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The effects from total knee replacement followed by non-surgical treatment on pain sensitization and clinical pain - a pre-defined ancillary analysis from a randomized controlled trial

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Conflict of interest: None to declare.

What's already know about this topic?

- Sensitization is important in knee osteoarthritis, but high quality evidence on its treatment is missing

What does this study add?

- Knee replacement followed by non-surgical treatment is more effective in reducing sensitization, but not other pain-related measures, as compared to non-surgical treatment alone at 3 months.

ABSTRACT

Background: The objective was to compare the effect of total knee replacement (TKR) followed by a 3-month non-surgical treatment with the non-surgical treatment alone in reducing pain sensitization and other pain-related measures in patients with knee osteoarthritis (OA).

Methods: One hundred patients were randomized to 1) TKR followed by a non-surgical treatment of neuromuscular exercise, education, diet, insoles and pain medication or 2) the non-surgical treatment alone. Outcomes assessed at baseline and after 3 months were: 1) pain sensitization assessed as pressure pain thresholds (PPTs) at the knee (localized sensitization) and the lower leg (spreading sensitization), 2) peak pain intensity during the previous 24h, 3) pain intensity after 30 min of walking, 4) pain location and pattern, 5) spreading of pain on a region-divided body chart, and 6) the usage of pain medication.

Results: There was a statistical significant mean difference (95% CI) in change in PPTs from baseline to 3 months between groups in the crude analysis of 71 kPa (21-121) and of 75 kPa (33-117) when adjusting for baseline PPT, age, gender and BMI, favoring the group having TKR. There were no significant between-group differences in change in the pain-related measures from baseline to 3 months (P = 0.15-0.27). Both groups improved in most of the pain-related measures ($P < 0.05$).

Conclusions: At 3 months, TKR followed by non-surgical treatment is more effective in reducing localized and spreading pain sensitization than non-surgical treatment alone. Both treatments are equally efficacious in reducing the pain-related measures of this study.

Trial registration: NCT01410409

Keywords (4-6): Knee; Osteoarthritis; Clinical trial; Pain; Sensitization

INTRODUCTION

Pain is the hallmark symptom of knee osteoarthritis (OA) and is believed to be a complex phenomenon encompassing several mechanisms (Dieppe and Lohmander, 2005). Recently, sensitization has emerged as an important pain mechanism in knee OA, especially in patients with more advanced disease severity (Arendt-Nielsen and Graven-Nielsen, 2011,Arendt-Nielsen et al., 2015b,Skou et al., 2014). The International Association for the Study of Pain (IASP) defines sensitization as *increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs* (International Association for the Study of Pain,).

Using a mechanism-based approach sensitization can be assessed in patients with knee OA applying quantitative sensory testing (QST) (Suokas et al., 2012), involving an assessment of the somatosensory response evoked from a controlled painful or non-painful stimuli (Graven-Nielsen and Arendt-Nielsen, 2010). Pressure algometry is one of the most widely used techniques for QST. Pressure pain sensitivity in patients (compared to pain free controls) demonstrated locally at the affected body part can be related to local and/or spreading sensitization (central sensitization) (Arendt-Nielsen and Graven-Nielsen, 2011,Graven-Nielsen and Arendt-Nielsen, 2010). Local and spreading sensitization have previously been demonstrated in patients with knee OA compared to pain-free controls (Arendt-Nielsen et al., 2010,Imamura et al., 2008,Lee et al., 2011,Graven-Nielsen et al., 2012,Kosek et al., 2013,Wylde et al., 2012).

Previous studies assessing the effects of total knee replacement (TKR) on sensitization have demonstrated inconsistent results (Graven-Nielsen et al., 2012,Kosek et al., 2013) and have only been case series thereby being associated with potential bias (Moher et al., 2010). Furthermore, due to the complexity of pain, assessing the effects of TKR on other pain-related measures, such as pain

intensity, usage of pain medication, pain pattern and spreading of pain, could contribute with additional important information for future treatment of patients with knee OA.

Recently, a high-quality randomized controlled trial (RCT) demonstrated that TKR followed by a non-surgical treatment program (exercise, education, weight loss, insoles and pain medication) resulted in greater improvements in pain, function and quality of life as compared to non-surgical treatment alone (Skou et al., 2015). In the RCT, other secondary outcomes were collected to allow for pre-specified ancillary analyses, including an analysis of the effects from the treatment on sensitization and pain (Skou et al., 2014). The aim of this pre-specified ancillary analysis from the RCT was to investigate the effects of TKR followed by the non-surgical treatment program in improving sensitization and other pain-related measures (pain intensity, pain location and pattern, spreading of pain and usage of pain medication) after 3 months compared to the non-surgical treatment alone. The hypothesis was that TKR followed by non-surgical treatment program would improve sensitization and pain more than non-surgical treatment program alone.

