



■ GENERAL ORTHOPAEDICS

Inpatient and outpatient opioid requirements after total joint replacement are strongly influenced by patient and surgical factors

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Aims

Currently, there is no single, comprehensive national guideline for analgesic strategies for total joint replacement. We compared inpatient and outpatient opioid requirements following total hip arthroplasty (THA) versus total knee arthroplasty (TKA) in order to determine risk factors for increased inpatient and outpatient opioid requirements following total hip or knee arthroplasty.

Methods

Outcomes after 92 primary total knee (n = 49) and hip (n = 43) arthroplasties were analyzed. Patients with repeat surgery within 90 days were excluded. Opioid use was recorded while inpatient and 90 days postoperatively. Outcomes included total opioid use, refills, use beyond 90 days, and unplanned clinical encounters for uncontrolled pain. Multivariate modelling determined the effect of surgery, regional nerve block (RNB) or neuraxial anesthesia (NA), and non-opioid medications after adjusting for demographics, length of stay, and baseline opioid use.

Results

TKAs had higher daily inpatient opioid use than THAs (in 5 mg oxycodone pill equivalents: median 12.0 vs 7.0; $p < 0.001$), and greater 90 day use (median 224.0 vs 100.5; $p < 0.001$). Opioid refills were more likely in TKA (84% vs 33%; $p < 0.001$). Patient who underwent TKA had higher independent risk of opioid use beyond 90 days than THA (adjusted OR 7.64; 95% SE 1.23 to 47.5; $p = 0.01$). Inpatient opioid use 24 hours before discharge was the strongest independent predictor of 90-day opioid use ($p < 0.001$). Surgical procedure, demographics, and baseline opioid use have greater influence on in/outpatient opioid demand than RNB, NA, or non-opioid analgesics.

Conclusion

Opioid use following TKA and THA is most strongly predicted by surgical and patient factors. TKA was associated with higher postoperative opioid requirements than THA. RNB and NA did not diminish total inpatient or 90-day postoperative opioid consumption. The use of acetaminophen, gabapentin, or NSAIDs did not significantly alter inpatient opioid requirements.

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Keywords: postoperative opioid requirements, total joint arthroplasty, total knee arthroplasty, total hip arthroplasty, opioid, postoperative pain control, regional anesthesia, spinal anesthesia, multimodal analgesia, total joint replacement

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Introduction

Amid the current opioid epidemic within the USA, orthopaedic surgeons face mounting challenges in managing patients' postoperative analgesia.¹ Without an evidence-based set of guidelines to maximize efficacy,

safety, and responsible use, orthopaedic surgeons have little support managing analgesic needs across a varied scope of practice.^{2,3} As it currently stands, orthopaedic surgeons are the third-largest prescribers of opioids (behind primary-care providers

and internists), accounting for approximately 8% of all prescribed doses.²⁻⁴ With over one million total knee arthroplasties (TKAs) and total hip arthroplasties (THAs) performed every year, these procedures compose a significant amount of prescribed opioids within the USA.⁵ Historically, it has been suggested that TKA is associated with higher levels of postoperative pain and opioid requirements than THA.⁶⁻⁸ Though these procedures historically required weeks of inpatient hospitalization with limited peri-operative analgesic options,^{9,10} TKAs and THAs now employ far shorter hospital stays,¹¹ and are even becoming outpatient procedures.¹² These changes further necessitate the investigation of modern approaches to pain management in order to best meet the complex analgesic needs of patients.

Components of multimodal analgesia for total joint replacement (TJR) can be applied before, during, and after surgery. Supported by a host of literature, intraoperative analgesia is transitioning from the exclusive implementation of general anesthesia to neuraxial anesthesia (NA) either alone or adjunctively, especially for TKA.^{9,10} Gaining traction in more recent years are regional nerve blocks (RNB); while the literature does support RNB, there is no consensus as to which combination of NA and RNB is most efficacious, or whether these interventions have any effect on postoperative opioid consumption.¹³⁻¹⁹ Implementation of non-opioid analgesia has led to targeting the postoperative inflammatory response via increased implementation of cyclooxygenase (COX) inhibitors, most notably the selective COX-2 inhibitors.²⁰⁻²⁴ Additionally, the use of neuromodulators like gabapentin and pregabalin has become increasingly common for TJR, though the beneficial effect of these medications is unclear.^{9,25-34}

