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## Predictors of Postoperative Movement and Resting Pain following Total Knee Replacement

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### Abstract

This study determined preoperative predictors of movement and resting pain following total knee replacement (TKR). We hypothesized that younger patients with higher preoperative pain intensity, pain sensitivity, trait anxiety, pain catastrophizing, and depression would be more likely to experience higher postoperative movement pain than older patients with lower scores on these variables prior to surgery and that predictors would be similar for resting pain. Demographics, analgesic intake, anxiety, depression, pain catastrophizing, resting pain, movement pain (i.e., during active knee range of motion), and quantitative sensory tests, were performed preoperatively on 215 participants scheduled for a unilateral TKR. On postoperative day 2 (POD2), analgesic intake, resting pain, and movement pain were again assessed. Significant predictors of moderate or severe *movement pain* were higher preoperative movement pain, von Frey pain intensity (VFPI) and heat pain threshold (HPT). People with severe movement pain preoperatively were 20 times more likely to have severe movement pain postoperatively. When the influence of preoperative movement pain was removed, depression became a predictor. Significant predictors of moderate to severe *resting pain* were higher preoperative resting pain, depression, and younger age. These results suggest that patients with higher preoperative pain and depression are more likely to have higher pain following TKR and younger patients may have higher resting pain. Cutaneous pain sensitivity predicted movement pain but not resting pain, suggesting that mechanisms underlying movement pain are different from resting pain. Aggressive management

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#### Conflict of Interest

The authors have no conflicts of interest to disclose.

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of preoperative pain, pain sensitivity, and depression prior to surgery may facilitate postoperative recovery.

## Keywords

Postoperative Pain; Movement Pain; Total Knee Replacement; Pain Sensitivity

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## 1. Introduction

It is estimated that over 500,000 total knee replacements (TKR) are performed each year in the U.S. [43,46]. The pain caused by this procedure can be severe during the immediate postoperative period and the severity of this early pain is predictive of persistent pain 4–22 months following knee arthroplasty [52]. Movement pain is more severe than resting pain [20], significantly correlates with a patient's ability to perform postoperative recovery activities [25,53] and accounts for a significant portion of the variance in functional outcomes two months after orthopedic surgery [20]. No study has investigated predictors of postoperative movement pain independent from resting pain. It is, therefore, unknown what characteristics predict the more severe pain associated with postoperative recovery.

Studies evaluating predictors of pain after TKR have largely focused on psychological traits and the prediction of overall pain 6 months to 1 year following surgery [7,16,54]. Higher preoperative pain intensity, depression, anxiety, and pain catastrophizing have predicted chronic pain following TKR [7,16,29,49,51,54]. One study investigated psychological predictors of immediate postoperative pain following TKR finding higher pain catastrophizing and negative mood to be significant predictors [58]. No study has included physiologic measures of pain sensitivity as possible predictors of pain following TKR. It is, therefore, unknown if preoperative pain sensitivity predicts pain following TKR and how this response influences the contribution of psychological traits, particularly during the immediate postoperative period.

Studies that have included pain sensitivity measures as possible predictors of pain following obstetrics and gynecology surgery consistently identify higher thermal pain sensitivity to be predictive of postoperative pain [5,48,59,64]. A systematic review of 43 studies with 23,057 patients undergoing a variety of surgical procedures found that higher preoperative pain and anxiety, younger age, and abdominal, orthopedic, and thoracic surgery consistently predicted higher postoperative pain. All studies including pain sensitivity measures in this review showed a significant influence on postoperative pain but this factor was mainly examined in obstetrics and gynecology surgery and not across multiple surgeries. The coefficient of determination of the predictive models in this review was less than 54% suggesting that more vigorous studies with robust statistics and validated designs are needed to investigate this field of interest [37]. A comprehensive approach that includes both physiological and psychological measures as possible predictors of acute postoperative pain is needed to fully understand and target patients at risk for uncontrolled postoperative pain so that appropriate treatments can be implemented to promote recovery and improve functional outcomes, particularly after TKR which requires aggressive physical therapy to reach functional goals.

The purpose of this study was to determine which preoperative characteristics predict moderate to severe movement and resting pain immediately following TKR using a comprehensive set of physiological and psychological variables. We hypothesized that younger patients with higher preoperative pain intensity, pain sensitivity, trait anxiety, pain catastrophizing, and depression would be more likely to experience moderate to severe

postoperative movement pain than older patients with lower scores on these variables preoperatively and that these predictors would be similar for resting pain.

## 1. Methods

### 2.1. Participants

Participants recruited for this prospective, cohort study were enrolled as part of a larger trial examining the effectiveness of transcutaneous electrical nerve stimulation (TENS) on pain and function after TKR (TANK, TENS After New Knee, Study). Data were collected on 215 participants during a preoperative visit 1 week prior to surgery in the orthopedic clinic and on postoperative day 2 (POD2) in the subject's room prior to the morning physical therapy session, after approval by the local Institutional Review Board. Five hundred eleven patients met inclusion criteria (i.e., were 30 years old with knee osteoarthritis, spoke English, and were indicated for a primary unilateral TKR at either the University of Iowa Hospitals and Clinics or the Iowa City Veteran's Affairs Medical Center) and were approached to participate in this study. Patients were excluded if they: (1) had used a TENS unit within the last five years (N=73); (2) had a condition that precluded the use of TENS (e.g., pacemaker or allergy to nickel electrodes; N=22); (3) had severe chronic uncontrolled pain at a site other than the surgical knee (N=29); (4) had a stroke or other CNS disorder (N=19); (5) were unable to provide informed consent (prisoners or cognitively challenged; N=12); (6) were confined to a wheelchair (N=3); or (7) were unable to correctly identify sharp and dull stimuli on their affected leg (N=10). Of the 343 patients who were eligible, 100 declined to participate and 15 had scheduling issues preventing preoperative testing. Following surgery, 13 participants were excluded due to surgical complications (i.e., excessive numbness determined by sharp and dull identification at the testing areas, post-operative disorientation measured by a subset of questions from the Mini Mental Status Questionnaire, or illness), leaving 215 participants in the final dataset. This recruitment rate (63%) is consistent with other studies on this topic that report recruitment rates (49% to 68%) [5,54,58]. Prior to participation, the study was explained, informed consent was obtained, and demographic information was recorded.

