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Abstract

Chronic postoperative pain following total knee replacement (TKR) in knee osteoarthritis (KOA) implies clinical challenges. Widespread hyperalgesia, facilitated temporal summation of pain (TSP), and impaired conditioning pain modulation (CPM) have been found in painful KOA. This exploratory study investigated postoperative pain relief 12 months after TKR in 4 sub-groups of patients preoperatively profiled by mechanistic quantitative sensory testing.

In 103 KOA patients pressure pain detection and tolerance thresholds (PDT, PTT) were assessed at the lower leg using cuff algometry. TSP was measured as an increase in pain intensity scores during 10 repeated (2 seconds intervals) painful cuff stimuli. CPM was calculated as the relative increase in PDT during painful conditioning stimulation. The grand averages of TSP and CPM were calculated and values below or above were used for sub-grouping. Facilitated TSP/impaired CPM (Group-A, N=16), facilitated TSP/normal CPM (Group-B, N=15), normal TSP/impaired CPM (Group-C, N=44), and normal TSP/normal CPM (Group-D, N=28). Clinical VAS pain intensity score were collected before and 12 months after TKR-surgery and the pain relief calculated. Less pain relief was found in Group A (52.0±14.0% pain relief) compared with Group B (81.1±3.5%, P=0.023) and Group C (79.6±4.4%, P=0.007), but not Group D (69.4±7.9%, P=0.087). Low preoperative PDT was associated with a less postoperative pain relief (R=-0.222, P=0.034) whereas TSP or CPM alone showed no associations with postoperative pain relief.

This explorative study indicated that OA patients with facilitated TSP together with impaired CPM are more vulnerable to experience less pain relief after TKR.

Manuscript

Preoperative pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain relief after total knee replacement

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1. Introduction

Patients with osteoarthritis (OA) may eventually suffer from chronic pain leading to disabilities of the individual and associated costs for public health care systems [20]. OA is the most frequent painful musculoskeletal condition in the elderly population [26]. The end-stage treatment of knee OA (KOA) is total knee replacement (TKR) of which approximately 500,000 are performed in the US every year, and this number is estimated to increase sevenfold by 2030 [41]. Evidence suggests that around 20% of KOA patients will develop chronic postoperative pain after TKR [7,29].

Quantitative sensory testing (QST) is widely used to characterise the underlying mechanisms of KOA pain [3,4,13,30]. KOA patients have decreased pressure pain thresholds (PPTs) around the knee and at extra-segmental sites compared with healthy controls [3,4,13] known as local and widespread hyperalgesia [14]. Patients with chronic e.g. OA [3,4,13], fibromyalgia [15], or low back pain [19] show facilitated pain responses to repeated painful stimulation (temporal summation of pain:TSP) compared with controls. This indicates that the central integrative mechanisms are facilitated potentially due to sensitization processes. A measure for the status of the descending pain control system is conditioned pain modulation (CPM) [5] which is impaired in patients with, e.g. KOA [3,4,13], fibromyalgia [21,23], chronic tension-type headache [36], or chronic pancreatitis [27].

Cuff algometry is widely used for assessment of the deep somatic tissue pain sensitivity [26] in addition to single-point algometry which stimulates more localized superficial somatic structures [12]. Computer controlled cuff algometry has previously been used to assess PPT, TSP, and CPM [4,13,33,40] and offers the advantage of being user independent [33] and has a good test-retest reliability [16].

Accumulated findings suggest that preoperative pain and sensitization play a role in the development of chronic postoperative pain. Impaired CPM before thoracotomy [49] and abdominal [47] surgery has shown to be predictive for the risk of developing chronic postoperative pain. Recently, it was demonstrated that patients who developed severe chronic postoperative pain after TKR had a fourfold increase in preoperative TSP compared with patients who did not develop chronic pain [30]. Another study showed that the degree of widespread hyperalgesia predicted postoperative pain in patients after total hip replacement [48]. Subgrouping KOA patients based on radiographic characterization and pain reveals different sub-groups [10] emphasizing that subgrouping of patients may play a major role in understanding the involvement of different pain mechanisms in KOA and hence possible how vulnerable they are to develop chronic pain after surgery. No studies have investigated the possible value of combined preoperative mechanistic QST parameters (e.g. TSP and CPM) in KOA patients before TKR and the associations to chronic postoperative pain outcomes.

The aims of this exploratory study were (1) preoperative profiling of KOA patients based on spreading hyperalgesia, TSP, and CPM characteristics, (2) to investigate 4 sub-groups of patients preoperatively profiled by mechanistic quantitative sensory testing (TSP, and CPM) and the relation to chronic postoperative pain relief 12 months after TKR, and (3) to investigate the associations between preoperative widespread hyperalgesia and the development of the chronic postoperative pain relief.

2. Methods

2.1 Patients

KOA patients (N=135) scheduled for unilateral TKR from the outpatient clinic at Hospital Vendsyssel, Frederikshavn, Denmark, were invited to join the study. Radiological KOA progression was evaluated using the Kellgren & Lawrence (KL) score [22]. Patients with other diagnosed pain problems (e.g., hip OA, rheumatoid arthritis, fibromyalgia, neuropathic pain), sensory dysfunction, or mental impairment were excluded from the study. The study was approved by The North Denmark Region Committee on Health Research Ethics (N-20120015) and conducted in accordance with the Helsinki Declaration. All patients read and signed an informed consent. This cohort of patients has not previous been included in any other scientific publications.

