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Original research

Evaluation of Low-Dose Versus High-Dose Opioid Pathway in Opioid-Naïve Patients After Total Knee Arthroplasty

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ABSTRACT

Background: Pain control after total knee arthroplasty (TKA) remains challenging. Tramadol is a weak opioid with potentially lower side effects and risk for dependency than stronger opioids. The purpose of this study was to evaluate efficacy and safety of tramadol after TKA in opioid-naïve patients compared with stronger opioids.

Methods: A retrospective review of patients who underwent primary TKA was performed. In September 2018, opioid-naïve patients were prescribed tramadol instead of oxycodone. Patients receiving tramadol (low-opioid group) were matched to patients discharged with oxycodone before this transition (high-opioid group). We compared morphine milligram equivalent (MME) consumption and outcomes up to 3 months postoperatively.

Results: Two-hundred and five patients underwent TKA, with 126 receiving tramadol. Fourteen patients were converted to stronger opioid (11.2% conversion rate). Seventy patients from the low-opioid group were matched to 70 patients in the high-opioid group. Average daily inpatient MME consumption was higher in the high-opioid group (40.0 ± 27.4 vs 16.3 ± 10.9, $P = .000$). Outpatient prescribed MME was significantly higher in the high-opioid group (135.5 ± 71.5 vs 75.3 ± 51.3, $P = .000$) along with a higher number of refills (0.53 ± 1.1 vs 0.886 ± 0.94, $P = .041$). Knee range of motion was not statistically different at any timepoint postoperatively. There was higher adverse event rate in the low-opioid group (8.6% vs 5.7%) but not statically significant.

Conclusions: Low opioid regimen following TKA showed lower MME consumption than high opioid regimen with no effect on outcomes up to 3 months. Use of low opioid regimen should be considered for TKA surgery.

Introduction

Pain control after total knee arthroplasty (TKA) is one of the most challenging realms of patient care and frequent reason for patient dissatisfaction after surgery [1,2]. Orthopedic surgeons have become the highest opioid prescribers of all surgical specialties and the third highest prescribers of all physicians [3]. This is of particular concern for surgeons performing TKA surgery, which has been recognized as one of the most painful surgical procedures [4]. Postoperative opioid prescribing is highly variable among surgeons with no current standardization on appropriate dosage and the number of pills that should be prescribed [5,6]. Studies have demonstrated that most patients receive an excess of opioids on discharge from the hospital and have poor education on how to dispose of unused pills [7,8]. Advances in multimodal pain regimens and local analgesia have greatly helped in reducing opioid consumption postoperatively [9-11]. Despite this, prolonged opioid use after TKA remains a significant problem further contributing to the opioid epidemic.

Although opioids can be effective in pain management, they also exert serious adverse effects and can predispose patients to opioid

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dependency. These side effects, including respiratory depression, overdose, constipation, nausea, and balance issues, are of particular concern in the elderly population who are more sensitive to the systemic effects [12]. Furthermore, prolonged use of opioids after TKA has been correlated with an increased risk of short- and long-term postoperative complications including infection, stiffness, and need for revision [13,14]. There are also data demonstrating that opioid-naïve patients still requiring opioids at 3 months postoperatively are at a significantly increased risk for prolonged opioids at 6 months and longer [15]. There is great interest in finding alternative pain management options to decrease patients' opioid consumption and decrease complications associated with their use.

Tramadol is an analgesic medication that has both opioid-receptor agonist activity and inhibition of monoaminergic reuptake [16]. It was first developed in the 1970s in Germany and became Food and Drug Administration–approved in the US in 1995 as a nonscheduled opioid [16]. In 2014 under the Controlled Substances Act (CSA), tramadol became a schedule IV controlled substance and was categorized as an opioid [17]. Despite receiving a strong recommendation from the American Association of Orthopaedic Surgeons in clinical practice guidelines for management of symptomatic knee osteoarthritis [18], tramadol is an underutilized pain management modality relative to other treatment options [19]. Furthermore, tramadol has shown to be a far more cost-effective medication than both opioids and even nonsteroidal anti-inflammatory drugs for management of osteoarthritis [19]. The efficacy of tramadol in the management of postoperative pain control after TKA has not been well established [20]. One study evaluating IV tramadol's efficacy compared with patient-controlled analgesia pump with oxycodone in management of maxillofacial surgery found tramadol to have similar pain control to oxycodone but with lower incidence of respiratory depression [21]. No direct comparative studies on tramadol's efficacy and safety for pain control have been performed in the arthroplasty literature.

