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Tramadol in Knee Osteoarthritis: Does Preoperative Use Affect Patient-Reported Outcomes After Total Knee Arthroplasty?

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ABSTRACT

Background: The 2013 American Academy of Orthopedic Surgeons evidence-based guidelines recommend against the use of preoperative narcotics in the management of symptomatic osteoarthritic knees; however, the guidelines strongly recommend tramadol in this patient population. To our knowledge, no study to date has evaluated outcomes in patients who use tramadol exclusively as compared with narcotics naive patients.

Methods: This is a retrospective study of prospectively collected data for patients who underwent unilateral primary total knee arthroplasty between January 2017 and March 2018. PRO scores were obtained using a novel electronic patient rehabilitation application, which pushed PRO surveys via email and mobile devices within 1 month prior to surgery and 3 months postoperatively.

Results: One hundred and thirty-six patients were opiate naïve, while 63 had obtained narcotics before the index operation. Of those, 21 patients received tramadol. The average preoperative Knee Disability and Osteoarthritis Outcome Scores were 50.4, 49.95, and 48.01 for the naïve, tramadol, and narcotic populations, respectively, ($P = .60$). The tramadol cohort had the least gain in 3 months postoperative Knee Disability and Osteoarthritis Outcome Scores, improving on average 12.5 points in comparison to the 19.1 and 20.1 improvements seen in the narcotic and naïve cohorts, respectively ($P = .09$). This difference was statistically significant when comparing the naïve and tramadol populations alone in post hoc analysis ($P = .016$).

Conclusions: When comparing patients who took tramadol preoperatively to patients who were opiate naïve, patients that used tramadol trended toward significantly less improvement in functional outcomes in the short-term postoperative period.

In 2017, in the face of a rapid growth in opioid abuse and opioid-related deaths, the United States officially declared a state of national emergency [1]. In 2014 alone, 47,055 individuals died in the United States from an opioid overdose. This burden is associated not only with increased morbidity and mortality but also with a large financial cost. In 2015, the White House Council of Economic Advisers estimated the economic loss because of the opioid crisis was $504 billion USD, representing 2.8% of the United States' Gross Domestic Product, with over $1.5 billion spent annually on prescription opioids for patients suffering from knee osteoarthritis (OA) [2,3]. If current conditions persist, an additional $500 billion is estimated to cost the country. Though regulatory bodies have attempted to curb this epidemic through limiting prescriptions, interstate monitoring systems, and enforcing digital prescribing/password protections, these measures have largely been ineffective [4,5]. The responsibility of narcotic gatekeeper thus continues to fall to healthcare providers.

One unique and commonly prescribed controlled narcotic is tramadol. Tramadol is a centrally acting synthetic opiate which is thought to induce its anesthetic effects through antagonism of the μ-opioid receptors, as well as its inhibition of the norepinephrine and serotonin neurotransmitters reuptake pathways [6]. With a morphine equivalent dose of 0.1, tramadol is an opiate with a low potential for abuse and favorable side-effect profile, demonstrated by its low incidence of

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respiratory depression, constipation, and/or sedation [7]. As a result of its seemingly minor side-effects and potential for pain relief, tramadol prescription rates doubled between 2003 and 2009. This accounted for approximately 10% of all narcotic prescriptions and costed an estimated $150 million in US national healthcare expenditures [8].

Due in part to its rapid growth in popularity and favorable analgesic effects, the 2013 American Academy of Orthopedic Surgeons Evidence-Based Guidelines provided strong recommendations for the administration of nonsteroidal anti-inflammatory drugs or tramadol in the nonoperative treatment of symptomatic knee OA [9]. It should be noted that these same guidelines did not recommend against the use of preoperative narcotics but rather gave an "inconclusive rating". These guidelines were supported by several studies that demonstrated improvement in patient-reported outcomes (PROs), such as the Western Ontario and McMaster Universities Arthritis Index pain and stiffness subscale scores, in patients with symptomatic knee arthritis receiving tramadol compared with placebo [10–14]. The clinical significance of these findings was underscored by studies which demonstrated a lack of efficacy for acetaminophen in a similar cohorts of patients [15]. Since then, tramadol has become one of the most commonly used opioids prescribed for the conservative treatment of knee OA [3,8].

