The Combination of Preoperative Pain, Conditioned Pain Modulation, and Pain Catastrophizing Predicts Postoperative Pain 12 Months After Total Knee Arthroplasty

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Abstract

Objectives: Approximately 20% of knee osteoarthritis (OA) patients undergoing total knee arthroplasty (TKA) report chronic postoperative pain. Studies suggests that preoperative variables such as impaired descending pain control, catastrophizing, function, and neuropathic-like symptoms may predict postoperative pain 12 months after TKA, but the combined prediction value of these factors has not been tested. The current prospective cohort study aimed to combine preoperative risk factors to investigate the predictive value for postoperative pain 12 months after TKA.

Design: Prospective cohort with follow-up 12 months after surgery.

Patients: A consecutive sample of 131 knee OA patients undergoing TKA.

Methods: Pain intensity, Pain Catastrophizing Scale (PCS) scores, PainDetect, conditioned pain modulation (CPM), and Oxford Knee Score (OKS) were obtained before and 12 months after TKA.

Results: TKA improved pain ($p<0.001$), PCS score ($p<0.001$), PainDetect Questionnaire scores ($p<0.001$), and OKS scores ($p<0.001$). Preoperative pain correlated with preoperative PCS ($r=0.38$, $p<0.001$), PainDetect ($r=0.53$, $p<0.001$), and OKS ($r=-0.25$, $p=0.001$). Preoperative PainDetect was associated with preoperative PCS ($r=0.53$, $p<0.001$), and OKS ($r=-0.25$, $p=0.002$). Higher postoperative pain was correlated with high preoperative pain ($r=0.424$, $p<0.001$), PCS ($r=0.33$, $p<0.001$), PainDetect ($r=0.298$, $p=0.001$), and lower CPM ($r=-0.18$, $p=0.04$). The combination of preoperative pain, PCS score, and CPM explained 20.5% of variance in follow-up pain. PCS had a significant effect on pain trajectory when accounting for patient variance ($t=14.41$, $p<0.0005$).

Conclusion: The combination of high preoperative clinical pain intensity, high pain catastrophizing thoughts, and impaired CPM, may predict long-term postoperative pain 12 months after surgery.

Keywords: **Osteoarthritis, conditioned pain modulation, pain catastrophizing, total knee arthroplasty, knee osteoarthritis**

Introduction

Knee osteoarthritis (OA) is a highly prevalent painful musculoskeletal disorder in the elderly (1) and the end-stage treatment is total knee arthroplasties (TKA). 20% of patients suffer from chronic pain after TKA (2) and since the number of TKA surgeries is expected to grow in the coming years (3), it is important to delineate potential preoperative factors for chronic postoperative pain.

A recent translational study on the assessment of conditioned pain modulation (CPM) in humans and diffuse noxious inhibitory control in rodents reported similar responses (4), indicating that CPM might be a measure of descending pain inhibitory function. CPM is impaired in severe knee OA pain compared to healthy subjects (5–7) and impaired preoperative CPM has been associated with the chronic postoperative pain following thoracotomy (8), abdominal surgery (9), and TKA (10) although conflicting evidence exists (11–13). Furthermore, preoperative widespread pressure hyperalgesia was associated with chronic postoperative pain after TKA (7,14,15) and widespread hyperalgesia has been suggested to be a result of impairment of descending pain inhibitory control (16), which further indicates that preoperative CPM might be a predictor for chronic postoperative pain after TKA.

Preoperative pain catastrophizing was shown to predict the presence of pain six (17) and 24 months after TKA (18) and pain catastrophizing may impact CPM (18,19), indicating an interplay between cognitive factors and descending pain inhibitory control.

A recent study found preoperative neuropathic pain-like symptoms predictive of chronic postoperative pain six months after TKA (11) and knee OA patients with positive neuropathic pain-like symptoms have been reported to present with widespread pressure hyperalgesia and impaired function compared with knee OA patients who show negative neuropathic pain-like symptoms (20).

These studies indicate an interaction between CPM, PCS, neuropathic pain-like symptoms and function and may be predictive of chronic postoperative pain after TKA. It is currently unknown if these

preoperative risk factors hold independent predictive value for postoperative pain 12 months after TKA and therefore, the aim of this exploratory study was to investigate the impact of the combination of preoperative factors CPM, PCS, neuropathic pain-like symptoms, and function on pain 12 months after TKA.

