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Preemptive Analgesia for Pain Management in Total Knee Arthroplasty: An Asian Perspective

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Abstract

Background: Knee osteoarthritis is a debilitating condition affecting up to 11% of individuals in Singapore. Total knee arthroplasty (TKA) is one of the most effective treatments for this condition. However, it is also associated with significant post-operative pain that can limit post-operative rehabilitation and outcomes. Preemptive analgesia (PA) is a proactive approach to pain management and has shown promising outcomes.

Objective: To study the short-term outcomes of Preemptive analgesia in patients undergoing TKA.

Method: A retrospective review of a database from January 2022 to December 2022 identified all TKA cases performed by one senior orthopaedic surgeon. Eligible patients were divided into those who received PA and those who did not receive PA. The PA group received oral medications consisting of 50 mg tramadol, 200 mg celecoxib, 1000 mg paracetamol, and 300 mg gabapentin one hour before surgery. No preoperative analgesia was given in the non-PA group. Outcome assessments included VAS scores at 6 and 24 hours postoperatively, degree of active range of motion (ROM) of the knee and the ability to perform a straight leg raise (SLR) 24 hours after surgery, requirement of breakthrough analgesia and length of stay (LOS) in the hospital.

Results: 104 patients were identified, with 53 patients in the PA group and 51 patients in the non-PA group. The PA group had lower VAS scores at 6 hours (1.94 vs. 2.24), but higher VAS scores at 24 hours compared to the non-PA group (3.75 vs. 3.43). Differences in VAS scores were not statistically significant. The ROM and SLR were similar between the PA and the non-PA group (83.4° vs. 81.3°, P = 0.44) and (77.4% vs. 68.6%, P = 0.25). There was no significant difference in requirements of breakthrough analgesia between both groups. LOS was comparable between both groups as well.

Conclusion: The use of Preemptive analgesia with a combination of tramadol, celecoxib, paracetamol, and gabapentin did not significantly reduce postoperative pain after TKA.

Introduction

Osteoarthritis (OA) is one of the leading causes of long-term pain and disability[1], with OA of the knee being the most common, accounting for approximately 85% of burden of osteoarthritis worldwide[2]. In Singapore, the estimated national prevalence of knee OA is 11%, with a prevalence of 19.7% for those aged 60 years and above[3]. More recent studies have shown that symptomatic knee osteoarthritis affects 1 in 10 people over the age of 50 in Singapore[4,5]. With the lifetime risk of symptomatic knee OA estimated to be 44.7%[6], total knee arthroplasty (TKA) has been proven to be an effective treatment in tackling this disease. However, issues of significant post-operative pain are still a major complaint that can influence overall outcomes[7].

Poorly controlled pain post TKA is associated with dissatisfaction, slower recovery, and rehabilitation, along with increased cost and length of stay[8]. According to Ranawat *et al.*, postoperative pain may even result in arthrofibrosis which diminishes range of motion[9]. It is therefore pertinent to establish an effective pain management model to allow satisfactory functional recovery after TKA.

Preemptive analgesia (PA) is a proactive approach to pain management, aiming to control postoperative pain by preventing the development of central sensitization, incisional, and inflammatory damage through the administration of analgesia before surgical incision[10]. By inhibiting pain mediators in both the peripheral and central nervous systems, PA is postulated to reduce the duration and intensity of postoperative pain, offering sustained relief beyond the normal pharmacological duration of action[11]. The utilization of PA has demonstrated promising outcomes in pain management[12]. As the concept of PA is gaining more recognition, our study aims to evaluate the use of PA in a local context to determine its effectiveness in reducing postoperative pain and to also assess the impact that it may have on short-term postoperative outcomes for TKA patients.

Materials and Methods

All procedures undertaken in this study were approved by the institutional review board on human subject research and by the ethics committee at our institution. Verbal and written informed consent were obtained before the study.

