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1 **Systematic review**

2 Is Knee joint distraction a viable treatment option for knee OA? - a literature review and
3 meta-analysis

4

5 **Abstract**

6 **Background:** Knee joint distraction (KJD) is a new application of an established
7 technique to regenerate native cartilage using an external fixator. The purpose of this
8 study is to perform a systematic review and meta-analysis of the literature to determine
9 whether KJD is beneficial for knee osteoarthritis and how results compare to established
10 treatments.

11 **Methods:** Studies assessing the outcomes of KJD were retrieved, with three studies
12 (one cohort, two randomized controlled trials), 62 knees, meeting inclusion criteria. The
13 primary outcome was functional outcome, assessed using a validated outcome score, at
14 one year. Secondary outcomes included: pain scores, structural assessment of the joint
15 and adverse events.

16 **Results:** KJD is associated with improvements in WOMAC from baseline to one year
17 as well as reductions in pain scores and improvements in structural parameters assessed
18 radiographically and by MRI. KJD is not associated with decreased knee flexion, but is
19 associated with a high risk of pin site infection. In patients aged 65 years or under at one
20 year no differences in WOMAC or pain scores was detected between patients managed
21 with KJD compared to high tibial osteotomy or total knee arthroplasty.

22 **Conclusions:** KJD may represent a potential treatments for knee arthritis though further
23 trials with longer term follow up are required to establish its efficacy compared to
24 contemporary treatments.

25

26 **Keywords:**

27 Knee osteoarthritis; knee joint distraction; total knee arthroplasty; high tibial osteotomy;
28 outcomes; complications.

29

30 **Level of evidence:** Level I (systematic review and meta-analysis)

31

32 **Introduction**

33 Knee osteoarthritis (OA) is the most common musculoskeletal disease
34 estimated to affect 3.8% of the world's population [1]. Considered a disease of the
35 whole joint, knee OA is characterized by loss of cartilage, bone remodeling and
36 inflammation. Cumulative joint degeneration eventually leads to substantial loss of
37 function and quality of life, and represents a major cause of global disability [1,2]. The
38 burden of OA is set to increase with rising obesity levels and an ageing population [1,3].
39 Gold standard treatment for OA of significant severity is joint arthroplasty after initial
40 conservative treatment. Beyond arthroplasty, no other treatment is proven effective in
41 halting or reversing disease progression. Globally, the prevalence of knee OA peaks at
42 50 years [1]. However, both patients and surgeons are reluctant to replace joints where
43 the patient is expected to outlive the lifespan of the prosthesis as there is a greater risk
44 of revision surgery [4-6].

45 Consequently, there is an increasing need for alternative treatments for this
46 younger OA population. Not least because of the increased failure risk [5] but also
47 because in some cases arthroplasty may result in poor clinical outcomes [7]. Following

48 injury and osteoarthritis in the ankle, ankle joint distraction has provided a useful means
49 of reducing pain, improving function and increasing radiological joint space [8].
50 Likewise basilar thumb arthritis has been effectively treated with joint distraction and
51 debridement in small prospective studies [9]. There are a certain risks of infection at pin
52 sites and related bone infection often observed in any surgical procedure using external
53 frame and pins or wires, however, such joint sparing alternatives are useful for patients
54 who wish to preserve the native joint.

55 A similar approach has been adopted to treat knee OA with knee joint
56 distraction (KJD). KJD uses an external fixator to unload the joint by distracting the
57 tibia and femur [10]. It is reported that this temporary mechanical unloading allows
58 natural intrinsic repair processes to regenerate cartilaginous tissue evidenced by a
59 sustained clinical benefit and increase in joint width space [11]. With KJD being a joint
60 sparing procedure aimed at postponing a first prosthesis, successful clinical adoption
61 could significantly improve patients' quality of life and thus reduce the long-term
62 healthcare costs associated with knee OA.

63 The aims of this systematic review are to identify and examine the current

64 evidence for the use of KJD focusing on clinical and radiological outcomes. This review
65 will also help to identify gaps in our understanding and so inform future clinical and
66 scientific studies.