Although tramadol is effective in reducing pain and potentially delaying the need for total knee arthroplasty (TKA), studies have failed to evaluate if preoperative exposure to tramadol is deleterious. Recent publications have demonstrated that narcotic naïve patients have improved outcomes following TKA when compared with patients who used narcotics preoperatively for pain control, suggesting opioid use may have damaging effects prior to TKA. However, these studies either did not subanalyze tramadol independently or failed to include tramadol in their study completely [3,16,17].

To our knowledge, no study to date has evaluated outcomes in patients that use tramadol exclusively as compared with narcotic naive patients. The purpose of this study is to therefore compare PROs following TKA among 3 distinct cohorts: (1) opiate naïve patients, (2) tramadol-exposed patients, and (3) other opiate-exposed patients. We hypothesized that preoperative exposure to tramadol will result in poorer PROs when compared with opiate naïve patients and equivalent PROs compared with other opiate-exposed patients.

Patients/Methods

This was a retrospective study of prospectively collected data from an urban, academic, tertiary orthopedic hospital including patients who underwent unilateral primary TKA between January 2017 and March 2018. Patients were preoperatively registered for an electronic patient rehabilitation application (EPRA; Force Therapeutics, New York, NY) by surgical coordinators at the time of surgical scheduling as part of our institution's standard of care. By utilizing an EPRA, patients received push notifications to their mobile devices and e-mails requesting PRO surveys to be completed at set time intervals: within 1-month prior to TKA and at 3 months postoperatively. PROs collected through the EPRA included the Knee Disability and Osteoarthritis Outcome Score Jr. (KOOS, JR.), the Veterans Rand 12-Item Health Survey (VR-12), Physical Component Score (PCS), and the Mental Component Summary (MCS) surveys. Patients with incomplete PRO surveys preoperatively or postoperatively were excluded from the study. A manual chart review, utilizing prescribing data, was performed to categorize patients into 1 of 3 groups: (1) opiate naïve patients, (2) preoperative tramadol users, and (3) preoperative opiate users (excluding tramadol). Other preoperative opioids used include hydrocodone/acetaminophen, oxycodone/acetaminophen, hydrocodone/paracetamol, oxycodone and Dilaudid. Multiple sources of data were reviewed for each patient, including prescription history, clinical notes, and medication lists. All patient who had any additional surgical procedures up to 3 years prior to TKA were excluded from this study.

During the study time frame, there were 694 total knee arthroplasties performed at our institution through the faculty group practice. Of those, 84 were removed as they were bilateral cases. We excluded all patient who did not have preoperative and postoperative PRO scores (n = 419). Therefore, this left 191 patients available for our analysis.

All patients underwent the same initial multimodal perioperative pain protocol. Our routine approach throughout our institution included a 1-time preoperative administration of oral analgesics (celecoxib, acetaminophen, and pregabalin). No selective nerve blocks were performed on this cohort. Spinal vs general anesthesia was performed using shared decision between the patient and the anesthesiologist. Intraoperatively, all patients received an intraoperative analgesic cocktail injection consisting of Marcaine, Toradol, and liposomal bupivacaine unless contraindicated. All patients postoperatively were placed on oral narcotics (oxycodone) for maintenance and breakthrough pain as needed. Discharge medications included a prescription for Percocet for breakthrough pain only.

To determine how many patients were needed to detect a difference between the tramadol and opiate naïve cohorts, a power analysis was calculated using the standard deviation 4.3 and group means of 27 and 33.6 from the study *Impact of Preoperative Opioid Use on Total Knee Arthroplasty Outcomes* [18]. Setting alpha to 0.05 and beta at 0.2 (80% power), we determined we would need at least 14 patients in each cohort. It has been shown in prior works that a minimal clinical difference for the KOOS Jr is between 2.21-8.16, which is well within our power analysis [19].

A separate query of our electronic database, Epic Caboodle (version 15, Epic, Verona, WI), was then performed using Microsoft SQL Server Management Studio 2017 (Microsoft, Redmond, WA) to obtain patient specific variables from our institution's electronic health record system. These variables included patient demographics (age, gender, body mass index [BMI], race, marital status, smoking status, insurance type, and American Society of Anesthesiologists [ASA] score) and perioperative variables (length of stay), surgical time, and discharge disposition. This information can be found in Table 1.

Statistical Analysis

Data sets from the EPRA and our database query were joined, statistically analyzed utilizing MatLab 2018a (MathWorks, Natick, MA). Descriptive statistics were performed for all baseline characteristics. Independent Student's t-tests and Chi-squared tests were utilized to evaluate continuous and categorical variables, respectively. One-way analysis of variance testing with pairwise comparisons was used for statistical analysis of our primary outcome of interest. Significance was set at $P < .05$.

