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ORIGINAL RESEARCH

Joint distraction using a purpose-built device for knee osteoarthritis: a prospective 2-year follow-up

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ABSTRACT

Objective Knee distraction treatment for end-stage osteoarthritis successfully postpones arthroplasty for years. Studies performed thus far used general intended use, patient-personalised or custom-made devices. In this study, for the first time, a device specifically designed for knee distraction is evaluated.

Design 65 patients (≤65 years) with end-stage knee osteoarthritis indicated for arthroplasty received knee distraction. Before, 1-year and 2-year post-treatment, questionnaires were filled out and knee radiographs made. Adverse events and self-reported pain medication were registered.

Results Forty-nine patients completed 2-year follow-up: one patient did not complete treatment, three patients received arthroplasty in the first and four patients in the second year follow-up. Eight patients were lost to follow-up in the second year. The total Western Ontario and McMaster Universities Osteoarthritis Index score showed a clinically relevant improvement at 1 and 2 years (+26 and +24 points), as did all subscales (all p<0.001). The minimum radiographic joint space width improved over 1 (+0.5 mm; p<0.001) and 2 (+0.4 mm; p=0.015) years, as did the physical Short-Form 36 (+10 points; p<0.001). The most common adverse event was pin tract infection, experienced by 66% of patients, in 88% successfully treated with oral antibiotics. In two cases, hospitalisation and/or intravenous antibiotics were needed. Eight patients experienced device-related complications. None of the complications influenced 2-year outcomes. Before treatment, 42% of patients used pain medication, which had nearly been halved 1 (23%; p=0.02) and 2 years (29%; p=0.27) post-treatment.

Conclusions Patients treated with a general applicable, for knee distraction purpose-built device showed, despite adverse events, significant clinical and structural improvement over 2 years.

Trial registration number NL7986.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Knee distraction treatment for end-stage osteoarthritis results in clinical and structural improvement and successfully postpones arthroplasty for years, but has thus far been performed using general intended use, patient-personalised or custom-made devices in relatively small clinical trials.

WHAT THIS STUDY ADDS

⇒ In this biggest knee distraction trial thus far conducted, 65 knee osteoarthritis patients were treated with 6-week knee distraction using a dedicated distraction device, developed specifically for knee distraction treatment and appropriate for use in regular care. Treatment resulted in significant structural and clinical improvement, as well as a significant reduction in use of pain medication at 1 and 2 years after treatment compared with pretreatment use. Despite the significant burden of treatment, including often occurring pin tract skin infections, knee distraction treatment can be an alternative to arthroplasty for relatively young patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Results from this study are important for implementation of knee distraction treatment in regular clinical care, but also for implementation of other joint-preserving treatments or newly developed dedicated devices.

INTRODUCTION

Knee distraction (KD) is a surgical technique increasing the joint space width (JSW) around 5 mm for a minimum of 6 weeks by use of an externally applied distraction device. This treatment for end-stage knee osteoarthritis (OA) under the age of 65 years is clinically effective in reducing pain and improving function as experienced by patients, and results in joint tissue repair activity, according to systematic reviews and meta-analyses of multiple open prospective studies and randomised controlled trials (level I evidence).[1 2] Postponement of initially indicated knee arthroplasty (KA) was reached for over 5 years up to even 10 years in three-quarters and half of the treated patients,

Figure 1 The purpose-built distraction device as used.

respectively, providing a relevant alternative treatment modality for the younger patient.[3 4] As a result, this joint-saving treatment can prevent revision arthroplasty in significant numbers,[5] making KD treatment a potentially cost-effective alternative.[6]

However, most studies have been performed with a 'proof-of-concept' medical device intended for a wide variety of orthopaedic and trauma applications (Monotube Triax External Fixation System, Stryker, Switzerland),[7 8] with Ilizarov ring fixators,[9] or in case series with personalised custom-made devices.[10] None of these devices were specifically intended for KD in the general population and all were lacking optimisation with respect to usability, which could potentially reduce treatment burden for patients during the 6-week distraction period. Moreover, the surgical procedure with these devices is unnecessarily complex for general implementation of KD treatment.[10] The University Medical Center Utrecht (UMC Utrecht, Utrecht, The Netherlands), therefore, developed a device specifically intended for KD treatment,[11–13] which has been licensed to a UMC Utrecht spin-off company (ArthroSave BV, Culemborg, The Netherlands). This device (shown in figure 1) incorporates relevant mechanical characteristics and important usability aspects, including the surgical technique, based on knowledge from previous studies.

