Retrospective Review

β-blocker Use is Associated with a Reduction in Opioid Use 30 Days After Total Knee Arthroplasty

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Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 02-22-2019
Revised manuscript received: 03-26-2019
Accepted for publication: 03-28-2019

Free full manuscript: www.painphysicianjournal.com

Background: Total knee arthroplasty (TKA) can lead to chronic pain and prolonged postoperative opioid use. There are few evidence-based interventions to prevent these outcomes. Recently, β-blockers have emerged as possible novel analgesics.

Objectives: The objective of this study was to determine whether perioperative β-blocker use is associated with reduced prolonged postoperative opioid use after TKA.

Study Design: This study used a retrospective cohort design.

Setting: The research took place within Department of Veterans Affairs hospitals in the United States between April 2012 and April 2016.

Methods: Patients: IRB approval was obtained to examine the records of Veterans Affairs (VA) patients undergoing TKA. Patients using opioids 60 days before surgery were excluded.

Intervention: The intervention being investigated was perioperative β-blocker use, overall and by class.

Measurement: Oral morphine equivalent usage through postoperative day 1 and prescription opioid refills through 30, 90, and 365 days after TKA were recorded. Adjusted models were created controlling for relevant demographic and comorbidity covariates. A secondary analysis examined the same outcomes separated by β-blocker class.

Results: The cohort was 93.8% male with a mean age of 66 years. Among the 11,614 TKAs that comprised the cohort, 2,604 (22.4%) were performed on patients using β-blockers. After adjustment, β-blocker use was associated with reduced opioid use through 30 days after surgery (odds ratio [OR] 0.89 [95% confidence interval (CI), 0.80-0.99], $P = .026$). Selective β-blockers were associated with reduced opioid use at 30 days (OR 0.88 [95% CI, 0.78-0.98], $P = .021$), and nonselective β-blockers were associated with reduced oral morphine equivalent usage through postoperative day 1 (β = -17.9 [95% CI, -29.9 to -5.8], $P = .004$).

Limitations: Generalizability of these findings is uncertain, because this study was performed on a cohort of predominantly white, male VA patients. This study also measured opioid use, but opioid use is not a perfect surrogate for pain. Nevertheless, opioid use offers value as an objective measure of pain persistence in a national cohort for which patient-reported outcomes are otherwise unavailable.

Conclusions: Perioperative β-blocker use was associated with reduced prescription opioid use at 30 days after surgery. Both selective and nonselective β-blockers were associated with reduced opioid use when analyzed individually.

Key words: Analgesics, opioid, arthroplasty, replacement, knee, adrenergic beta-antagonists, pain management

Pain Physician 2019: 22:E395-E406

Chronic postsurgical pain (CPSP) is a major source of morbidity, affecting 10% to 40% of patients depending on the surgical population, which can lead to prolonged postoperative opioid use in those with more severe symptoms (1-4). Despite undergoing total knee arthroplasty (TKA), a surgery intended to alleviate pain and improve function, a recent study from Kaiser Permanente found that over 40% of their patients still required opioids 90 days after surgery (5). Considering that over 700,000 patients underwent a TKA in the United States in 2010, and more than half of the US population suffering osteoarthritis is projected to receive a TKA, this is an enormous challenge facing our health care system (6,7). Furthermore, evidence-based interventions to prevent CPSP or reduce its severity, and subsequent opioid use, are limited (8-10).

Recently, through animal and human studies, beta-adrenergic receptor antagonists (β-blockers) have emerged as possible novel analgesics. For instance, metoprolol reduced acute pain sensation in mice (11). Used intraoperatively in humans, esmolol infusions substantially reduce opioid requirements postoperatively (12). Even in chronic pain syndromes like fibromyalgia and temporomandibular disorders, propranolol has analgesic effects (13-15). Some of the postulated mechanisms for these effects are direct antagonism of sympathetic afferents, anti-inflammatory properties, and inhibition of catechol-O-methyltransferase (COMT)-dependent pain, though the mechanism may depend on the class of β-blocker investigated (15-18).

While β-blockers are a relatively safe and commonly used class of medication, whether their pain-modulating properties mitigate the risk of CPSP or prolonged postoperative opioid use is unknown. Considering these observations and reports, this study's hypothesis was that perioperative β-blocker use would be associated with reduced rates of prolonged postoperative opioid use in Department of Veterans Affairs (VA) patients undergoing TKA.