### 2.2. Pain Intensity (resting and movement) and ROM

Participants were asked to rate the pain in their surgical knee on a vertical, 21-point numerical rating scale (NRS) where 0 was "no pain" and 20 was "the most intense pain imaginable." Resting pain intensity was measured prior to any study procedures. Movement pain was measured during active flexion and extension of the arthritic knee. For active extension, a towel roll was placed under the ankle of the surgical leg and participants straightened their leg as far as possible by pressing their knee toward the exam table. Pain intensity was rated when participants reached their maximum extension and degrees of extension were measured using a goniometer with the stationary arm of the goniometer aligned with the greater trochanter and the lateral malleolus used as the landmark to align the movable arm of the goniometer. For active flexion, participants flexed their surgical knee as far as possible while keeping their foot flat on the exam table. Participants were asked to rate the intensity of the pain in the surgical knee when maximum flexion was reached and degrees of flexion were measured with the same goniometer and landmarks. The 0–20 NRS has been previously shown to be easier to use and associated with higher compliance and lower failure rates in older adults when compared to the Visual Analogue Scale [32]. NRSs have established validity and reliability for assessing acute [13,31,38,47] and postoperative [23] pain and correlate well with the Visual Analogue Scale during the postoperative period (.90 to .95) [14,23,34]. A 21-point scale was used (versus a 0–10 NRS) based on evidence that 21 points provide a sufficient and needed level of discrimination [39]. Goniometer measures have concordant validity with radiography of 0.97 to 0.99 [8].

### 2.3. Quantitative Sensory Testing

Three quantitative sensory tests were used to measure pain sensitivity to mechanical and thermal stimuli.

1. *Cutaneous mechanical pain sensitivity* was measured with Von Frey Pain intensities (VFPI). A standardized von Frey monofilament (Stoelting Co., Wood Dale, IL) was pressed at a right angle to the skin's surface with a standard force (451 mN) sufficient to bend the filament and participants were asked to rate the pain intensity caused by this force on the 0–20 NRS (described above).
2. *Cutaneous thermal pain sensitivity* was measured with heat pain thresholds (HPT). A TSA-II Neurosensory Analyzer with a 16×16 mm Peltier thermode (Medoc, Israel) starting at a baseline temperature of 34°C and increased at a rate of 1°C/s to a maximum 52°C. Participants were instructed to press a button when the heat sensation was first perceived as painful. If the temperature reached 52°C, that temperature was recorded as the HPT.
3. *Pressure pain thresholds* (PPT) were used to measure deep mechanical pain sensitivity using a hand-held pressure algometer (Somedic AB, Farsta, Sweden) with a 1cm<sup>2</sup> digital probe applied at 40kPa/s. The probe was pressed perpendicularly to the skin and the subject was asked to press a button when the pressure was first perceived as painful.

All measurements were performed on three sites 4cm apart and 4cm medial to the center of the patella (i.e., proposed incision site) on both knees. The average of the scores at these 3 sites was used as the final value for each measure to obtain a representative measure of pain sensitivity at the affected knee. Each subject had one familiarization test for each measure performed on the forearm prior to data collection. These quantitative sensory measurements have been previously used to determine increased sensitivity to pain [21,30,56,69]. Intra-class correlations ranged from 0.92–0.97 for VFPI, 0.70–0.92 for HPT, and 0.87–0.97 for PPT (inter-rater reliability).

### 2.4. Analgesic medications

All analgesic medications taken by the subject preoperatively and 24 hours prior to data collection on POD2 were recorded (i.e., name, route, dose, date/time of each dose). All opioid medications (oral and intravenous) were converted into an equianalgesic dosage of oral morphine [26,41,50,63]. Non-opioid analgesic medications were converted to acetaminophen equivalents using the conversion table [1]. Combination opioid and non-opioid analgesic medications were sub-divided into each component (opioid/non-opioid), and then separately calculated in the appropriate category. For example, Percocet (5mg oxycodone/325mg acetaminophen) was separated into the appropriate opioid (oxycodone) and non-opioid (acetaminophen) categories. The 5mg of oxycodone was converted into a 7.5mg oral morphine equivalent, and the 325mg of acetaminophen required no conversion in the non-opioid category [6,42]. Celecoxib 200mg PO and oxycodone 10mg PO were routinely given once prior to surgery and BID while hospitalized after surgery. Oxycodone/acetaminophen 5/325mg 1–2 tablets PRN and/or morphine 1mg IV every 30 minutes PRN was used for breakthrough pain after surgery. Intraoperative anesthesia included regional anesthesia with bupivacaine and/or general anesthesia with propofol followed by isoflurane or sevoflurane. Intraoperative analgesia included femoral analgesia using ropivacaine with or without IV narcotics. These data were categorized and evaluated as a possible control variable.

## 2.5. Psychological Variables

Anxiety, depression, and pain catastrophizing were measured during the preoperative clinic visit using the Trait Anxiety Form of the State Trait Anxiety Inventory (STAI), the Geriatric Depression Scale (GDS), and the Pain Catastrophizing Scale (PCS), respectively.

The *Trait Anxiety scale* (STAI Form Y-2) consists of twenty statements that assess how respondents generally respond to perceived threats in the environment [4,60,61] rated on a 4-point scale ranging from “almost never” to “almost always.” The STAI has good test-retest reliability (STAI Trait 0.88; STAI State 0.70), and moderate to strong correlations with other measures of anxiety (Depression Anxiety Stress Scale – Anxiety subscale 0.47; Beck Anxiety Inventory 0.68) [17]. This instrument has been used in studies examining patients following hip or knee replacement [19].

The *Geriatric Depression Scale* (GDS) is a five item-screening tool for depression in the older population. Participants are considered to screen positive for depression if they answer positive to two or more questions. The GDS has shown high inter-rater reliability (0.84), sensitivity (0.925–0.94), and specificity (0.77–0.81) [35,45,55].

The *Pain Catastrophizing Scale* (PCS) is a 13 item survey designed to measure rumination, magnification, and helplessness responses of the subject [67]. Participants rate their thoughts and feelings about pain using a 5-point scale ranging from “not at all” to “all the time.” The PCS has shown high internal consistency ( $\alpha=0.77-0.87$ ) for adults [65,66,70]. A recent analysis of the PCS in patients with low back pain demonstrated that all items on this scale loaded exclusively on a scale factor distinguishing pain catastrophizing from other factors related to low back pain (factor loadings between 0.466 and 0.816) [24].