This study evaluates the efficacy of this purpose-built device over 2 years after treatment, based on changes in clinical outcomes, cartilage thickness (radiographic JSW), quality of life, adverse events and pain medication use. While 2 years is a relatively short follow-up and future longer follow-up will be necessary, a large treatment effect has previously been seen 2 years after KD treatment. As such, the hypothesis was that KD with this purpose-built device provides relevant benefit to patients 2 years after treatment, thereby providing a joint-preserving technique in the treatment of end-stage knee OA at a relatively young age.

METHODS

Patients

Patients with end-stage knee OA, defined by persisting, conventional treatment-resistant pain with significant cartilage tissue damage, in general practice considered for KA or high tibial osteotomy (with axis deviation up to 10 °), were offered KD by the orthopaedic surgeon as alternative joint-preserving treatment. Patients (n=65) were included in five hospitals: Martini Hospital Groningen (n=23), University Medical Center Utrecht (n=21), Amphia Hospital Breda (n=11), Antwerp University Hospital (n=7) and Maastricht University Medical Center (n=3). An aim of 75 included patients was described in the original research protocol (WHO trial ID NL7986). Because of a low inclusion rate this number was lowered to 65 which, according to the original sample size calculation as described in the protocol, remained sufficient. With an alpha of 0.05, power of 0.8 and effect size of 0.46 based on results from previous studies (based on a 5-year change in JSW, which previously showed the lowest effect size, of 0.43 mm with SD 0.94),[14] the required sample size was 40 patients.

Inclusion criteria were as follows: age ≤65 years, body mass index <35 kg/m^2 with max 110 kg body weight, normal-good physical condition (judged by the orthopaedic surgeon), sufficient knee joint stability (judged by the orthopaedic surgeon), sufficient range of motion (judged by orthopaedic surgeon), radiographic signs of joint damage: Kellgren-Lawrence (K-L) grades 2–4 (judged by the orthopaedic surgeon) and a Numeric Rating Scale (NRS) for pain >4/10 (conservative treatment resistant).

Exclusion criteria were as follows: patients who would not be considered for arthroplasty or osteotomy because of psychosocial condition, comorbidities that would compromise the efficacy of KD (judged by the orthopaedic surgeon), history of inflammatory or septic arthritis, knee malalignment of more than 10 degrees; previous surgical interventions of the index knee <6 months ago, absence of any radiographic JSW on both sides (medial and lateral), presence of an endoprostheses elsewhere.

Inclusion and exclusion criteria corresponded to instructions for use of the purpose-built device and were applied as they would be in regular care (eg, a patient with K-L grade 2 as judged by orthopaedic surgeon as in regular care would be included; central reading on the baseline study radiograph was not used for this).

Intervention

Patients were treated with KD according to a standardised protocol and with a distraction device built for KD (KneeReviver, ArthroSave BV, The Netherlands; ArthroSave BV was not involved in financing, design, nor conduction of the study). Distraction was performed by fixating two distraction elements, bridging the joint medially and laterally, according to instructions for use as provided by the manufacturer using a total of eight bone pins. A distraction distance of 2 mm was applied intraoperatively and gradually distracted further, twice a day by 0.5 mm, until 5 mm distraction was reached within 3 days after surgery.[15] During the distraction period weight-bearing was encouraged. After 6 weeks, the distraction device was removed, and knee manipulation under anaesthetic was performed at day treatment.