Methods

Patients

A total of 185 knee OA patients (82 men and 103 women; mean age ± SD: 68.8 ± 8.92 years) scheduled for unilateral TKA were included in the current study. The patients included here were enrolled in a randomized controlled trial to assess the effect of acute and 7 days postoperative administration of chlorzoxazone on postoperative pain 12 months after TKA. In short, chlorzoxazone is a muscle relaxant aimed to enhance acute postoperative pain recovery (21), which may improve postoperative pain (22), but the study demonstrated no effect of chlorzoxazone on acute and chronic postoperative pain compared to placebo (see (23)) and the patient groups were pooled for the current analysis. Sample size calculation was based on pain intensity after 5 mins of walk 48 hrs after TKA. Exclusion criteria involved use of gabapentinoids, glucocorticoids, opioids, anxiolytics, antipileptics or antidepressants; alcohol abuse; other pain treatments outside of standard care; malignant conditions; pregnancy; BMI > 40 kg/m^2; suffering from other peripheral or central acting diseases; allergy towards chlorzoxazone; per-operative complications (e.g. fractures) and liver diseases. All patients signed an informed consent prior to inclusion. The study was approved by the Danish Medicines Agency, the local ethics committee (VN-20150024) and Danish Data Protection Agency, preregistered at Clinicaltrials.gov (identifier number: NCT02405104) and conducted in accordance to the Declaration of Helsinki.

Quantitative Sensory Testing

Pressure pain sensitivity was evaluated by cuff pressure using a computer-controlled cuff algometer (Cortex Technology and Aalborg University, Denmark). A 13-cm wide tourniquet cuff (VBM, Sulz, Germany) was placed at the head of the gastrocnemius muscle of both legs. An electronic visual analogue scale (VAS) was used to continuously rate the pain on a 10 cm long sliding resistor and sampled at 10 Hz; 0 cm indicated "no pain" and 10 cm indicated "maximum pain".

First, the pressure in kPa was increased at a rate of 1 kPa/s at the ipsilateral lower leg to the surgical knee and patients were instructed to rate the pain on the electronic VAS until a pressure tolerance threshold (PTT) was reached. At this point, the patients were instructed to press a stop button. The pressure pain detection threshold (PDT) was defined as the pressure at which the VAS score exceeded 1 cm (24,25), which is similar to previous studies within this field. Following this, the same procedure was conducted on the contralateral lower leg.

Conditioned pain modulation

CPM was performed by having the tourniquet on the contralateral lower leg inflated to a level of 70% of PPT. Simultaneously, the cuff on the ipsilateral lower leg to the surgical knee was inflated by 1 kPa/sec and the patients were asked to rate their pain intensity on the electronic VAS. CPM was calculated as the absolute change for the conditioned versus non-conditioned PDT ($PDT_{conditioned}$-$PDT_{non\text{-}conditioned}$) where a negative value reflects inefficient CPM whereas a positive value reflects efficient CPM. Test-retest reliability on cuff algometry for CPM measures have shown interclass correlation coefficients (ICCs) of 0.75 – 0.87 (26) indicating good-to-excellent reliability.

Cognition, function, and pain intensity measures

Pre- and postoperative pain catastrophizing thoughts were assessed by the Pain Catastrophizing Scale (PCS) (27). The PCS contains 13 items (each scored from 0-4) reflecting the frequency of catastrophizing cognitions and is based on three subscales on rumination, magnification, and helplessness. PCS scores range from 0-52 and the PCS is validated in both chronic pain patients, pain-free samples (28,29) and the Danish version in clinical and non-clinical cohorts (30).

Preoperative pain and function were tested by the 12-item Oxford Knee Score (OKS) questionnaire which assesses everyday activity. The combined OKS score for function (5/12 items) and pain subscales (7/12 items) was used and have been shown to demonstrate excellent internal consistency (31). The 12 questions were rated on a 5-point Likert-scale ranging from "None" (4) to "Severe" (0). The total score ranges from 0-48 with higher values reflecting better outcome.

To detect possible neuropathic pain-like symptoms, the PainDetect (32) was completed preoperatively. The total score can range from 0-38, where PainDetect scores ≥ 19 indicates neuropathic pain-like symptoms, scores ≤ 12, representing nociceptive pain symptoms, and scores between 13 and 18, indicative of unclear symptoms (32). The PainDetect has been shown to have fair test-retest reliability in OA patients undergoing TKA(33).

Clinical pain was assessed as the pain intensity after 20 mins of rest and was rated on a visual analogue scale (VAS; 0-10 cm; referred to as pain from hereon). Clinical pain was assessed pre- and 12 months postoperatively.