This retrospective cohort study data was conducted to identify all primary TKAs performed for the indication of osteoarthritis between January 2022 to December 2022 by a single series surgeon in a tertiary institution. Patients were included in this study if they met all of the following eligibility criteria: had a primary diagnosis of osteoarthritis, were aged between 45 and 80 years, had visited the orthopaedic specialist clinic, and underwent a unilateral elective primary TKA. Patients were excluded if they had inflammatory arthritis, neurologic or psychiatric diseases that may influence pain perception, coagulopathy, ASA physical status of grade 4, and any allergy to analgesics chosen to be used as PA. In this single surgeon series, there were a total of 142 patients. Four were excluded due to being older than 80 years of age, five had some form of inflammatory arthritis, ten patients had allergies to the chosen analgesia for the preemptive analgesia regime, three had neurological or psychiatric conditions that could impact pain perception, 11 patients underwent a unicompartmental knee arthroplasty instead of a TKA, and five patients had missing data, leaving 104 patients for analysis (Figure 1).

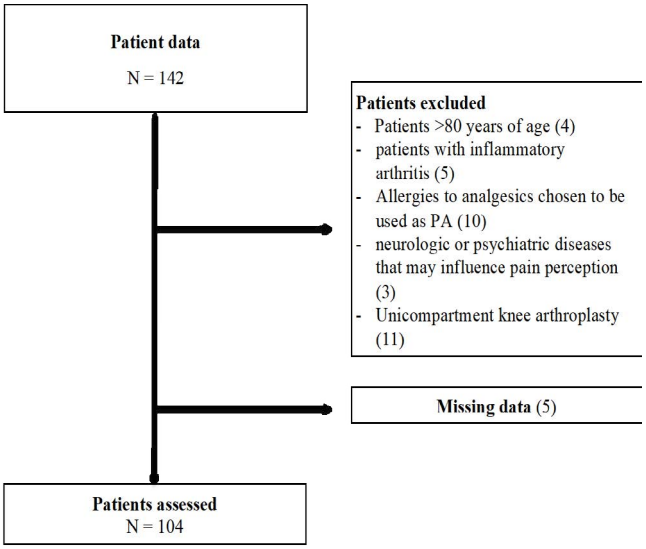

Figure 1: Flowchart of patient selection

Once the study population was finalized, eligible patients were divided into the 2 main study groups: patients who received PA and patients who did not receive any PA. For patients in the PA group, an analgesic cocktail of oral medications consisting of 50mg tramadol, 200mg celecoxib, 1000mg paracetamol and 300mg gabapentin was given one hour before surgery. No preoperative analgesia was given to patients in the non-PA group.

All surgeries were performed by one senior orthopaedic surgeon with an interest in arthroplasty, and surgeries were performed either under general anaesthesia or regional anaesthesia via a spinal nerve block. Pre-operatively, intravenous 1000mg Tranexamic acid and an adjusted dosage of intravenous dexamethasone to 4-8mg based on the patient's blood sugar control was given by the anaesthetist as per our institution's standardized protocol for all TKA patients. Intraoperative procedures were also standardised as well. All TKAs were performed under tourniquet control and used a standard medial parapatellar approach. A posterior-stabilized or medial congruent prosthesis was used in all cases, and all components were cemented. The patella was not resurfaced in any case, and no patient required stem extensions of the femoral or tibial component or any reconstruction for bone defects. Intraoperatively, a periarticular injection containing 150mg 1% Ropivacaine, 30mg Ketorolac and 0.5ml Adrenaline (1:1000) mixed with sterile normal saline solution to a combined volume of 100ml. The first 30ml of this mixture was injected before component implantation, into the posterior aspect of the joint capsule, medial and lateral collateral ligaments, soft tissue around the quadriceps tendon and patellar tendon, fat pad, and synovium. Before wound closure, the remaining 70ml was used to infiltrate fat and subcutaneous tissues. No drains were inserted. In the general ward, all patients received a standard postoperative regimen of oral medications consisting of 1g