Methods

This retrospective cohort study utilized the medical records of all adult patients nationally who underwent a TKA at a VA hospital between April 1, 2012 and April 1, 2016. This period was chosen because it occurred after recognition of the opioid crisis and the peak opioid prescribing rates seen in 2010 (19). IRB approval with a waiver of informed consent was obtained. VA Informatics and Computing Infrastructure (VINCI) data from January 1, 2012 to May 1, 2017 was incorporated to assess preoperative measures and postoperative outcomes after one year of follow-up. Patients were identified by screening medical and administrative data for the presence of the TKA Current Procedural Terminology (CPT) code 27447. Some patients underwent bilateral TKAs on different dates during this period, and each surgery was treated as a separate case. Because patients using opioids prior to a TKA are significantly more likely to use them chronically postoperatively, patients who filled a prescription for an opioid within 60 days prior to their surgeries were excluded from this analysis (20). These patients were also excluded to reduce the likelihood that future opioid prescriptions were written for conditions other than surgical pain.

Because patient-reported pain lasting at least 3 months after surgery, a common definition of CPSP, cannot be abstracted from VINCI records, this study used outpatient prescription opioid use through 30, 90, and 365 days and inpatient oral morphine equivalent use through postoperative day 1 as the outcomes of interest (21). This study's primary analysis focused on the effects of any β-blocker class use on these outcomes. Patients who filled outpatient prescriptions at the VA or reported non-VA opioid prescriptions between 30 and 60 days, between 90 and 120 days, and between 365 and 395 days after surgery were recorded as using opioids beyond 30, 90, and 365 days, respectively. For inpatient opioid use, all opioids administered outside of the operating room on postoperative days 0 and 1 were converted to morphine equivalents and summed (22,23). The VA inpatient drug administration database does not reliably record total doses administered via patient-controlled analgesia (PCA) devices, so all patients who received a PCA were excluded from the analysis of morphine equivalent use through postoperative day 1. Opioid prescriptions were identified by the VA national formulary class code for opioid analgesics, "CN101," or the following words or word-segments: "buprenorphine," "codeine," "codone," "fentanyl," "meperidine," "methadone," "morphine," "morphine," "tapentadol," and "tramadol."

Demographic and comorbidity data were obtained with VA Surgical Quality Improvement Program (VASQIP) data and supplemented with International Classification of Diseases, Ninth Revision (ICD-9) and ICD-10 codes within one year of each TKA. Data collection, variable definitions, and interobserver agreement from VASQIP have been previously reported (24,25). Demographic covariates in this study included age at time of surgery, death date (if any), body mass index

(BMI), sex, and race (African American, Other, Unknown, White). Anesthesia type was recorded as general or regional (epidural, local, monitored anesthesia care, other, regional, or spinal). Inpatient prescription records were used to determine binarily if patients received a non-opioid adjunct pain medication in the hospital: acetaminophen, gabapentin, pregabalin, celecoxib, diclofenac, etodolac, ibuprofen, indomethacin, ketoprofen, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, or sulindac. Outpatient prescription records and patient-reported non-VA prescriptions were also used to determine binarily if patients received postoperative non-opioid adjunct pain medications within 90 days. Comorbidities included: cerebrovascular disease (CVD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), depression, diabetes mellitus (DM), dysrhythmia, heart failure (HF), hypertension (HTN), ischemic heart disease (IHD, a composite of VASQIP angina and myocardial infarction variables), obstructive sleep apnea (OSA), posttraumatic stress disorder (PTSD), and tobacco use (any use within one year prior to surgery). The ICD codes used to supplement VASQIP are provided in Appendix Table 1b (26,27).