Based on the American Association of Orthopaedic Surgeons clinical guidelines, our institution started using oral tramadol in September 2018 routinely for pain control after TKA as part of a multimodal pain pathway in opioid-naïve patients without contraindications. The purpose of this study was to evaluate the efficacy and safety of tramadol in controlling postoperative pain after TKA compared with stronger opioids in this patient cohort.

Material and methods

This was a retrospective review of patients undergoing primary unilateral TKA at our institution between January 2017 and May 2019. Institutional review board approval from our institution was obtained before this study. All surgeries were performed by a senior fellowship-trained adult reconstructive surgeon. In September 2018, our practice transitioned from standard opioids (oxycodone) for postoperative pain control to low opioids (tramadol) in opioid-naïve patients without medication contraindications. Contraindications included those who were on antidepressant medications (due to adverse medication interaction) or had previous intolerance/side effects with tramadol use. We also excluded patients with a history of other illicit substance use/abuse as these patients may be using other nonprescribed or illicit substances for postoperative pain control. We limited our study population to opioid-naïve patients as our practice's experience with tramadol before this transition was that patients on preoperative opioids had higher tolerance and required stronger opioid to adequately control their pain, which has been supported by several studies in the literature [22-24]. There is limited literature to support this selection bias, but we felt it would be safer and more efficacious for our patient population to eliminate patients with preoperative opioid use.

Patients before the September 2018 transition who were prescribed oxycodone (high-opioid group) were age-, gender-, and body mass index (BMI)–matched to patients who received tramadol (low-opioid group) after this transition. As part of the multimodal perioperative regimen, all patients underwent spinal and adductor canal blocks by an anesthesiologist before TKA surgery. Preoperatively patients received 500 mg of oral acetaminophen, 15 mg of oral meloxicam (except those with renal/gastric contraindications), 5 mg of oral oxycodone, and 300 mg of gabapentin. A standardized periarticular local injection containing 25 mL of 0.5% ropivacaine, 0.25 mL of 1 mg/mL epinephrine, 0.4 mL of 1 mg/10 mL clonidine, 0.5 mL 30 mg/mL ketorolac (except those with renal disease), and 23.85 mL of sterile saline was also performed intraoperatively by the surgeon. While inpatient postoperatively, patients received 15 mg of intravenous ketorolac every 8 hours, 1000 mg of oral acetaminophen every 8 hours, 300 mg of gabapentin twice daily, and their designated opioid medication every 4 hours as needed (tramadol dose 50-100 mg and oxycodone dose 5-10 mg). All patients were discharged with the same standard postoperative multimodal pain regimen including Tylenol 500 mg every 6 hours, meloxicam 7.5 mg twice daily (except for patients with decreased renal function or stomach ulcers), and gabapentin 300 mg nightly. Tramadol was prescribed 50-100 mg every 4 hours as needed for pain, and oxycodone was prescribed 5-10 mg every 4 hours as needed for pain. The number of opioid pills was not standardized and varied from patient to patient.

