Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis

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Keywords:  
Osteoarthritis  
Knee  
Treatment  
Joint distraction  
Cartilage repair  
MRI

Summary

Background: Treatment of severe osteoarthritis (OA) in relatively young patients is challenging. Although successful, total knee prosthesis has a limited lifespan, with the risk of revision surgery, especially in active young patients. Knee joint distraction (KJD) provides clinical benefit and tissue structure modification at 1-year follow-up. The present study evaluates whether this benefit is preserved during the second year of follow-up.

Methods: Patients included in this study presented with end-stage knee OA and an indication for total knee replacement (TKR); they were less than 60 years old with a VAS pain ≥60 mm (n = 20). KJD was applied for 2 months (range 54–64 days) and clinical parameters assessed using the WOMAC questionnaire and VAS pain score. Changes in cartilage structure were measured using quantitative MRI, radiography, and biochemical analyses of collagen type II turnover (ELISA).

Results: Average follow-up was 24 (range 23–25) months. Clinical improvement compared with baseline (BL) was observed at 2-year follow-up: WOMAC improved by 74% (P < 0.001) and VAS pain decreased by 61% (P < 0.001). Cartilage thickness observed by MRI (2.35 mm (95%CI, 2.06–2.65) at BL) was significantly greater at 2-year follow-up (2.78 mm (2.50–3.09); P = 0.03). Radiographic minimum joint space width (JSW) (1.1 mm (0.5–1.7) at BL) was significantly increased at 2-year follow-up as well (1.7 mm (1.1–2.3); P = 0.03). The denuded area of subchondral bone visualized by MRI (22% (95%CI, 12.5–31.5) at BL) was significantly decreased at 2-year follow-up (8% (3.6–12.2); P = 0.004). The ratio of collagen type II synthesis over breakdown was increased at 2-year follow-up (P = 0.07).

Conclusion: Clinical improvement by KJD treatment is sustained for at least 2 years. Cartilage repair is still present after 2 years (MRI) and the newly formed tissue continues to be mechanically resilient as shown by an increased JSW under weight-bearing conditions.

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Introduction

Osteoarthritis (OA) is a slowly progressive joint disorder clinically characterized by pain, stiffness, and functional disabilities. Structural characteristics comprise cartilage damage and loss, changes in subchondral bone, and secondary synovial inflammation. These tissue changes are only partially associated with the clinical characteristics.1–3

The incidence of OA is increasing, due to an aging population and a rise of obesity.4–6. There is no cure for OA, and the first step in current treatment is conservative, predominantly focused on pain relief, minimizing functional disability, and limiting progression of structural joint changes. New treatments include cell transplantation techniques and disease modifying OA drugs (DMOADs).7–9. When conservative treatment fails and joint preserving surgery is not or no longer indicated, total knee replacement (TKR) of the affected joint is recommended. It is questionable, however, whether all options are routinely considered before replacement surgery is performed.10–13

TKR is a final option and although expensive, considered effective in relieving pain and regaining function.14–16. The total number of TKRs is increasing, as is the rate of revisions. It is remarkably that over 40% of all knee replacements and up to 44% of all total knee revisions are performed in patients ≤65 years of age, considering the known problems of limited lifespan of TKRs. This constitutes a
costly healthcare problem\textsuperscript{2,11}. Therefore, development of alternative treatment strategies for end-stage knee OA is necessary in order to preserve a patient’s joint.

For certain disease specific indications, joint preserving surgery is an option; these include arthroscopic debridement, subchondral bone stimulation, osteotomy, and more recently, knee joint distraction (KJD). Joint distraction has been effectively applied in ankle OA with prolonged clinical benefit and indications of tissue structure modification\textsuperscript{15–16}; there has also been a report of clinical benefit in the hip, published already years ago\textsuperscript{17}, although this has not been further explored. Recently, joint distraction was applied for severe end-stage knee OA, and a study by Deie M et al. reported positive clinical results with the use of hinged knee distraction over time\textsuperscript{18}. These treatment approaches are discussed in detail in a review that was recently published by our group\textsuperscript{19}.