METHODS

Study design

This was an ancillary analysis of the 3-month results from a two-arm parallel group assessor-blinded RCT conforming to the CONSORT statement for reporting RCTs (Moher et al., 2010). The analysis was pre-defined in the statistical analysis plan, which was made available before any analyses commenced (Skou et al., 2014).

Details of the study was published in the study protocol (Skou et al., 2012).

Patients

One hundred patients with radiographic (Kellgren and Lawrence score ≥2) (Schiphof et al., 2011) and symptomatic knee OA found eligible for TKR by an orthopedic surgeon were enrolled. Patients were recruited from two specialized, public outpatient clinics at Aalborg University Hospital in Denmark (Frederikshavn and Farsoe, 50 patients from each clinic) between 12 September 2011 and 6 December 2013. Major exclusion criteria were previous knee replacement on the same side; a need for bilateral simultaneous knee replacement; and a mean knee pain intensity in the previous above 60 mm on a 100 mm visual analogue scale (VAS).

All patients gave informed consent before being enrolled, and the study was conducted in accordance with the Helsinki declaration and was approved by the local Ethics Committee of The North Denmark Region (N-20110024). Furthermore, it was registered at ClinicalTrials.gov (NCT01410409).

Intervention

Total knee replacement (TKR)

Patients randomized to TKR followed by non-surgical treatment had a total cemented prosthesis with patellar resurfacing (NexGen, CR-Flex, fixed bearing or LPS-Flex, fixed bearing, Zimmer, Warsaw, Indiana, USA, applying standard methods (Endres, 2011).

Non-surgical treatment

Patients in both groups participated in the non-surgical treatment program at the same facility, but separately to avoid contamination and crossover between treatment groups. The 3-month non-surgical treatment included a prescription of education, exercise and insoles to everyone in the MEDIC group, while weight loss and/or pain medication were prescribed if indicated. The treatments were given by physiotherapists and dieticians at Aalborg University Hospital, Denmark.

Education

Two 60-min sessions actively engaging the patients and focusing on disease characteristics, OA pain and how to control and monitor it during exercise, treatment and help to self-help.

Exercise

The NEuroMuscular EXercise training program (NEMEX), previously found feasible in patients waitlisted for TKR (Ageberg et al., 2010b), was delivered twice weekly with each session lasting 60 min. The program is based on neuromuscular and biomechanical principles and has different levels of difficulty for each exercise (Ageberg et al., 2010b). The exercise program was followed by a transition period of 8 weeks to gradually accustom patients to continue exercising at home.

Dietary advice

Patients who had a body mass index (BMI) ≥25 at baseline underwent a dietary weight loss program based on principles from motivational interviewing (Miller and Rollnick, 2002), consisting of four 60-min sessions, with the aim of reducing body weight by at least 5% (Christensen et al., 2007).

Insoles

The patients received individually fitted full-length Formthotics Original Dual Medium (perforated) insoles with medial arch support (Foot Science International, Christchurch, New Zealand). A 4° lateral wedge was added to the insoles of patients with a knee-lateral-to-foot position (the knee moves over or lateral to the 5th toe in three or more of five trials) tested with the valid and reliable Single Limb Mini Squat Test (Ageberg et al., 2010a).

Pain medication

If indicated, paracetamol 1 g four times daily, ibuprofen 400 mg three times daily, and pantoprazole 20 mg daily were prescribed. The prescription was reassessed every 3 weeks to supervise the use and indications of the medication.

Outcomes

Baseline and 3-month follow-up were carried out at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Denmark. The assessor was unaffiliated with the treatment sites, and specifically trained in all aspects of the assessments. The assessor was blinded to treatment allocation by instructing patients to cover the study knee with three layers of white elastic tape covering a potential scar after TKR surgery before meeting the assessor.

Assessment of sensitization

Bilateral, pressure pain thresholds (PPTs) were obtained using a handheld algometer with a 1 cm^2 probe (Algometer Type II, Somedic AB, Hoerby, Sweden). Applied perpendicular to the skin at a constant rate of 30 kPa/s, pressure was increased until the patient felt the pressure change to pain and pressed a button defining the PPT. To ensure that the patient understood the procedure, one or two test assessments were performed at the dorsal aspect of the hand. A previous assessment of the test procedure in a test-retest reliability and agreement study with 20 patients with knee OA demonstrated intraclass correlation coefficients (2-way random-effects model, consistency-type) and 95 % limits of agreement (95% LOA; presented as the difference between the mean difference and the upper and lower LOA) ranging from 0.84 to 0.91 and 199.6 to 434.0 kPa for the different sites (Skou et al., 2015). The 95% LOA corresponds to the minimal detectable change (MDC) for the assessment method.

