Original Article

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Factors Associated with Early Postoperative Pain after Total Knee Arthroplasty

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Abstract:

Objective: Total knee arthroplasty (TKA) is a common operation for geriatric patients. Knowing the factors leading to acute post-TKA pain will lead to personalized pain care.

Material and Methods: We recruited 843 patients who underwent TKA. Preoperative, intraoperative, and postoperative data were obtained retrospectively.

Results: Moderate to severe postoperative pain in the first 24 hours was found in 87%. Factors associated with moderate to severe postoperative pain were being female [adjusted odd ratio (AOR) 2.34, 95% confidence interval (95% CI) 1.23–4.46], having an ASA physical status classification of II (AOR 9.22, 95% CI 1.9–44.67) or III (AOR 6.75, 95% CI 1.32–34.63), a longer tourniquet time (AOR 1.01, 95% CI 1.01–1.02), and postoperative use of aspirin (AOR 2.04, 95% CI 1.25–3.32). Factors found to be associated with mild postoperative pain were being younger (AOR 0.97, 95% CI 0.94–0.99), being given intrathecal fentanyl (AOR 0.3, 95% CI 0.12–0.73), having a peripheral nerve block (AOR 0.28, 95% CI 0.12–0.66), and taking a systemic corticosteroid (AOR 0.26, 95% CI 0.13–0.55), parecoxib (AOR 0.39, 95% CI 0.19–0.78) or ketorolac (AOR 0.47, 95% CI 0.23–0.99).

Conclusion: Being female, having an ASA physical status classification of II or III, a longer tourniquet time, and postoperative use of aspirin were significantly related to having moderate to severe postoperative pain within the first 24 hours after TKA. Factors associated with mild postoperative pain included being younger, intrathecal fentanyl, having a peripheral nerve block, receiving a systemic corticosteroid, and use of parecoxib and ketorolac.

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Introduction

Survival beyond 65 years of age is increasing worldwide. For example, a 65-year-old in 2015-2020 could anticipate living another 17 years on average. This is anticipated to increase to 19 additional years by the years 2045-2050. In addition, women currently live longer than men by 4.8 years, although this gender gap has been estimated to decrease slightly over the next 3 decades[1]. Multiple organ degeneration is an inevitable part of ageing. Osteoarthritis (OA) is the most predominant degenerative joint disease and has been noted to be the principal cause of disability worldwide[2]. Consistent with the findings regarding the aging of the world's population, the annual incidence and age-standardized point prevalence of OA in 2017 were 181 and 3,754 per 100,000, a rise of 8% and 9% from 1990, respectively[3]. It is estimated that in 2032, at least an additional 26,000 individuals per 1,000,000 population aged 45 years or older will have consulted a clinician due to OA of the peripheral joints compared with 2012[4].

Over the past few decades, total knee arthroplasty (TKA) has become the most popular joint replacement procedure globally. The prevalence of TKA generally increases with age: 1%, 3%, 7%, 10%, and 8% at 50, 60, 70, 80, and 90 years of age, respectively[5]. It is estimated that 3.48 million TKA operations will be performed annually by the year 2030 in the United States alone, which is 673% higher than the number performed in the year 2005[6].

TKA often results in significant acute postoperative pain. The mean rating of acute postoperative pain on 0-10 numerical scales is reported to range from 5.0 to 5.7 following TKA, which is in the moderate range[7-9] Average pain scores in the first 24 hours after TKA have been reported to range from 0.71-7.9[10]. It has been found that half of TKA patients experience at least moderate post-surgical pain intensity[7]. Another study found that 60% of patients undergoing TKA experience severe postoperative knee pain, while an additional 30% experience moderate pain[11]. Some patients postpone this surgical procedure due to fear of acute postoperative pain following TKA[12,13]. Acute post-TKA pain also places patients at risk for thromboembolism, and has been reported to interfere with early ambulation, rehabilitation, range of motion, patient satisfaction, and other important outcomes[13]. Moreover, a higher level of acute postoperative pain is also related to developing chronic postsurgical pain (CPSP)[14].