In 2006, our group started the first prospective evaluation of knee distraction in 20 patients with severe end-stage OA, who were considered for a TKR. In addition to evaluating clinical benefit, we also measured tissue structural repair using various imaging and biochemical markers. Analysis of the 1-year follow-up revealed positive clinical benefit and signs of cartilage repair\textsuperscript{20}. This paper examines whether these beneficial effects are preserved over the second year of follow-up.

Materials and methods

Patient selection

Twenty-three successive patients with end-stage OA (average age 49 ± 1 years, range 32–57 years), indicated for TKR surgery due to persistent loss of function and pain, not adequately responding to conventional treatments were selected at the Department of Orthopedics, University Medical Center Utrecht. In short, inclusion criteria were age <60 years, Visual Analogue Scale (VAS) of pain ≥60 mm, and radiographic signs of primarily tibio-femoral OA joint damage. Exclusion criteria were severe symptoms in both knees, primary patella-femoral OA, a history of inflammatory or septic arthritis, severe knee malalignment (≥10°) requiring surgical correction and inability to cope with an external fixator for 2 months. Patients had been referred from peripheral hospitals for a second opinion because the patient refused the indicated TKR for personal reasons mostly related to young age. Detailed clinical history of all patients has been previously described\textsuperscript{20}. Of the 23 successively selected patients, three were excluded: one based on bilateral OA; one because of remaining metal in the knee after anterior cruciate ligament (ACL) reconstruction; and one withdrew the informed consent directly after treatment. The 20 included patients were discharged from the hospital. Patients were allowed and encouraged to load the distracted joint with full weight-bearing capacity, supported with crutches. In case of superficial (skin) pin tract infections, treatment with oral antibiotics for 5–7 days was provided (Flucloxacinill). Every 2 weeks the patients returned to the hospital and the monotoles were temporarily removed. The knee was bent, for 3–4 h, in a continuous passive motion device, with pain at the pin sites determining the maximum degree of flexion; on average, 25° (15–80°) flexion and full extension was reached. The monotoles were replaced and sufficient distraction was confirmed by X-ray examination and adjusted if needed.

After 2 months (average duration 60 days, range 54–64 days), the tubes and pins were surgically removed and patients went home without imposed functional restrictions. After both surgeries, patients were treated with acetaminophen and NSAID as needed, according to the standard analgesia protocol of the UMCU. Upon discharge, pain medication, along with daily exercise and physical therapy, were regulated by the patient and not documented.

Follow-up

Patients visited the outpatient clinic twice before treatment (BL) and at 3 and 6 months, and subsequently every 6 months post-treatment. At these time points the WOMAC questionnaire\textsuperscript{21} and VAS pain score were assessed. For evaluation of structural improvement, blood and urine samples were collected at BL and at six, 12 and 24 months after distraction therapy and stored at −80°C. Standardized weight-bearing X-ray images according to the knee images digital analyses (KIDA) protocol\textsuperscript{22} and MRIs according to the Eckstein protocol\textsuperscript{23} were taken at BL, and at 1 and 2 years of follow-up.

Clinical outcome

To score clinical improvement, the WOMAC (version 3.0, normalized to a 100-point scale for total and subscales; 100 being the best score) was used as primary outcome parameter. The secondary clinical outcome parameter was the VAS pain score (0–100 mm; “0” meaning no pain). To identify actual responders, we used the Osteoarthritis Research Society International (OARSI) defined OARSI-OMERACT responder criteria, validated for drug-therapies\textsuperscript{24} and TKR\textsuperscript{25} in case of diagnosed knee OA.