Outcomes

The primary objective was to document clinical efficacy of KD with the purpose-built device by two main (coprimary) outcomes: an increase in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; main clinical outcome) score and increase in radiographic minimum JSW (min-JSW; main structural outcome) at 1-year and 2-year follow-up compared with baseline. Secondary objectives were to document changes in general well-being after distraction by the Short-Form 36 (SF-36) Physical Component Scale (PCS) and Mental Component Scale (MCS) and to document subsequent surgical procedures after distraction. Additional objectives were to document NRS pain, JSW per compartment (most affected and least affected tibiofemoral compartment; MAC, LAC determined at baseline), mean joint JSW, OA-related pain medication and intra-articular injections and adverse events.

The Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire was used to obtain WOMAC scores. Additionally, questionnaires were used for NRS pain and SF-36. For the WOMAC and NRS pain, the results at screening and just before surgery were averaged to obtain baseline values. SF-36 was only obtained at screening providing baseline values. For WOMAC and SF-36, higher values indicate a better condition, while for the NRS pain lower values indicate a better condition. All KOOS subscales were evaluated as well.

Tissue structure was evaluated by standardised weight-bearing, semiflexed posterior–anterior radiographs, performed according to the Buckland-Wright protocol at screening and at 1-year and 2-year follow-up.[16] Images of all included patients were checked per triplet for each patient for consistency of acquisition between all time points by two observers (MPJ and FL; blinded to time order). In case of technical inconsistencies between acquisitions, the radiographic outcome was omitted from analyses, which occurred in one case (designated as missing data). During this acquisition quality check, K-L grade was assessed by the same observers for all baseline images. All images were evaluated using knee images digital analysis software to analyse the JSW (minimum, mean of the MAC, mean of the LAC and mean total).[17] All image analyses were performed by a single, experienced observer (MM), blinded to patient characteristics. The intraobserver variation of this measurement method was shown to be good (for the main outcome min-JSW, intraclass correlation coefficient (ICC)=0.965).[18]

Adverse events were documented over the 2 years follow-up and are presented in different categories during distraction and during the first and second year of follow-up. Adverse events were defined as any undesirable experience occurring to a subject during the study, potentially related to the treatment. All events reported spontaneously by the subject or observed by the investigators or staff were recorded.

Self-reported pain medication was registered at baseline and at 1-year and 2-year follow-up. At each of the time points, patients were asked whether they had used pain medication during the last week before filling out the questionnaires and whether they obtained intra-articular injections. Three categories of pain medication were defined: paracetamol, opioids and non-steroidal anti-inflammatory drugs (NSAIDs), in addition to intra-articular injections.

Statistical analyses

Paired t-tests were used to calculate changes at 1- and 2 years compared with baseline for all parameters, except the change in pain medication use, which was analysed with McNemar symmetry χ^2 tests. The number of responders was calculated for the two main outcomes, using the OARSI-OMERACT criteria[19] for total WOMAC and smallest detectable difference (SDD)[18] for min-JSW; patients with follow-up surgery were counted as clinical non-responders as well. Missing data were not replaced. Specific sensitivity analyses were performed to address potential bias, comparing main and secondary outcomes between: patients with and without follow-up surgery after 1 or 2 years, patients who did and did not retrospectively meet inclusion criteria, patients with and without device-related complications, patients with and without pin tract infections, and patients who did and did not use pain medication before treatment. These analyses were descriptive (low numbers), except for patients with and without pin tract infections (sufficient numbers), where differences were analysed with independent t-tests. Correlations between changes in the two main outcome parameters, total WOMAC and min-JSW, were analysed with Pearson correlations. In all cases, p values<0.05 were considered statistically significant.

RESULTS

Patients and follow-up

The number of patients over the 2 years of follow-up is illustrated in figure 2. Due to a low inclusion rate within a confined inclusion period, 65 of the 75 patients intended for participation received distraction treatment. Lost to follow-up was reported after arthroplasties in three patients in the first (all unilateral KA; UKA) and four patients in the second (one UKA, three total KA; TKA) year; the reason why patients opted for follow-up arthroplasty soon after KD treatment was not documented. One patient did not receive full treatment, as the distraction device was removed halfway due to a broken pin. Partially the result of COVID restrictions, follow-up of 8 patients was missed for the second year of follow-up.

The baseline characteristics of the 65 included patients are shown in table 1.