Localized sensitization

PPTs from four sites at the knee, all in proximity to the patella were used to assess localized sensitization (peripheral sensitization): (1) 3 cm medial to the midpoint of the medial edge, (2) 2 cm proximal to the midpoint of the superior edge, (3) 3 cm lateral to the midpoint of the lateral, and (4) at the center (Arendt-Nielsen et al., 2010). PPTs were obtained twice at each site, and the mean of all four sites was used in the analyses.

Spreading sensitization

PPTs from the tibialis anterior muscle (lower leg: 5 cm distal to the tibial tuberosity) was used to assess spreading sensitization (central sensitization) (Arendt-Nielsen et al., 2010). PPTs were obtained twice and the mean was used in the analyses.

Assessment of pain

Peak pain intensity in the most affected knee during the previous 24 h was assessed on a 100 mm VAS with terminal descriptors of ‘no pain’ and ‘worst pain possible’ was chosen based on its frequent application in studies on sensitization in knee OA-related pain (Skou et al., 2014,Arendt-Nielsen et al., 2010,Skou et al., 2013). The VAS is a measure of pain widely used in patients with knee OA that is valid, reliable and responsive (Hawker et al., 2011).

Pain intensity during function

Knee pain intensity after 30 min of walking was assessed on a 100-mm VAS with terminal descriptors of ‘no pain’ and ‘worst pain possible’ was chosen, since it can serve as an indirect measure of how knee pain affects function.

Knee pain location and pattern

Using the reliable interviewer-administered questionnaire Knee Pain Map, previously applied in patients with knee OA (Thompson et al., 2009,Thompson et al., 2010), knee pain location and pattern in the most affected knee were assessed. The Knee Pain Map identifies areas of the knee, which are painful, and characterizes the pain as localized, regional or diffuse (Thompson et al., 2009,Thompson et al., 2010). Diffuse pain is indicative of a more progressed sensitization (Arendt-Nielsen and Graven-Nielsen, 2011), which is why pain location and pattern were dichotomized (yes/no to diffuse pain in the most affected knee).

Spreading of pain

The patients shaded body sites with pain in the previous 24 hours on a region-divided body chart (26 sites in total). The total number of pain sites was used to quantify the spreading of pain (Coggon et al., 2013).

Usage of pain medication

Defined as any pain medication taken on a regular basis during the last week at baseline and at the 3-month follow-up. Due to non-uniformity of the distribution of pain medication intake, the results were dichotomized (yes/no to pain medication).

Statistical analysis

Sample size

The sample size was powered for the primary RCT, based on the primary outcome the Knee injury and Osteoarthritis Outcome Score $(KOOS)_4$, with scores ranging from 0 (worst) to 100 (best). $KOOS_4$ is the mean score for the KOOS subscale scores for Pain, Symptoms, Function, daily living and Quality of life (Roos et al., 1998,Roos and Toksvig-Larsen, 2003). The sample size needed to detect a 10 point difference (SD 14) between groups in $KOOS_4$ was 41 patients in each group

(power of 90 % and a significance level at 0.05 (2-sided)). To account for crossovers to TKR from the non-surgical treatment only group, and for missing data, the dropout rate was set to 20%, and a total of 100 patients were randomized. In this pre-specified ancillary analysis we were interested in exploring the effects of TKR followed by non-surgical treatment or non-surgical treatment alone on sensitization and pain.

Ancillary analyses

Since this was an ancillary analysis, only patients staying in the group that they were randomized to during the 3-month follow-up with available data from both the baseline and 3-month follow-up were included in the analyses. As endorsed by The European Agency for the Evaluation of Medicinal Products when ancillary analyses are declared as supportive, no adjustments for multiplicity were done (The European Agency for the Evaluation of Medicinal Products, CPMP, 2002).