Given the impact of acute post-TKA pain on patients' psychological and physical function, it is important to understand the factors associated with this pain in order to more accurately determine who will benefit the most from preventive care. Many investigators have therefore sought to identify the patient factors that predict or are associated with chronic pain after TKA[15]. However, only a very few studies have sought to identify the factors that are associated with acute post-TKA pain. Among the factors that have been identified in this body of research as being positively associated with acute post-TKA pain are being younger and endorsing higher preoperative pain[16], having a higher body mass index (BMI)[10], having pain-related catastrophizing thoughts and negative moods[17], higher levels of cutaneous pain sensitivity[16], and higher levels of temporal summation of pain (TSP)[10].

Although the prior research has shown that it may be possible to predict postoperative pain after TKA, additional research is needed to determine which of the factors identified in these studies replicate in additional samples. This is particularly important in the case of TKA, given how

often TKA is being done, and the fact that increases in this procedure are very likely in the decades ahead. The primary aim of the current study was therefore to identify the factors associated with moderate to severe pain in the first 24 hours after TKA. We hypothesized that multiple preoperative, intraoperative, and postoperative variables would be associated factors for moderate to severe acute postoperative pain in patients undergoing TKA.

Material and Methods

Procedures

All data were collected retrospectively from each participant's medical record. A data record form was created and used to facilitate data collection. First, we identified all TKA cases conducted between October 2017 and December 2020 that were in our hospital information system. Next, one of the study investigators (TT) accessed the medical record and pulled the specific study variables from that record using the data record form. The study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Thailand (REC 64-117-8-4) before data collection commenced. Anonymity of the data was maintained, in accordance with the Declaration of Helsinki.

Participants

A total of 844 patients who underwent unilateral total knee arthroplasty (TKA) for primary osteoarthritis and met the other study inclusion criteria were identified. Among these, 843 (99.9%) had complete data in their medical records. Exclusion criteria included bilateral TKA, revision of knee replacement, patients receiving general anesthesia, and those with incomplete data in the hospital information system.

Surgical technique

All TKA procedures were performed by 3 experienced orthopedic joint surgeons. A minimally invasive medial parapatellar approach was used, employing a measured resection technique. Posterior-stabilized prosthetic components were implanted using bone cement.

Postoperative pain management

The hospital's postoperative pain management protocol for TKA patients includes regular administration of oral paracetamol, oral or intravenous nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors (COXIBs), peripheral nerve block (if not contraindicated), along with opioid injections (morphine or fentanyl) administered as needed. Periarticular infiltration or local infiltration analgesia (LIA) is optional. Other medications that patients used prior to surgery, such as gabapentin, pregabalin, and nortriptyline, were continued into the postoperative period.

Measures

Demographic data pulled from the patients' records included gender, age, weight, height, comorbidities, and the American Society of Anesthesiologists (ASA) physical status classification.

Preoperative data included preoperative pain intensity at rest as measured by a ward nurse using a verbal numerical rating score (VNRS) ranging from 0-10 (0="No pain", 10="Worst pain imaginable"). In addition, the research staff recorded all analgesics that the patients received on the day of surgery.

Intraoperative data comprised the type of anesthesia provided during the TKA, the presence or absence of peripheral nerve block, and both the tourniquet and operative times.

Postoperative data were the patients' ratings of worst postoperative pain intensity as measured by a Verbal Numerical Rating Scale (VNRS) at 0-6, 7-12, 13-18, and 19-24 hours postoperatively, analgesic consumption (including non-opioids and opioids as did or did not receive), and side effects, including nausea/vomiting, pruritus,

dizziness, respiratory depression, and urinary retention. The primary study outcome was a dichotomous variable at each assessment point representing no to mild pain (the mild pain group; worst pain rating 0–3 on the 0–10 scale) or moderate to severe pain (the high pain group; worst pain rating 4–10 on the 0–10 scale)[18].

Statistical analysis

We computed means and standard deviations of the continuous study variables with normal distributions, and medians and interquartile ranges for study variables with non-normal distributions to describe the sample and study variables. All parameters were first analyzed by univariate analysis. Parameters with p-value<0.20 from univariate analysis and known factors (non-opioids) were included in the multivariable analysis to predict outcome. Results from the multivariable analysis were reported as adjusted odds ratios and 95% confidence intervals (CIs). We identified multicollinearity by a variance inflation factor that exceeded 10 and was statistically significant at p-value<0.05. Data analyses were performed using the R program version 4.1.3 (Vienna, Austria).