Preoperative knee range of motion (ROM) was measured in clinic by one of our providers (surgeon or physician assistant) using a goniometer. Postoperative inpatient pain scores were assessed by nursing staff using the visual analog scale (VAS) on score of 1 (little pain) to 10 (high pain) at 6-hour intervals after surgery. Patients and nursing staff members were educated that the goal for pain control postoperatively was VAS level of 5 or less. If the patient had a pain score of 5 or less, they were encouraged to only take Tylenol. If the pain level was between 5 and 7, they were instructed to take either 50 mg of tramadol or 5 mg of oxycodone, and for pain level 8-10, they were instructed to take 100 mg of tramadol or 10 mg of oxycodone. If patients in the low-opioid pathway maximized their allowable tramadol dosage and frequency and still did not achieve adequate pain control at any point after surgery, they were switched to a stronger opioid medication (ie, oxycodone, Norco, Percocet, Vicodin, or Dilaudid). Any patient requiring conversion to a stronger opioid was excluded for this study, but the overall conversion rate during the study period was separately analyzed. These patients were eliminated from analysis of the low-opioid group as inclusion would lead to a heterogenous population where outcome measures would be harder to interpret. Thus, our data analysis was a per-protocol analysis of patients who completed the treatment to which they were initially allocated. The amount of inpatient opioid consumption was carefully tracked using the medication administration record. On discharge, patient opioid consumption was measured using the number of pills dispensed and the number of refills dispensed. The total morphine milligram equivalent (MME) quantity was calculated for each patient using conversion factors of 0.1 for each mg tramadol and 1.5 for every mg of oxycodone, up to 3 months after surgery. The number of opioids prescriptions filled was monitored and verified using Colorado Drug Monitoring Program that tracks any controlled substance dispensed by pharmacies within the state of Colorado. The total MME quantity consumed and the number of pain medication refills were compared between groups.

Patients were clinically assessed at 2 weeks, 6 weeks, and 3 months after surgery. Knee ROM was assessed at each session by the provider using a goniometer in similar fashion to the preoperative assessment. All patients underwent outpatient physical

therapy that began the week after surgery and consisted of 2-3 visits per week for 6-8 weeks depending on the patient's progress. All medical and surgical complications reported in the patients' charts were documented and compared between groups.

Results

From January 2017 to August 2018, 70 patients prescribed oxycodone after TKA surgery (high-opioid group) were age-, gender-, and BMI-matched to 70 patients prescribed tramadol (low-opioid group) between September 2018 and May 2019. The average patient age was 68.8 ± 8.2 years, and the average BMI was 28.8 ± 4.5 kg/m^2. The population consisted of 56% males and 44% females. Preoperative alcohol and tobacco usage by patients is reported in Tables 1 and 2, respectively. There was no significant difference between groups in terms of prior alcohol ($P = .596$) or tobacco use ($P = .980$). Postoperative inpatient VAS pain scores are shown in Table 3. There was no significant difference in pain scores at the 6-hr, 12-hr, or 18-hr timepoints. There was slightly higher pain rating at the 24-hr timepoint in the high-opioid group (3.27 vs 2.52 in the low-opioid group) which was statistically significant but not determined to be clinically relevant ($P = .048$). Of note, the VAS ratings were not available on all patients at all timepoints. The pain scores in the high-opioid group were more consistently reported than in the low-opioid group. This may have been affected by shorter length of stay that was observed in the low-opioid group (1.1 ± 0.4 days) than in the high-opioid group (1.4 ± 0.5 days) ($P = .000$).

The total daily inpatient MMEs consumed by patients and the overall amount of outpatient MMEs dispensed are shown in Table 4. There was significantly higher daily inpatient MME consumption in the high-opioid group (40.0 MMEs) than in the low-opioid group (16.3 MMEs) ($P = .000$). Similarly, the total amount of outpatient prescribed MMEs was significantly higher in the high opioid group (135.5 MMEs) than in the low-opioid group (75.3 MMEs) ($P = .000$). We also saw a higher number of refills in the high-opioid group at 0.886 refills compared with 0.53 refills in the low-opioid group ($P = .041$).

