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# Characterization of Patients with Difficult-to-Treat Acute Pain Following Total Knee Arthroplasty Using Multi-Modal Analgesia

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**Abstract:** *Objective*: To determine the efficacy of post-operative pain control over the first 24 hours in patients undergoing unilateral total knee arthroplasty (TKA) using a multi-modal analgesia protocol including femoral nerve catheters (FNC). *Materials and Methods*: 119 patients who underwent unilateral TKA between 2009 and 2010 under regional anesthesia with FNC were studied. Electronic charts were reviewed for numerical rating scale (NRS) pain scores at baseline, from the time the patients entered the post-operative care unit and every 4 hours thereafter until FNC was discontinued at 24 hours post-surgery. Opioid usage was also recorded during the same time period. *Results*: Analysis of average NRS pain scores from all patients demonstrated that 69% had NRS pain scores ≤ 5 ('low pain' (LP) group) and 31% had NRS pain scores ≥ 6 ('high pain' (HP) group). Time analysis showed that HP patients' high pain scores persisted for 24 hours post-surgery and they were characterized by being younger when compared to the LP patients.The majority of HP patients were female. Further analysis demonstrated that the average body mass index (BMI) of the female HP patients was significantly greater than females with LP. *Conclusions*: In spite of a diverse multi-modal analgesia protocol designed for TKA surgery, 31% of our patients had 'difficult-to-treat' pain (NRS pain scores ≥ 6) for 24hours post-surgery. Our analysis implicates age, pre-operative pain scores, female gender and obesity as potential risk factors for experiencing insufficient pain control with the currently evaluated multimodal pain protocol post-TKA surgery.

**Keywords:** Acute pain, female, multi-modal analgesia, obesity, post-operative pain, total knee arthroplasty.

## INTRODUCTION

Clinical data confirm that total knee arthroplasty (TKA) is a painful procedure, and numerical pain rating scale (NRS) scores (with 0 signifying no pain and 10 the worst pain) over the first 24 hours post-surgery can be as high as 5-7 depending on the anesthesia and post-surgical pain management techniques used [1-5]. Health related websites have been created to educate prospective patients about what to expect in regard to pain following TKA surgery. Within these websites statements are posted such as "pain after knee surgery is quite variable and not entirely predictable" [6] or "recovering from knee replacement surgery can be painful" [7].

In most clinical anesthesia practices standardized opioid-sparing, multimodal analgesia protocols [8] that include regional anesthesia techniques (e.g. femoral nerve catheters [9-12]), non-opioid analgesics (e.g. Cox-2 inhibitors [5], pregabalin [13]), intrathecal [14-16] and systemic opioids have been shown to be relatively effective in controlling pain for orthopedic procedures such as TKA. In line with these practice guidelines, at our institution TKA patients are offered a multimodal peri-operative analgesia regimen comprising non-opioid analgesics, opioids and spinal anesthesia in combination with femoral nerve blockade plus indwelling femoral nerve catheter (FNC) [17]. Our clinical goal has been to provide adequate acute post-operative pain control for our TKA patients and based on the literature defined as average NRS pain scores ≤ 5, using an11-point verbal NRS scale over the first 24 hours post-surgery. To validate our clinical expectations in regard to analgesia management in our patients we executed a retrospective study to characterize pain profiles over the first 24 hours in 119 patients undergoing unilateral TKA.

## MATERIALS AND METHODOLOGY

Approval for this retrospective study was received from the local institutional review board (IRB), and consent from the patients to access their electronic medical records was waived by the IRB. Electronic medical charts for 119 patients who underwent elective unilateral TKA during 2009-2010 were reviewed. Patients were excluded from the study collection review if they had undergone TKA under general anesthesia, if they were on opioid therapy at the time of surgery or if there was documented failure of the FNC during the first 24 hours post-surgery. Data collection forms included demographic data, past medical and surgical history, peri-operative vital signs, pre-surgical baseline NRS pain scores, NRS pain scores from the post-anesthesia care unit (PACU), and those reported by the ward nurse every 4 hours until the FNC was discontinued by the acute pain team