Currently, there is no single, comprehensive national guideline for analgesic strategies for TJR.³⁵ Individual institutional guidelines for standardization of postoperative opioid prescribing after TKA and THA have been employed with successful reduction in 30-day postoperative prescription amounts.² However, risk factors throughout the 90-day global postoperative period and continued use of opioids beyond 90 days after TJR are only recently beginning to be understood.³⁶ Better understanding of the patient and surgical risk factors would allow institutions to more effectively create their own "procedure guideline" of postoperative analgesia. Therefore, the primary purpose of the present study is to determine differences in inpatient and outpatient opioid requirements within 90 days following primary TKA versus THA. Secondary aims of the study are to determine patient risk factors for increased opioid requirements or use of opioids beyond 90 days post-surgery. We hypothesized that TKA will have greater inpatient and outpatient opioid requirements than THA. We also hypothesize that the use of both regional and/or spinal

anesthesia as well as non-opioid analgesics will decrease opioid requirements in patients following TKA and THA at our institution.

Methods

Institutional Review Board approval was obtained. A total of 92 patients underwent unilateral primary THA or TKA between 2 January 2018 and 24 April 2018. All operations were performed in an inpatient setting at a single academic medical centre by one of two adult reconstruction fellowship-trained orthopaedic surgeons. Revision total knee and hip arthroplasties were excluded. Simultaneous bilateral arthroplasties were excluded from the study. Additionally, patients undergoing any surgery within 90 days after TJR were excluded, as residual pain from the initial procedure or pain with the additional procedure would influence overall pain level and opioid consumption. Subsequent non-TJR procedures that disqualified patients included: closed or open reduction for instability; procedures for postoperative stiffness (closed manipulation, open lysis of adhesions, or arthroscopic lysis of adhesions); irrigation and debridement of postoperative wounds; explant and antibiotic spacer placement for infection; and periprosthetic fracture stabilization procedures. Although a total of 113 consecutive cases between 2 January 2018, and 24 April 2018 were screened, 21 were excluded due to meeting one or more of the preceding exclusion criteria. This resulted in the final sample size of 92 patients in the study analysis. All data were obtained from existing medical records. No patients were contacted for the purpose of the current study.

According to an a priori power analysis, the sample size of 92 patients ($n = 43$ THA; $n = 49$ TKA) is adequate to assess the primary study aim. There is no established clinically significant difference in daily inpatient opioid use or total 90-day postoperative opioid use following TJR; in our opinion, we would consider a 15 morphine milligram equivalent (MME) difference in daily inpatient opioid use to be clinically meaningful, which is equivalent to 2 pills of 5 mg oxycodone. Over the entire 90-day postoperative period we could consider a 150 MME difference (equivalent to 20 pills of 5 mg oxycodone) to be clinically meaningful. The power analysis determined that the sample is adequate to detect a mean 15 MME difference in daily inpatient opioid use (standard deviation (SD) 20) at 95% power and $\alpha = 0.05$; the sample is also adequate to detect a mean 150 MME difference (equivalent to 20 pills of 5 mg oxycodone) in total 90-day opioid use (SD 250) at 82% power and $\alpha = 0.05$.

Outcomes were collected for 90 days after surgery, as this corresponds with the global postoperative period for insurers. Continued use of opioids beyond 90 days after surgery was also recorded. Baseline opioid and chronic opioid use were defined as opioid consumption for

greater than 90 days pre-operatively and postoperatively, respectively. Opioid prescribing patterns were collected via four separate measurements, all in MME. For ease of understanding, all MME values were converted to the equivalent quantity of 5 mg oxycodone pills as this is a commonly prescribed medication and strength per pill. The average MME per day was recorded for the inpatient stay, from admission to 24 hours prior to the last inpatient opioid administration. The last 24 hours of inpatient opioid administration were measured separately in an effort to elicit whether the opioid consumption just prior to discharge predicts the opioid consumption in the outpatient setting. Furthermore, due to the variability of the time of day at which patients are discharged, calculation of the final 24 hours of inpatient opioid consumption instead of the final calendar day allowed for more accurate comparisons between patients. The equivalent of 5 mg oxycodone pills on the initial outpatient prescription were recorded as well as all refills within 90 days of surgery.