Paracetamol four times daily, 200mg Celecoxib two times daily, and 300mg Gabapentin every night. 5mg Oxycodone Hydrochloride was given every 6 hours as needed for breakthrough, and this was determined via the visual analogue scale (VAS). VAS was assessed using an 11-point Likert scale where 0 was equivalent to no pain and 10 was equivalent to the worst possible pain. When the VAS score exceeded 4, or upon patient request, oxycodone was given. The first dose of analgesia was given 6 hours after completing surgery and the regimen continued throughout the patient's hospital stay. The quality of postoperative pain relief was determined by VAS scores. Active and passive knee range of motion exercises and mobilisation were initiated immediately after surgery by a physiotherapist.

Outcome assessment using VAS was done 6 hours after surgery, and again 24 hours after surgery. Any requirement for breakthrough analgesia in the form of oxycodone within the first 24hrs post-surgery was also recorded. Other parameters studied to determine outcomes were the degree of active range of motion (ROM) of the knee, as well as the ability to perform a straight leg raise (SLR). Range of motion was measured using a goniometer with the patient in a supine position and SLR was defined as the ability of the patient to hold the operated leg off the bed, regardless of height raised and hold time. These parameters were recorded 24 hours postoperatively. Lastly, we also recorded the overall length of stay (LOS) of all recruited patients.

Statistical Analysis

Statistical analysis was performed with SPSS Statistics version 28.0 (IBM-SPSS, New York, USA). Continuous variables are reported as mean ± standard deviation. Demographic and clinical variables were compared using ANOVA and Fisher's exact test. The normality of distribution for the outcome variables such as such as VAS, ROM and LOS, ability to SLR and requirement for breakthrough analgesia was assessed by the Shapiro-Wilk test. Accordingly, the outcome variables are presented as means with SD or medians with interquartile range (95% CI). The data was tested using a one-way ANOVA if the data were normally distributed and with the Kruskal-Wallis test and the Mann-Witney U test if they were not normally distributed. The level of statistical significance was set at 0.05.

Results

Patients

104 eligible patients were identified for this study. 53 patients were in the PA group and 51 patients were in the non-PA group. The most relevant demographic data, including age, laterality, gender distribution, racial profiles, and American Society of Anesthesiologist (ASA) grades are presented in Table 1.

Intra-operative factors

Regarding intra-operative factors, both groups were comparable in terms of the type of anesthesia used, method of knee replacement and their mean tourniquet times. The results are presented in Table 2.

Outcomes

The various outcomes assessed are presented in Tables 3, 4, 5.

Visual Analogue Scale (VAS) scores

At 6 hours postoperatively, the VAS scores in the PA group were lower than the non-PA group (1.94 and 2.24 respectively). However, this difference was not statistically significant (P = 0.537). When VAS scores were recorded again at 24 hours postoperatively, individuals in the PA group exhibited higher VAS scores compared to the non-PA group (3.75 and 3.43 respectively). This difference between the two groups was again not statistically significant (P = 0.548).

Table 1: Comparison table of biodemographic of Preemptive analgesia vs non Preemptive analgesia cases

Variables	PA Group (n=53)	Non-PA Group (n=51)	p-value
	Mean ± SD	Mean ± SD	
Age	66.7 ± 7.74	66.6 ± 7.92	0.79
Laterality of procedure	L: 24 (45.3%)	L: 21 (41.2%)	0.60
	R: 29 (54.7%)	R: 30 (58.8%)	
Gender	F: 27 (40%)	F: 28 (54.9%)	0.06
	M: 13 (24.5%)	M: 23 (45.1%)	
Race	Chinese - 40 (81.1%)	Chinese - 37 (72.5%)	0.80
	Indian - 5 (9.4%)	Indian - 9 (17.6%)	
	Malay - 5 (9.4%)	Malay - 5 (9.8%)	
ASA grade	2.20 (1-3)	2.23 (1-3)	0.08