2.2 Protocol

The peak pain intensity within the last 24 hours (visual analogue scale, VAS), body mass index (BMI), and QST recordings (pressure pain sensitivity, TSP and CPM) were collected before surgery by handheld pressure algomery and cuff algometry. The patients were asked not to take any analgesic medication 24 hours prior to the examination. Moreover, the patients were contacted 12 months after surgery to collect the VAS score of the peak pain intensity within the last 24 hours (VAS). Pain relief was calculated as the percentage difference between pre- and postoperative VAS and used as the main outcome measure.

2.3 Cuff Algometry

Deep-tissue pain sensitivity was evaluated by cuff pressure stimuli using a computer-controlled cuff algometer (NociTech and Aalborg University, Denmark) including a 13-cm wide tourniquet cuff (VBM, Sulz, Germany) and an electronic VAS (Aalborg University, Denmark) for recording of the pain intensity. The cuff was placed at the level of the head of the gastrocnemius muscle of the leg most affected by KOA. The electronic continuous VAS (sliding resistor) was 10 cm long and sampled at 10 Hz; 0 cm indicated “no pain” and 10 cm indicated “maximum pain”.

Pressure Detection and Tolerance Threshold

The pressure was increased by 1 kPa/s and the patient was instructed to rate the pain intensity continuously on the electronic VAS until the tolerance level was reached and, further, the patient was instructed to press a stop button after which the pressure was released immediately. The pressure pain detection threshold (PDT) was defined as the pressure where the VAS score exceeded 2 cm[43] and the pain tolerance threshold (PTT) was defined when the patient pressed the stop button. The measures were repeated three times and the average was used for further analysis.

Temporal Summation of Pain

The concept of temporal summation is an increase in the pain ratings during a series of e.g. 10 identical painful stimuli delivered at a rate of e.g. 0.5 Hz. The automatic cuff algometer was used to elicit temporal summation [16].

A total of 10 repeated mechanical pressure stimuli at the average of the PDT and PTT levels were delivered at 0.5 Hz (1 s stimulus duration and 1 s interval between stimuli) to the lower leg. A constant pressure between the individual pressure stimuli of 1 kPa was applied to avoid movement of the cuff. During the 10 repeated stimuli, the patients rated continuously the pain intensity on a 10 cm continuous VAS (sliding resistor) (“0” represented “no pain”, and “10” represented “maximal pain”).

For analysis of TSP, the mean VAS score was calculated in the interval from the first to the end of the 4th stimulus (VAS-I) and in the interval from the 8th to the end of the 10th stimulus (VAS-II). TSP was defined as the difference between VAS-I and VAS-II (i.e. VAS-II minus VAS-I) [44].

Conditioned Pain Modulation

The concept of CPM is that a tonic painful stimulus (conditioning stimulus) will inhibit pain evoked simultaneously from another site (test stimulus).

The painful conditioned stimulus was initially set to the level of 60 kPa as this value was found equivalent to a general pain perception of 5 cm on the VAS in a preliminary assessment. If not tolerated, the conditioned stimulus was reduced to 30 kPa. Simultaneously, assessment of PDT was performed using a single chamber cuff on the ipsilateral lower leg (test stimulus). The conditioned stimulus was terminated right after the PDT was assessed. CPM was defined as the difference between PDT during and before conditioned pain (i.e. "during" minus "before").

2.4 Handheld Algometry

A handheld algometer (Somedic AB, Sweden) was used for measuring PPT. A 1-cm^2 probe was used and placed perpendicularly to the skin. The pressure was applied at 30 kPa/s until the patient identified the pressure as pain and pressed a button. The algometry was performed on 7 sites at the most affected knee with two distant sites at the tibialis anterior muscle (TA, 5 cm distal to the tibial tuberosity) and at the extensor carpi radialis longus muscle (arm, 5 cm distal to the lateral epicondyle of humerus). The sites in the peripatellar regions were: 2 cm distal to the inferior medial edge of patella (Site 1); 2 cm distal to the inferior lateral edge of patella (Site 2): 3 cm lateral to the midpoint of the lateral edge of patella (Site 3); 2 cm proximal to the superior lateral edge of patella (Site 4): 2 cm proximal to the superior edge of patella (Site 5); 2 cm proximal to the superior medial edge of patella (Site 6); 3 cm medial to the midpoint of the medial edge of patella (Site 7). An average of the seven peripatellar PPTs was used for further analysis [3].

2.5 Statistics

To phenotype patients with a high degree of central sensitization, i.e., facilitated TSP and impaired CPM, the patients were arbitrarily divided into four groups based on a mean cut-off splits of preoperative TSP and CPM defined by facilitated TSP and impaired CPM (Group A), facilitated TSP and normal (defined as the average of the group) CPM (Group B), normal TSP and impaired CPM (Group C), and normal TSP and normal CPM (Group D). Later studies should be designed to optimize these cut-off splits. The data are presented as mean and standard error of the mean (SEM) if not otherwise stated. A one-way analysis of variance (ANOVA) was performed to compare preoperative parameters and the postoperative pain relief for the four groups. The Fisher post-hoc test was used in case of significant differences. Pearson's correlation was used for correlation analysis. Linear regression, including significant correlating parameters from the Pearson's correlations, was used to categorize independent parameters. A previous study showed that cuff measurement in KOA patients is age-dependent, for which reason all analyses were adjusted for age [11]. $P<0.05$ was considered significant.