## 2.6. Data Collection Protocol

At the preoperative clinic visit, consented participants completed a demographic form and the psychological questionnaires (STAI, GDS, PCS). Pain intensity at rest was measured and then quantitative sensory tests were performed as described above on the surgical and contralateral knees. Active extension and flexion were then performed and the subject rated the intensity of pain caused by these movements in the surgical knee. Postoperatively, the intraoperative anesthesia and analgesia intake was extracted from the electronic medical record. Pain intensity at rest and during active extension and flexion was measured again the morning of POD2 prior to any physical therapy, along with degrees of active flexion and extension, and postoperative analgesic intake was recorded.

## 2.7. Statistical Analysis

Descriptive statistics were used to describe preoperative and postoperative pain variables using percentages for categorical variables, and mean  $\pm$  SD or median (25<sup>th</sup>–75<sup>th</sup> percentile) for continuous variables. Movement pain was determined by averaging the pain intensity ratings during active extension and flexion on POD2. These scores were then coded as mild, moderate, or severe pain using cutoff points established in the literature [7]. Mild pain = 0–7 (equivalent to 0–3.5 on a 0–10 NRS), moderate pain = 8–14 (equivalent to 4–7 on a 0–10 NRS), and severe pain = 15–20 (equivalent to 7.5–10 on a 0–10 NRS). This variable was categorized because the data had a bimodal distribution and were not normally distributed, making this approach more appropriate. Peak cut-off points in the distribution were consistent with standard cut offs for mild, moderate, and severe pain providing confirmation for the appropriateness of these cut-offs. This approach also provided clinically meaningful results (i.e., clinicians can identify with patients who have severe pain versus an average pain rating of an 8 on a 0–10 NRS). A similar approach was used for resting pain. However, due to the large number of participants with “0” resting pain and the small number of

participants with severe resting pain, the data were coded as none, mild, and moderate to severe. None = 0–2 (0–1 on a 0–10 NRS), mild pain = 3–7 (1.5–3.5 on a 0–10 NRS), and moderate to severe pain = 8–20 (4–10 on a 0–10 NRS). For each candidate explanatory variable (see Table 1 for a list of all candidate explanatory variables), a generalized logit model for pain with movement and pain at rest was fitted which included the candidate variable as the independent variable adjusted for the treatment received. Odds ratios for mild (resting only), moderate and severe pain, using mild pain as reference for movement pain and none as reference for resting pain, were calculated for each variable. Those variables with  $p < 0.10$  were then included in a stepwise logistic regression analysis with criteria of  $p < 0.10$  for entry and  $p > 0.10$  for removal from the model. Quantitative sensory tests on the contralateral knee were highly correlated with the affected knee (PPT  $r = .65$ ,  $p < .0001$ ; VFPI  $r = .70$ ,  $p < .0001$ ; HPT  $r = .75$ ,  $p < .0001$ ) so the contralateral knee data were not included in these analyses.

### 3. Results

#### 3.1. Preoperative Assessment

The 215 participants enrolled in the study had a mean age of  $61.68 \pm 9.82$  years, a mean body mass index of  $38.18 \pm 11.43$ , were primarily female ( $n = 125$ , 58%), white ( $n = 200$ , 98%), college educated ( $n = 130$ , 61%), and married ( $n = 119$ , 55.3%). The affected knee in the majority of participants had an OA grade of 3 or higher ( $n = 172$ , 80%), had been painful for  $> 5$  years (6–20 years), and participants rated the pain intensity (0–20 NRS) during the preoperative visit in this affected knee at a median of 2 (IQR 0–5) at rest and 7.5 (IQR 3.5–12) with movement (ROM). Descriptive statistics are provided for all preoperative variables in Table 1, along with distributions of these variables across postoperative pain groups (as described below).

#### 3.2. Postoperative Assessment

On POD2, 58 (27%) participants had mild pain, 98 (46%) moderate pain, and 59 (27%) severe pain during active joint movement. In contrast, 85 (40%) participants had no resting pain, 53 (25%) mild pain, and 77 (36%) moderate to severe pain. Median resting pain intensity was 4 (IQR 1–10) and increased with movement to 12 (7–15). Postoperative resting and movement pain were significantly correlated (Spearman rho  $r = .54$ ,  $p < .0001$ ). The type of intraoperative anesthesia and analgesia participants received did not differ significantly between postoperative pain groups ( $p = 0.11$  to  $0.88$  and  $p = 0.30$  to  $0.90$ , respectively). Participants received a total of 103.68 (75.6–134.4) mg opioid oral morphine equivalents during the 24 hours prior to POD2 assessment and a similar amount of opioids were received across pain groups (mild pain, median 103.68, IQR 75.12–126.96; moderate pain, median 102.24, IQR 71.52–144; and severe pain, median 103.68, IQR 78.96–126.24). In contrast, the total acetaminophen equivalents of non-opioid analgesic medications received during the 24 hours prior to POD2 assessment were 3799.2 (IQR 2664.72–5093.76) mg and participants with higher postoperative movement pain received smaller amounts than participants with lower movement pain (mild pain, median 4026, IQR 3232.08–5314.56; moderate pain, median 3698.16, IQR 2609.04–4968.72; and severe pain, median 3615.12, IQR 2200.56–4597.92). These differences, however, were not significant (see Table 2). The degree of active extension on POD2 averaged  $-10.26 \pm 6.34$  (degrees from 0, full extension) and significantly correlated with pain during active extension ( $r = .22$ ,  $p = 0.001$ ). The degree of active flexion on POD2 averaged  $56.68 \pm 17.70$  but did not significantly correlate with pain during active flexion ( $r = -0.09$ ,  $p = 0.189$ ).

### 3.3. Single Factor Model

To screen variables for possible inclusion in the multi-factor model, a generalized logit model for postoperative movement pain (severe, moderate, and mild as reference) was fitted to include one independent variable of interest, adjusted for treatment received. Odds ratios (with 95% CI), and p-values obtained from these models are presented in Table 3. Variables with  $p < 0.10$  for association with moderate or severe movement pain were preoperative movement pain, resting pain, von frey pain intensity (VFPI), heat pain threshold (HPT), pressure pain threshold (PPT), age, marital status, OA grade, depression, anxiety, and pain catastrophizing. Gender, educational level, BMI, pain duration prior to surgery, and analgesia intake (opioid and non-opioid) were not significantly associated with postoperative movement pain ( $p > 0.10$ ).

A similar approach was used for postoperative resting pain (moderate to severe, mild, and none as reference, see Table 4). Variables with  $p < 0.10$  for association with mild or moderate to severe resting pain were (preoperative resting pain, movement pain, age, education, depression, anxiety, pain catastrophizing, and VFPI). Gender, BMI, OA grade, pain duration prior to surgery, HPT, PPT, and analgesia intake (opioid and non-opioid) were not significantly associated with postoperative resting pain ( $p > 0.10$ ).