We observed an improvement in knee ROM in both groups at the 6-week and 3-month clinical evaluations compared with preoperative evaluation (Table 5). There was no significant difference in knee ROM values at any timepoint preoperatively or postoperatively between groups, indicating no detrimental impact on knee motion based on pain medication received. All documented adverse outcomes or effects were recorded and compared between groups (Table 6). We found higher rates of adverse reactions in the low-opioid group at 8.6% vs 5.7% in the high-opioid group, but this was no statistically significant ($P = .7447$). The adverse effects in the low-opioid group included nausea (2), dizziness (1), shortness of breath (2), and gastrointestinal bleeding (1). The adverse effects in the high-opioid group included gastrointestinal intolerance (2), rash (1), and rapid response for unresponsiveness (1). None of the adverse reactions in the low-opioid group were considered urgent or life-threatening, whereas the rapid response in the high-opioid group was considered a life-threatening reaction. The same patient who had a rapid response for unresponsiveness required repeat surgical intervention for arthrotomy dehiscence from a fall. There were no other major medical or surgical complications that required readmission or repeat surgery in the early postoperative period.

From the start of our protocol transition in September 2018 to November 2019, we performed 205 primary unilateral TKAs, of which 126 patients were prescribed tramadol (only 70 of which were able to be matched to historical cohort for the purposes of this study). There were 14 patients converted to stronger opioid in the postoperative period, leading to a conversion rate of 11.2%. The majority of these conversions to stronger opioid were for inadequate pain control with tramadol.

Discussion

Pain control after TKA surgery remains challenging despite advances in postoperative pain management. The use of opioids can have serious side effects, particularly in elderly populations, and risk for opioid dependence postoperatively [12,25]. There has been growing interest in the use of alternative medications for pain control, with minimal data available on utility of weaker opioids such as tramadol in the setting of TKA surgery [20]. This is one of the first studies to evaluate both the efficacy and safety of tramadol for postoperative pain after TKA surgery compared with stronger opioids. Overall, we found that a low-opioid regimen with tramadol as part of a multimodal pain protocol showed to have lower overall opioid consumption than high-opioid regimen and no apparent detrimental impact on early postoperative pain scores or functional outcomes. Our data supports that tramadol should be considered as an alternative to stronger opioids in patients without medical contraindications or prior opioids use.

There is limited literature on performance of tramadol for pain management after TKA surgery [20]. Hannon et al [20] recently performed a systematic review and meta-analysis on efficacy and safety of various opioids after total joint arthroplasty. They found only 2 studies evaluating tramadol that met their inclusion criteria. One study by Stiller et al [26] studied effects of tramadol vs saline when combined with a morphine patient-controlled analgesia after TKA and found lower opioid consumption in the tramadol group. Another study by Stubhaug et al [27] found no improved analgesic effect of tramadol after total hip replacement compared with placebo or stronger opioid. This later study was performed in 1995 when perioperative pain control protocols were arguably quite

Table 1
Comparison of preoperative alcohol usage between low- and high-dose opioid groups.

	Frequency	Low opioid, N (%)	High opioid, N (%)	
Alcohol usage	None	15 (21.4)	16 (22.9)	$P = .596$
	Yes, <1 a week	23 (32.9)	18 (25.7)	
	Yes, 2-7 a week	28 (40.0)	34 (48.6)	
	Not reported	4 (5.7)	2 (2.8)	

Table 2
Comparison of preoperative tobaccol usage between low- and high-dose opioid groups.

	Frequency	Low opioid, N (%)	High opioid, N (%)	
Tobacco use	Never	53 (75.71)	52 (74.29)	$P = .980$
	Previous	16 (22.86)	17 (24.29)	
	Current	1 (1.43)	1 (1.43)	

Table 3
Inpatient VAS pain scores at various timepoints after surgery.

Timepoint	Low opioid (N) VAS score	High opioid (N) VAS score	
6 h postoperatively	(64) 2.11 ± 1.39	(62) 2.6 ± 1.95	$P = .110$
12 h postoperatively	(36) 2.08 ± 1.48	(48) 2.4 ± 1.63	$P = .363$
18 h postoperatively	(40) 2.15 ± 1.61	(47) 2.77 ± 1.55	$P = .074$
24 h postoperatively	(48) 2.52 ± 1.86	(55) 3.27 ± 1.96	$\mathbf{P = .048}$

Bold values indicate statistical significance.