To evaluate change in pain intensity and number of pain sites between and within groups a Student's t-test was applied. A 3-way analysis of variance (ANOVA) was used to evaluate change in PPT from baseline to 3 months using the fixed factors *group (TKR + non-surgical, non-surgical)*, *site (knee, lower leg)* and *side (most affected, contralateral)*. The analysis was conducted both unadjusted and adjusted (baseline PPT, gender, age and BMI). Within-group changes in PPTs due to the treatment were further assessed using a repeated measures ANOVA with *time (baseline, 3 months), site (knee, lower leg)* and *side (most affected, contralateral)* as the within-subject factors for both the TKR + non-surgical group and the non-surgical group. The assumption of homogeneity of variance was tested using Levene's test ($P > 0.05$), and the assumption of normal distribution was tested by visual inspection of Q-Q plots. Tukey-Kramer was used as a post hoc test if ANOVA factors or interactions were significant.

The relative risks for usage of pain medication and diffuse pain were estimated and compared between groups using a Poisson regression model with a robust error variance for the confidence intervals.

All analyses were performed in either IBM SPSS Statistics (Version 22, IBM Corporation, Armonk, NY, USA) or Stata 13 (StataCorp, College Station, TX, USA). The significance level was set at $P < 0.05$.

RESULTS

In all, 1,470 patients seen in secondary care by an orthopedic surgeon were assessed for eligibility, 1,348 were ineligible, and 27 did not want to participate. The primary reasons for ineligibility were being ineligible for a TKR (n = 544), OA not severe enough (Kellgren-Lawrence score < 2; n = 197), not able to participate in intervention (n=180), and unable to come to treatment site (n=145). One hundred patients were randomized, with 41/50 (82%; one patient did not undergo TKR) in the TKR + non-surgical group and 46/50 (92%; one patient underwent TKR during the 3 months) in the non-surgical group completing both baseline and 3-month follow-up. For further information on the study flow (including Flow diagram), please refer to (Skou et al., 2015). Patient characteristics are presented in Table 1 and pain location and pattern at baseline are presented in Table 2.

Between-group analyses

Localized and spreading sensitization

There was a statistically significant mean difference (95% CI) in change in PPTs from baseline to 3 months between groups in the crude analysis of 71 kPa (21-121), $F(1,304) = 7.897$, $P = 0.005$ (Fig. 1). The difference remained significant when adjusting for baseline PPT, age, gender and BMI with

a mean difference (95% CI) of 75 kPa (33-117), F(1,300) = 12.091, *P* = 0.001. Both the crude and adjusted analysis favored the TKR + non-surgical group. Neither site nor side had a statistically significant effect on the results.

Peak pain intensity

The difference in change (95 % CI) from baseline to 3 months of 7.9 (-6.1 to 21.0) millimeter in peak pain intensity in favor of the TKR + non-surgical group was not statistically significant (*P* = 0.27).

Pain intensity during function

The difference in change (95 % CI) from baseline to 3 months of 9.5 (-5.1 to 24.1) millimeter in pain intensity during function in favor of the TKR + non-surgical group was not statistically significant (*P* = 0.20).

Knee pain location and pattern

There was no significant difference between groups in the number of patients with diffuse pain at 3 months compared to baseline (Table 3).

Spreading of pain

The difference in change (95 % CI) from baseline to 3 months of 0.7 (-0.3 to 1.8) in the number of body sites with pain in favor of the TKR + non-surgical group was not statistically significant (*P* = 0.15).

Fig. 2 illustrates the difference in body sites with pain at baseline and after 3 months in the TKR + non-surgical group and the non-surgical group.

Usage of pain medication

There was no significant difference between groups in the usage of pain medication at 3 months compared to baseline (Table 4).

Within-group analyses

Within-group results are presented in Tables 3–5.

DISCUSSION

The present study showed that TKR followed by a 3-month non-surgical treatment program was associated with greater improvements in localized and spreading sensitization, but not pain intensity, pain location and pattern, spreading of pain and usage of pain medication after 3 months as compared to non-surgical treatment alone. Due to the exploratory nature of the analysis, the results must be interpreted with caution.

The two previous non-randomized reports on the effects of TKR on sensitization had conflicting result (Graven-Nielsen et al., 2012,Kosek et al., 2013). While Graven-Nielsen et al. demonstrated a normalization of a range of measures of sensitization (Graven-Nielsen et al., 2012), including PPTs from the lower leg of the operated and non-operated leg, Kosek et al. found no effects of TKR on PPTs from a range of body sites, including the knee of the operated and non-operated leg (Kosek et al., 2013). The present high-quality RCT extends the findings from Graven-Nielsen et al. (Graven-Nielsen et al., 2012) with improvements in PPTs from the knee and lower leg of the operated and non-operated leg of patients with knee OA undergoing TKR followed by non-surgical treatment when compared to patients undergoing non-surgical treatment alone. A previous RCT in patients with knee OA not eligible for TKR demonstrated that even though PPTs from the knee, lower leg