Statistics

All data were assessed for normality by Shapiro-Wilk test. Additional assumptions for multiple backward linear regressions were tested based on Durbin-Watson values and collinearity variance

inflation factor (VIF) and tolerance. Paired samples t-tests were performed to assess changes between pre and postoperative clinical pain, PCS scores, OKS score, PainDetect, and CPM.

Pearson correlation analyses were used to investigate the associations between the preoperative factors as well as correlations between preoperative factors and postoperative pain. A multiple backward linear regression was performed with postoperative pain as the dependent factor and utilizing preoperative CPM, PCS scores, PainDetect, and OKS score as the potential predictors. Backwards selection was applied to the linear regressions to identify predictors using cut-offs for statistical independence and inclusion of 0.05 and exclusion of 0.157, respectively, according to Akaike's Information Criterion for prognostic models (34). For the analysis, all collinearity tolerance and VIF levels were above 0.1 and below 10 (35), respectively, indicating no collinearity or multicollinearity among the independent variables. To take into account patient variability and the effects of PCS and CPM on the individual patient pain trajectories, a mixed effect model was performed, with patients as random factor and baseline PCS and CPM as putative moderator variables on pain intensity change over time. Maximum likelihood estimation was used to estimate the parameter probability distribution and –log2 likelihood was used for information criterion.

All analyses were performed in Statistical Package for Social Sciences (v. 25, IBM). A p-value < 0.05 was considered statistically significant. All data is presented as mean ± SEM unless otherwise stated.

Results

A total of 131 of the 185 knee OA patients (mean age ± SD: 67.73 ± 8.98 years; 73 women) had all preoperative data available and were included in the analyses. The included patients did not differ from the excluded patients on gender ratio ($\chi^2 < 0.001$, $p = 0.98$) but the included group (mean ± SD: 67.73 ±

8.98 years) was significantly younger than the excluded group (mean ± SD: 71.41 ± 8.28, t_{183} = -2.6, p = 0.01). Missing preoperative data included pain intensity (n=4), PCS score (n=21), PainDetect (n=15), CPM (n=12), and OKS score (n=17).

TKA significantly reduced clinical pain intensity (t_{130} = 13.1, p < 0.001), PCS score (t_{125} > 15.143 p < 0.001), PainDetect scores (t_{120} = 9.6, p < 0.001), and improved OKS scores (t_{130} = -2.5, p = 0.013). No significant changes were found when comparing CPM (t_{125} = -0.26, p = 0.79), see TABLE 1. The number of patients reporting postoperative pain 12 months after surgery is presented in TABLE 2, where different cut-offs have been included with their associated percentage out of the full cohort.

Correlations between preoperative risk factors

Preoperative clinical pain intensity correlated with preoperative PCS (r = 0.38, p < 0.001), PainDetect (r = 0.53, p < 0.001), and OKS (r = -0.25, p = 0.001). Furthermore, preoperative PainDetect was associated with preoperative PCS (r = 0.53, p < 0.001), and OKS (r = -0.25, p = 0.002). Preoperative PCS and CPM did not correlate (r = -0.01, p = 0.92).

Correlations between preoperative risk factors and postoperative pain

Higher postoperative clinical pain intensity was associated with higher preoperative clinical pain intensity (r = 0.424, p < 0.001, R^2 = 0.1798, Figure 1A), higher preoperative PCS score (r = 0.33, all p ≤ 0.001, R^2 = 0.1089, Figure 1B), lower preoperative CPM (r = -0.18, p = 0.04, R^2 = 0.0324, Figure 1C), and higher preoperative PainDetect scores (r = 0.298, p = 0.001, R^2 = 0.0889, Figure 1D). Conversely, preoperative OKS score (r = -0.13, p = 0.13) was not significantly associated with postoperative pain.

Independent preoperative factors for 12 months postoperative pain

Model 1 of the multiple regression analysis was significant ($F_{5,125} = 7.26$, $p < 0.001$) and explained 19.4% of postoperative clinical pain intensity variance. After applying backwards selection, model 2 ($F_{3,127} = 12.17$, $p < 0.001$) explained 20.5% (Adj. $R^2 = 0.205$) of the variance in postoperative clinical pain intensity, with significant independent predictors preoperative clinical pain intensity ($\beta = 0.32$, $p < 0.01$), and preoperative PCS score ($\beta = 0.196$, $p = 0.025$). Preoperative CPM ($\beta = -0.124$, $p = 0.122$) contributed to the variance explanation, but was not an independent factor (TABLE 2).