Table 4
Inpatient VAS pain scores at various timepoints after surgery.

	Low opioid	High opioid	
Inpatient			
Daily MMEs	16.3 ± 10.9	40.0 ± 27.4	***P* = .000**
Outpatient			
# of refills	0.53 ± 1.10	0.886 ± 0.941	***P* = .041**
Total prescribed MMEs	75.3 ± 51.3	135.5 ± 71.5	***P* = .000**

MME, morphine milligram equivalents.
Bold values indicate statistical significance.

different than the present day. A more recent study by Fleischman et al [28] showed that a multimodal regimen incorporating low supply of tramadol correlated with better pain control, less opioid use, and lower side effects than regimens that used traditional supplies of oxycodone after hip replacement surgery. Of note, the groups receiving tramadol were prescribed an equal number of oxycodone pills, so this study was not able to evaluate the true efficacy and safety of a tramadol-only regimen. A similar study has not yet been performed for knee surgery. Cumulatively there remains very little quality literature to support our findings that tramadol may be suitable analgesic medication after joint replacement surgery.

One finding from our study that has been previously demonstrated is that tramadol has higher rates of minor adverse effects [20,21], albeit maybe not as severe or life-threatening as stronger opioids. Some of the most common side effects reported with tramadol include dry mouth, dizziness, nausea, vomiting, and hyponatremia [20,29]. Hannon et al [20] showed in their limited meta-analysis that rates of dizziness and dry mouth were higher with tramadol than in controls; however, studies showing higher rates of nausea and vomiting had too much heterogeneity to perform an accurate meta-analysis. The adverse effects reported in our study were similar, with the most common ones being nausea and dizziness. We observed no serious or life-threatening side effects in the tramadol group, whereas the high-opioid group had one patient requiring rapid response for unresponsiveness. The dangers of stronger opioids are well known, and one could argue that a higher adverse side effect profile with tramadol may be acceptable as long as the severity of the adverse effects is lower than that of stronger opioids.

One of the concerns shared by patients and providers with switching from high opioids to low opioids is that tramadol may not be strong enough for controlling pain after TKA surgery. An internal analysis of our patient population after the September 2018 transition to low-opioid medications revealed that the conversion rate from tramadol to stronger opioid over a 1-year period was 11.2% . We have not yet performed detailed analysis to determine if risk factors can be identified to predict one's likelihood of converting to stronger opioid, but this is an intended area of future study. Despite this, we feel that an 88% success rate with tramadol use is promising, particularly after total knee replacement. Our data have shown no detrimental impact of tramadol over oxycodone use in the first 3 months after TKA in terms of inpatient pain scores and knee motion. We recognize that more data points including standardized survey information are needed to verify our preliminary findings, which is another area of research moving forward.

Table 5
Patient knee ROM at various timepoints before and after surgery.

	Low opioid ROM (in °)	High opioid ROM (in °)	
Preoperatively	114.5 ± 11.8	112.2 ± 11.6	*P* = .240
2 weeks	102.8 ± 17.2	101.3 ± 12.2	*P* = .599
6 weeks	121.24 ± 9.05	120.59 ± 8.88	*P* = .679
3 months	123.2 ± 7.1	123.7 ± 6.5	*P* = .742

Table 6
Postoperative adverse drug effects or medical/surgical complications.