3. Results

3.1 Demographics

Of the 135 patients recruited, 32 patients (24%) were lost at the 12 month follow-up where three patients could not be reached, two patients had undergone major surgery within the last month, one patient had developed Alzheimer, and 26 patients did not attend the follow-up despite several phone calls. In total 103 patients were included in the current analysis. All patients had technically successful TKRs at follow-up.

Four groups were initially suggested based on the arbitrary QST cut-off levels below or above the grand average of TSP (1.55 ± 0.17 cm) and CPM (5.40 ± 1.05 kPa), respectively.

Group A: facilitated TSP and impaired CPM (N=16).

Group B: facilitated TSP and normal CPM (N=15).

Group C: normal TSP and impaired CPM (N=44).

Group D: normal TSP and normal CPM (N=28).

Group B showed higher BMI compared with Group D (ANOVA: $F=4.772$, $P<0.002$, Fisher: $P=0.020$) (Table 1). Otherwise the groups were identical.

3.2 Postoperative Pain Relief

No difference between preoperative VAS scores was found among the four groups (Table 1; ANOVA: $F=1.86$, $P=0.13$). Group A had significantly (Table 1; ANOVA: $F=2.55$, $P<0.045$) less postoperative pain relief as compared with Group B (Fisher: $P=0.023$) and C (Fisher: $P=0.007$) but not with Group D (Fisher: $P=0.087$).

3.3 Cuff Algometry

Pressure Pain Detection and Tolerance Thresholds

Group D showed significantly higher PDT values compared with Group A and Group B (Figure 1; ANOVA: $F=3.62$, $P<0.005$, Fisher: $P<0.016$) and higher PTT values compared with Group A (ANOVA: $F=2.86$, $P<0.028$, Fisher: $P<0.027$).

Temporal Summation of Pain

A significant interaction was found between groups and TSP (ANOVA: F=52.53, P<0.001) showing less TSP in Group B (Fishers, P=0.002), Group C (Fishers, P<0.001) and Group D (Fishers, P<0.001) compared with Group A, and less TSP in Group C (Fishers, P<0.001) and Group D (Fishers, P<0.001) compared with Group B (Figure 1). TSP alone did not predict postoperative pain relief.

Conditioned Pain Modulation

Group A and Group C showed significantly impaired CPM compared with Group B and Group D (ANOVA: F=25.6, P<0.001, Fisher: P<0.001), but no significant difference was found between the groups with facilitated and normal TSP (i.e., Group A and Group C or Group B and Group D) (Figure 1. CPM alone did not predict postoperative pain relief.

3.4 Handheld Pressure Algometry

No significant difference in PPTs was found between the groups in the peripatellar area (Figure 2; ANOVA: F=0.59, P=0.67), TA (ANOVA: F=1.41, P=0.24), or on the arm (ANOVA: F=0.49, P=0.75). PPTs alone did not predict postoperative pain relief.

3.5 Correlations

A positive correlation was found between postoperative pain relief and preoperative pain (R=0.241, P=0.009). A significant negative correlation was found between postoperative pain relief and preoperative PDT (R=-0.216, P=0.021). A linear stepwise regression analysis, including preoperative VAS and PDT (Table 2), was performed to investigate the possible prediction of postoperative pain relief. The analysis showed that PDT was an independent parameter (R=-0.222, P=0.034) and a trend towards an independent parameter was found for preoperative pain

(R=0.263, P=0.080). As such PDT, independently of preoperative pain, could predict postoperative pain relief.

No significant correlations between the postoperative pain relief and the preoperative TSP, CPM, or handheld algometry, respectively, were found.

4. Discussion

This preliminary study showed that preoperative subgrouping of KOA patients based on TSP and CPM can identify vulnerable groups experiencing less postoperative pain relief 12 months after TKR. Reduced preoperative pressure pain detection thresholds at the lower leg were as a single parameter associated with pain relief 12 months after TKR.

4.1 Preoperative Pain Biomarkers and associations for Postoperative Pain Relief

Sensitization in OA is often characterized by widespread hyperalgesia, impaired descending pain control, and increased facilitation of temporal summation [6,25,42]. As in the present study preoperative widespread hyperalgesia has been shown to predict postoperative pain outcome after total hip replacement [48]. Yarnitsky et al. [49] suggested that impaired CPM was associated with a higher risk of chronic pain after thoracotomy and Wilder-Smith et al. [47] showed similar results in patients after abdominal surgery. Preoperatively facilitated TSP has been shown to predict chronic postoperative pain after abdominal surgery [46] and, recently also after TKR [30]. An increasing number of studies suggest that subgrouping of KOA patients based on clinical and experimental pain assessment parameters can reveal groups of specifically sensitized patients [2,3,10] which could be the patients more vulnerable to experience less pain relief after TKR. The present study confirmed this suggestion and found that subgrouping KOA patients based on preoperatively facilitated TSP and impaired CPM revealed a sub-group of KOA patients with the least pain relief after TKR. This group had less postoperative pain relief as compared with patients showing either showing 1) facilitated TSP but normal CPM or 2) impaired CPM but normal TSP. This indicates that a preoperative multimodal pain mechanistic QST approach is important for predicting the chronic postoperative pain outcome. Drugs designed to block the N-methyl-D-aspartate (NMDA) receptors have shown to reduce TSP [34,45], and drugs promoting the re-uptake of serotonin and norephinephrine have shown to strengthen CPM [32] suggesting that such drugs in combination may be used for selected vulnerable KOA patients before TKR, but future randomized control trials are needed to confirm the hypothesis of such a targeted individualized treatment regime.