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**Table 1. Multi-Modal Anesthesia Regimen for TKA Patients**

| Technique & Route of administration | Medications | Dose | Start | End |
|---|---|---|---|---|
| Oral | Celebrex | 200mg q 12 hrs | Morning of Surgery | 48 hrs post-surgery |
| Oral | Oxycontin <70 years of age | 20mg q 12 hrs | Morning of Surgery | 1 week post operatively |
| Oral | Oxycontin ≥70 years of age | 10mg q 12 hrs | Morning of Surgery | 1 week post operatively |
| Spinal anesthesia | 0.75% hyperbaric bupivacaine | 10-15mg | Intra-operatively | N/A |
| Femoral Nerve Catheter (FNC) | Ropivacaine | 40cc bolus (0.5% Ropivacaine) pre-operatively | Upon recovery of motor function: infusion via FNC: 0.2% Ropivacain at 10cc/hr | at 24 hrs post-surgery |
| Oral | Pregabalin | 75 mg q 12 hrs | Evening on day of surgery | 48 hrs post-surgery |

at 24 hours post-surgery. In addition, FNC removal time (including total local anesthetic infusion time via the FNC) and opioid usage was recorded (defined as the amount of morphine equivalents recorded in milligrams administered to the patient during the first 24 hrs).

### Multi-Modal Analgesia TKA Protocol

The multi-modal anesthesia regimen used for the TKA patients comprised several different medications, anesthesia techniques and timing of medication administration as shown in Table **1**. Celecoxib (Celebrex®) and oxycontin were started on the morning of surgery (Table **1**) and for surgical anesthesia all patients received lumbar spinal anesthesia with hyperbaric 0.75% bupivacaine in addition to a femoral nerve block with a bolus of 40cc of 0.5% ropivacaine administered via an indwelling FNC placed using ultrasound and electrical nerve stimulation guidance. Intra-operatively, all patients were sedated with intravenous propofol only. Post-operatively, the patients were transferred for recovery to the PACU and upon return of their lower extremity motor function (defined as the ability to move feet; lift and bend the non-operated leg) 0.2% ropivacaine at an infusion rate of 10cc/hr was started via the FNC. Finally, after the patients were transferred from the PACU to the orthopedic floor they received 75mg Pregabalin (Lyrica®) orally in the evening (Table **1**). At our institution, a dedicated acute pain management team led by anesthesiologists manages patients' pain post-operatively. For breakthrough pain the patients were given oxycodone 5-10mg orally every 4 hours as needed. On the floor the patients typically start rehabilitation on the first post-operative day via a continuous passive motion machine (CPM) for 2 hour blocks up to 4 hours during the first 24 hours.

### Data and Statistical Analysis

All data from the case report forms were transcribed onto electronic spreadsheets and subsequently analyzed using SAS statistical software (v. 9.2, SAS Institute, NC). As our clinical intention was to maintain a pain score at $\leq 5$ we divided patients into a low pain group (LP) if the average NRS pain score over 24 hours was $\leq 5$ or a high pain group (HP) if the average pain was $\geq 6$. These two groups were then compared in regard to differences in NRS pain scores over time using repeated measures analysis of variance (ANOVA). To characterize potential underlying factors that distinguished LP from HP patients we performed the following analyses: a) a chi-square test on gender, b) 2-sided independent t-test on age, BMI, baseline NRS pain scores and duration of surgery, and c) logistic regression on 24 hour average NRS pain scores from HP and LP patients with gender, age, BMI and baseline NRS pain scores as predictors. Stepwise selection at a significance level of 0.05 was applied to determine the best model. Differences in comorbidity between the two groups were tested using the Fisher's exact test with post-hoc corrections for multiple comparisons. Opioid consumption between the two groups was compared using a one-way analysis of covariates (ANCOVA) to compare opioid consumption between the two groups with age as a covariate.

### Results

Of the 119 patients who underwent TKA during the pre-determined time period, a total of 106 electronic patient charts were reviewed (13 patients were excluded due to documented opioid usage prior to surgery).

### Post-Operative Pain Profiles Over 24 Hours

We first calculated the average NRS pain scores for each TKA patient from the time the patients were transferred to the orthopedic ward by averaging NRS pain scores reported via the electronic records at 4, 8, 12, 16, 20 and 24 hours. The frequency distributions of the average NRS pain scores from all patients are shown in Fig. (**1**) and demonstrate that 69% of the patients had average NRS pain scores $\leq 5$ and 31% had average NRS pain scores $\geq 6$. Patients with NRS pain scores $\leq 5$ were assigned to the 'low pain' (LP) group and those with NRS pain scores $\geq 6$ were assigned to the 'high pain' (HP) group. Fig. (**2**) shows the time-course of NRS pain scores in the LP and HP groups measured from the time of PACU discharge and every 4 hours over 24 hours and demonstrates that NRS pain scores remained elevated in the HP group over the entire time period, in contrast to the LP group which had adequate pain control ($\leq 5$) according to