PA: Preemptive analgesia; SD = Standard deviation

Table 2: Comparison of intra-operative factors

Variables	PA group (n=53)	Non-PA group (n=51)	p-value
Type of anaesthesia	General anaesthesia (21) Spinal (32)	General anaesthesia (28) Spine (23)	0.11
Method of knee replacement	Conventional (3) Navigated (23) Robotic (27)	Conventional (3) Navigated (16) Robotic (32)	0.31
Mean tourniquet times (min)	112.6 ± 21.3	115.3 ± 21.7	0.53

PA: Preemptive analgesia; SD = Standard deviation

Table 3: VAS scores on POD 0 and POD 1

Variables	PA Group (n=53)	Non-PA Group (n=51)	p-value
	Mean ± SD	Mean ± SD	
VAS POD 0	1.94 ± 1.69	2.24 ± 1.86	0.537
VAS POD 1	3.75 ± 1.94	3.43 ± 2.28	0.548

PA: Preemptive analgesia; Non-PA: Non-Preemptive analgesia; SD = Standard deviation

The data was not normally distributed.

The p-value was measured using the Kruskal-Wallis non-parametric test.

Table 4: ROM on POD 1 and LOS

Variables	PA Group (n=53)	Non-PA Group (n=51)	p-value
ROM POD 1	83.89 Degrees ± 19.32	81.27 Degrees ± 19.76	0.497
Length of stay	4.00 days	2.69 Days	0.534

PA: Preemptive analgesia; Non-PA: Non-Preemptive analgesia; SD = Standard deviation

The data for ROM on POD 1 was normally distributed.

The p-value was measured using the ANOVA parametric test.

Table 5: The ability to straight leg raise (SLR) on POD 1 and the requirement of breakthrough analgesia within the first 24hrs post-surgery

Variables	PA Group (n=53)	Non-PA Group (n=51)	p-value
	Mean ± SD	Mean ± SD	
SLR POD 1	41 (77.4%)	35 (68.6%)	0.316
Required breakthrough analgesia	25 (47.2%)	30 (58.8%)	0.172

PA: Preemptive analgesia; Non-PA: Non-Preemptive analgesia; SD = Standard deviation

The data was not normally distributed.

The p-value was measured using the Mann-Whitney U-test.

Range of Motion (ROM)

Patients in the PA group were able to achieve 83.4° ROM when evaluated at 24 hours postoperatively, this was slightly better as compared to patients in the non-PA group who only achieved 81.3° ROM at 24 hours postoperatively. However, there was no statistically significant difference between the two groups (P = 0.497).

Length of Stay (LOS)

There was no significant difference in LOS among both groups (P = 0.534), with the average LOS of the PA group being 4.00 as compared to 2.67 days in the non-PA group.

Straight Leg Raise (SLR)

41 patients in the PA group were able to perform SLR when evaluated at 24 hours postoperatively compared to 35 patients in the non-PA group. This difference was not statistically significant (P = 0.253).

Requirement for breakthrough analgesia

25 patients in the PA group required breakthrough analgesia during the first 24hrs post-surgery compared to 30 in the non-PA group. This difference was not statistically significant (P = 0.172).

Discussion

Effective pain management after TKA is a significant clinical issue in facilitating postoperative rehabilitation and improving outcomes for patients. Studies such as the network meta-analysis done in 2022 have shown that PA was more efficacious compared to traditional pain management methods in reducing postoperative pain and opioid consumption[13]. However, this study did not account for variability in procedures and did not have additional analyses of drug doses, which would be an important consideration. Through our study, we aimed to evaluate the efficacy of PA in reducing postoperative pain through standardized perioperative procedures and medication doses. Our study also aimed to determine the influence on short-term outcomes in patients post-TKA specifically. Through our analysis, our study shows that the efficacy of PA in TKA is comparable to patients who did not receive PA in terms of management of postoperative pain as well as other outcome parameters.

