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PREOPERATIVE HYPOALGESIA AFTER COLD PRESSOR TEST AND AEROBIC EXERCISE IS ASSOCIATED WITH PAIN RELIEF SIX MONTHS AFTER TOTAL KNEE REPLACEMENT

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ABSTRACT

Objectives: Chronic pain after total knee replacement (TKR) is not uncommon. Preoperative impaired conditioning pain modulation (CPM) has been used to predict chronic postoperative pain. Interestingly, exercises reduce pain sensitivity in patients with knee osteoarthritis. This pilot study investigated the association between exercise-induced hypoalgesia (EIH) and CPM on post-TKR pain relief.

Methods: Before and six months post-TKR, 14 patients with chronic knee osteoarthritis performed the cold pressor test on the non-affected leg and two exercise conditions (bicycling and isometric knee extension), randomized and counterbalanced. Before and during the cold pressor test and after exercises test-stimuli were applied to extract the pain

sensitivity difference: Computer-controlled cuff inflation on the affected lower leg until the subjects detected the cuff pain threshold (cPPT) and subsequently the pain tolerance threshold (cPTT). 2) Manual pressure pain thresholds (PPTs) at the legs, arm and shoulder. Clinical pain intensity (numerical rating scale) and psychological distress (questionnaires) were assessed.

Results: Clinical pain intensity, psychological distress, cPPT and PPT at the affected leg improved post-TKR compared with pre-TKR ($P<0.05$). Preoperatively, the CPM and bicycling EIH assessed by the increase in cPTT correlated with reduction in NRS pain scores post-TKR ($P<0.05$). Improved CPM and EIH responses after TKR were significantly correlated with reduction in NRS pain scores post-TKR ($P<0.05$).

Discussion: In knee osteoarthritis patients, hypoalgesia after cold pressor stimulation and aerobic exercise assessed preoperatively by cuff algometry was associated with pain relief six months after TKR. EIH as a novel preoperative screening tool should be further investigated in larger studies.

Keywords: Osteoarthritis, exercise-induced hypoalgesia, conditioned pain modulation, total knee replacement, chronic postoperative pain

1. INTRODUCTION

Knee osteoarthritis (KOA) is a common and painful disease in the elderly population (1). Total knee replacement (TKR) is considered to be an effective end-stage treatment to relieve chronic knee pain (2). However, not all patients benefit from TKR and approximately 20% continues to suffer from chronic pain (3). With an increasing number of TKR performed each year (4), effective preoperative screening tools identifying patients likely to benefit from TKR is warranted to reduce the prevalence of chronic pain after TKR.

In KOA patients altered pain processing has been demonstrated including increased pain sensitivity (5, 6) and impaired conditioned pain modulation (CPM) (5, 6). Moreover, preoperative assessment of experimental pain sensitivity can help predicting postoperative chronic pain after TKR (6, 7). Less efficient CPM assessed before surgery predicted chronic pain in patients after thoracotomy (8) and abdominal surgery (9), although this association was not demonstrated in patients with KOA (6). In addition, normalization of pain processing has been demonstrated after successful TKR (10) indicating a relationship between clinical pain and pain sensitivity in KOA. However, the association between postoperative clinical pain and preoperative pain thresholds is not consistent with some studies demonstrating an association (7, 11) and others no association (6, 12). It has however been recommended to include a range of stimulus intensities in the assessment of experimental pain sensitivity to reveal potential effects that are manifested with more painful stimuli (13) in addition to assessment of pain thresholds.

Recently, moderate effectiveness of exercise on clinical pain intensity in KOA has been demonstrated (14). Still, the current knowledge on the hypoalgesic response immediately after exercise in KOA is sparse. Exercise-induced hypoalgesia (EIH), another measure of descending pain modulation (15, 16) can be assessed with recordings of pain sensitivity before and after an exercise condition. In patients with knee and hip OA it was demonstrated that isometric exercise involving the painful extremity produced hypoalgesia before and three months after surgery to a degree comparable with healthy controls (17). In contrast, a recent study in patients with KOA found no significant hypoalgesia after lower body resistance exercise, although upper-body exercise produced EIH (18). No studies have investigated whether preoperative assessment of EIH is associated with postoperative pain following TKR. A recent study in rats demonstrated that a reduced EIH response after

aerobic exercise was predictive of increased pain severity following nerve injury (19) and it may be hypothesized that preoperative impaired EIH is associated with less pain reduction after surgery. Moreover, no studies have investigated the hypoalgesic effect of different types of exercise (e.g. aerobic and isometric) in KOA. Such a comparison will significantly contribute to the understanding of how physical activity influences pain perception, which is necessary to optimize the clinical utility of physical activity as a method of pain management in KOA. The primary aim of this pilot study was to investigate whether the effect of cold pressor test and different exercises on pressure pain thresholds and pain tolerance assessed preoperatively in patients with KOA were associated with pain relief six months after TKR. A secondary aim was to investigate the effect of TKR on clinical pain, pain sensitivity, CPM and EIH responses. It was hypothesized that 1) clinical pain and pain sensitivity would be reduced six months after TKR, 2) the degree of CPM and EIH responses assessed before surgery were associated with reduction of pain after TKR, and 3) the cold pressor test (CPM) and exercises (EIH) produce hypoalgesia six months after but not before TKR.

2. MATERIALS AND METHODS

2.1 Subjects

Fifteen patients with KOA scheduled for unilateral TKR (mean age of 66.3 ± 5.9 years; 7 women) were included in this study. For inclusion in the study, radiographic confirmed knee osteoarthritis with a score of ≥ 2 on the Kellgren–Lawrence scale (20) and eligibility for TKR determined by an experienced orthopedic surgeon was required. Furthermore, patients should be able to use a stationary bicycle, which was assessed by the orthopedic surgeon. Patients fulfilling the inclusion criteria were recruited from the Orthopedic Department at Odense University Hospital, Denmark. Moreover, all recruited patients

completed pain drawings to identify other painful body areas that could influence the results. None of the included patients suffered from neurological, psychiatric, cardiovascular diseases, or other chronic pain conditions and all patients were asked to refrain from regular physical exercises, coffee, alcohol, and nicotine on the days of participation. No restrictions were made on analgesic consumption (Table 1). The study was conducted in accordance with the Declaration of Helsinki, approved by the local ethical committee (S-20110070) and all patients provided written informed consent.