67

68 **Material and methods**

69 **Inclusion and exclusion criteria**

70 Eligible studies included those involving patients aged 18 years or older with
71 knee arthritis that compared surgical KJD against other surgical procedures for knee
72 arthritis. There were no exclusions based study design or duration of distraction.

73

74 **Information Sources and Search Strategy**

75 Electronic databases (MEDLINE (Ovid), EMBASE (Ovid), Web of Science
76 (ISI Web of Knowledge)) were searched from their inception until 25 February 2018 for
77 studies meeting inclusion criteria. Searches were tailored to individual databases with
78 the search strategy for MEDLINE shown in Appendix 1. In addition, reference lists of
79 reviews and retrieved articles were assessed for further studies as were registers of
80 controlled clinical trials (metaRegister of controlled trials (mRCT)
81 (www.controlled-trials.com/mrct), clinicaltrials.gov (www.clinicaltrials.gov) and the
82 World Health Organization (WHO) International Clinical Trials Registry Platform

83 (ICTRP) (<http://apps.who.int/trialsearch/>). No restrictions were applied based on the
84 publication status. Where necessary authors were contacted for additional information.

85 Studies were assessed independently in duplicate for eligibility and data from
86 eligible studies extracted independently in duplicate into an electronic database (TT,
87 TWH). A risk of bias assessment was performed on included studies.

88

89 **Outcome measures assessed**

90 To assess the outcome of KJD improvements from baseline to one year post
91 intervention were assessed. To compare KJD with other surgical interventions outcomes
92 at one year post intervention were assessed.

93 The primary outcome assessed was functional outcome, assessed using a
94 validated outcome score, at one year following surgical intervention. Secondary
95 outcomes included: pain scores, assessed using a validated pain score, structural
96 assessment of the joint, both radiographic and with MRI and assessment of adverse
97 events. All secondary outcomes were assessed at one year following surgical
98 intervention.

99

100 **Statistical analysis**

101 Heterogeneity of included studies was assessed using the I² statistic and in the
102 event of substantial heterogeneity (I²>85%) a meta-analysis was not be performed. As a
103 degree of variability was expected due to the subjectivity of the outcome measures a
104 random-effects model was used in all cases. For continuous data the mean difference
105 (MD) was calculated along with 95% confidence-intervals (95%CI), calculated using
106 the inverse variance method. For dichotomous data the risk difference along with
107 95%CI was calculated using the Mantel-Haenszel method. Data analysis was performed
108 using standard statistical techniques as described in the Cochrane Handbook for
109 Systematic Reviews of Interventions, using Review Manager-5.3 (The Nordic Cochrane
110 Centre, The Cochrane Collaboration, 2014).

111

112 **Results**

113 Three studies consisting of one cohort study and two
114 randomized controlled trials were identified as meeting inclusion criteria [11-13].
115 Figure 1. The results of the cohort study were reported across three papers with relevant
116 data extracted where reported [11,14,15]. Included studies are outlined in **Table 1** with
117 an assessment of risk of bias presented in Figure 2. All studies were considered at high
118 risk of performance and detection bias as it was not possible to blind surgeons,
119 participants or outcome assessors as to the treatment received. Attrition and reporting
120 bias was assessed as low risk with no loss to follow up at one year reported. As all three
121 studies originate from the same research group it was consider that this presented an
122 unclear risk of bias.

123 Two studies were excluded as they reported the results of arthroscopic
124 microfracture in combination with KJD and it was the authors opinion that, as
125 microfracture is already an established treatment for cartilaginous loss, it would not be
126 possible to delineate any treatment effect seen [16,17]. The first of these studies by Deie

127 *et al.* (2007) reported the outcomes of six knees managed with KJD and microfracture
128 and found at a mean 3 year follow up significant improvements in Japanese Orthopaedic
129 Association Score, VAS pain score and radiographic joint space width [16]. The second,
130 by Aly *et al.* (2011), reported the outcomes of 61 knees, 19 managed with KJD, joint
131 debridement and microfracture and 42 managed with joint debridement and
132 microfracture and found that at a mean follow up of 3 to 5 years the group managed
133 with KJD, joint debridement and microfracture had significantly improved pain,
134 walking capacity, stair climbing and radiographic joint space width compared to
135 baseline whereas those treated with joint debridement and microfracture without KJD
136 did not [17].