In a similar study done by Lubis *et al.*, results showed that VAS in the PA group was lower than that in the group who did not receive any PA[14]. The study also showed that VAS scores decreased from day 1 to day 3 postoperatively. This contrasts with our results in which VAS scores were higher at 24 hours postoperatively as compared to 6 hours postoperatively. Of note, in the study done by Lubis *et al.*, the PA chosen consisted of celecoxib and pregabalin only whereas ours also included an opioid. The addition of an opioid to our PA regimen may be a contributory factor to higher VAS scores, as seen in a study by Cooper *et al.*[15] Cooper's study found that patients who received PA with oxycodone had a greater VAS score on postoperative day 1 compared to those who did not receive an opioid. The patients who received preemptive opioids experienced more pain and demonstrated impaired early function by ambulating shorter distances and required greater morphine equivalents postoperatively. The authors suggested that this could be attributable to opioid-induced hyperalgesia (OIH)[16], a condition in which individuals develop increased sensitivity to painful stimuli because of opioid use. Therefore, when considering PA regimens, it may be beneficial to reconsider the use of opioids. Alternatives to opioids to the PA regimen include cyclooxygenase-2 (COX-2) inhibitors such as celecoxib, and anticonvulsants such as gabapentin and pregabalin which have shown promise, either as individual therapy or as a combination with other medications. For example, studies by Liu *et al.*[17] and Wang *et al.*[18] demonstrate that preemptive use of celecoxib alone resulted in lower pain scores and better knee ROM postoperatively. In Lubis's study, a combination

of pregabalin and celecoxib was used for their synergic effects[14]. This multimodal analgesic approach was also seen in a study by Passias *et al.*, in which a combination of acetaminophen, celecoxib, and gabapentin was given 30 to 60 minutes before total joint arthroplasty and patients demonstrated lower pain scores and a reduction in opioid requirements postoperatively[19]. Given the range of possible drug combinations, further research is required to determine the ideal preemptive medication regime. Our Preemptive analgesia cocktail was formulated due to the known synergistic effects of having a nonsteroidal anti-inflammatory drug, acetaminophen, gabapentin, and short-acting oral narcotic as part of an effective multi-modal pain regimen[20]. Possible research into the most favorable approach when prescribing PA (for example, as a single dose before surgery versus multiple doses in the days leading up to surgery) or to evaluate and compare individual medications against a combination of medications to determine which regime would result in more favorable outcomes.

Rehabilitation after TKA is important for recovery and it has been shown that early mobilisation following a TKA results in lower morbidity and shorter LOS[21]. Several studies have demonstrated that post-operative knee flexion ROM is positively associated with knee function and that the greater the ROM, the better the clinical outcomes in terms of better functional ability and improved patient satisfaction[22-26]. Lower post-TKA knee ROM at the time of discharge, has been shown to have greater risk of requiring manipulation under anaesthesia postoperatively to treat persistent knee stiffness[27]. Similarly, SLR is correlated with functional performance. SLR is a surrogate evaluation of quadriceps muscle strength. Quadriceps muscle strength after TKA is more strongly related to functional outcomes as compared to ROM or pain[28]. The ability to perform SLR on postoperative day 1 has been associated with shorter LOS and time to ambulation and thus is used to prognosticate early recovery and discharge from the hospital[29]. Therefore, to evaluate short-term outcomes post-TKA, we chose to study ROM and SLR at 24 hours post-TKA.