Perioperative β-blocker use was determined with outpatient prescription records, patient-reported non-VA prescriptions, and inpatient prescription records. β-blocker use was recorded by class: selective β1-antagonists (acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nebivolol), nonselective β-antagonists (nadolol, penbutolol, pindolol, propranolol, sotalol), and mixed α/β-antagonists (carvedilol, labetalol). For the analysis of prolonged postoperative opioid use, to be classified as using a β-blocker, patients were required to fill a prescription for a β-blocker within 90 days prior to surgery, receive a β-blocker as an inpatient on postoperative day 0 or 1, and fill a prescription for a β-blocker within 90 days after surgery. For the analysis of morphine equivalent use, all requirements were the same, except patients were not required to fill an outpatient prescription after surgery. Due to these different definitions of which patients classified as β-blocker users, as well as the exclusion of PCA users from morphine equivalent calculations, the cohort analyzed for morphine equivalent usage was different than the cohort analyzed for prolonged postoperative opioid use (Fig. 1).

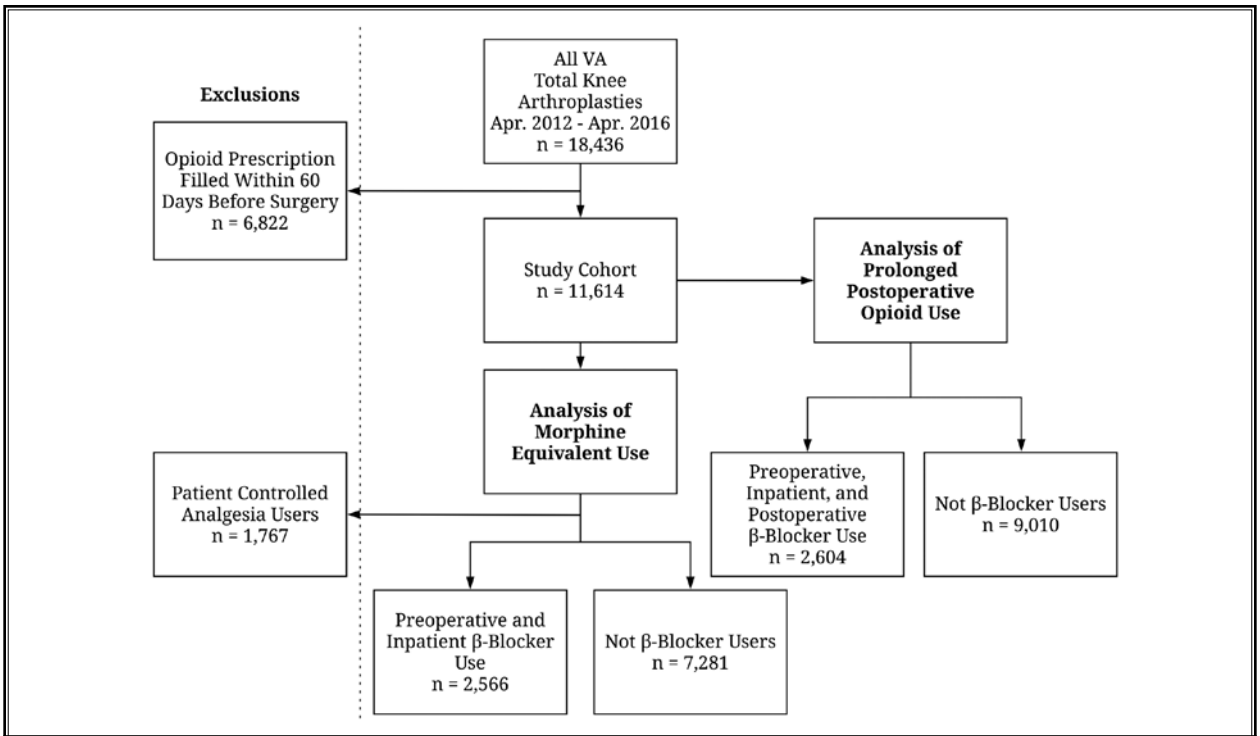

Fig. 1. *A flowchart depicting study inclusion criteria, exclusion criteria, and the definitions for patients to be considered β-blocker users in each analysis cohort.*

A secondary analysis was undertaken examining associations between each β-blocker class and prescription opioid use at each follow-up time. To be recorded as taking a selective β-blocker, for example, a patient must have fulfilled the same criteria for β-blocker use as in the primary analysis, but all criteria had to be met with a selective β-blocker specifically. The same was true for nonselective and α/β-blockers.