Parameter estimation of PCS and CPM on pain trajectory after surgery

The mixed effect model demonstrated that PCS remained a statistically significant moderator variable for pain intensity change over time ($t = 14.41$, $p < 0.0005$) with a 1-unit increase in PCS resulting in an estimated increase of 0.128 in pain intensity. Conversely, CPM did not significantly impact pain intensity change over time when taking into consideration patients as a random factor ($t = -0.91$, $p = 0.36$). No interaction between PCS and CPM was found ($t = -0.458$, $p = 0.65$).

Discussion

The current study is the first larger report to show that preoperative impaired CPM, higher preoperative clinical pain intensity, higher preoperative PainDetect scores and higher preoperative PCS are all associated with postoperative pain 12 months after TKA. When using these preoperative factors in a backward regression analysis only higher preoperative clinical pain intensity and higher preoperative PCS were shown to be independent predictors for higher postoperative pain intensities 12 months after TKA with preoperative CPM contributing to the prediction value.

Preoperative pain and pain catastrophizing predict pain 12 months after surgery

It is well-documented that preoperative pain is associated with chronic postoperative pain after TKA (36) but recent studies have provided contradicting results (15,37), indicating that other preoperative factors may be important. The current study corroborates earlier findings that preoperative pain intensity is predictive of postoperative pain 12 months after TKA, and further extends this by showing that preoperative inefficient CPM and high pain catastrophizing are important factors to consider. This supports the notion that combining a range of preoperative risk factors yields a more comprehensive understanding of useful preoperative parameters to consider when predicting postoperative pain 12 months after surgery (7,13,38).

A recent study demonstrated that high pain catastrophizing and pain expectation were associated with reduced CPM effect (39). It is generally accepted that chronic pain patients (18) who report high pain catastrophizing also report higher pain intensity and poorer pain-related outcomes possibly due to e.g. maladaptive coping approaches and increased central pain processing (29,40). At present, pain catastrophizing is considered an important factor to consider when predicting poor outcome after surgery (41), though some past reports have questioned its influence (42). A recent study demonstrated that increased preoperative PCS scores were predictive for moderate-to-severe postoperative pain 24 hours after TKA (43). Prospectively, Forsythe et al. (18) reported that those suffering from higher chronic postoperative pain 24 months after TKA had higher preoperative PCS. Additionally, a study found that high preoperative pain catastrophizing was associated with worse preoperative function and predicted poor pain outcome 6 months after TKA (17). These studies are supported by the current findings, in that preoperative PCS score was an independent factor for postoperative pain. Preliminary evidence suggests that interventions targeted at reducing catastrophizing thoughts may improve

outcomes such as self-reported pain and function (44). However, a recent large multisite randomized clinical trial demonstrated that preoperative reduction of PCS by pain coping therapy did not decrease the prevalence of chronic postoperative pain when compared to a non-treated group and this does question if modifying preoperative pain catastrophizing improves the postoperative outcome (45). This is supported by a recent study demonstrating that cognitive behavioral therapy based pain education did not improve postoperative pain compared to usual care at three or 12 months after TKA (46). Therefore, strategies aimed at enhancing recovery after TKA in the most vulnerable subgroup of patients remain unclear and require further studies.

Preoperative CPM contribute to variance explanation in postoperative pain after TKA

Descending pain pathways, have been studied in animals and humans for decades and in patients with chronic pain it seems evident that impairment of descending pain pathways is associated with higher pain intensities (47) and impaired CPM has been found in patients suffering knee OA (5–7). Furthermore, CPM has been shown predictive of chronic postoperative pain six months after thoracic surgery (8), abdominal surgery (9), and TKA (10,48), and CPM predicted pharmaceutical treatment effect of duloxetine in painful diabetic neuropathy (49) and non-steroidal anti-inflammatory drug treatment in knee osteoarthritis (50,51). Two studies in OA patients undergoing TKA found that in 14 (10) and 47 (48) knee OA patients, impaired preoperative CPM was correlated with postoperative pain 6 months after TKA. However, the majority of studies including CPM as a preoperative predictor for chronic postoperative pain after TKA report poor prediction value and several studies have been unable to demonstrate associations between preoperative CPM and chronic postoperative pain (52). The current study supports this in that preoperative CPM and postoperative pain 12 months after TKA were correlated, but CPM was not an independent risk factor for chronic postoperative pain after TKA. This

finding may indicate that identification of additional preoperative risk factors is needed to better predict chronic postoperative pain 12 months after TKA.