The occurrence of unexpected pain-related interventions within 90 days of surgery was also recorded. These events included visits to the emergency department (ED) or clinic visits with a provider other than the surgeon for pain control, phone calls or web-based messages to the surgeon's clinic concerning pain, or requests by the patient for refills of prescription opioids.

The patients in the current study were managed post-operatively by a teaching service at an academic medical centre. In general, a combination of oral and intravenous analgesics including opiates, acetaminophen, ketorolac and/or an oral non-steroidal anti-inflammatory drugs (NSAIDs), and gabapentin or pregabalin are utilized for acute postoperative pain control. Patients who did not receive the above non-opioid analgesics usually, but not always, had a medical contraindication to the withheld medication. We routinely utilize cryotherapy in the immediate postoperative period for TKAs but not for THAs. We also routinely administer a standard local infiltration of an analgesic cocktail (ropivacaine with the addition of ketorolac, if no medical contraindications to NSAIDs) into the periarticular tissues at the completion of both TKAs and THAs. All TKA (but not THA) patients were offered the option of an adductor block. All patients were instructed to continue acetaminophen and an NSAID in the acute postoperative period once discharged from the hospital, except in some cases of a concurrent enoxaparin prescription and the presence of any medical contraindications. Based on insurance status and patient preference, patients were given either physical prescription papers versus instructions to obtain non-opioid analgesics from an outpatient pharmacy. This practice explains the seemingly low number of patients prescribed acetaminophen and/or NSAIDs at the time of discharge.

Statistical analysis. Analyses were performed in a standard statistical software package (JMP 14.0; SAS institute, Cary, North Carolina, USA). Descriptive statistics were generated for the entire sample. A bivariate analysis was performed comparing opioid usage rates as well as opioid-related outcomes (refill requests, ER or clinic visits for pain, clinic calls for pain, and opioid use beyond 90 days) between hip and knee arthroplasties; chi-squared and Wilcoxon rank-sum tests were performed as appropriate. Opioid usage rates and distance traveled had highly non-normal distributions as assessed by visual inspection and Shapiro-Wilk W test for normal distribution; therefore, prior to performing a multivariate analysis, Johnson S^u transformations were applied to achieve more normal distributions of these data. A series of multivariate linear regression models were created to determine independent risk factors for average daily inpatient opioid use and total 90 day postoperative opioid use. Effect sizes were reported as β coefficients. A multivariate logistic regression model was created to determine independent risk factors for continued use of opioids beyond 90 days.

Potential covariates considered in the multivariate models included age, sex, employment, insurance, surgical procedure, length of procedure, length of inpatient stay, use of regional anesthesia, use of spinal anesthesia, inpatient use of IV ketorolac or oral NSAIDs other than aspirin, inpatient use of acetaminophen, inpatient use of gabapentin or pregabalin, discharge opioid prescription (amount prescribed), and discharge prescription of acetaminophen, gabapentin/pregabalin, or an NSAID other than aspirin. A backwards selection method was utilized for the multivariate models with an exit criterion of $p > 0.05$. Interaction terms between surgical site (hip or knee) and use of regional and/or spinal anesthesia were also tested and were non-significant ($p > 0.05$), indicating that the effect of spinal and/or regional anesthetic on outcomes was not dependent on surgical site (hip or knee) in all analyses.

Results

Summary statistics. The mean age of the sample population was 61.9 years (SD 11.7) with more females (57%) than males (43%) (Table I). Length of surgery was an average of 137.1 minutes (SD 29.5) and length of inpatient stay was 2.3 days (SD 1.4).

Most patients received the following while inpatient: oral or intravenous NSAIDs (84%), acetaminophen (90%), gabapentin or pregabalin (76%); however, only acetaminophen was prescribed a majority of the time at discharge (65%). A total of 63% of patients received a regional block and/or spinal anesthesia. The total number of opioids prescribed within 90 days varied widely with a median of 157.2 pills of 5 mg oxycodone (25th percentile 97.2 and 75th percentile 322.1). More than half (60%) of patients required an opioid refill. Among patients

Table 1. Summary statistics.