The patients who received arthroplasty during the follow-up did not differ significantly in baseline characteristics from the overall population (online supplemental table S1), except for both subscales of the SF-36, which were statistically significantly lower (worse condition) for the patients who got an arthroplasty. Note that seven

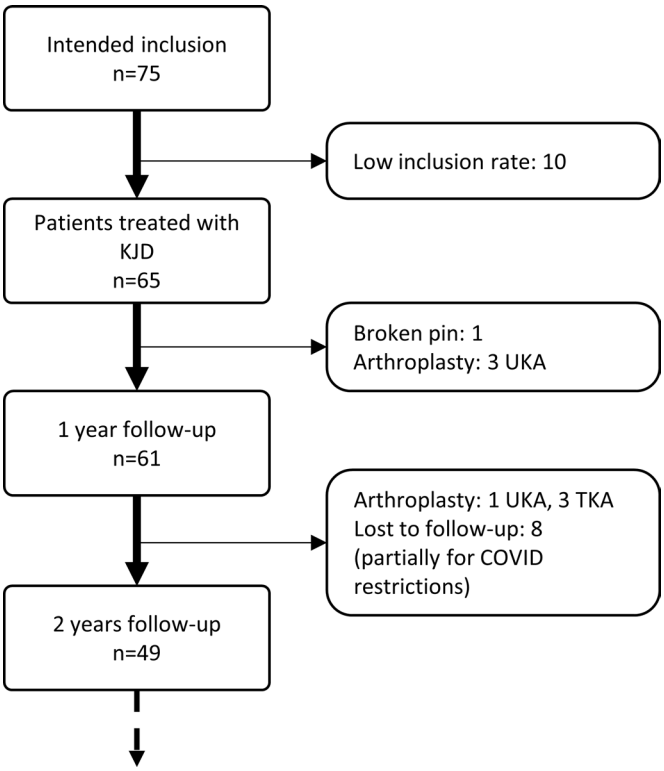

Figure 2 Overview of the number of patients involved during the first 2 years of follow-up. Of the total of 75 patients intended, 65 were included within the assigned inclusion period. One patient did not complete treatment due to a broken pin. Three patients received an unicompartmental knee arthroplasty (UKA) due to unsatisfactory response to distraction in the first year after distraction treatment. One patient received an UKA and three patients a total knee arthroplasty (TKA) between the first and second year after distraction treatment. Eight patients were lost to follow-up at 2 years, partially due to COVID-19 restrictions.

Table 1 Baseline characteristics of the 65 included patients

Parameter	Unit	Mean±SD or n (%)
Age	Years	53.3±6.7
Male sex, n (%)	n (%)	38 (59)
BMI	kg/m^2	28.0±3.3
WOMAC total	0–100	43.5±17.2
WOMAC pain	0–100	45.5±17.4
WOMAC stiffness	0–100	38.6±21.6
WOMAC function	0–100	46.7±16.8
NRS pain	10–0	6.8±1.5
JSW minimum	mm	0.9±1.2
JSW mean MAC	mm	2.6±1.8
JSW mean LAC	mm	7.7±2.0
JSW mean total	mm	5.1±1.1
SF-36 PCS	0–100	32.6±7.1
SF-36 MCS	0–100	53.2±10.8
Medial MAC	n (%)	58 (89)
Kellgren-Lawrence grade	n (%)	
0/1/		0 (0)/7 (11)/
2/3/4		26 (40)/23 (35)/9 (14)

The mean and SD or number of patients and percentage are given. BMI, body mass index; JSW, joint space width; LAC, least affected compartment; MAC, most affected compartment; MCS, Mental Component Scale; NRS, Numeric Rating Scale; PCS, Physical Component Scale; SF-36, Short-Form 36; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

patients had a K-L grade of 1 according to centralised reading, whereas they were included by judgement of the orthopaedic surgeon with a K-L grade of 2 (or higher) according to inclusion criteria. This might have been the result of different radiographic acquisitions before and during study inclusion, as K-L grade could have been judged (without official grading) by the orthopaedic surgeon on knee radiographs performed with Rosenberg view (clinical care radiographs), while central K-L reading was performed on radiographs performed with Buckland-Wright view (trial radiographs).