2.2 Procedure

Before TKR surgery, patients participated in two sessions approximately at the same time of the day and separated by 1-3 weeks. This time frame was chosen to avoid potential carry-over effects between sessions as well as to avoid further development in the chronic pain condition. In each session, pressure pain thresholds were recorded from both legs, the arm, and shoulder, and pressure pain tolerance was recorded from the affected lower leg. In addition, all patients performed a total of 4 different conditions over the two sessions: 1) a control condition, 2) a cold pressor test, 3) an aerobic bicycling exercise, and 4) an isometric muscle contraction.

In the first session patients completed the control condition which was 15 min of quiet rest. Following the rest condition, age-related target heart rates corresponding to 50 % VO_{2max} and 75 % VO_{2max} to be used in the second session for the bicycling condition was determined (see below). Moreover, the maximal voluntary contraction (MVC) in the dominant quadriceps femoris muscle was determined for the isometric contraction condition. Data were also collected on age, height, weight, pain duration, and all patients completed the following pain related questionnaires at home between session 1 and session 2: Patients were asked to indicate clinical peak pain intensity ("Please rate the intensity of

pain that best describes your pain in the knee at its worst in the last 24 hours"), general pain with movement ("Please rate the intensity of pain that best describes your pain in the knee when you are moving your leg in the last 24 hours"), and pain during rest ("Please rate the intensity of pain that best describes your pain in the knee at its least in the last 24 hours") on 0-10 numerical rating scales (NRS) with 0 defined as "no pain" and 10 "as worst imaginable pain", Hospital Anxiety and Depression Scale (HADS), Pain Catastrophizing Scale (PCS) and Tampa Scale of Kinesiophobia (TSK).

In the second session, a cold pressor test on the foot of the non-affected leg was used to assess CPM and an aerobic bicycling condition as well as an isometric muscle contraction condition was used to assess EIH. The order of the conditions in the second session was randomized and counterbalanced. Each session lasted approximately 2 hours. The hypoalgesic response after cold pressor test and exercise has previously been shown to be short-lasting (15, 21) and a 20 min recovery interval was kept between the three conditions to avoid carry-over effects (Fig. 1).

Six months after TKR, all patients completed a cold pressor test on the foot, an aerobic bicycling condition, as well as an isometric muscle contraction condition in the same randomized and counterbalanced order as before surgery and the same pain related questionnaires were completed. MVC in the dominant quadriceps femoris muscle was re-assessed six months after TKR and questionnaires were completed prior to performing cold pressor test and exercises so the clinical pain reporting was not influenced by the pain testing procedures.

2.3 Pain sensitivity assessment

Manual pressure algometry and computer-controlled cuff algometry were used to assess pain sensitivity before and after rest as well as before, immediately after, and 15 min after

cold pressor test and exercise conditions. Manual pressure algometry was also performed during the cold pressor test as recommended when assessing CPM (22). The rest condition was included to test the effect of repeated pain sensitivity assessments. As it has previously been recommended to include a range of stimulus intensities in the assessment of experimental pain sensitivity, assessments of pressure pain threshold and pressure pain tolerance were included in this study.

2.3.1 Assessment of manual pressure pain thresholds

Manual pressure pain thresholds (PPT) were assessed using handheld pressure algometry (Somedic Hörby, Sweden) with a stimulation area of 1 cm^2. The increment rate of pressure was kept at approximately 30 kPa/s and the first time the pressure was perceived as pain, the patient pressed a button and the pressure intensity defined the PPT. Two PPT assessments were completed for each site and the average used for further analysis. Twenty-second intervals between assessments were retained.

Four assessment sites were located and marked. Site one was located in the middle of the quadriceps femoris muscle of the affected leg, twenty centimeters proximal to the base of patella. Site two was located in the middle of the quadriceps femoris muscle in the non-affected leg, twenty centimeters proximal to the base of patella. Site three was located in the middle of the dominant biceps brachii muscle, ten centimeters proximal to the cubital fossa. Site four was located in the non-dominant upper trapezius muscle, ten centimeters from the acromion in direct line with the neck. Test–retest reliability of manual pressure algometry has previously demonstrated excellent ICC values in patients with chronic pain (23) and healthy subjects (24).

2.3.2 Assessment of cuff pressure pain threshold and tolerance

Cuff pressure pain threshold (cPPT) and pressure pain tolerance (cPTT) were assessed on the affected leg by computer-controlled cuff algometry (NociTech, and Aalborg University, Denmark) (25). A 13-cm wide silicone tourniquet cuff (VBM, Sulz, Germany) with an equal-sized proximal and distal chamber was wrapped around the lower leg. The cuff was mounted with a 5 cm distance between its upper rim and the tibial tuberosity. The cuff pressure was increased at a rate of 1 kPa/s in both chambers and the maximal pressure limit was 100 kPa. The maximal pressure limit was based on the maximum capacity of the system. Air was supplied from a 200 liters external air tank to avoid loud noises from the cuff system during assessment. Patients used an electronic visual analogue scale (VAS) to rate their pressure-induced pain intensity and a button to release the pressure. The electronic VAS was sampled at 10 Hz. Zero and 10 cm extremes on the VAS were defined as "no pain" and "maximal pain", respectively. Patients were instructed to rate the pain intensity continuously on the electronic VAS from when the pressure was defined as first sensation of pain and to press the pressure release button when the pain was perceived as intolerable. The pressure value, when the patient rated the sensation of pain as 1 cm on the VAS was defined as cPPT, and when the patient terminated the pressure inflation, the pressure value was defined as cPTT. In case the maximum pressure stimulation was achieved before reaching the pain tolerance, 80 kPa was used for further analysis as a conservative estimate (relevant for one patient). Good test-retest reliability and sensitivity of computer-controlled cuff algometry for assessment of pain sensitivity and pain modulation has been demonstrated in patients with chronic pain (23) and healthy subjects (24).

2.4 Cold pressor test

The cold pressor test was performed with the patient comfortably seated while immersing the foot on the non-affected leg into a tank containing circulating ice water at 1-2ºC. The patient immersed the foot five centimeters above the ankle joint for 2 min. Just before removing the foot from the ice water the patient was instructed to rate the pain intensity caused by the cold water on a 0-10 NRS, with 0 defined as "no pain" and 10 "as worst imaginable pain".

