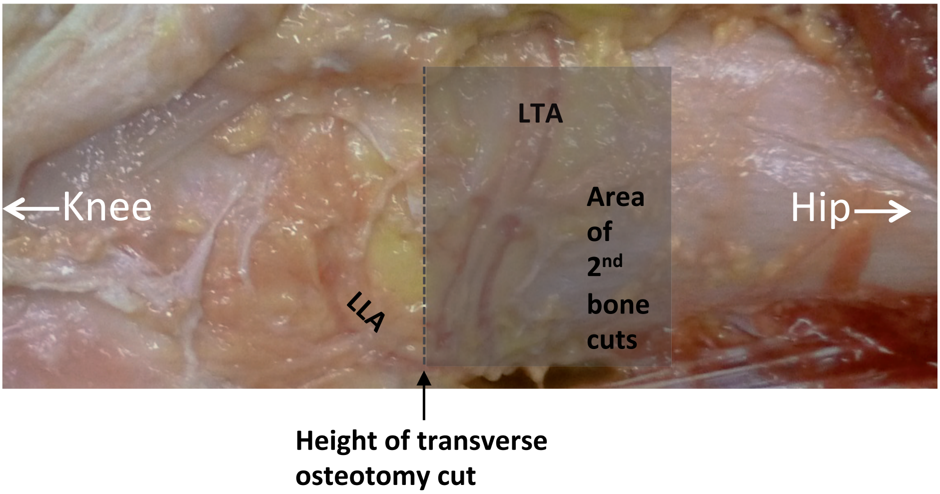

Figure 4. Lateral side of a left distal femur with the branching of the superior lateral genicular artery. The lateral transverse artery (LTA) is the transversely travelling artery and is accompanied by two venae comitantes. The LLA is the lateral longitudinal artery. The dotted line represents the height of the first transverse osteotomy cut (lateral open- and closed-wedge distal femoral osteotomies) and the proximal grey zone is an example of the area were the second transverse bone cuts are positioned in lateral closed-wedge distal femoral osteotomies (depending of pre-planned distance).

Relation of the vascular structures to location of osteotomy cuts

A constant branch pattern of the vascular supply of the medial and lateral femoral condyle, related to the height of the transverse osteotomy cuts in distal femoral osteotomies was observed. Each of the arteries is accompanied by two venae comitantes, which make them easily recognizable (see also Figures 2 and 4). The UTA and LTA are located in the area 6.5 cm proximal to the medial and lateral knee joint line respectively, where transverse cuts for medial and lateral open-wedge and closed-wedge osteotomies are positioned. In osteotomy surgery of the distal femur the UTA and LTA can serve as consistent landmarks for transverse osteotomy height position.

DISCUSSION

The most important finding in this study is that the vascularization of the medial and lateral aspect of the femoral condyle is highly consistent and characterized by anastomoses between the UTA, the LTA and the longitudinal arch of the femoral shaft. Moreover, the height of both the UTA (on the medial side) and the LTA (on the lateral side) are in line with the height of the osteotomy cuts in distal femoral osteotomies and thus can serve as an intra-operative landmark for orthopedic surgeons.

Intra-operative landmarks are an important help for the surgeon, not only in standard "open" approaches of the distal femur[2,5] but even more in mini-invasive approaches.[4,21,22] Especially in the latter approach only a keyhole view is present of the bone area for positioning of the osteotomy cuts. Precise positioning of the transverse osteotomy cuts is crucial to the success of the surgical technique and a consistent landmark on the bone helps the surgeon in addition to fluoroscopic assistance. In this study it was found that if the guiding wires for the osteotomy cuts are positioned immediately distal to the UTA and LTA the optimal medial, respectively, lateral starting points for open-wedge osteotomies are used. The second transverse bone cut used in closing-wedge techniques will be started more proximal at a preplanned distance from the first osteotomy cut. In both osteotomy techniques it is safe to coagulate the landmark-vessels to prevent bleeding as the anastomoses prevent vascular insufficiency of the medial and lateral femoral condyle.

To our knowledge, in the past only one study was conducted that described the presence and distances to the knee joint of the UTA. No earlier work describing the presence and distances to the knee joint of the LTA has been published yet. Hugon et al.[16] described the UTA in 100 % of the knees (16) they dissected. In those 16 knees the mean distance between the origination of the UTA and the knee joint line averaged 7.2 cm, with a minimum distance of 5.4 cm and a maximum distance of 8.9 cm. This is in line with our average of 6.9 cm, minimum of 5.9 cm and maximum of 7.9 cm. In the current study, the DGA was present in 87.5 % of the dissected knees. This is in line with earlier reports, which state a presence of 85– 100 %.[14,16,23]

In 1950, Rogers and Gladstone[24] were the first to review the intra- and extra-osseous blood supply of the distal femur. They stated that the medial condyle arteries originate from the DGA and the SMGA and those were richly anastomosing and ultimately perforating the cortex to vascularize the bone. Later, Shim and Leung[25] confirmed this with a microangiographic study. Hugon et al.[16] also described many anastomoses between the branching of the periosteal vascularization of the medial femoral condyle with the SLGA, the muscular branches of the vastus intermedius and the longitudinal arch of the femoral shaft. In addition, they even noticed that they found numerous arteries entering the bone posteriorly and connecting with the periosteal arteries, without forming any form of watershed line. The findings of these studies are in line with the anastomoses we described between the UTA, LTA, and the longitudinal arch of the femoral shaft. Regarding risk areas for vascular insufficiency, our study did not focus on this topic. However, in literature this has been extensively described. Reddy and Frederick[18] reported a relative watershed region in the anterior portion of the medial condyle. Furthermore, they stated that subchondral bone of the lateral femoral condyle is well supplied and has a richer circulation with more collateral supply than the medial side. In a similar study Lankes et al.[19] found the region of the femoral insertion of the posterior cruciate ligament (anteriorly in the intercondylar fossa) to be avascular. They did not describe the relative watershed as mentioned by Reddy and Frederick. Vascular insufficiency manifested i.e. by osteonecrosis has not been cited in the literature as a postoperative occurrence after femoral osteotomies[20] nor as a complication after corticopertiosteal vascularized grafting from the medial femoral metaphysis.[26-28]

A limitation of this study is the limited amount of knees that were dissected and investigated. This may have led to a type II error. However, the relatively small population size of n=8 is not unusual in labor-intensive anatomic research.[29-30] The findings were consistent and therefore the sample size was sufficient to meet the purpose of this study. Furthermore, we found a high correlation with the results of previously reported studies on distal femur vascularization. Another limitation is the possible length variability of each cadaver. One of the possibilities to address this issue would be to use the relative distance of the lower limb or femur for interpretation. However, the legs were already amputated prior the dissection and sectioning, so this data was not available. We did not use any in- or exclusion criteria for the knees, and the dissected knees population in this study did not contain severely arthritic knees. Relationships between arteries and bony landmarks can change in osteoarthritis of the knee.[31] However, these differences are reported to be minimal in the sagittal and coronal plane (0.8– 1.6 mm) and therefore its clinical implications are questionable.[31] So, even if there had been knees included with a high-grade osteoarthritis, this would not have biased the results of our study.

CONCLUSIONS

In conclusion, in this study the vascularization of the medial and lateral aspect of the femoral condyle was found to be highly consistent. Both the UTA, on the medial side, and the LTA, on the lateral side, can serve as a landmark for orthopedic surgeons in determining the height of the transverse cuts in open- and closed-wedge distal femoral osteotomies. The UTA and LTA can be cauterized in a safe way, and bone cuts can be made at the level of these vessels since there are many anastomoses in the periosteal vascularization of the medial and lateral femoral condyle.

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Chapter

4

Knee joint distraction compared with high tibial osteotomy: a randomized controlled trial

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ABSTRACT

Purpose: Both, knee joint distraction as a relatively new approach and valgus-producing opening-wedge high tibial osteotomy (HTO), are knee-preserving treatments for knee osteoarthritis (OA). The efficacy of knee joint distraction compared to HTO has not been reported.

Methods: Sixty-nine patients with medial knee joint OA with a varus axis deviation of <10° were randomized to either knee joint distraction (n=23) or HTO (n=46). Questionnaires were assessed at baseline and 3, 6, and 12 months. Joint space width (JSW) as a surrogate measure for cartilage thickness was determined on standardized semi-flexed radiographs at baseline and 1-year follow-up.

Results: All patient-reported outcome measures (PROMS) improved significantly over 1 year (at 1 year p<0.02) in both groups. At 1 year, the HTO group showed slightly greater improvement in 4 of the 16 PROMS (p<0.05). The minimum medial compartment JSW increased 0.8±1.0 mm in the knee joint distraction group (p=0.001) and 0.4±0.5 mm in the HTO group (p<0.001), with minimum JSW improvement in favour of knee joint distraction (p=0.05). The lateral compartment showed a small increase in the knee joint distraction group and a small decrease in the HTO group, leading to a significant increase in mean JSW for knee joint distraction only (p<0.02).

Conclusion: Cartilaginous repair activity, as indicated by JSW, and clinical outcome improvement occurred with both, knee joint distraction and HTO. These findings suggest that knee joint distraction may be an alternative therapy for medial compartmental OA with a limited mechanical leg malalignment.

Level of evidence: Randomized controlled trial, Level I.

INTRODUCTION

Historically, the treatment of knee osteoarthritis (OA) was limited to total knee arthroplasty (TKA) in the event of conservative treatment failure. However, there is an increasing recognition that even in advanced knee OA, joint repair may occur. For example, high tibial osteotomy (HTO) is a well-established surgical procedure for medial compartment knee OA in varus malalignment[26,27] with an 87–99% 5-year survival and a 66–84% 10-year survival[6,7,10,13,34] and can thus defer TKA in OA. Evidence for intrinsic cartilage repair after opening-wedge HTO is sparse. Four studies evaluated cartilage quality after opening-wedge HTO by second-look arthroscopic assessment. Jung et al. performed two retrospective, sequential reviews. In the first, they found partial coverage of the medial femoral condyle in 92% of the knees, but only maturation in 4% of the knees 2 years after HTO.[17] In the second study, two groups were compared: one group was treated with HTO alone, and in the other group, HTO was combined with subchondral bone drilling. Grade II fibrocartilage formation in both groups was equal (90% in HTO vs. 94% with additional drilling).[18] Spahn et al.[42] reported, one and a half years after HTO, restoration of deep cartilage lesions in 60%. Koh et al.[20] compared HTO with additional mesenchymal stem cell therapy or plasma therapy. Evaluation showed partial or even fibrocartilage coverage in 50% of the patients with additional mesenchymal stem cell therapy, but in only 10 % of the patients in the plasma group.

Knee joint distraction is a more recently developed surgical joint-preserving treatment that also appears to be associated with joint tissue repair. Joint distraction for OA has been reported for several joints including the knee.[1,2,11,12,15,31] Only one of these studies prospectively evaluated patients[15]; however, all studies showed radiographic joint space width (JSW) improvement. The first prospective open uncontrolled study reported substantial clinical improvement and cartilage repair by knee joint distraction resulting in the planned TKA being postponed for at least 5 years.[15,23,45] This was associated with MRI-determined cartilaginous repair 2 years later and associated increased radiographic JSW under weight-bearing conditions.[45] The increase in JSW was maintained at 5 years as compared to the natural progression of cartilage loss.[23]

Both knee joint distraction and HTO are based on unloading of the affected joint compartment cartilage, which is thought to be beneficial in OA.[24] The therapeutic rationale is that abnormal loading is a major cause of OA development and progression, and joint unloading may slow or prevent OA progression, or even lead to repair. Because both HTO and knee joint distraction make use of (partial/temporarily) joint unloading, both are associated with JSW improvement, and both reported to result in prolonged clinical benefit, we compared these treatments in a randomized controlled trial. It was hypothesized that there was no clinical important difference in efficacy between knee joint distraction and HTO treatment.

MATERIALS AND METHODS

The 69 patients with medial knee compartmental OA were recruited between 2011 and 2013 in this prospective, two-centre, randomized controlled trial comparing HTO with knee joint distraction. Fifty-five patients were included at the Maartenskliniek Woerden, and fourteen patients were included at the University Medical Center Utrecht. Randomization of 2:1 for HTO versus knee joint distraction was performed in blocks of six at each of the institutes using standard randomization software. In order to minimize the number of knee joint distraction treatments, the medical ethics committee, considering knee joint distraction an experimental treatment, obligated this randomization ratio. This resulted in 46 patients randomized to HTO, and 23 to knee joint distraction.

Patients and physicians were aware of treatment assignment after allocation. Inclusion criteria were OA of the medial compartment of the knee with a tibiofemoral angle of less than 10° of varus, age <65 years, intact knee ligaments, normal range of motion (minimum of 120° flexion) and a body mass index (BMI) <35. Patients with contralateral knee OA needing treatment were excluded, as were those with primary patellofemoral OA, bi-compartmental OA, a history of inflammatory or septic arthritis, a (partial) lateral meniscectomy, inability to cope with an external fixator, complete joint space absence on X-ray, post-traumatic fibrosis due to a fracture of the tibial plateau, inability to undergo MRI examination or previous surgery on the same knee within the past 6 months.

Treatments

In HTO, the goal was to shift the weight-bearing line laterally, with the post-operative mechanical axis running laterally through the tibial plateau, at 62% of its entire width (measured from the medial side). Using standing whole leg radiographs, the amount of needed correction was determined using the Miniaci method.[33] At the Maartenskliniek Woerden, a specialized osteotomy clinic, two experienced surgeons (RH, SS) performed 36 HTO's. At the University Medical Center Utrecht, one experienced surgeon (PR) performed nine HTO's. Bi-plane medial based opening-wedge osteotomy was performed, including a distal release of the superficial fibres of the medial collateral ligament. TomoFix medial high tibial plates and screws (DePuy Synthes, Switzerland) or Synthes locking compression plate (LCP) system (DePuy Synthes, Switzerland) were used for fixation. In three cases, in the University Medical Center Utrecht, autologous iliac bone grafts were applied to fill the osteotomy gap. Post-operative partial weight bearing (maximum of 20 kg) was allowed for 6 weeks; thereafter, all patients started gradual full weight bearing. Subcutaneous low molecular weight heparin thromboembolism prophylaxis was used for 6 weeks.

Knee joint distraction was performed by use of a proof of concept external distraction device, normally used for bone lengthening or fracture stabilization. Two dynamic monotubes (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 1), bridging the knee joint at the lateral and medial side. Intra-operatively, the tubes were distracted 2 mm. Post-operatively, every day the tubes were 1 mm distracted, until 5-mm distraction was reached. At day 4, distraction was checked by weight-bearing radiographs and adapted if needed. Hereafter, patients were discharged from the hospital and allowed full weight bearing with crutches (for stability). At 3 weeks, patients visited the outpatient department for radiographic evaluation of the distraction and pin tract evaluation. After 6 weeks (average duration 43 days, range 39–50 days), the frame and pins were surgically removed. Partial weight bearing (maximum 20 kg) was allowed, and patients were discharged the same day. Gradually, they regained normal full loading in approximately 6 weeks (expansion of 15 kg every week). Low molecular weight heparin as thrombosis prophylaxis was given for 9 weeks (during distraction treatment and for 3 weeks after frame removal).

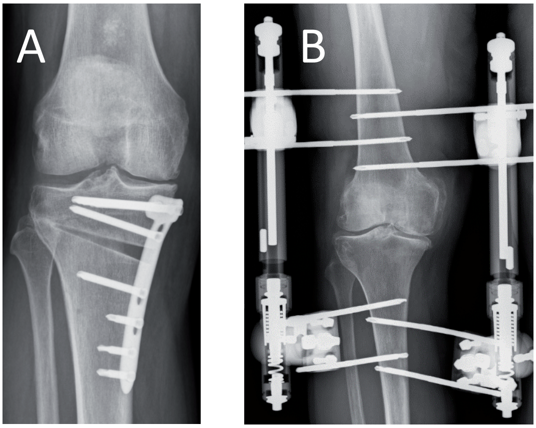

Figure 1. Example of a post-operative radiograph, **a** patient treated with HTO, **b** patient treated with knee joint distraction.

Clinical outcome

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, version 3.1) and the validated Dutch knee injury and osteoarthritis outcome score (KOOS) were used to score clinical improvement, normalized to a 100-point scale; 100 being the best condition. Both questionnaires were used to make comparison with other studies, using either of the two, possible. The intermittent and constant osteoarthritis pain score (ICOAP) for the knee was the secondary clinical outcome parameter (0–100, 0 meaning no pain). A visual analogue scale for pain (VAS pain; 0–100 mm, 0 meaning no pain) was the tertiary clinical outcome parameter. The EQ-5D-3L was used to assess improvement of quality of life. The obtained questionnaire was transformed to an EQ-5D index score (0–1, 1 being the best). The Short Form 36 (SF-36) health survey was used to measure the health status of the patients. The SF-36 items were transformed to the physical (PCS) and mental (MCS) component summary score. At baseline and 3, 6, and 12 months, the KOOS/WOMAC questionnaire, ICOAP questionnaire, the VAS pain, and the EQ-5D-3L questionnaire were assessed. At baseline and 6 and, 12 months, the SF-36 was assessed.

Structural outcome

To assess structural outcome, knee radiographs were obtained at baseline and 12 months post-operatively. The knee images were standardized weight-bearing, semiflexed posterior–anterior radiographic views according to the protocol of Buckland-Wright and were evaluated by the use of knee images digital analyses (KIDA) validated software.[30] This is a fully mathematical method to analyse the mean and minimum joint space width (JSW) of the knee. The minimum JSW was measured as the shortest distance between the femur and the tibia. The mean JSW of the medial compartment is defined as the mean of four predefined locations. In case of possible magnification of the radiograph, an aluminium step-wedge is used for correction. The method has frequently been used and reported on, inter-observer reproducibility is very high (R=0.85–0.90), and the intra-observer variation (ICC=0.73–0.99) good.[19,30] Image analyses were performed blinded to the order of acquisition and patient characteristics. The mean and minimum JSWs are given for the medial and lateral compartment in millimetre, rounded to one decimal. No MRI analyses were performed at 1 year because the presence of the plates (removed after 18 months) in the HTO group.

The medical ethics committee of the University Medical Center Utrecht approved this level I, prospectively, randomized, controlled study (No. 11/072), the site-specific institutional review boards of the Maartenskliniek Woerden and University Medical Center Utrecht approved the study protocol before study initiation, and it was registered on the Netherlands National Trial Register (NTR2900). All patients provided written informed consent before enrolment.

Statistical analyses

A sample size calculation was performed based on non-inferiority using a power of 80%.[47] To account for possible dropout and/or insufficient data quality, the sample size was increased by 15%. Two-sided paired tests (normally distributed data sets) were used to evaluate whether the follow-up values differed from the baseline values. To compare the changes between 1 year and baseline between both groups, independent samples t test was used (normally distributed data sets). For difference between Kellgren and Lawrence grade, Chi-square test for trend was used. Tests were two-sided, and probability $p<0.05$ was considered statistically significant. SPSS software version 22.0 was used to perform statistical analyses.

RESULTS

Of the 69 randomized patients enrolled, 23 were assigned to knee joint distraction and 46 to HTO. After randomization, one knee joint distraction and one HTO assigned patient were excluded (see Figure 2). Of the remaining 67 patients, the baseline characteristics and an overview of previous knee surgery of the affected knee are given in Table 1. In the HTO group, the mean mechanical tibiofemoral axis was preoperatively 6.2°±2.3° (mean±SD) of varus and post-operatively 2.4°±1.8° of valgus. The mean medial proximal tibia angle changed from 86.5°±1.9° preoperatively to 94.0°±4.7° post-operatively.

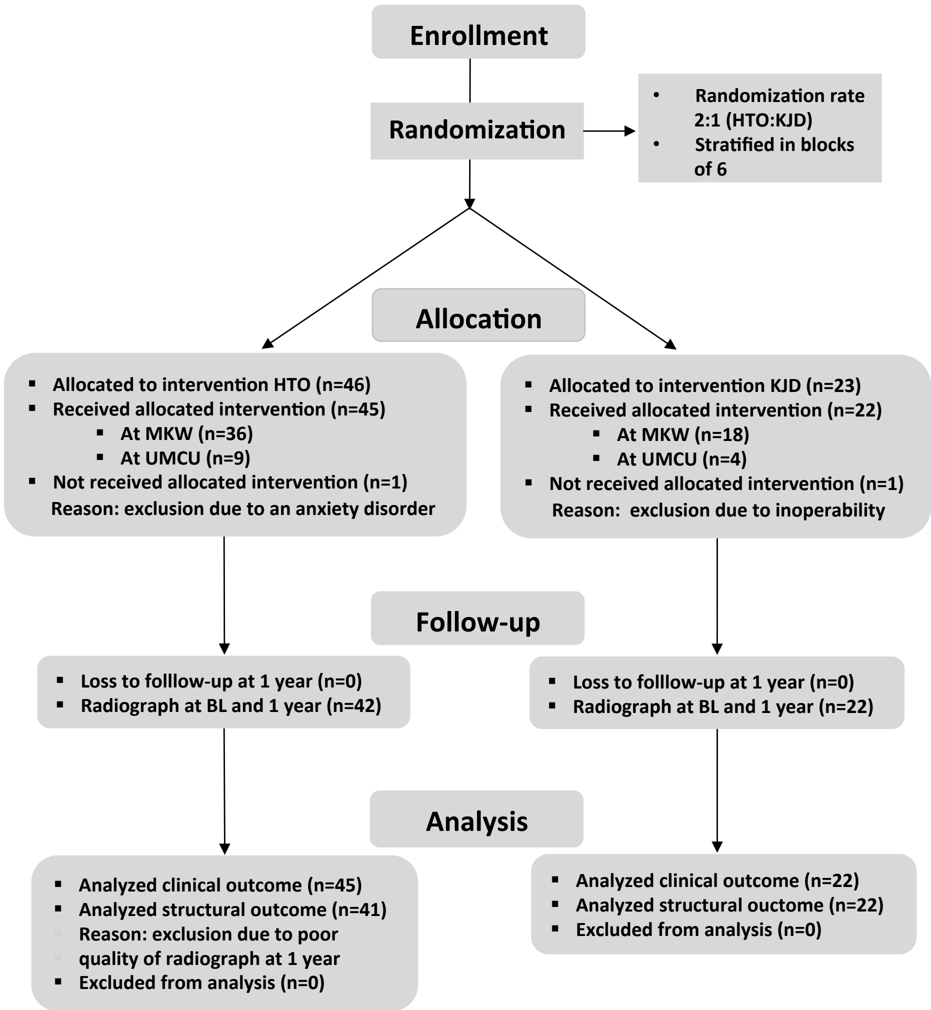

Figure 2. Flow chart including the numbers of excluded patients, as well allocation of the randomized treatment and the analysed patients per treatment arm. KJD: knee joint distraction, MKW: Maartenskliniek Woerden, UMCU: University Medical Center Utrecht.

Table 1. Baseline characteristics

Characteristics Mean (± SEM)	High tibial osteotomy (n=45)	Knee joint distraction (n=22)	p value
Male gender (n)	27/45 (60%)	16/22 (73%)	n.s.
Height (cm) ig	177 ± 2	178 ± 2	n.s.
Weight (kg)	85.2 ± 2.1	87.2 ± 2.8	n.s.
Body mass index (kg/m^2)	27.2 ± 0.5	27.5 ± 0.7	n.s.
Affected knee (left)	20/45 (44%)	10/22 (45%)	n.s.
Age at surgery (yr)	49.4 ± 1.0	51.2 ± 1.1	n.s.
Kellgren & Lawrence (median)	3	3	n.s.
Grade 0 (n)	1 (2%)	0 (0%) 6	
Grade 1 (n)	5 (11%)	6 (27%)	
Grade 2 (n)	12 (27%)	4 (18%)	
Grade 3 (n)	23 (51%)	11 (50%)	
Grade 4 (n)	4 (9%)	1 (5%)	
Tibiofemoral axis (°)	6.2 ± 0.3	5.8 ± 0.6	n.s.
Previous surgery **Operation (number)**			
ACL Reconstruction (n)	4	2	
High Tibial Osteotomy (n)	2	0	
Arthroscopy:	31	16	
Partial meniscectomy (n)	18	12	
Arthroscopic joint lavage (n)	13	4	
Open Medial Meniscectomy (n)	3	1	
Tibial Crest Transposition(n)	1	0	
Fixation Osteochondritis Dissecans lesion (n)	1	0	

Clinical outcome

A clear clinical improvement, based on the total WOMAC score (Figure 3) and KOOS (Figure 4), was noted in both groups. For the five subscales of the KOOS, the three individual components of the WOMAC index, the ICOAP for the knee, the physical component scale (PCS) of the SF-36, the VAS pain score and the EQ-5D similar improvements were found (Table 2).

The HTO group showed statistically significantly greater improvements in the mean change of the KOOS subscale quality of life (p=0.002), the WOMAC subscale stiffness (p=0.028), the VAS pain score (p=0.006) and SF-36 PCS (p=0.024).

Knee flexion in both the knee joint distraction and the HTO group equalled to baseline levels (132° in the knee joint distraction group and 128° in the HTO group) at 12-month follow-up. After an initial fall in joint flexion, levels returned to baseline levels after 6 months of knee joint distraction.

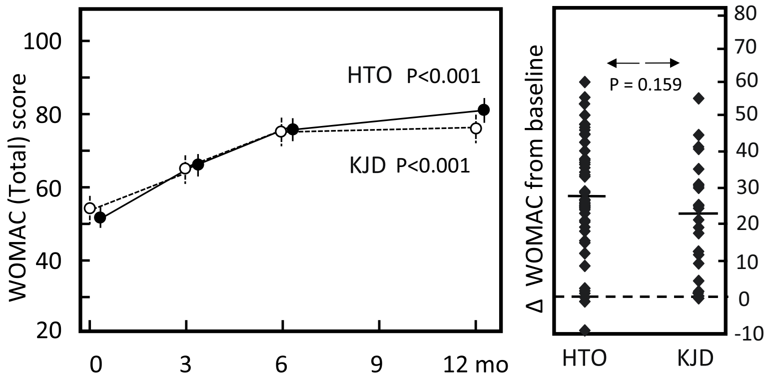

Figure 3. WOMAC total. Dotted line represents the knee joint distraction group (n=22), solid line represents the HTO group (n=45). Mean values ± SEM are given. P values show statistical difference in values at 1-year follow-up compared to pretreatment values. Mean change of WOMAC total (right): for both groups (average: dash) and for every individual patient (squares).

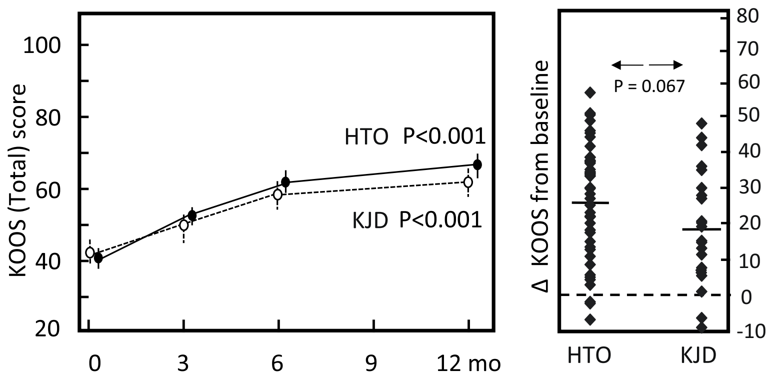

Figure 4. KOOS total. Dotted line represents the knee joint distraction group (n=22), solid line represents the HTO group (n=45). Mean values ± SEM are shown. P values show statistical difference in values at 1-year follow-up compared to pre-treatment values. Mean change of KOOS total score (right): for both groups (average: dash) and for every individual patient (squares).

Structural outcome

The mean JSW of the medial compartment in the knee joint distraction group increased significantly from 2.0±1.4 mm (mean±SD) towards 2.8±1.3 mm at 1 year (p=0.004), whereas the minimum JSW increased 0.8±1.0 mm (p=0.001). In the HTO group, both the mean and minimum medial compartment showed a less striking trend with the mean JSW increasing from 2.0±1.2 mm at baseline to 2.4±1.3 mm at 1 year (p<0.001). The minimum JSW increased on average 0.4±0.5 mm (p<0.001). See also Figure 5 a-c.