It is well known that pain in KOA varies throughout the day (e.g. during walking, while climbing stairs, or when the patient is at rest)[4,29]. To avoid misinterpretation of an e.g. lower current pain while the patients were examined in the laboratory, the peak pain intensity within the last 24 hours is, as in the present study, often applied to assess the knee OA pain [2-4,30,31,35,37,38]. Pain ratings during rest, during the last 24 hours, or during the last 8 days are strongly correlated in patients with hip and knee OA [28].

The present was not designed to predict if patients developed chronic postoperative pain or not and hence the sub-grouping of patients were not optimized for this purpose. However the combination of mechanistic QST parameters for assessing central pain processing may be indicative of possibly biologically important contributions for the postoperative outcome. In case of specific sensitive patients (group A) red flags should be raised prior to surgery to indicate that a given patient could be more vulnerable for developing less postoperative pain relief.

4.2 Temporal Summation of Pain and Conditioned Pain Modulation

Previous studies have shown that patients with KOA have enhanced temporal summation compared with healthy controls [4] and that patients with pain after revision TKR have continued enhanced temporal summation as compared with patients without pain [39]. Preoperative temporal summation has been associated with postoperative chronic pain after TKR [30]. The current study defined two groups with facilitated preoperative TSP, and the group with the most facilitated TSP showed the least pain relief after TKR surgery. Patients with KOA have shown a less efficient CPM system compared with healthy controls [4] but the CPM normalises after pain free recovery after TKR surgery [13]. Dysfunctional preoperative CPM has been suggested to have a predictive value for which patients may develop chronic postoperative pain [47,49], for which reason the current study focused on combining these two apparently important pain mechanisms. It should be stated that neither TSP nor CPM individually as parameters could be associated with postoperative outcomes. The present preliminary study arbitrarily selected cut-off levels of the different QST parameters used for sub-grouping patients and further studies should investigate if these cut-off levels could be further optimised and hence increase the ability to predict postoperative outcomes.

Cuff algometry has previously been widely used to study pain mechanisms in KOA, such as pressure pain thresholds, TSP, and CPM [13,39,40], and offers the advantage of being user-independent [33]. Pain sensitivity has been shown to be related with age for which reason the analysis in the present study was adjusted for age [11]. In addition, studies have shown that increased BMI is associated with increased inflammation [24] and increased inflammation is associated sensitization of the peripheral nociceptors [1], why BMI is important to adjust for in the statistical analysis as done in the present study.

4.3 Widespread Hyperalgesia

Cuff assessment performed on the lower part of the leg in KOA is suggested a proxy for widespread hyperalgesia. The current study showed that KOA patients with preoperatively facilitated TSP and impaired CPM and patients with facilitated TSP had a decreased pressure detection threshold measured by cuff algometry compared with the other groups. Patients with normal CPM combined with normal TSP (normal defined as the grand average in the present population) did not show widespread hyperalgesia compared with the other groups which may suggest that facilitated TSP and widespread hyperalgesia somehow reflect the same pain mechanisms.

Preoperative widespread hyperalgesia measured by handheld pressure algometry has been shown in KOA patients compared with healthy controls [4,8,9,13,17,18,30]. A recent study found that preoperative widespread hyperalgesia measured by pressure algometry did not, as a single parameter, predict postoperative pain after total knee replacement [48]. The present study did confirm that preoperative widespread hyperalgesia as assessed by handheld algometry is not capable of predicting the postoperative pain relief after TKR.

In addition, this study illustrated that widespread hyperalgesia measured by cuff and handheld algometry yielded different sensory profiles which had different predictive values for postoperative KOA patients and hence argue for the value of multi-modal, mechanism based sensory testing.

4.4 Limitations

This study presented a 24% dropout at follow-up limiting the study results by the low sample size of the groups, but these patients are most likely the patients with no pain. This lowers the sensitivity of the current study, and the findings should be replicated in large studies before the clinical implications can be concluded. The study was designed as an explorative study and as such no firm statistical plan was formulated *à priori* which further highlight the preliminary nature at the study. The findings should therefore be replicated in future studies before the findings can be suggested as indicative for diagnosis and treatment of patients before TKR.

The groups were initially established based on arbitrary selected cut-off limits of the mechanistic QST parameters which should be optimised to enhance the sensitivity of the sub-grouping. The current study did not include a healthy control group, and therefore, the terms "normal" TSP and "normal" CPM is used in contrast to "facilitated" TSP and "impaired" CPM.

The present preliminary study can be indicative of how possibly biologically important sensitization processes may contribute to the continued postoperative pain problems in KOA patients and hence provide clinically important pre-operative indications for specifically vulnerable patients.

The clinical outcome parameter in the present study was based on the peak pain intensity in the last 24 hours as this has been shown as a reliable clinical parameter in characterizing KOA pain. If this is the most sensitive parameter to be associated with mechanistic QST parameters is not known and should be further investigated.