Variable	Mean and SD or percentage
Age (yrs)	61.9; SD 11.7
Male	n = 40 (43%)
Female	n = 52 (57%)
Total hip arthroplasty	n = 43 (47%)
Total knee arthroplasty	n = 49 (53%)
Currently employed	n = 50 (54%)
Baseline opioid use	n = 20 (22%)
History of mental health disorder	n = 31 (34%)
Distance traveled (miles)	25.9; SD 28.8
Private Insurance	n = 49 (53%)
Government Insurance	n = 47 (43%)
Length of surgery (mins)	137.0; SD 29.5
Peri-operative nerve block	n = 51 (55%)
Spinal anesthesia	n = 35 (38%)
Peri-operative nerve block and/or spinal anesthesia	n = 58 (63%)
Length of stay (days)	2.3; SD 1.4
Peri-operative ketorolac	n = 41 (45%)
Inpatient gabapentin or pregabalin	n = 70 (76%)
Inpatient oral NSAID other than aspirin)	n = 73 (79%)
Inpatient NSAID, oral or IV, other than aspirin	n = 77 (84%)
Inpatient acetaminophen	n = 83 (90%)
Discharged with acetaminophen	n = 60 (65%)
Discharged with gabapentin or pregabalin	n = 11 (12%)
Discharged with NSAID (other than aspirin)	n = 8 (9%)
Mean equivalents of 5 mg oxycodone pills per 24 hours while inpatient	10.1; SD 5.8
Equivalents of 5 mg oxycodone pills for last 24 hours prior to discharge	9.8; SD 6.6
Equivalents of 5 mg oxycodone pills in prescription on day of discharge	77.0; SD 28.9
Patient required a opioid refill	n = 55 (60%)
Total equivalents of 5 mg oxycodone pills refilled up until 90 days postoperative	305; SD 362
Trips to ED for pain	n = 6 (7%)
Clinic visit with provider other than surgeon for pain	n = 22 (24%)
Trips to ED or and/or clinic visit with provider other than surgeon for pain	n = 24 (26%)
Calls to surgeon's clinic related to pain	n = 33 (36%)
Opioid use beyond 90 days after surgery	n = 16 (17%)

SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug; ED, emergency department.

without baseline (pre-operative) opioid use, 7% (n = 5/72) utilized opioids greater than 90 day after surgery; among baseline opioid users, 55% (n = 11/20) utilized opioids greater than 90 days after surgery.

Opioid use and outcomes after THA versus TKA. In the bivariate analysis, without adjusting for potential confounding variables, TKAs had substantially higher opioid consumption than THAs (Table II). Specifically, TKAs had higher daily inpatient opioid use (TKA median 12.0 vs THA

median 7.0 pills of 5 mg oxycodone; p < 0.001) and had a higher total 90 day number of opioids prescribed (knee: median 224.0 vs hip: median 100.5 pills of 5 mg oxycodone; p < 0.001). Furthermore, TKAs were significantly more likely to request an opioid refill after discharge (THA 33%; TKA 84%; p < 0.001). TKAs trended towards more chronic opioid use 90 days after surgery (THA 9%; TKA 24%; p = 0.05).

Independent predictors of total 90-day opioid consumption. The best independent predictor of total opioids consumed within 90 days of surgery is the rate of opioid consumption within the last 24 hours of the postoperative hospital stay (effect size 0.41 SE 0.09; p < 0.001) (Table III). This was followed by TKA as the procedure performed versus THA (effect size 0.29 SE 0.08; p = 0.001). Older patients required less opioids (per five-year increase: effect size -0.13 SE 0.03; p < 0.001), and unemployed patients required more opioids (effect size 0.16 SE 0.08; p = 0.04). These independent predictors, in combination, explained 42% of the variance in 90 day opioid consumption (R² = 0.42).

Predictors of opioid use during postoperative inpatient stay. TKAs (p < 0.001) and younger patients (p < 0.001) required statistically significant greater average number of opioids per day while inpatient (Table IV) and these factors explained 25% of the variation in opioid use rates (R² = 0.25). Patients who had received a regional or spinal block had no difference in average opioid consumption across the entire inpatient stay (p = 0.25).