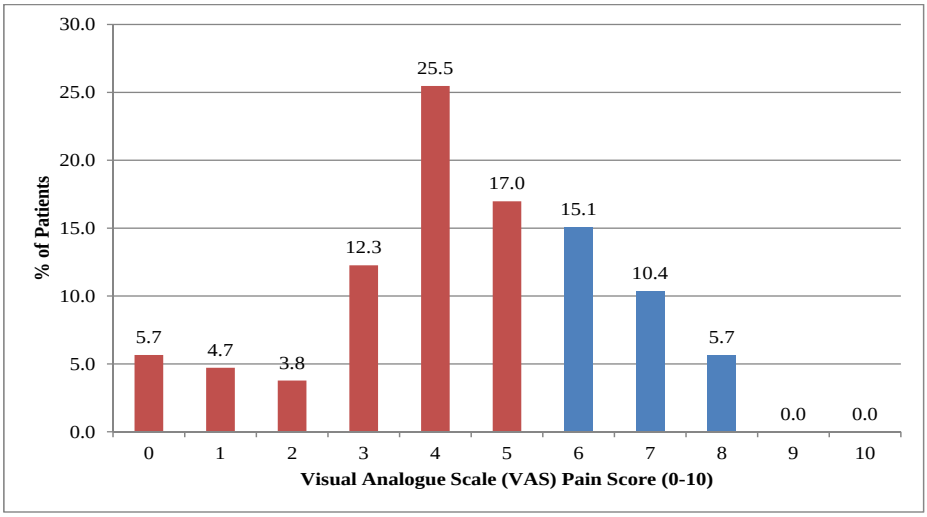


**Fig. (1).** Frequency Distributions of Average VAS Pain Scores in TKA Patients over first 24 hrs post-surgery.

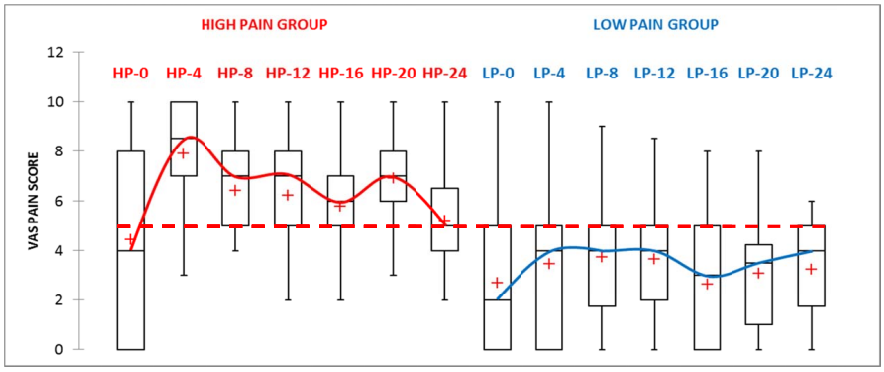


**Fig. (2).** Time-course of NRS pain scores in the LP and HP groups measured from the time of PACU discharge and every 4 hours over 24 hours.

clinical expectation. Changes in pain scores within and between LP and HP groups over time were found to be significant. Specifically, the change in pain over time was different between the two groups (Group * Time interaction effect, $p<0.0001$); and post-hoc analysis revealed that except for the time at PACU discharge, median NRS pain scores in the HP group were significantly different from the LP group at 4, 8, 16 and 20 hours post-operatively. Importantly, data analysis in regard to the FNC showed that in the high pain (HP) and low pain (LP) patient groups the average infusion time before the FNC was discontinued was 23.8 ± 6.2 hrs and 22.6 ± 4.1 hrs, respectively (no significant difference, p-value =0.28), suggesting that malfunction of the FNC did not contribute to differences in pain profiles between the two groups.

### Comparison of Demographics, Pre-operative NRS Pain Scores and Co-Morbidity Between LP and HP Groups

Table **2** shows that age was significantly different between the two groups and younger age characterized patients in the HP group (LP: 69.7 ± 11.1 years versus HP 62.5 ± 8.7 years, p=0.001) as well as higher baseline NRS pain scores. To further validate this finding we performed a logistic regression on 24 hour average NRS pain scores from the two groups with gender, age, BMI and baseline NRS pain scores as predictors. The regression coefficients for age and baseline NRS pain scores were –0.063 and 1.14, respectively, and both were significant (p=0.01 for age and p=0.04 for baseline NRS pain). Explicitly, the model predicted that for patients 40 years or older the log odds ratio of getting a NRS pain score of 6 or greater for a given patient would decrease with increasing age (6.1%/year) and increase with higher pre-surgical NRS pain scores. In regard to comorbidity, Table **2** shows that except for cardiac disease (stable coronary artery disease), which was significantly higher in the LP group, co-morbidity was matched between the two groups.