2.5 Bicycling exercise

Patients performed a 15 min bicycling exercise. Based on the linear relationship between maximal heart rate (HR) and VO_{2max} (% HR_{max} = (0.636 x % VO_{2max}) + 38.2), which has been demonstrated in a previous study (26), the age-related target heart rates corresponding to 50 % and 75 % of VO_{2max} were determined. HR_{max} was calculated as 220 beats/min minus the age of the patient. The seat post of the stationary cycle (Ergomedic 928E, Monark Exercise AB, Vansbro, Sweden) was adjusted so that the patient had approximately five degree bend at the knee during the bottom phase of the pedal stroke. A heart rate monitor (Monark Heart Rate Monitor) was strapped around the patient's chest. Patients were instructed to maintain a pedal rate as close to seventy rounds per min (RPM) as possible throughout the 15 min bicycling exercise. Patients could see the RPMs during bicycling in order to maintain the desired pedal rate. The first 2 min was used as warm-up and the intensity was kept below a heart rate corresponding to 50 % VO_{2max}. Resistance was then increased over the next 3 min until the target heart rate corresponding to 75 % VO_{2max} was achieved by the beginning of the fifth min where after the patient continued bicycling for 10 min. This intensity was chosen based on previous studies in healthy subjects (15, 27, 28) and patients with chronic musculoskeletal pain (23), which have shown robust EIH at this intensity. HR was monitored constantly, and

resistance manipulated if necessary to keep the HR at the desired level. Rating of Perceived Exertion (RPE: 6-20), Watt and HR (beats/min) were obtained just before reaching the 15 min of bicycling.

2.6 Isometric muscle contractions

In the first session, patients were seated on a table with full support of the thighs. The dominant leg was strapped above the ankle to the force transducer (Commander Muscle Tester, Powertrack II, JTECH Medical, USA). The MVC during isometric knee extension was determined in a position of ninety degrees of knee flexion. Two maximal contractions, separated by one min, were performed and the average was used to determine the sub-maximal value of 30 % MVC.

In the second session, patients performed a sustained 90 s isometric muscle contraction with the dominant quadriceps femoris muscle (knee extension) at a sub-maximal intensity corresponding to 30 % MVC. The muscle contraction intensity was chosen based on previous studies showing robust EIH at this intensity and duration in healthy subjects (15, 29) and patients with chronic musculoskeletal pain (23). During the sustained sub-maximal isometric contraction, each subject was required to match the target force as displayed on the monitor of the force transducer. The subjects were verbally encouraged to sustain the force throughout the 90 s.

2.7 Statistics

Results in text are presented as mean and standard deviation (SD) unless otherwise specified. Potential differences in clinical pain (NRS scores), psychological distress (questionnaire scores), baseline PPTs, cPPT and cPTT before surgery compared with six months post-TKR were analyzed with paired t-test for the normally distributed variables

and with the non-parametric Wilcoxon test for non-normally distributed variables (when the Shapiro-Wilk demonstrated $P < 0.05$).

Pearson's product moment correlations were performed to determine the relationship between CPM and EIH responses assessed before surgery and the change in clinical pain intensity (positive value indicates a NRS reduction in pain at follow-up) six months after TKR. In the correlation analysis, CPM and EIH response was calculated as percentage change (i.e. 100*after/before) in manual and cuff algometry parameters during or immediately after cold pressor test and exercises with manual algometry averaged between the four assessment sites. The effect of the control condition (quiet rest) on PPTs, cPPT, and cPTT was analyzed with repeated measures analysis of variance (RM-ANOVA) with the factor *time* (before, and immediately after) as repeated measures. Furthermore, RM-ANOVAs were used to compare the effect of cold pressor test, and exercise conditions on algometry parameters before and after surgery with the factors *pre/post* (before TKR, and 6 months after TKR), and *time* (before, [*PPTs also during cold pressor test*], immediately after, and 15 min after) as repeated measures. In the analysis of PPTs, assessment sites (quadriceps sites, biceps site, and trapezius site) were added to the RM-ANOVAs. Furthermore, the percentage change in CPM and EIH responses before and six months after TKR was compared with RM-ANOVAs. Finally, the percentage change in PPTs, cPPT, and cPTT after each of the three active conditions before and after TKR were compared with two-way ANOVAs with the factor *pre/post* (before TKR, and 6 months after TKR), and *condition* (cold pressor test, bicycling, and isometric knee extension). In case of significant factors or interactions, Bonferroni corrected pairwise comparisons were used. Partial η^2 for each ANOVA were examined and effect sizes were calculated based on

Cohen's D, with correction of the correlation between observations due to the within-subject design. *P*-values less than 0.05 were considered significant.

3. **RESULTS**

3.1 Baseline and follow-up

Fifteen patients with KOA were assessed prior to surgery. One patient did not attend follow-up six months after TKR due to personal issues. Fourteen patients completed the assessment at six months follow-up and were included in the analysis. Although, 4 patients still reported some knee pain during rest and eleven patients reported some knee pain during general movement fewer patients used analgesics at follow-up compared with baseline. Moreover, patients reported less clinical pain intensity and psychological distress, as well as increased cPPT and PPT at the affected leg at follow-up compared with baseline (Table 1).

3.2 Quiet rest (control condition, baseline)

There was no significant main effect of time in the ANOVAs of PPT, cPPT, and cPTT ($F(1,13) < 3.4$, $P > 0.08$, partial $\eta^2 < 0.12$), indicating that quiet rest did not affect pain sensitivity assessed with handheld or cuff pressure algometry.

3.3 CPM at baseline and follow-up

All 14 patients completed the cold pressor test before and after TKR. The pain intensities reported during the cold pressor test at baseline and follow-up were not significantly different (Table 1; Wilcoxon: $P > 0.2$).

There was a significant main effect of time in the ANOVA of PPTs of all sites (Table 2; $F(3,39) = 5.41$, $P = 0.003$, partial $\eta^2 = 0.29$) although no pre/post TKR effects, with post-hoc test showing significantly increased PPTs during cold pressor test compared with before cold pressor test ($P < 0.05$). The ANOVA of the percentage difference in PPTs

during cold pressor stimulation demonstrated a significant main effect of site ($F(3,39) = 3.03$, $P < 0.04$, partial $\eta^2 = 0.19$) and no pre/post TKR effects, with post-hoc test showing significantly larger CPM response at the biceps site compared with the other three assessment sites ($P < 0.05$). There was no significant interactions or main effects for cPPT, cPTT or percentage difference in cPPT and cPTT (Table 2, $F(2,26) < 2.44$, $P > 0.11$, partial $\eta^2 < 0.16$).