The mean HTO lateral compartment JSW (Figure 5 d) showed a decline of 0.2±1.3 mm (n.s.), whereas the knee joint distraction group showed an increase of 0.2±1.4 mm (n.s.). The mean JSW of the whole joint (medial and lateral compartment averaged) increased

Table 2. KOOS, WOMAC, and SF-36 scores pre-operative and the post-operative follow-up moments for both both groups

		High tibial osteotomy					Knee joint distraction				
Score (± SD)		BL	3m	6m	12m	BL→1Y	BL	3m	6m	12m	BL→1Y
KOOS	Pain	46±18	64±17*	72±19*	77+19*	32±19	47±18	61±22*	71±21*	72±18*	25±19
(0-100)	Symptom	54±15	63±14*	71±15*	73±16*	19±18	56±19	54±20	63±20	68±19*	13±17
	ADL	54±17	68±14*	76±18*	82±17*	28±17	55±21	65±22	75±19*	78±19*	24±17
	Sport/Rec	23±19	31±22*	47±25*	53±31*	29±24	29±19	36±30	44±25*	49±27*	21±24
	QOL	27±15	37±17*	47±21*	55±25*	28±19#	32±16	30±17	43±21*	44±20*	12±17
	Total	41±13	53±14*	63±17*	68±19*	27±16	43±17	50±18	60±18*	62±18*	19±16
WOMAC	Pain	50±21	68±17*	76±19*	81±18*	31±19	54±21	69±23*	76±20*	76±15*	23±21
(0-100)	Stiffness	46±21	58±21*	64±23*	69±19*	22±21#	50±20	56±21	58±19	60±18	10±24
	Function	54±17	68±14*	76±18*	82±17*	28±17	55±21	65±22	75±19*	78±19*	24±17
	Total	52±17	67±14*	75±17*	81±16*	29±17	54±20	65±20	74±18*	76±17*	22±16
ICOAP	Constant	48±21	34±24*	29±27*	19±24*	-29±24	50±20	35±31	24±25*	23±20*	-27±21
(100-0)	Intermittent	54±22	33±22*	35±26*	23±24*	-31±31	50±20	38±29	34±24*	34±22*	-17±20
	Combined	51±20	34±21*	32±26*	21±23*	-30±26	50±20	36±29	30±24*	29±19*	-22±18
VAS	Pain	65±21	47±26*	37±24*	27±23*	-38±26#	55±24	46±29	34±23*	36±26*	-19±26
(0-100)											
EQ-5D	Index score	0.64±.2	0.68±.2#	0.68±.3	0.79±.3*	0.15±.3	0.63±.2	0.52±.3	0.69±.2	0.77±.1*	0.14±.3
(0-1)											
SF-36	PCS	36±8		42±10*	46±10*	10±9#	37±7		40±10	42±10*	5±8
	MCS	55±8		53±11	54±10	-1±8	56±8		56±8	54±9	-1±9
Flexion	Knee	132±8	127±10	128±8	128±8		130±7	115±17	128±9	132±8	
(Degree)											

* p<0.05 relative to the preoperative score
# p<0.05 difference between HTO and knee joint distraction

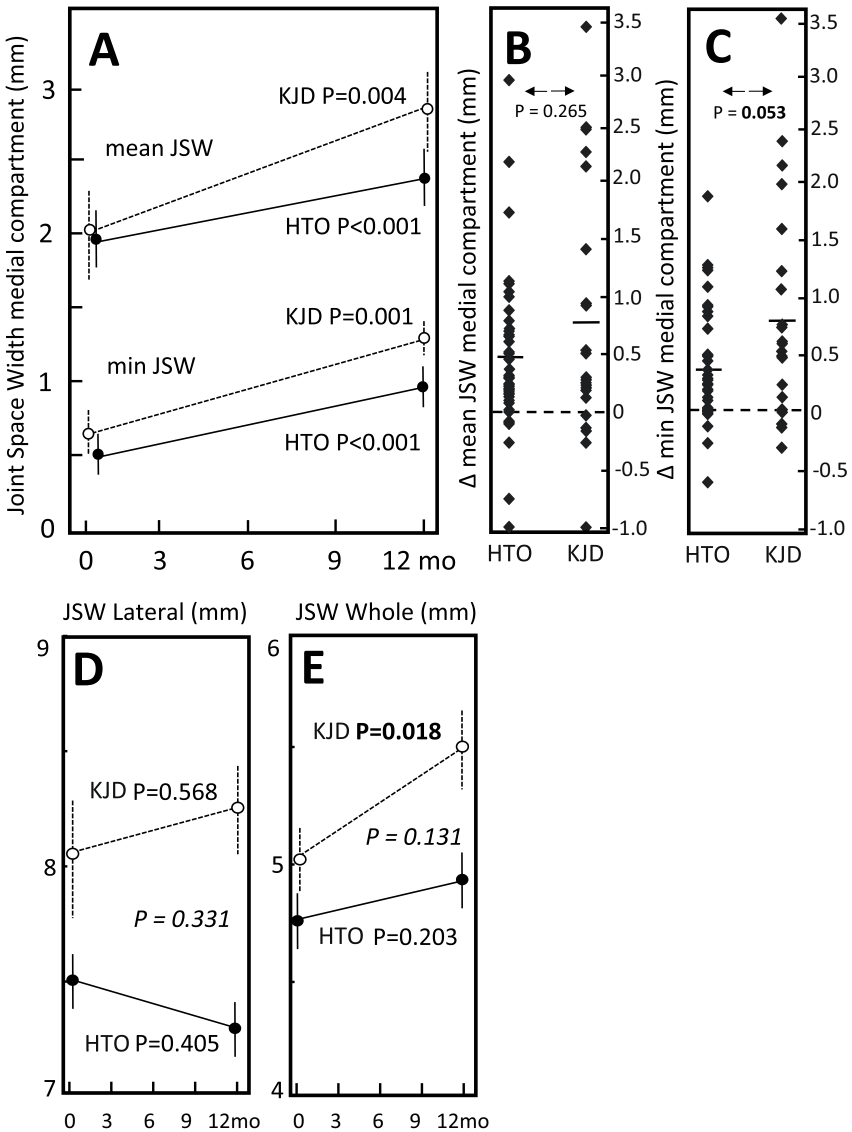

Figure 5. a, Mean quantitative radiograph analyses of the medial (affected) compartment of both treatment groups. The solid line represents HTO group (n = 41), and the dotted line represents the knee joint distraction group (n = 22). Mean values ± SEM are presented. P values show statistical difference in values at 1-year followup compared to pre-treatment values. **b**, Mean change of mean JSW of medial compartment. For both groups (average: dash) and for every individual patient (squares). **c**, Mean change of minimum JSW of medial compartment. For both groups (average: dash) and for every individual patient (squares). **d**, Mean JSW of the lateral (least affected) compartment of both treatment groups. **e,** Mean JSW of the whole joint of the both treatment groups. The p value in italic shows statistical difference in change over 1 year between the two treatment groups.

0.5±0.9 mm in the knee joint distraction group (p=0.018) and showed no significant increase in the HTO group (+0.2±0.8 mm, see also Figure 5 e).

The increase in the minimum JSW neared statistical significant difference between the two groups (p=0.053), whereas the increase in the mean JSW of the medial compartment and of the whole joint showed no statistical significant difference between the two groups.

Adverse events

An overview of the adverse events is given in Table 3. In the knee joint distraction group, thirteen patients (59%) had single or multiple pin tract infections, nine of which were treated adequately with oral antibiotics. In the HTO group, two patients (4.4%) had a post-operative wound infection.

Table 3. Overview of adverse events

Knee joint distraction	
Pin tract infection	
Antibiotics oral	9
Antibiotics intravenous	3
with surgical irrigation and debridement	2
Osteomyelitis (3 weeks post frame removal)	
Antibiotics intravenous with surgica irrigation and debridement l	1
Monotube failure (re-fixation)	1
Breaking of bone pin during fixation	1
Manipulation knee under anesthesia (17 days after removal frame)	1
High tibial osteotomy	
Wound infection	
Antibiotics oral	1
Antibiotics intravenous	1
Erysipelas	
Antibiotics intravenous	1
Partial medial meniscectomy (affected knee, <6 months)	1

DISCUSSION

This study showed that knee joint distraction was non-inferior to HTO for clinical symptoms and for JSW improvement in knee joint OA. In addition, in both treatment groups, all the domains of the KOOS, the EQ-5D index and the SF-36 PCS subscale demonstrated significant improvements at 1-year follow-up. Cartilage repair activity as indicated by

JSW on radiographs was slightly better for knee joint distraction, whereas clinical parameters improved slightly more in the case of HTO.

This is the first study comparing knee joint distraction in randomized set-up with another knee joint-preserving surgical strategy. With respect to knee joint distraction, one previous prospective uncontrolled study of twenty patients showed efficacy.[15,45] In the present study, patients treated with knee joint distraction showed similar outcome at 1-year follow-up on the WOMAC (76±17, n=22 and 77±21, n=20). However, the baseline values in the present study for knee joint distraction were higher (better condition) than in the previous uncontrolled study (54±20 and 45±16 points, respectively).

This difference at baseline and similarity for 1 year's outcome was also seen for VAS pain. This may be explained by the fact that in the present randomized controlled trial, patients were in general practice considered for HTO, whereas in the previous prospective uncontrolled knee joint distraction study, patients were treated with a new experimental technique and only severe end-stage knee OA was considered. This difference in disease activity was reflected by a difference in disease severity (joint damage). In the knee joint distraction population of the uncontrolled study, 55% had Kellgren & Lawrence (KLG) grade 3 at baseline and 10% had grade 4. In the present study, 50% had grade 3 and 5% had grade 4. The presently treated group of patients treated with knee joint distraction had medial compartment osteoarthritis and participated on a higher level in daily society than the patients in the previously uncontrolled study. These results show that even in younger patients, who undertake high-demanding activities for the knee (e.g. recreational sports), knee joint distraction treatment may lead to clinical relevant improvement.

A number of previous prospective studies utilizing valgus-producing opening-wedge HTO using KOOS and VAS pain scores have been carried out.[8,14,32,40,43] In these studies, the KOOS score was between 60 and 63 points[8,32,40], and VAS pain was between 21 and 25 mm at 12 months.[14,43] Clinical outcome of the HTO treated patients in the present study was 68±19 points for KOOS and 27±23 mm for VAS pain, which is comparable to those of previous studies. Also the rate of superficial (2.2%) and deep (2.2%) wound infections in the HTO group is in line with the literature, which showed a rate of 1–9% for superficial wound infections and 0.5–4.7% for deep infections.[3] As expected, the rate of pin tract infections in the knee joint distraction group was relatively high. In general, external fixation infection varies from as low as 3% to over 80%, depending of the used external fixator and the various definitions of pin site infections.[16] All patients observed with a pin tract infection were adequately treated with antibiotics, but minimizing such infections is desirable.

In general, it is difficult to judge differences in burden between both treatments. Not unexpectedly, external fixation causes patient discomfort, and the knee joint distraction group were asked about this. In general, activities of daily living, such as showering, walking and sleeping, did not give much discomfort. Patients having a clerical job were even able to continue the work during the distraction treatment. Most patients indicated that they would undergo knee joint distraction treatment again. Moreover, some patients subsequently received knee joint distraction of their contralateral osteoarthritic knee some time later.

For both HTO and knee joint distraction, a significant increase in radiographic JSW was observed (see Figure 6 for representative examples). For knee joint distraction, this was not confined to the medial (affected) compartment, but also, although less pronounced, in the lateral compartment. In case of knee joint distraction, the JSW on weight-bearing radiographs is considered to represent thickness of resilient cartilage tissue (weight-bearing radiographs), since it is not anticipated that knee joint distraction alters the alignment of the knee joint significantly. This cartilage regenerating capacity was supported by MRI data.[24,25] In case of HTO, the change from varus alignment to valgus alignment may have created a joint space at the medial site not representing cartilage thickness per se. Moreover, this shift in alignment resulted in a decrease in JSW at the lateral side. Earlier studies showed similar widening of the medial compartment (ranging from + 0.4 mm till + 1.1 mm) and a decrease in the lateral compartment.[5,25,37] Longer-term follow-up and MRI analyses (first follow-up after 2 years because of plate interference) in the present study will reveal what the outcome on cartilage regeneration between the two approaches will be.

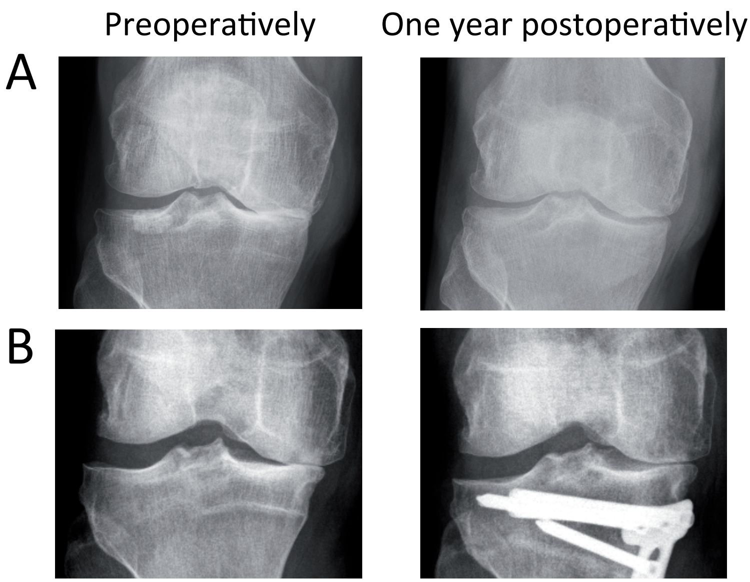

Figure 6. a, Radiograph preoperatively (left) and 1 year post-operatively (right) of a representative patient treated with knee joint distraction. **b,** Radiograph preoperatively (left) and 1 year post-operatively (right) of a representative patient treated with HTO.

This trial had incomplete blinding and lack of a placebo. However, numerous surgical practices have evolved into standard of care without being randomized against placebo/sham intervention.[22] Adding a placebo-control arm to our RCT would hardly be ethical: active, relatively young patients with symptomatic medial compartmental OA would be deprived of standard operative care for several years. Secondly, the homeostatic joint mechanisms implicated in the effects of joint distraction are clearly understood and described in vitro human cartilage models and in vivo canine models of knee joint distraction.[4,46] Thirdly, both treatments have shown persistent clinical benefit up till 5 years after treatment.[9,23] Finally, an eventual placebo effect would be expected to be equal in both groups.

For medial compartment OA, a load-bypassing knee support system has been reported (KineSpring System). Although initial studies reported joint pain and function improvement[29], later studies reported serious risks including development of intra- and extra-articular metallosis, medial joint capsule and medial collateral ligament/medial joint instability after device removal.[39] Furthermore, studies comparing the KineSpring with HTO are lacking. Other treatment options would be unicompartimental knee arthroplasty or TKA, the latter being less favourable in our relative young patients. Register studies[21,35] showed a higher rate of aseptic loosening of unicompartimental knee arthroplasties, so it is not advised to perform this procedure in patients younger than 55 years.[28] International register studies described even more unfavourable results in patients aged below 65 years after TKA.[36] Clearly, a TKA at relatively young age should be postponed as long as possible to prevent patients from revision surgery.

This study has some limitations, as there is a high heterogeneity in the patient's parameters at baseline (Table 1). In the HTO group, 51% of the patients had OA of grade 3 and even 9% of the patients had OA of grade 4. In the literature, the ideal candidate for HTO has a maximum KLG of 2, and it is described that a KLG (3 or 4) is associated with a poorer clinical outcome and as a risk factor for conversion to arthroplasty 10 years after HTO.[41,42,44] On the other hand, in a study of 91 patients (average age patients 50.4 years) with KLG 3 and 4, the 5-year knee survival rate was 95.2%.[38] Other factors negatively influencing the outcome of HTO are female gender and obesity.[41,44] Noteworthy is the difference in female gender between the HTO group and the knee joint distraction group (40 vs. 27%). One could imagine that this relative difference influenced the outcome in the HTO group. Furthermore, in the HTO group, two patients were included who had a previous HTO that led to an undercorrection (persistent varus malalignment). For the knee joint distraction group, there was the same heterogeneity; however, since this is a relatively new treatment, specific patient parameters influencing clinical outcome currently remain unknown. Nevertheless, in our study, all patients had a clear varus deformity in the proximal tibia with a varus malalignment and medial compartment OA resistant to conservative treatment with no other joint-preserving treatment options and would have been considered in general practice for HTO.

In general, it may be concluded that knee joint distraction may be considered in case of varus malalignment as an alternative to HTO. After the short follow-up time in this study, choosing between HTO and knee joint distraction will be based on personal preference, based on experience, and personal 'belief'. Burden of patients should be considered as well, leaving space for improvement of the distraction device. Midterm and long-term results of knee joint distraction treatment are mandatory to make an evidence-based decision.

CONCLUSION

Knee joint distraction is an effective and valuable treatment option in patients with knee OA, even with a varus deviation of up to 10°, providing structural and clinical improvement in this relative young patient category.

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Part II

Knee joint distraction

Chapter

5

Five-year follow-up of knee joint distraction; clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study

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ABSTRACT

Objective: In end stage knee osteoarthritis, total knee arthroplasty (TKA) may finally become inevitable. At a relatively young age this comes with the risk of future revision surgery. Therefore, in these cases, joint preserving surgery such as knee joint distraction (KJD) is preferred. Here we present five-year follow-up data of KJD.

Design: Patients (n=20; <60yrs) with conservative therapy resistant tibio-femoral osteoarthritis considered for TKA were treated. Clinical evaluation was performed by questionnaires. Change in cartilage thickness was quantified on radiographs and MRIs. The five-year changes after KJD were evaluated and compared with the natural progression of osteoarthritis using OsteoArthritis-Initiative data.

Results: Five-years posttreatment, patients still reported clinical improvement from baseline: ΔWOMAC (Western Ontario and McMaster Universities Arthritis Index) +21.1 points (95% CI +8.9 to +33.3; P = 0.002), ΔVAS (visual analogue scale score) pain 27.6 mm (95%CI 13.3 to 42.0; P < 0.001), and minimum radiographic joint space width (JSW) of the most affected compartment (MAC) remained increased as well: Δ +0.43 mm (95% CI +0.02 to +0.84; P = 0.040). Improvement of mean JSW (x-ray) and mean cartilage thickness (MRI) of the MAC, were not statistically different from baseline anymore (Δ +0.26 mm; P = 0.370, and Δ +0.23 mm; P = 0.177). Multivariable linear regression analysis indicated that KJD treatment was associated with significantly less progression in mean and min JSW (x-ray) and mean cartilage thickness (MRI) compared with natural progression (all Ps <0.001).

Conclusions: KJD treatment results in prolonged clinical benefit, potentially explained by an initial boost of cartilaginous tissue repair that provides a long-term tissue structure benefit as compared to natural progression.

Level of evidence: Prospective study, Level II.

INTRODUCTION

Tibiofemoral knee osteoarthritis is a progressive degenerative joint disease affecting all joint tissues, most prominently the articular cartilage. The disease is characterized by persistent pain, soft tissue impairment, subchondral bone changes, and cartilage tissue damage and loss (visualized on radiographs and/or MRI), all together reducing joint function.[1] The disease has a major impact on healthcare costs and a major impact on quality of life, significantly affecting labor participation. Accurate data on incidence and prevalence of knee osteoarthritis in literature are lacking because of absence of a clear definition of the disease. Yet, knee osteoarthritis is considered the most common type of osteoarthritis and affects approximately 6% of the adult population worldwide, with increasing age reaching up to 40% for those over 70 years of age.[2] Furthermore, more recent data show that 13.8% of the population >45 years is diagnosed with symptomatic knee osteoarthritis, and this number is predicted to increase to 15.7% in 2032.[3] The incidence is significantly increasing due to aging of the population, with a preferred active lifestyle at a relatively older age, as well as the significant increase in obesity at younger age, both being important predictors for disease development and progression.[4]

If conservative treatment fails and pain or joint function becomes unbearable, several surgical options are indicated. In case of relatively young and physically active patients (<65 years), joint preserving surgery is preferred.[5] This is because a total knee arthroplasty (TKA) at this age, where patients still have an active lifestyle, is less successful than in the elderly, with high revision rates of up to 44% later in life.[6,7]

Recently knee joint distraction (KJD) treatment has been proposed as an effective and joint saving treatment. It is an experimental surgical procedure in which the two bony ends of a joint are gradually separated to a certain extent for a certain period of time, by use of an external fixation frame.[8,9] It was demonstrated that this treatment results in cartilaginous tissue repair by use of digitally analyzed standardized radiography, quantitative MRI analyses, and biochemical analysis of collagen type II up till two years after distraction.[10-15] However, the durability of this clinical effect as well as of the cartilage tissue structure repair has not yet been evaluated.

In the present study we have followed the first 20 KJD-patients to evaluate the durability of the clinical benefit and the observed cartilaginous tissue repair, abutting the earlier reported one-year and two-years follow-up.[14,15] Additionally, a control group was selected, using data from the Osteoarthritis Initiative (OAI), to compare cartilaginous tissue repair over time after KJD with the natural progression rate of cartilage damage in case of no or conservative treatment.

MATERIALS AND METHODS

Patients selection

From 2006-2008 a total of 20 patients with primarily tibiofemoral knee osteoarthritis and with persistent pain refractory to conservative therapy (average age 48.5 years, range 32-57 years; 45% females; body mass index [BMI] 29.6 kg/m2, range, 25-36 kg/m2) were included at the Department of Orthopedics, University Medical Center Utrecht (UMCU). Patient characteristics have been described in detail previously.[15] These patients were referred and indicated by their orthopedic surgeon for TKA, based on clinical examination (Visual Analogue Score (VAS) for pain of ≥60mm) and radiographic examination (signs of primarily tibiofemoral cartilage tissue loss), and they had to be less than 60 years of age. Because of their relative young age, KJD was proposed as an experimental alternative for the indicated TKA. Patients were excluded in case of primary patella-femoral OA, if a history of inflammatory or septic arthritis existed, in case of severe varus/valgus malalignment (>10°), and in case of psychological inabilities to cope with an external fixation fame. The medical ethical committee of the UMCU approved the study (No. 04/086). All patients gave written informed consent.

Distraction method

The distraction method was applied as previously described by Intema et al.[14], using a proof-of-concept distraction device consisting of two external bilaterally placed dynamic monotubes, fixed on two bone-pins at each end, bridging the knee joint (see Figure 1). Distraction was applied in stages until 5mm was reached, confirmed by radiography. KJD treatment lasted for two months (average 60 days, range 54-64 days) and was every two weeks shortly interrupted during which continuous passive motion (CPM) was performed (average 25° flexion, range 15-80°). After reinstalling the distraction tubes actual distraction was checked by radiography. Throughout the whole treatment patients were allowed and encouraged to load the distracted joint with full weight bearing capacity, supported with crutches if needed. Pin-tract infections were successfully treated with Flucloxacillin for 5-7 days. After removal of the tubes and pins at daycare surgery, patients were discharged without imposed functional restrictions.

Follow-up

Patient reported outcome measurements (PROMs) were collected twice at baseline and at 3, 6, 12, 18, and 24 months follow-up as reported[14,15] and subsequently every year. Structural outcome parameters were assessed at baseline and one, two, and five years follow-up. No data were gathered over time on post-treatment medication or physiotherapy as this was on personal demand.

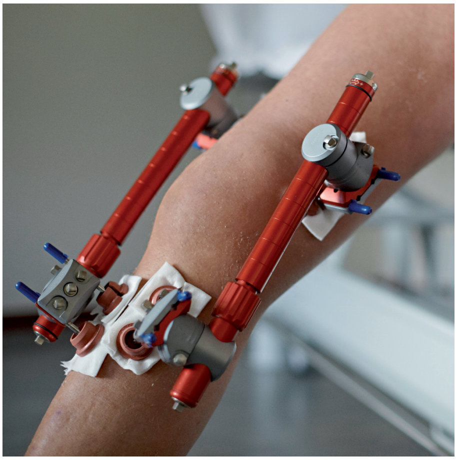

Figure 1. The bilateral external fixation frame used for knee joint distraction treatment.

Clinical outcome, PROMs

The WOMAC questionnaire (version 3.0, normalized to a 100-point scale for total and subscales; "100" being the best score) including 3 domains (pain, function, and stiffness) was used as primary outcome parameter.[16] The secondary clinical outcome parameter was the VAS pain score (0-100 mm; "0" meaning no pain).

Structural outcome

Radiographic analysis

Standing, weight bearing, semi-flexed, posterior-anterior radiographs were taken, with a magnification/density reference in view, according to the KIDA (knee images digital analyses) protocol.[17] Images were digitally mathematically analyzed independent of subjective clinical reader interpretation, by an experienced observer. Minimum and mean JSW of the most affected compartment (MAC; medial n=18, lateral n=2) are presented. Reproducibility of this technique has been reported.[17]

Quantitative MRI analysis

MRI analyses were performed as described earlier[15] with the use of custom software (Chondrometrics GmbH., Ainring, Germany). In short: coronal MRIs of the tibiofemoral cartilage plates were acquired using a 1.5 T Philips Achieva, with a SENSE T/R knee coil and a 3D spoiled gradient recalled (SPGR) imaging sequence with fat suppression (repetition time 20ms; echo time 9ms; flip angle 15°; slice thickness 1.5mm; in-plane resolution 0.3125x0.3125mm.[18] Similar as for the one-year follow-up analyses[14], five-year follow-up images were segmented with reference to the baseline images, which were segmented again to minimize intra- and inter-observer variability, and to ensure blinding of the reader and quality control reader to the temporal sequence of the images.

The primary outcome parameter was the mean cartilage thickness over the total subchondral bone area (ThCtAB) and the percentage of denuded subchondral bone area (dABp), i.e. without cartilage coverage.[19] All parameters were calculated for the most affected compartment (MAC). The reproducibility of this type of analyses has been published before in detail.[20-22]

Control group from the OsteoArthritis-Initiative

The control group was composed from the OsteoArthritis-Initiative (OAI) database. The OAI is an ongoing multi-center study (http://www.oai.ucsf.edu) targeted at identifying sensitive biomarkers of onset and progression of knee osteoarthritis.[23]

Data was selected from the progression sub-cohort (n=1390), in order to select a group comparable at baseline with our KJD patients. In this sub-cohort the patients had at least one knee with definite osteophytes (Kellgren and Lawrence grade; KLG≥2) and frequent knee symptoms at baseline. All patients below ≤60 years of age, without TKA during follow-up and with available radiographic JSW measurements at four years follow-up, and/or quantitative MRI measurements (ThCtAB and dABp) available at two years follow-up (longest follow-up for both parameters available) were selected. This resulted in 138 patients for the OAI control group (baseline characteristics, Table 1).

Since in the OAI radiographic measurements were only available up to four years and quantitative MRI measurements up to two years, the value of outcomes and change scores (for radiographic mean and min JSW and the quantitative MRI measurements (ThCtAB and dABp) of the MAC) at five year follow-up was calculated assuming a linear progression over time.[24,25]

Table 1. Demographics and baseline characteristics of distraction patients and OAI controls

Characteristics	KJD group (n=20)	OAI group (n=138)	p value
Age at surgery, yr (± SEM)	48.5 ± 1.3	51.2 ± 0.3	0.054
Male gender, n (%)	11(55%)	59 (43%)	0.303
Body mass index, kg/m^2 (± SEM)	29.6 ± 0.8	31.1 ± 0.5	0.214
Affected knee, n left knees (%)	11 (55%)	72 (52%)	0.549
Most affected compartment, n medial (%)	18 (90%)	109 (79%)	0.246
Kellgren & Lawrence, mean (± SEM)	2.6 ± 0.2	2.4 ± 0.04	0.330
Grade 0, n (%)	0 (0%)	0 (0%)	
Grade 1, n (%)	3 (15%)	0 (0%)	
Grade 2, n (%)	4 (20%)	83 (60%)	
Grade 3, n (%)	11 (55%)	55 (40%)	
Grade 4, n (%)	2 (10 %)	0 (0%)	

Statistical analysis

For all parameters mean values ± SEM are given, at each time-point. In case of double baseline measurements, these were averaged. Statistics for comparison of post-treatment follow-up outcomes with baseline values was performed by two-sided paired t-tests. For comparison of changes in structural outcome parameters over 5 years between patients after KJD and controls multivariable regression analysis was used, with adjustment for the respective baseline values for the outcome and confounders. A stepwise selection procedure was used starting with all baseline variables (Table 1) and removing them one-by-one based on change (≤ 5%) of the regression coefficient of the variable 'group' (KJD group or OAI group). Mean changes are presented with a 95% confidence interval (95%CI). A P-value ≤ 0.05 was considered statistically significant. For all statistical tests, IBM SPSS Statistics version 20.0.0 was used.

RESULTS

Patients

In total two patients withdrew consent for further follow-up, one after two years and one just before five years follow-up. Three other patients underwent TKA because of unsatisfactory/declining clinical benefit, at 3.8, 4.4, and 4.8 years (mean 4.3±0.5) after KJD treatment. For all missing data the last observation was carried forward for evaluation.

Clinical benefit

As for the published one and two years follow-up (Intema et al. 2011[14], Wiegant et al. 2013[15]), at three to five years follow-up the WOMAC scores were statistically significant improved as compared to pre-treatment values (Table 2a; Figure 2a), although over time the clinical benefit tended to decrease (not statistically significant). WOMAC total scores were at baseline: 43.9±3.3 vs. 72.9±5.6 ($p<0.001$) at three years follow-up; vs. 73.0±5.4 ($p<0.001$) at four years follow-up; vs. 65.1±5.6 ($p=0.002$) at five years follow-up. The changes compared to baseline for each patient, presented as mean with 95%CI for the whole group are presented in Figure 2a and Table 2b.

Values for the three WOMAC sub-scores were statistically significant improved over three to five years follow-up as well (Table 2a); baseline vs. five years follow-up for pain (45.3±3.5 vs. 65.6±5.5 ($p=0.003$)), for stiffness (43.9±3.9 vs. 63.8±6.1 ($p=0.002$)), and for function (43.1±3.2 vs. 65.0 ±5.7 ($p=0.002$)). The changes compared to baseline for each patient, presented as mean with 95%CI for the whole group are presented in Table 2b.

As for WOMAC scores, the VAS pain score was statistically significantly improved at three, four, and five years follow-up as compared to pre-treatment values: 72.9±2.1 vs. 37.0±6.1 ($p<0.001$) at three years follow-up; vs. 33.3±5.8 ($p<0.001$) at four years follow-

Table 2a. Overview of all clinical and structural parameters at baseline and at one, two and five year(s) of follow-up for the KJD group.

Parameter	Pre-surg	1yr post	2yrs post	5yrs post
WOMAC total (0-100)	43.9 ± 3.3	76.3 ± 4.8	76.5 ± 5.4	65.1 ± 5.6
P compared to pre-surg.		<0.001	<0.001	0.002
WOMAC pain (0-100)	45.3 ± 3.5	79.4 ± 4.8	78.2 ± 4.8	65.6 ± 5.5
P compared to pre-surg.		<0.001	<0.001	0.003
WOMAC function (0-100)	43.1 ± 3.2	77.7 ± 4.9	77.1 ± 5.4	65.0 ± 5.7
P compared to pre-surg.		<0.001	<0.001	0.002
WOMAC stiffness (0-100)	43.9 ± 3.9	65.6 ± 5.5	63.8 ± 5.9	63.8 ± 6.1
P compared to pre-surg.		<0.001	0.003	0.002
VAS pain (mm)	72.9 ± 2.1	30.5 ± 5.8	28.3 ± 6.0	45.3 ± 6.1
P compared to pre-surg.		<0.001	<0.001	0.001
X-ray min JSW MAC (mm)	1.2 ± 0.3	1.7 ± 0.3	1.7 ± 0.3	1.6 ± 0.3
P compared to pre- surg.		0.018	0.024	0.040
X-ray mean JSW MAC (mm)	2.6 ± 0.3	3.2 ± 0.2	3.1 ± 0.3	2.9 ± 0.3
P compared to surg.		0.036	0.104	0.370
MRI ThCtAB MAC (mm)	2.3 ± 0.1	3.0 ± 0.1	2.8 ± 0.1	2.5 ± 0.1
P compared to surg.		<0.001	0.017	0.177
MRI dABp MAC (percentage)	21.8 ± 4.3	4.5 ± 1.9	7.9 ± 2.1	16.1 ± 3.5
P compared to surg.		<0.001	0.002	0.139

Mean values ±SEM are given. P-values show statistical difference compared to baseline (paired analyses).