Structural outcome

Quantitative MRI analysis

MRI acquisition was performed with a 1.5 T Philips Achieva, using a 3D spoiled gradient recalled (SPGR) sequence with fat suppression (repetition time 20 ms; echo time 9 ms; flip angle 15°; slice thickness 1.5 mm; in-plane resolution 0.3125 × 0.3125 mm), which has been previously validated for the purpose of quantitative measurement of cartilage thickness and volume\textsuperscript{25}. Coronal images were used to segment the tibio-femoral cartilage plates and bone surface, including denuded areas. The operator (SC) and quality control reader (FE) were blinded to the sequence of the BL and the 1-year follow-up images\textsuperscript{26}; 2-year follow-up images were segmented independently, without reference to the BL or 1-year follow-up images, in order to exclude reading bias, and prevent overestimation of results. Cartilage parameters in the medial and the lateral compartment were computed using custom software (Chondrometrics GmbH., Airing, Germany). The primary structural outcomes were cartilage thickness over the total subchondral bone area (ThCCAB; cartilage thickness with areas of denuded bone included, counting as 0 mm thickness) and the percentage of denuded subchondral bone area (dABp)\textsuperscript{27}. The secondary structural outcome parameter was cartilage thickness over cartilaginous area of subchondral bone (ThCCAB; cartilage thickness with areas of
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**Ratio** 11/9 (M/F) 11/9 (L/R) 18/2 (M/L) 49 ± 1 3 44.9 ± 3.6 45.2 ± 3.5 14.4 ± 4.0 42.8 ± 3.4 1.1 ± 0.3 2.8 ± 0.4 6.8 ± 0.3 2.4 ± 0.1 22.0 ± 4.5 2.9 ± 0.1

Gender: M = male, F = female; affected knee: L = left, R = right; M = medial, L = lateral; K&L = Kellgren and Lawrence grade; WOMAC: Western Ontario and McMaster Universities Osteoarthritis index version 3.0 score range 0–100, 0 being worst 100 being best; JSW MAC: joint space width MAC, min = minimal; JSW LAC: joint space width least affected compartment. ThCtAB — cartilage thickness over total subchondral bone area. dABp — percentage of denuded subchondral bone area. ThCcAB — cartilage thickness over cartilaginous area of subchondral bone.
Samples were analyzed in duplicate, and longitudinal samples for each time point of a patient were analyzed in the same assay plate. Average intra-plate and inter-plate variability were 3.8% and 10.9%, respectively.

**Statistical methods**

Non-parametric statistics (two-sided paired test) were used for all parameters, to evaluate whether the follow-up values significantly differed from the BL values. Double BL values were averaged. Spearman correlation coefficients and unpaired non-parametric comparison of dichotomized data were used to relate/compare longitudinal changes over 2 years for different outcome parameters. Means and 95% confidence intervals (95%CI) are given for the 20 patients; a $P \leq 0.05$ was considered a statistically significant difference. There were no missing data. For all statistical tests, IBM SPSS Statistics version 20.0.0 was used.

**Results**

**Adverse events**

As a result of treatment with the external fixation frame, 17 patients suffered from a pin tract infection, all adequately treated with antibiotics (Flucloxacillin), and no further complaints reported. No deep vein thromboembolism was diagnosed. Two patients suffered from a pulmonary embolism, adequately treated with oral anticoagulates (Sintrom) for 6 months. Limited flexion limitation was observed directly after treatment ($-31.6^\circ$ of flexion, (95%CI $-43.9$ to $-19.2$)), within 6 months the patients recovered to acceptable levels ($-7.2^\circ$ of flexion, ($-15.2$ to $11$)) and flexion range fully normalized within 1-year follow-up ($+2.9^\circ$ of flexion, ($-3.3$ to $9.1$)).

**Clinical benefit**

A quick clinical improvement, based on the total WOMAC index, was already observed at 3 months reaching a plateau within 6 months, and was sustained until 2-year post-treatment [Fig. 2(A)]. The relative improvement from BL to 1- and 2-year follow-up was 70% (95%CI $38.6$–$152.5$%) and 74% (45.8–161.6), respectively, both $P < 0.001$ compared to BL. Also, the individual components of the WOMAC score [pain, stiffness, and function; dotted lines in Fig. 2(B)] all improved statistically significantly ($all P < 0.005$ at each time point) in a similar manner.

VAS pain decreased almost instantly (at 3 months) and stayed low through the 2-year follow-up, which is a relative decrease in comparison to BL of $-58\%$ (95%CI $-73.8$ to $-39.3$) at 1 year and $-61\%$ (78.3 to $-39.3$) at 2 years post-treatment.