This study was conducted in a single hospital and a multi-centre study should confirm the findings of this study. In addition, the patients were end-stage KOA patients and the criteria for eligibility for surgery may vary from country to country.

5. Conclusions

KOA patients with preoperatively facilitated TSP and impaired CPM constitute a group of vulnerable patients who experience less postoperative pain relief 12 months after TKR as compared with patients with either only facilitated TSP or impaired CPM alone. Widespread hyperalgesia assessed by cuff algometry may be a predictive preoperative mechanistic QST parameter for the postoperative pain relief after TKR.

Conflicts of Interest

NociTech is partly owned by Aalborg University and KKP is partly employed by NociTech.

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References

[1] Andrew D, Greenspan JD. Mechanical and heat sensitization of cutaneous nociceptors after peripheral inflammation in the rat. J Neurophysiol 1999;82:2649-2656.

[2] Arendt-Nielsen L, Egsgaard L, Petersen K, Eskehave T, Graven-Nielsen T, Hoeck H, Simonsen O. A mechanism-based pain sensitivity index to characterize knee osteoarthritis patients with different disease stages and pain levels. Eur J Pain 2015;19(10):1406-1417.

[3] Arendt-Nielsen L, Eskehave TN, Egsgaard LL, Petersen KK, Graven-Nielsen T, Hoeck HC, Simonsen O, Siebuhr AS, Karsdal M, Bay-Jensen AC. Association Between Experimental Pain Biomarkers and Serologic Markers in Patients With Different Degrees of Painful Knee Osteoarthritis. Arthritis Rheumatol 2014;66:3317-3326.

[4] Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, Graven-Nielsen T. Sensitization in patients with painful knee osteoarthritis. Pain 2010;149:573-581.

[5] Arendt-Nielsen L, Graven-Nielsen T. Translational musculoskeletal pain research. Best Prac Res Clin Rheumatol 2011;25:209-226.

[6] Arendt-Nielsen L, Skou ST, Nielsen TA, Petersen KK. Altered Central Sensitization and Pain Modulation in the CNS in Chronic Joint Pain. Curr Osteoporos Rep. 2015;13(4):225-234.

[7] Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open 2012;2:e000435-2011-000435.

[8] Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. Ann Intern Med 1988;109:18-24.

[9] Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Fremingham Study. Ann Intern Med 1992;116:535-539.

[10] Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, Campbell CM, Haythornthwaite JA, Edwards RR, Smith MT. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthritis Rheum 2013;65:363-372.

[11] Finocchietti S, Arendt-Nielsen L, Petersen KK, Simonsen O, Graven-Nielsen T. Cuff algometry to assess sensitization in elderly patients with severe knee osteoarthritis compared with controls**.** The 15th World Congress on Pain, 6-11 October 2014, Buenos Aires, Argentina. International Association for the Study of Pain/IASP Press, 2014. s. No. PT232

[12] Finocchietti S, Takahashi K, Okada K, Watanabe Y, Graven-Nielsen T, Mizumura K. Deformation and pressure propagation in deep tissue during mechanical painful pressure stimulation. Med Biol Eng Comput 2013;51:113-122.

[13] Graven-Nielsen T, Wodehouse T, Langford R, Arendt-Nielsen L, Kidd B. Normalisation of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. Arthritis Rheum 2012;64:2907-2916.

[14] Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 2010;6:599-606.

[15] Graven-Nielsen T, Aspegren Kendall S, Henriksson KG, Bengtsson M, Sörensen J, Johnson A, Gerdle B, Arendt-Nielsen L. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. Pain 2000;85:483-491.

[16] Graven-Nielsen T, Vaegter HB, Finocchietti S, Handberg G, Arendt-Nielsen L. Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry: A reliability study. Pain 2015;156(11):2193-202.

[17] Harden RN, Bruehl S, Stanos S, Brander V, Chung OY, Saltz S, Adams A, Stulberg SD. Prospective examination of pain-related and psychological predictors of CRPS-like phenomena following total knee arthroplasty: a preliminary study. Pain 2003;106:393-400.

[18] Hawker G, Davis A, French M, Cibere J, Jordan J, March L, Suarez-Almazor M, Katz J, Dieppe P. Development and preliminary psychometric testing of a new OA pain measure–an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16:409-414.

[19] Hübscher M, Moloney N, Leaver A, Rebbeck T, McAuley JH, Refshauge KM. Relationship between quantitative sensory testing and pain or disability in people with spinal pain—A systematic review and meta-analysis. Pain 2013;154:1497-1504.

[20] Jinks C, Jordan K, Croft P. Osteoarthritis as a public health problem: the impact of developing knee pain on physical function in adults living in the community: (KNEST 3). Rheumatology (Oxford) 2007;46:877-881.

[21] Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 2005;114:295-302.

[22] Kellgren J, Lawrence J. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494.

[23] Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. Pain 1997;70:41-51.

[24] Lee YC, Lu B, Bathon JM, Haythornthwaite JA, Smith MT, Page GG, Edwards RR. Pain sensitivity and pain reactivity in osteoarthritis. Arthritis Care Res 2011;63:320-327.

[25] Lluch E, Torres R, Nijs J, Van Oosterwijck J. Evidence for central sensitization in patients with osteoarthritis pain: A systematic literature review. Eur J Pain 2014;18(10):1367-1375.