3.4 EIH after aerobic exercise at baseline and follow-up after TKR

The bicycling intensities, heart rate, and rating of perceived exertion during bicycling at baseline and follow-up after TKR were not significantly different (Table 1; Wilcoxon: $P > 0.2$).

There was a significant main effect of time in the ANOVA of PPTs (Table 2; $F(2,26) = 12.83$, $P < 0.001$, partial $\eta^2 = 0.50$) although no pre/post TKR effects, with post-hoc test showing significantly increased PPTs immediately after bicycling compared with before and 15 min after bicycling ($P < 0.002$). There was no significant interactions or main effects for the percentage difference in PPTs ($F(3,39) < 1.24$, $P > 0.31$, partial $\eta^2 < 0.15$). There was no significant interactions or main effects of time for cPPT, cPTT or percentage difference in cPPT and cPTT ($F(2,26) < 1.18$, $P > 0.32$, partial $\eta^2 < 0.07$).

3.5 EIH after isometric exercise at baseline and follow-up

The MVC was significantly increased at follow-up compared with baseline (Table 1; Wilcoxon: $P < 0.02$).

The ANOVA of PPTs demonstrated a significant main effect of time (Table 2; $F(2,26) = 4.00$, $P < 0.03$, partial $\eta^2 = 0.24$) but no pre/post TKR effects, with post-hoc test showing significantly increased PPTs immediately after isometric exercise compared with before and 15 min after isometric exercise ($P < 0.05$). There was no significant interactions

or main effects for the percentage difference in PPTs ($F(3,39) < 0.82$, $P > 0.49$, partial $\eta^2 < 0.1$). There was no significant interactions or main effects of time for cPPT, cPTT or percentage difference in cPPT and cPTT ($F(2,26) < 3.50$, $P > 0.10$, partial $\eta^2 < 0.2$).

3.6 Comparison of cold pressor test, bicycling and isometric knee extension

There was a statistically significant difference in the ANOVA for percentage change in PPT at the quadriceps muscle in the non-affected leg ($F(2,26) = 8.11$, $P = 0.002$, partial $\eta^2 = 0.38$). Post hoc test showed a significant percentage increase in PTT after bicycling compared with isometric knee extension ($P = 0.009$). There was no significant interactions or main effects for the percentage difference in cPPT, cPTT, and PPTs at the other assessment sites ($F(2,26) < 2.29$, $P > 0.12$, partial $\eta^2 < 0.15$).

3.7 Correlational analyses

As illustrated in Table 3, reduction in NRS scores of clinical pain during rest after TKR was significantly correlated with the preoperative increase in cPTT after the cold pressor test (Fig. 2A; $r(13) = 0.57$, $P < 0.04$). Likewise, reduction in NRS scores of clinical peak pain after TKR was significantly correlated with the preoperative increase in cPPT (Fig. 2B; $r(13) = 0.53$, $P < 0.05$) and cPTT (Fig. 2C; $r(13) = 0.53$, $P < 0.05$) after bicycling.

Moreover, there was a correlation between the reduction in NRS scores of the clinical peak pain intensity and the change in CPM response ($r(13) = 0.67$, $P < 0.008$), and the change in EIH response after bicycling ($r(13) = 0.68$, $P = 0.008$) assessed post-TKR.

4. DISCUSSION

This pilot study is the first to investigate the association between preoperative EIH in patients with KOA and pain relief after TKR. Clinical pain intensity, psychological distress, cPPT and PPT at the affected leg improved six months post TKR surgery compared with before TKR. Hypoalgesia after aerobic exercise and cold pressor test

assessed preoperatively were associated with pain relief six months post TKR. Despite the increase in muscle strength and the pain reduction following surgery, the hypoalgesic response after cold pressor test and exercises were comparable before and six months after TKR. However, the change in CPM and EIH post TKR was significantly correlated with reduction in clinical pain intensity after TKR, indicating that the magnitude of the CPM and EIH responses were associated with the intensity of knee pain. If replicated in larger studies, these findings could have important clinical implications for the decision-making process indicating which patients with KOA that would profit the most after TKR.

4.1 Pressure pain thresholds and clinical pain six months after surgery

In general, PPTs were increased, and levels of peak pain intensity, pain during movement, and rest were reduced six months after surgery. The increase in PPTs after TKR is in agreement with a previous study (10). However some patients still reported knee pain during rest and or during movement. This is consistent with a previous systematic review concluding that a significant proportion of people continue to have painful joints post TKR (3) and further addresses the need for preoperative determinants of good and bad outcomes after joint replacement surgery.

4.2 CPM

The cold pressor stimulation increased PPTs heterotopically and homotopically, although a larger effect was found when assessed on the biceps sites compared with the lower extremities. Similar findings have been demonstrated in healthy subjects (15, 30). A significant CPM effect based on increased PPTs was only observed *during* the cold pressor stimulation. This is in agreement with previous studies, reporting increases in PPT during noxious thermal stimulation but not after (23, 31-33). No significant difference in the magnitude of CPM was found when comparing before and six months post TKR. This is in

agreement with a previous study in 78 KOA patients undergoing TKR, demonstrating increased PPTs after the cold pressor test preoperatively and 12 months post-surgery (6). Another study including 15 patients with hip osteoarthritis demonstrated a less-efficient CPM response before total hip replacement, which was restored in pain free patients 6-14 months after surgery (33). A possible reason for this discrepancy is the use of different CPM testing paradigms. In the study by Kosek and Ordeberg (33) the conditioning stimulus was applied using the upper extremity submaximal effort tourniquet test whereas the cold pressor test was used in the current study and by Petersen and colleagues (6).

The CPM response assessed preoperatively by cuff algometry was significantly associated with the degree of pain relief six months post TKR. In other populations previous studies have also demonstrated that less efficient CPM assessed before surgery was associated with the presence of chronic pain in patients after thoracotomy (8) and abdominal surgery (9). Although an association between hypoalgesia after cold pressor test and aerobic exercise assessed preoperatively by cuff algometry and pain relief six months after TKR was found, no significant association between the increase in manual PPTs after cold pressor test and aerobic exercise assessed preoperatively and pain relief six months post TKR was found. This is in agreement with the findings from Petersen et al. (6), where the CPM response to the cold pressor test was assessed with manual algometry and not found significantly associated with pain 12 months post-TKR. The equivocal results on the associations of the CPM and EIH responses between manual pressure algometry and cuff algometry may be due to the different area of pressure stimulation which is considerably larger with cuff algometry compared with manual algometry. Moreover, cuff algometry may also be more sensitive to individual changes in pain modulation compared with manual algometry. This is supported by a recent study demonstrating differences in EIH

and CPM responses assessed with cuff algometry between subgroups of chronic musculoskeletal pain patients, but not for manual algometry (23).