The interaction between preoperative risk factors for chronic postoperative pain

Preoperative clinical pain intensity has been shown to predict chronic postoperative pain in multiple lines of evidence (7,13,53,54). High pain catastrophizers in general report higher pain intensity (18) and preoperative pain catastrophizing has been shown to predict presence of pain six (17) and 24 months after TKA (18). Furthermore, chronic postoperative pain after TKA is associated with preoperative widespread pressure hyperalgesia (13–15,55). Since impairment of descending pain inhibitory control may lead to widespread hyperalgesia (16) this further supports the notion that CPM may be important to consider when predicting chronic postoperative pain. The reliability of CPM assessment have been questioned (56,57) and it is evident that different CPM paradigms will yield different results (26), which complicates the generalizability of the current evidence. The predictive value of have been highlighted in a few studies (8,10,49–51) but a recent systematic review questions this predictive value (52). The current findings demonstrated an association between preoperative CPM and pain assessed at 12-months follow-up, but CPM was not an independent predictor and therefore the current study adds to the ongoing debate whether CPM holds predictive value for future pain.

Additionally, neuropathic pain-like symptoms predict chronic postoperative pain six months after TKA (11), and knee OA patients with signs of neuropathic pain-like symptoms also exhibit widespread pressure hyperalgesia and impaired function when comparing with patients with no signs of neuropathic pain-like symptoms (20). This study supports that preoperative clinical pain intensity and PCS are independent predictors for chronic postoperative pain following TKA and there might be an association between preoperative CPM and PainDetect and chronic postoperative pain after TKA.

Limitations

The current study is limited by missing data from approx. 30% of the patients, which resulted in exclusion, however, this is a common phenomenon in these longitudinal studies (12,42,45). The excluded patients were significantly older than the included and it is known that younger age prior to TKA is associated with higher risk of chronic postoperative pain. It was, however, recently shown in a large-scale study that CPM is unaffected by age (58) but the results from the current study should be interpreted with care due to this limitation. The total variance explained by the included preoperative factors was 20.5% indicating only a modest prediction value but is the first to demonstrate the potential in combining readily available variables such as preoperative pain and PCS, with mechanistic pain profiling such as CPM.

Conclusions

The current study demonstrates correlations between high preoperative clinical pain intensity, high preoperative pain catastrophizing thoughts, high preoperative neuropathic pain-like symptoms and impaired CPM and high clinical pain intensity 12 months after TKA. The combination of preoperative high clinical pain scores, high levels of pain catastrophizing thoughts, and impaired descending pain modulation predicted 20.5% variance in pain at rest 12 months after TKA with preoperative clinical pain intensity and pain catastrophizing scores as independent predictors. Future studies should explore, how adding additional preoperative risk factors could increase the prediction value and if modification of these preoperative risk factors in combination reduces the risk of chronic postoperative pain.

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Author contributions

KKP, ML, OS, and LAN contributed to the conceptual development of the study. Data were collected by ML and OS and analyzed by DBL. All authors interpreted and discussed the data. DBL wrote the first draft which was critically revised by KKP, RRE, LAN, OS, and ML. All authors approved the final version.

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Figure legends:

FIGURE 1. Scatter plots of the associations between preoperative factors and postoperative pain. A positive association between preoperative pain intensity (A), PCS (B), PainDetect (D), and postoperative pain intensity was found. Conversely, CPM demonstrated a significant negative correlation to postoperative pain (C). *PCS: Pain Catastrophizing Scale; CPM: Conditioned Pain Modulation*

Table legends

TABLE 1. Preoperative versus postoperative differences in included variables - Mean ± SD. 12 months after TKA, patients had significantly lower pain, PCS scores, PainDetect scores, and OKS scores. CPM did not change after TKA.*TKA: Total knee arthroplasty; PCS: Pain Catastrophizing Scale; OKS: Oxford Knee Scale; CPM: Conditioned Pain Modulation*.