A multivariable logistic regression model was created to control for patient baseline characteristics, including age, gender, BMI, ASA, marital status, race type, insurance type, and preoperative narcotic use to determine independent risk factors for worse short-term PROs.

Results

In total, 191 unilateral TKA patients were included in this study. One hundred thirty-six patients were opiate naïve, 21 patients

Table 1
Demographics and Inpatient Factors.

Variables	None (n = 136)	Tramadol (n = 21)	Other Opiates (n = 42)	*P* Value
Age	66.60 ± 8.33	65.05 ± 7.14	63.48 ± 9.27	.10
Gender				.25
Female	78 (57.35%)	16 (76.19%)	26 (61.90%)	
Male	58 (42.65%)	5 (23.81%)	16 (38.10%)	
BMI	30.77 ± 6.32	33.48 ± 6.49	32.83 ± 6.36	.07
ASA				.66
1	2 (1.47%)	1 (4.76%)	1 (2.38%)	
2	77 (56.62%)	9 (42.86%)	21 (50.00%)	
3	54 (39.71%)	10 (47.62%)	20 (47.62%)	
4	3 (2.21%)	1 (4.76%)	0	
Race				.66
African American (Black)	17 (12.50%)	5 (23.81%)	5 (11.90%)	
Asian	2 (1.47%)	0	1 (2.38%)	
White	105 (77.21%)	15 (71.43%)	30 (71.43%)	
Other	12 (8.82%)	1 (4.76%)	6 (14.29%)	
Smoking status				.84
Current smoker	8 (5.88%)	2 (9.52%)	2 (4.76%)	
Former smoker	53 (38.97%)	10 (47.62%)	17 (40.48%)	
Never smoker	75 (55.15%)	9 (42.86%)	23 (54.76%)	
Insurance type				.70
Commercial	57 (41.91%)	8 (38.10%)	22 (52.38%)	
Medicaid	3 (2.21%)	1 (4.76%)	1 (2.38%)	
Medicare	76 (55.88%)	12 (57.14%)	19 (45.24%)	
Marital status				.15
Divorced/separated	13 (9.56%)	3 (14.29%)	2 (4.76%)	
Married/partner	84 (61.76%)	8 (38.10%)	22 (52.38%)	
Single/widowed	39 (28.68%)	10 (47.62%)	18 (42.86%)	
Surgical time (min)	109.66 ± 31.43	102.86 ± 18.07	107.05 ± 35.30	.62
Length of stay (d)	2.19 ± 1.20	2.52 ± 1.50	2.19 ± 1.45	.53
Discharge				<.05
Acute rehabilitation facility	2 (1.47%)	0	2 (4.76%)	
Home with services	121 (88.97%)	17 (80.95%)	32 (76.19%)	
Home with self-care	7 (5.15%)	0	6 (14.29%)	
Skilled nursing facility	4 (2.94%)	3 (14.29%)	1 (2.38%)	
Unknown	2 (1.47%)	1 (4.76%)	1 (2.38%)	

ASA, American Society of Anesthesiologists; BMI, body mass index.

received tramadol, and the remaining 42 had received alternate forms of narcotic pain medication. Among the three cohorts, patients taking tramadol or other opiates tended to be younger ([None vs Tramadol vs Other Narcotics]; 66.60 ± 8.33 vs 65.05 ± 7.14 vs 63.48 ± 9.27; $P = .10$) and have higher BMIs (30.77 ± 6.32 vs 33.48 ± 6.49 vs 32.83 ± 6.36; $P = .07$), than opiate naïve patients, though these trends did not reach significance. Discharge to skilled nursing facility was also significantly higher in tramadol patients (2.94% vs 14.29% vs 2.38%; $P < .05$), while discharge home with services was lower (88.97% vs 80.95% vs 76.19%; $P < .05$). Gender, ASA, race, smoking status, insurance type, marital status, surgical time, and length of stay were otherwise not significantly different among the three groups.