Complication	Low opioid, N (%)	High opioid, N (%)	
Yes	6 (8.6)	4 (5.7)	*P* = .7447
No	64 (91.4)	66 (94.3)	

There are several limitations to our study. This was a retrospective review comparing a historical cohort to a more recent cohort of patients. Our analysis was a per-protocol analysis of patients who completed their initial treatment protocol allocated. This limits interpretation of our data; however, we felt that including patients requiring conversion to stronger opioid would create heterogeneous population and affect analysis of primary outcome measures. All patients were age-, gender-, and BMI-matched to create as comparable and homogeneous a patient population for comparison as possible. However, by nature of this study design, we cannot account for temporal changes in patient care between time periods. There has been gradually increasing trend toward outpatient TKA surgery, which may in part explain the lower number of inpatient VAS scores reported and the lower overall inpatient MME consumption in the low-opioid group. We restricted our study period to as consecutive a period of time as possible to help control for any temporal changes in patient care that may have had an impact on opioid consumption. Furthermore, the multimodal pain regimen (other than the opioid) remained standardized over the entire study period as did the periarticular injections and anesthesia blocks performed which helps in maintaining consistency. Another limitation to the retrospective design is that we were not able to monitor outpatient opioid consumption as accurately as we could with a prospective design. Our calculation on total outpatient MME consumption was based on the number of pills prescribed to each patient. We certainly recognize that some patients may not have used all the pills they were prescribed which means that our calculation may have overestimated actual consumption in both the low- and high-opioid groups. Furthermore, some patients may have been taking other pain medications not prescribed by our providers for pain control. We attempted to control this by verifying all prescriptions through the Colorado Drug Monitoring Program, but this would not capture prescriptions patients had in their possession from historical prescribers or prescribers from out of state. We also recognize that reporting of adverse effects may be inaccurate if certain reactions were not documented in the patients' charts. The rate of adverse effects may certainly have been underestimated owing to incomplete documentation. We feel confident that we were able to capture the more serious complications during admission and those requiring emergency room visit or readmission after discharge. Finally, patients in the low-opioid group were limited to those who were opioid-naïve and had no medication contraindications to tramadol use which does lead to selection bias. Therefore, we cannot generalize our results to the efficacy and safety of low-opioid protocol for patients in these groups. While there is the potential for selection bias based on our selection criteria, we would recommend that these are the same selection criteria surgeons should consider when selecting tramadol as the primary analgesic. Further research is needed to determine optimal patient population for tramadol use to minimize need for conversion to stronger medication and tramadol side effects.

Although our results are limited, this study establishes a good foundation that tramadol can be safely and effectively used for

postoperative pain control in patients without contraindications after TKA surgery. There is a need for quality prospective controlled trials to verify our findings and help identify which patients would not do well with low-opioid regimen after surgery. Furthermore, the safety profile of tramadol in patients with certain medications such as anxiolytics and antidepressants needs to be further evaluated.

Conflicts of interest

The authors declare that there are no conflicts of interest.

For full disclosure statements refer to https://doi.org/10.1016/j.artd.2021.11.019.

References

[1] Gunaratne RP, Banda DN, Fick J, et al. Patient dissatisfaction following total knee arthroplasty: a systematic review of the literature. J Arthroplasty 2017;32:3854.

[2] Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiol Clin North Am 2005;23:21.

[3] Volkow ND, McLellan TA, Cotto JH, et al. Characteristics of opioid prescriptions in 2009. JAMA 2011;305:1299.

[4] Gerbershagen HJ, Aduckathil S, van Wijck AJM, et al. Pain intensity on the first day after surgery. Anesthesiology 2013;118:934.

[5] Wyles CC, Hevesi M, Trousdale ER, et al. The 2018 Chitranjan S. Ranawat, MD Award: developing and implementing a novel institutional guideline strategy reduced postoperative opioid prescribing after TKA and THA. Clin Orthop Relat Res 2019;477:104.

[6] Sabatino MJ, Kunkel ST, Ramkumar DB, et al. Excess opioid medication and variation in prescribing patterns following common orthopaedic procedures. J Bone Joint Surg Am 2018;100:180.

[7] Hernandez NM, Parry JA, Taunton MJ. Patients at risk: large opioid prescriptions after total knee arthroplasty. J Arthroplasty 2017;32:2395.

[8] Huang PS, Copp SN. Oral opioids are overprescribed in the opiate-naive patient undergoing total joint arthroplasty. J Am Acad Orthop Surg 2019;27:E702.