Sample size calculation

The sample size was calculated to identify any potential factors associated with moderate to severe pain, based on risk factors reported in the previous literature[19], with Type I and Type II errors set at 0.05 and 0.2, respectively. The estimated total sample size was 759 patients. Considering an anticipated 10% dropout rate, we aimed to collect data from 843 patients.

Results

We collected data from 843 eligible patients who had TKA from October 2017 to December 2020. One patient was excluded due to incomplete data (lack of tourniquet time). One hundred and seven patients had mild acute postoperative pain, while the majority, 736 patients (87%), endorsed having moderate to severe pain following TKA (Figure 1).

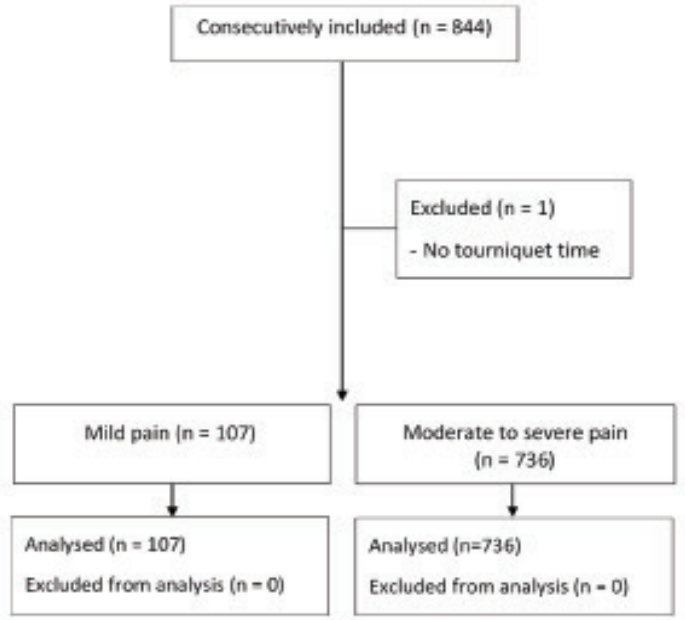

Figure 1 The consort flow chart

Demographic data are shown in Table 1. The 2 groups (mild pain group vs high pain group) had similar characteristics in terms of gender, age, body mass index (BMI), ASA classification (4 patients with ASA classification I were in each group) and comorbidities, including asthma, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, and chronic kidney disease. However, more participants in the high pain group met the criteria for a depressive disorder (per diagnosis in their chart) [none (0%) in the mild pain group vs 28 patients (4%) in the high pain group, p-value=0.039] and endorsed having preoperative pain at rest [35 patients (33%) in the mild pain group vs 335 patients (46%) in the high pain group, p-value=0.017].

Regarding analgesics and adjuvants that the patients received on the day of surgery, but before the surgery (i.e., premedication), a higher percentage of the patients with mild postoperative pain consumed non-steroidal anti-inflammatory drugs (NSAIDs) in comparison to those with moderate to severe postoperative pain [70 patients (65%) in the mild pain group vs 297 patients (40%) in the moderate to severe pain group, p-value<0.001], as can be seen in Table 2.

As can be seen in Table 3, a higher percentage of the patients in the mild pain group received intrathecal opioids [10 patients (9%) vs 26 patients (4%), p-value=0.015], peripheral nerve block (either adductor canal block, femoral nerve block or fascia iliaca block) [100 patients (93.5%) vs 626 patients (84.9%), p-value=0.026], and systemic corticosteroid [13 patients (12.1%) vs 38 patients (5.2%), p-value=0.009] in comparison to the patients in the high pain group. In contrast, the patients in the high pain group had longer surgeries [90 (80, 115) minutes vs 85 (75, 100) minutes, p-value=0.002] and tourniquet time [70 (55, 100) minutes vs 55 (45, 75) minutes, p-value<0.001] than those in the mild pain group.