[26] Manafi-Khanian B, Arendt-Nielsen L, Frøkjær J, Graven-Nielsen T. Deformation and pressure propagation in deep somatic tissue during painful cuff algometry. Eur J Pain 2015;19(10):1456-1466.

[27] Olesen SS, Brock C, Krarup AL, Funch–Jensen P, Arendt–Nielsen L, Wilder–Smith OH, Drewes AM. Descending inhibitory pain modulation is impaired in patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2010;8:724-730.

[28] Perrot S, Poiraudeau S, Kabir-Ahmadi M, Rannou F. Correlates of pain intensity in men and women with hip and knee osteoarthritis. Results of a national survey: The French ARTHRIX study. Clin J Pain 2009;25:767-772.

[29] Petersen KK, Simonsen O, Laursen MB, Nielsen TA, Rasmussen S, Arendt-Nielsen L. Chronic Postoperative Pain After Primary and Revision Total Knee Arthroplasty. Clin J Pain 2015;31:1-6.

[30] Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB. Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. Pain 2015;156:55-61.

[31] Petersen KK, Siebuhr AS, Graven-Nielsen T, Simonsen O, Boesen M, Gudbergsen H, Karsdal M, Bay-Jensen AC, Arendt-Nielsen L. Sensitization and Serological Biomarkers in Knee Osteoarthritis Patients With Different Degrees of Synovitis. Clin J Pain 2015 [Epub ahead of print].

[32] Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states–maybe it is all in their head. Best Prac Res Clin Rheumatol 2011;25:141-154.

[33] Polianskis R, Graven-Nielsen T, Arendt-Nielsen L. Computer-controlled pneumatic pressure algometry—a new technique for quantitative sensory testing. Eur J Pain 2001;5:267-277.

[34] Price DD, Mao J, Frenk H, Mayer DJ. The N-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. Pain 1994;59:165-174.

[35] Rathleff MS, Petersen KK, Arendt-Nielsen L, Thorborg K, Graven-Nielsen T. Impaired Conditioned Pain Modulation in Young Female Adults with Long-Standing Patellofemoral Pain: A Single Blinded Cross-Sectional Study. Pain Medicine 2015 [Epub ahead of print].

[36] Sandrini G, Rossi P, Milanov I, Serrao M, Cecchini A, Nappi G. Abnormal modulatory influence of diffuse noxious inhibitory controls in migraine and chronic tension-type headache patients. Cephalalgia 2006;26:782-789.

[37] Siebuhr AS, Bay-Jensen AC, Leeming DJ, Plat A, Byrjalsen I, Christiansen C, van de Heijde D, Karsdal MA. Serological identification of fast progressors of structural damage with rheumatoid arthritis. Arthritis Res Ther 2013;14;15(4):R86

[38] Siebuhr A, Petersen KK, Arendt-Nielsen L, Egsgaard LL, Eskehave T, Christiansen C, Simonsen O, Hoeck HC, Karsdal MA, Bay-Jensen AC. Identification and characterisation of osteoarthritis patients with inflammation derived tissue turnover. Osteoarthritis Cartilage 2014;22(1):44-50.

[39] Skou ST, Graven-Nielsen T, Rasmussen S, Simonsen O, Laursen MB, Arendt-Nielsen L. Widespread sensitization in patients with chronic pain after revision total knee arthroplasty. Pain 2013;154(9):1588-1594.

[40] Skou S, Graven-Nielsen T, Rasmussen S, Simonsen O, Laursen M, Arendt-Nielsen L. Facilitation of pain sensitization in knee osteoarthritis and persistent post-operative pain: A cross-sectional study. Eur J Pain 2014;18(7):1024-1031

[41] Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89:780-785.

[42] Suokas A, Walsh D, McWilliams D, Condon L, Moreton B, Wylde V, Arendt-Nielsen L, Zhang W. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2012;20(10):1075-1085.

[43] Uchida Y, Petersen K, Graven-Nielsen T, Arendt-Nielsen L. Within and between daily session reliability of computer-controlled pressure cuff algometry. Abstract book of the 9th Congress of the European Pain Federation, EFIC vol. PO28 No. 363. pp. EFIC5-0373.

[44] Vægter HB, Handberg G, Graven-Nielsen T. Isometric exercises reduce temporal summation of pressure pain in humans. Eur J Pain 2015;19(7):973-983.

[45] Vierck CJ,Jr, Cannon RL, Fry G, Maixner W, Whitsel BL. Characteristics of temporal summation of second pain sensations elicited by brief contact of glabrous skin by a preheated thermode. J Neurophysiol 1997;78:992-1002.

[46] Weissman-Fogel I, Granovsky Y, Crispel Y, Ben-Nun A, Best LA, Yarnitsky D, Granot M. Enhanced presurgical pain temporal summation response predicts post-thoracotomy pain intensity during the acute postoperative phase. J Pain 2009;10:628-636.

[47] Wilder-Smith OH, Schreyer T, Scheffer GJ, Arendt-Nielsen L. Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: a pilot study. J Pain Palliat Care Pharmacother 2010;24:119-128.

[48] Wylde V, Sayers A, Lenguerrand E, Gooberman-Hill R, Pyke M, Beswick AD, Dieppe P, Blom AW. Preoperative widespread pain sensitization and chronic pain after hip and knee replacement: a cohort analysis. Pain 2015;156(1):47-54.

[49] Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best L, Granot M. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. Pain 2008;138:22-28.