4.3 Exercise-induced hypoalgesia

This pilot study showed that patients with smaller EIH responses after aerobic exercise preoperatively had less pain reduction 6 months after TKR. This association has not previously been studied in humans, but the results are comparable with a recent study demonstrating that the EIH response after aerobic exercise was predictive of pain severity following nerve injury in rats (19). The exact mechanisms of EIH are still unknown. Several studies have investigated the contribution of an opioid mechanism by administering naloxone, an opioid antagonist prior to aerobic exercise with some studies demonstrating reduced EIH (34, 35) and others that naloxone did not affect hypoalgesia (36, 37). In addition to an opioid mechanism, it has been suggested that non-opioid mechanisms may also be involved in the hypoalgesic response produced by exercise, and several non-opioid mechanisms have been proposed. A non-opioid mechanism potentially contributing to EIH after aerobic exercise is the effect of proprioception, where limb movement during exercise may excite proprioceptive pathways inhibiting nociceptive processes (38). In healthy subjects, passive movements induced hypoalgesia compared with a control condition, indicating a potential role of joint movement or proprioception in EIH (39). Partly different mechanisms for the EIH responses after aerobic and isometric exercises may explain why only EIH after aerobic exercise was associated with pain relief post-TKR. The EIH response has also been linked to the CPM response. Recently, studies demonstrated that healthy subjects with a greater CPM response were more likely to report a greater EIH response after isometric exercise (40) and aerobic exercise (23). Yet, EIH and CPM demonstrate differences in temporal and spatial manifestations (15), and

hypoalgesia has also been demonstrated after non-painful aerobic exercise (16), indicating that EIH and CPM are not identical phenomena.

The magnitude of EIH was not different before and six months post-TKR. This is the first study to compare hypoalgesia produced by aerobic exercise before and after TKR and further research is warranted. The hypoalgesic effect of isometric lower-body exercise before and after joint replacement surgery has previously been investigated in 107 patients with knee or hip osteoarthritis and in line with the current study no statistically significant effect of surgery on EIH was found (17). However, a smaller study including 11 patients with KOA performing resistance exercises demonstrated no EIH response when exercises were performed with the lower-body, indicating that exercises with painful body parts reduces the EIH response (41). Different contraction durations between studies may explain the equivocal results. In the study by Burrows and colleagues (41), exercises were performed for 60 seconds, whereas exercises in the study by Kosek and colleagues (17) as well as in the current study had longer durations. This is supported by a previous study demonstrating a greater increase in PPT after a low-intensity and long duration isometric contraction compared with contractions of shorter duration (42).

4.4 Future directions

This pilot study indicated that hypoalgesia after aerobic exercise and cold pressor test assessed preoperatively had a moderate positive relationship with pain relief six months post TKR. With pain being one of the main complaints for patients undergoing TKR, the goal of TKR is generally to alleviate pain. Determination of a threshold for the CPM or EIH response to predict whether TKR would provide pain relief to a given patient would be of great interest. However, several issues need to be considered. First, a previous study on patients with KOA undergoing TKR have demonstrated the average minimal important

change (MIC) in patient-reported pain relief as 22 points on a 0-100 NRS (43); however, patients may have different MICs for what constitutes a successful outcome after TKR depending on the level of pain before TKR (44). Secondly, there is no consensus on a normal CPM or EIH response and no studies have yet determined reference values for the CPM and EIH responses assessed with cuff algometry which is warranted. In this study, 7 and 6 patients reported a change in peak pain and resting pain, respectively of more than 2 points on a 0-10 NRS with the majority of these patients also demonstrating hypoalgesia to some degree after cold pressor test and aerobic exercise, whereas the majority of patients reporting pain relief of less than 2 points demonstrated a hyperalgesic response to cold pressor test and aerobic exercise. Larger studies are warranted to define cutoff values for CPM and EIH responses in order to determine whether TKR is likely to provide a successful outcome based on individual MIC in a given patient.

4.5 Limitations

This study was intended as a pilot study and is as such limited by the small sample size. Limitations include lack of statistical power as well as risk of false positive results and the results, especially the comparison of EIH and CPM before and after surgery as well as the association between EIH, CPM and pain reduction six months after TKR, should be interpreted with care. Larger studies should confirm the findings of this study.

Although the order of cold pressor test and exercise conditions was randomized between subjects, the control condition was always performed first, which may have permitted an order effect. This study did not include a healthy control group and it may be that although cold pressor test and exercises produced hypoalgesia, the CPM and EIH responses may be markedly impaired compared to healthy controls. Hypoalgesia up to 30 min after exercise has been demonstrated (45) causing a risk of carry-over effect in the

current experimental design. However, most studies demonstrate hypoalgesia for less than 15 min after aerobic and isometric exercise (15, 46). The intensity of aerobic exercise was not based on an exhaustive physical performance test and determination of VO_2max and the duration at the desired intensity was limited to 15 min, which may create some concern in terms of interpretation of the findings. Finally, the use of opioid analgesic before TKR (3 patients) was not restricted prior to assessment of CPM and EIH. Reduced pain inhibition has been reported in humans and animals treated with opioids (47, 48) potentially influencing the preoperative CPM and EIH responses.

4.6 Conclusion

This pilot study demonstrated that reduced hypoalgesia after cold pressor test and aerobic exercise assessed preoperatively by cuff algometry was associated with less pain relief six months after total knee replacement. Exercise-induced hypoalgesia as a preoperative screening tool should be further investigated in larger studies in various patient populations.

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Figure legends

Fig. 1: Illustration of the experimental procedures performed on both testing days. On day 2, three different conditions (cold pressor test [CPM], bicycling [BIKE], and isometric muscle contraction [ISOMETRIC]) were performed in randomized and counterbalanced order. Pain sensitivity was assessed with manual pressure algometry (pressure pain thresholds) at four assessment sites (bilateral thighs, upper arm and shoulder) and computer-controlled cuff algometry (affected lower leg). The pain sensitivity was assessed before and immediately after quiet rest [REST] as well as before, immediately after, and 15 min after cold pressor test, bicycling and isometric muscle contraction (solid arrow). Assessment with manual pressure algometry was also performed during cold pressor test (broken arrow).