Table 2b. Overview of all changes at five years compared to baseline for all clinical parameters for the KJD group.

Outcome	KJD group (n=20)		
	Δ 5 yrs	**95%CI**	***P***
WOMAC total (0-100)	+21.1	+8.9 to + 33.3	0.002
WOMAC pain (0-100)	+20.3	+7.6 to + 33.0	0.003
WOMAC function (0-100)	+21.9	+9.4 to + 34.4	0.002
WOMAC stiffness (0-100)	+19.9	+8.0 to + 31.8	0.002
VAS pain (mm)	-27.6	-13.3 to – 42.0	0.001

Mean values with 95%CI and P-values (paired analyses) are given.

Table 2c. Overview of all changes at five years compared to baseline for all structural parameters for the KJD group and the OAI group.

Outcome	KJD group (n=20)			OAI group (n=138)		
	Δ 5 yrs	**95%CI**	***P***	**Δ 5 yrs**	**95%CI**	***P***
X-ray min JSW (mm)	+0.43	+0.02 to + 0.84	0.040	-0.67	-0.76 to – 0.59	<0.001
X-ray MAC mean JSW (mm)	+0.26	-0.33 to + 0.85	0.370	-0.80	-0.88 to – 0.72	<0.001
MRI ThCtAB MAC (mm)	+0.23	-0.11 to + 0.57	0.177	-0.25	-0.28 to – 0.22	<0.001
MRI dABp MAC (%)	-5.72	-13.50 to + 2.03	0.139	+4.17	+2.64 to + 5.71	<0.001

Mean values with 95%CI and P-values (Multivariable linear regression analysis) are given.

up; and vs. 45.3±6.1 (p<0.001) at five years follow-up respectively (Figure 2b; Table 2a,b for absolute values and changes from baseline, respectively).

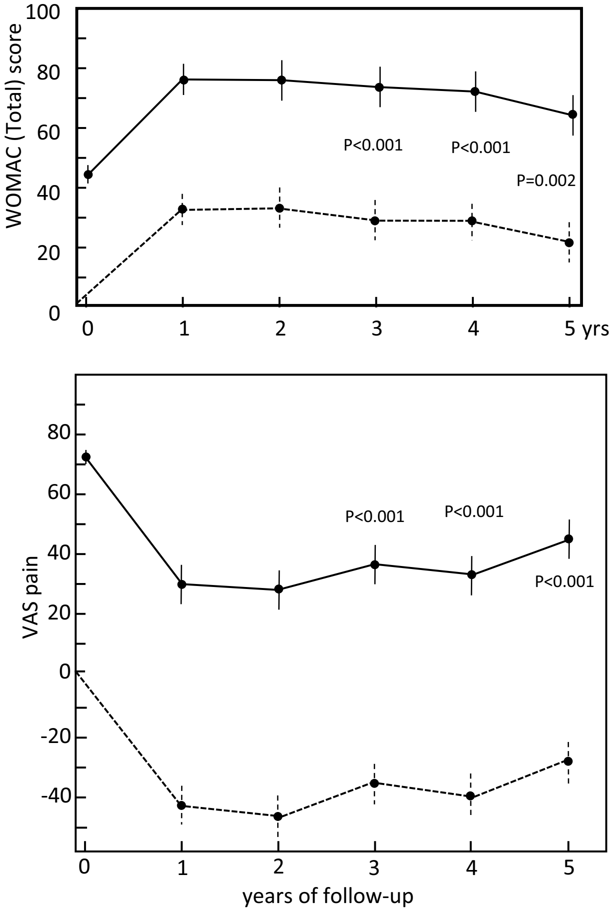

Figure 2. Clinical outcome parameters. WOMAC total (**a**) and VAS pain score (**b**) of all 20 patients (last value carried forward in case of lost to follow-up). Mean values ±SEM are given. P-values show statistical difference of values compared to baseline values. The dotted line represents the mean improvement from baseline for each patients at each year of follow-up and averaged for all 20 patients subsequently.

Structural outcome

Minimum JSW of the MAC at five years post-treatment was still increased as compared to pre-treatment values (BL: 1.2±0.3mm vs 5yrs: 1.6±0.3mm; Δ+0.43mm, 95%CI:+0.02 to +0.84mm; p=0.040) (Figure 3a; Table 2a,c). Mean JSW of the MAC was not statistically significant different from pre-treatment values anymore (BL: 2.6±0.3mm vs. 5yrs: 2.9±0.3mm; Δ+0.26mm, 95%CI:-0.33 to +0.85mm; p=0.370) (Figure 3b, Table 2a,c).

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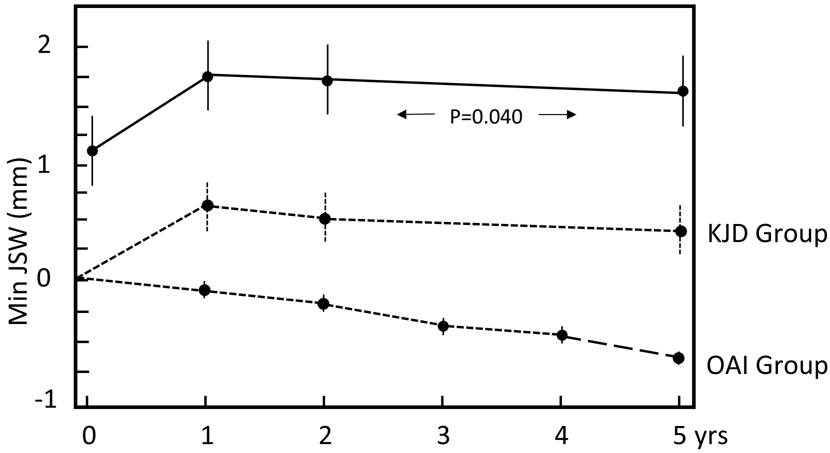

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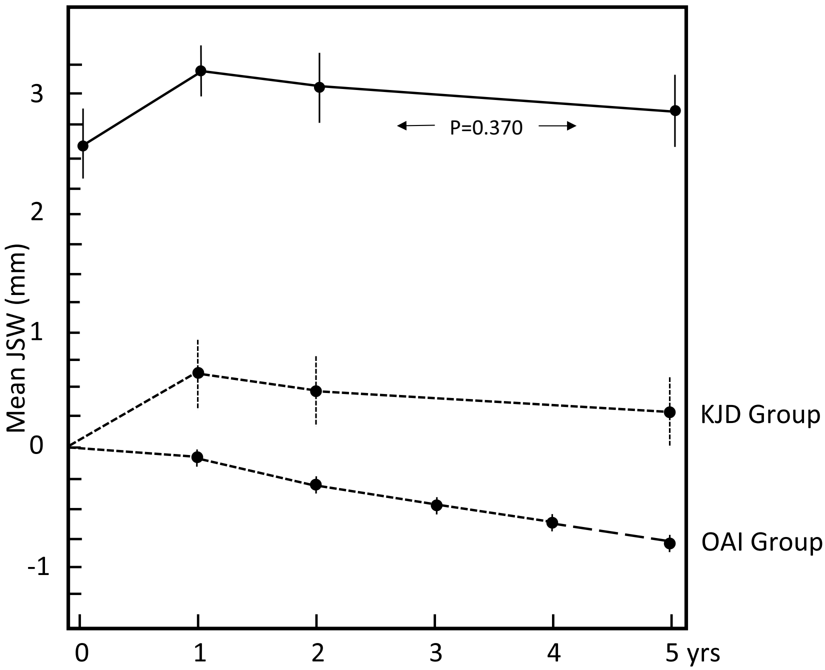


Figure 3. Radiographic structural outcome parameters. Minimum (**a**) and mean (**b**) (for MAC) joint space width (JSW) of all 20 patients (last value carried forward in case of lost to follow-up). Mean values ±SEM are given. P-values with arrows show statistical difference of values compared to baseline values; The dotted line represents the mean improvement from baseline calculated for each patient for each year after surgery for the KJD group and the OAI group. The dotted line between 4 and 5 years for the OAI group represents extrapolation based on linear progression. MAC: most affected compartment. JSW: joint space width. OAI: Osteoarthritis Initiative.

The quantitative MRI analysis showed at five years follow-up that the mean cartilage thickness of the MAC on MRI was not statistically significant different from pre-treatment values anymore (ThCtAB: BL: 2.3±0.1mm vs. 5yrs: 2.5±0.1mm; Δ+0.23mm, 95%CI:-0.11 to + 0.57mm; p=0.177), due to a gradual decrease of the initial increase at 1 and 2 years (Intema et al. 2011[14], Wiegant et al. 2013[15]) (Figure 4a, Table 2a,c). The same was observed for the average percentage denuded bone area of the MAC on the MRI images (dABp: BL: 21.8±4.3% vs. 5yrs: 16.1±3.5 %; Δ-5.72%, 95%CI:-13.50 to +2.03%; p=0.139) (Figure 4b, Table 2a,c).

Adverse events

During distraction treatment, 17 out of the 20 patients had had single or multiple pin tract infections, and could be treated adequately with antibiotics. Two patients suffered from pulmonary embolism, treated according to guidelines with oral anticoagulants for six months. At six-month follow-up, knee flexion was still decreased by 9° (±4.5). After this initial fall in joint flexion, levels returned to baseline levels after one year (121°±4.0 at baseline, and 123°±3.7 at one year). These levels of joint flexion were maintained at the two year follow-up (123°±3.3).

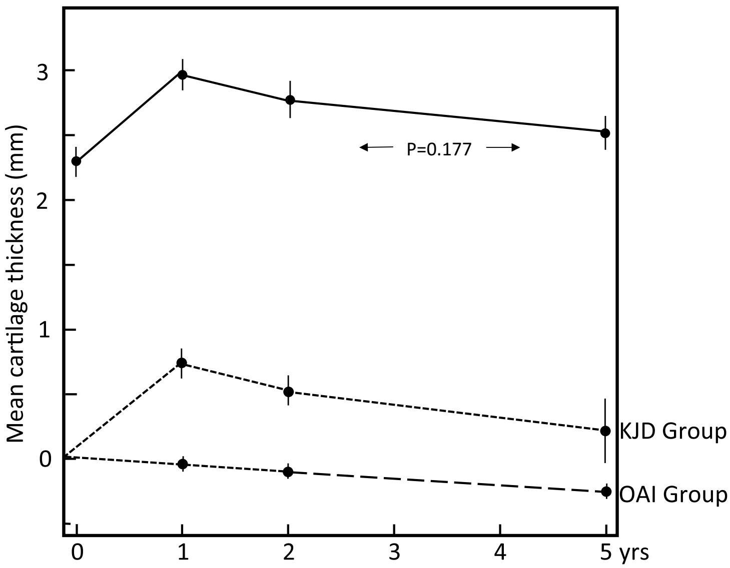
Comparison with OAI group

The KJD group and OAI control group were not statistically significantly different regarding demographic baseline values and severity of osteoarthritis (Table 1).

In the OAI group the mean JSW of the MAC decreased from 4.93±0.12 mm at BL to an extrapolated value of 4.13±0.14 mm at 5yrs (Δ-0.80mm, 95%CI:-0.88 to –0.72mm) (Figure 3b, Table 2c). The min JSW of the MAC showed similar results, with a decrease from 4.20±0.14 mm at BL to a extrapolated value of 3.52±0.14 mm at 5yrs (Δ-0.67mm, 95%CI:-0.76 to –0.59mm) (Figure 3a, Table 2c).The mean cartilage thickness (ThCtAB) of the MAC decreased from 3.47±0.06 mm at BL to an extrapolated value of 3.22±0.06 mm at 5yrs (Δ-0.25mm, 95%CI:-0.28 to –0.22mm) in the OAI group (Figure 4a, Table 2c). The same was observed for the extrapolated average percentage denuded bone area of the MAC on the MRI images (dABp: BL:4.0±0.8% vs. an extrapolated value at 5yrs: 8.1±1.5 %; Δ4.17%, 95%CI:2.64 to +5.71%) (Figure 4b, Table 2c).

Multivariable linear regression analysis indicated that KJD treatment was associated with significantly less progression in mean JSW, min JSW, mean cartilage thickness, and average percentage denuded bone area (adjusted for the respective baseline values and confounders age, and KL grade) when compared to the 'natural progression' in the OAI group over five years. The 'regression coefficient' (β) for KJD was negative for dABp (-17.49), indicating that patients in the KJD group would on average have a 17.49 percent (95%CI=-21.96 to -13.03, p<0.001) lower progression of percentage denuded bone area when compared to patients in the OAI group. For mean JSW, the β for KJD

A



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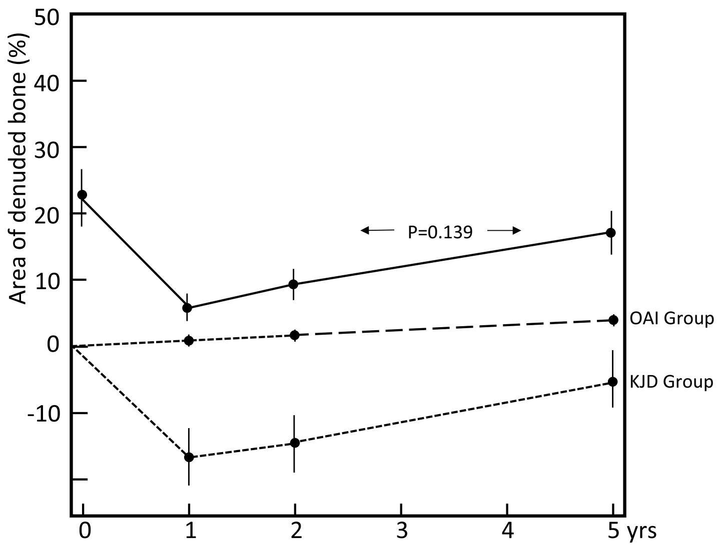

Figure 4. MRI structural outcome parameters. Mean cartilage thickness (**a**) and percentage area of denuded bone (**b**) (for MAC) of all 20 patients (last value carried forward in case of lost to follow-up). Mean values ±SEM are given. P-values with arrows show statistical difference of values compared to baseline values; The dotted line represents the mean improvement from baseline for each year after surgery for the KJD group and the OAI group. The dotted line between 2 and 5 years for the OAI group represents an anticipated linear extrapolated progression. MAC: most affected compartment. OAI: Osteoarthritis Initiative.

was positive (0.76), indicating that patients in the KJD group have on average a 0.76 mm (95%CI=0.50 to 1.02, $p<0.001$) lower progression of the mean JSW when compared to patients in the OAI group. The β for KJD in the analysis of min JSW was 0.83 (95%CI=0.59 to 1.08, $p<0.001$) and for mean cartilage thickness (ThCtAB) it was 0.35 (95%CI=0.24 to 0.46, $p<0.001$).

DISCUSSION

Five years after KJD, >80% of patients were still satisfied. There appeared to be a sustained clinical benefit and most patients lack the need for additional surgical intervention. Three out of 18 patients underwent TKA within the five years of follow-up (on average >4 years after KJD). Moreover, in two of the three secondary TKAs (all performed without any complications and with good results), WOMAC and pain scores were, despite of being decreased over the last year of follow-up, still significantly improved compared to pre-treatment values (individual data not shown). Apparently a relative worsening of physical condition and pain, despite still improved compared to pre-treatment conditions, is sufficient to prefer a subsequent alternative treatment.

The question is whether failure over time to KJD can be predicted by e.g. patient's demographics or clinical condition? Unfortunately, no predictors could be identified in this still limited numbers of patients treated. Recently 42 patients have been treated with KJD in two RCTs comparing KJD with high tibial osteotomy and with TKA.[26] Based on such numbers a prediction of failure to KJD might be found in the future. However, in over a 110 patients treated with joint distraction in case of ankle osteoarthritis only female gender appeared predictive of failure.[27] Finding reliable predictors would narrow criteria for treatment and facilitate implementation, because failure upon such a demanding treatment should be avoided.

Another issue is whether KJD, in case clinical benefit is declining over the years, can be repeated or followed by other joint preserving surgical treatments such as osteotomy? This might be relevant in case patients are still below the age of 65 years and joint preserving treatment is still favorable. A second joint distraction procedure has been performed sporadically in cases of ankle OA[28], several years after the first treatment, with good clinical results. Whether this is also possible for knee osteoarthritis needs future study. This approach seems worthwhile to explore based on the initial one-to-two years cartilaginous repair followed by progression of damage with a rate very similar to natural progression.

Although patients have a stiff knee joint for eight weeks, which limits their activities in daily life, almost all patients consider the treatment "worth the investment". Also the frequently occurring pin-tract infections (reported on previously[14,15] needing antibiotic treatment) were not considered of such a burden that patients would have refused KJD treatment. At present even subsequent treatment of the other osteoarthritic knee is performed on patient's request. Clearly factual information to patients about durability, burden, and risks is a prerequisite before general implementation can be started. Clearly, proper pin tract care protocols and anti-coagulation to prevent embolism, as well as care to regain full joint motion after treatment are of utmost importance.

Originally, in the present study no control group was included. In fact this is difficult, as patients need treatment in one or the other way in this debilitating stage of the disease. Therefore, in this study natural progression of osteoarthritis was determined in a control group with comparable patients characteristics (demographic and severity of osteoarthritis) at baseline. Although both groups were comparable at baseline there were also some limitations with this approach. The OAI control group only had radiographic measurements available up to four years and quantitative MRI measurements up to two years. Therefore the five-year follow-up date of the most affected compartment (MAC) for the OAI patients were calculated considering the natural progression rate to be linear over time, which is a reasonable assumption according to recent literature.[24,25] Patients in the OAI group were slightly older (on average 2.3 years). It may be debated if in younger patients the progression rate will be higher considering the higher activity level of such younger patients. In that case we may have overestimated the natural progression in the OAI group. On the other hand patients that underwent TKA in the OAI group were excluded (worst cases) probably leading to an underestimation of actual progression in this group. Irrespectively, this population is the only one with comparable baseline characteristics and with longitudinal MRI and X-ray data available and as such might be considered the best available control.

Interestingly, after the first initial substantial increase in JSW on radiographs, and substantial increase in cartilage thickness on MRI upon KJD, the subsequent gradual decrease in these parameters over time seem to parallel with the rate of progression in the OAI group. Apparently, the cartilaginous tissue repair takes place in the first (two) year(s) and subsequently natural progression proceeds again. Irrespectively, the head start in the first year is maintained (statistically significant) over the subsequent five years.

In summary, KJD results in prolonged clinical benefit, potentially explained by an initial boost of cartilaginous tissue repair that provides long-term tissue structure benefit as compared to natural progression in the OAI group. KJD therefore represents a promising therapeutic option for young patients with severe knee osteoarthritis.

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Chapter

6

Knee joint distraction compared to total knee arthroplasty for treatment of end stage osteoarthritis: Simulating long-term outcomes and cost-effectiveness

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ABSTRACT

Objective: In end-stage knee osteoarthritis the treatment of choice is total knee arthroplasty (TKA). An alternative treatment is knee joint distraction (KJD), suggested to postpone TKA. Several studies reported significant and prolonged clinical improvement of KJD. To make an appropriate decision regarding the position of this treatment, a cost-effectiveness and cost-utility analysis from healthcare perspective for different age and gender categories was performed.

Methods: A treatment strategy starting with TKA and a strategy starting with KJD for patients of different age and gender was simulated. To extrapolate outcomes to long-term health and economic outcomes a Markov (Health state) model was used. The number of surgeries, QALYs, and treatment costs per strategy were calculated. Costs-effectiveness is expressed using the cost-effectiveness plane and cost-effectiveness acceptability curves.

Results: Starting with KJD the number of knee replacing procedures could be reduced, most clearly in the younger age categories; especially revision surgery. This resulted in the KJD strategy being dominant (more effective with cost-savings) in about 80% of simulations (with only inferiority in about 1%) in these age categories when compared to TKA. At a willingness to pay of 20.000 Euro per QALY gained, the probability of starting with KJD to be cost-effective compared to starting with a TKA was already found to be over 75% for all age categories and over 90–95% for the younger age categories.

Conclusion: A treatment strategy starting with knee joint distraction for knee osteoarthritis has a large potential for being a cost-effective intervention, especially for the relatively young patient.

INTRODUCTION

In the event of failure of conservative treatment in generalized knee osteoarthritis the treatment of choice is often a total knee arthroplasty (TKA). TKA is now generally regarded as the gold standard for generalized knee osteoarthritis, being a safe and (cost)-effective procedure.[1] However, in younger and middle aged patients there are some legitimate concerns regarding the effectiveness of TKA related to the time to failure of TKA and need for revision surgery.[2] Younger patients (< 55) have an almost five times higher risk of revision, one of main reasons being aseptic loosening.[3-5] The increasing rate of primary and revision TKAs is a considerable healthcare burden.[6] For young and middle aged patients with generalized knee osteoarthritis alternative treatment strategies are therefore needed. One of those alternatives is knee joint distraction (KJD). KJD is a surgical procedure in which an external fixation frame is used to extend the tibiofemoral joint for 6–8 weeks.

In short the distraction treatment comes down to the following; two dynamic monotubes are placed on either side of the knee joint (lateral and medial) and are fixed to femur and tibia with two bone pins each. The knee joint is distracted for ~5 mm and patients are allowed to fully load the distracted knee if needed supported with crutches. After 6– 8 weeks the frame and pins are removed.[7] The scientific rationale is that full mechanical unloading of the knee joint prevents further wear and tear and enables intrinsic cartilaginous tissue repair.[8] In the past one prospective uncontrolled study was conducted, treating 20 patients originally considered for TKA. Results were promising, with prolonged clinical benefit and cartilaginous tissue repair on radiographs and magnetic resonance images.[7,9] Currently RCTs are being conducted, comparing KJD with hight tibial osteotomy and TKA.[10] To make appropriate decisions regarding the specific position of KJD for generalized knee osteoarthritis, the long-term health effects and cost-effectiveness needs to be compared to the current treatment standard for this condition (TKA). Even though currently long-term data on KJD is limited, early information on these issues can help to guide optimal implementation of KJD for patients and society, e.g. selection of patients for further studies. Therefore we set out an (early) cost-effectiveness evaluation comparing KJD with TKA from a healthcare perspective.[11] In addition, we determined the influence of age and gender in this comparison.

MATERIALS AND METHODS

Patients and treatment data

The target population for our analysis consisted of patients with advanced, generalized knee osteoarthritis indicated for TKA. However, follow-up data for KJD is still limited.

Before KJD multiple studies have been conducted with joint distraction as treatment for severe ankle osteoarthritis.[8] Since ankle and knee distraction are conceptually comparable with no statistically significant difference in survival, we decided to combine these data to strengthen the modeling over a longer time, for time to KJD failure.[12]

For KJD, data was derived from a feasibility study (six patients) and a prospective follow-up study (twenty patients). These 26 patients were treated with KJD between 2002 and 2008 at the University Medical Center Utrecht (UMCU). To strengthen this limited follow-up and number of patients treated, data from an open prospective multicenter study in patients who underwent distraction as a treatment for severe ankle osteoarthritis was added. Seventy-four patients underwent joint distraction of the ankle between 1993 and 2001. An overview of these studies, with mean age and survival time is given in Table 1.

All studies were approved by the medical ethics review committee of the UMCU and all clinical investigations have been conducted according to the principles expressed in the Declaration of Helsinki. All patients gave written informed consent.

Regarding time to failure for TKA and revision TKA we used published data up to 12 years from the Australian Orthopedic Association National Joint Replacement Registry (AOANJRR) stratified by age category and gender, as no such suitable Dutch or European data (from e.g. Scandinavian registries) were available.[13,14]

Table 1. Overview of studies used to derive data for KJD regarding time to failure

Type of study	Number of patients	Average age (range)	% Female	Lost to follow-up	Number of failures	Mean survival time failures (range)
Feasibility study and prospective follow-up (Knee Joint Distraction)	26	48.3 yrs (32-57 yrs)	42%	3	5	61 months (45-84 months)
Prospective multi-center study (Ankle Distraction)	74	43.3 yrs (18-65 yrs)	45%	6	25	38 months (6-120 months)

Time to failure for the different treatments

To extrapolate the obtained short and intermediate term failure probabilities for the different treatments to long-term failure times a parametric (Weibull) regression analysis was performed on the recreated individual patient data. To fit this model as close as possible to the (published) survival curve(s), recreated individual patient data was simulated assuming no censoring.[15] Figures 1a, 1b and 1c present survival curves based on a parametric Weibull distribution, fitted to extrapolate the time to failure for the different procedures. Time to failure was only stratified (age and gender) for TKA, as for both KJD and revision TKA no data for subgroups was available.

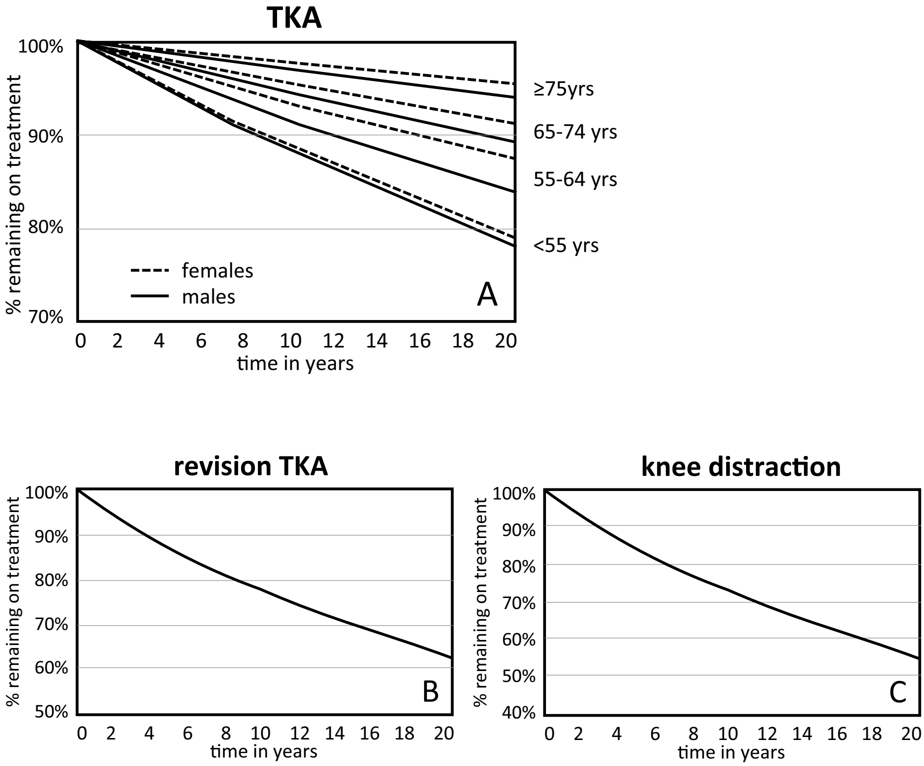

Figure 1. Survival curves. A Parametric Weibull distribution was fitted to extrapolate the time to failure for the different procedures (per age- gender category): for TKA **(a)**, revision TKA **(b)**, and knee distraction **(c)**.

Health Economic simulation model

To simulate a treatment strategy starting with TKA and a treatment strategy starting with KJD for patients of different age and gender and to extrapolate outcomes to long-term health and economic outcomes a simulation model was used. This individual patient Markov (or Health state) model evaluates the effectiveness of introducing KJD as first treatment compared to TKA over twenty years. This time horizon was considered adequate to capture the long-term impact (i.e. on revision surgery) of a treatment strategy starting with KJD as compared to TKA without going too much beyond the available follow-up data for the different surgical procedures, and a conservative approach as the longer time span the more chance on revision surgery. In the model a cohort of 200 patients was simulated to start with KJD (KJD strategy) and another (similar) cohort was simulated to start with TKA. After failure of KJD a TKA was performed (only for KJD arm) and after failure of TKA, revision TKA was performed in the model. When the revision TKA fails a second revision TKA or best supportive care was performed (Figure 2). Best supportive care (BSC) refers to care given after failure of revision surgery (if a 2nd revision is not performed, i.e. analgesic therapy, a knee brace, or even knee arthrodesis). After the 2nd TKA, it was assumed in the model that the patient remains in the 'post 2nd revision TKA/BSC' state until twenty-year follow-up (or death, see below), since no data was available for time to failure after 2nd revision. Movement to the (absorbing) state of death is also possible in the model. Overall survival (life years left) was based on data stratified by gender and age for the Dutch population from the central bureau of statistics of the Netherlands, assuming the life expectancy of osteoarthritis patients to be equal to the general population (i.e. osteoarthritis and treatment specific mortality is assumed to be zero).[16] In both cohorts patients are distributed over the health states according to the probabilities of failing of the different surgical procedures and the probability of dying over time with a cycle time (time interval over which a transition to another state can occur) of one year. The different health states (see Figure 2) are assigned a cost-value and utility value to obtain the total costs and quality adjusted life years over the total time horizon of twenty years.

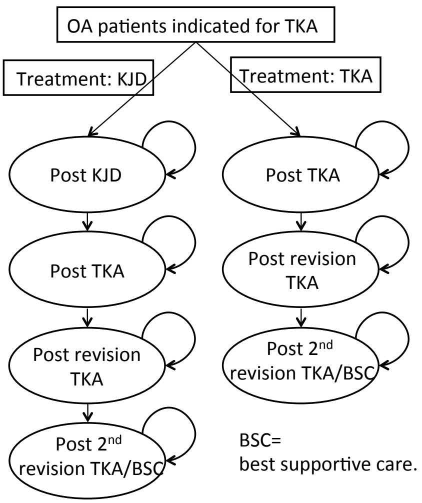

Figure 2. Overview of the health state model. Over the 20-year horizon analysis of the model patients are at risk of dying, so they can move to the absorbing state death from each other state. State death not shown in figure. BSC = Best Supportive Care.