Analysis of variance testing of KOOS JR. scores demonstrated similar preoperative scores among the 3 cohorts (50.40 ± 13.22 vs 49.95 ± 13.16 vs 48.01 ± 13.89; $P = .60$). However, 12-week postoperative KOOS, JR. scores were significantly lower in the tramadol and other opiate cohorts (70.47 ± 12.89 vs 62.47 ± 11.02 vs 67.14 ± 13.62; $P < .05$), while ΔKOOS, JR. trended toward lower increases in scores (20.08 ± 15.76 vs 12.52 ± 16.34 vs 19.13 ± 14.93; $P = .12$). When evaluating VR-12 PCS scores, preoperative scores demonstrated significantly lower scores for tramadol and other opiate patients (33.39 ± 8.63 vs 29.01 ± 7.69 vs 30.51 ± 7.97; $P < .05$), with a trend for lower tramadol and other narcotic scores at 12 weeks (40.72 ± 8.04 vs 36.18 ± 7.50 vs 39.71 ± 8.26; $P = .09$). ΔVR-12 PCS were not significantly different between the groups. Lastly, VR-12

Table 2
Univariable Patient-Reported Outcomes.

Variables	None	Tramadol	Other Narcotics	*P* Value
KOOS, JR.				
KOOS, JR. baseline	50.40 ± 13.22	*49.95 ± 13.16*	*48.01 ± 13.89*	.60
KOOS, JR. 12 wk	70.47 ± 12.89	*62.47 ± 11.02*	*67.14 ± 13.62*	<.05
ΔKOOS Jr	20.08 ± 15.76	*12.52 ± 16.34*	*19.13 ± 14.93*	.12
VR-12 PCS				
VR-12 PCS baseline	33.39 ± 8.63	*29.01 ± 7.69*	*30.51 ± 7.97*	<.05
VR-12 PCS 12 wk	40.72 ± 8.04	*36.18 ± 7.50*	*39.71 ± 8.26*	.09
ΔVR12 PCS	7.32 ± 9.54	*7.17 ± 8.27*	**9.20 ± 8.51**	.52
VR-12 MCS				
VR-12 MCS baseline	50.43 ± 11.13	*47.45 ± 11.80*	*47.46 ± 13.93*	.29
VR-12 MCS 12 wk	54.76 ± 8.93	*49.54 ± 10.75*	*52.21 ± 10.86*	.05
ΔVR12 MCS	4.33 ± 11.37	*2.09 ± 9.02*	**4.75 ± 9.70**	.68

Italic indicates lower scores and bold indicates higher scores or changes in scores compared with no narcotic pain medications (control group) preoperatively.
KOOS, JR., Knee Disability and Osteoarthritis Outcome Score Jr.; PCS, Physical Component Score; VR-12, the Veterans Rand 12-Item Health Survey; MCS, Mental Component Summary.

Table 3
Multivariable Adjusted Patient-Reported Outcomes.

Variables	None	Tramadol	*P* Value	Other Narcotics	*P* Value
KOOS, JR.					
KOOS, JR. baseline	Reference	**0.86 ± 2.95**	.77	**0.44 ± 2.34**	0.84
KOOS, JR. 12 wk	Reference	*−6.23 ± 3.05*	<.05	*−0.34 ± 2.42*	0.88
ΔKOOS, JR.	Reference	*−7.09 ± 3.69*	.06	*−0.78 ± 2.92*	0.79
VR-12 PCS					
VR-12 PCS baseline	Reference	*−3.52 ± 2.07*	.09	*−2.13 ± 1.54*	0.17
VR-12 PCS 12 wk	Reference	*−3.71 ± 1.95*	.06	*−0.37 ± 1.54*	0.81
ΔVR-12 PCS	Reference	**0.02 ± 2.41**	.99	**1.94 ± 1.75**	0.27
VR-12 MCS					
VR-12 MCS baseline	Reference	*−2.68 ± 3.14*	.39	*−2.29 ± 2.33*	0.33
VR-12 MCS 12 wk	Reference	*−4.42 ± 2.34*	.06	**2.09 ± 9.02**	0.27
ΔVR-12 MCS	Reference	*−2.98 ± 2.63*	.32	**0.26 ± 2.16**	0.90

Italic indicates lower scores and bold indicates higher scores or changes in scores compared with no narcotic pain medications (control group) preoperatively.
KOOS, JR., Knee Disability and Osteoarthritis Outcome Score Jr.; VR-12, the Veterans Rand 12-Item Health Survey; PCS, Physical Component Score.

MCS scores demonstrated a strong trend lower scores at 12 weeks for previous tramadol use (54.76 ± 8.93 vs 49.54 ± 10.75 vs 52.21 ± 10.86; $P = .05$), though it did not reach significance. Preoperative and ΔVR-12 MCS otherwise did not reach significance. See Table 2 for more details.