### 3.4. Multi-factor Model Postoperative Movement Pain

As mentioned above, variables with  $p < 0.10$  for either moderate or severe postoperative movement pain from the single factor models were included in the stepwise logistic regression. The final fitted model was based on  $n=179$  participants (54 mild, 78 moderate, and 47 severe). Participants with missing data were excluded from the analysis. Missing data were primarily due to lack of heat pain thresholds caused by limited availability of the thermode machine during preoperative clinic visits at the VAMC site. Participants with missing data were primarily male, had a lower education level, received less acetaminophen equivalents postoperatively and had higher preoperative resting pain. None of these variables were significantly different between groups in the single factor models except for preoperative resting pain which was highly correlated with preoperative movement pain, a significant predictor in our model. Therefore, the results would not have been different if these participants had been included in the analyses.

The fitted final model is presented in Table 5. Significant predictors included preoperative movement pain, VFPI and HPT. The highest odds ratio indicated that people with severe movement pain preoperatively were 20 times more likely to have severe movement pain postoperatively. Figures 1–3 illustrate the percentage of participants with mild and severe postoperative movement pain based on these preoperative variables. Due to the large influence of preoperative movement pain on the variability in postoperative movement pain, a second model was fitted excluding this variable to determine if other variables were predictive of postoperative movement pain apart from preoperative pain levels. This model is presented in Table 6. In this model, depression loaded as a significant predictor, along with the same two pain sensitivity variables (VFPI and HPT). Participants who were screened as depressed prior to surgery were 2.7 times more likely to experience severe postoperative movement pain. Preoperative movement pain was significantly different between participants who were depressed and those who were not depressed ( $p=0.021$ ) with the median pain score reported by depressed participants being 10 (IQR 6–14.75) versus 6.75 (3–11.5) in non-depressed participants.

The other candidate variables that were considered for possible inclusion in the stepwise regression analysis but did not enter into the final model were preoperative resting pain, age, marital status, OA grade, anxiety, pain catastrophizing, and PPT. Further examination of

association of these variables with the variables that were included in the final model showed significant correlations between preoperative resting pain and preoperative movement pain (Spearman rho  $r=0.34$ ,  $p<0.0001$ ), age and preoperative movement pain (Spearman rho  $r=-0.17$ ,  $p=.0137$ ), age and VFPI (Spearman rho  $r=0.15$ ,  $p=.0320$ ), marital status and preoperative movement pain ( $p=0.0003$ ), marital status and depression ( $p=0.092$ ), anxiety and VFPI (Spearman rho  $r=0.19$ ,  $p=0.0072$ ), PPT and VFPI (Spearman rho  $r=0.43$ ,  $p<0.0001$ ), and PPT and HPT (Spearman rho  $r=0.37$ ,  $p<0.0001$ ). Pain catastrophizing and OA grade were not significantly correlated with predictor variables.

### 3.5. Multi-factor Model – Postoperative Resting Pain

Variables with  $p<0.10$  for either mild or moderate to severe postoperative resting pain from the single factor models were included in the stepwise logistic regression. The final fitted model was based on  $n=199$  participants (78 none, 52 mild, and 69 moderate to severe). This model is presented in Table 7. Significant predictors included preoperative resting pain, depression, and age. The highest odds ratio indicated that people with moderate to severe resting pain preoperatively were 9 times more likely to have moderate to severe resting pain postoperatively.

The other candidate variables that were considered for possible inclusion in the stepwise regression analysis but did not enter into the final model were preoperative movement pain, education, marital status, anxiety, pain catastrophizing, and VFPI. As mentioned above, preoperative movement pain was significantly correlated with preoperative resting pain (Spearman rho  $r=0.34$ ,  $p<0.0001$ ). Further examination of association of other variables with the variables that were included in the final model showed significant correlations between resting pain and marital status ( $p=0.044$ ), anxiety ( $p=.0034$ ), pain catastrophizing ( $p=0.0058$ ) and VFPI ( $p=0.0019$ ). Marital status was also significantly correlated with depression ( $p=0.092$ ). Education was not significantly correlated with predictor variables.

## 4. Discussion

This study examined, for the first time, both physiological and psychological predictors of postoperative pain following TKR. Unique to this study was the focus on movement pain which is most problematic for patient recovery after surgery and, therefore, an appropriate target for improving patient care. Movement pain on POD2 was highly correlated with resting pain, suggesting that movement pain is additive and builds on the level of resting pain (i.e., movement serves as a trigger that intensifies resting pain and the higher the resting pain, the higher the movement pain).

### 4.1. Preoperative pain predicts postoperative pain

High preoperative pain was a significant predictor of high pain (at rest and during movement) following TKR. These results suggest the more intense a patient's pain prior to surgery, the more likely the patient is to have intense pain after surgery. Preoperative movement pain was the largest predictor of postoperative movement pain and had the highest odds ratio. The same was true for resting pain. This strong relationship has also been found in other studies evaluating predictors of postoperative pain [27,28] and was found to be a consistent predictor in a systematic review of this literature [37]. This evidence suggests that strategies, such as earlier surgery or aggressive pain management prior to surgery, may prevent the occurrence of intense postoperative pain. Decreasing movement pain postoperatively can decrease a patient's risk of poor recovery and/or delayed functional outcomes following surgery [11,44,71,73]. Further research is needed to test the effect of strategies aimed at reducing preoperative pain for their effect on postoperative pain.



## 4.2. Preoperative cutaneous pain sensitivity predicts postoperative movement but not resting pain

Preoperative cutaneous pain sensitivity to force and heat stimuli significantly predicted postoperative movement pain but not resting pain. While studies have found preoperative HPT and cold pressor pain to predict acute resting pain after cesarean section [48,64], laparoscopic tubal ligation [59], and laparoscopic cholecystectomy [5], other studies have demonstrated a direct relationship between pain sensitivity and movement pain but not resting pain [15,18,40,72]. A reduction in pricking pain thresholds corresponded to lower movement pain but not resting pain in patients after renal surgery [72], and a reduction in von frey pain thresholds correlated with movement pain but not resting pain after major gynecologic surgery [40]. Investigators comparing the effects of gabapentin, an anti-hyperalgesic agent, to placebo after breast surgery found that movement pain was significantly reduced, but not resting pain, further supporting this relationship [15,18]. These results suggest that movement pain may involve sensitivity of the nociceptive response and mechanisms underlying movement pain are distinctly different from resting pain. If this is confirmed, strategies that focus on decreasing pain sensitivity may prevent high movement pain after surgery.