137

138 **Outcomes of KJD improvement from baseline to one year post intervention**

139 **Primary Outcome**

140 The Western Ontario and McMaster Universities Osteoarthritis Index
141 (WOMAC) scores at baseline and one year post KJD were reported in all 3 studies, 62
142 patients, with a significant improvement in WOMAC scores, mean difference 28.7

143 points ($p<0.001$; 95%CI 22.6 to 34.8), between baseline and one year post surgery
144 observed. Figure 3. Improvements were seen across all subdomains of WOMAC: pain
145 ($p=<0.001$; MD 29.3 points 95%CI 21.9 to 36.5), stiffness ($p=<0.001$; MD 19.5 points
146 95%CI 8.4 to 30.6) and function ($p=<0.001$; MD 29.5 points 95%CI 23.6 to 35.4).

147 KOOS, ICOAP, EQ-5D and SF-36 were reported in 2 studies, 42 patients.
148 Significant improvements between baseline and one year scores were observed for
149 KOOS ($p<0.001$, MD 23.2 points 95%CI 15.4 to 31.1), ICOAP ($p<0.001$, MD 26.7
150 points 95%CI 17.0 to 36.4) and EQ-5D ($p<0.001$, MD 0.15 points 95%CI 0.06 to 0.23)
151 and all subdomains. Significant improvements between baseline and one year SF-36
152 physical component score ($p=0.009$, MD 7.8 points 95%CI 1.9 to 13.7), but not mental
153 component score ($p=0.41$, MD -1.5 points 95%CI -5.0 to 2.0) were observed.

154

155 **Secondary outcomes**

156 Pain score, assessed using a pain visual analogue score (VAS) 0 to 100 where
157 0 was equivalent to no pain, were reported in all 3 studies, 62 patients. Patients

158 managed with KJD reported significant improvements in pain VAS of 33.3 points
159 ($p < 0.001$; 95%CI 19.7 to 46.9) from baseline to one year post surgery. Figure 4.
160 Structural assessment of the joint was performed radiographically in all 3 studies, 59
161 patients, and by MRI in one study, 20 patients. Between baseline and one year
162 following KJD the radiographic minimum joint space width increased by 0.8mm
163 ($p < 0.001$; 95%CI 0.5 to 1.0; Figure 5) and mean joint space width increased by 0.8mm
164 ($p = 0.003$; 95%CI 0.3 to 1.3). On MRI the mean cartilage thickness over the total
165 subchondral bone area increased from 1.4mm (SD 0.3) to 1.6mm (SD 0.3; $p = 0.03$) on
166 the tibia and from 1.0mm (SD 0.4) to 1.4mm (SD 0.3; $p < 0.001$) on the femur. The
167 percentage of denuded subchondral bone decreased from 16.7% (SD 17.2) to 4.8% (SD
168 8.3; $p = 0.006$) on the tibia and from 27.3% (SD 25.6) to 4.2% (SD 10.2; $p < 0.001$) on the
169 femur.

170

171 **Adverse events**

172 Knee flexion was reported in 2 studies, 42 patients. No change in knee flexion
173 between baseline and one year following KJD was observed ($p = 0.18$; MD 2.4° 95%CI

174 -1.1 to 5.9) from baseline to one year post surgery. Across all three studies, 62 patients,
175 one patient was reported as requiring manipulation under anesthetic at 17 days
176 following frame removal for stiffness.

177 Across all three studies, 62 patients, 42 patients developed single or multiple
178 pin site infection requiring antibiotics. Overall, the risk of developing pin site infection
179 was 69% (95%CI 51 to 87). Figure 6. The risk of developing pin site infection requiring
180 oral antibiotics was 57% (95%CI 33 to 82). The risk of developing pin site infection
181 requiring intravenous antibiotics was 10% (95%CI 1 to 18%). Overall two patients
182 required surgical irrigation and debridement with one developing osteomyelitis three
183 weeks following frame removal.