Main and secondary outcomes

Changes from baseline to 1 year and to 2 years follow-up are provided for all parameters, including baseline values in online supplemental table S2. Joint distraction resulted on average in a statistically significant (p<0.001) and clinically relevant (>15 points on the WOMAC scale[20] improvement (figure 3A,B). The effect sustained for 2 years. After 1 year 72% of patients were clinical responders, at 2 years this was reduced to 55%.

All WOMAC subscales, KOOS scales, as well as NRS pain, showed similar, statistically significant and clinically relevant results (see online supplemental table S2 and online supplemental figure S1).

Joint distraction resulted on average in a statistically significant (p<0.001) increase in min-JSW (figure 3C,D) that sustained for 2 years. Also, for mean JSW of the MAC and total JSW a statistically significant increase was observed (see online supplemental table S2). In 38% and 29% of the patients an increase in min-JSW of more than the SDD (0.61 mm) was reached at 1-year and 2-year follow-up, respectively.[18]

A statistically significant (p<0.001) increase in SF-36 PCS (figure 4A,B) was observed that sustained for 2 years. The SF-36 MCS (figure 4C,D) did not change statistically significantly.

Complications

Complications registered within the first 2 years of follow-up are categorised and -summarised in table 2 for the period during treatment, after treatment within 1-year follow-up, and between the first and second year of follow-up. The most common complications were directly related to the distraction device and the surgical technique, with pin tract skin infections occurring most frequently, in 66% of treated patients, comparable to