Cost calculation

Costs of KJD are calculated based on the actual/observed surgical equipment used, time spend on the surgery by the orthopedic surgeon and other personnel, hospital stay (on average 5 days) administrative hospital costs (i.e. overhead) and physical therapy costs (three months) of individual patients undergoing KJD, based on the presently available (limited and between hospitals variable) data. Additional non-surgical costs in the year of treatment are considered not different between both treatments and negligible compared to the surgery related costs. Resource use was valued using the Dutch manual for costing and Costs were measured in 2013 Euros.[17] Costs of TKA are based on tariffs for knee prosthesis cited by specific hospitals (Orthopedium Delft and Maartenskliniek, noting that cost may differ between different Dutch hospitals). Costs of revision TKA are based on expert opinion (SP, RvH, PvR, RC) and report from the Dutch health care insurer Achmea.[18] Costs as used in the analysis are shown in Table 2.

Since costs for TKA and revision TKAs are based on tariffs and no tariff yet exists for KJD, the costs based on actual observed costs were increased with a 10% markup. For the costs in the years after the procedure only for revision operation costs were assumed given the worse outcomes of these procedures and related care, for 2nd revision these were assumed lower given the fewer treatment options available (Table 2), although this is conservative and may be an underestimation for costs of such a 2nd revision. As such costs represent costs from a health care perspective (and not a societal perspective). Future costs were discounted using a constant annual rate of 4 percent.[17]

Table 2. Input data mean cost and utility per health state, point estimate with range as used in PSA

	Costs		
	1st year (range)	**Yearly thereafter (range)**	**Source**
Distraction	€8.000 (€4.573-€12.370)	€0 (€0-€0)	Based on actual/observed costs with 10% markup
TKA	€12.000 (€8.405-€16.226)	€0 (€0-€0)	Based on tariffs cited by specific hospitals
Revision	€20.000 (€16.273-€24.106)	€1.000 (€376-€1.923)	Reference 18
BSC	€25.000 (€21.234-€29.069)	€100 (€38-€192)	Reference 18
	Utility		
	1st year (range)	**Yearly thereafter (range)**	**Source**
Distraction	0.73 (0.70-0.75)	0.82 (0.79-0.85)	EQ-5D RCT comparing knee distraction with TKA[10]
TKA	0.76 (0.73-0.79)	0.79 (0.76-0.82)	Reference 19-21
Revision	0.73 (0.70-0.76)	0.75 (0.72-0.78)	Reference 19-21
BSC	0.70 (0.67-0.73)	0.72 (0.69-0.75)	Reference 19-21

Utility estimation

Quality adjusted life years (QALY) takes into account both quantity and quality of life. For the different procedures QALYs were based on assigning a utility value for the year of the procedure (after) and one for the years thereafter the procedure. For KJD this utility value was based on the presently available data on the EuroQoL 5 dimension scale (EQ-5D) in a currently ongoing RCT, comparing KJD with TKA.[10] Utility for the other surgical procedures (in the year of the procedure and the years thereafter) are based on (changes in) scores after these procedures from the literature, as this contains more robust data for TKA than can be obtained from the before mentioned RCT.[19-21] For the utilities a discount rate of 1.5 percent was used.[17] Utility values as used in the model analysis are shown in Table 2.

Analysis

The total number of operations, QALYs and treatment costs, and ICER's expressing the costs per TKA saved, costs per revision operation saved, costs per 2nd revision/BSC saved, and costs per QALY as accumulated in the model per treatment strategy were calculated and the differences therein. This was done separately for gender and age categories (45–49, 50–54, 55–59, 60–64, 65–69). We used age and gender categories, since we also meant to get information on the 'best place/indication' for the treatment. Costs-effectiveness was also expressed using the cost-effectiveness plane. To obtain an (point) estimate as well as the uncertainty therein for the outcomes of the model a probabilistic sensitivity analysis (PSA) was performed. In this analysis for each individual patient in the simulation cohort a time to failure for KJD, TKA, revision TKA, and death is sampled

Table 3. Differences between strategy starting with KJD and TKA after 20-years

	No. TKAs prevented by KJD (95% CI)	No. of 1st revisions prevented by KJD (95% CI)	No. of 2nd revisions prevented by KJD (95% CI)	No. of Years on BSC prevented by KJD (95% CI)	Costs saved by starting with KJD (95% CI)
Females					
45 – 49	107 (93-121)	30 (18-43)	6 (1-13)	48 (1-103)	€681.740 (€-371.853 - €1.649.483)
50 – 54	108 (94-122)	32 (20-44)	7 (1-13)	48 (2-100)	€744.004 (€-285.500 - €1.715.557)
55 – 59	110 (96-124)	18 (8-28)	4 (0-8)	26 (-6 – 67)	€402.671 (€-618.273 - €1.347.240)
60 – 64	113 (99-127)	18 (8-28)	4 (0-8)	24 (-5 – 62)	€421.703 (€-600.873 - €1.370.455)
65 – 69	118 (104-132)	11 (3-20)	2 (-1-6)	14 (-8 – 44)	€297.486 (€-722.089 - €1.231.619)
Males					
45 – 49	107 (93-121)	31 (19-44)	7 (1-13)	49 (1-104)	€729.266 (€-312.521 - €1.768.484)
50 – 54	109 (96-123)	32 (20-44)	7 (1-13)	48 (4-100)	€753.401 (€-307.230 - €1.709.497)
55 – 59	112 (98-126)	22 (11-33)	4 (0-9)	31 (-6-76)	€520.600 (€-521.532 - €1.469.602)
60 – 64	117 (103-131)	21 (11-32)	4 (0-9)	28 (-4-68)	€542.960 (€-486.280 - €1.498.937)
65 – 69	125 (110-139)	14 (5-27)	2 (-1-7)	15 (-7-48)	€413.259 (€-630.412 - €1.381.296)
Overall					
	115 (101-129)	20 (12-31)	4 (0-9)	27 (-5-67)	€480.330 (€-550.213 - €1.434.335)

Overall result: weighted average with weights according to the proportion of patients in the different gender and age categories undergoing TKA in the Netherlands.[22]

and model outcomes are calculated. This simulation is repeated 5000 times for each age and gender category, in which also the cost inputs and the utility inputs are varied over a suitable range resulting in average estimates with 95% percent confidence ranges for the outcomes. The range for the average health state costs and health state utility in the PSA were varied using a uniform distribution for the cost inputs given the uncertainty in these input (Table 2). This analysis was performed for each gender and age category separately. Results are presented in cost-effectiveness acceptability curves. Apart from the PSA a deterministic sensitivity analyses (DSA), in which specific input variables are varied individually, was performed on:

- Time to failure for KJD (base failure time on data of KJD only, excluding ankle data)

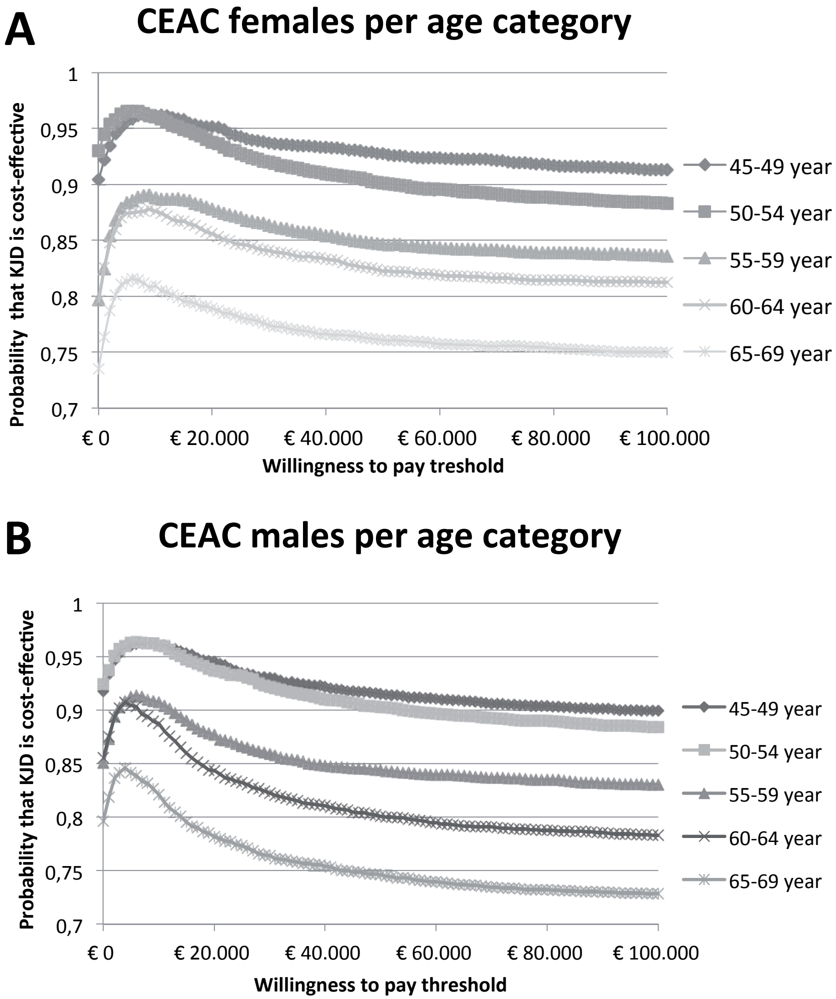

Figure 3. Cost-effectiveness acceptability curves. Females (**a**) and males (**b**) per age category.

- The cost of KJD procedure (using € 10.000 instead of € 8.000)
- Utility of KJD (using utility values in year of procedure and thereafter equal to TKA)
- The cost in years after revision and 2nd revision surgery (set to € 0 instead of € 1.000 and € 100 respectively)

RESULTS

Over 100 TKA' s are prevented by KJD over twenty years irrespective of age/gender category. Around 30 revision TKAs are prevented by KJD in the younger age groups (< 55 years). Only few 2nd revision operations are saved due to the low number of 2nd revisions occurring over this (conservative but still reliable) time horizon. In general, starting with KJD saved costs. For detailed numbers of all age/gender categories see Table 3. Similar results in favor of KJD were seen for the average costs and QALY' s per person (Table 4). Furthermore, KJD strategy was dominant in about 80% of simulations (with only inferi-

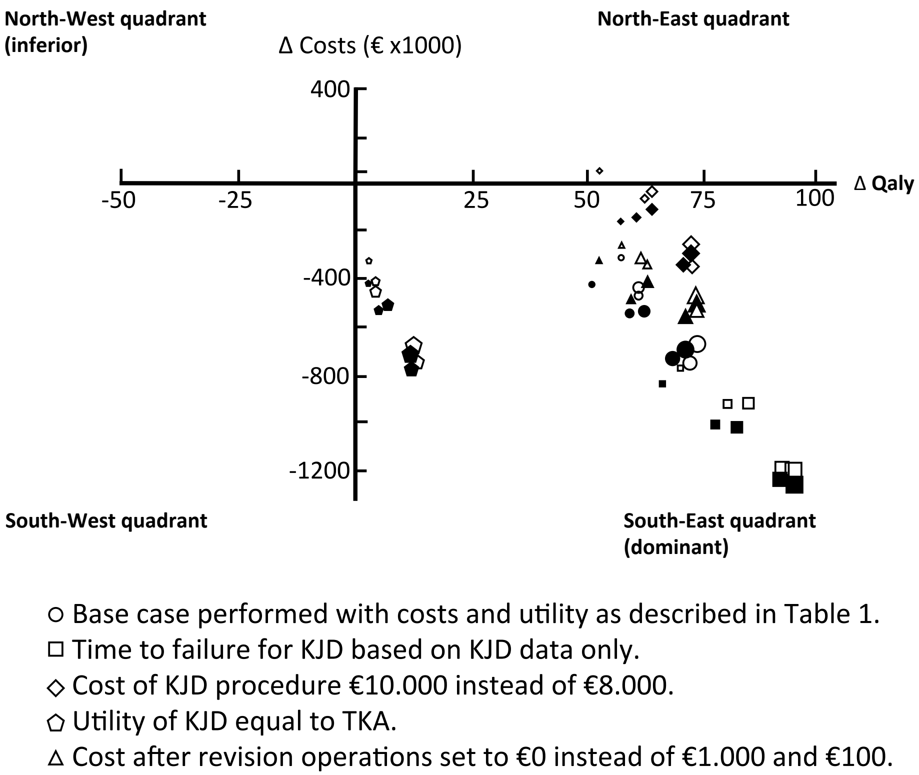

Figure 4. Deterministic sensitivity analyses. Females (open symbols) and males (filled symbols) per age category. The larger the symbol the younger the patient category.

ority in around 1%) in the younger age categories (45– 49 and 50– 54) when compared to directly starting with TKA (see Table 4). At a willingness to pay a threshold of 20.000 Euro per QALY gained, the probability that KJD is cost-effective was already found to be over 75% for all age categories and over 90– 95% for the younger age categories (Figure 3). The results of the DSA (Figure 4) also confirm the cost-effectiveness of this approach,

Table 4. Average costs per person, average QALY per person with 95% confidence limits, and the proportion of the results of the simulations per quadrant of the cost-effectiveness plane after 20-years

	Strategy starting with TKA		**Strategy starting with KJD**		**Proportions CE-plane**			
Category	Average Costs per person (95% CI)	Average QALYs per person (95% CI)	Average Costs per person (95% CI)	Average QALYs per person (95% CI))	%NE	%SE (dom)	%NW (inf)	%SW
Females								
45 - 49	€16.700 (€12.600-€21.100)	13.2 (12.7-13.7)	€13.200 (€9.300-€18.000)	13.6 (13.1-14.1)	8.6%	80.7%	1.0%	9.7%
50 - 54	€16.600 (€12.700-€21.200)	13.0 (12.4-13.6)	€12.900 (€9.100-€17.600)	13.4 (12.9-13.8)	7.0%	79.9%	0.9%	12.2%
55 - 59	€14.700 (€10.900- €19.200)	12.7 (12.1-13.3)	€12.700 (€8.900-€17.400)	13.0 (12.5-13.6)	16.3%	66.4%	3.7%	13.7%
60 - 64	€14.600 (€10.800-€19.100)	12.2 (11.5-12.9)	€12.500 (€8.700-€17.200)	12.5 (11.8-13.1)	16.1%	63.6%	3.6%	16.7%
65 - 69	€13.600 (€9.800-€17.900)	11.3 (10.5-12.2)	€12.200 (€8.400-€16.500)	11.6 (10.8-12.4)	19.9%	53.5%	7.2%	19.4%
Males								
45 – 49	€16.900 (€13.000-€21.500)	13.1 (12.5-13.6)	€13.300 (€9.300-€17.900)	13.5 (13.0-13.9)	6.7%	80.7%	1.1%	11.5%
50 – 54	€16.700 (€12.800-€21.100)	12.7 (12.1-13.3)	€13.000 (€9.300-€17.700)	13.1 (12.6-13.6)	6.9%	78.7%	1.2%	13.3%
55 – 59	€15.300 (€11.400-€19.700)	12.3 (11.6-12.9)	€12.700 (€8.900-€17.300)	12.6 (11.9-13.2)	12.5%	68.4%	2.7%	16.4%
60 – 64	€15.100 (€11.400-€19.600)	11.5 (10.6-12.3)	€12.400 (€8.600-€16.800)	12.2 (10.9-12.5)	15.2%	64.6%	4.0%	16.2%
65 – 69	€14.100 (€10.200-€18.400)	10.2 (9.3-11.2)	€12.000 (€8.200-€16.700)	10.5 (9.5-11.5)	15.6%	55.5%	5.8%	23.1%
Overall								
	€14.100 (€11.100-€19.300)	12.0 (11.2-12.7)	€12.500 (€8.700-€17.100)	12.3 (11.5-12.9)	14.6%	64,8%	4.0%	16.6%

Overall result: weighted average with weights according to the proportion of patients in the different gender and age categories undergoing TKA in the Netherlands.[22] Proportions CE-plane: The North-East (NE) quadrant indicates that the KJD strategy is more effective but also more costly than the TKA strategy. A result in the South East (SE) quadrant means that KJD is dominant. A result in the South West (SW) quadrant means that KJD is less costly but also less effective, and a result in the North West (NW) quadrant means that KJD is less effective and more costly (inferior).

with the KJD strategy on average being dominant (i.e. costs savings with QALY gain) in all scenarios in all age/gender categories except for females 65– 69 years old for scenario two where the costs for the KJD procedure were increased from € 8.000 to € 10.000. The most cost-effective scenario was the one where time to failure was based on KJD data only (leaving ankle distraction data out).

DISCUSSION

This study found that when patients with generalized knee osteoarthritis are first treated with KJD before TKA, this leads to delay of revision TKA surgeries, and effectiveness in terms of quality adjusted life years. Moreover starting with KJD saves costs. This resulted in a very high likelihood for the KJD strategy to be cost-effective, in specifically the younger age categories (45–54 years). Even if the costs for KJD were increased to €10.000, KJD still dominates TKA (except in females aged between 65–69).

Less favorable outcomes on cost and effects were seen for the older age categories. This makes sense because it is less likely that elderly need (more costly) revision surgery during their lifetime, consequently these operations cannot be prevented by KJD when performed at a later age (i.e. 65–70 years). Nevertheless, in all age categories the KJD treatment strategy was found to be dominant or cost-effective. Given the sizable burden of osteoarthritis especially in the ageing and obese population, KJD can substantially contribute to the improvement in quality of life in this population. Females benefit slightly less than males as a result from the slightly more benefit (in terms of time to failure) they have from TKA.

Early assessment of medical technology is an important step. As shown by Steuten et al.[23], an early HTA analysis can provide critical insights for technologies in development using this decision analytic approach. An important part of such an early technology assessments is often a cost-effectiveness (CE) analysis. Such CE analyses give insight into whether new technologies (such as in this case KJD) have potential in terms of cost and clinical effects (i.e. value for money) and also in which situation(s) (i.e. setting and patient population). In that way it can be determined what the patient and social impact likely will be and also what the likely returns on investment in further development of the new technology would be.[23] Our analysis made a number of assumptions and clearly has some limitations. First assumptions were made regarding the costs of the KJD procedure, due to lack of an available tariff (as used for the TKA procedure). However, for the costs of KJD, data on medical consumption (i.e. personnel material etc.) was used from the clinical setting where the frame was used and a markup of 10% was used to obtain comparable cost data, which is an often-used way of determining tariffs. Other costs were based on tariffs or estimations of tariffs from clinical experts and a health insurer. As such the perspective of the cost-effectiveness analysis was that of the health care system. This analysis did not consider high tibial osteotomy or unicompartimental knee prosthesis as part of the treatment standard, since these procedures are performed solely in patients with unicompartimental disease, whereas the KJD patient population concerned patients considered for an initial TKA with (mainly) bicompartmental knee osteoarthritis.

As we estimated costs from the healthcare perspective, no productivity costs were included in the analysis. This can be seen as a limitation, since patients with knee osteoarthritis requiring surgery often have cost due to lost productivity.[24] However, hospital treatment costs comprehend most of the cost and adding costs due to lost productivity would probably have led to similar results as we do not expect that during the procedures and in the years after effective procedures these costs are significant different between TKA and KJD. This is expected even if the loss of labor during the six weeks distraction for some patients will be included, since also TKA patients will not regain labor directly after surgery. Although patients receiving KJD overall have more operations (extra KJD procedure for removing of the distraction frame) the higher number of revision surgery and/or complications at earlier age will lead to higher loss if productivity. Another limitation was that the survivorship of knee implants was based on historical data. This could have led to an underestimation of the current survivorship given the technological advancement in recent years. However, this may also be the case for KJD as a relative novel technique, still further improving in its technology (e.g. pin tract infections are significantly reduced, treatment is changed from three months in the first study toward six weeks in the present studies) and with that potential better clinical outcome. In addition, since we used a twenty-year time horizon, this could lead to an underestimation of lifelong revision TKA surgeries and costs, since it is reasonable to assume that after this twenty-years the number of TKA failures increases and therefore more revisions might be prevented by first performing KJD. Furthermore one has to bear in mind that KJD is not the final stadium for a patient. If, after KJD, patients still have knee pain (or even an relative increase in knee pain) another good treatment option, namely TKA, is available and this step is then easily made. After TKA, only less optimal treatment options are available which makes the step from TKA to revision TKA not as easy.[25] After TKA about 80% of the patients is satisfied, meaning that as many as 20% remains to have persisting problems.[26,27] This reflects itself in the fact that the number of patients dissatisfied with the outcome after TKA is higher than the number of patients requiring revision.

Our model also had some other limitations. Since we meant to obtain information on the 'best place/indication' for KJD, we decided to report results per age and gender category. However, for KJD and revision TKA no (sufficient) data was available for specific estimates of time to failure per gender and age category. Therefore the same input for time to failure was used for all gender and age categories for KJD and revision TKA in the model (Figure 1). However, for life expectancy and time to failure for TKA specific estimates per gender and age category was available and used in the model.

This is the first analysis systematically evaluating the likely health gains and costs (savings) of implementing KJD as new treatment for osteoarthritis in current clinical practice using the best available data present. Although results are inherently uncertain this analysis shows high potential in effectively postponing TKA and preventing revision surgery. This will definitely improve quality of life of patients with a very high probability of cost-effectiveness. Additionally, in case of KJD the patient' s own knee is saved, whereas a TKA is at the expense of the original joint.

In conclusion, the findings suggest that a treatment strategy starting with knee joint distraction for osteoarthritis shows large potential for being a cost-effective intervention, especially in relatively young patients. Future studies should focus on this population first.

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Chapter

7

Six weeks of continuous joint distraction appears sufficient for clinical benefit and cartilaginous tissue repair in the treatment of knee osteoarthritis

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ABSTRACT

Background: Knee joint distraction (KJD) is a surgical joint-preserving treatment in which the knee joint is temporarily distracted by an external frame. It is associated with joint tissue repair and clinical improvement. Initially, patients were submitted to an eight-week distraction period, and currently patients are submitted to a six-week distraction period. This study evaluates whether a shorter distraction period influences the outcome.

Methods: Both groups consisted of 20 patients. Clinical outcome was assessed by WOMAC questionnaires and VAS-pain. Cartilaginous tissue repair was assessed by radiographic joint space width (JSW) and MRI-observed cartilage thickness.

Results: Baseline data between both groups were comparable. Both groups showed an increase in total WOMAC score; 24±4 in the six-week group and 32±5 in the eight-week group (both p b 0.001). Mean JSW increased 0.9±0.3mmin the six-week group and 1.1±0.3mmin the eight-week group (p=0.729 between groups). The increase in mean cartilage thickness on MRI was 0.6±0.2mmin the eight-week group and 0.4±0.1mm in the six-week group (p=0.277).

Conclusions: A shorter distraction period does not influence short-term clinical and structural outcomes statistically significantly, although effect sizes tend to be smaller in six week KJD as compared to eight week KJD.

INTRODUCTION

In generalized knee osteoarthritis (OA) with persistent severe pain, a total knee arthroplasty (TKA) is often indicated.[1] Nevertheless, joint replacement has its drawbacks. Especially in young and active patients results of TKA are less satisfactory with higher revision rates due to mechanical, aseptic loosening.[2,3] Therefore, in these patients alternative joint-preserving treatment strategies are required. Among these alternatives, knee joint distraction (KJD) is increasingly investigated. In KJD, an external fixation frame of two bilaterally placed monotubes is put in place and gradually separates the femur and tibia for several weeks. Goals of the distraction are reducing mechanical stress on the cartilage, preventing further wear and tear, and stimulating chondrocytes to initiate cartilaginous tissue repair.[4] Moreover, springs in the distraction frame increase synovial fluid pressure changes in the knee during walking. This might improve nutrition of the cartilage and further stimulate chondrocytes.[5]

KJD was associated with both joint tissue repair and clinical benefit (pain and function) in several clinical studies in knee OA patients.[6-11] Benefits were maximum between the first and second year post-operatively[6,7] and resulted in the planned TKA being postponed for at least five years in the vast majority of patients.[8] In these studies, distraction was performed for eight weeks and combined with returning visits to the hospital every two weeks. During these visits, distraction tubes were temporarily removed from the frame and the knee was passively exercised on a continuous passive motion (CPM) device in order to prevent contractures. Since patients experienced these returning visits as a significant burden, KJD is nowadays performed for six weeks and without frame removal and CPM. However, it remains to be studied whether this shorter distraction period influences outcome. Therefore, in the present study we compared one-year structural and functional outcomes between eight-week intermittent distraction and six-week continuous distraction.

MATERIALS AND METHODS

Patients

The eight-week intermittent (eight-week) group consisted of twenty end-stage knee OA patients with an indication for a TKA. These subjects are part of an observational cohort study and were included between 2006 and 2008 at the University Medical Center Utrecht. Inclusion criteria were: age <60 years, Visual Analogue Scale (VAS) ≥60 mm and primarily tibiofemoral OA at radiographs. Exclusion criteria were: contralateral knee OA requiring treatment, primarily patellofemoral OA, severe knee malalignment (>10° varus or valgus), a history of inflammatory or septic arthritis, and inability to cope with an external fixator.

The six-week continuous (six-week) group consisted of twenty patients that were part of two ongoing randomized controlled trials and were included at the Maartenskliniek Woerden.[12] In these trials, KJD is compared with TKA and high tibial osteotomy (HTO). In the KJD-TKA trial patients in clinical practice considered for TKA were included and in the KJD-HTO trial patients considered in general clinical practice for HTO (with an axis deviation <10° varus) were included. Inclusion and exclusion criteria were comparable to the eight-week intermittent group: age <65 years, intact knee ligaments, normal range-of-motion (ROM; minimum of 120° flexion) and a Body Mass Index (BMI) <35. The medical ethical review committee of the University Medical Center Utrecht approved all studies (Nos. 04/086, 10/359/E, and 11/072) and all patients gave their written informed consent.

Distraction method

KJD was performed as previously described by Intema et al.[6] In short, a commercially available proof-of-concept distraction device was used, consisting of two bilaterally placed dynamic monotubes (Triax/Stryker), fixed on two bone pins at each end, bridging the knee joint at the lateral and medial side. Distraction was gradually increased to five millimeters and confirmed radiographically (see Figure 1). Instructions about pin-site care and physical therapy (on demand) were given. Patients were instructed to fully load the distracted joint, supported with crutches.

For subjects in the eight-week group, return visits to the hospital were planned every two weeks. During these visits, the monotubes were temporarily removed from the

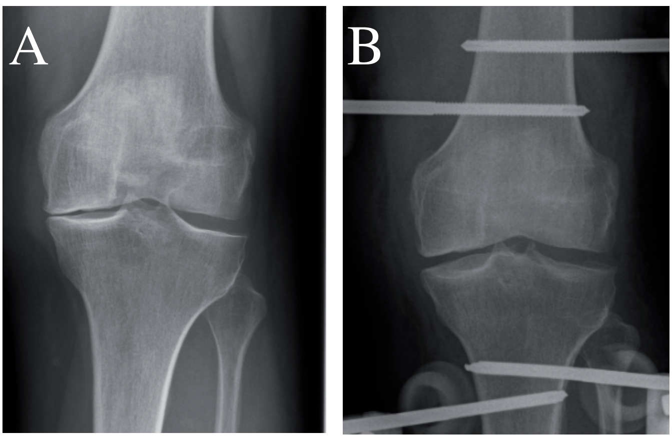

Figure 1. Example of a pre-operative radiograph (**a**) of a patient treated with knee joint distraction. Radiograph (**b**) of the same patient during distraction treatment with five millimeters of distraction.

bone pins and they received CPM exercise for three to four hours. The maximum degree of knee flexion averaged 25° (15 to 80°) and full extension was reached. The monotubes were re-installed after exercising and distraction was confirmed radiographically. At the end of the eight-week period (average duration 59 days, range 54 to 64 days), frame and pins were removed at day care. Patients returned home without any functional restrictions, and with physiotherapy and pain medication on demand (the latter two were not registered).

In the six-week group, frame and pins were surgically removed after six weeks (average duration 42 days, range 39 to 47 days). As the ROM of the knee joints was limited due to adhesions in the surrounding soft tissues, the knee joints were flexed gradually by hand under anesthesia. At the first post-operative day, partial weight-bearing (maximum 20 kg) was allowed. After discharge, patients gradually regained normal full loading in approximately six weeks (expansion of 15 kg every week). Physiotherapy and pain medication were used on demand (not registered). For details see Wiegant et al.[12] The skin surrounding bone pins was treated to minimize pin tract infection.[13] Prophylactic low-molecular-weight heparin was prescribed for nine weeks (six-week distraction period and three weeks after). At three to four weeks, patients visited the outpatient department for radiographic evaluation of the distraction and pin tract.

Clinical outcome

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to score clinical improvement, normalized to a 100-point scale; 100 being the best condition. A visual analogue scale for pain (VAS-pain; 0 to 100 mm, 0 meaning no pain) was the secondary clinical outcome parameter. At baseline, three, six, and twelve months the WOMAC questionnaire, and the VAS-pain were assessed.

Cartilaginous repair activity

Radiographic analysis

Standardized weight-bearing, semi-flexed (seven degrees to 10° flexion) posterior-anterior knee radiographs, according to Buckland-Wright, were obtained at baseline and twelve months post-operatively. Radiographic parameters were quantified by using 'knee images digital analyses' (KIDA) software, performed by one experienced observer, blinded to order of acquisition and patient characteristics, in a single session (to prevent bias from a learning curve between radiographs that were sequentially obtained during study periods).[14] Mean JSW of the most affected compartment (MAC), the least affected compartment, and the minimum JSW are given in mm. Intra-observer reproducibility for mean and minimum joint space width (JSW) have been demonstrated to be very high.[14] The intra-class correlation coefficient between the original and reevaluation was 0.97.