184 Additional adverse events reported with the use of KJD included pulmonary
185 emboli (2 of 20 patients (10%) in one study), post-operative foot drop managed with
186 ankle foot orthosis (1 patient), failure of the KJD distraction device (1 patient) and
187 breaking of a bone pin during application (1 patient).

188

189 **Outcomes of KJD compared to other treatments**

190 **Primary Outcome**

191 Two randomized controlled trials assessed the outcomes of KJD against other
192 treatments for arthritis, one against high tibial osteotomy, one against total knee
193 arthroplasty. Both studies were conducted in patients aged 65 years and under. At one
194 year no difference in total WOMAC score, or across subdomains, was seen between
195 knees managed with KJD and those managed with HTO ($p=0.25$; MD -5.0 points,
196 95%CI -13.5 to 3.5) or TKA ($p=0.53$; MD -3.0 points, 95%CI -12.5 to 6.5). Figure 7. At
197 one year no difference was seen in KOOS, ICOAP, EQ-5D or SF-36 between treatment
198 groups.

199 Pain score, assessed using a pain VAS 0 to 100 were reported in both studies.
200 At one year no difference in pain VAS was seen between knees managed with KJD and
201 those managed with HTO ($p=0.17$; MD 9.0 points, 95%CI -3.8 to 21.8) or TKA
202 ($p=0.13$; MD 10.0 points, 95%CI -3.0 to 23.0). Figure 8.

203

204 **Adverse events**

205 At one year no difference in knee flexion was seen between knees managed
206 with KJD and those managed with HTO ($p=0.05$; MD 4.0 degrees, 95%CI -0.1 to 8.1)
207 or TKA ($p=0.07$; MD 5.0 degrees, 95%CI -0.3 to 10.3). No difference in the rate of
208 manipulation under anesthetic (MUA) was seen between KJD and HTO ($p=0.40$; RD
209 0.05 95%CI -0.1 to 0.2). A higher rate of MUA was seen with TKA compared to KJD
210 ($p=0.04$; RD 0.14 95%CI 0 to 0.3).

211 The risk of developing infection requiring antibiotics was significantly higher
212 following KJD compared to both HTO ($p<0.01$; RD 0.5 95%CI 0.3 to 0.8) and TKA
213 ($p<0.01$; RD 0.6 95%CI 0.4 to 0.8). This is likely to be secondary to associated risks of
214 using pins which provide a communication between the external environment and lower
215 limb bones into which they are placed.

216

217

218 **Discussion**

219 The main findings of this systematic review are that KJD is associated in
220 significant improvements in functional scores, pain scores and radiographic measures of
221 cartilage thickness at one year post-operatively and in patients aged 65 years or younger
222 has comparable functional outcomes to HTO and TKA. The main limitation of KJD is
223 the occurrence of pin-tract infection was reported in 69% (95%CI 51 to 87) of patients
224 and was significantly higher than that seen in HTO or TKA. At one year no difference
225 in knee flexion, compared to baseline flexion and flexion one year following HTO and
226 TKA, was seen. Whilst MUA following KJD has been reported (one case across three
227 studies, 62 patients) the rate of MUA was found to be significantly lower than the rate
228 observed following TKA.

229 Compared to older patients, in young patients managed with arthroplasty, the
230 risk of implant failure, and subsequent revision burden is high and any intervention that
231 can postpone or reduce the need for the index procedure in this group, and other groups
232 at risk of poor outcomes, is worth considering. This review has found that KJD appears
233 to be a potential alternative treatment option in managing knee OA, and in patients aged

234 65 years or younger the results appear to be as good as HTO and TKA at one year.
235 Whilst these results are promising, the high rate of pin site infection following KJD is a
236 concern because both HTO and TKA can give lower rate of post-operative infection.
237 Despite in the majority of these cases resolution of infection was achieved with oral
238 antibiotics. In very few instances, osteomyelitis has been reported, and surgeons may
239 well have concerns about performing arthroplasty in these cases should KJD fail.
240 However, Wiegant K, *et al.* [18] described the safety to perform TKA following KJD
241 and concluded that it appears safe to treat patients several years following KJD with a
242 TKA.