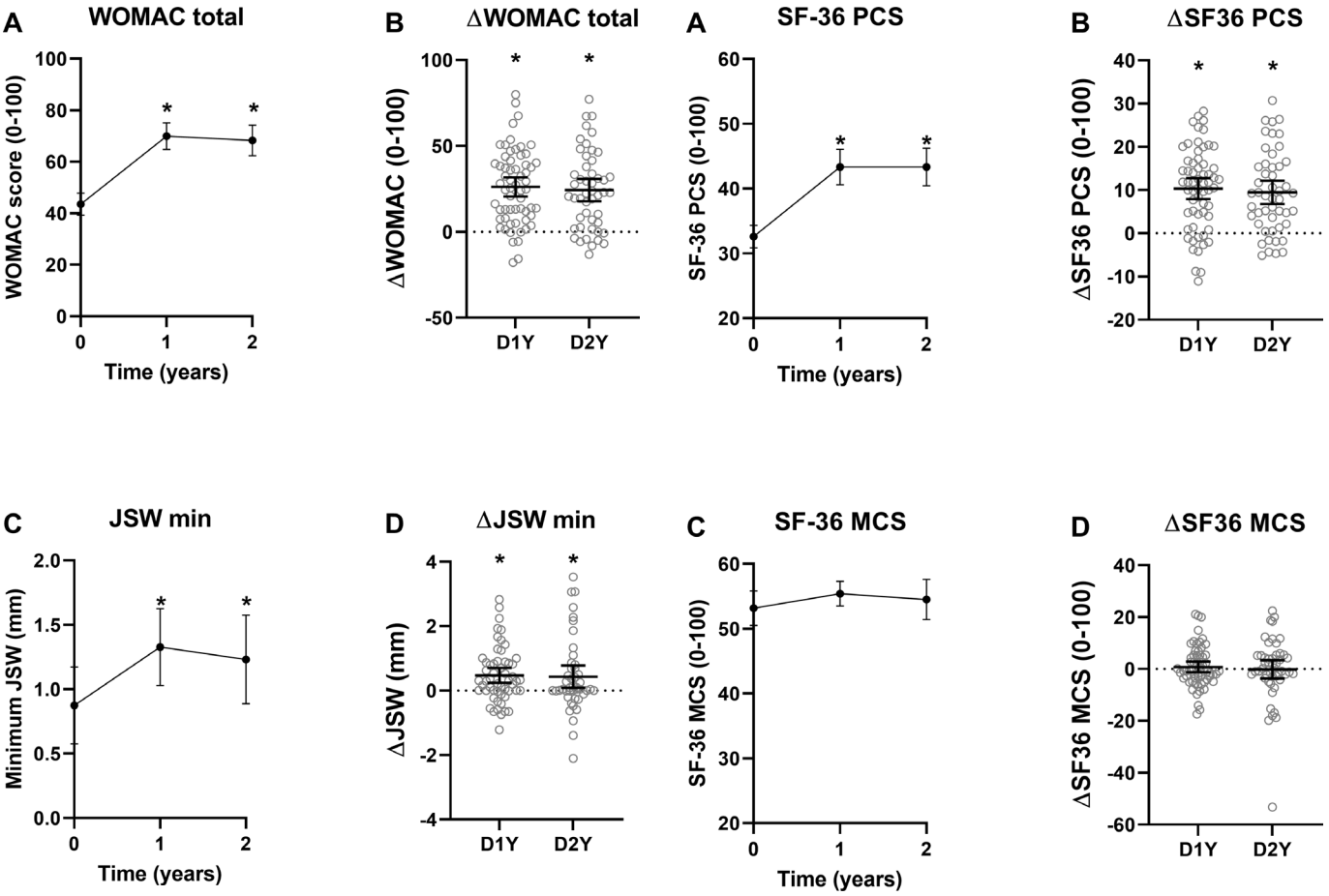

Figure 3 Total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score (A) and minimum joint space width (JSW) (C) at baseline (pretreatment) and 1-year and 2-year follow-up as well as the change from baseline to 1 year and baseline to 2 years of follow-up for both parameters (B and D, respectively). The mean and 95% CI are shown in all panels, with markers in B and D representing individual patients. Asterisks indicate statistically significant differences (p<0.05) from baseline values.

Figure 4 The Short-Form 36 (SF-36) Physical Component Scale (PCS) (A) and Mental Component Scale (MCS) (C) at baseline (pretreatment) and 1 and 2 years follow-up as well as the change from baseline to 1 year and baseline to 2 years of follow-up for both parameters (B and D, respectively). The 95% CIs are shown in all panels, with markers in B and D representing individual patients. Asterisks in A and B indicate statistically significant differences (p<0.05) from baseline values.

previous KD studies.[21] In most cases (88% of infection cases) infections could be treated successfully with oral antibiotics, although in two patients (3% of total patients) intravenous antibiotics and corresponding hospital admission were needed, which is somewhat less than the 10% reported in previous studies.[21]

Pain medication

Self-reported use of pain medication during the week prior to surgery, 1 year and 2 years follow-up is provided in table 3. A 33%–50% reduction in use of pain medication (excluding injections) compared with baseline was achieved at 1 (p=0.02) and 2 years (p=0.27). Additionally, intra-articular injections were documented based on patient report (table 3).

Sensitivity analyses

For all main and secondary clinical and structural outcomes, patients who were lost to follow-up between 1 and 2 years after treatment showed similar 1-year results as the other patients (online supplemental figure S2). However, patients who received an arthroplasty in the second year, clearly showed worse 1-year results for the total WOMAC and SF-36.

Patients who had a K-L grade of 1, and thus retrospectively did not meet inclusion criteria, did not differ from the other patients in the main and secondary clinical and structural outcome at both 1 and 2 years after treatment (online supplemental figure S3).

None of the complications related to the device (item 7 in table 2) were found to (negatively) relate to the main/secondary outcome (online supplemental figure S4). Patients with pin tract-related complications (item 1 in table 2) did not show significant differences in response for the main and secondary outcomes either (all p>0.11; online supplemental figure S5).

Use of pain medication at baseline did seem to affect main and secondary outcomes (online supplemental figure S6).