Quantitative MRI analysis

MRI analyses were performed as was described previously[7], using custom-made software (Chondrometrics GmbH, Ainring, Germany). In short, tibiofemoral cartilage surfaces and bone cartilage interfaces were segmented (SM) on coronal images, with the reader being blinded to the time sequence of the image acquisitions. Primary structural outcomes in this study were cartilage thickness over the total subchondral bone area (ThCtAB; cartilage thickness, including denuded bone areas), the percentage of denuded bone area (dABp), and cartilage thickness over cartilaginous area of subchondral bone (ThCcAB; cartilage thickness excluding denuded bone areas). The reproducibility of these assessments has been published before.[15-17]

Statistical analysis

All continuous variables were normally distributed. Unpaired two-sided Student's t-tests and Chi-square tests were used to compare preoperative parameters between groups. Kellgren and Lawrence grades (KLG) were compared using Chi-square tests. Paired two-sided t-tests were used to compare continuous variables between baseline and one-year follow-up. The average changes during the study period were compared between the eight-week and six-week group using two-sided unpaired Student's t-tests. p-Value of below 0.05 was considered statistically significant. SPSS software version 22.0 was used to perform statistical analyses.

RESULTS

The baseline demographics, clinical, and structural parameters and an overview of previous knee surgery for the eight-week group and the six-week group is given in Table 1. In general both groups are comparable. In the six-week group, eleven patients were from the KJD–TKA study and nine were from the KJD–HTO study. One patient in the six-week group continued to have disabling pain and functional impairment despite KJD and underwent TKA seven months post-distraction. For this patient, clinical and radiographic parameters that were obtained at six-month follow-up were carried forward. For MRI no follow-up data were available and the average of nineteen patients was used for comparison.

Clinical outcome

The total WOMAC score increased in both groups (Figure 2); 24±4.0 points (mean±SEM) in the six-week group and 32±5.0 points in the eight-week group (both $p<0.001$). The WOMAC subscales for pain, stiffness, and function all improved similarly in both groups at the different follow-up moments ($p<0.02$, except for the stiffness subscale at three

Table 1. Baseline characteristics

Characteristics Mean (± SEM)	**8-wks KJD (n=20)**	**6-wks KJD (n=20)**	**p value**
Male gender (n)	11/20	10/20	0.752
Height (cm)	175 ± 2	176 ± 2	0.752
Weight (kg)	90.5 ± 2.7	82.6 ± 3.7	0.095
Body mass index (kg/m^2)	29.6 ± 0.8	26.4 ± 0.8	0.009*
Affected knee (left)	11/20	9/20	0.527
Most affected compartment (medial)	18/20	17/20	0.633
Age at surgery (yr)	48.5 ± 1.3	54.6 ± 1.7	0.007*
Kellgren & Lawrence (median)	3	3	0.229
Grade 1 (n)	3 (15%)	2 (10%)	
Grade 2 (n)	4 (20%)	3 (15%)	
Grade 3 (n)	11 (55%)	9 (45%)	
Grade 4 (n)	2 (10%)	6 (30%)	
Duration distraction (days)	59.1 ± 0.8	42.1 ± 0.4	<0.001*
Clinical parameters at baseline Mean (± SEM)			
WOMAC Total	43.9±3.3	51.8±3.7	0.122
WOMAC, subscale stiffness	43.9±3.9	44.7±5.2	0.899
WOMAC, subscale pain	45.3±3.5	51.2±4.2	0.284
WOMAC, subscale function	43.1±3.2	52.8±3.5	0.051
VAS pain	74±1.9	60±4.5	0.012*
Knee flexion (degrees)	121±4.0	126±2.0	0.297
Cartilaginous parameters at baseline Mean mm (± SEM)			
Mean JSW MAC	2.63±0.4	1.80±0.4	0.110
Min JSW MAC	1.03±0.3	0.54±0.2	0.196
Mean JSW whole joint	4.78±0.2	4.77±0.2	0.969
Mean JSW LAC	6.92±0.4	7.73±0.4	0.135
Cartilaginous parameters at baseline Mean (± SEM)			
ThCtAB MAC (mm)	2.37±0.1	2.15±0.2	0.406
dABp MAC(%)	22.0±4.5	31.6±5.1	0.168
ThCcAB MAC (mm)	2.96±0.1	2.93±0.1	0.871
Previous surgery Operation (number)			
ACL Reconstruction (n)	1	2	
High Tibial Osteotomy (n)	4	4	
Arthroscopy:	15	11	
Partial meniscectomy (n)	12	7	
Arthroscopic joint lavage (n)	3	4	
Open Meniscectomy (n)	0	2	
Excision loose bodies (n)	0	1	

months in the six-week group; Figure 3). The change of the total WOMAC score and of the subscales between baseline and one-year follow-up was similar between groups (right panels Figures 2 and 3). Sixteen patients from the eight-week group and 14 patients from the six-week group could be identified as clinical responders according to the OARSI-OMERACT responder criteria[18] (not statistically significant different between both groups).

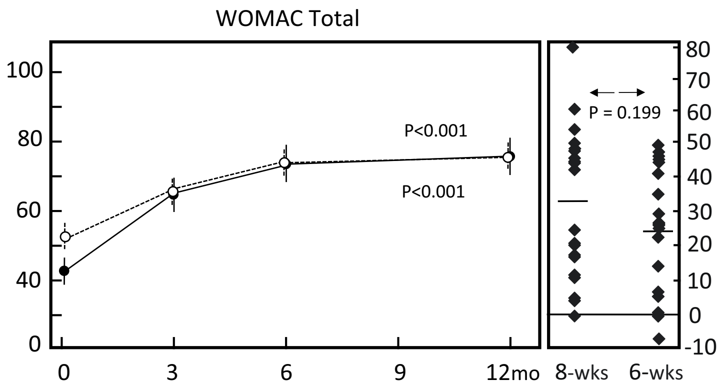

Figure 2. WOMAC total (**left**) dotted line represents the six-week group, solid line represents the eight-week group. Mean values ± SEM are shown. p-Values show statistical difference of values at one year compared to pre-treatment values (for the other time points p<0.02). Mean change of WOMAC total (**right**) for both groups (dash: mean value) and for every individual patient (squares), with p-value for difference between change in both groups.

The VAS-pain decreased from 74±1.9 mm at baseline to 31±5.8 mm (p<0.001) at one-year follow-up in the eight-week group, and from 60±4.5 mm to 37±5.4 mm (p=0.002) in the six-week group. Average change was 43±6.3 mm in the eight-week group and 23±6.6 mm in the six-week group (p=0.032).

At six-month follow-up, knee flexion was similar to baseline in the six-week group, but was still decreased by nine degrees (±4.5) in the eight-week group (see Figure 4). At 12-month follow-up, flexion was not different from baseline in both groups.

Cartilaginous repair activity

Radiographic analysis

At one-year follow-up, mean JSW of the MAC in the six-week group had significantly increased from 1.8±0.4 mm to 2.9±0.4 mm (increase 1.1±0.3 mm, p=0.001) (Figure 5). This was similar to the eight-week group in which mean JSW of the MAC increased 0.9±0.3 mm, from 2.6±0.4 to 3.6±0.2 mm (p=0.006). The increase in mean JSW at one-year follow-up was not statistically significantly different between groups (p=0.729).

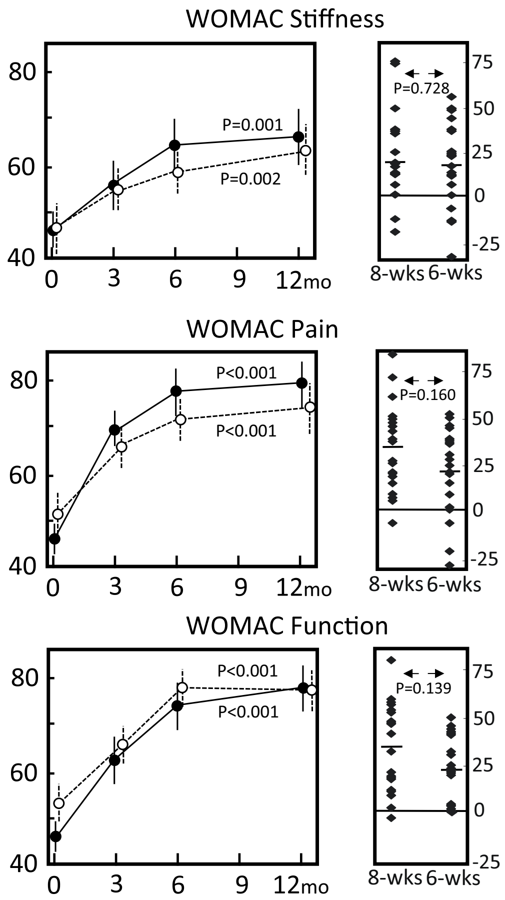

Figure 3. The left panel shows the different subscales of the WOMAC index (stiffness, pain, and function). The solid line represents the eight-week group, the dotted line the six-week group. Mean values ± SEM are given. p-Values show statistical difference of values compared to pre-treatment values (for the other time points p<0.02, except for stiffness at three months in the six-week group). The right panel shows the mean change of all parameters (dash) of the WOMAC index and of the individual patients (squares).

Minimum JSW showed a similar trend, increasing in both groups (Figure 5 left panel). In the six-week group the change in min JSW was 0.9±0.2 mm and in the eight-week group 1.1±0.2 mm (p=0.463 between groups; Figure 5 right panel).

Quantitative MRI analysis

ThCtAB of the MAC increased by 0.4±0.1 mm in the six-week group, from 2.2±0.2 mm to 2.6±0.2 mm at one-year follow-up (p=0.002), and increased 0.6±0.2 mm in the eight-week group, from 2.4±0.1 mm to 3.0±0.1 mm (p<0.001) (Figure 6). dABP decreased from 31.6±5.1% to 16.3±3.5% at one-year follow-up in the six-week group (p<0.001) and decreased from 22.0±4.5% to 4.6±1.9% in the eight-week group (p<0.001) (Figure 6 lower panels). The ThCcAB did not change significantly in both groups (from 2.9±0.1 mm to 3.0±0.1 in the six-week group, p=0.621; from 3.0±0.1 mm to 3.1±0.1 mm in the eight-week group, p=0.062). The increase of ThCtAB and ThCcAB as well as the decrease of dABP were not statistically significantly different between the two treatment groups (p=0.277, p=0.123, and p=0.715, respectively).

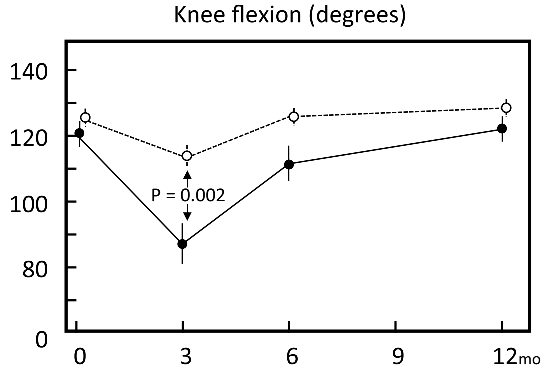

Figure 4. Overview of knee flexion. Solid line represents the eight-week group, dotted line represents the six-week group. Mean values±SEM are given. Except for three months of post-treatment no statistical significant differences.

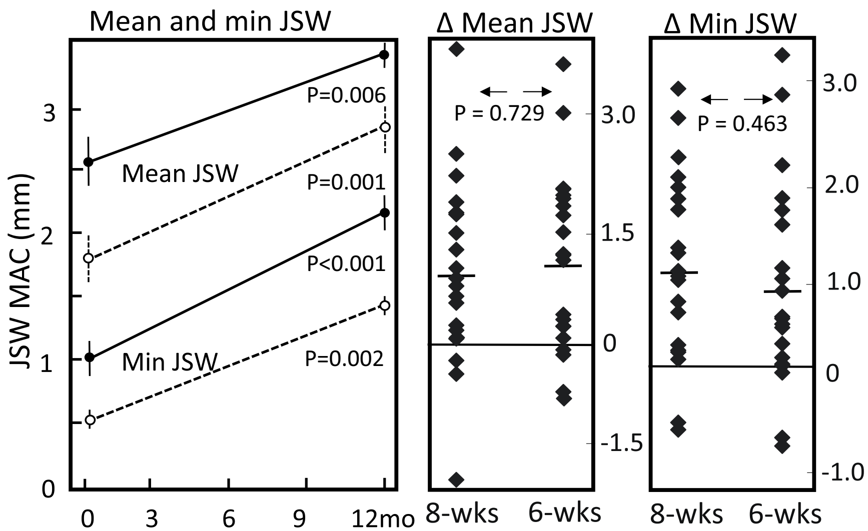

Figure 5. The left panel shows the mean and min JSW on radiographs of the most affected compartment (MAC) of both distraction groups. The solid line represents the eight-week group and the dotted lines represent the six-week group. Mean values ± SEM are given. p-Values show statistical difference of values compared to pre-treatment values. The right panels show the mean change (dashes) of both parameters and the individual patients (squares). The p-value between the arrows depicts difference between the two groups.

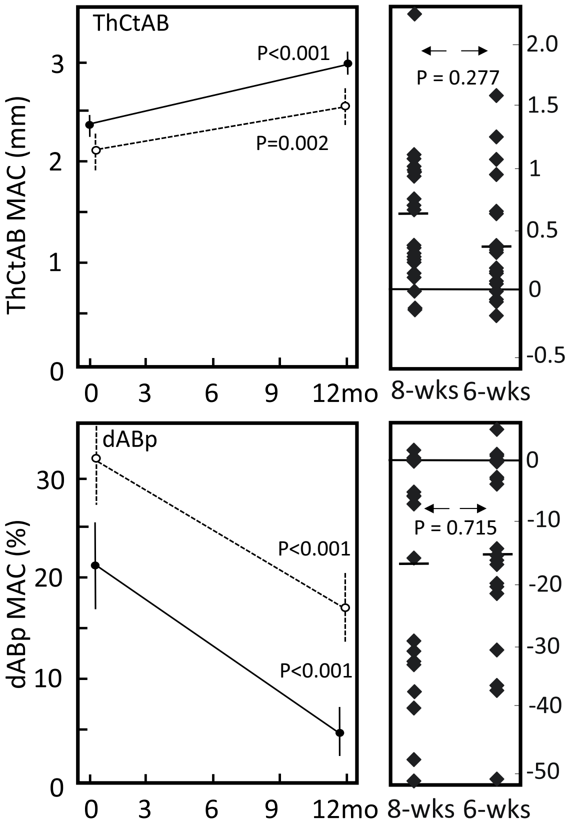

Figure 6. The upper left panel shows the mean ThCtAB and the lower left panel the mean dABp of the most affected compartment (MAC) of both distraction groups. Solid lines represent the eight-week group and the dotted lines represent the six-week group. Mean values ± SEM are given. p-Values show statistical difference of values compared to pre-treatment values. The right panel represents the individual change of patients (squares) as well as the mean change (dashes). The p-value between the arrows depicts difference between the two groups.

Adverse events

In the eight-week group, 17 out of 20 patients (85%) had single or multiple pin tract infections, 16 of which could be treated adequately with oral antibiotics. None of the patients had signs of osteomyelitis. Two patients suffered from pulmonary embolism, treated according to guidelines with oral anticoagulants for six months. For further details on adverse events in the eight-week group see Intema et al.[6]

In comparison, 11 out of 20 (55%) patients in the six-week group had single or multiple pin tract infections during the distraction period, which was statistically significantly less than in the eight-week groups (p<0.038). One patient developed sepsis with positive Staphylococcus aureus blood cultures shortly after removal of the frame and could be adequately treated with intravenous antibiotics for two weeks. Other pin tract infections could be treated adequately with oral antibiotics. One patient needed surgical revision during the distraction period, due to loosening of one of the monotubes that impaired distraction. One patient developed peroneal nerve injury with an ipsilateral dropfoot after placement of the monotubes. Although a clear serious adverse effect, the patient regained normal function in daily live with the use of an ankle-foot orthosis. One patient continued to have disabling pain and functional impairment and received within one year after KJD (seven months post-surgery) a TKA.

DISCUSSION

The current study shows that six-week continuous KJD has similar efficacy to eight-week intermittent KJD in treating knee OA in young and active patients. Clinical outcome parameters, radiographic JSW, and mean cartilage thickness on MRI all improved equally between groups. However, although not statistically significantly different, effects tended to be more pronounced in the eight-week intermittent than in the six-week continuously treated group. It is therefore concluded that six weeks is a minimum distraction time for optimal effect in relation to treatment burden.

Both groups showed a similar increase in radiographic mean and minimum JSW of the MAC (Figure 6 and 7). However, mean JSW at baseline was 1.6 mm less in the six-week

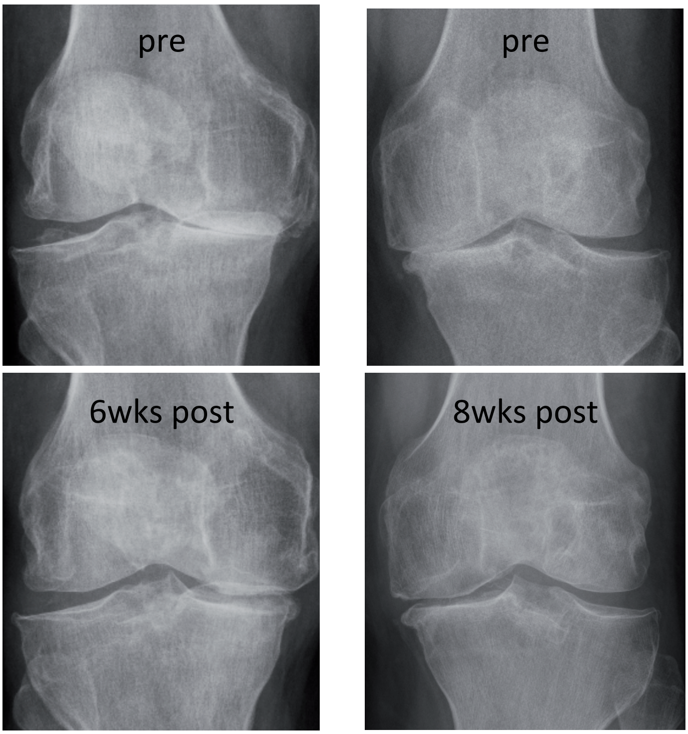

Figure 7. Representative standardized radiographs of two patients at baseline (upper radiograph) and one year after treatment (lower radiograph). Left row one patient from the six-week continuous group, right row one patient from the eight-week intermittent group.

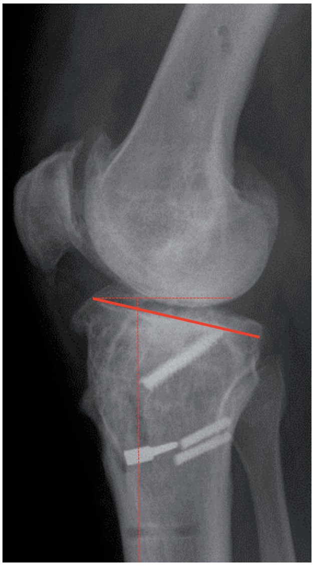

Figure 8. Radiograph of knee (lateral view) after failed distraction treatment with posterior tibial slope >15º.

group, probably because subjects in the six-week group were older in comparison with the eight-week group (55 years vs. 49 years) and had higher baseline KLG (30% KLG 4 vs. 10%). An analytical review showed a mean annual progression in KLG of 5.6%±4.9% and described a mean rate of joint space narrowing of 0.1±0.2 mm/year, which might explain the difference in JSW at baseline between both groups.[19]

Increase of the radiographic JSW was corroborated by the increase in mean cartilage thickness on MRI demonstrating two opposing cartilage layers. The quality of the newly formed cartilaginous tissue, however, remains unknown and it might be, in part, fibro-cartilaginous tissue. Direct observations of cartilage repair are lacking, since patients are not willing to undergo articular cartilage biopsy after distraction treatment. Indirect observations include imaging and biochemical marker analyses.[6,7] Biochemical marker analyses have shown a positive and over time increasing ratio for collagen type II synthesis over breakdown, which is suggestive of hyaline cartilage formation. Moreover, the newly formed tissue showed to be mechanically resilient, as all radiographs have been taken under weight-bearing conditions demonstrating a significantly increased JSW.[6,7] Most recently dGEMRIC MRI evaluation supported quality cartilage tissue repair two years after distraction (data to be published). Also distraction in case of experimentally induced OA in a canine model demonstrated cartilage tissue repair by cartilage GAG content and collagen damage as outcome parameters.[20]

Pin tract infection is a clear adverse event in KJD. Although still quite frequent, pin tract infections occurred less in the six-week groups as compared to the eight-week group (55% versus 85%). This might be due to different factors. First, protocols for treating the skin surrounding bone pins had been improved in the six-week group.[13] Second, CPM therapy in the eight-week distraction group results in extra skin movement around pins. One could argue that latent pin tract infection could pose a higher infection risk in case of future TKA. However, bone pins are placed only extra-articular and outside the knee joint capsule. Furthermore, five-year follow-up data in the eight-week group, showed that none of the three patients that underwent TKA suffered from prosthetic joint infection and that TKA outcome was similar to primary TKA in matched controls.[21] Still, pin tract care protocols need further attention.

Patients in the six-week group were interviewed about the discomfort they experienced during the distraction period. It appeared that the external frame did not interfere with activities in daily life (e.g. walking, showering, and sleeping). Patients having a clerical job could even continue their job during the distraction period. Most discomfort resulted from pin tract infection.

One serious adverse event that occurred in this study was the neuropathy of the common peroneal nerve and paralysis of the tibialis anterior muscle, directly after the tourniquet-less placement of the external frame. Theoretically, when placing bone pins (approximately 10 cm below the knee joint) from medial to lateral and in a perpendicular fashion, the deep peroneal nerve can be injured.[22,23] Although less likely, the dropfoot could have resulted from the pre-operative single-shot sciatic and femoral nerve block. Neuropathy is described to occur in 0.02% after a sciatic nerve block.[24]

One patient in the six-week group underwent TKA within one year after KJD, despite a 1.1 mm increase in mean JSW of the affected compartment. In retrospect, this patient had an abnormal posterior slope >15° and had previously been treated with two ACL reconstructions and an opening-wedge high tibial osteotomy (see Figure 8). This increased posterior tibial slope results in an increase in anterior tibial translation, tibial shear force, and ACL force in walking, standing, and squatting.[25,26] An increased tibial slope has serious consequences for cartilage pressure[27] and the increased shear stresses definitely contributed to the functional impairment in this osteoarthritic knee. In retrospect, this patient should have been considered ineligible for KJD.

Clinical improvement and radiographic and MRI outcome tended to be less pronounced in the six-week group although not statistically significantly different. Theoretically, KJD could lose efficacy when performed for less than six weeks. It remains to be determined whether long-term outcomes are similar between six-week and eight-week treatment. Long-term follow-up of the six-week group will demonstrate whether shortening the treatment with two weeks will lead to a less beneficial long-term outcome. Long-term follow-up data is available for the eight-week group, since they were treated between 2006 and 2008. At five-year follow-up in the eight-week group, patients still reported clinical relevant improvement (ΔWOMAC+21 points) and only three of the 20 patients received a TKA.[8]

In conclusion, this study revealed that six-week continuous KJD does not decrease short-term outcomes as compared to eight-week intermittent KJD. Both cartilaginous repair activity, as indicated by an increase in radiographic JSW and MRI-observed cartilage thickness, and improvement of clinical performance were similar between groups. Moreover, six weeks of continuous distraction treatment does not lead to a stiffer knee in comparison with the 'intermittent' eight-week treatment. Despite the fact that patients in the six-week group were older and had a higher KLG as compared to the eight-week group, this did not influence cartilaginous tissue repair. This suggests that cartilaginous tissue repair is even possible in severely damaged joints.

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Chapter

8

Knee joint distraction compared with total knee arthroplasty: a randomized controlled trial

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ABSTRACT

Aims: Knee joint distraction (KJD) is a relatively new, knee-joint preserving procedure with the goal to postpone a first total knee arthroplasty (TKA) in specifically young and middle-aged patients, to decrease the chance for revision surgery later in life. However, the clinical efficacy of KJD has never been compared to TKA.

Patients and Methods: Sixty patients ≤65 years with end-stage knee osteoarthritis were randomized to either KJD (n=20) or TKA (n=40). Questionnaires were assessed at baseline, three, six, nine, and twelve months. In the KJD-group, radiographic joint space width (JSW), representing cartilage thickness, was determined as well.

Results: Fifty-six patients received the allocated intervention (TKA=36, KJD=20). All patient reported outcome measures improved significantly over one year (at one year $p<0.02$) in both groups. At one year, the TKA-group showed a greater improvement in only 1 out of the 16 PROMS assessed ($p<0.05$). OARSI-OMERACT clinical response was 83% after TKA and 80% after KJD. Twelve patients (60%) in the KJD-group suffered from pin tract infections. In the KJD-group both minimum (+0.9±1.1mm) and mean JSW (+1.2±1.1mm) increased significantly ($p<0.01$).

Conclusions: In relatively young patients with end-stage knee osteoarthritis treatment with KJD did not demonstrate relevant inferiority in efficacy compared to TKA.

INTRODUCTION

In case of end-stage knee osteoarthritis (OA) a total knee arthroplasty (TKA) is generally indicated.[1] TKA was first performed in the 1970s and is now generally regarded as the gold standard for end-stage knee OA, being a (cost)-effective treatment.[2] Nevertheless, in the younger and more active patients joint replacement has its drawbacks. First of all, after TKA, up to 20% of the patients are dissatisfied with their knee replacement.[3-5] Even more patients (44%) reported that they experienced persistent postsurgical pain of any severity after TKA, with 15% of the patients reporting severe-extreme persistent pain.[6] In addition, registries have shown that the younger the patient, the higher the risk of revision, with patients younger than 55 years having almost a five times higher risk of revision surgery than those aged 75 years or older.[7] One of the main reasons why younger patients have a higher rate of revision is aseptic loosening, a characteristic of implant wear, which is responsible for more than 30% of the revisions.[7,8] Since wear increases with both time and activity, this legitimates concerns regarding the results and survivorship of TKA in young and middle aged, relatively high physical demanding patients.[9] As such the increasing number of primary and revision TKA's (on average 40% below the age of 65 years) clearly provides a huge healthcare burden of knee OA in young patients.[10]

Therefore, in case of generalized knee OA in young and middle aged, physically active patients, alternative, joint preserving treatments strategies are a necessity. However, joint preserving treatments are scarce. Arthroscopic debridement is not recommended anymore, because studies showed that the improvement in symptoms could be attributable to a placebo effect.[11] Osteotomies are mainly considered in unicompartmental knee OA.[12] Recently the KineSpring has been introduced for only medial compartmental knee OA as well, but its place in general practice has still to be defined.[13]

A more recently proposed joint-saving treatment is knee joint distraction (KJD). KJD is a treatment for persisting, painful, conservative treatment-resistant knee OA at a relatively young age, with the goal to postpone TKA and thereby decreasing the risk for revision surgery later in life. It considers a 6-8 weeks, 5 mm distraction of the tibio-femoral joint by use of a temporarily placed externally distraction frame. Thus far, twenty patients (aged <60 years), originally indicated for TKA were treated in a prospective open uncontrolled study.[14] The follow-up of this study reported substantial clinical improvement and cartilaginous tissue repair by KJD in about 80% of patients treated. The original planned TKA could be postponed for at least five years[14-16], and even over 10 years if the six patients of the original feasibility study are included.[17] Radiographic and MRI evaluations showed that cartilaginous repair was induced and maintained over the follow-up period.[14-16] The cartilaginous repair tissue was considered mechanically resilient, as shown by the increased radiographic JSW under weight-bearing conditions.[15] It was also demonstrated that a TKA in the cases of subsequent failure of KJD gives similar clinical benefit as a primary TKA and no risk for e.g. infections were observed.[17]

Thus far, no comparative data on clinical efficacy between TKA and KJD are available. Therefore, an RCT was set out to compare KJD with TKA. It was hypothesized that there would be no clinical important difference in efficacy between KJD and TKA one year after treatment.

PATIENTS AND METHODS

The sixty patients with end-stage knee OA were recruited between 2011 and 2014 in this prospective, two-center, randomized controlled trial comparing KJD with TKA. Fifty-one patients were included at the Maartenskliniek Woerden (MKW) and nine patients were included at the Maastricht University Medical Center (MUMC). Randomization of 2:1 for TKA versus KJD was performed in blocks of six at each of the institutes using standard randomization software and were concealed in sequentially numbered, sealed, opaque envelopes. The medical ethics committee considered KJD an experimental treatment and obligated this randomization ratio, in order to reduce the number of KJD treatments. Group size calculation was based on a non-inferiority hypothesis. The sample size was estimated based on the primary outcome parameter (WOMAC), 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).[18] To account for possible drop-out and/or insufficient data quality, the sample size was increased by 15%. A change in WOMAC score of more than 15 points (SD±16.7) compared to the TKA-group was considered clinically relevant.[19] This resulted in 40 patients randomised to TKA and 20 to KJD. Patient numbers were assigned sequentially. After inclusion, the envelope with the allocated treatment was opened. Patients and physicians were aware of treatment assignment after allocation.

Patients and physicians were aware of treatment assignment after allocation. Inclusion criteria were knee OA considered for TKA according to regular clinical practice with an age ≤65 years (considered a population at risk for revision surgery later in life), functionally intact knee ligaments, near normal range-of-motion (minimum of 120° flexion), and a Body Mass Index (BMI) <35. Patients with primary patella-femoral OA were excluded, as were those with a history of inflammatory or septic arthritis, inability to cope with an external fixator, absence of any joint space on radiographs, post-traumatic fibrosis due to a fracture of the tibial plateau, previous surgery on the same knee within the past six months or previous joint replacements. The medical ethics committee of the University Medical Center Utrecht approved the study (No 10/359/E) and the site-specific institutional review board of the MKW and the MUMC approved the study protocol before study initiation. The study was registered on the Netherlands National Trial Register (NTR2809). All patients provided written informed consent before enrollment.

Three experienced surgeons (RJvH, SS, and PJE) performed all total knee arthroplasties and knee joint distractions using the technique described below.

Treatments

In patients allocated to TKA, the Genesis II posterior stabilized system was used (Smith and Nephew, Warsaw, IN, USA). For fixation GentaPalacos (Heraeus, Hanau, Hessen, Germany) cement was used. 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 low molecular weight heparin as thrombosis prophylaxis, until six weeks post-operative.