Fig. 2: Scatter plots of the association between hypoalgesia after cold pressor test assessed preoperatively by cuff algometry and change in pain during rest six months post-TKR (cPTT; **A**) as well as associations between hypoalgesia after aerobic exercise assessed preoperatively by cuff algometry (cPPT; **B**, and cPTT; **C**) and change in peak pain intensity six months post-TKR. Linear regression line (solid line).

Table 1: Mean ± SD and range (n=14) demographics, clinical pain scores, psychological variables, experimental pain sensitivity, variables related to the cold pressor test and exercise conditions, and use of analgesics before and six months after total knee replacement (TKR). Significant difference between baseline and follow-up (six months post TKR) (*, $P < 0.05$). Effect sizes are based on Cohen's D, with correction of the correlation between observations due to the within-subject design. 'BMI': Body Mass Index. 'NRS': Numerical Rating Scale. 'HAD': Hospital Anxiety and Depression Scale. 'PCS': Pain Catastrophizing Scale. 'TSK': Tampa Scale of Kinesiophobia. 'PPT': Manual Pressure Pain Threshold. 'cPPT': Cuff Pressure Pain Threshold. 'cPTT': Cuff Pressure Pain Tolerance.

Domain	Variable	OA (N=14)		Effect size
		Baseline	Follow-up	
Demographics	Age (years)	65.2±5.8 (56-79)	65.8±5.8 (57-80)	-
	BMI (kg/m^2)	28.3±3.1 (23.87-33.43)	27.3±3.4 (22.5-33.1)*	0.8
Clinical pain intensity	Peak pain (NRS: 0-10)	5.9±1.3 (5-9)	2.7±2.1 (0-6)*	1.5
	During movement (NRS: 0-10)	6.4±2.2 (1-9)	2.4±2.0 (0-6)*	1.3
	During rest (NRS: 0-10)	3.2±2.0 (0-6)	0.9±1.7 (0-6)*	0.8
Psychological variables	Anxiety (HAD: 0-21)	2.2±2.2 (0-6)	1.1±1.5 (0-5)*	0.6
	Depression (HAD: 0-21)	2.3±1.9 (1-6)	0.6±0.9 (0-3)*	1.2
	Pain Catastrophizing (PCS: 0-52)	10.7±7.2 (1-28)	4.5±3.9 (0-12)*	1.0
	Fear of movement (TSK: 17-68)	35.0±6.2 (23-47)	31.4±5.4 (21-38)*	0.7
Experimental pain sensitivity	PPT Quadriceps dominant(kPa)	500.1±214.9 (285-1027)	574.8±248.7 (349-1325)*	0.7
	PPT Quadriceps non-dominant (kPa)	577.0±315.2 (250-1512)	549.2±238.4 (258-1225)	-0.3
	PPT Biceps (kPa)	288.9±121.5 (160-516)	288.6±130.0 (225-576)	0.0
	PPT Trapezius (kPa)	389.0±134.3 (243-662)	397.4±163.2 (158-797)	0.1
	cPPT (kPa)	19.4±13.7 (6.58-40.98)	24.4±12.9 (7.85-48.2)*	0.9
	cPTT (kPa)	49.9±20.8 (21.4-82.1)	46.3±21.7 (20.9-80.5)	-0.4
CPM and EIH conditions	Pain intensity during cold pressor test (NRS: 0-10)	5.7±2.0 (3-9)	5.4±1.9 (2-8)	0.2
	Intensity during bicycling (Watt)	90.0±25.0 (55-135)	91.4±30.5 (40-140)	0.1
	Heart rate during bicycling (beats/min)	141.4±5.8 (133-154)	142.1±5.6 (133-154)	0.2
	Rating of perceived exertion (Borg: 6-20)	14.6±1.2 (12-16)	14.5±0.9 (13-16)	0.1
	Maximal voluntary contraction (N)	216.4±113.8 (99-462)	227.2±124.0 (88-489)*	0.2
Analgesics	Frequency using analgesics (%)	11 (78.6 %)	7 (50 %)	-
	- Opioids (count, %)	3 (21.4 %)	0 (0 %)	-
	- NSAIDs (count, %)	4 (28.6) %	3 (21.4 %)	-
	- Paracetamol (count, %)	9 (64.3 %)	7 (50 %)	-

Table 2: Algometry parameters (mean ± SD, n=14) for cold pressor test and exercises before and six months after total knee replacement (TKR). Significantly different compared with baseline values (*, P < 0.05). Effect sizes are based on Cohen's D, with correction of the correlation between observations due to the within-subject design. 'PPT': Manual Pressure Pain Threshold. 'cPPT': Cuff Pressure Pain Threshold. 'cPTT': Cuff Pressure Pain Tolerance.