Only pain sensitivity to cutaneous stimuli (force and heat) was predictive of postoperative movement pain. Preoperative PPT, another measure of pain sensitivity using deep mechanical stimuli, while significantly correlated with severe postoperative pain in the bivariate analyses, was not predictive of postoperative movement or resting pain in the logistic regressions. These results are consistent with other studies showing a significant correlation between preoperative PPT and pain intensity post-cesarean section [9] and lower abdominal gynecology surgery [36] but not predictive in regression analyses. In the current study, PPT was significantly correlated with both VFPI and HPT, reducing its unique influence. Further research is needed to evaluate the unique contribution of PPT on postoperative pain.

Unique to this study was the measurement of pain intensity to cutaneous mechanical stimuli (i.e. 451mN force) which was found to significantly predict postoperative movement pain. This test is easy to perform with the same von Frey filament used to clinically evaluate diabetic neuropathy. This test may provide an easy method of predicting a patient's risk for high movement pain after surgery and help target patients requiring more aggressive pain management. The intensity of pain caused by this force was mild (equivalent to 0.5 on a 0–10 NRS). This force was based on the average pain threshold at the surgical knee in pilot participants. Therefore, these ratings are consistent with pain thresholds and any pain intensity rating > 0, using this filament, indicates pain sensitivity.

## 4.3. Positive depression screening predicts postoperative pain

Screening positive for depression prior to surgery was a significant predictor of postoperative resting pain and postoperative movement pain when preoperative movement pain was removed from the analysis. This finding is consistent with studies evaluating depression as a predictor of chronic pain following TKR [7,16] and other orthopedic surgery [2,33]. This finding also supports previous studies showing depression and pain as common comorbidities, sharing biological pathways and neurotransmitters [3,57]. Dysfunction at the level of the serotonergic and noradrenergic neurons results in the psychological and somatic symptoms of depression and causes routine sensory input that is not normally felt to become interpreted as disagreeable or even painful [62]. If a person's depression is not addressed preoperatively, these effects may persist after surgery, increasing their risk for higher postoperative pain [10]. Furthermore, additive impairments in mobility and activity are seen when depression and pain coexist [3]. Therefore, it is essential for treatment success to

recognize the comorbidity of pain and depression and to treat both disorders in affected individuals [57].

#### 4.4. Age predicts postoperative resting pain

Age was a significant predictor of postoperative resting pain which is consistent with prior studies [5,12,22]. In contrast, while significantly correlated with postoperative movement pain in the bivariate analyses, age did not predict movement pain. This may be due to a reduced unique influence of age caused by its significant correlation with both preoperative movement pain and VFPI. The variability in age was also limited in this study. The youngest participant was 40 years of age compared to 18 – 20 years in studies where age was found to significantly predict postoperative pain [5,12,22]. These results suggest that younger patients are at a greater risk of high resting pain but all ages are at equal risk for high movement pain following TKR.

#### 4.5. Other psychological variables do not predict postoperative pain

While preoperative anxiety was significantly associated with both postoperative movement and resting pain in the bivariate analyses and pain catastrophizing was associated with movement pain, neither of these variables were significant predictors of pain in the regression models. These results are contrary to studies showing these variables predict pain after TKR [7,16,29,54]. Prior studies did not include quantitative sensory tests and primarily examined the development of chronic pain 6 months to 1 year after TKR. It is possible that peripheral sensitivity outweighed the effects of these psychological traits when predicting the variability in postoperative pain. The unique influence of these traits was also reduced due to their significant correlation with depression and pain in this sample. It is possible that chronic pain is more influenced by these traits than immediate postoperative pain. While these traits were not predictive of postoperative pain, anxiety was predictive of preoperative pain in a previous analysis [68] and thus be an important target of intervention.

#### 4.6. Limitations

This sample was largely white, educated, cognitively intact, with no postoperative confusion. Generalizability of these findings is limited to similar patients. Depression was measured with the GDS, based on an expectation that participants would be older adults. Forty seven participants were < 55 years possibly influencing the results. However, the percentage of these participants screening positive for depression (13%) was similar to older (> 55 years) participants (14%) suggesting that this tool worked equally well in younger adults. Caffeine intake was not assessed due to limited consumption during the immediate postoperative period but should be considered in future studies. The focus of this study was pain during the immediate postoperative period. It will be important for future studies to consider a longer post-surgical follow-up period to determine if preoperative pain, pain sensitivity, age and depression continue to predict pain throughout rehabilitation. In addition, this study focused on measures of peripheral pain sensitivity. Future research should include measures of central pain sensitivity to determine if changes in both peripheral and central processing influence postoperative pain or if this is strictly a peripheral phenomenon. Finally, participants were grouped by their average pain intensity during range of motion of the affected knee. Future research should explore if similar results are obtained with other types of movement (e.g., walking, leg lifts) to determine if targeting preoperative pain, hyperalgesia, and depression is appropriate for controlling pain during all aspects of rehabilitation following TKR.

## 4.7. Summary

These results suggest that younger patients with higher preoperative pain and depression are more likely to have higher pain following TKR. Cutaneous pain sensitivity predicted movement pain but not resting pain, suggesting that mechanisms underlying movement pain are different from resting pain. Pain catastrophizing and anxiety were not predictive of postoperative pain as hypothesized. Movement is essential to recovery and improved functional outcomes following TKR. Efforts to prevent or decrease preoperative pain, cutaneous pain sensitivity and depression, such as earlier surgery or aggressive use of combination therapies prior to surgery may facilitate postoperative pain control and improve functional outcomes following TKR.