### Opioid Consumption Between LP and HP Groups

As expected, the average opioid consumption as defined by morphine equivalents in mg over 24 hours post-operatively in the HP group was significantly higher when compared to the LP group (28.7 ± 20.8mg versus 17.5 ± 15.1mg, p=0.002). However, opioid consumption over the first 24 hours in the two groups fluctuated widely as indicated by the high standard deviations (SD). After controlling for age, opioid consumption was still significantly different between the two groups (group effect: p-value = 0.016) but the estimated SDs on opioid usage between the two groups were greatly reduced after age

**Table 2. Patient Characteristics**

| Characteristics | | High Pain Group N=33 | Lower Pain Group N=73 | P-value |
|---|---|---|---|---|
| Gender | **Male (N, %)** | 13, 39 | 26, 36 | 0.71 |
| | **Female (N, %)** | 20, 61 | 47, 64 | |
| Mean (SD) Age, Years | | 62.5 (8.7) | 69.7 (11.1) | 0.001 |
| Mean (SD) BMI | | 33.8 (7.1) | 32.0 (6.2) | 0.21 |
| Mean (SD) Body Weight, kg | | 93.7 (15.4) | 88.6 (18.9) | 0.18 |
| Baseline NRS Pain Score Median (95% CI) | | 4 (0, 8.5) | 0 (0, 7.7) | 0.02 |
| Duration of Surgery, hours Mean (SD) | | 2.1 (0.6) | 1.9 (0.5) | 0.19 |
| **Disease** | | **High Pain Group N=33** | **Lower Pain Group N=73** | **P-value** |
| Hypertension (N, %) | | 25, 80 | 54, 70 | 1 |
| Cardiac disease (N, %) | | 1, 0 | 17, 23 | 0.01 |
| Hypercholesterolemia (N, %) | | 14, 42 | 36, 49 | 0.53 |
| Diabetes Mellitus, Type 2 (N, %) | | 8, 24 | 6, 0.8 | 0.03 |
| Hypothyroidism (N, %) | | 8, 24 | 17, 23 | 1 |
| Depression or anxiety (N, %) | | 10, 30 | 19, 26 | 0.65 |

N=number of subjects.

adjustment, as shown in Fig. (**3**). However 'age' in itself was not a significant factor in regard to opioid consumption (p=0.08).

### Female TKA Patients

Although gender distributions were matched between the LP and HP groups, we were interested in looking specifically at characteristics of female patients in the HP groups given that the majority of TKA patients are female (Table **2**) and further that the post-operative pain has been reported to be more severe in female patients [18]. We therefore compared age, BMI and duration of surgery between the two groups using a 2-sided independent *t*-test while correcting for multiple comparisons. Interestingly, this analysis demonstrated that the BMI of the female patients in the HP group was 12% greater than the LP group (HP BMI: 37.3 ± 6.4 versus LP BMI: 33.1 ± 6.1, p=0.01). Explicitly, 30% of the female patients in the HP group were characterized by a BMI ≥ 40; in comparison to only 17% in the LP group. This statistical difference also held true when body weights were compared (HP body weight: 96.6 ± 15.5 kg versus LP body weight: 85.9 ± 18.3, p=0.03). In regard to co-morbidity, there were no significant differences between the LP and HP female patients. However, 46% of the obese patients in the HP group were treated for depression in comparison to only 21% in the LP group (not significant).

## DISCUSSION

This retrospective analysis of 106 patients demonstrated that the multi-modal analgesia protocol we implemented for patients undergoing unilateral TKA did not provide uniform pain control over the first 24-hours post-operatively. Guided by the clinical literature we defined 'acceptable' average NRS pain scores to be ≤ 5 over the first 24 hours, and the majority of TKA patients fell into this category. However, 31% of the TKA patients had NRS pain scores ≥ 6 over the first 20 hours after PACU discharge in spite of the multi-modal approach. Frequency analysis further demonstrated that as many as 16% of the patients had NRS scores ≥ 7 which from a quality care point of view is unacceptable. Several studies have characterized acute post-operative pain in TKA patients treated with and without femoral nerve blockade and reported NRS pain scores similar to those reported here acutely after surgery [19-23]. For example; in the study by Wang and colleagues, the TKA patients' mean NRS pain score was reported to be 3 and 6 during rest and rehabilitation, respectively, 20-24 hours post-surgery [23]. As previously mentioned, at our institution, the TKA patients start rehabilitation on the first post-operative day via a continuous passive motion machine (CPM) for 2 hours during the first 24 hours, and the NRS pain scores reported by the ward nurse every 4 hours are incorporated in the CPM routine. However, we were unable to separate 'rest' from 'rehabilitation' NRS scores based on the retrospective data collection.