When utilizing multivariable linear regression and adjusting for patient factors, KOOS. JR. demonstrated significantly lower scores by approximately −6.23 ± 3.05 ($P < .05$), with a trend toward smaller ΔKOOS, JR. scores increases (−7.09; $P = .06$). All other KOOS Jr scores for tramadol and other opiates were otherwise similar to that of opiate naïve patients. For VR-12 PCS, 12-week scores trended toward a decrease of −3.71 points lower than opiate naïve patients. All other recorded VR-12 PCS scores were otherwise nonsignificant. Lastly, VR-12 MCS scores also trended toward lower scores by −4.42 points ($P = .06$). All other scores were otherwise similar to their narcotic naïve counterparts and can be seen in Table 3.

Discussion

Patients who consume tramadol preoperatively had worse outcomes in comparison to patients who are opiate naïve. This expands upon previous orthopedic literature that found patients that take opioids preoperatively have significantly less proportional pain relief postoperatively, and improved outcomes [20–22]. However, to our knowledge, this is the first study to demonstrate differences with the use of tramadol alone. Preoperative tramadol use was a predictor of worse outcomes as measured by the KOOS, JR. both when investigated through univariable analysis, as well as in a multivariable regression model adjusted for comorbidities, albeit this trended toward significance. The fact that the cohort that received other forms of opioids also did significantly worse than the opioid naïve group (a known finding) demonstrates validity of the study. However, it was interesting to note that the other opioid cohort had better improvement post operatively compared with tramadol users.

We observed a trend toward statistically significant change in the KOOS, JR. scores vs the VR-12 PCS and VR-12 MCS scores. The KOOS, JR. specifically targets knee pain associated with OA while the VR-12 PCS and the VR-12 MCS are global assessments on physical function and mental health functioning, respectively. We expected patients receiving a TKA to have some improvement in these assessments, but dramatic changes are not expected after 3 months.

While opioid consumption results in smaller improvements in outcomes after TKA, as well as higher prevalence of in-hospital complications, such as ileus or challenging postoperative pain control (as a result of hyperalgesia), it is surprising to find that tramadol had worse outcomes with its described improved side-effect profile. Previous studies have demonstrated that preoperative TKA opioid use is more closely associated with pain catastrophizing than with preoperative baseline pain. Smith et al created a multivariable analysis that adjusted for comorbidity and Western Ontario and McMaster Universities Arthritis Index pain scores that demonstrated that pain catastrophizing was the only factor associated with opioid use before a TKA. Additionally, the study found those who used opioids had a mean pain catastrophizing scale score of 15.5 points compared with opioid naïve patients that had a score of 10.7 points [18]. Our study unfortunately did not capture this scale and therefore could not determine if it was directly related to the functional outcome changes seen. Providers should be wary of pain catastrophizing and a higher incidence of narcotic prescriptions to prevent the development of opioid tolerance and hyperalgesia.

Limitations

There are several limitations of this study to be considered. Primarily, it is difficult to accurately record outpatient medication consumption. As opioid utilization was obtained through prescription information from the medical record, we are unable to verify frequency that these medications were consumed. It is also well recognized that patients may receive prescriptions from other providers, report false medication consumption rates, or redistribute medications among their colleagues, friends, or family members. Furthermore, nonopioid postoperative pain medications were not accounted for and could have also skewed postoperative pain and outcome scores.

Additionally, we were not able to track the indications for opioid pain medication from providers outside of our institution. This was a minority of patients, but we cannot differentiate the effects of preoperative opioid use for other sources of pain vs opioids for knee pain with this data.

We could also not confirm the duration of medication exposure. The retrospective nature of our study could have skewed our results, especially as our results were limited to 3-month follow-up and did maintain preoperative pain scores to control for. We did not collect data of postoperative opioid use, which also could have skewed our results. However, all patients were given the same postoperative pain regimen, which would mitigate this variability.

Conclusion

When compared to their opioid naïve counterparts, patients with documented tramadol use prior to TKA are at risk for worse

12-week postoperative PROs, even when adjusting for patient-related risk factors. Owing to the potential limitations of this retrospective study, future randomized control trials are required to confirm this potential causal relationship. However, given the conflicting evidence presented in this study and despite the 2013 American Academy of Orthopedic Surgeons Clinical Practice Guidelines, it is recommended providers remain very conservative in their administration of outpatient narcotics including tramadol prior to surgery.

Conflict of Interest

None of the authors have financial or institutional disclosures to report related to the research in this article.

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