Predictors of opioid use beyond 90 days after surgery. Baseline opioid use was a strong predictor of continued opioid use more than 90 days after TJR (adjusted odds ratio (OR) 29.2, 95% confidence interval (CI) 5.54 to 153; p < 0.001) (Table V). The next strongest independent predictor was performance of TKA compared with THA (adjusted OR 7.64, 95% CI 1.23 to 47.5; p = 0.01) followed by the number of opioids provided on the initial discharge prescript from the hospital (per 10 pills increase in 5 mg oxycodone: adjusted OR 1.45, 95% CI 1.01 to 2.09; p = 0.02) and history of mental health disorder (adjusted OR 5.06, 95% CI 1.10 to 23.4; p = 0.03).

Discussion

The most important finding of the current study is the significant difference in opioid prescription between TKAs and THAs, with TKAs consistently requiring more opioids than THAs. Inpatient opioid use in the last 24 hours prior to discharge is the single best predictor of total 90 day opioid use and demand for either TKA or THA. The planned surgical procedure and patient factors, such as demographics and baseline opioid use, have a much greater influence on inpatient and outpatient opioid demand than the use of regional nerve blocks, neuraxial anesthesia, or the use of inpatient non-opioid analgesics.

Table II. Opioid usage outcomes among THA versus TKA patients.

Variable	THA (n = 43)	TKA (n = 49)	p-value
Median postoperative inpatient equivalents of 5 mg oxycodone pills per 24 hrs	7.0 (IQR 10.3 to 3.8)	12.0 (IQR 15.6 to 8.2)	< 0.001*
Mean postoperative equivalents of 5 mg oxycodone pills during last 24 hrs of inpatient stay	6.0 (IQR 12.0 to 3.0)	10.2 (IQR 15.2 to 7.5)	0.009*
Total 90 day equivalents of 5 mg oxycodone pills	100.5 (IQR 163.8 to 65.2)	224.0 (IQR 384.6 to 123.3)	< 0.001*
Request for opioid refill	33%	84%	< 0.001†
Call to surgeon's clinic for pain related complaint	19%	51%	0.001†
Trips to ED or and/or clinic visit with provider other than surgeon for pain	19%	33%	0.13†
Use of opioids beyond 90 days after surgery	9%	24%	0.05†

THA, total hip arthroplasty; TKA, total knee arthroplasty; IQR, interquartile range; ED, emergency department.

*Wilcoxon rank-sum.

†chi-squared test.

Table III. Independent predictors of 90-day requirement for opioids.

Independent risk factor	Effect size (β estimate) and SE	Log worth	p-value
Requirement opioids in last 24 hrs prior to discharge	0.41; SE 0.09	4.7	< 0.001
Total knee arthroplasty	0.29; SE 0.08	3.6	0.001
Total hip arthroplasty	0 (referent)		
Age: per five-year increase	-0.13; SE 0.03	3.6	0.001
Unemployment	0.16; SE 0.08	2.1	0.04

Whole model $R^2 = 0.42$; $p < 0.001$.

SE, standard error.

Table IV. Independent of mean inpatient requirement for opioids per 24 hours throughout entire inpatient stay.

Independent risk factor	Effect size (β estimate) and SE	Log worth	p-value
Total knee arthroplasty	0.38; SE 0.08	4.7	< 0.001
Total hip arthroplasty			
Patient age (per 5 yrs)	-0.13; SE 0.03	3.8	< 0.001

Whole model $R^2 = 0.25$; $p < 0.001$.

SE, standard error.

This study adds to the existing literature comparing opioid requirements in THAs versus TKAs.^{6,7} The underlying factors influencing the increase in opioid requirements of TKAs compared with THAs have not been fully elucidated. More studies are needed to understand this interesting finding so that appropriate analgesic adjuncts can be added for our TKA patients, in particular. In the interim, adding low-risk adjuncts such as cryotherapy or gabapentinoids may be an appropriate start.³⁵ Interestingly, the number of opioids needed in the last 24 hours prior to discharge was the best predictor of 90-day opioid demand. This factor is easily calculated and should help guide prescribing patterns upon discharge.

Surprisingly, relatively little impact was noted on inpatient opioid use with the implementation of RNAs, NA, and non-opioid analgesics. This is not to imply that we should abandon these treatments. Studies have shown that compared with general anesthesia, NA is associated with decreased operative times, decreased risk for many major early postoperative complications, decreased

Table V. Independent predictors of opioid use beyond 90 days after surgery.