Statistical Analysis

All statistical analyses were performed with R Version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) (28). Descriptive statistics were obtained for all covariates stratified by any β-blocker use, as well as by β-blocker class. Student t test, Pearson chi-squared test, and Fisher exact test were utilized for univariate testing as appropriate. For these univariate tests, patients not using β-blockers were always the comparison group. Separate testing was required for the prolonged postoperative opioid use cohort and the morphine equivalent use cohort.

To perform the adjusted analyses for the 4 time points of interest, a separate generalized linear model (GLM) was constructed for each outcome using an identity link for morphine equivalent use and logit links for prolonged postoperative opioid use. Patients with missing data were excluded, as well as patients who died prior to the follow-up outcome time being examined. All GLMs initially adjusted for all covariates. Of note, prolonged postoperative opioid was adjusted for a postoperative non-opioid adjunct prescription, while morphine equivalent use was adjusted for inpatient non-opioid adjunct use. To avoid collinearity, the variance inflation factor (VIF) for each covariate in each GLM was calculated using the R package HH (29). No VIFs in any GLM were greater than 5, so no covariates were removed (29). The GLMs were used to determine odds ratios (prolonged postoperative opioid use) or coefficients (morphine equivalent use), confidence intervals, and *P* values.

For the secondary analysis, the same methods were used for adjustment but isolated to each class of β-blocker. Again, each β-blocker class was only compared to patients not using β-blockers.

Results

This study's VINCI query yielded 18,436 TKAs performed on 16,895 unique patients. After excluding patients using opioids preoperatively, the final cohort consisted of 11,614 TKAs performed on 10,841 unique patients.

In the prolonged postoperative opioid use cohort, 2,604 surgeries (24.3%) were performed on patients using β-blockers. The cohort was 93.8% male and 78.2% white with a mean age of 66 years. Patients using β-blockers were significantly more likely to have all comorbidities recorded except for depression, PTSD, and current tobacco use. This was especially notable for dysrhythmias, HF, HTN, IHD, and OSA. Full demographic descriptions and univariate testing results are in Table 1. The only covariate with missing values was BMI (n = 3). For opioid use at 30 days, 23 patients died prior to this follow-up time. For opioid use at 90 and 365 days, a total of 27 and 31 patients died prior to these follow-up times, respectively.

The morphine equivalent use cohort excluded 1,767 patients due to PCA use, for a total of 9,847 patients. Surgeries were performed on 2,566 patients (26.1%) using β-blockers. The cohort was 93.8% male and 79.1% white with a mean age of 67 years. Comorbidity distributions were consistent with the prolonged postoperative opioid use cohort. Full demographic descriptions and univariate testing results are in Supplemental Table 1. The only covariate with missing values was BMI (n = 3).

Unadjusted and adjusted results comparing opioid use at each follow-up time by perioperative β-blocker use are presented in Table 2. Prior to adjustment, β-blocker users required slightly fewer morphine equivalents (86.1 vs 90.4, *P* = .004) and had a lower rate of opioid use 30 days after surgery (27.4% vs 30.0%, *P* = .010). β-blocker users had similar rates of opioid use compared to patients not using β-blockers at 90 and 365 days after surgery.

After adjustment for age, BMI, gender, race, anesthesia type, non-opioid adjunct use, CKD, COPD, CVD, depression, DM, dysrhythmia, HF, HTN, IHD, OSA, PTSD, and tobacco use, β-blocker use remained associated with reduced opioid use at 30 days after surgery (OR = 0.89 [95% confidence interval (CI) 0.80-0.99], *P* = .026). Morphine equivalent use and opioid use at 90 and 365 days were not different between the 2 groups.

Secondary Analysis

Of the 2,604 TKAs in the prolonged postoperative opioid use cohort in which β-blockers were taken perioperatively, selective β-blockers were solely used in 2,219 (85.2%); nonselective β-blockers were solely used in 103 (4.0%); and α/β-blockers were solely used in 265 (10.2%). Seventeen patients (0.7%) used more than one class and were excluded from the β-blocker class-

Table 1. *Baseline cohort characteristics separated by patients using any β-blocker perioperatively*