On the individual level, 15 patients (75%) could be designated as actual clinical responder according to the OARSI-OMERACT responder criteria. Responders are defined as an increase of $>50\%$ in WOMAC pain OR function with $>20$ points of improvement in either category, or an increase of $>20\%$ of WOMAC pain AND function with $10$ points improvement in each category. Moreover, 10 patients at 1-year follow-up and nine patients at 2-year follow-up achieved an increase of $>50\%$ in WOMAC pain AND function, with at least $20$ points of improvement for both categories.

**Structural outcome**

**Quantitative MRI**

Figure 3(A) shows representative images of a patient, clearly indicating an increase in cartilage thickness over time in the MAC of the knee joint while the least affected compartment remained unchanged. Quantification of these MRIs showed a strong increase...
in mean cartilage thickness (ThCtAB) of the MAC of 0.6 mm (95%CI, 0.24–1.22; \(P = 0.002\)) from BL to 1-year follow-up, and 0.4 mm (0.06–0.83; \(P = 0.030\)) from BL to 2-year follow-up \[Fig. 3(B)\].

After distraction, on average, the subchondral bone area that was denuded (dABp) in the MAC decreased from 22% (12.5–31.5) at BL to 5% (0.4–8.6; \(P = 0.001\)) and 8% (3.6–12.2; \(P = 0.004\)) at 1- and 2-year follow-up, respectively \[P-values compared to BL; Fig. 3(C)\]. No statistically significant differences in dABp were identified between 1- and 2-year follow-ups.

Moreover, the mean ThCcAB did not change over time \[Fig. 3(D)\], implying that newly formed cartilaginous tissue (filling in of denuded areas) was not at the expense of thickness of existing cartilage pre-treatment.

In the least affected compartments no clear changes in cartilage structure were observed and no statistically significant changes at 1- and 2-year follow-up were found compared to BL (data not shown). Changes calculated for the whole joint, showed an improvement in cartilage structure as well, which was most evident and statistically significant for dABp (Table II).

**Radiographic analysis**

Radiographic analysis corroborated the MRI data. The minimum JSW in the MAC showed a statistically significant gradual increase over the 2 years: 51% (0.55 mm, 95%CI 0.09–1.02; \(P = 0.03\)) at 1 year and 59% (0.57 mm, 0.09–1.06; \(P = 0.03\)) at 2 years \(\text{Fig. 4}\). The mean JSW of the MAC shows a similar trend, albeit less striking, with an increase of 24% (0.66 mm, 0.06–1.26; \(P = 0.03\)) and 21% (0.36 mm, -0.13 to 0.85; \(P = 0.11\)) at 1 and 2 years, respectively. A tendency towards a gradual increase in JSW was also observed at the least affected compartment, although the change was not statistically significant \(\text{Fig. 4}\). Averaged JSW of the whole joint also increased \(\text{Table II}\), and subchondral bone density normalized after
a decrease in the first year until just below BL levels at 2-year follow-up (data not shown).

The increase in radiographic mean JSW in the MAC over 2 years demonstrated a good linear correlation with an increase in ThCtAB ($r = 0.67, P < 0.001$) and an inverse correlation with a decrease in dABp on MRI over 2 years ($r = -0.66, P = 0.004$).

**Biomarker analysis**

From 6 months until 2 years of follow-up, a tendency for an increase in collagen type II synthesis marker PIIANP (from 329 ng/mmol creat (249–1977) to 1856 ng/mL (1642–2071); +3% (−8 to 18); P = 0.69), and a clear decrease in collagen type II breakdown marker CTXII (from 329 ng/mmol creat (249–410) to 229 ng/mmol creat (188–269); −31% (−37 to −1); P = 0.006) was found. When expressed as a ratio of PIIANP/CTXII for each patient at each time point, an increase of collagen type II synthesis of 25% (18–103) (from 7.5 (5.2–9.9) to 9.4 (7.7–11.1); P = 0.07) at 2-year follow-up was calculated.