Figure Legends

Figure 1. A: Mean (±SEM) preoperative pressure detection thresholds (PDTs, red bars, [kPa]), pressure pain tolerance thresholds (PTTs, yellow bars, [kPa]), conditioned pain modulation (CPM, green bars, [kPa]) and temporal summation of pain (TSP, blue bars, [VAS]) were measured using cuff algometry at the lower leg. Groups are defined by: facilitated TSP and impaired CPM (Group A, N=16), facilitated TSP and normal CPM (Group B, N=15), normal TSP and impaired CPM (Group C, N=44), and normal TSP and normal CPM (Group D, N=28). B: Mean (±SEM) pain relief from the four groups after total knee replacement. * indicates significant difference ($P<0.05$) compared with group A, and # indicates significant difference ($P<0.05$) compared with group B.

Figure 2. Mean (±SEM) preoperative pressure pain thresholds (PPTs) measured using handheld pressure algometry at the peripatellar area (knee), the tibialis anterior muscle (TA), and the extensor carpi radialis longus muscle (Arm). No significant differences were found between groups.

Summary

Knee osteoarthritis patients with low conditioned pain modulation and high temporal summation have more pain 12 months after total knee replacement surgery.

Figure 1

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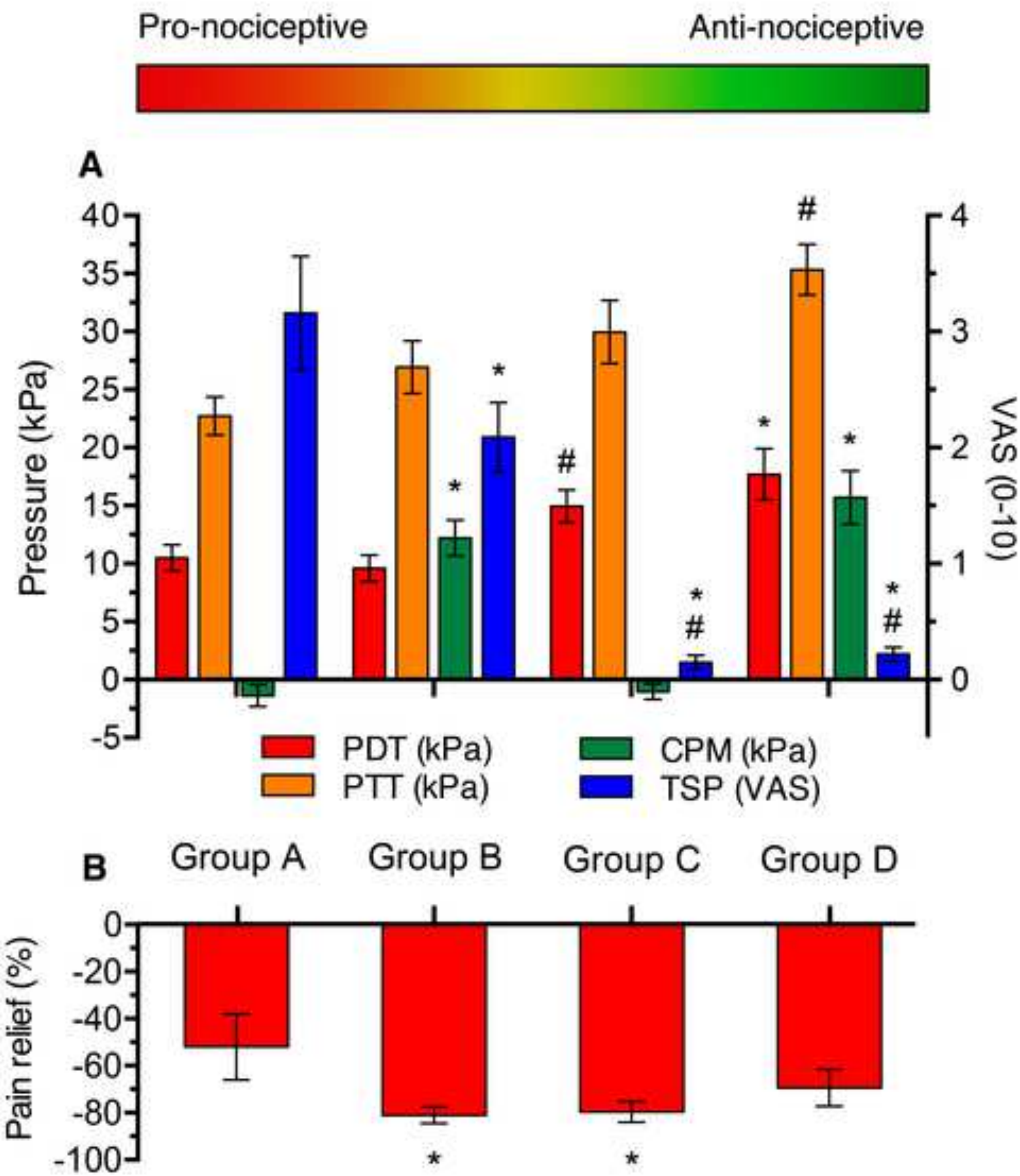