	Overall (n = 11,614)	No β-Blocker Use (n = 9,010)	β-Blocker Use (n = 2,604)	*P* Value*
Age (mean, SD)	66.4 (8.3)	65.9 (8.4)	68.3 (7.4)	< .001
BMI (mean, SD)	31.5 (4.9)	31.2 (4.9)	32.3 (4.8)	< .001
Male (n, %)	10,898 (93.8)	8,394 (93.2)	2,504 (96.2)	< .001
Race (n, %)				< .001
African American	1,251 (10.8)	1,030 (11.4)	221 (8.5)	
Other	257 (2.2)	205 (2.3)	52 (2.0)	
Unknown	1,029 (8.9)	834 (9.3)	195 (7.5)	
White	9,077 (78.2)	6,941 (77.0)	2,136 (82.0)	
General Anesthesia (n, %)	7,187 (61.9)	5,601 (62.2)	1,586 (60.9)	.244
Postoperative Adjunct (n, %)	9,740 (83.9)	7,546 (83.8)	2,194 (84.3)	.538
CKD (n, %)	1,033 (8.9)	673 (7.5)	360 (13.8)	< .001
COPD (n, %)	1,086 (9.4)	775 (8.6)	311 (11.9)	< .001
CVD (n, %)	566 (4.9)	376 (4.2)	190 (7.3)	< .001
Depression (n, %)	4,585 (39.5)	3,551 (39.4)	1,034 (39.7)	.785
DM (n, %)	3,435 (29.6)	2,448 (27.2)	987 (37.9)	< .001
Dysrhythmia (n, %)	3,787 (32.6)	2,621 (29.1)	1,166 (44.8)	< .001
HF (n, %)	1,542 (13.3)	890 (9.9)	652 (25.0)	< .001
HTN (n, %)	9,623 (82.9)	7,085 (78.6)	2,538 (97.5)	< .001
IHD (n, %)	1,860 (16.0)	1,037 (11.5)	823 (31.6)	< .001
OSA (n, %)	3,552 (30.6)	2,574 (28.6)	978 (37.6)	< .001
PTSD (n, %)	2,634 (22.7)	2,068 (23.0)	566 (21.7)	.192
Tobacco Use (n, %)	1,808 (15.6)	1,455 (16.1)	353 (13.6)	.001

*P values were obtained with Student t test and Pearson chi-squared test as appropriate.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; IHD, ischemic heart disease; OSA, obstructive sleep apnea; PTSD, posttraumatic stress disorder; SD, standard deviation.

Table 2. *Unadjusted and adjusted results for postoperative opioid use stratified by perioperative β-blocker use.*

	Overall	No β-Blocker	β-Blocker	*P* Value
Unadjusted Results				
Postoperative Morphine Equivalents* (mean, SD)	89.3 (65.8)	90.4 (66.4)	86.1 (63.9)	.004
30-Day Opioid Use (n, %)	3,411 (29.4)	2,698 (30.0)	713 (27.4)	.010
90-Day Opioid Use (n, %)	1,475 (12.7)	1,139 (12.7)	336 (12.9)	.750
365-Day Opioid Use (n, %)	1,356 (11.7)	1,033 (11.5)	323 (12.4)	.200
Adjusted Results for β-Blocker Users†			**95% CI**	
Postoperative Morphine Equivalents* (β)	-1.9		-5.0-1.1	.217
30-Day Opioid Use (OR)	0.89		0.80-0.99	.026
90-Day Opioid Use (OR)	1.00		0.87-1.15	.965
365-Day Opioid Use (OR)	1.04		0.90-1.20	.547

*These are the morphine equivalents patients used on postoperative days zero and one, excluding patients who used patient-controlled analgesia.
†Results were adjusted for age, body mass index, race, sex, anesthesia type, non-opioid adjunct use, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular disease, depression, diabetes mellitus, dysrhythmia, heart failure, hypertension, ischemic heart disease, posttraumatic stress disorder, obstructive sleep apnea, and tobacco use.
Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation

specific analyses. When stratified by β-blocker class, the characteristics of patients mirrored the results for all β–blocker users. Notably, patients using nonselective β-blockers had higher rates of depression and PTSD, while patients using α/β-blockers had higher rates of HF and IHD. Full demographic descriptions and univariate testing results are in Table 3.