Table 2 Overview of registered complications

	During treatment	Within 1 year after treatment	Between 1 and 2 years after treatment
	n (%)	n (%)	n (%)
Pin tract infection—action:	**43 (66)**	**1 (2)**	–
Oral antibiotics	38 (59)	1 (2)	–
Hospitalisation and/or intravenous antibiotics	2 (3)	–	–
Wound cleaning at day care	1 (2)	–	–
Day care without follow-up needed	1 (2)	–	–
Undefined	1 (2)	–	
Pain/discomfort treated knee—action:	**9 (14)**	**2 (3)**	
Pain medication	2 (3)	–	
No action	7 (11)	2 (3)	
Flexion limitation	**–**	**2 (3)**	–
Pain/discomfort elsewhere	**3 (5)**	**1 (2)**	**2 (3)**
Contralateral knee	–	–	2 (3)
Back and bladder	1 (2)	–	–
Other	1 (2)	1 (2)	–
Cardiovascular	**2 (3)**	–	–
Thrombosis with additional anticlotting	1 (2)	-	–
Suspected vain complications+pain medication	1 (2)	–	–
Defect tibia cortex	**–**	**1 (2)**	–
Device related	**8 (12)**		
Distraction distance deviation	4 (6)		
Loose bone pin(s)	1 (2)		
Broken bone pin(s)	1 (2)		
Device repositioned	1 (2)		
Device failure	1 (2)		

Complications are shown within the first 2 years of follow-up in seven categories during treatment, after treatment until 1-year follow-up, and between the first and second year of follow-up. The number and percentage of patients are given. Bolt numbers represent the total complications per category. Detailed explanation of device related complications: (1) Deviation of the initially set amount of distraction (5 mm) was reported for four cases; distraction was restored for the remaining treatment period. (2) Remarkable loosening of bone pins in the bones was reported for one patient. From oral communications with involved surgeons, it appeared that reduced bone pin fixation at removal after 6 weeks treatment was observed regularly, which was considered inevitable aspect of the surgical technique. (3) Broken bone pins were observed in one case halfway the distraction period (at 3 weeks); the distraction device was subsequently removed and KD treatment was not completed. The pin fragments did not protrude from the outer cortex and were kept in place. (4) Device failure consisted of a broken tube, discovered at frame removal and not affecting treatment.

DISCUSSION

As hypothesised, patients treated with KD using the purpose-built device showed clinical benefit at 1 year which was maintained over the second year of follow-up. WOMAC score increased on average statistically significant and the relevant number of patients was clinical responder, suggesting a clinically meaningful improvement. Min JSW increased in a smaller but still relevant number of patients with more than the SDD at patient level, on average statistically significant. Of the secondary outcome paraments the only parameter that did not show a significant change was the SF-36 MCS. This was anticipated since this parameter is insensitive to knee OA treatments in general. In previous studies high tibial osteotomy and TKA did not induce a change in this parameter either.[8 22 23]

In short, outcomes after KD treatment with the purpose-built device were overall quite similarly as previously reported with general use devices.[1] Compared with the general use device, the purpose-built device appeared more user-friendly and reduced surgery time by 20%, but that has been reported previously and was not the focus of the current study.[24]

A limited number of patients (11%) received arthroplasty within 2 years post-treatment. Those receiving arthroplasty in the second year showed worst WOMAC and SF-36 PCS outcomes after 1 year. Interestingly, patients who received a prothesis shortly after KD had a

Table 3 Overview of self-reported use of pain medication

	Screening	1 year	2 years
	n (%)	n (%)	n (%)
	n=65	n=61	n=49
Pain medication used	28 (43)	14 (23)	14 (29)
		p=0.02	p=0.27
Paracetamol	**20 (31)**	**11 (18)**	**8 (16)**
On demand	11 (17)	7(11)	4(8)
Daily	9(14)	4 (6)	4 (8)
Opioids (incl oxynorm, oxycontin, tramadol)	**3 (5)**	**2 (3)**	**1 (2)**
On demand	2 (3)	2 (3)	–
Daily	2 (3)	–	1 (2)
NSAIDs (including arcoxia, meloxicam, peroxicam, diclofenac, ibuprofen)	**16 (25)**	**9 (15)**	**9 (18)**
On demand	8 (12)	4 (6)	3 (6)
Daily	9 (14)	5 (8)	6 (12)
Injection	**12 (18)**	**1 (2)**	**1 (2)**
Steroids	5 (8)	–	–
Hyaluronic acid	3 (5)	–	1(2)
Undefined	4 (6)	1 (2)	-