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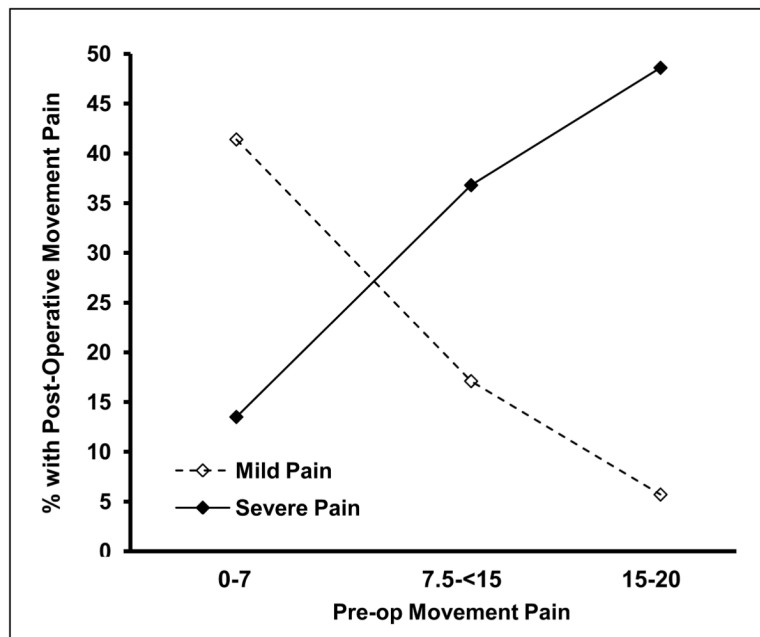
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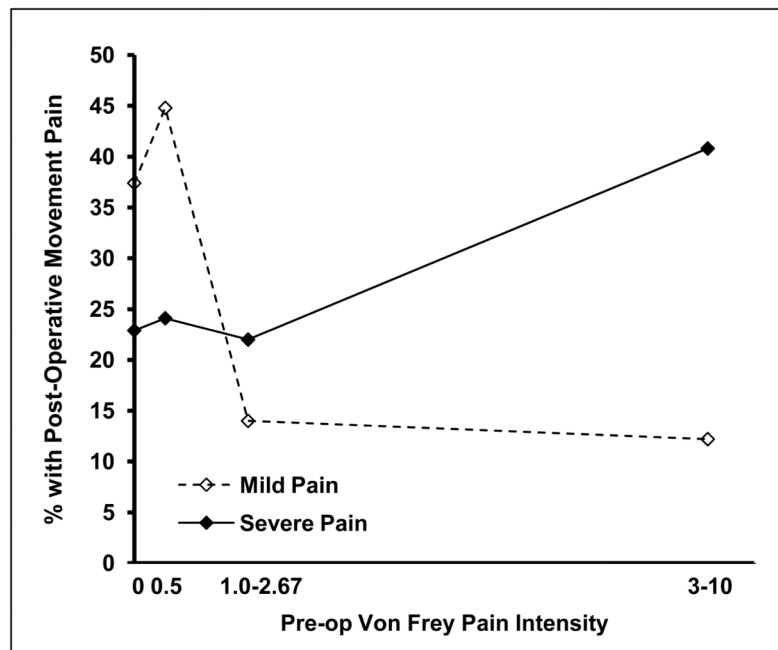
### **SUMMARY STATEMENT**

Patients with higher pain, increased pain sensitivity, and depression prior to total knee replacement are more likely to have higher movement pain postoperatively.





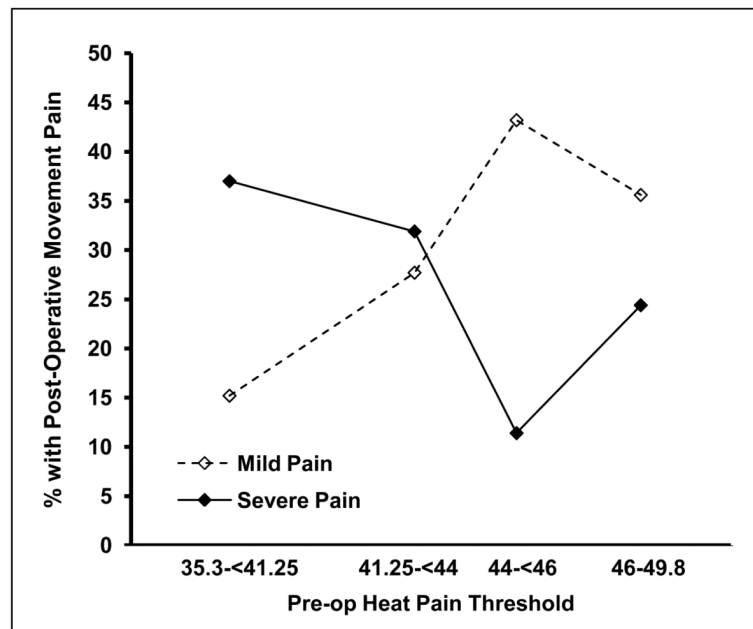
**Figure 1.** Percent of Participants with Mild or Severe Postoperative Movement Pain Based On Preoperative Movement Pain Levels\*  
\*=A larger percentage of participants with mild postoperative movement pain rated their preoperative movement pain low (0-7) while a larger percentage of participants with severe postoperative movement pain rated their preoperative movement pain high (15-20).



**Figure 2.**

Percent of Participants with Mild or Severe Postoperative Movement Pain Based On Preoperative Von Frey Pain Intensity Levels\*

\*=A larger percentage of participants with mild postoperative movement pain rated the pain intensity to a standard von frey stimulus low (0–1) while a larger percentage of participants with severe postoperative movement pain rated the pain intensity to a standard von frey stimulus high (9–10). Von Frey pain intensities were grouped, based on data quartiles, and mean scores for each quartile were plotted.



**Figure 3.** Percent of Participants with Mild or Severe Postoperative Movement Pain Based On Preoperative Heat Pain Threshold Levels\*

\*=A larger percentage of participants with mild postoperative movement pain had high preoperative heat pain thresholds (45–48) while a larger percentage of participants with severe postoperative movement pain had low heat pain thresholds (38–43). Heat pain thresholds were grouped, based on data quartiles, and mean scores for each quartile were plotted.