Table 1 Demographic data of recruited patients

	Mild pain (n=107)	Moderate to severe pain (n=736)	p-value
Gender			0.203
Male (n, %)	16 (15)	76 (10.3)	
Female (n, %)	91 (85)	661 (89.7)	
Age (years), median (IQR)	70 (64, 75)	69 (63, 74)	0.132
BMI (kg/m^2), median (IQR)	27.2 (24.3, 29.6)	27.6 (24.7, 30.4)	0.148
ASA physical status (n, %)			0.005*
I	4 (3.7)	4 (0.5)	
II	79 (73.8)	582 (79)	
III	24 (22.4)	151 (20.5)	
Hypertension (n, %)	63 (58.9)	463 (62.8)	0.497
Diabetes mellitus (n, %)	22 (20.6)	136 (18.5)	0.697
COPD (n, %)	0 (0)	1 (0.1)	1
Asthma (n, %)	4 (3.7)	41 (5.6)	0.579
Chronic kidney disease (n, %)	9 (8.4)	69 (9.4)	0.89
Coronary artery disease (n, %)	4 (3.7)	25 (3.4)	0.778
Cerebrovascular disease (n, %)	1 (0.9)	36 (4.9)	0.074
Depressive disorder (n, %)	0 (0)	28 (3.8)	0.039*
Preoperative pain at rest (n, %)	35 (32.7)	335 (45.5)	0.017*

*p-value<0.05, ASA=American Society of Anesthesiologists, BMI=body mass index, COPD=chronic obstructive pulmonary disease

Table 2 Preoperative administration of analgesics (premedication)

	Mild pain (n=107)	Moderate to severe pain (n=736)	p-value
Premedication (n, %)	73 (68)	348 (47.2)	<0.001
Benzodiazepine	1 (1)	20 (2.7)	0.502
Paracetamol	7 (7)	43 (5.8)	0.944
NSAIDs	70 (65)	297 (40.3)	<0.001
Gabapentin	3 (3)	28 (3.8)	0.787
Pregabalin	1 (1)	5 (0.7)	0.558

NSAIDs=non-steroidal anti-inflammatory drugs

Table 3 Anesthetic techniques and intraoperative analgesic administration

	Mild pain (n=107)	Moderate to severe pain (n=736)	p-value
General anesthesia (n, %)	3 (2.8)	48 (6.5)	0.198
Spinal anesthesia (n, %)	104 (97.2)	696 (94.4)	0.333
Intrathecal opioid (n, %)			0.015*
Morphine	0 (0)	4 (0.5)	
Fentanyl	10 (9.3)	22 (3)	
Periarticular infiltration (n, %)	31 (29)	260 (35.3)	0.241
Peripheral nerve block (n, %)	100 (93.5)	626 (84.9)	0.026*
Systemic corticosteroid (n, %)	13 (12.1)	38 (5.2)	0.009*
Operative time (min), median (IQR)	85 (75, 100)	90 (80, 115)	0.002*
Tourniquet time (min), median (IQR)	55 (45, 75)	70 (55, 100)	<0.001*

*p-value<0.05

The patients in the high pain group required higher doses of opioids (morphine and fentanyl) in the first 24 hrs after the operation in comparison to those in the mild pain group [morphine 0 (0, 3) vs 10 (6, 18), p-value<0.001 and fentanyl 0 (0, 160) vs 150 (77.5, 240), p-value<0.001)]. A higher proportion of the high pain group patients also received postoperative aspirin, naproxen, and meloxicam, while the higher proportion of participants in the mild pain group received ketorolac (Table 4).

Table 5 shows the results from univariate analysis (crude odds ratios) and multivariable analysis (adjusted odds ratios). As can be seen, a number of variables distinguished participants in the mild pain group from those in the high pain group at p-value<0.200 in the univariate analysis, including gender, age, BMI, presence of cerebrovascular disease, ASA physical status classification, preoperative pain at rest, preoperative use of NSAIDs, and intraoperative use of the following procedures or medications: general anesthesia, intrathecal fentanyl, peripheral nerve block, and systemic corticosteroid. Operative time and tourniquet time were also different between the 2 groups. Moreover, the use of the following medications during the postoperative period differed between the 2 groups: aspirin, naproxen, meloxicam, ketorolac, and gabapentin. Periarticular infiltration or local infiltration analgesia (LIA) and postoperative use of parecoxib were forced into the multivariable analysis because these

2 factors had p-values very close to 0.200, and they were of particular interest for affecting postoperative pain intensity. We could not include depressive disorders in the multivariable analysis because no patient in the mild pain group had this diagnosis.