Further analysis of the post-surgical NRS scores demonstrated that patients in the HP group were defined as being slightly younger and having higher pre-surgical pain scores. Logistic regression analysis revealed that the odds of falling into the HP group were 6.6% lower for every year of 'aging' (assuming constant pre-surgical pain levels over time). This finding of younger age being a predictor of severe pain acutely after surgery is not novel and has been previously reported [24, 25]. In fact, Kalkman and coworkers [25] recently characterized predictors for

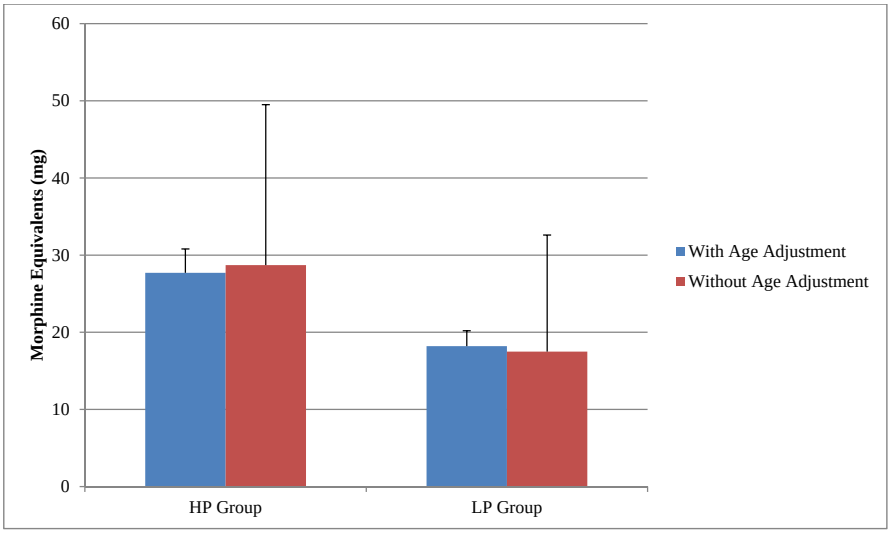


**Fig. (3).** Opioid Usage in TKA patients with high and low NRS pain scores.

developing post-operative pain for a wide variety of surgical procedures including orthopedic procedures in a large series of surgical inpatients undergoing general anesthesia with either an inhalational anesthetic or propofol [25]. While there was no difference in the number of patients with severe pain between the two anesthesia techniques, younger age, female gender and high pre-operative pain scores were among the most significant predictors of 'presence of severe pain' post-surgery [25]. These classifiers have been confirmed in other studies as well [26, 27], although some studies do not find gender to be a significant factor in acute pain [28].

Our retrospective analysis also demonstrated that the majority of the female TKA patients with high, 'difficult-to-treat' post-operative pain were characterized by being more obese (BMI = 37.7 ± 6.1), in contrast to the female patients in the low pain group who had an average BMI of 34.4 ± 5.9. To the best of our knowledge, there are no clinical studies in the literature demonstrating or suggesting that obese female patients are at higher risk for developing unmanageable, acute pain post-surgery. However, there is a growing body of literature on the role of fat itself and its many pathophysiological consequences. Previously, adipocytes were considered to be little more than storage cells for fat, but it is now clear that fat tissue functions as an active endocrine organ that produces many pro-inflammatory substances such as tumor necrosis factor alpha (TNFα), interleukin 6 (LI-6) and leptin [29-33] which interact with many physiological processes. For example, leptin is produced by adipocytes and is a hormone that regulates food intake; leptin also can act as a cytokine and induce a heightened inflammatory state [34]. In this context it is also important to emphasize that plasma levels of leptin in obese subjects have been shown to correlate positively with BMI [35, 36] and that leptin levels are higher in females [37]. A current working hypothesis now associates obesity with a chronic inflammatory state, in other words, as individuals become obese and their adipocytes enlarge, adipose tissue undergoes molecular and cellular alterations that change body metabolism and induce a general inflammatory state [38, 39]. Based on this evidence in the literature, it is possible that obesity in the female TKA patients may have played a role in regards to higher NRS pain scores post-operatively.

However, there are many other factors that potentially explain our findings and which could not be controlled for (e.g. oral rather than parenteral administration of opioids and other predisposing factors) in this retrospective study. Clearly, further investigation of the potential role of obesity and pre-operative inflammatory status on post-operative acute pain following TKA, including measurements of serum leptin levels, will be needed to provide further support and validation for our findings.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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