Of the 2,566 TKAs in the morphine equivalent use cohort in which β-blockers were taken perioperatively, selective β-blockers were solely used in 2,179 (84.9%); nonselective β-blockers were solely used in 110 (4.3%); and α/β-blockers were solely used in 266 (10.4%). Eleven patients (0.4%) used more than one class and were excluded from the β-blocker class-specific analyses. Again, comorbidity distributions were consistent with the prolonged postoperative opioid use cohort. Full demographic descriptions and univariate testing results are in Supplemental Table 2.

Unadjusted and adjusted results comparing opioid use at each follow-up time by perioperative β-blocker class are presented in Table 4. Because such a large proportion of patients were using selective β-blockers, the selective β-blocker results were consistent with the primary analysis. Prior to adjustment, selective β-blocker users required fewer morphine equivalents (86.2 vs 90.4, $P = .007$) and had a lower rate of opioid use 30 days after surgery (26.9% vs 30.0%, $P = .004$). Additionally, nonselective β-blocker use was associated

Table 3. *Descriptive characteristics of patients separated by which of the 3 β-blocker classes they received perioperatively.*

	Selective β-Blocker Use (n = 2,219)	*P* Value	Nonselective β-Blocker Use (n = 103)	*P* Value	α/β-Blocker Use (n = 265)	*P* Value*
Age (mean, SD)	68.5 (7.4)	< .001	64.4 (7.4)	.044	67.8 (7.3)	< .001
BMI (mean, SD)	32.2 (4.8)	< .001	33.1 (5.0)	< .001	32.6 (5.0)	< .001
Male (n, %)	2,139 (96.4)	< .001	94 (91.3)	.448	255 (96.2)	.050
Race (n, %)		< .001		.263		.442
African American	185 (8.3)		7 (6.8)		28 (10.6)	
Other	46 (2.1)		2 (1.9)		4 (1.5)	
Unknown	169 (7.6)		6 (5.8)		18 (6.8)	
White	1,819 (82.0)		88 (85.4)		215 (81.1)	
General Anesthesia (n, %)	1,359 (61.2)	.424	56 (54.4)	.105	160 (60.4)	.554
Postoperative Adjunct (n, %)	1,860 (83.8)	.936	89 (86.4)	.467	230 (86.8)	.185
CKD (n, %)	289 (13.0)	< .001	16 (15.5)	.002	50 (18.9)	< .001
COPD (n, %)	265 (11.9)	< .001	8 (7.8)	.764	36 (13.6)	.005
CVD (n, %)	161 (7.3)	< .001	6 (5.8)	.405	21 (7.9)	.003
Depression (n, %)	857 (38.6)	.494	66 (64.1)	< .001	105 (39.6)	.945
DM (n, %)	831 (37.4)	< .001	32 (31.1)	.377	118 (44.5)	< .001
Dysrhythmia (n, %)	971 (43.8)	< .001	47 (45.6)	< .001	137 (51.7)	< .001
HF (n, %)	484 (21.8)	< .001	25 (24.3)	< .001	135 (50.9)	< .001
HTN (n, %)	2,173 (97.9)	< .001	93 (90.3)	.004	255 (96.2)	< .001
IHD (n, %)	695 (31.3)	< .001	21 (20.4)	.005	102 (38.5)	< .001
OSA (n, %)	813 (36.6)	< .001	45 (43.7)	.001	113 (42.6)	< .001
PTSD (n, %)	465 (21.0)	.044	33 (32.0)	.029	65 (24.5)	.548
Tobacco Use (n, %)	307 (13.8)	.007	13 (12.6)	.333	30 (11.3)	.035

**P* values were obtained by comparing each medication use group against patients not taking any β-blocker. Student t test, Pearson chi-squared test, and Fisher exact test were used as appropriate.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; IHD, ischemic heart disease; OSA, obstructive sleep apnea; PTSD, posttraumatic stress disorder; SD, standard deviation

Table 4. *Unadjusted and adjusted results for postoperative opioid use stratified by class of perioperative β-blocker use.*