Condition	Time	Pain sensitivity parameter	Before (mean ± SD)	During/IA (mean ± SD)	After (mean ± SD)	Effect size
Cold pressor test (CPM)	Pre-TKR	PPT Quadriceps (dominant)	469.0±337.5	508.4±285.9*	474.5±266.2	0.3
		PPT Quadriceps (non-dominant)	479.0±307.8	527.4±295.2*	494.1±271.7	0.4
		PPT Biceps	246.7±145.2	329.0±217.7*	291.0±198.7	1.0
		PPT Trapezius	367.9±193.1	406.0±164.3*	373.5±167.7	0.5
		cPPT (kPa)	22.0±17.3	25.7±18.9	21.9±16.8	0.2
		cPTT (kPa)	48.6±22.5	45.6±23.9	52.3±21.9	-0.2
			512.6±278.5	570.8±264.3*	546.6±249.6	0.5
	Post-TKR	PPT Quadriceps (dominant)	549.4±252.0	589.4±312.6*	596.3±318.2	0.3
		PPT Quadriceps (non-dominant)	262.3±111.4	331.8±161.9*	320.3±153.4	1.1
		PPT Biceps	414.5±165.1	465.3±221.5*	447.1±203.6	0.6
		PPT Trapezius	22.5±14.2	24.2±16.7	23.4±16.4	0.2
		cPPT (kPa)	47.2±22.5	48.1±18.7	52.1±20.9	0.1
		cPTT (kPa)				
Bicycling (EIH)	Pre-TKR	PPT Quadriceps (dominant)	440.3±240.5	582.6±442.6*	519.6±408.5	0.9
		PPT Quadriceps (non-dominant)	468.9±303.7	607.5±355.5*	509.9±352.2	0.9
		PPT Biceps	263.5±144.5	285.9±123.7*	250.2±111.4	0.4
		PPT Trapezius	387.4±213.6	430.4±196.5*	378.0±184.4	0.5
		cPPT (kPa)	17.7±9.3	20.0±12.1	20.5±13.9	0.4
		cPTT (kPa)	47.8±18.6	50.2±22.6	51.5±20.7	0.2
			497.8±226.9	625.4±358.4*	565.4±396.7	1.0
	Post-TKR	PPT Quadriceps (dominant)	555.9±308.1	700.0±413.5*	625.1±432.6	0.9
		PPT Quadriceps (non-dominant)	264.1±134.7	330.3±111.7*	261.8±124.2	1.2
		PPT Biceps	380.4±182.5	442.6±188.2*	381.2±154.9	0.7
		PPT Trapezius	25.6±14.8	27.3±16.3	25.7±16.2	0.2
		cPPT (kPa)	51.3±20.0	52.5±21.1	50.4±21.0	0.1
		cPTT (kPa)				
Isometric quadriceps contractions (EIH)	Pre-TKR	PPT Quadriceps (dominant)	452.6±276.7	504.1±392.0*	415.5±255.0	0.3
		PPT Quadriceps (non-dominant)	492.5±349.6	499.0±385.2*	458.0±312.8	0.1
		PPT Biceps	251.8±122.9	269.3±154.4*	231.7±132.4	0.3
		PPT Trapezius	368.2±197.8	376.4±217.7*	367.8±213.8	0.1
		cPPT (kPa)	20.5±13.7	21.1±14.4	23.5±17.6	0.1
		cPTT (kPa)	48.8±22.3	46.7±24.0	52.5±22.1	-0.2
			501.1±295.5	496.5±237.3*	473.7±224.0	0.0
	Post-TKR	PPT Quadriceps (dominant)	573.0±408.3	601.6±356.1*	559.9±305.3	0.2
		PPT Quadriceps (non-dominant)	262.6±108.0	310.5±158.1*	263.4±116.9	0.8
		PPT Biceps	402.9±173.6	440.5±205.5*	415.0±182.5	0.5
		PPT Trapezius	26.7±14.6	23.2±15.3	25.4±14.3	-0.5
		cPPT (kPa)	50.7±20.8	49.4±21.4	53.6±20.3	-0.1
		cPTT (kPa)				

Table 3: Pearson's product moment correlations (n = 14 patients with knee osteoarthritis) between changes in clinical pain scores six months after total knee replacement and preoperative response to cold pressor test and exercises (aerobic and isometric). 'CPM': Conditioned pain modulation. 'EIH': Exercise-induced hypoalgesia. 'PPT': Manual pressure pain thresholds averaged across 4 assessment sites (legs, arm, and shoulder). 'cPPT': cuff pressure pain threshold assessed on the affected lower leg. 'cPTT': cuff pressure pain tolerance assessed on the affected lower leg.

Variables	Correlation	CPM (PPT)	CPM (cPPT)	CPM (cPTT)	Bike EIH (PPT)	Bike EIH (cPPT)	Bike EIH (cPTT)	Isometric EIH (PPT)	Isometric EIH (cPPT)	Isometric EIH (cPTT)
Change in clinical peak pain	R P-value	0.08 0.78	-0.06 0.83	0.18 0.53	-0.23 0.44	0.53 0.049	0.53 0.049	-0.08 0.78	0.19 0.53	-0.06 0.85
Change in clinical movement pain	R P-value	0.07 0.81	0.04 0.90	0.42 0.14	-0.11 0.70	0.19 0.51	0.51 0.06	0.15 0.62	0.37 0.20	0.26 0.37
Change in clinical resting pain	R P-value	-0.37 0.19	-0.02 0.96	0.57 0.035	0.03 0.92	0.09 0.76	0.40 0.15	-0.02 0.94	0.22 0.45	0.10 0.73