**Relation between clinical benefit and structural changes**

No clear statistically significant correlations between the change in clinical parameters and the change in structural parameters were observed in this small group of patients. There was a slight correlation between the decrease in VAS pain score and the change in subchondral bone density at 2-year follow-up ($r = 0.31, P = 0.06$); at 1-year follow-up the correlation was significant ($r = 0.29, P = 0.05$) (data not shown).

**Discussion**

The present prospective open uncontrolled study demonstrates that joint distraction results in substantial clinical and structural improvement in relatively young patients with end-stage knee OA in such a manner that the original planned total knee prosthesis could be postponed for at least 2 years in all patients. The significant reduction of pain and significant improvement of function is sustained for at least 2 years, and further follow-up is ongoing. Assuming that prolonged benefit of the treatment of these relatively young and active patients, may lead to prevention of revision surgery in time.

Distraction therapy might be perceived as a burdensome treatment for patients because they experience 2 months of joint stiffness and potential pin tract pain/infection during the distraction period. Despite these side effects, the clinical benefit appeared worth the “investment”, as reported by all patients. Moreover, alternative surgical interventions such as osteotomy are at least as burdensome.

One of the most impressive and maybe unexpected results was that the denuded bone areas (dABp) were diminished, and filled with tissue that has the same signal intensity as cartilage, when estimated by MR imaging. This challenges the dogma that intrinsic cartilage repair is not possible. It is difficult to envision that this effect is solely due to an increased matrix synthesis of resident chondrocytes. As such it is postulated that resident mesenchymal stem cells (MSCs) in the joint are important for intra-articular repair activity. Contribution appears to consist of metabolic stimulation of existing chondrocytes or differentiation in an osteogenic manner into new chondrocytes. Hydrostatic dynamic pressure (1–10 kPa), as measured intra-articular during knee and ankle joint distraction when applied in vitro, can stimulate MSCs in coculture with cartilage, leading to cartilage matrix synthesis.

Filling up denuded bone areas contributes to the mechanical competence of the cartilage, as demonstrated by increased JSW under weight-bearing conditions (X-ray). After 2 years of unrestricted loading/mobility, this newly formed tissue is still present, as seen on MR images of the participants, and has functional capabilities. No other treatment at present can induce and preserve such changes in cartilage quantity and morphology.

We can only speculate on the quality of the newly formed cartilaginous tissue; it might be, in part, fibrocartilaginous tissue. Compositional MRI acquisitions, such as dGEMRIC, which could potentially provide clues on the biochemical and structural composition of the newly formed tissue, were not included in the
In conclusion, this study shows that clinical improvement by KJD treatment is sustained for at least 2 years and the partially, newly formed cartilage-like tissue is stable and mechanically effective to the extent that the JSW increases at radiographic examination under weight-bearing conditions. As a result, KJD can postpone a TKR for at least 2 years and, assuming prolonged benefit, possibly prevent revision surgery. Ideally, this new joint sparing treatment should be further investigated in comparison to, or in combination with, other treatments such as DMOADs and cell-based therapies. Next steps for joint distraction should include prolonged follow-up and randomized controlled trials in which KJD is compared with currently used surgical treatments such as TKR and osteotomy. This will provide more knowledge on the ‘position’ of KJD as a treatment option for end-stage knee OA for relatively young patients.

Contributions

KW collected, analyzed and interpreted the data, drafted the first version of the manuscript and performed the statistical analysis. PMR designed the study and provided patients. FI designed the study and collected data. SC and FE offered technical support and analyzed and interpreted the data. SCM analyzed and interpreted the data, supported the statistical analysis and offered technical and logistical support. PPJG obtained the funding, designed the study, analyzed and interpreted the data and supported the statistical analysis.

All authors contributed in the critical revision of the article for important intellectual content and all authors approved the final manuscript.

Role of funding source

This study was funded by the Dutch Arthritis Association.

Competing interests

FE is co-owner and CEO of Chondrometics GmbH.

Acknowledgments

We thank Ms. Sarah Opitz for spelling and grammar corrections.

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