The results of the multivariable analysis indicate that the following factors were associated with moderate to severe post-TKA pain: being female [adjusted odds ratio (AOR) 2.34, 95% confidence interval (CI) 1.23, 4.46], age [0.97 (0.94, 0.99)], having an ASA physical status of II [9.22 (1.9, 44.67)] or III [6.75 (1.32, 34.63)] with ASA class I as reference, having a longer tourniquet time [1.01 (1.01, 1.02)], and postoperative use of aspirin [2.04 (1.25, 3.32)]. Conversely, having received intrathecal fentanyl [0.3 (0.12, 0.73)], a peripheral nerve block [0.28 (0.12, 0.66)], and a systemic corticosteroid [0.26 (0.13, 0.55)], as well as the postoperative use of parecoxib [0.39 (0.19, 0.78)] and ketorolac [0.47 (0.23, 0.99)], were identified as being more likely to have mild pain than moderate or severe postoperative pain in the first 24 hours after TKA.

Regarding adverse events, the participants in the mild pain group had a lower incidence of nausea [19 patients (17.8%) in the mild pain group vs 254 patients (34.5%) in the moderate to severe pain group, p-value<0.001] and vomiting [18 patients (16.8%) in the mild pain group vs 226 patients (30.7%) in the moderate to severe pain group, p-value=0.005] in comparison to those with moderate to severe pain as shown in Table 6. The incidence of dizziness, pruritus, and urinary retention was low and did not differ significantly between the 2 groups.

Discussion

The purpose of this study was to identify the factors associated with moderate to severe pain in the first 24 hours after TKA. The key findings were that being female, having an ASA physical status classification of II or III (as

Table 4 Analgesic and medication use in the first 24 hours after TKA

	Mild pain (n=107)	Moderate to severe pain (n=736)	p-value
Morphine (mg/day), median (IQR)	0 (0, 3)	10 (6, 18)	<0.001*
Fentanyl (mcg/day), median (IQR)	0 (0, 160)	150 (77.5, 240)	<0.001*
Tramadol (mg/day), median (IQR)	100 (100, 100)	100 (100, 150)	0.382
NSAIDs (n, %)	104 (97.2)	721 (97.8)	0.723
Aspirin	58 (55.8)	509 (70.6)	0.003*
Naproxen	2 (1.9)	73 (10.1)	0.011*
Meloxicam	7 (6.7)	124 (17.2)	0.01*
Ibuprofen	0 (0)	7 (1)	0.605
Diclofenac	1 (1)	2 (0.3)	0.333
Celecoxib	9 (8.7)	63 (8.7)	1
Etoricoxib	1 (1)	12 (1.7)	1
Parecoxib	52 (50)	310 (43)	0.215
Ketorolac	37 (35.6)	164 (22.7)	0.006*
Paracetamol (n, %)	103 (96.3)	686 (93.1)	0.3
Nortriptyline (n, %)	23 (21.5)	156 (21.2)	1
Gabapentin (n, %)	76 (71)	425 (57.7)	0.012*
Pregabalin (n, %)	5 (4.7)	63 (8.5)	0.236

*p-value<0.05, NSAIDs=non-steroidal anti-inflammatory drugs, TKA=total knee arthroplasty

Table 5 Associated factors for moderate to severe postoperative pain in the first 24 hours after TKA