TABLE 2. Ratio of patients presenting with pain > 0, 1, 2, and 3 at 12 months follow-up after TKA. Considerable difference in the percentage of patients that were classified as having postoperative pain 12 months after TKA, depending on threshold for pain presence. *TKA: Total knee arthroplasty*

TABLE 3. Multiple backward linear regression analysis including 131 patients. Model 1 containing all preoperative predictors explained 19.4% of the postoperative pain variance. Model 2 explained 20.5% of the postoperative pain variance and revealed preoperative pain and PCS score as significant independent predictors for postoperative pain, whereas preoperative CPM contributed non-significantly to the variance explanation. *PCS: Pain Catastrophizing Scale; CPM: Conditioned Pain Modulation; OKS: Oxford Knee Score, R^2: R-squared, proportion of variance explained by independent predictors*

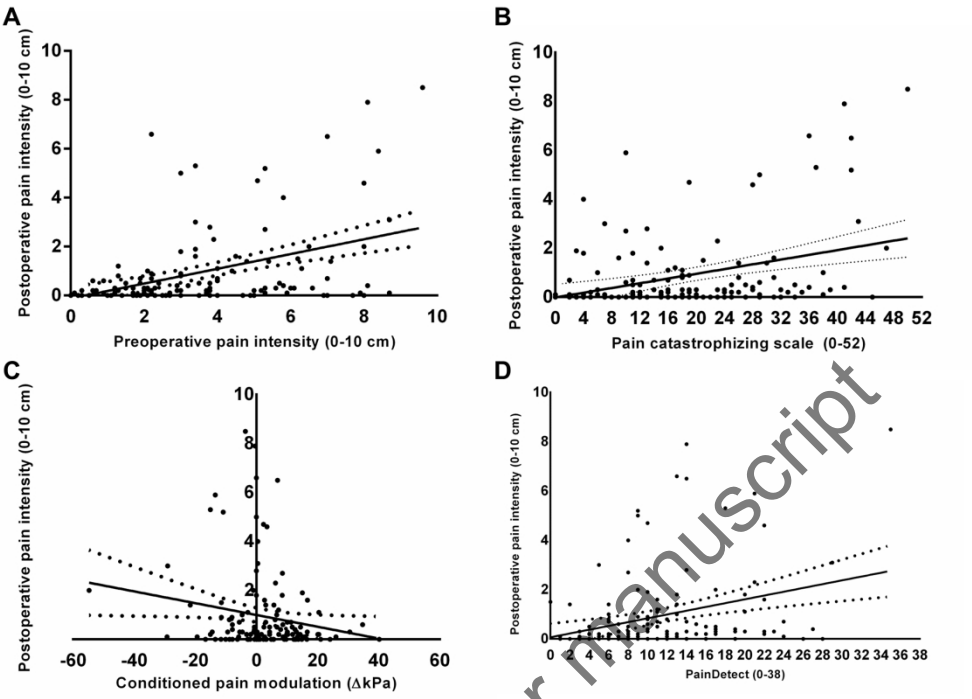

FIGURE 1. Scatter plots of the associations between preoperative factors and postoperative pain. A positive association between preoperative pain intensity (A), PCS (B), PainDetect (D), and postoperative pain intensity was found. Conversely, CPM demonstrated a significant negative correlation to postoperative pain (C). PCS: Pain Catastrophizing Scale; CPM: Conditioned Pain Modulation

254x190mm (300 x 300 DPI)

TABLE 1.

	Preoperative	Postoperative	*p**
Pain	3.5 ± 2.35	0.94 ± 1.67	**< 0.001**
Total PCS score	19.99 ± 11.48	4.01 ± 6.94	**< 0.001**
PainDetect	11.41 ± 6.71	4.91 ± 4.89	**< 0.001**
CPM	2.27 ± 12.56	2.64 ± 13.39	0.79
OKS scores	33.47 ± 9.17	35.03 ± 12.59	**0.013**

** Paired-samples t-tests*

TABLE 3.

	Yes	No	Percentage of patients with postoperative pain 12 months after surgery
Pain intensity at rest > 0	94	37	71.8%
Pain intensity at rest > 1	32	99	24.43%
Pain intensity at rest > 2	16	115	13.9%
Pain intensity at rest > 3	13	118	9.92%

TABLE 3.

Model	Pre-operative factor	Pain after 20 mins of rest (follow-up) Standardized coefficient	*P*	R^2
1				0.194
	Pain	**0.29**	**0.003**	
	CPM	-0.133	0.113	
	Total PCS score	0.175	0.07	
	PainDetect	0.059	0.58	
	OKS	0.008	0.93	
2				0.205
	Pain	**0.32**	**< 0.001**	
	CPM	-0.124	0.12	
	Total PCS score	**0.196**	**0.025**	

** Based on 0.157 removal criterion (AIC)*