From our study, ROM in patients who received PA was comparable to patients who did not receive PA. This was also seen in studies by Lubis *et al.* and Ssamy *et al.*, where there was no significant difference observed in the ROM between patients who were provided with PA and those who were not[14,30]. However, early postoperative ROM at 24 hours post-TKA may not be reflective of mid- to long-term ROM outcomes. A study by Tomohiro *et al.* found that measuring ROM 5 days postoperatively was significant and demonstrated high specificity when predicting 12-month ROM, although the predictive accuracy at 1 month was higher than that at 5 days[31]. Given this, it may be beneficial to expand this study by observing more data points by evaluating ROM between the PA and non-PA group at longer intervals post-surgery to look into mid- to long-term outcomes. However, some studies dispute the use of early ROM as an outcome parameter because knee ROM is not only affected by pain but is also influenced by other factors such as preoperative ROM, knee alignment and soft tissues, and muscle strength. In a study by Köglberger *et al*., there were negligible correlations between ROM in the early postoperative days (days 4, 7, 10) and ROM at 12 months postoperative[32]. Similarly, Bade *et al.* reported limited prognostic value in acute measures of knee ROM post-TKA but instead found that measures of functional performance, such as the TUG (Timed Up and Go) test or the 6-minute walk test, were of more useful prognostic value[33]. Future expansions of our study can include evaluating the effect of PA on functional performance markers as these may be more capable of predicting outcomes and long-term function.

Our study showed no significant difference between the PA and non-PA groups in performing SLR at 24 hours post TKA. To our knowledge, few other studies have investigated the effect of PA specifically on SLR. Majority of research studying the effects of analgesia on post-TKA patients using SLR as an outcome measure mainly evaluates intraoperative use of nerve blocks or intra-articular injections.

PA has been shown to decrease hospital LOS and reduce the likelihood of patients being discharged to step-down facilities[34]. Both ROM and SLR are also directly affected by postoperative pain, therefore it is implied that by reducing postoperative pain with PA, ROM and SLR rates will improve, and this would then translate to early mobilisation rates. As mentioned above, LOS is reduced with early mobilisation[35-37]. In our study, the LOS of patients who received PA was contrarily higher than that of patients who did not receive PA, although this difference was not statistically significant. It is important to consider that LOS is a multifactorial outcome parameter that is not only affected by surgical and rehabilitation factors, but patient and social circumstances as well. Several factors that are associated with prolonged LOS after TKA are age, race, income level, premorbid functional status, medical and surgical complications, and inadequate home environment[38,39]. The limitation of this study is that these patient and social factors were not fully accounted for, and it is possible that the LOS in our patient groups were affected by these factors.

Our study has some other limitations. Firstly, there may have been selection bias as this was a retrospective single-centre study with a relatively small sample size. A multi-centre study with a larger sample size would be beneficial to provide further analysis. For better comparison between a PA and non-PA group, a randomized study could have yielded more significant results. Secondly, our research

was limited to 24 hours after surgery. Thus, we were unable to assess if this then would translate to long-term knee function recovery. Lastly, the use of analgesia, with special attention to opioids in particular, prior to surgery was not accounted for and this may have influenced postoperative outcomes. Multiple studies have found a correlation between opioid use prior to surgery and negative outcomes following TKA. To name a few, negative outcomes were in the form of less pain relief, higher requirements of opioids after surgery, and longer LOS[40-43]. Further studies with a detailed assessment of prior analgesic use should be done to better interpret study outcomes.

Optimal pain control after TKA is imperative to achieve better postoperative outcomes. At present, there is no standardized clinical guideline which informs the most efficacious medications, doses, and pattern of administration. Therefore, it is important to further investigate the topic of preemptive analgesia in hopes of optimizing perioperative pain management. Further studies will be needed to establish a better, more comprehensive approach.

Conclusion

The use of preemptive analgesia with the combination of tramadol, celecoxib, paracetamol and gabapentin did not significantly reduce postoperative pain after total knee arthroplasty. Additionally, this combination of preemptive analgesia did not show significant improvement in the VAS score, requirements for breakthrough analgesia, range of motion and performing a straight leg raise.

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Contributions

All authors had equal contribution in this study, and all approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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