	Crude OR (95% CI)	p-value	Adjust OR (95% CI)	p-value
Female (vs male)	1.53 (0.85, 2.74)	0.153	2.34 (1.23, 4.46)	0.01
Age (years)	0.98 (0.95, 1.01)	0.153	0.97 (0.94, 0.99)	0.045
BMI (kg/m^2)	1.04 (0.99, 1.09)	0.112		
Cerebrovascular disease (ref: no)	5.44 (0.74, 40.12)	0.096		
ASA physical status				
I	1		1	
II	7.37 (1.81, 30.05)	0.005	9.22 (1.9, 44.67)	0.006
III	6.29 (1.47, 26.86)	0.013	6.75 (1.32, 34.63)	0.022
Preoperative pain at rest (ref: no)	1.71 (1.12, 2.63)	0.014		
Premedication with NSAIDs (ref: no)	0.36 (0.23, 0.55)	<0.001		
General anesthesia (ref: no)	2.42 (0.74, 7.89)	0.145		
Intrathecal fentanyl (ref: no)	0.3 (0.14, 0.65)	0.002	0.3 (0.12, 0.73)	0.008
Peripheral nerve block (ref: no)	0.39 (0.18, 0.87)	0.022	0.28 (0.12, 0.66)	0.003
Periarticular infiltration (ref: no)	1.34 (0.86, 2.08)	0.201		
Systemic cortocosteroid (ref: no)	0.39 (0.2, 0.76)	0.006	0.26 (0.13, 0.55)	<0.001
Operative time (min)	1.01 (1, 1.02)	0.005		
Tourniquet time (min)	1.02 (1.01, 1.02)	<0.001	1.01 (1.01, 1.02)	0.028
Postoperative use of aspirin (ref: no)	1.89 (1.25, 2.85)	0.002	2.04 (1.25, 3.32)	0.004
Postoperative use of naproxen (ref: no)	5.77 (1.4, 23.87)	0.016		
Postoperative use of meloxicam (ref: no)	2.89 (1.31, 6.37)	0.008		
Postoperative use of parecoxib (ref: no)	0.77 (0.51, 1.15)	0.203	0.39 (0.19, 0.78)	0.008
Postoperative use of ketorolac (ref: no)	0.54 (0.35, 0.84)	0.006	0.47 (0.23, 0.99)	0.047
Postoperative use of gabapentin (ref: no)	0.56 (0.36, 0.86)	0.009		

ASA=American Society of Anesthesiologists, BMI=body mass index, NSAIDs=non-steroidal anti-inflammatory drugs, TKA=total knee arthroplasty

Table 6 Adverse events

	Mild pain (n=107)	Moderate to severe pain (n=736)	p-value
Dizziness (n, %)	0 (0)	5 (0.7)	1
Nausea (n, %)	19 (17.8)	254 (34.5)	<0.001*
Vomiting (n, %)	18 (16.8)	226 (30.7)	0.005*
Pruritis (n, %)	0 (0)	5 (0.7)	1
Urinary retention (n, %)	0 (0)	5 (0.7)	1

*p-value<0.05

opposed to a classification of I), having a longer tourniquet time, and postoperative use of aspirin were all significantly related to having moderate to severe postoperative pain within the first 24 hours after TKA. Factors associated with having mild postoperative pain included being younger and receiving intrathecal fentanyl, a peripheral nerve block, a systemic corticosteroid, parecoxib, or ketorolac. These findings have important implications for understanding the

factors that could determine who is most at risk for having moderate to severe post-TKA pain, and for developing potential approaches to minimize that pain.

A previous study on the incidence and risks of postoperative pain after knee replacement showed that its incidence of moderate to severe pain on the first postoperative day was approximately 50%, and the primary risk factors were preoperative pain intensity and type of anesthesia provided[19]. Differences in the prevalence and the method of variable selection may have contributed to the differing sets of potential risk factors between our study and the previous one[19]. Our study found more factors contributing to acute moderate to severe postoperative pain in the first 24 hours after TKA. We also found potential protective factors against this acute pain.