KJD was performed by use of a proof-of-concept external distraction device, in general used for bone lengthening or fracture stabilization. Two dynamic mono-tubes with internal coil springs (Triax, Stryker, 45 kg spring with 2.5mm displacement, Kalamazoo, MI, USA) were placed bridging the knee joint at the lateral and medial side. Each mono-tube was fixed to two bone pins on each side (eight pin sites in total) and the internal coil spring was present for dynamization, see also figure 1. Intra-operatively the tubes were distracted 2 mm. Postoperatively, every day the tubes were gradually 1 mm distracted, until 5 mm distraction was reached. At day four, distraction was checked by weight bearing radiographs. Hereafter patients were discharged from the hospital and allowed full weight bearing with crutches (if needed for stability). At approximately three weeks, patients visited the outpatient department for radiographic evaluation of the distraction and pin tract evaluation. After six weeks the frame and pins were surgically removed. Partial weight bearing (maximum twenty kg) was allowed and patients were discharged the same day. Gradually they regained normal full loading in approximately six weeks (expansion of fifteen kg every week). Low molecular weight heparin as thrombosis prophylaxis was given during nine weeks (during distraction treatment and for three weeks after frame removal).

Follow-up

After randomization baseline values were taken for both groups. A secondary baseline survey was filled in the day prior to surgery. Subsequently, both groups visited the outpatient department three, six, nine and twelve months postoperatively.

Clinical outcome

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, version 3.1) and the validated Dutch knee injury and osteoarthritis outcome score (KOOS) were used to score clinical improvement, normalized to a 100-point scale; 100 being the

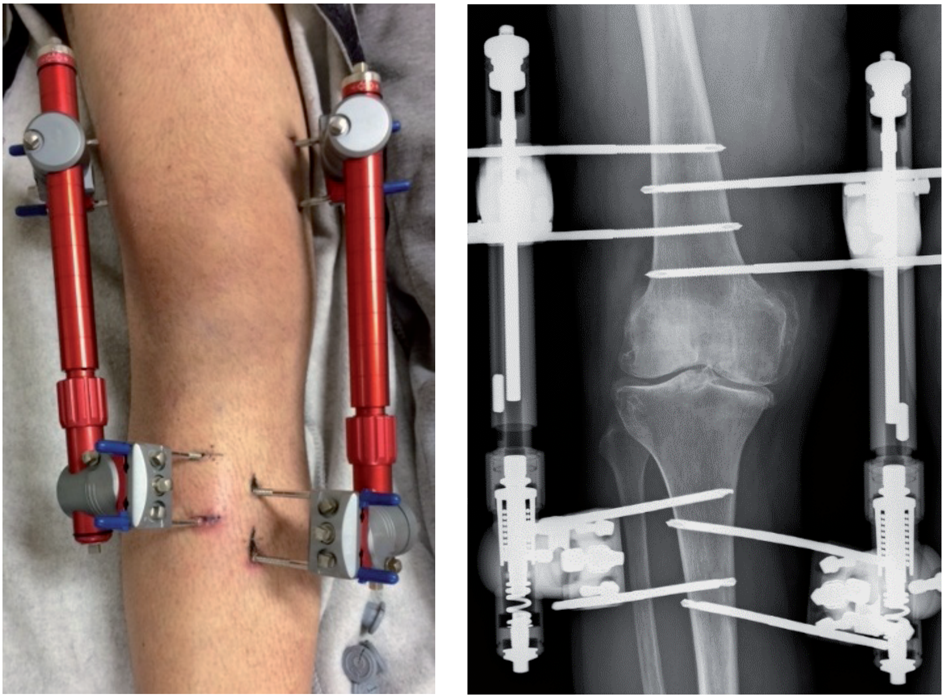

Figure 1. Example of the bilateral external fixation frame used for knee joint distraction treatment (left) and an example of a radiograph (right) during distraction treatment with five millimeters of distraction.

best condition. The WOMAC was used as primary outcome parameter. The intermittent and constant osteoarthritis pain score (ICOAP) for the knee was the secondary clinical outcome parameter (0-100, 0 meaning no pain). A visual analogue scale for pain (VAS-pain; 0-100 mm, 0 meaning no pain) was the tertiary clinical outcome parameter. The EQ-5D-3L was used to assess improvement of quality of life. The obtained questionnaire was transformed to an EQ-5D index score (0-1, 1 being the best). The Short Form 36 (SF-36) health survey was used to measure the health status of the patients. The SF-36 items were transformed to the physical (PCS) and mental (MCS) component summary score. At baseline, three, six, nine and twelve months the KOOS/WOMAC, ICOAP, and EQ-5D-3L questionnaire as well as the VAS-pain were assessed. At baseline, six, and twelve months the SF-36 was assessed.

Structural outcome

To assess structural outcome, knee radiographs of only the KJD-group were obtained at baseline and twelve months postoperatively. The knee images were standardized weight-bearing, semi-flexed (7°-10° flexion) posterior-anterior radiographic views according to Buckland-Wright, with a reference aluminum step wedge close to the knee within the field of exposure. Images were evaluated using knee images digital analyses (KIDA) software.[20] This is a fully mathematical method to analyze amongst others the mean and minimum joint space width (JSW) of the knee.[20] The min JSW was measured as the smallest distance between the femur and the tibia. The mean JSW of each compartment is defined as the mean of 4 predefined locations. For potential differences in magnification, the step-wedge on the radiographs was used for correction. The method has frequently been used and reported on, with high inter-observer reproducibility (R=0.85-0.90) and very small intra-observer variation.[20] Image analyses were performed blinded to the order of acquisition and patient characteristics by one single experienced observer. The mean JSW of the most affected compartment (MAC) and the least affected compartment, and the minimum JSW are given in mm, rounded at one decimal.

Statistical analyses

Two-sided paired tests (normally distributed data sets) were used to evaluate whether the follow-up values differed from the baseline values. To compare the changes from baseline to one year between both treatment groups two-sided independent-samples T-test was used (normally distributed data sets) with $p<0.05$ considered statistically significant. SPSS software version 22.0 was used to perform statistical analyses.

RESULTS

Of the 60 patients enrolled in the randomized controlled trial, 20 were assigned to KJD and 40 to TKA. After randomization four TKA assigned patients withdrew consent, because they were not willing to undergo a total knee replacement (Figure 2). Of the remaining 56 patients the baseline characteristics and an overview of previous knee surgery of the affected knee is given in Table 1. One patient in the KJD-group continued to have disabling pain and functional impairment and received a TKA within one year. For clinical outcome the last data at six months were carried forward.

Clinical outcome

A clear clinical improvement, based on the primary outcome parameter (total WOMAC score, figure 3), was noted in both groups. For the WOMAC score the KJD-group improved 30±17 points (mean±SD), and the TKA-group improved by 36±19 points over 12 months ($p<0.001$ for both). The WOMAC subscales for pain, stiffness, and function showed a similar trend (table 2). On the individual level, 16 patients (80%) in the KJD-group and 30 patients (83%) in the TKA-group could be designated as actual clinical responders according to the OARSI-OMERACT responder criteria.[21] Responders are defined as an increase of >50% in WOMAC pain OR function with >20 points of improve-

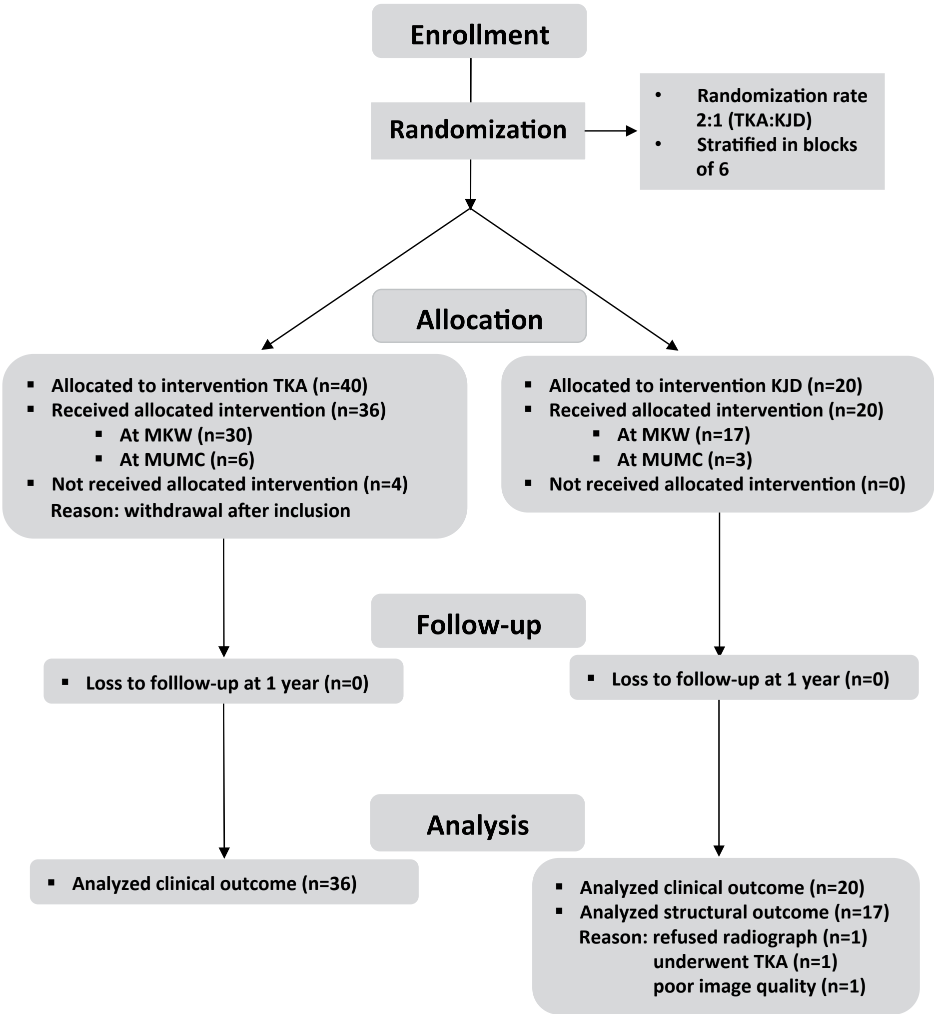

Figure 2. Flow chart including the numbers of excluded patients, as well allocation of the randomized treatment and the analysed patients per treatment arm. KJD: knee joint distraction, MKW: Maartenskliniek Woerden, MUMCU: Maastricht University Medical Center.

ment in either category, or an increase of >20% of WOMAC pain AND function with 10 points improvement in each category. The change of the total WOMAC score between baseline and one year follow-up was not different for both treatment groups (p=0.273; right panel figure 3)

The total KOOS improved significantly at one year follow-up compared to baseline in both treatment groups (p<0.001) (figure 4). The change of the total KOOS score between baseline and one year follow-up was not different for both treatment groups (p=0.065; right panel figure 4)

Table 1. Baseline characteristics

Characteristics Mean (± SEM)	Total knee arthroplasty (n=36)	Knee joint distraction (n=20)
Male gender (n)	13/36 (36%)	9/20 (45%)
Height (cm)	173 ± 1.7	175 ± 2.2
Weight (kg)	88.3 ± 2.3	83.9 ± 3.6
Body mass index (kg/m^2)	29.4 ± 0.6	27.4 ± 0.9
Affected knee (left)	17/36 (47%)	6/20 (30%)
Age at surgery (yr)	55.2 ± 1.0	54.9 ± 1.8
Kellgren & Lawrence (median)	3	4
Grade 0 (n)	0 (0%)	0 (0%)
Grade 1 (n)	0 (0%)	0 (0%)
Grade 2 (n)	9 (25%)	1 (5%)
Grade 3 (n)	21 (58%)	8 (40%)
Grade 4 (n)	6 (17%)	11 (55%)
Previous surgery **Operation (number)**		
ACL Reconstruction (n)	5	3
High Tibial Osteotomy (n)	4	4
Arthroscopy:	17	13
Partial meniscectomy (n)	4	7
Arthroscopic joint lavage (n)	13	6
Open Meniscectomy (n)	7	6
Perichondriumplasty(n)	1	0

Also the five subscales of the KOOS all improved significant at the one year follow-up compared to baseline in the both treatment groups ($p<0.001$) (table 2). Similar results were seen for the ICOAP for the knee, the Physical Component Scale (PCS) of the SF-36, the VAS-pain score and the EQ-5D (see table 2). The TKA-group only showed significantly greater improvements in the mean change of the KOOS subscale quality of life ($p=0.021$) (table 2).

Knee flexion in the KJD-group equaled to baseline levels (125°) at 12 months follow-up. After an initial fall in joint flexion, levels returned to baseline levels after 6 months of KJD. Knee flexion in the TKA-group showed a significant decline of 5° of knee flexion at one year follow-up (124° at baseline, and 120° at one year; $p=0.013$, see figure 5). The mean changes were statistically significant different between both group ($p=0.024$) in favor of KJD.

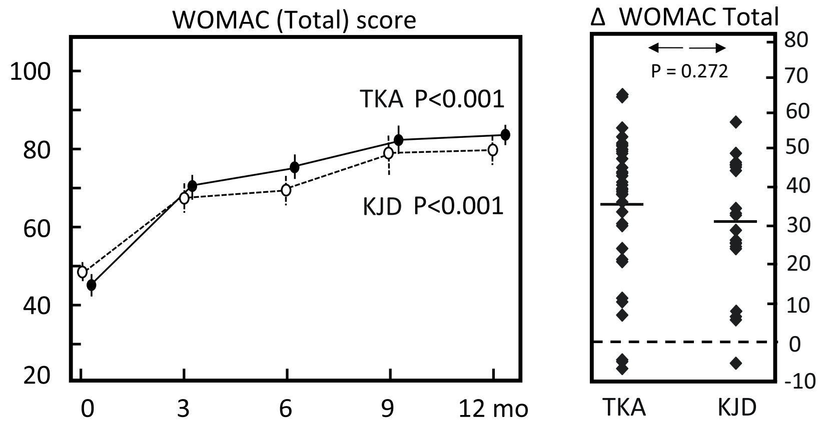

Figure 3. WOMAC Total. Dotted line (**left**) represents the KJD group (n=20), solid line represents the TKA group (n=36). Mean values ± SEM are shown. P values show statistical difference of values at 1 year follow-up compared to pre-treatment values. Mean change of WOMAC Total score (**right**): For both groups (average: dash) and for every individual patient (squares); no statistical significant difference in clinical efficacy was observed.

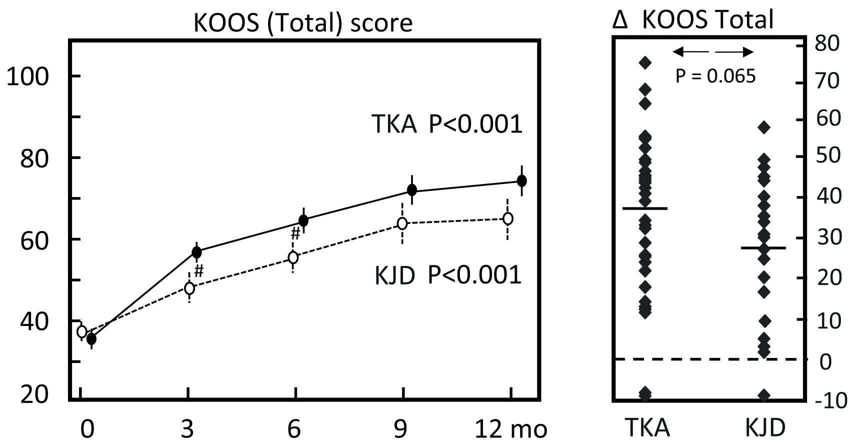

Figure 4. KOOS Total. Dotted line (**left**) represents the KJD group (n=20), solid line represents the TKA group (n=36). Mean values ± SEM are shown. P values show statistical difference of values at 1 year follow-up compared to pre-treatment values. # indicates a significant difference between TKA and KJD. Mean change of KOOS Total score (**right**): For both groups (average: dash) and for every individual patient (squares); no statistical significant difference in clinical efficacy was observed.

Table 2. KOOS, WOMAC, ICOAP, VAS, EQ-5D and SF-36 scores pre-operative and the post-operative follow-up moments for both groups.

Score (± SD)		Total knee arthroplasty						Knee joint distraction					
		BL	3m	6m	9m	12m	BL→1Y	BL	3m	6m	9m	12m	BL→1Y
KOOS	Pain	42±14	68±18*	76±19*#	84±17*	82±17*	40±23	43±11	60±17*	63±23*	74±23*	74±21*	31±19
(0-100)	Symptom	45±16	58±16*	67±15*	72±15*	75±15*	30±19	45±15	54±21	61±21*	67±19*	68±20*	23±17
	ADL	47±12	72±14*	77±17*	83±17*	84±15*	36±18	51±11	69±16*	73±19*	82±19*	81±16*	30±16
	Sport/Rec	20±13	43±23*#	54±27*#	55±28*	61±27*	42±28	22±16	25±22	39±27*	53±30*	52±31*	30±27
	QOL	27±13	44±17*#	50±18*#	64±22*#	67±23*#	39±25#	28±11	30±16	37±20*	47±21*	51±24*	23±24
	Total	36±12	57±13*#	65±16*#	72±17*	74±17*	37±20	38±9	48±15*	55±19*	64±20*	65±20*	27±18
WOMAC	Pain	46±16	73±17*	79±18*#	85±17*	85±15*	39±22	48±13	69±19*	67±25*	78±23*	80±20*	32±20
(0-100)	Stiffness	45±20	53±18	62±25*	70±21*	71±23*	26±28	38±16	54±23*	54±21*	64±23*	67±29*	29±25
	Function	47±12	72±14*	77±17*	83±17*	84±15*	36±18	51±11	69±16*	73±19*	82±19*	81±16*	30±16
	Total	47±13	71±14*	76±17*	83±17*	83±16*	36±19	49±11	68±17*	70±19*	79±19*	80±18*	30±17
ICOAP	Constant	55±21	33±25*	23±22*	14±20*	12±16*	-43±27	46±18	36±19	28±25*	20±22*	12±14*	-34±23
(100-0)	Intermittent	55±17	33±22*	24±22*	17±21*	16±16*	-40±22	47±15	35±16*	27±21*	23±23*	17±14*	-30±21
	Combined	55±18	33±22*	24±21*	16±20*	14±16*	-41±24	46±16	35±17*	27±20*	22±22*	15±13*	-32±21
VAS	Pain	71±17	39±26*	28±22*#	21±22*	18±19*	-53±28	65±19	44±27*	41±26*	32±32*	28±26*	-36±32
(0-100)													
EQ-5D	Index score												
(0-1)		0.52±.3	0.71±.2*	0.74±.2*#	0.81±.2*	0.87±.1*	0.35±.3	0.58±.3	0.62±.2	0.60±.3	0.68±.3	0.76±.3*	0.18±.3
SF-36	PCS												
	MCS	32±7		42±9*#		47±9*	15±10	33±9		37±10		44±10*	11±8
Flexion	Knee	54±10		55±8		53±10	-1±13	54±8		54±7		53±8	-1±11
(Degree)		124±7	113±15*	116±12*	118±11*	120±11*	-5±11	122±9	113±11*	122±9	123±10	125±9	2±11#

* p<0.05 relative to the preoperative score # p<0.05 difference between TKA and KJD

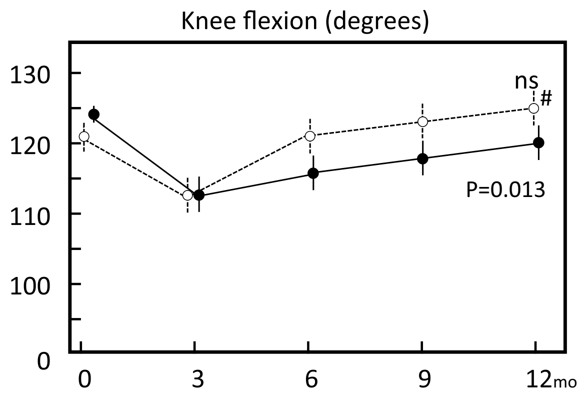

Figure 5. Overview of knee flexion. Dotted line represents the KJD-group (n=20), solid line represents the TKA-group (n=36). Mean values ±SEM are given. For the TKA group flexion was still significantly reduced compared to pre-treatment values, which was not observed for KJD. # indicates a significant difference between KJD and TKA.

Structural outcome

Eighteen patients of the KJD-group had radiographs available at baseline and one year follow-up (one patient received a TKA, and one patient refused the radiograph; see figure 2). One patient's radiographs were of insufficient quality for analysis. In the remaining seventeen patients the mean JSW of the most affected compartment increased significantly from 1.9±2.1 mm towards 3.2±2.1 mm at one year ($p<0.001$). In line with this, the minimum JSW increased 0.9±1.1 mm, from 0.6±1.2 mm at baseline to 1.5±1.1 mm at one year ($p=0.004$), see figure 6. The mean JSW of the least affected compartment increased from 7.1±2.0 mm towards 7.4±2.1 mm at one year ($p=0.422$).

Adverse events

In the KJD-group twelve patients (60%) had single or multiple pin tract infections, 10 of which were treated adequately with oral antibiotics. One patient was admitted to the hospital shortly after removal of the frame, to receive intravenous antibiotics for two weeks, due to a sepsis based on a positive Staphylococcus aureus blood culture. One other patient had high fever of unknown origin after removal of the frame and received as well intravenous antibiotics for two weeks. Both patients fully recovered. In one patient, after placement of the monotubes, an ipsilateral dropfoot occurred. With the use of an ankle-foot orthosis the patient regained normal function in daily live.

In the TKA-group five patients developed knee stiffness and consequently had a reduced knee flexion. To improve the range of motion they underwent manipulation under anesthesia. One TKA patient had a myocardial infarction within six days after surgery, which was treated with a percutaneous coronary intervention and subsequent pacemaker implantation.

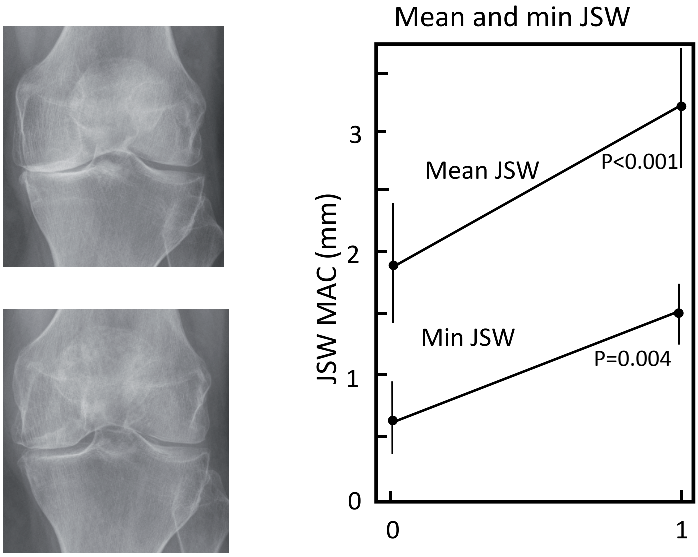

Figure 6. The left panel shows representative standardized radiographs of a representative patient at BL (upper radiograph) and 1 year after treatment (lower radiograph). The right panel shows the mean and min JSW on radiographs of the most affected compartment (MAC) of the KJD-group (n=17). Mean values ±SEM are given. P values show statistical difference of values compared to pre-treatment values.

DISCUSSION

This study showed that KJD was not different from TKA with respect to clinical efficacy. In both groups all patient related outcome measures (primary outcome parameter WOMAC, KOOS, VAS-pain, ICOAP for the knee, EQ-5d index, and the SF-36 PCS sub-scale) improved significantly. Only one clinical parameter showed significantly greater improvements in the TKA-group (mean change of the KOOS subscale quality of life). None of the other changes in PROMS were different between both groups. Recovery of flexion was better for KJD than for TKA. Furthermore, there was no difference between the actual clinical responders in both groups (80% vs. 83% for KJD vs. TKA) according to the OARSI-OMERACT responder criteria. [21] TKA was at the expense of the original joint, whereas KJD lead to a substantial increase of JSW.

This is the first study comparing KJD in a randomized set-up with TKA. With respect to KJD, there is so far one prospective uncontrolled study conducted in which twenty patients, originally considered for TKA, received KJD for eight weeks.[14-16] The results of the twenty patients, even with one failure (last data carried forward), in the current study were comparable at one-year (uncontrolled study: WOMAC total 77±21 points vs. 80±18 points in this RCT and VAS-pain 31±26 mm vs. 28±26 mm in this RCT; not statistically significant different). The slightly better outcome in the present RCT for both parameters could be attributed to a difference in BMI (27.4 kg/m^2 in the RCT-group vs. 29.6 kg/m^2 in the uncontrolled study) although not statistically significant different (p=0.077). It is well documented that preoperative overweight increases the risk of poor outcome on quality of life and physical function after TKA. [22]

In the past, a number of prospective studies/trials were conducted, which treated patients with TKA and clinical outcome was measured using the same outcome parameters as used in this study.[4,23,24] In one study, at one year follow-up the KOOS score of the subscale pain was 83 points and of the subscale ADL 85 points[24], WOMAC total was 82 points [4], and the EQ-5D index was between 0.76 and 0.87.[23,24] Clinical outcome of the TKA treated patients in the present study was 82±17 for subscale pain, 84±15 for the subscale ADL, 83±16 for the WOMAC total, and 0.87±0.14 for the EQ-5D index. So results for TKA in the present study were comparable to those of previous studies.

Of concern is the high number of pin tract infections in the KJD-group, measuring 60% although mostly successfully treatable with oral antibiotics. Two patients had two be treated with intravenous antibiotics for two weeks. In comparison with the prospective uncontrolled study the infection rate is substantially lower (85% in the uncontrolled study vs. 60% in the RCT). This may be the result of a more dedicated pin tract care guideline for nursing of the pins and skin around the pinholes, to minimize pin-tract infections in the present study.[25,26] The high risk of developing infections is not uncommon, with the percutaneous passage of pins through muscles and into bone. An overall pin track infection rate of 27% and deep infection rates of 16% have been reported in literature, with 4% developing chronic osteomyelitis.[27,28] This is in line with the 10% deep infection rate (two patients treated with intravenous antibiotics) in our KJD-group. Possible explanation for the higher pin tract infection rate is the encouraged full weight bearing during distraction treatment and advised muscle contraction and relaxation to prevent thrombosis. It is established that excessive patient activity leads to pin irritation and infection. One study reported a greater infection rate when pin placement was periarticular, possibly due to the increased soft tissue motion, and sites with greater soft tissue thickness over bone (as the femoral side in KJD) have been implicated as at higher risk of infection.[29] Irrespective of the usage of a more dedicated pin tract care guideline, in the future these numbers should be minimized further. Important is a meticulous surgical technique during pin insertion. After completion of the procedure, all pin sites must be free of skin tenting and soft tissue impingement, so pin sites are encouraged to heal around the pins.[30] Furthermore, the usage of coated pins is likely to inhibit biofilm formation and thus preventing pin tract infections. Novel approaches to reduce pin-tract infection for KJD are at presently under development. [31,32]

Despite the absence of a pin site infection at the moment of subsequent TKA surgery, one could still argue that there is a latent infection risk with higher risk of periprosthetic joint infection during subsequent TKA surgery. However, to minimize such risk the bone pins are placed extra-articular and extra-synovial, outside the area that is involved in TKA.[17] Moreover, registry of follow-up data in the uncontrolled study, showed that three patients received a TKA within five-year after treatment. None of these patients suffered from a prosthetic joint infection and outcome of these TKA surgeries were similar to that of matched primary TKA controls.[17] Also the patient from the present study that did receive a TKA 6 months after KJD did not demonstrate any problems. As reported earlier[33], this patient had an abnormal posterior slope, which, despite a 1.1 mm increase in mean JSW, definitely contributed to the functional impairment and therefore this patient should have been considered not eligible for KJD.

In the KJD-group one patient had directly after the tourniquet-less placement of the external frame an ipsilateral dropfoot. A performed electromyogram showed neuropathy of the common peroneal nerve and great loss in function of the tibialis anterior muscle. However, when placing bone pins, the innervation of the tibial anterior muscle is not directly at risk.[33] An alternative option would be that the dropfoot was caused by the concomitant single-shot sciatic and femoral nerve block, which the patient received prior to the surgery.[33]

Our study has its limitations. We did not include a sham-surgery control group or placebo control group; as surgery, and to a lesser extent non-surgical treatments, are associated with placebo effects.[34] Findings in this study may thus overestimate effects of both surgical treatments. Recently, one RCT comparing TKA with a nonsurgical-treatment group was published.[24] In this study one group underwent TKA followed by twelve weeks of nonsurgical treatment, while the other group only received twelve weeks of nonsurgical treatment (consisting of exercise, education, dietary advice, insoles, and pain medication). After one year the TKA-group showed greater pain relief and functional improvement. The nonsurgical-treatment group showed a clinically relevant mean improvement of 17 points on the KOOS subscale pain, 11 points on the subscale symptoms, and 18 points on the subscale ADL. When comparing these mean improvements with both groups in our study (mean improvement in KJD-group of 31 points for subscale pain, 23 points for subscale symptoms and 30 points for subscale ADL; mean improvement in TKA-group of 40 points for subscale pain, 30 points for subscale symptoms and 36 points for subscale ADL), both KJD and TKA show at least an extra 10 points improvement in these KOOS subscales. For KOOS subscales a minimal clinically important difference of 10 points is considered relevant.[35] Both KJD and TKA seem to be more efficacious than nonsurgical treatment in providing pain relief and improving function and quality of life. Another limitation is the short follow-up. KJD has proven its survival on the longer term only in relatively small numbers (approximately 80% after five years (n=23) and 65% after ten years (n=6)).[16,17] It is therefore possible that KJD would not maintain its benefit over time. In general it could be stated that patients with insufficient satisfaction within five years after KJD treatment should be transferred to a TKA (clearly they did not experienced the intended benefit from KJD). On the other hand, in patients who could be stated as an OARSI-OMERACT responder and who experience a decline in benefit years after distraction treatment KJD could be repeated again. In a survey, most patients indicated, with clear knowledge of the discomfort during distraction treatment, that they would undergo KJD again. However, mid-term and long term results of KJD treatment still are mandatory to make an evidence based decision.