243 The mechanism by which KJD works is unclear. In the clinical studies of KJD
244 increased radiographic JSW and coverage of denuded bone assessed by MRI were
245 reported. Biomarker analysis has reported that following KJD a decrease in the collagen
246 type II breakdown marker (CTXII) is observed coupled with an increase in the collagen
247 type II synthesis marker (PIIANP) [14,15]. Whilst these findings would suggest that
248 KJD changes the intra-articular environment to one that favors cartilage repair. It is
249 likely that the conflicting results obtained in animal experiments are due to a variety of

250 reasons such as differences in experimental set up, type of surrogate endpoints used to
251 assess cartilage repair and limited follow up. Some studies have shown promising
252 results with evidence of bone and cartilage repair whilst others have failed to
253 demonstrate any advantage with KJD, with some even reporting adverse effect on the
254 cartilage integrity. It is clear from these conflicting observations that more work is
255 needed to establish indeed when and how joint distraction works and in which scenarios
256 [19-26].

257 Alongside the mechanism of action of KJD there are several other areas of
258 uncertainty around this treatment. In the present studies static distraction was applied
259 using two 45 kg springs to permit some degree of joint loading. Whether this represent
260 the optimum distraction force, and whether a hinged distractor, which has been
261 demonstrated to be superior for ankle OA, still needs to be assessed [27,28].
262 Additionally, the patient population most likely to benefit from distraction and optimum
263 duration of distraction remains to be defined. Early reports suggest that men with more
264 severe arthritis are most likely to respond to treatment, and six weeks distraction
265 provides equivalent clinical outcomes to eight weeks distraction however these findings

266 are based on limited data, and appropriately powered trials comparing the outcomes of
267 KJD to other treatments for knee OA are required [29,30]. Finally, further information
268 on the long term efficacy of KJD is required. Current data suggests that, at five years
269 the functional outcomes and structural assessments of joint remain improved compared
270 to baseline, about 70% of the patients treated still have their own knee instead of the
271 initially planned joint prosthesis [11]. At 9 years post distraction, still 50% of the
272 patients continue to manage with their own knee and thereby the need for an artificial
273 joint is avoided. Remarkably mostly women seem to drop out and opt for further
274 intervention although there is no clear explanation for this gender difference [31].

275 The strengths of this systematic review are that is a comprehensive
276 assessment of the efficacy of KJD for the treatment of knee arthritis. The weakness of
277 this review is that it is limited by the data available, with only three studies available for
278 inclusion, with all originating from the same research group.

279 This study has highlighted that KJD may be a valid alternative to HTO and
280 TKA in the treatment of knee arthritis in the young, resulting in improvements in
281 functional and pain as well as evidence of structural improvements within the joint

282 lasting beyond one year. However, further work is required to optimize the technique of
283 KJD, define the optimum population for its use as well as develop methods to reduce
284 the risk of pin site infection, the major complication associated with this technique.
285 Ultimately KJD needs to be assessed pragmatically through appropriately powered
286 multi-center studies designed to assess its long term effectiveness and comparative
287 efficacy against other established treatments for knee OA.

288 **List of abbreviations**

289 EF: External Fixator

290 EQ-5D: EuroQol five dimensions questionnaire

291 HTO: High Tibial Osteotomy

292 JOA: Japanese Orthopaedic Association

293 KJD: Knee Joint Distraction

294 KOOS: Knee Injury and Osteoarthritis Outcome Score

295 PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

296 PROM: Patient Reported Outcome Measures

297 RCT: Randomized Controlled Trial

298 ROM: Range Of Motion

299 TKA: Total Knee Arthroplasty

300 VAS: Visual Analogue Scale

301 WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index

302

303

304 **Conflict of interest**

305 The authors have no financial conflict of interest in this study.

306

307 **Funding**

308 None.

309

310 **Ethical approval**

311 This is a systematic review so ethical approval was waived.

312

313 **Written informed consent**

314 Not applicable.

315

316

317 **Appendix 1: MEDLINE (Ovid) Search Strategy**

318 1. Knee joint/

319 2. distraction.mp. OR arthrodiatasis.mp

320 3. 1. AND 2.

321

322

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