We will discuss each factor in our findings one by one, starting with gender. Our study shows that being female is associated with a higher risk for moderate to severe postoperative pain following TKA. In general, more females have knee OA and TKA compared to males. The prevalence of symptomatic knee OA in Americans aged 60 years or older was 13% in females and 10% in males[20]. Data from India have revealed that the prevalence of knee OA was significantly higher in females than males (51% vs 33%)[21]. In the USA, white females possessed the highest incidence rate of TKA at 2.3%, while non-white males possessed the lowest rate at 0.9%[22]. Being female was also identified as an independent predictor for early postoperative pain following TKA by Lo and colleagues[23]. Moreover, females were found to report higher levels of pain intensity during the first 2 weeks after TKA than males[24]. Females have been found to constantly report marginally higher pain scores (0.29 point out of 10), regardless of the type of operation[25]. A study performed in orthopedic patients demonstrated that females endorsed significantly higher worst postoperative pain scores than males. Subgroup analysis showed that this sex effect was larger for older (i.e., >50 years of age) than younger patients[26]. A large variety of experimental pain models also suggest sex differences in pain[27]. The mechanisms that explain these consistent sex effects are not yet known. It has been postulated that biological differences, such as sex hormones[28,29], along with psychological[30] and sociocultural[31] parameters, may all contribute to this effect. Future research is needed to identify the mechanisms underlying these sex differences, as such research may inform the development of treatments that could reduce post-surgical pain in women.

We found that higher ASA physical status (II or III) was associated with a greater risk factor for having moderate to severe postoperative pain after TKA. To the best of our knowledge, no other researchers have examined the ASA physical status classification and severity of postoperative pain. However, one study found that a higher ASA classification was associated with lower satisfaction in patients undergoing total hip arthroplasty[32]. Higher ASA score was shown to be associated with increased opioid consumption in inpatients and discharge prescriptions[33]. It is possible that these latter findings may be explained by the role that the ASA score has in predicting the risk of post-surgical pain.

We also found that tourniquet time was associated with a greater risk of having moderate to severe post-TKA pain. This finding is consistent with the results of a systematic review of randomized controlled trials (RCTs), which showed that on the third day following TKA, pain was significantly higher in patients on whom a tourniquet was used intraoperatively compared to those without a tourniquet[34]. A cohort study demonstrated that tourniquet use during ankle surgery led to a 20% increase in postoperative opioid requirement, or by 0.43 mg for every 10 minutes of tourniquet time[35]. A tourniquet can cause a number of local and systemic derangements, including tissue ischemia, no-

reflow phenomenon, and post-tourniquet syndrome[36]. As a group, these findings suggest that the use of tourniquets should be for as little time as possible.

Many of the study participants received a low dose of aspirin (81 mg per day) postoperatively for venous thromboembolism (VTE) prophylaxis. However, we found that the use of this drug was a significant risk factor for having moderate to severe post-TKA pain. To the best of our knowledge, this is the first study that has examined low-dose aspirin as a potential risk factor for post-surgical pain. It seems likely that a low dose of aspirin at 81 mg per day is too low to exert any noticeable analgesic effects (a regular dose of aspirin for pain relief is 300-600 mg every 4-6 hours). However, it is possible that this dose of aspirin may be enough to interfere with the pharmacokinetics of other traditional NSAIDs and selective cyclo-oxygenase 2 (COX-2) inhibitors (COXIBs), thereby compromising the analgesic effects of the latter. At the same time, NSAIDs can interfere with aspirin's efficacy to prevent VTE following total joint arthroplasty. It is thought that the binding of NSAIDs to the COX-1 receptor may prevent aspirin's platelet inhibition via effective competition, most probably at the level of platelet COX-1[37]. In any case, these findings support the need for more research to evaluate the interaction of aspirin on NSAIDs/COXIBs and vice versa.

All of our recruited patients' ages ranged from 63-75 years old, and we found that those in the younger age group were associated with having mild (as opposed to moderate or severe) post-TKA pain. However, this result is inconsistent with those from other studies, which showed that being younger was associated with higher levels of post-surgical pain following total joint arthroplasty[38]. A retrospective cohort study as part of the international PAIN OUT program found that with 4 common operations (hip or knee replacement, spinal surgery and laparoscopic cholecystectomy), postoperative pain lessened with advancing age. However, the change was small and of questionable clinical significance[39].