Medication at the week prior to surgery, 1 year and 2 years of follow-up. The number of patients with percentage is provided for all defined medication categories: paracetamol, opioids, NSAIDs and injections. Bolt numbers show the total use of each type of pain medication (excluding intra-articular injections). At 1 year, a statistically significant reduction in use of pain medication of 47% (p=0.02) was observed. The 33% reduction at 2 years was not statistically significant compared with baseline (p=0.27).
NSAIDs, Non-steroidal anti-inflammatory drugs.

statistically significantly worse mental and physical health (SF-36 score) before KD treatment. This suggest that preoperative evaluation of well-being and mental status is relevant for effective treatment of an individual patient with KD. These patients may have a neuropathic pain component in which the pain is less related to the cartilage tissue damage but with the same functional limitations and may be less eligible for KJD.[25]

A clear reduction of up to ~50% in general pain medication after KD in the first year was observed, which sustained in the second year postdistraction treatment, although not statistically significant. This indicates a reduction in pain after treatment and confirms the improvements seen in NRS pain and WOMAC pain scores. It also shows for the first time that these changes in patient reported outcomes after KJD are not driven by an increase in pain medication.

The most common complication was pin tract skin infection, as has been reported previously for KD treatment and use of external fixation frames in general.[21] Especially for the two patients who required hospital admission with intravenous drug administration, these pin tract infections greatly increase the burden KD treatment places on the patient. Reducing infections remains an important improvement to patient experience, in which care protocols may be effective.[26] Also, while device-related complications occurred in 12% of patients, only in one case (the broken pin) this resulted in patient discomfort, and neither pin tract infections nor device-related complications were shown to affect treatment primary outcomes or physical health.

While these first analyses show positive results for the purpose-built device, the long-term results are still unknown. About half of patients (42%) had a min-JSW increase of more than 0.5 mm. This has previously been concluded an indicator for long-term up to 9 years clinical benefit.[3]

Although both the main outcomes (the total WOMAC score and min-JSW) improved significantly at 1 and 2 years, the correlation between the changes in both were poor and not statistically significant (R=0.141; p=0.355). This could point to independent pathological pathways that apparently can both be influenced independently by KD. This could be related to different subtypes of knee OA, for example, a bone changes-enhanced pain phenotype in which KD influences pain via bone changes[27–29] or a synovial changes-enhanced cartilage damage phenotype, in which KD influences JSW via synovial stem cell recruitment and activation.[30] Clearly, this is all speculative and needs further study.

This study had several limitations. First, a clear limitation was that patients were not randomised with the standard of care such as a joint arthroplasty or osteotomy nor with other devices (eg, the Stryker Monotubes) used in earlier studies. The ethical committee of the UMC Utrecht did not allow a direct comparison with the previously used device, since the purpose-built device was considered more user-friendly according to self-reported data.[24] The absence of a randomisation and comparison with arthroplasty may have resulted in a selection of patients who preferred distraction treatment maintaining their native knee as compared with replacement by metal and plastic. This specific motivation may have led to a bias in the clinical outcome after treatment. Therefore, randomisation to standard of care treatment for future studies is still warranted. The uncontrolled setup of the study, without a control group receiving sham surgery, might have resulted in a placebo effect for clinical improvement. However, clear structural improvement was also observed, which is less likely to be affected by the placebo effect.

Another limitation was the patients lost to follow-up. Data of a reduced number of patients were analysed at 2 years follow-up, which was partially due to COVID-19 restrictions. The data set, however, remained sufficiently powered for statistical analyses on the main outcomes, although secondary outcomes should be considered more exploratory as the study was not primarily powered for those outcomes. Also, data of these patients at 1-year

follow-up were equally distributed over the total group, indicating that the data obtained at 2-year follow-up remain representative for the entire group of treated patients.

In conclusion, the presently studied purpose-built device, generally applicable with intended use 'KD', enables successful KD treatment for relatively young patients as an alternative to arthroplasty with good clinical and structural improvement over at least 2 years, despite the significant burden of treatment. Long-term follow-up as well as randomisation to KA studies are still warranted.

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