	Selective β-Blocker	P Value	Nonselective β-Blocker	P Value	α/β-Blocker	*P* Value
Unadjusted Results						
Postoperative Morphine Equivalents (mean, SD)*	86.2 (63.4)	.007	78.3 (55.5)	.026	88.9 (70.2)	.742
30-Day Opioid Use (n, %)	597 (26.9)	.004	31 (30.1)	.986	78 (29.4)	.838
90-Day Opioid Use (n, %)	270 (12.2)	.526	17 (16.5)	.246	44 (16.6)	.059
365-Day Opioid Use (n, %)	267 (12.0)	.471	17 (16.5)	.114	37 (14.0)	.217
Adjusted Results†						
Postoperative Morphine Equivalents (β, 95% CI)*	-1.2 (-4.4-2.0)	.468	-17.9 (-29.9 to -5.8)	.004	-0.7 (-8.8-7.5)	.875
30-Day Opioid Use (OR, 95% CI)	0.88 (0.78-0.98)	.021	0.90 (0.58-1.37)	.636	0.92 (0.69-1.22)	.567
90-Day Opioid Use (OR, 95% CI)	0.96 (0.82-1.11)	.560	1.20 (0.68-1.99)	.500	1.28 (0.90-1.80)	.158
365-Day Opioid Use (OR, 95% CI)	1.04 (0.89-1.20)	.649	1.30 (0.74-2.15)	.339	1.15 (0.78-1.64)	.460

*These are the morphine equivalents patients used on the day of surgery and postoperative day 1.
†Results were adjusted for age, body mass index, race, sex, anesthesia type, non-opioid adjunct use, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular disease, depression, diabetes mellitus, dysrhythmia, heart failure, hypertension, ischemic heart disease, post-traumatic stress disorder, obstructive sleep apnea, and tobacco use.
Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

with receiving fewer morphine equivalents (78.3 vs 90.4, *P* = .026).

After adjustment for all covariates, selective β-blocker use remained associated with reduced opioid use at 30 days after surgery (OR = 0.88 [95% CI, 0.78-0.98], *P* = .021). Nonselective β-blocker use also remained associated with reduced morphine equivalent use (β = -17.9 morphine equivalents [(95% CI, -29.9 to -5.8), *P* = .004]). There were no other associations between the outcomes of interest and β-blocker use by class.

Discussion

This retrospective study of a cohort of patients undergoing TKAs at the VA found perioperative β-blocker use to be associated with reduced prescription opioid use at 30 days after surgery. When separated by β-blocker class, the same was true of selective β-blockers, and nonselective β-blockers were associated with a 17.9-morphine equivalent use reduction through postoperative day one.

These findings are consistent with a growing body of basic research and clinical studies indicating analgesic properties of β-blockers (11,12,14,15,18,30-36). For instance, clinical trials of intraoperative esmolol infusions have shown reduced opioid requirements in the immediate postoperative period (12,31). Additionally, in a prospective cohort of patients with chronic pain from knee and hip osteoarthritis, β-blockers prescribed for hypertension were associated with reduced pain scores, analgesic use, and opioid use (30). To our knowledge, however, this is the first study to suggest that the effects of β-blockers on acute pain are associated with subsequent reduced postoperative opioid use.

Several proposed mechanisms for analgesia from β-blockers exist, and, in fact, multiple mechanisms may exist depending on the cause of pain (11,13,15-18,33,34). Notably, both selective and nonselective β-blockers were associated with reduced opioid use to different extents. If future, prospective research were to suggest these associations are causal, β1- and β2-adrenergic receptor antagonism may be involved.

As a retrospective database review, this study has

innate limitations. The quality of any data analysis is dependent on the data available. In this case, VASQIP data is considered to be reliable (25). Nevertheless, unmeasured confounders are always a threat, despite the inclusion of many relevant comorbidities. Because this study was performed on a cohort of predominantly white, male VA patients, generalizability of these findings is also uncertain.

Another concern is that, while patients were classified based on prescription records, patients may have not taken prescriptions they filled or taken medications that were not prescribed. However, there is no reason to believe that patients prescribed β-blockers were systematically more inclined to either take unprescribed opioids or not take prescribed opioids. Thus, the net result of misclassifications for these reasons should not favor rejecting the null hypothesis. This study measured inpatient opioid use and opioid prescription refills as the outcomes of interest, but they are also not perfect surrogates for pain. Some patients may have used opioids without significant pain, and some may have avoided opioids despite significant pain. Nevertheless, these measures offer value as objective measures of pain persistence over time in a large, national cohort for which patient-reported outcomes are otherwise unavailable.