[9] Lamplot JD, Wagner ER, Manning DW. Multimodal pain management in total knee arthroplasty. J Arthroplasty 2014;29:329.

[10] Jenstrup MT, Jaeger P, Lund J, et al. Effects of Adductor-Canal-Blockade on pain and ambulation after total knee arthroplasty: a randomized study. Acta Anaesthesiol Scand 2012;56:357.

[11] Vendittoli P-A, Makinen P, Drolet P, et al. A multimodal analgesia protocol for total knee arthroplasty. A randomized, controlled study. J Bone Joint Surg Am 2006;88:282.

[12] Martin CM, Forrester CS. Anticipating and managing opioid side effects in the elderly. Consult Pharm 2013;28:150.

[13] Cancienne JM, Patel KJ, Browne JA, Werner BC. Narcotic use and total knee arthroplasty. J Arthroplasty 2018;33:113.

[14] Namba RS, Inacio MCS, Pratt NL, et al. Persistent opioid use following total knee arthroplasty: a signal for close surveillance. J Arthroplasty 2018;33:331.

[15] Goesling J, Moser SE, Zaidi B, et al. Trends and predictors of opioid use after total knee and total hip arthroplasty. Pain 2016;157:1259.

[16] Miotto K, Cho AK, Khalil MA, et al. Trends in tramadol. Anesth Analg 2017;124:44.

[17] U.S Department of Justice Drug Enforcement Administration Diversion Control Division: 2014 - final rule: placement of tramadol into schedule IV. https://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0702.htm. [Accessed 16 November 2021].

[18] Jevsevar DS, Brown GA, Jones DL, et al. The American Academy of Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the knee, 2nd edition. J Bone Joint Surg Am 2013;95:1885.

[19] Bedard NA, Dowdle SB, Anthony CA, et al. The AAHKS clinical research Award: what are the costs of knee osteoarthritis in the year prior to total knee arthroplasty? J Arthroplasty 2017;32:S8.

[20] Hannon CP, Fillingham YA, Nam D, et al. The efficacy and safety of opioids in total joint arthroplasty: systematic review and direct meta-analysis. J Arthroplasty 2020;35:2759.

[21] Silvasti M, Tarkkila P, Tuominen M, et al. Efficacy and side effects of tramadol versus oxycodone for patient-controlled analgesia after maxillofacial surgery. Eur J Anaesthesiol 1999;16:834.

[22] Aasvang EK, Lunn TH, Hansen TB, et al. Chronic pre-operative opioid use and acute pain after fast-track total knee arthroplasty. Acta Anaesthesiol Scand 2016;60:529.

[23] Bedard NA, DeMik DE, Dowdle SB, Callaghan JJ. Trends and risk factors for prolonged opioid use after unicompartmental knee arthroplasty. Bone Joint J 2018;100-B:62.

[24] Franklin PD, Karbassi JA, Li W, et al. Reduction in narcotic use after primary total knee arthroplasty and association with patient pain relief and satisfaction. J Arthroplasty 2010;25:12.

[25] Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet 2004;43:879.

[26] Stiller C-O, Lundblad H, Weidenhielm L, et al. The addition of tramadol to morphine via patient-controlled analgesia does not lead to better postoperative pain relief after total knee arthroplasty. Acta Anaesthesiol Scand 2007;51:322.

[27] Stubhaug A, Grimstad J, Breivik H. Lack of analgesic effect of 50 and 100 mg oral tramadol after orthopaedic surgery: a randomized, double-blind, placebo and standard active drug comparison. Pain 1995;62:111.

[28] Fleischman AN, Tarabichi M, Foltz C, et al. Cluster-randomized trial of opiate-sparing analgesia after discharge from elective hip surgery. J Am Coll Surg 2019;229:335.

[29] Udy A, Deacy N, Barnes D, Sigston P. Tramadol-induced hyponatraemia following unicompartmental knee replacement surgery. Anaesthesia 2005;60:814.