**Table 1**  
Preoperative Variables According to Mild, Moderate, & Severe Postoperative Movement Pain Intensity

	Mean ± SD, Percentage, or Median (IQR)		Mild pain (n=58)		Moderate pain (n=98)		Severe pain (n=59)		TOTAL (N=215)	
	n	data	n	data	n	data	n	data	n	data
Age	58	60.8 ± 9.2	98	63.6 ± 10.4	59	59.3 ± 9.0	215	61.7 ± 9.8	215	61.7 ± 9.8
Body Mass Index (BMI)	58	35.5 ± 9.2	98	39.2 ± 12.7	59	38.9 ± 10.8	215	38.2 ± 11.4	215	38.2 ± 11.4
Sex	35	Female	55	60.3%	35	56.1%	125	58.1%	125	58.1%
Racial Heritage	56	White	93	96.6%	51	94.9%	200	93.0%	200	93.0%
Education*	16	High School	28	29.6%	21	31.8%	65	33.3%	65	33.3%
	31	Some college/college grad	46	57.4%	46	52.3%	98	50.3%	98	50.3%
	7	Post-grad school	14	13%	11	15.9%	32	16.4%	32	16.4%
Marital Status	23	Married or Living w/SO	61	39.7%	35	62.2%	119	55.3%	119	55.3%
OA Grade**	0	Grade 2	0	0%	5	9.1%	5	2.6%	5	2.6%
	12	Grade 3	24	24%	18	26.7%	54	27.7%	54	27.7%
	38	Grade 4	66	76%	32	73.3%	136	69.7%	136	69.7%
Pain Duration***	2	< 1 year	6	3.9%	2	7.6%	2	3.9%	10	5.5%
	14	1- < 3 years	13	27.5%	7	16.5%	34	18.8%	34	18.8%
	10	3- 5 years	13	19.6%	15	16.5%	38	21%	38	21%
	25	> 5 years	47	49%	27	59.5%	99	54.7%	99	54.7%
Depressed (GDS)****	6	Yes	10	10.7%	16	11%	32	16.1%	32	16.1%
Anxiety (STAI)	54	32.5 (26-36)	92	32 (27-38.5)	53	36 (30-45)	199	33 (27-39)	199	33 (27-39)
Pain Catastrophizing (PCS)	56	9 (4.5-14.5)	89	8 (4-12)	53	12 (7-19)	198	9 (5-15)	198	9 (5-15)
Resting Pain (0-20NRS)	58	1 (0-4)	98	2 (0-5)	59	4 (0-8)	215	2 (0-5)	215	2 (0-5)
Movement Pain (0-20NRS)	58	3 (1-7.5)	98	7.5 (4-11)	59	10.5 (7.5-15)	215	7.5 (3.5-12)	215	7.5 (3.5-12)
VFPI (0-20NRS)	57	0 (0-67)	97	1 (0-2.67)	57	1 (0-4)	211	.67 (0-2.67)	211	.67 (0-2.67)
HPT (° C)	55	44.6 (42.9-46.4)	79	43.9 (41.13-45.7)	48	42.2 (45.8-48.5)	182	43.9 (41.2-45.8)	182	43.9 (41.2-45.8)
PPT (kPa)	58	295.5 (207-379.7)	98	249.7 (186.3-348.3)	59	211.3 (164.7-290.7)	215	247.3 (177-347)	215	247.3 (177-347)
Opioid Intake (MSO4 equiv) <sup>†</sup>	45	0 (0-7.5)	80	0 (0-5)	47	0 (0-10)	172	0 (0-7.5)	172	0 (0-7.5)
Non-opioid Intake (acetaminophen equiv)	45	650 (486-1000)	80	536 (325-1000)	47	572 (325-1000)	172	572 (325-1000)	172	572 (325-1000)

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\* Education data available for n=195 (mild=54, moderate=88, severe=53)

\*\* OA Grade data available for n=195 (mild=50, moderate=90, severe=55)

Uses the Kellgren-Lawrence classification of osteoarthritis from radiographic images:

3 = moderate multiple osteophytes, narrowing of joint space, some sclerosis, possible deformity of bone

4 = large osteophytes, marked narrowing of joint space, severe sclerosis, definite deformity of bone

\*\*\*

Pain Duration data available for n=181 (mild=51, moderate=79, severe=51)

\*\*\*\*

Depression data available for n=199 (mild=56, moderate=91, severe=52)

<sup>†</sup>Morphine equivalents

**Table 2**

Odds ratios of postoperative analgesia on moderate and severe postoperative pain with movement (ref: mild pain)

Postop Variable	n	Moderate Pain (vs. Mild Pain)		Severe Pain (vs. Mild Pain)	
		Odds Ratio	95% CI of OR	Odds Ratio	95% CI of OR
Acetaminophen equiv. (per +10)	207	0.97	0.93, 1.02	0.96	0.91, 1.02
Morphine equiv. (per +10)	211	0.81	0.50, 1.30	0.81	0.45, 1.46
					p-value
					0.153
					0.481

**Table 3**

Odds ratios of individual preoperative variables on moderate and severe postoperative movement pain (ref: mild pain)

Preop Variable	n	Moderate Pain (vs. Mild Pain)			Severe Pain (vs. Mild Pain)		
		Odds Ratio	95% CI of OR	p-value	Odds Ratio	95% CI of OR	p-value
Age (ref: +5 years)	215	1.17	0.99, 1.39	<b>0.072</b>	0.92	0.76, 1.12	0.409
BMI (ref: <25)	208						
25-<30		0.76	0.20, 2.85	0.684	4.87	0.49, 48.32	0.176
30-<40		1.24	0.37, 4.18	0.723	5.96	0.64, 55.22	0.116
40		0.74	0.20, 2.68	0.642	6.29	0.66, 60.16	0.110
Sex (Female/Male)	215	0.82	0.42, 1.59	0.548	0.92	0.44, 1.94	0.830
Education (ref: college/post grad)	195						
HS/HS grad		1.27	0.55, 2.92	0.572	1.74	0.70, 4.35	0.511
Some College		1.32	0.58, 3.03	0.237	1.24	0.47, 3.22	0.666
Marital Status	215	2.02	0.98, 4.20	<b>0.058</b>	3.13	1.32, 7.44	<b>0.010</b>
OA grade (2-3/4)	195	1.14	0.51, 2.54	0.745	2.24	0.96, 5.24	<b>0.062</b>
Pain duration (ref: <1year)	181						
1-<3 years		0.25	0.04, 1.51	0.131	0.40	0.04, 3.53	0.406
3-5 years		0.33	0.05, 2.05	0.234	1.15	0.14, 9.76	0.900
>5 years		0.51	0.09, 2.75	0.433	0.87	0.11, 6.77	0.894
Depression	199	0.99	0.34, 2.91	0.984	3.59	1.27, 10.11	<b>0.016</b>
Anxiety	199	1.02	0.98, 1.06	0.375	1.06	1.01, 1.10	<b>0.009</b>
Pain Catastrophizing	198	0.99	0.96, 1.04	0.888	1.04	1.00, 1.08	<b>0.052</b>
Movement Pain (ROM)	215	1.19	1.10, 1.30	<b>&lt;0.0001</b>	1.32	1.20, 1.44	<b>&lt;0.0001</b>
Resting Pain	215	1.13	1.02, 1.25	<b>0.020</b>	1.21	1.09, 1.35	<b>0.0004</b>
Von Frey Pain Intensity (VFPI)	211	1.32	1.07, 1.63	<b>0.010</b>	1.42	1.14, 1.77	<b>0.001</b>