CONCLUSION

In relatively young middle-aged patients with end-stage knee osteoarthritis, who are eligible for TKA and because of their age are at risk of revision surgery later in life, treatment with KJD results in comparable clinical benefit after one year when compared with TKA. However, the rate of pin tract infections was high in the KJD-group and it is desirable to minimize such infections in the future. As KJD preserves the knee joint, it represents a promising therapeutic option in postponing a first TKA potentially preventing revision surgery later in life.

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Chapter 9

Prediction of cartilaginous tissue repair after knee joint distraction

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ABSTRACT

Background: For young patients (<65 years), knee joint distraction (KJD) may be a joint-saving treatment option for end-stage knee osteoarthritis. Distracting femur from tibia for five millimeters for six to eight weeks using an external fixation frame results, in addition to clinical benefit, also in cartilaginous tissue repair. This study is a first attempt to predict the degree of cartilaginous tissue repair after KJD.

Methods: Fifty-seven consecutive patients received KJD. At baseline and at one year of follow-up, mean and minimum joint space width (JSW) of the most affected compartment was determined on standardized radiographs. To evaluate the predictive ability of baseline characteristics for JSW at one year of follow-up, multivariable linear regression analysis was performed.

Results: Mean JSW±SD of the most affected compartment increased with 0.95 ± 1.23mm to 3.08 ± 1.43mm at one year ($p<0.001$). The min JSW increased with 0.94 ± 1.03 mm to 1.63 ± 1.21 mm at one year of follow-up ($p<0.001$). For a larger mean JSW one year after KJD, only Kellgren and Lawrence grade (KLG) at baseline was predictive (regression coefficient (β)=0.47, 95% CI = 0.18–0.77, $p=0.002$). For a larger min JSW, KLG ($\beta=0.46$, 95% CI=0.19–0.73, $p=0.001$) and male gender ($\beta=0.52$, 95% CI=0.06–0.99, $p=0.028$) were statistically predictive. Eight weeks of distraction time neared significance ($\beta=0.44$, 95% CI=−0.05–0.93, $p=0.080$).

Conclusions: In our cohort of patients treated with KJD, males with higher KLG had the best chance for cartilaginous tissue repair by distraction.

INTRODUCTION

Knee osteoarthritis is a chronic joint disease, clinically characterized by pain and functional limitation. Structural changes associated with knee osteoarthritis are progressive degradation of cartilage, low-grade inflammation of synovial tissue, osteophyte formation and subchondral bone changes.[1,2] In the case of persistent, conservative treatment resistant, pain accompanied by cartilage tissue damage, the treatment of choice is often a total knee replacement. However, in the case of relative young patients (<65 years) knee joint distraction, being a joint-sparing treatment, is to be considered an alternative, postponing arthroplasty for a prolonged time in at least three-quarter of the patients.[3,4] This surgical procedure provides a six to eight weeks of biomechanical joint homeostasis, by distracting the femur from the tibia for five millimeters by use of an external fixation frame, which appeared to facilitate cartilage repair activity.[5] In the past, five studies[3,6-9] have been performed using knee distraction. Only one of those studies was based on prospective evaluation.[3] Though, all showed significant increases in the radiographic joint space width (JSW). Most convincing, Wiegant et al.[4] showed that the newly formed cartilage-like tissue was stable and mechanically resilient under weight-bearing conditions over two-years of follow-up in twenty patients. However, cartilaginous tissue repair by use of joint distraction is still controversial, and it is not clear which patients favor the most of this treatment regarding this cartilage tissue repair. Knowledge in this respect may add to acceptance of distraction and may refine indications for treatment. Therefore, this paper is a first attempt to identify patient's characteristics predicting cartilage tissue repair after KJD treatment.

MATERIALS AND METHODS

Patients

Fifty-seven consecutive patients received KJD between April 2006 and July 2013 (24 at the University Medical Center Utrecht and 33 at the Sint Maartenskliniek Woerden, The Netherlands). Twenty patients were included in an open prospective study and had end-stage knee osteoarthritis, initially considered for total knee arthroplasty (TKA) and received eight weeks of distraction. The remaining thirty-seven patients were included in ongoing randomized controlled trials (RCTs). These RCTs compare KJD with presently applied surgical alternatives (TKA or high tibial osteotomy; HTO).[10] These patients were as such indicated for TKA or for HTO (with a deviation of <10°) and received six weeks of distraction. In addition, all patients had to have an age below 65 years, body mass index of <35 kg/m^2, intact knee ligaments and a normal range of motion (minimum of 120° flexion). Exclusion criteria were primary patellofemoral osteoarthritis, severe knee malalignment (>10° varus or valgus), a history of inflammatory or septic arthritis, inability to cope with an external fixator, and posttraumatic fibrosis due to a fracture of the tibial plateau. The medical ethical review committee of the University Medical Center Utrecht approved all studies (Nos. 04/086, 10/359/E and 11/072), all patients gave written informed consent and all studies were performed in accordance with the ethical principles laid out in the Declaration of Helsinki.

Distraction method

The applied distraction method has been described in detail previously.[3] In short: two dynamic monotubes were placed on either side of the knee joint, at both sides (lateral and medial) fixed to femur and tibia with two bone pins each. The knee joint was distracted for ~5 mm. Patients were allowed to fully load the distracted knee if needed support with crutches. After a mean of 49 (±8) days of distraction the frame and pins were removed, patients were discharged and rehabilitated in their own environment with the help of a physiotherapist and pain medication on demand.

Outcome

The outcome parameters (dependent variables) were, minimum (min) JSW and mean JSW of the most affected compartment (MAC) at one year after KJD.[3,4] Both radiographic parameters were determined at baseline and at one year follow-up on standardized weight-bearing, semi-flexed posterior–anterior radiographs. These were taken according to the protocol of Buckland-Wright (7° to 10° of knee flexion).[11] This method has proven to produce accurate and precise measurements and that technicians are able to reliably and consistently place the knee in the correct position.[12,13] The digital radiographs were taken with an aluminum step wedge on the lateral side close to the knee, against the detector (film) within the field of exposure. KIDA software was used to determine mean and min JSW.[14] This is a fully mathematical method to analyze the mean and min JSW of the knee. The aluminum step wedge reference (15 cm × 3 cm) is included in the analysis in order to correct for e.g. magnification of the radiograph. The min JSW was measured as the smallest distance between the femur and the tibia. The mean JSW of the MAC was defined as the mean of 4 predefined locations in the most affected compartment. The tibio-femoral joint angle was defined as the angle between the femoral and tibial knee joint lines in the frontal plane. A negative angle indicates a medially converging joint line. The image analyses were performed blinded to the order of acquisition and patient characteristics. Interobserver reproducibility has proven to be high, and the intra-observer variation revealed good variability in the past.[14,15] Intra-observer variation, tested by random reanalyses of 29 radiographs in the present study showed good correlations between the two observations (Pearson's R, 0.97 and 0.91 for mean JSW and min JSW, respectively). Baseline (pre-treatment) patient characteristics assessed for their predictive ability for the outcome were gender, distraction time (six or eight weeks of distraction performed), HTO or TKA indication, age, BMI, min JSW, mean JSW of the MAC, and Kellgren & Lawrence grade (KLG). There were no statistical significant correlations between all those parameters. Clinical outcome was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, version 3.0 and 3.1), normalized to a 100-point scale; 100 being the best condition. Furthermore, a visual analog scale for pain (VAS-pain; 0 to 100 mm, 0 meaning no pain) was used.

Statistical analysis

Two-sided paired tests were used to evaluate whether outcomes variables changed from baseline to one year posttreatment. To obtain (a combination of) variables predictive for radiographic outcome, multivariable linear regression analyses were used. The effect of predictors on change in the outcome was assessed by using min JSW and mean JSW at one year as dependent variable and adjust the analysis for the respective baseline values. A stepwise selection procedure was used starting with all variables and removing them one-by-one based on p-value and change in explained variance of the model (R^2 change >3%). SPSS software version 22.0 was used for statistical analysis and a p-value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the whole cohort are given in Table 1. A mean±SD clinical improvement of 28.3±18.8 points, based on the WOMAC total was observed for this cohort. The WOMAC total increased from 50.0±17.0 points at baseline, towards 78.3±17.7 points at one year (p<0.001). In line with this, the VAS-pain decreased from 64.2±18.7 mm towards 30.9±24.4 mm at one year (p<0.001) after joint distraction. For this cohort on average the mean±SD JSW of the MAC increased with 0.95±1.23mm, from 2.13±1.62 mm at baseline to 3.08±1.43 mm at one year (p<0.001). Min JSW increased with 0.94±1.03 mm, from 0.69±1.08 at baseline to 1.63±1.21 mm at one year of follow-up (p<0.001). In the patients with at baseline a medially converging joint line, the tibio-femoral joint angle changed from −6.98±2.90° to −6.07±3.18° at one year (n=52, p=0.001). In the patients with at baseline a laterally converging joint line, the tibio-femoral joint angle changed from 3.59±1.65° to 2.38±1.10° at one year (n=5, p=0.010). Multivariable linear regression analysis revealed that only higher KLG was predictive for a higher mean JSW (in addition to mean JSW at baseline; Table 2A). For mean JSW the regression coefficient (=β) of KLG measured 0.47 mm (95% CI = 0.18–0.77, p=0.002), meaning that the mean JSW after one year would be 0.47 mm higher if the patient had a higher KLG at baseline (e.g. grade IV instead of grade III). For min JSW, higher KLG and male gender were statistically signifi-

Table 1. Baseline characteristics

Characteristics	KJD (n=57)
Male gender, n (%)	33 (58%)
Height, cm (±SD, range)	176 ± 9.4 (156 – 197)
Weight, kg (±SD, range)	86.8 ± 13.6 (55 – 117)
Body mass index, kg/m^2 (±SD, range)	27.9 ± 3.7 (19 – 36)
Affected knee, n left knees (%)	26 (46%)
Most affected compartment, n medial (%)	51 (90%)
Age at surgery, yr (±SD, range)	52.1 ± 6.8 (32 – 65)
Kellgren & Lawrence, median	3
Grade 0, n (%)	0 (0%)
Grade 1, n (%)	9 (16%)
Grade 2, n (%)	9 (16%)
Grade 3, n (%)	27 (47%)
Grade 4, n (%)	12 (21%)
Tibio-femoral angle joint (±SD, range)	-6,1 ± 4.1 (-13,1 – 5,8)
Initial indication TKA/HTO	35/22
Duration of distraction 6/8	37/20

Table 2A. Multivariable linear regression analysis with mean JSW (mm) as dependent variable

R^2=0.55	ß (95% CI)	P
KLG	0.47 (0.18 – 0.77)	0.002
Mean JSW baseline value	0.72 (0.55 – 0.90)	<0.001

Table 2B. Multivariable linear regression analysis with min JSW (mm) as dependent variable

R^2=0.53	ß (95% CI)	P
KLG	0.46 (0.19 – 0.73)	0.001
Gender (male)	0.52 (0.06 – 0.99)	0.028
Distraction time (eight weeks)	0.44 (–0.05 – 0.93)	0.080
Min JSW baseline value	0.84 (0.59 – 1.08)	<0.001

Table 2C. Multivariable linear regression analysis with mean JSW (mm) as dependent variable

R^2=0.58	ß (95% CI)	P
KLG	0.49 (0.19 – 0.78)	0.002
Gender (male)	0.36 (-0.16 – 0.88)	0.174
Distraction time (eight weeks)	0.30 (-0.26 – 0.85)	0.287
Mean JSW baseline value	0.70 (0.52 – 0.88)	<0.001

β = the regression coefficient. Example: the min JSW would be 0.52 mm higher if the patient was male.

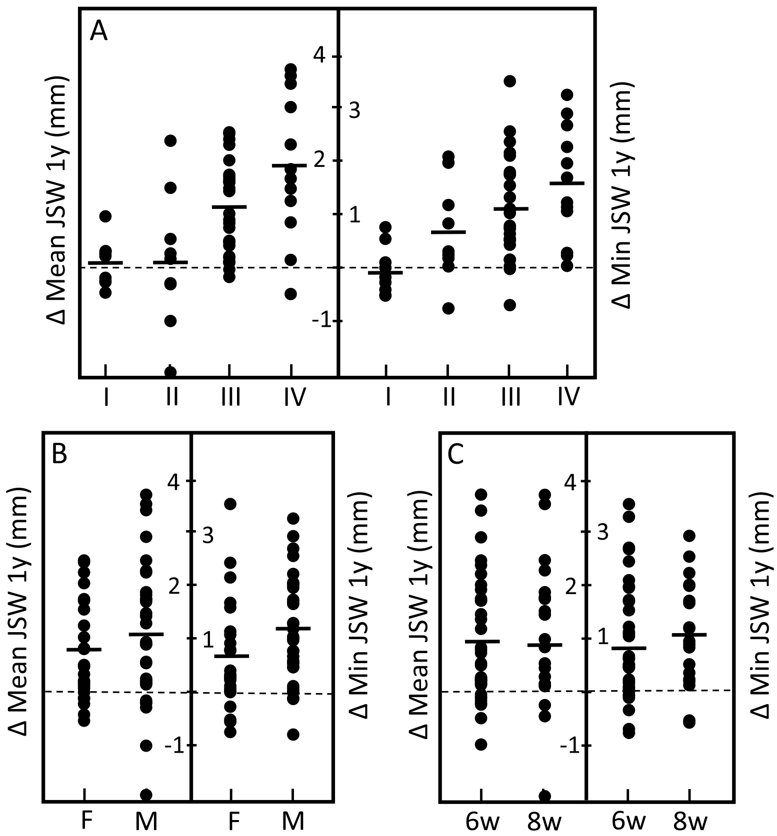

Figure 1. The upper panel (**a**) shows the mean change of the mean and min JSW (mm) at one-year for every patient per KLG grade. The lower panels (**b/c**) show the mean change of the mean and min JSW (mm) at one-year for every patient per gender and distraction time.

cantly positively related. Eight weeks of distraction time neared significance (Table 2B). Because mean JSW of the MAC and min JSW are related, age and distraction time were also added to the model of mean JSW, although both were not statistically significant the direction and order of magnitude of the regression coefficients were comparable and they increased explained variance (R^2=0.55 to R^2=0.58; Table 2C). Figure 1A–C gives a visualization of the change in mean JSW of the MAC and min JSW separated for baseline KLG, gender, or distraction time.

DISCUSSION

This study is the first to demonstrate that KLG, (male gender, and distraction time) of osteoarthritis patients treated with KJD predicts radiographic determined cartilaginous thickness one year after treatment. Upon correction for JSW at baseline, the final JSW at one year posttreatment can be explained by the degree of joint damage at baseline, the more severe the damage (higher KLG) the greater the cartilaginous tissue repair. It appeared that knees with KLG III and IV showed normalization of the JSW to a JSW not distinguishable from those with a KLG I at baseline (data not shown). Regarding normal values few data have been reported for the Caucasian population. Based on literature, normal values of the mean JSW are between 4.8 to 5.1 mm and 6.0 to 6.1 mm (medial and lateral compartment respectively) and the normal value of the min JSW would be 3.1 mm.[15,16] This means that, despite the increase of JSW, the mean and min JSW in our patients is still below these normal values. Regarding rates of cartilage loss, more data is published. An analytic review found a mean rate of joint space narrowing of 0.13±0.15 mm/year.[17] Taken into account the increase in mean JSW (0.95±0.16 mm) in our population, a profit of over fourteen years in JSW has been gained by KJD. The mechanical competence of the cartilage-like tissue at one year after distraction is demonstrated by the fact that the radiographs were obtained under weight-bearing conditions after unrestricted posttreatment loading over the one year follow-up. The reason for the severity of joint damage being a predictor of cartilage repair can only be speculated on. One reason could be that it has been shown that there is cartilaginous repair activity in the osteoarthritic joint (e.g. increased matrix synthesis activity) but that this repair activity is ineffective (limited retention of the newly formed matrix molecules).[18] It could be that the more severe the joint is affected, the higher the repair activity. Note that KLG does not only refer to cartilage loss (atrophic activity), but also to osteophyte formation being a major component of the KLG and considered to be a hypertrophic activity.[19] This higher repair activity may become effective by providing the proper joint biomechanical homeostasis during joint distraction. Another reason could be that the higher the KLG the larger the area of denuded bone. It has been reported that the bone cartilage interface in case of osteoarthritis is penetrated by blood vessels entering the cartilage from the subchondral bone.[20] So in the case of denuded bone there may be an increased area of nourishment from the bone side.[21] This is supported by the observation that denuded bone areas are filled in by cartilaginous tissue upon knee joint distraction.[3] Patient characteristics, such as age and BMI are known risk factors for progression of osteoarthritis.[22] However, they did not add significantly to prediction of cartilage repair after KJD. Male gender appeared to be a positive indicator for JSW one year after treatment. This corroborates previous observation for ankle distraction, where clinical outcome was positively predicted by male gender.[23] Interestingly, in the model also eight weeks of distraction as compared to six weeks of distraction was positively associated with JSW one year after treatment, although not statistically significant. In a study where outcome between six weeks of distraction was compared to those of eight weeks of distraction (n=20 patients each), no statistically significant benefit of eight weeks of distraction was found, although a small average benefit for eight weeks of distraction was visible comparing the graphs.[24] It might be that the power of this and the present analyses is still too small to make the statement. Clearly future studies should take duration of distraction time into account.

In conclusion, for the first patients treated with KJD, a higher KLG, male gender, and eight weeks of distraction are positive predictors for cartilaginous tissue repair one year after treatment.

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Chapter

10

Summary and general discussion

In the young and active population results after knee replacement are less satisfactory with higher rates of revision due to mechanical, aseptic loosening.[1-4] Therefore, in case of persisting, painful, conservative treatment-resistant knee osteoarthritis at relative young age, alternative, joint preserving, treatments strategies are a necessity. In this population the surgical treatment should focus on reversing the mechanical factors associated with the development and progression of knee osteoarthritis. An option in this respect is (temporarily) unloading the knee joint. Depending on the severity of the osteoarthritis (unicompartmental or bicompartmental) and malalignment, unloading of the knee joint is possible by performing an osteotomy (partial unloading) or by knee joint distraction (temporarily unloading). Therefore, this thesis aimed to improve the knowledge regarding knee joint preserving treatments, such as valgus-producing distal femoral osteotomy (DFO) and knee joint distraction (KJD). In this way a better understanding of what the optimal treatment will be in relatively young patients with conservative treatment-resistant knee osteoarthritis may be found. In the introduction (**chapter 1**) the specific aims in this approach were described.

FEMORAL OSTEOTOMIES

Chapter 2 involved a retrospective analysis of fifteen patients (sixteen knees) who underwent a closed-wedge valgus-producing DFO for the treatment of symptomatic femoral varus deformity. Either a lateral uniplanar or biplanar closed-wedge technique was used, which resulted in accurate corrections (mechanical lateral distal femoral angle changed from 95.9° (±2.7°) preoperatively to 89.3° (±2.9°) postoperatively and the mean mechanical tibiofemoral axis changed from 10.0° (±2.6°) of varus to 3.1° (±2.6°) of varus postoperatively) in these patients. The aims for correction differed from unloading in case of medial osteoarthritis, decrease of varus to normal varus or decrease to leg alignment symmetrical to the contralateral leg. Carefully preplanned single plane and biplane osteotomies resulted in significant pain relief, increase in function, and a high survival rate. At a mean of 40 months (±30) postoperatively the VAS-pain averaged 2.5 (±2.4), the total WOMAC score 80 (±20) points and the osteotomy survival rate was 94%.

These encouraging results support our opinion that each deformity should be corrected at its source (i.e. tailored approach); otherwise joint-line obliquity will be the result.[5] This is not desirable for two reasons. Firstly, it results in increased shear stresses at the cartilage joint surface and even tibiofemoral subluxation. Second, it may hamper subsequent joint replacement surgery. As mentioned both uniplanar or biplanar techniques have been used in correcting the femoral varus deformity in these patients. Mean bone healing time of biplanar osteotomies (4±3 months) was shorter than in the uniplanar osteotomies (6±3 months), which confirmed the findings in saw model studies that biplane closing-wedge technique has the best bone healing potential compared to other DFO techniques.[6] Regarding bone healing time evaluation, the intervals of follow up hampers an accurate registration of bone healing time. A next step would be a prospective study with a monthly follow-up for more accurate information on bone healing time.

Chapter 3 investigated the periosteal vessels location as intra-operative landmarks in distal femoral osteotomies and focused on the branching pattern of the vascular supply of the medial and lateral femoral condyle, its consistency, and the relationship to the height of distal femoral osteotomies. A human cadaver dissection study was conducted, in which surgical dissection was performed in eight knees.

A constant branch pattern was observed of the vascular supply of the medial and lateral femoral condyle, related to the height of the transverse osteotomy cuts in distal femoral osteotomies. At the medial side this was the upper transverse artery (UTA) and at the lateral side of the femur the lateral transverse artery (LTA). Each of the arteries is accompanied by two accompanying veins, which make them easily recognizable. The UTA and LTA are located in the area 6.5 cm proximal to the medial and lateral knee joint line, respectively, where transverse cuts for medial and lateral open-wedge and closed-wedge osteotomies are positioned. For orthopaedic surgeons during osteotomy surgery of the distal femur, in addition to fluoroscopic assistance, the UTA and LTA can serve as an intra-operative landmark. In both open-wedge and closed-wedge DFO techniques it is safe to coagulate the landmark-vessels (UTA and LTA) to prevent bleeding and bone cuts can be made at the level of these vessels, since there are many anastomoses in the periosteal vascularization of the medial and lateral femoral condyle.

HIGH TIBIAL OSTEOTOMY VERSUS KNEE JOINT DISTRACTION

In the field of joint preserving surgical treatment for unicompartmental osteoarthritis comparative data between high tibial osteotomy (HTO) and KJD is lacking. Therefore we recruited 69 patients (age <65 years) with medial knee compartmental osteoarthritis in a prospective, two-center, randomized controlled trial (RCT) comparing these two treatments (**chapter 4**). A biplane medial based opening-wedge HTO was performed in 45 patients and 22 patients underwent KJD. At one year all patient reported outcome measures (PROMS) improved significantly in both groups ($p<0.02$), and the patients treated with HTO showed slightly greater improvement in 4 of the 16 PROMS ($p<0.05$). Cartilage repair activity, as indicated by joint space width (JSW) on radiographs, was better for KJD with the mean JSW of the whole joint significantly increasing in the KJD group (+0.5±0.9 mm, $p=0.018$), and not significantly increasing in the HTO group (+0.2±0.8 mm). In general it may be concluded that KJD was non-inferior to HTO and may be considered as an alternative in case of varus malalignement. A clear limitation is the short follow-up, and the relatively high number (thirteen patients) of pin tract infections.

Of particular interest and the most challenging step in the surgical treatment of conservative-treatment resistant unicompartmental osteoarthritis is selecting the appropriate treatment for the patient and determining the exact place of KJD as surgical option. Important factors to consider are radiographic severity of the osteoarthritis, activity level and age of the patient. In the past the choice was either HTO or unicompartmental knee arthroplasty (UKA). Patients considered for UKA should have bone-on-bone anteromedial osteoarthritis with a correctable intra-articular varus deformity, functionally intact knee ligaments (cruciate and collateral) and full thickness cartilage preserved in the lateral compartment.[7,8] In general it is advised to be reserved with performing UKA in younger patients, since significantly higher rates of revision have been reported in patients younger than 55 years.[9-11] Patients considered for HTO should have a typical, extra-articular, metaphyseal varus deformity of the proximal tibia.[12] Performing an HTO in knees with a normal alignment induces a valgus deformity of the proximal tibia which leads to increased shear stresses, a relative lower clinical outcome and a shorter survival of the knee joint. [5,13-15] Furthermore, it is also not advised to perform osteotomies in knees with a 'pagoda deformity' or with a previous (partial) lateral meniscectomy.[11-13]

Taking into consideration the above mentioned and based on the results as presented in **chapter 4**, patients less or not suitable for HTO can be considered for KJD. In ideal HTO candidates KJD can be considered as an alternative, however the orthopaedic surgeon has to bear in mind the relatively short follow-up (one year) of this RCT. At this moment the two year follow-up data of both groups is being gathered and analysed. The first results are very promising, with an increase of almost all KOOS subscales in the KJD-group in the second year after treatment (Symptoms +3, Pain +2, ADL -1, Sport/Rec +5, and QOL +4 points). In the same period the HTO-group showed a less striking increase of the KOOS subscales (Symptoms +1, Pain -2, ADL +0, Sport/Rec +2 and QOL +3 points). With HTO being a well-established surgical procedure with an 87-99% five year survival, longer follow-up still is necessary to determine the long-term treatment effect of KJD compared to HTO.

In patients eligible for UKA the exact place of KJD as alternative treatment remains unclear, since comparative studies are lacking. In general it could be stated that in patients without bone-on-bone anteromedial osteoarthritis, and thus not suitable for UKA, KJD can be considered.

In the last years, for medial compartment osteoarthritis, a load-bypassing knee support system has been reported (KineSpring System). Initial studies reported clinical improvement[16], while later studies reported serious risks, including development of intra- and extra-articular metallosis, medial joint capsule and medial collateral ligament/

medial joint instability after device removal.[17] Studies comparing the KineSpring with HTO or UKA are even lacking.

Despite the improvement of clinical scores and radiographic JSW, the effects of HTO and KJD on cartilage quality remain unknown. At present there is a clear academic and clinical debate on the actual quality of the cartilage formed during and after HTO and KJD and whether the regeneration of articular cartilage leads to hyaline cartilage or fibrocartilage, the latter having inferior biomechanical properties compared to hyaline cartilage. dGEMRIC (delayed gadolinium-enhanced magnetic resonance imaging of cartilage) enables a non-invasive assessment of cartilage quality. In the past, three studies investigated cartilage quality after HTO using dGEMRIC, which is a surrogate measure for glycosaminoglycan (GAG) content in cartilage.[18-20] Two of them detected no changes due to HTO within knee compartments before and after HTO.[18,19] The third study found higher T_1 values (increased GAG content) in the lateral compartment, compared with the medial compartment at baseline and increased T_1 values in the medial compartment two years after HTO, indicating recovery of cartilage with respect to GAG content.[20] The first preliminary evaluations of the cartilage quality after KJD also showed a GAG content of the newly formed cartilage similar to the pre-treatment condition or even better. The final data have to be awaited here. Another similarity is that both KJD and HTO result in significant bone activity (bone turnover). In KJD a significant decrease of subchondral density (increased in case of osteoarthritis; osteosclerosis) of the affected compartment after treatment is described.[21] Similar results were seen after HTO, where it was noted that osteosclerosis of the affected medial condyle decreased compared with that of the lateral condyle after correction of a varus deformity.[22] Identifying what structural changes are responsible for the clinical benefit of KJD and HTO however remains to be established.

So, as it is important to gain more insight in the quality of the cartilage formed and in the changes of subchondral bone, twenty KJD and twenty HTO patients were also included in an observational study, in which cartilage changes are evaluated between pre- and two years post treatment by using, amongst others, the dGEMRIC (GAG content) and T2 relaxation (collagen structure) MRI, as well as CT (bone structure) procedure. From a clinical point of view the actual quality of the cartilage and bone formed is of major importance to predict long-term clinical outcome. It is anticipated that the higher the quality of the cartilage formed (normal or near normal amount of proteoglycans and collagen type II is associated with hyaline-like cartilage tissue), and the higher the bone quality (diminished osteosclerosis and diminishment of bone marrow edema) the longer the clinical benefit will be. The two-year results of this observational study will provide important new insights to the ongoing debate of joint regeneration and cartilage regeneration specifically after HTO and KJD.

KNEE JOINT DISTRACTION

In the past, one clinical study[21], performed by Dr. P.M. van Roermund, explored distraction treatment for knee osteoarthritis. In this, prospective open uncontrolled study twenty patients aged <60 years, originally considered for TKA, were included and treated with distraction between 2006 and 2008. As it is important in new surgical treatments to evaluate the long-term effect, we have followed these first KJD-patients to evaluate the durability of the clinical benefit five years after treatment and how the change in cartilaginous tissue repair compares to the natural course of degeneration (**chapter 5**).

Of these twenty patients, two withdrew consent for further follow-up, one after two years and one just before five years follow-up. Three other patients underwent TKA because of unsatisfactory/declining clinical benefit, at a mean of 4.3±0.5 years after distraction treatment (knee joint survival was 83% after five years). For the cases that withdrew consent or received a TKA, the last observation was carried forward. Although over time the clinical benefit tended to decrease, still an impressively mean change of +21.1 points for the total WOMAC score was noted (43.9±3.3 points at baseline and 65.1±5.6 points at five years follow-up, p=0.002). Similar scores were noted for the WOMAC subscales and VAS-pain (at five year p<0.01). Of the fifteen patients with five-year follow-up data available, even eleven patients (73%) were still actual clinical responders according to the OARSI-OMERACT responder criteria.

Minimum radiographic JSW of the most affected compartment remained increased as well: Δ+0.43mm (p=0.040). Improvement of mean JSW and mean cartilage thickness (MRI), were not statistically different from baseline anymore (Δ+0.26mm; p=0.370, and Δ+0.23mm; p=0.177). To compare cartilaginous tissue repair over time after KJD with the natural progression rate of cartilage damage in case of no or conservative treatment a control group was selected, using data from the OsteoArthritis-Initiative (OAI). The OAI control group (n=138) was comparable with our KJD group regarding demographic baseline values and severity of osteoarthritis. Multivariable linear regression analysis indicated that KJD treatment was associated with significantly less progression in mean and min JSW (X-ray) and mean cartilage thickness (MRI) compared to natural progression in the OAI group (all P<0.001). It can be concluded that KJD results in prolonged clinical relevant benefit and most patients lack the need for additional surgical intervention. Furthermore, the initial observed one-to-two years cartilaginous repair followed by a subsequent gradual decrease with a rate not worse from the natural progression. This is surprising and could mean that the newly formed cartilage is rather hyaline-like cartilage tissue, than fibrocartilage. As mentioned above, the latter has inferior biomechanical properties compared to hyaline cartilage and one would expect a higher progression rate in case of fibrocartilage, rather than the comparable progression rate we established.