Figure 1

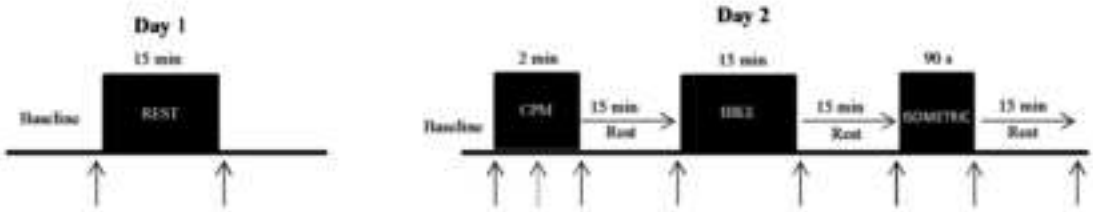

Figure 2A

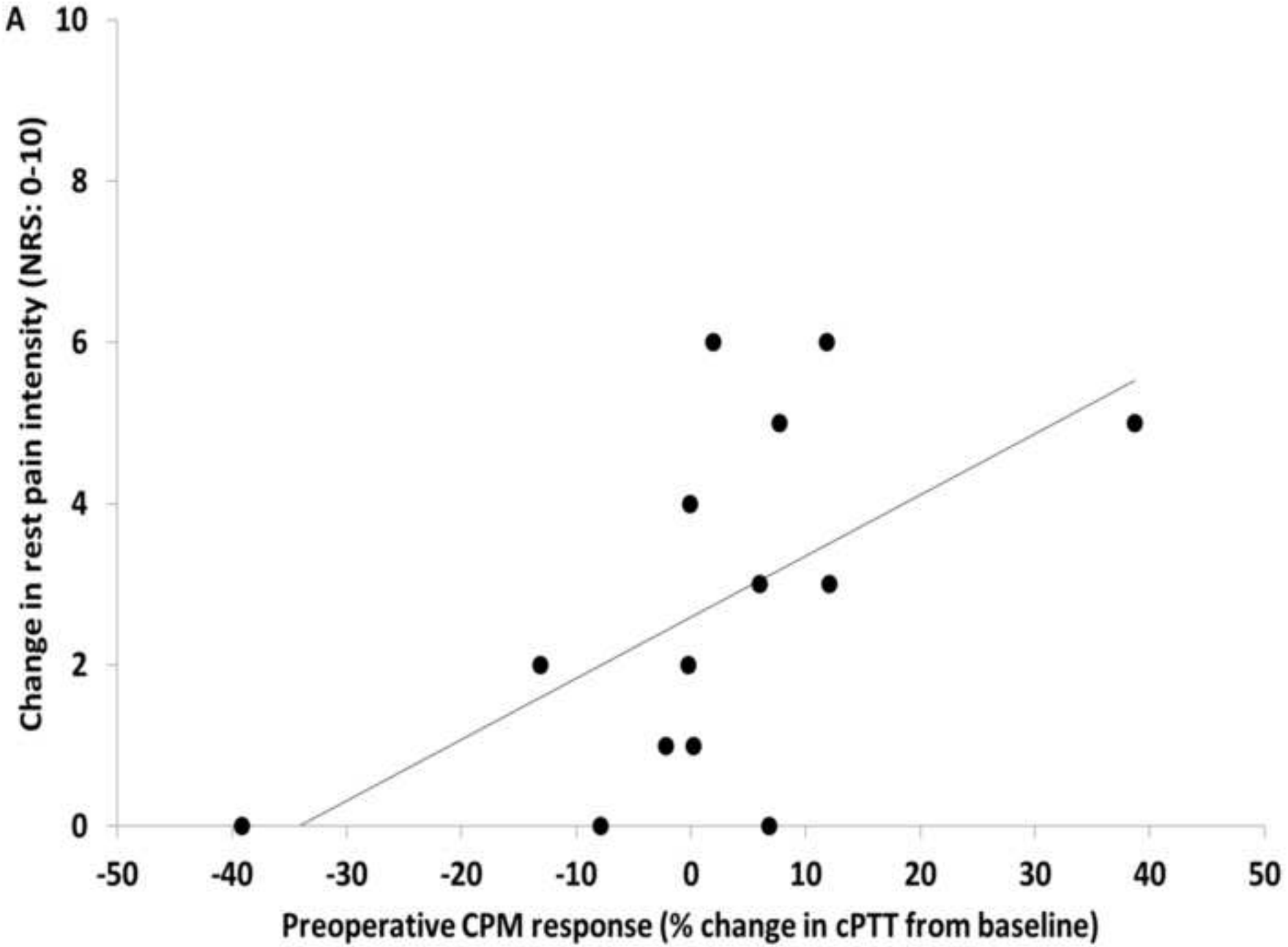

Figure 2B

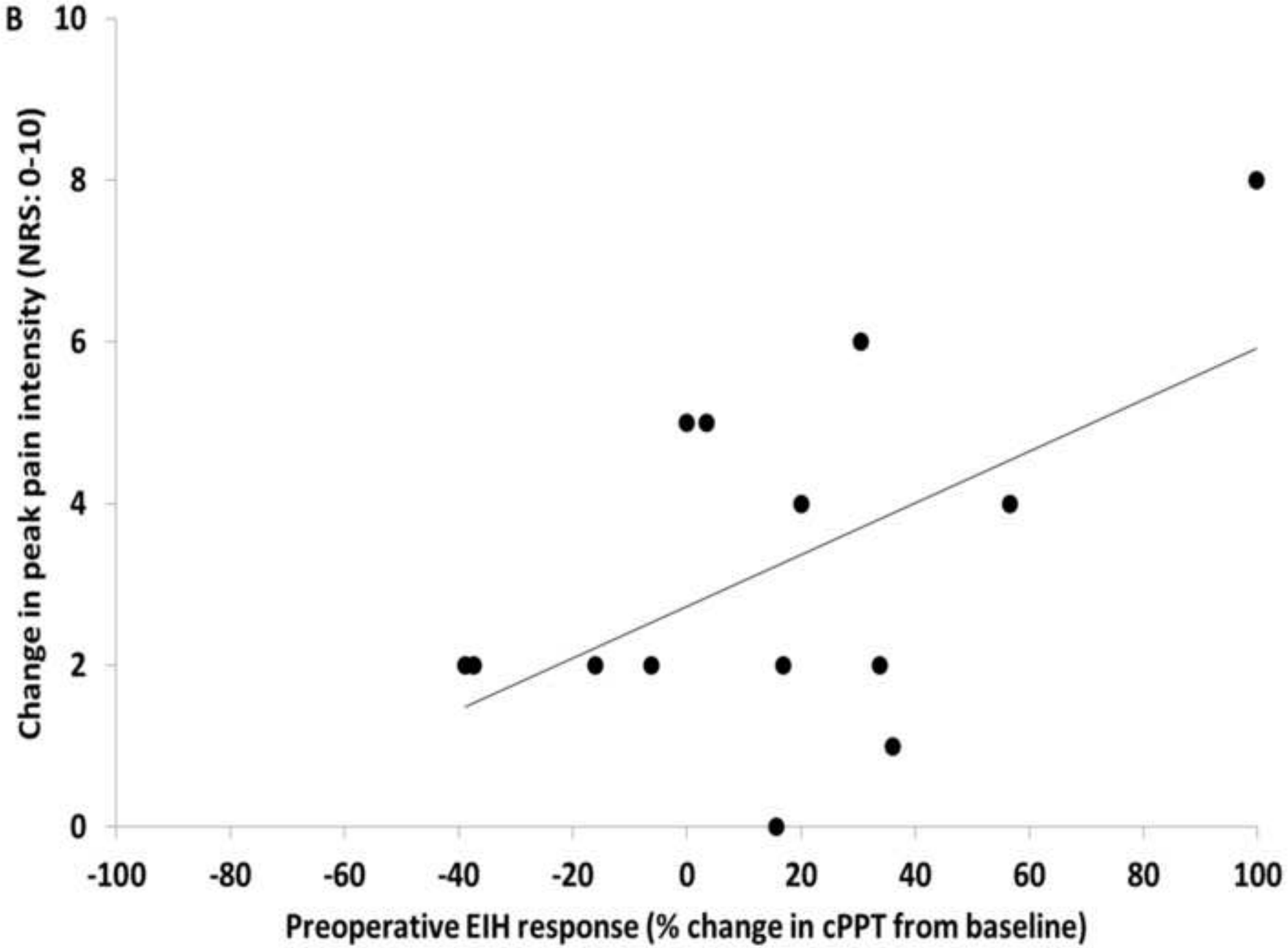

Figure 2C