Preop Variable	n	Moderate Pain (vs. Mild Pain)			Severe Pain (vs. Mild Pain)		
		Odds Ratio	95% CI of OR	p-value	Odds Ratio	95% CI of OR	p-value
Heat Pain Threshold (HPT)	182	0.90	0.80, 1.01	<b>0.076</b>	0.83	0.73, 0.95	<b>0.007</b>
Pressure Pain Threshold (PPT)	215	0.85	0.70, 1.03	0.100	0.66	0.50, 0.87	<b>0.003</b>
Opioids (MSO4 equiv, per 10mgs)	172	.881	0.50, 1.54	.656	1.37	0.80, 2.36	.249
Non-opioids (acetaminophen equiv, per 325 mg)	172	.924	0.74, 1.16	.488	.902	0.70, 1.16	.421



**Table 4**

Odds ratios of individual preoperative variables on mild and moderate/severe postoperative resting pain (ref: none)

Preop Variable	n	Mild (vs. none)			Moderate/Severe (vs. none)		
		Odds Ratio	95% CI of OR	p-value	Odds Ratio	95% CI of OR	p-value
Age (per +5 years)	215	0.86	0.72, 1.03	0.102	0.80	0.68, 0.94	<b>0.008</b>
BMI (ref: <25)	208						
25-<30		1.56	0.33, 7.29	0.572	0.85	0.21, 3.37	0.813
30-<40		1.49	0.35, 6.31	0.586	1.54	0.45, 5.19	0.491
40		2.20	0.51, 9.48	0.289	1.92	0.55, 6.70	0.305
Sex (Female/Male)	215	0.86	0.43, 1.71	0.660	0.77	0.41, 1.45	0.418
Education (ref: college graduate/post graduate)	195						
HS/HS graduate		0.51	0.20, 1.32	0.165	2.01	0.92, 4.41	<b>0.082</b>
Some College		1.50	0.66, 3.42	0.334	1.50	0.64, 3.54	0.356
Marital status (ref: married or with partner)	199	1.77	0.85, 3.68	0.126	1.93	0.99, 3.75	<b>0.054</b>
OA grade (2-3/4)	195	1.70	0.77, 3.74	0.190	1.79	0.86, 3.70	0.119
Pain duration – (ref: 3 yrs)	190	1.01	0.89, 1.14	0.914	1.03	0.92, 1.16	0.573
Depression	199	1.34	0.42, 4.19	0.633	3.55	1.38, 9.14	<b>0.009</b>
Anxiety	199	1.02	0.98, 1.06	0.478	1.05	1.01, 1.09	<b>0.006</b>
Pain Catastrophizing	198	1.02	0.99, 1.06	0.207	1.03	0.99, 1.06	<b>0.093</b>
Resting pain	215	1.03	0.92, 1.16	0.578	1.28	1.16, 1.42	<b>&lt;0.0001</b>
Movement pain (ROM)	215	1.03	0.96, 1.11	0.387	1.11	1.04, 1.17	<b>0.001</b>
Von Frey Pain Intensity (VFPI)	211	1.07	0.92, 1.24	0.390	1.16	1.02, 1.32	<b>0.023</b>
Heat Pain Threshold (HPT)	182	1.03	0.91, 1.16	0.656	0.92	0.83, 1.03	0.145
Pressure Pain Threshold (PPT)	215	1.02	0.82, 1.27	0.853	0.84	0.67, 1.05	0.117

Preop Variable	n	Mild (vs. none)			Moderate/Severe (vs. none)		
		Odds Ratio	95% CI of OR	p-value	Odds Ratio	95% CI of OR	p-value
Opioids (MSO4 equivalents per 10mgs)	211	0.54	0.14, 2.11	0.375	0.91	0.64, 1.30	0.602
Non-opioids (acetaminophen equivalents per 325mgs)	207	1.00	0.95, 1.05	0.952	0.97	0.93, 1.02	0.230

BMI=Body Mass Index; HS=High School; OA=osteoarthritis; ROM=Range of Motion; MSO4=morphine

**Table 5**  
 Logistic Regression of Severe and Moderate Postoperative Pain with Movement (compared to mild pain) (n=179)

Preop Variable	Moderate Pain (vs. Mild Pain)		Severe Pain (vs. Mild Pain)	
	Odds Ratio	95% CI of OR	Odds Ratio	95% CI of OR
Pain with movement (reference: mild pain)				
Moderate Pain	2.10	0.90, 4.88	6.34	2.31, 17.41
Severe Pain	5.00	1.00, 25.02	<b>20.06</b>	3.71, 108.6
Von Frey Pain Intensity	1.30	1.04, 1.63	1.27	1.00, 1.61
Thermal Pain Threshold	0.88	0.77, 1.01	0.85	0.73, 0.98
				p-value
				0.0003
				0.0005
				0.050
				0.031

**Table 6**

Logistic Regression of Severe and Moderate Postoperative Pain with Movement (compared to mild pain) without Preoperative Movement Pain in Model (n=179)

Preop Variable	Moderate Pain (vs. Mild Pain)		Severe Pain (vs. Mild Pain)	
	Odds Ratio	95% CI of OR	Odds Ratio	95% CI of OR
Depression	0.96	0.29, 3.10	2.70	0.83, 8.79
VF surg knee pre	1.31	1.04, 1.64	1.38	1.09, 1.76
Thermal Pain Threshold surg. Knee pre	0.88	0.78, 1.00	0.83	0.72, 0.96
				p-value
				0.098
				0.007
				0.014

**Table 7**  
 Logistic Regression of Mild and Moderate/Severe Postoperative Resting Pain (compared to no pain) (n=199)

Preop Variable	Mild Pain (vs. None)		Moderate/Severe Pain (vs. None)	
	Odds Ratio	95% CI of OR	Odds Ratio	95% CI of OR
Resting pain (reference: none)				
Mild Pain	1.06	0.48, 2.34	2.86	1.29, 6.35
Moderate/Severe Pain	0.98	0.25, 3.79	9.31	3.19, 27.2
Depression	1.32	0.41, 4.22	2.87	1.04, 7.97
Age (ref. + 5 yrs)	0.87	0.72, 1.06	0.86	0.71, 1.03
				p-value
				0.010
				<.0001
				0.042
				0.106