and arm improved from the same non-surgical treatment as in this trial, the improvements were not larger than those seen in patients receiving information and advice on treatment only (Skou et al., 2016). In the present trial, patients randomized to non-surgical treatment alone did not improve in sensitization. It is possible that the conflicting results could be caused by a type II error, since this study was not powered to detect this difference. However, since the group randomized to TKR followed by non-surgical treatment improved, it seems reasonable that the type, and perhaps the invasiveness, of the treatment plays an important role when it comes to improving sensitization. TKR is a major surgery involving replacement of joint surfaces of the affected knee (Carr et al., 2012), which are likely to cause major changes in the environment of the joint, potentially being of a sufficient dose to reduce sensitization in knee OA. Future confirmatory trials and studies looking at mechanisms behind this change are needed.

The primary report from this RCT demonstrated that, albeit associated with more serious adverse events, TKR followed by non-surgical treatment reduced pain during activities with 17.1 units more that non-surgical treatment alone on a 0-100 scale (Skou et al., 2015). Both treatment groups of the trial had clinically relevant improvements in pain at 12-month follow-up (Skou et al., 2015) and this study confirms the difference between groups being initiated already at 3 months. However, the difference in change between groups at 3 months was not significant for any of the pain-related measures (risk of type II error). Since pain has the potential to improve for at least 12 months after TKR (Nilsdotter et al., 2009), the full effects from the surgery are not manifested after 3 months potentially explaining the non-significant findings. In addition many different pain mechanisms and sensitization process are involved in painful end-stage OA (Arendt-Nielsen et al., 2015b,Arendt-Nielsen et al., 2015a,Egsgaard et al., 2015) and hence a variety of mechanistic pain assessment tools are needed to tease out the contribution of the various mechanisms (Arendt-Nielsen et al.,

2015b,Skou et al., 2014,Skou et al., 2013,Arendt-Nielsen et al., 2015a,Egsgaard et al., 2015,Dworkin et al., 2005).

The present study has some limitations. First of all, it is important to acknowledge, that since the sample size was powered based on the primary RCT, the non-significant findings of this analysis could merely be a result of a type II error. Furthermore, since the non-surgical treatment consisted of several non-surgical treatments that were delivered in an individualized fashion with regards to specific content and intensity, there could have been systematic differences between groups. We did not adjust for all potential confounders in the analysis of PPTs. As recommended by the European Medicines Agency we decided to include only a few of the most important covariates, including the baseline PPT (The European Medicines Agency, 2015). Additionally, the multimodal nature of the non-surgical treatment, preclude the possibility to differentiate the effects of the individual treatment modalities. However, as the intervention was standardized and delivered by the same physiotherapists and dieticians, and as the multimodal approach individualized to patient is recommended in clinical guidelines on the treatment of knee OA (Fernandes et al., 2013,McAlindon et al., 2014), the generalizability of the results is strengthened.

Conclusions

TKR followed by a non-surgical treatment program is more effective in reducing localized and spreading sensitization, but not other pain-related measures, as compared to the non-surgical program alone in patients with knee OA. Both treatment options demonstrated clinically relevant changes in pain-related measures, highlighting their applicability in clinical practice.

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AUTHOR CONTRIBUTIONS

Study conception and design. Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Simonsen, Rasmussen

Acquisition of data. Skou.

Analysis and interpretation of data. Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Simonsen, Rasmussen.

Drafting the article or revising it critically for important intellectual content. Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Simonsen, Rasmussen

Final approval of the article. Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Simonsen, Rasmussen

All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE LEGENDS

Figure 1. Pressure pain thresholds on the most affected side. Mean pressure pain thresholds (PPT) measured in kPa using a handheld algometer on the knee and lower leg. The TKR + non-surgical group had significantly larger improvements in pressure pain thresholds from baseline to 3 months compared to the non-surgical group ($P < 0.05$). Furthermore, while the TKR + non-surgical group had significantly higher PPTs (*; $P < 0.05$) after 3 months compared to baseline the non-surgical had not. Error bars indicate 95% confidence intervals.

Figure 2. Pain sites. Sites of the body where at least 10% of the patients in the TKR + non-surgical group (A) and in the non-surgical group (B) reported pain during the previous 24 hours. A black shade indicates that at least 10% reported pain at both baseline and at the 3-month follow-up, while a grey shade indicates that at least 10% reported pain at baseline, but not at the 3-month follow-up. The right side of the body in the figures has been set as the side mostly affected by knee osteoarthritis. Less than 10% in the TKR + non-surgical group had pain in the foot of the most affected leg at baseline, while 10% had it at 3-month follow-up.