Biomarker analysis (showing an increase in the ratio of collagen type II synthesis/ breakdown) and the changes observed by histo- and biochemistry in an animal study, support the possible formation of hyaline-like cartilage tissue.[21,23]

The knee joint survival of 83% after five years is very encouraging, certainly as one takes in account that these patients, with generalized knee osteoarthritis, originally were considered for a total knee replacement. The question remains what the overall survival rate will be with longer follow-up (e.g. ten years). Previous to the prospective uncontrolled study, a feasibility study was conducted with six patients (clinical outcome was not scored). Of these six patients one could not be traced and four were without TKA twelve years after distraction treatment (survival rate of 67%).[24] Supportive of prolonged clinical benefit after 5 years survival is the fact that failure to treatment after ankle distraction (n=111) was highest in the first five years of follow-up.[25]

To guide optimal implementation of KJD for patients and society, in **chapter 6** a model is created to predict the impact of distraction treatment on cost-effectiveness compared to TKA. A cost-effectiveness and cost-utility analysis from healthcare perspective for different age and gender categories was performed, in which a treatment strategy starting with TKA (n=200) and a strategy starting with KJD (n=200) for patients of different age and gender was simulated. This study found that when patients with generalized knee osteoarthritis are first treated with KJD before TKA, this leads to delay of revision TKA surgeries, and effectiveness in terms of quality adjusted life years. Moreover, starting with KJD clearly saves costs. This resulted in a very high likelihood for the KJD strategy to be cost-effective, in specifically the younger age categories (45-54 years). Less favorable outcomes on cost and effects were seen for the older age categories (>65 years). This makes sense because it is less likely that elderly need (more costly) revision surgery during their lifetime, consequently these operations cannot be prevented by KJD when performed at a later age (i.e. 65-70 years). Further improvement of cost-effectiveness of KJD can be accomplished by developing a more "user-friendly" version of the distraction device. The UMC Utrecht has developed recently such a "user-friendly" distractor. In this way the surgery time can be reduced and maybe the duration of hospital stay shortened. Currently patients are hospitalized four days (till five mm of distraction is reached three days after surgery). With a more dedicated distraction device it might be possible to reduce the length of stay. Moreover, such device may be friendlier for patients to wear and for the orthopedic surgeon easier to place. The UMC Utrecht has started a spin-off company (ArthroSave BV) intending to valuate and market this new device.

In the RCTs comparing KJD with HTO and TKA the duration of distraction was, based on empirical knowledge, shortened to six weeks and performed continuously. To determine whether this adjustment in distraction treatment influences the outcome (one year) after treatment, **chapter 7** compares the twenty patients treated in the prospective open uncontrolled study[21] with the first twenty KJD patients, which were included in one of two RCTs (eleven patients were from the KJD-TKA (see **chapter 8** below) study and nine were from the KJD-HTO study). Duration of the distraction period differed from eight weeks in the patients of the prospective study (average 59 days, range 54-64 days), to six weeks in the first twenty patients included in the RCTs (average duration 42 days, range 39-47 days).

This study revealed that, after one year, shortening the distraction period to six weeks does not significantly decrease short-term outcomes. Both cartilaginous repair activity, as indicated by an increase in radiographic JSW and MRI-observed cartilage thickness, and improvement of clinical performance were not different between groups. However, although not statistically significantly different, clinical improvement and radiographic and MRI outcome tended to be less pronounced in the 6-wks group. Theoretically, KJD could lose efficacy when performed for less than six weeks. It remains to be determined whether long-term outcomes are similar between six-week and eight-week treatment. Clearly shorter distraction periods are not advocated.

KNEE JOINT DISTRACTION VERSUS TOTAL KNEE ARTHROPLASTY

Since the original study (in which twenty patients were treated with distraction between 2006 and 2008) was a prospective, uncontrolled study and lacking a control group, no comparative data on efficacy between KJD and TKA is available. To determine the optimal place of KJD as surgical treatment in bicompartmental knee osteoarthritis we executed a well-designed, sufficiently powered randomized controlled clinical trial comparing KJD with TKA (**chapter 8**).

Sixty patients (age <65 years) with end-stage knee osteoarthritis were enrolled in this RCT and randomized to either KJD (n=20) or TKA (n=40). After randomization four TKA assigned patients withdrew consent, because they were not willing to undergo a total knee replacement. After treatment, one patient in the KJD group continued to have disabling pain and functional impairment and received a TKA within one year after distraction treatment. Even with this failure in the KJD group, treatment with KJD resulted in comparable clinical benefit after one year when compared with TKA. For example, in the KJD group WOMAC score improved 30±17 points, while the TKA group improved by 36±19 points over 12 months ($p<0.001$ for both). All other patient reported outcome measures (KOOS, ICOAP, VAS-pain, EQ-5D, and the Physical Component Scale of the SF-36) also improved significantly over one year (at one year $p<0.02$) in both groups. Only one of the sixteen clinical parameters showed significantly greater improvements in the TKA-group (mean change of the KOOS subscale quality of life). Furthermore, there was no difference between the actual clinical responders in both groups (80% vs. 83% for KJD vs. TKA) according to the OARSI-OMERACT responder criteria. TKA was at the expense of the original joint, whereas KJD lead to a substantial increase of radiographic JSW. The mean JSW of the most affected compartment increased significantly from 1.9±2.1 mm towards 3.2±2.1 mm at one year ($p<0.001$). In line with this, the minimum JSW increased from 0.6±1.2 mm at baseline to 1.5±1.1 mm at one year ($p=0.004$). It can be concluded that in these relative young patients with conservative treatment-resistant generalized knee osteoarthritis KJD represents a promising therapeutic option in postponing a first TKA and potentially preventing revision surgery later in life.

Of special concern is the high rate of pin tract infections in the KJD group, measuring 60% (twelve patients). Two of these twelve patients even had two be treated with intravenous antibiotics for two weeks. The high risk of developing infections is clear, with the percutaneous passage of pins into muscle and bone. Minimizing pin tract infections is desirable, as it represents a considerable burden for the patients. In interviews KJD patients indicated that most discomfort experienced during the distraction period resulted from pin tract infections. Furthermore, pin tract infections could be seen as a latent infection risk with higher risk of infection during subsequent TKA surgery. However, bone pins are placed only extra-articular and outside the knee joint capsule. Furthermore, follow-up data of the KJD failures from **chapter 5** showed that none of the three patients that underwent TKA suffered from prosthetic joint infection and that TKA outcome was similar to primary TKA in matched controls.[23]

Regarding the pin tract infection rate, in comparison with the prospective uncontrolled study the infection rate is already substantially lower (85% vs. 60%), since a more dedicated pin tract care guideline for nursing of the pins and skin around the pinholes was used. Irrespective, in the future these numbers should be minimized further. Important is a meticulous surgical technique during pin insertion. After completion of the procedure, all pin sites must be free of skin tenting and soft tissue impingement, so pin sites are encouraged to heal around the pins.[26] Also, novel approaches to reduce pin-tract infection should be explored. In recent literature a few approaches are opted.[27-29] Firstly, usage of coated external fixation pins is likely to inhibit biofilm formation. One study[27] evaluated the use of iodine-coated external fixation pins in patients (mean duration external fixation six months). They reported an infection rate as low as 2.5% for grade 1, and 1.1% for grade 2 infections according to the Checketts–Otterburn classification. Another promising technique is the use of bactericidal micron-thin sol-gel films on the pins. One study used sol-gel films that continuously released triclosan in vitro for durations exceeding 8 weeks. In an in vivo rabbit study they successfully prevented pin tract infections (no signs infections in the animals receiving coated pins vs. up to 100% infection rate in rabbits with control, uncoated pins).[28] Finally, a most promising approach seemed the usage of small electric currents. In one study two pins where inserted into the lateral right tibia of nine goats. Both pins were infected with a *S. epidermidis* strain of which one pin was subjected to a small electric current. After 21 days, infection developed in 89% of the pin sites without electric current, whereas only 11% of the pin sites in the current group showed infection.[29] These novel approaches are promising and future studies should focus on the clinical applicability of them.

PREDICTION OF EFFICACY OF KNEE JOINT DISTRACTION

As a next step we identified parameters that can predict the degree of cartilaginous tissue repair after KJD in **chapter 9.**

In retrospect we included 57 consecutively treated KJD patients. Twenty patients were included in the open prospective study and had end-stage knee osteoarthritis, initially considered for TKA and received eight weeks distraction (**chapter 7**). The remaining thirty-seven patients were included in one of the two RCTs (**chapter 4 and 8**). Baseline (pre-treatment) patient characteristics assessed for their predictive ability for the outcome were gender, distraction time (six or eight weeks of distraction performed), HTO or TKA indication, age, BMI, min JSW, mean JSW of the most affected compartment, and Kellgren & Lawrence grade (KLG). At baseline and at one year of follow-up, mean and minimum JSW of the most affected compartment was determined on standardized weight-bearing radiographs by use of interactive KIDA software.[30]

Multivariable linear regression analysis revealed that only higher KLG (more severe joint damage) was predictive for a higher mean JSW when corrected for baseline JSW (increase in cartilage thickness). For mean JSW the regression coefficient of KLG measured 0.47 mm (95% CI=0.18–0.77, p=0.002), meaning that the mean JSW after one-year would be 0.47 mm higher if the patient had a higher KLG at baseline (e.g. grade IV instead of grade III). For min JSW, higher KLG and male gender were statistically significantly positively related. Eight weeks of distraction time neared significance. It is unclear why a low correlation exists between clinical symptoms of OA and histological, radiographic or MRI parameters of cartilage quality, studied as well. Finding the answer would give insight in how cartilaginous tissue repair or structural changes improve clinical outcome and would help in identifying which patients (characteristics) would benefit best from distraction treatment.

CONCLUSION

This thesis has given new insights in the use of DFOs and KJD. We have shown that a distal lateral closed-wedge valgus osteotomy of the femur for the treatment of varus deformity of the knee is a valuable procedure when the deformity is localized in the femur and using a biplane technique shortens bone healing time. In the cadaveric study we found that the periosteal vascularization of medial and lateral aspect of the distal femur is highly constant, safely can be cauterized, and can serve as a landmark for orthopaedic surgeons in determining the height of the osteotomy cuts in distal femoral osteotomies.

In the field of KJD we demonstrated that KJD results in prolonged clinical relevant benefit, even five years after distraction, with a high survival rate of 83%. Starting with KJD (when compared with TKA) is cost-effective, specifically in the younger age categories (45-54 years), a shorter distraction period (six instead of eight weeks) does not influence short-term outcome but with six weeks seeming the minimal duration, and higher KLG and male gender were predictive for radiographic determined cartilaginous thickness one year after distraction treatment.

Furthermore, in case of unicompartmental osteoarthritis KJD was non-inferior to HTO one year after treatment, and thus KJD can be considered as alternative treatment option. Even more impressive, in end-stage knee osteoarthritis, treatment with KJD resulted in comparable clinical benefit after one year when compared with TKA. Combined with the high five-year survival rate and the established cost-effectiveness in the younger age categories, it can be concluded that KJD is a promising joint-preserving surgical treatment, which can effectively postpone a TKA and revision TKA burden in young patients with conservative treatment-resistant end-stage knee osteoarthritis.

Future studies should focus on improving the distraction device and exploring novel approaches to minimize pin tract infections, lowering the burden of the distraction period for the patient. Exploring mechanisms of action of the observed cartilaginous repair using distraction as a 'gold standard' for cartilaginous tissue repair (e.g. by taking synovial fluid samples during and after distraction or extending in vivo animal studies) might provide novel tools for treatment of this high incidence and invalidating disease.

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Chapter

10

Dutch summary / Nederlandse samenvatting

Slijtage van het kniegewricht, artrose, is een langzaam voortschrijdend proces. Het uit zich in pijn en functionele beperkingen in het dagelijkse leven (van wandelen tot sporten). Veel factoren dragen bij aan het ontstaan en het verergeren van de artrose, waarbij een van de meest belangrijke mechanische factoren de stand van het been is (een O-been of X-been). De initiële behandeling van artrose van de knie bestaat uit conservatieve maatregelen (zoals leefstijladviezen, gewichtsreductie bij overgewicht, pijnstilling en indien nodig ontstekingsremming). Wanneer deze maatregelen onvoldoende resultaat geven kan een operatie noodzakelijk zijn. Bij artrose aan de binnenzijde of buitenzijde van de knie kan een standscorrectie van het been overwogen worden. Als de artrose aan zowel de binnenzijde als de buitenzijde van de knie zit, is een totale knie prothese (TKP) vaak een laatste redmiddel. Echter een TKP heeft ook nadelen, zeker voor de relatief jonge (<65 jaar) patiënt. Deze nog relatief actieve patiënten zijn lang niet altijd tevreden met een totale knie prothese en de duur dat de totale knie prothese functioneel blijft (slijtage en loslating) is korter in vergelijking met die bij de oudere patiënt. Voor specifiek deze relatief jonge en nog actieve populatie zijn gewricht sparende chirurgische ingrepen dan ook wenselijk indien conservatieve behandeling onvoldoende effectief is. In deze patiëntenpopulatie zou de behandeling gericht moeten zijn op het voorkomen van verdere schade door het verminderen van de mechanische overbelasting van het beschadigde kraakbeen. Dit kan, op verschillende manieren, door het mechanisch ontlasten van het kniegewricht. Afhankelijk van de mate van artrose (alleen binnenzijde of buitenzijde, of de gehele knie) kan dit gedaan worden met een beenstandcorrectie indien er sprake is van een duidelijke afwijking van de beenstand (gedeeltelijke permanente ontlasting). Indien er sprake is van artrose aan beide zijden van het gewricht of bij eenzijdige artrose met beperkte of afwezige standsafwijking kan kniedistractie als behandeling worden overwogen (tijdelijke volledige ontlasting).

De belangrijkste indicatie voor een beenstandcorrectie in geval van knie artrose is kraakbeenschade van één van beide compartimenten van de knie (alleen binnenzijde of buitenzijde). Bij een standscorrectie wordt de belasting van het aangedane kraakbeen verlegd naar het gezondere kraakbeen van de knie. Deze 'betere' verdeling van de belasting van het kniegewricht zorgt voor verlichting van de pijn, leidt tot een verbetering van het functioneren in het dagelijks leven en stelt een gewrichtsvervangende operatie (TKP) uit. Daarnaast zijn er ook aanwijzingen dat een beenstandcorrectie zorgt voor kraakbeenherstel waarbij nieuw kraakbeenweefsel gemaakt wordt. Afhankelijk van de bron van de afwijkende beenstand (op het niveau van het bovenbeen of het niveau van het onderbeen), dient de correctie ook plaats te vinden op dat niveau. Indien dat niet gedaan wordt kan worden kan dit leiden tot een scheve kniegewrichtsspleet en juist weer zorgen voor een toename van de klachten.

Een andere mogelijkheid bij enkelzijdige of tweezijdige knie kraakbeenschade is kniedistractie. Dit is een behandeling waarbij de uiteinden van het kniegewricht voor zes tot acht weken lang van elkaar gehouden worden. Dit gebeurt met behulp van twee telescopische buizen die aan binnen- en buitenkant van de knie worden vastgeschroefd aan pennen bevestigd in het bot van het boven- en onderbeen. In de telescopische buizen zit een veer die op spanning gedraaid wordt. Na het plaatsen van dit "frame" worden, in de drie dagen na de operatie, de telescopische buizen steeds iets verder verlengt, waardoor er in het kniegewricht een ruimte (ca. 5 mm) tussen het boven- en onderbeen ontstaat. Dit leidt tot mechanische ontlasting van het kraakbeen in het kniegewricht. Gedurende de behandeling met het frame worden patiënten aangemoedigd het been volledig te belasten zodat de vering in de telescopische buizen resulteert in een wisselende vloeistofdruk in het gewricht en daarmee doorvoeding van het kraakbeen. Na verwijdering van het frame (na zes tot acht weken) moet het geopereerde been opbouwend belast worden en wordt deze belasting al dan niet onder begeleiding van de fysiotherapeut geleidelijk opgevoerd. Tussen 2006 en 2008 is een eerste groep van twintig patiënten met deze behandelmethode geholpen. In deze groep zorgde kniedistractie voor een verbetering van de pijn- en functieklachten van de patiënt, zelfs tot twee jaar na de ingreep, en dus tot uitstel van een TKP. Daarnaast bleek dat het versleten kraakbeenweefsel herstelde en zelfs in dikte toenam (regeneratie).

Deze studie was de eerste prospectieve follow-up studie naar kniedistractie wereldwijd. Vergelijkende studies met andere operatieve behandelingen van de knie (zoals een beenstandcorrectie of een TKP) waren nog niet uitgevoerd. Ook was nog niet bekend wat de lange termijn effecten van kniedistractie zijn, of kniedistractie kosteneffectief is, wat de optimale behandelduur met het frame is en of er specifieke factoren zijn die de uitkomst op kraakbeenherstel kunnen voorspellen.

Dit proefschrift bestaat uit twee delen. In het eerste deel kijken we naar een groep patiënten die een weinig voorkomende standscorrectie aan de buitenzijde van het bovenbeen (DFO: distale femur osteotomie) hebben ondergaan bij een O-been, beschrijven we een anatomische studie naar de vaatvoorziening van het bovenbeen in relatie tot de hoogte van de standscorrecties in het bovenbeen en vergelijken we 45 patiënten die een standscorrectie van het scheenbeen (TKO: tibiakop osteotomie) hebben ondergaan met 22 patiënten die kniedistractie hebben ondergaan in een gerandomiseerde studie.

In het tweede deel behandelen we verschillende vragen rondom kniedistractie. Zo gaan we in op de optimale behandelduur van distractie (zes of acht weken?), beschrijven we de langetermijnresultaten (vijf jaar follow-up) van de behandelde patiënten in de open follow-up studie, bepalen we de kosteneffectiviteit van kniedistractie (vergeleken met TKP), vergelijken we 36 patiënten die een TKP hebben ondergaan met 20 patiënten die kniedistractie hebben ondergaan in een gerandomiseerde studie en identificeren we kenmerken die het kraakbeenherstel kunnen voorspellen na kniedistractie.

Beenstandcorrecties

In **hoofdstuk 2** beschrijven we retrospectief een groep van vijftien patiënten die een standscorrectie van het bovenbeen hebben ondergaan bij een O-been stand. Bij een deel van de patiënten werd botzaagsnedes gebruikt in één vlak voor de correctie (monoplanair) en bij het andere deel van de patiënten werden botzaagsneden gebruikt in twee vlakken (biplanair). Met de beschrijving van deze groep patiënten laten we zien dat als de oorzaak van het O-been een standsafwijking in het bovenbeen is het belangrijk is om de standscorrectie dan ook op die plek uit te voeren (en niet, zoals vaak gebruikelijk, een standscorrectie van het onderbeen te verrichten). Gemiddeld 40 maanden na de operatie was er nog steeds sprake van afgenomen pijn en toegenomen functie bij deze patiënten. Daarnaast vonden we een snellere botgenezing in de groep van patiënten waarbij de biplanaire standscorrecties werden uitgevoerd vergeleken met de groep waarbij de monoplanaire techniek was uitgevoerd.

Aanvullend laten we in **hoofdstuk 3** zien dat de bloedvoorziening in het uiteinde van het bovenbeen in de supracondylaire regio net boven de knie in onderzochte kniepre-paraten vergelijkbaar (consistent) is. Ook werd bevestigd dat zowel aan de binnenzijde als aan de buitenzijde bloedvaten gebruikt kunnen worden als referentiepuntpunt voor een optimale localisatie van botzaagsnedehoogte in het bovenbeen. Doorsnijding van deze bloedvaten bij uitvoering van standscorrecties is niet schadelijk omdat andere bloedvaten de bloedvoorziening van het bot kunnen verzorgen.
Als alternatief voor een beenstandcorrectie kan ook een knie distractie behandeling overwogen worden. Daarom is er een klinische gerandomiseerde studie opgezet waarin we beenstandcorrectie vergelijken met kniedistractie. In **hoofdstuk 4** beschrijven we de resultaten één jaar na de operatie van patiënten met een beperkte beenstandafwijking behandeld hetzij met een beenstandcorrectie hetzij met een kniedistractie. In totaal werden 22 patiënten behandeld met kniedistractie en 45 patiënten ondergingen een beenstandcorrectie. Patiënten waren allemaal jonger dan 65 jaar. Als wordt gekeken naar pijn, functie en stijfheid van de knie door middel van vragenlijsten die de patiënt zelf rapporteert, dan laten al deze gerapporteerde metingen een significante verbete-ring zien in de beide patiëntengroepen. Ten aanzien van kraakbeenherstel (gemeten op röntgenfoto's) liet de kniedistractie groep een significante toename van kraakbeenweef-sel zien (toename van de gewrichtsspleetruimte op een röntgen opname), waar er in de beenstandcorrectie-groep geen significante toename te zien was. Over het algemeen kan geconcludeerd worden dat kniedistractie zeker toegepast kan worden in patiënten met eenzijdige knie artrose met een beperkte beenstandafwijking. Wel moet men zich bedenken dat de follow-up duur nog relatief kort (één jaar) is.

Kniedistractie

In 2006 is de eerste prospectieve klinische follow-up studie gestart naar de effecten van kniedistractie. Twintig patiënten jonger dan 60 jaar, die op basis van hun klachten en kraakbeenschade op de röntgenfoto in aanmerking kwamen voor een TKP, werden geïncludeerd en behandeld met kniedistractie gedurende acht weken. In **hoofdstuk 5** beschrijven we de resultaten van deze groep patiënten na vijf jaar. Van de achttien patiënten die nog meededen aan de trial, hadden vijftien patiënten nog steeds geen knieprothese. Pijn en functie waren nog steeds verbeterd ten opzichte van de conditie voor de behandeling. De dikte van het geregenereerde kraakbeen was wel afgenomen ten opzichte van de initiële "groei" in de eerste twee jaren. Als we de toename in kraakbeendikte vergelijken met een groep van patiënten met dezelfde mate van artrose vóór behandeling maar die geen operatieve behandeling van de knie hadden ondergaan en waarbij de kraakbeen dikte over de jaren verder afneemt, dan is er nog steeds sprake van een winst in kraakbeendikte als gevolg van kniedistractie 5 jaar na behandeling. In **hoofdstuk 6** onderzoeken we de kosten-effectiviteit van kniedistractie als nieuwe behandeling en als mogelijk alternatief voor een TKP. Wanneer patiënten met ernstige artrose eerst worden behandeld met kniedistractie voordat zij een totale knie prothese ontvangen (als het effect van de kniedistractie afneemt) in vergeleken worden met patiënten bij wie direct een totale knie prothese wordt geplaatst, leidt dit tot vermindering van het aantal revisie knie protheses en is daarmee de kosteneffectiviteit bewezen. Kniedistractie is duidelijk kosteneffectief in de jongere patiënten categorieën (<65 jaar). Minder gunstige uitkomsten werden gezien bij de oudere patiënten categorieën (>65 jaar).

In **hoofdstuk 7** bestuderen we de duur van de distractieperiode in relatie tot het klinisch effect. De eerste patiënten (2006) zijn behandeld voor een periode van acht weken. Hierbij moesten patiënten elke twee weken terugkomen naar het ziekenhuis waarbij het frame voor een aantal uur verwijderd werd en de knie passief bewogen werd. De patiënten vonden deze frequente bezoeken erg belastend. Hierop werd empirisch de behandelduur teruggebracht naar zes weken in de twee gerandomiseerde studies die ik in mijn proefschrift beschrijf. Om te onderzoeken of deze verkorte en permanente distractie even effectief was als de acht weken intermitterende distractie zijn de eerste twintig patiënten uit de twee gerandomiseerde studies (behandelduur zes weken permanent) vergeleken met de twintig patiënten die tussen 2006 en 2008 gedurende acht weken intermitterend behandeld zijn met kniedistractie. Eén jaar na behandeling blijkt de kortere distractie periode niet te hebben geresulteerd tot belangrijke verschillen in uitkomsten als pijn, functie en kraakbeenherstel op röntgenfoto's en MRI. Er zijn wel aanwijzingen dat zes weken de minimale behandelduur met kniedistractie moet zijn.

In **hoofdstuk 8** wordt in een gerandomiseerd studie, de effectiviteit van het plaatsen van een TKP vergeleken met kniedistractie. In totaal zijn er 60 patiënten geïncludeerd, allemaal jonger dan 65 jaar. Twintig patiënten werden behandeld met kniedistractie en 36 patiënten kregen een totale knie prothese. Vier patiënten werden na inclusie alsnog geëxcludeerd. Na behandeling bleek bij één patiënt kniedistractie onvoldoende effectief te zijn geweest en is er alsnog een totale knie prothese geplaatst. Zelfs met deze patiënt erbij waren er geen significante verschillen in de door de patiënt gerapporteerde vragen over pijn, stijfheid, dagelijks functioneren of kwaliteit van leven. We hebben dan ook kunnen concluderen dat in deze relatief “jonge” patiënten populatie (jonger dan 65 jaar) kniedistractie een veelbelovende gewricht sparende therapie is, waarmee een eerste knie prothese kan worden uitgesteld en een revisie operatie op latere leeftijd mogelijk kan worden voorkomen. Net zoals bij de gerandomiseerde studie waarbij kniedistractie vergeleken wordt met een beenstandcorrectie, geldt ook hier dat de follow-up duur nog relatief kort (één jaar) is. Ook is in beide studies gebleken dat ondanks een flinke reductie van het aantal pengatinfecties tijdens de behandeling in de twee gerandomiseerde studies (60%) ten opzichte van de eerste open prospectieve follow-up studie (85%), het aantal patiënten dat dergelijke infecties doormaakt nog steeds erg hoog is. Ondanks dat deze infecties over het algemeen goed te behandelen zijn met antibiotica en niet zorgen voor een verhoogde kans op een infectie indien alsnog een knie prothese wordt geplaatst, ondervinden patiënten toch veel hinder van deze pengat infecties. Voor toekomstig onderzoek zal dan ook gekeken moeten worden hoe het aantal pengatinfecties kan worden verminderd, om de behandeling verder te verbeteren.

Tot slot hebben we in **hoofdstuk 9** nog gekeken naar factoren die mogelijk het kraakbeenherstel beïnvloeden na een behandeling met kniedistractie. Hierbij werden retrospectief alle 57 patiënten bekeken die vanaf 2006 kniedistractie hebben ondergaan. Aan de hand van metingen op röntgenfoto’s (minimale en gemiddelde kraakbeendikte) één jaar na behandeling werd gekeken welke patiënt-kenmerken bijdragen aan herstel en toename van kraakbeenweefsel. Na analyse bleek dat mannen en ernstigere artrose van de knie positief voorspellend zijn voor de toename van de op röntgenfoto’s’ gemeten gewrichtsspleetruimte één jaar na kniedistractie.

Conclusies

Dit proefschrift heeft nieuwe inzichten gegeven in het gebruik van standscorrecties van het bovenbeen en van kniedistractie. Zo hebben we laten zien dat bij patiënten met een O-beenstand gelocaliseerd in het bovenbeen een laterale distale femur osteotomie een waardevolle en effectieve procedure is met snellere botgenezing wanneer een biplanaire operatietechniek wordt gebruikt. Daarnaast laat de verrichte anatomische studie zien dat de vaatvoorziening van het bovenbeen in de regio waar standscorrecties worden uitgevoerd een vaste consistente positie kent, dat specifieke bloedvaten kunnen dienen als referentiepunt bij het bepalen van de hoogte van standscorrecties, en deze bloedvaten veilig doorgenomen kunnen worden omdat andere bloedvaten de bloedvoorziening kunnen overnemen.

Op het gebied van kniedistractie hebben wij laten zien dat kniedistractie langdurig (meer dan 5 jaar) vermindering van de pijnklachten geeft en toename van de mobiliteit bij het grootste deel van de patiënten. Het maakt daarbij niet uit of patiënten zes of acht weken behandeld worden voor het resultaat. Vergelijking met een beenstandcorrectie en met een TKP toont dat kniedistractie gelijkwaardige resultaten oplevert één jaar na de operatie, waarbij kraakbeenherstel bij kniedistractie ten opzichte van beide andere behandelingen een meerwaarde heeft. In vergelijking met een totale knie prothese is kniedistractie kosteneffectief. Het beste herstel van kraakbeen lijkt op te treden bij mannen met ernstigere artrose van de knie. Kortom, kniedistractie is een veelbelovende behandeling voor jonge patiënten met ernstige, invaliderende, artrose van de knie en maakt het mogelijk om een eerste knie prothese voor korte en middellange termijn uit te stellen in deze patiëntenpopulatie.

Chapter

10

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chapter

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Curriculum vitae

CURRICULUM VITAE

Jan-Ton van der Woude was born on December 20th 1985 in Woerden, the Netherlands. In 2004 he graduated from the Kalsbeek College (Gymnasium) in Woerden. After a gap year he began medical school at the Utrecht University in 2005, which he completed in 2011. In December of the same year he started his carreer as non-training resident at the department of Orthopaedic Surgery of the Maartenskliniek Woerden. In 2014 he started his PhD-project at the department of Rheumatology & Clinical Immunology of the University Medical Centre Utrecht (prof. dr. F.P.J.G. Lafeber and dr. S.C. Mastbergen) and the department of Orthopaedic Surgery of the Maartenskliniek Woerden (dr. R.J. van Heerwaarden). This research resulted in several poster- and oral presentations at (inter) national conferences and he won the young investigator award at the IWOAI of 2014 in Reykjavik and at the OARSI World Congress of 2016 in Amsterdam.

Currently he is working as non-training resident at the department of Orthopaedic Surgery of the Alrijne hospital in Leiden. At the beginning of 2016 he got accepted for the orthopaedic training program in the ROGO Rotterdam. As a part of this training program, he will start in January 2017 as a resident at the department of Surgery of the IJsselland hospital in Capelle aan den IJssel. He is expected to finish is his orthopaedic training program at the end of 2022. Jan-Ton lives in Woerden together with his wife Nicoline and their daughter Philippine.