Figure 2

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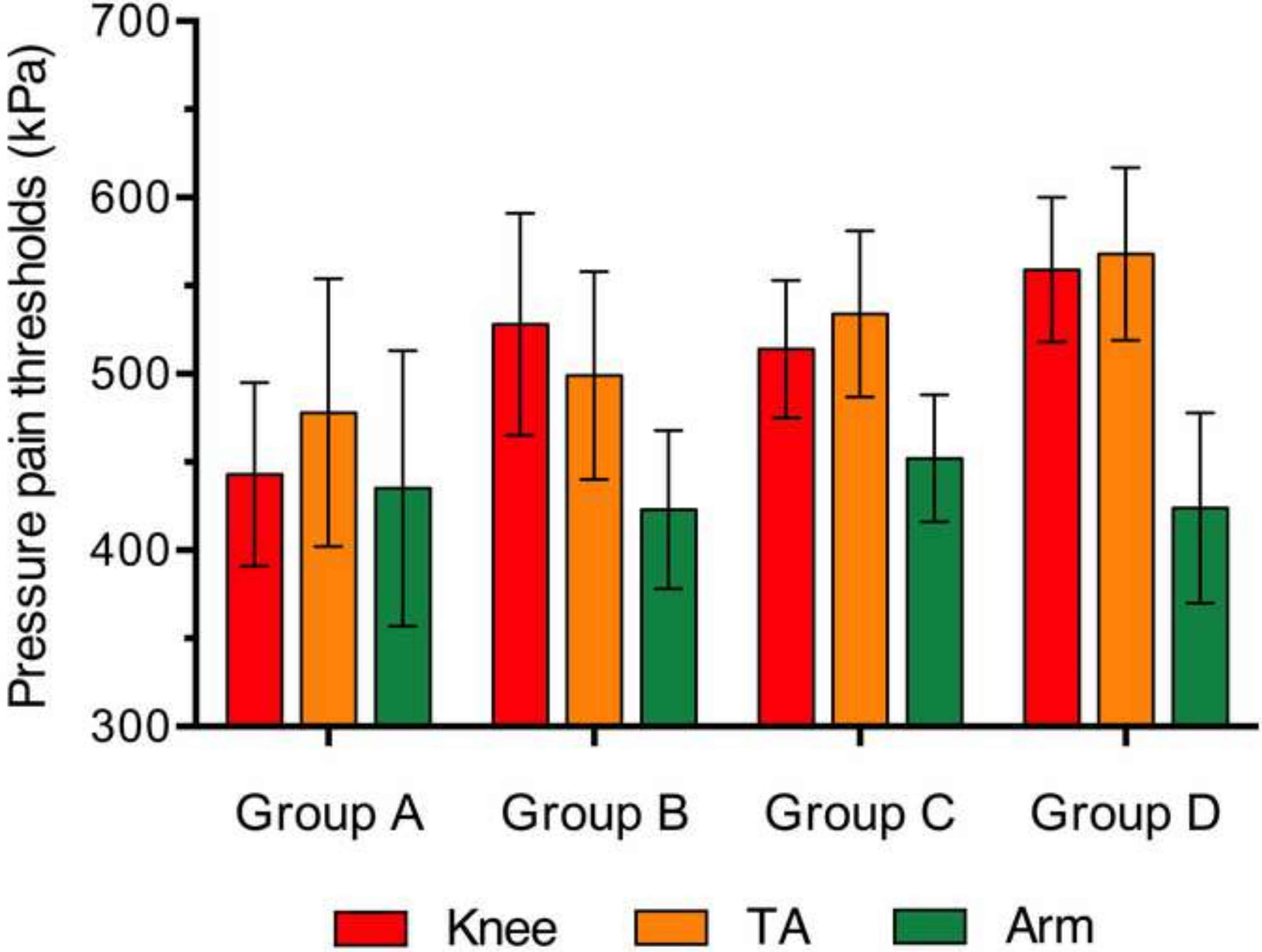

Table 1: Demographic characteristics of the subgrouped KOA patients

	Group A	Group B	Group C	Group D
Number (N) of patients	N=16	N=15	N=44	N=28
Preoperative pain VAS scores (cm, mean ± SEM)	6.6 ± 0.5	6.8 ± 0.5	6.8 ± 0.3	5.9 ± 0.4
BMI (kg/m^2, mean ± SEM)	28.5 ± 1.2	32.2 ± 1.7	30.4 ± 0.8	28.6 ± 1.1*
Age (years, mean ± SEM)	73.2 ± 2.1	69.6 ± 2.2	66.8 ± 1.7	67.0 ± 1.7
Sex (% female)	73.3%	57.1%	70.7%	51.9%
KL (mean (range))	3.7 (2-4)	3.9 (1-4)	3.7 (3-4)	3.8 (3-4)
Pain relief (% VAS reduction, mean ± SEM)	52.0 ± 14.0	81.1 ± 3.5[#]	79.6 ± 4.4[#]	69.4 ± 7.9

BMI: Body Mass Index. KL: Kellgren & Lawrence radiological scores. Significant difference compared with Group B (*, ANOVA: P = 0.020) or Group A (#; ANOVA: P < 0.023).

Table 2. The crude coefficient shows the result from the univariate logistic regression analysis between the postoperative pain relief and the preoperative pain and pressure detection threshold (PDT) measured by cuff algometry. The adjusted coefficient shows the results from the multivariate stepwise logistic regression analysis.

	Crude coefficient	P-value	Adjusted coefficient	P-value
Preoperative pain	0.263	0.005	0.183	0.080
PDT	-0.196	0.042	-0.222	0.034