We also found that having intrathecal fentanyl before the surgery was a protective factor against early moderate to severe postoperative pain following TKA. This finding is consistent with the conclusions from a systematic review and meta-analysis of RCTs, which showed the effectiveness and safety of spinal fentanyl in various kinds of surgery, including orthopedic procedures such as total hip arthroplasty[40]. Thus, providing intrathecal fentanyl would be worth considering when possible.

In addition, having received a peripheral nerve block prior to the survey was protective against moderate to severe post-TKA pain. This finding is consistent with the conclusions from a network meta-analysis, which found that single-shot and continuous femoral nerve blocks provided better postoperative pain relief at 24 hours in comparison to control[41]. Adductor canal blockade[42] and fascia iliaca block[43] have also been found to be effective adjuncts for postoperative pain relief in TKA patients.

Another potential protective factor against moderate to severe post-surgical pain identified in the current study was systemic corticosteroid. Again, this finding is consistent with the conclusions from a systematic review and meta-analysis of 1,671 TKA patients, which demonstrated that adding perioperative intravenous dexamethasone reduced postoperative pain, opioid consumption, and length of hospital stay[44].

Finally, we found that postoperative administration of either parecoxib or ketorolac was a protective factor against moderate to severe post-TKA pain. These findings are consistent with a study in Korean patients undergoing TKA that demonstrated parecoxib provided significantly better pain relief than a placebo[45]. Also, meta-analysis concluded that parecoxib was effective in decreasing postoperative pain and opioid requirements in TKA patients[46]. It has been shown that parecoxib provided comparable analgesia to ketorolac in TKA patients[47]. A retrospective study with

propensity score matching demonstrated that TKA patients with contraindications for NSAIDs had significantly higher postoperative pain intensity and required higher doses of morphine compared with those receiving NSAIDs[48]. As a group, these findings suggest that it would be useful to consider offering either ketorolac or parecoxib to patients who have undergone TKA.

The study has a number of limitations that should be considered when interpreting the results. Of most importance, it was a retrospective study, in that all of the data were collected after the TKA surgeries had been completed. That said, the variables examined as predictors were assessed and put into the patients' medical records prior to them having the surgery. Thus, although the study itself is retrospective, many of the key predictor variables studied here were not. This increases our confidence that the findings are reliable and were not impacted by the patient's (or clinician staff's) memories regarding the variables, or might have been influenced by the presence of significant post-surgical pain intensity. A second limitation is that we studied a large number of variables in a series of exploratory analyses. We did not control for multiple tests in these analyses. It is therefore possible – indeed it is probable – that some of the significant findings might have emerged due to chance alone. These variables would therefore need to be studied in additional samples of individuals who have had a TKA to determine which findings are reliable. Also, the sample contained many more women than men. Thus, the extent to which the findings generalize to men with TKA is not known. Again, additional research is needed, in particular in samples containing more men, to determine the overall generalizability of the results. Finally, the TKAs were performed by different surgeons, and anesthesia was administered by various anesthesiologists. Variations in pain management regimens (even if similar) could have been a significant factor contributing to differences in pain control between the mild and high pain groups.

Conclusion

Despite the study's limitations, the findings provide important new information regarding the factors associated with post-TKA pain. We identified a number of variables that predicted subsequent pain (i.e., factors assessed prior to the TKA) and that were associated with (i.e., factors assessed after the TKA) post-TKA pain. To the extent that these findings replicate in other samples of individuals who have undergone TKA surgery, the findings may be used to make it possible to deliver more effective pain management for these subjects (e.g., a personalized pain relief strategy), and to make them more comfortable for both the short term and long term following TKA.

Authors' contributions:

Sasikaan Nimmaanrat was involved in the study design, proposal writing, Ethics Committee application, data collection, data analysis and interpretation, manuscript writing, and submission for publication.

Thara Tantichamnankul was involved in the study design, proposal writing, Ethics Committee application, data collection, data analysis and interpretation, and manuscript writing.

Mark P. Jensen was involved in data interpretation, manuscript writing, and submission for publication.

Sirikarn Siripruekpong was involved in data collection and manuscript writing.

Sumidtra Prathep was involved in data collection and manuscript writing.

Khanin Iamthanaporn was involved in data collection and manuscript writing.

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Conflict of interest

None to declare.

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