Independent risk factor	Adjusted OR, 95% CI	Log worth	p-value
Baseline opioid use	29.2; CI 5.54 to 153	5.5	< 0.001
Total equivalents of 5 mg oxycodone pills in prescription provided on day of discharge	Per 10 pills of 5 mg oxycodone: 1.45; CI 1.01 to 2.09	1.7	0.02
Total knee arthroplasty	7.64; CI 1.23 to 47.5	1.9	0.01
Total hip arthroplasty	1.0 (referent)		
History of mental health disorder	5.06; CI 1.10 to 23.4	1.5	0.03

Whole model area under receiver-operator curve (ROC) = 0.92; $p < 0.001$.

OR, odds ratio; SE, standard error; CI, confidence interval.

30 day mortality, and equivalent analgesic efficacy.^{13,37} Furthermore, the literature does support the pain and opioid reducing benefits of RNA implementation unless specifically contraindicated.¹³⁻¹⁹ Selective COX-2 inhibitors have also shown efficacy in reducing postoperative pain and opioid consumption when added to multimodal pain regimens.^{7,19-23} The lack of effect of inpatient non-opioid analgesics on inpatient opioid demand in our study could in part be due to a culture of 'give opioids first' for postoperative pain. This could be an important opportunity from a quality improvement standpoint to ensure that all non-opioids are scheduled with opioids only given as needed for breakthrough pain.

In our multivariate analysis, it was generally the case that increased analgesic requirements and/or refills of opioids were associated with factors such as TKA (vs THA), a larger number of opioids prescribed at the time of discharge, baseline opioid use, a history of a mental health disorder, and lower patient age. Of these risk factors, the specific indicators for chronic opioid use beyond 90 days following TJR were TKA (vs THA), baseline opioid use, history of mental health disorder, and the total amount of opioids prescribed at the time of discharge. Many of these risk factors, such as baseline opioid use, history of a mental health disorder, substance abuse, are consistent with the risk factors in the current arthroplasty literature for chronic opioid use postoperatively.^{8,38-43}

Most concerning among these, however, is the finding that the quantity of opioid pills prescribed at the time of discharge is a major independent predictor of postoperative chronic opioid use. This finding, in addition to several prospective studies indicating that patients are prescribed too many opioids after TJR, suggests that the quantity of opioid pills prescribed at the time of discharge should be limited as much as possible.^{44,45} Following an initial prescription at discharge, only patients with a more robust opioid requirement could be provided with smaller-quantity prescriptions given at more frequent intervals. This would allow for the most optimal titration of opioids, and perhaps a heightened emphasis on a multimodal regimen.

Limitations. The present study is not without its associated limitations. Based upon the data collection process, patients with minimal postoperative analgesic requirements were not adequately identified due to the practice of recording only the total number of prescribed pills. This would mean that any patient who did not fully complete the postoperative prescription was analyzed as having taken the full prescribed amount. However, less than 20% of the patient cohort did not receive a refill following their original discharge prescription, which places a minority of patients into this possible scenario. Cryotherapy and infiltration of local analgesics into periarticular tissues may be useful adjuncts; however, because all patients received this adjunct if medically able, we did not include this in our analysis. Furthermore, cryotherapy was not able to be controlled in statistical analyses since these therapies are currently applied only in TKAs and not in THAs.

Although all patients were instructed to take acetaminophen and an NSAID following discharge if there were no medical contraindications, not all patients received a physical prescription paper. It is for this reason that the effect of the multimodal analgesic regimen is certainly underestimated in the outpatient setting. A significant degree of variability in prescribing practices at the time of discharge is further accounted for by the many different residents that rotate through the lower limb adult reconstruction inpatient service at our institution. Although our multivariate analysis identified several risk factors for continued opioid use past 90 days, we did not have enough patients who used opioids past 90 days (17% of study population) to adequately power a direct comparison between no opioid use after 90 days and continued opioid use past 90 days. Further studies with larger numbers of patients who use opioids past 90 days may be helpful to better understand risk factors for continued opioid use.

Conclusion

In conclusion, opioid use following TKA and THA is most strongly predicted by surgical and patient factors. TKA

was associated with higher postoperative opioid requirements than THA. Regional nerve blocks and neuraxial anesthesia did not diminish total inpatient or 90-day postoperative opioid consumption. The use of acetaminophen, gabapentin, or NSAIDs did not significantly alter inpatient opioid requirements.

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