In this study, β–blockers were associated with reduced opioid use 30 days after a TKA. It would be premature to recommend perioperative β-blocker administration as a non-opioid adjunct currently, especially with their history of increasing mortality in the POISE trial (37). However, prospective research efforts are warranted to elucidate if there is a role for β-blockers to help reduce CPSP after high-risk procedures.

Acknowledgements:

We would like to thank the editorial board of Pain Physician for review and criticism in improving the manuscript.

Conflict of Interest: All authors have no conflicts of interest to report. None of the authors of the manuscript received any remuneration. Further, the authors have not received any reimbursement or honorarium in any other manner.

Supplemental Table 1: *Baseline cohort characteristics separated by patients using any β-blocker preoperatively and through the hospital stay, but not necessarily post-operatively. Patients using patient-controlled analgesia were excluded due to unknown dosages delivered.*

	Overall (n = 9,847)	No β-Blocker Use (n = 7,281)	β-Blocker Use (n = 2,566)	P-value*
Age (mean, SD)	66.6 (8.3)	65.9 (8.4)	68.4 (7.5)	< 0.001
BMI (mean, SD)	31.5 (4.9)	31.2 (4.9)	32.3 (4.9)	< 0.001
Male (n, %)	9,236 (93.8)	6,760 (92.8)	2,476 (96.5)	< 0.001
Race (n, %)				< 0.001
African American	1,019 (10.3)	810 (11.1)	209 (8.1)	
Other	217 (2.2)	166 (2.3)	51 (2.0)	
Unknown	823 (8.4)	635 (8.7)	188 (7.3)	
White	7,788 (79.1)	5,670 (77.9)	2,118 (82.5)	
General Anesthesia (n, %)	6,213 (63.1)	4,595 (63.1)	1,618 (63.1)	0.961
Inpatient Adjunct (n, %)	8,590 (87.2)	6,366 (87.4)	2,224 (86.7)	0.320
CKD (n, %)	879 (8.9)	536 (7.4)	343 (13.4)	< 0.001
COPD (n, %)	928 (9.4)	619 (8.5)	309 (12.0)	< 0.001
CVD (n, %)	484 (4.9)	294 (4.0)	190 (7.4)	< 0.001
Depression (n, %)	3,867 (39.3)	2,850 (39.1)	1,017 (39.6)	0.662
DM (n, %)	2,856 (29.0)	1,914 (26.3)	942 (36.7)	< 0.001
Dysrhythmia (n, %)	3,192 (32.4)	2,055 (28.2)	1,137 (44.3)	< 0.001
HF (n, %)	1,296 (13.2)	664 (9.1)	632 (24.6)	< 0.001
HTN (n, %)	8,182 (83.1)	5,675 (77.9)	2,507 (97.7)	< 0.001
IHD (n, %)	1,560 (15.8)	762 (10.5)	798 (31.1)	< 0.001
OSA (n, %)	3,055 (31.0)	2,086 (28.6)	969 (37.8)	< 0.001
PTSD (n, %)	2,232 (22.7)	1,664 (22.9)	568 (22.1)	0.455
Tobacco Use (n, %)	1,494 (15.2)	1,154 (15.8)	340 (13.3)	0.002

*P-values were obtained with Student's t-test and Pearson's chi-squared test as appropriate.
Abbreviations: BMI – body mass index, CKD – chronic kidney disease, COPD – chronic obstructive pulmonary disease, CVD – cerebrovascular disease, DM – diabetes mellitus, HF – heart failure, HTN – hypertension, IHD – ischemic heart disease, OSA – obstructive sleep apnea, PTSD – post-traumatic stress disorder.

Supplemental Table 2: *Baseline cohort characteristics separated by which β-blocker patients used preoperatively and through the hospital stay, but not necessarily post-operatively. Patients using patient-controlled analgesia were excluded due to unknown dosages delivered.*

	Selective β-Blocker Use (n = 2,179)	*P*-value	Non-Selective β-Blocker Use (n = 110)	*P*-value	α/β-Blocker Use (n = 266)	*P*-value*
Age (mean, SD)	68.6 (7.5)	< 0.001	65.1 (7.4)	0.293	68.4 (7.4)	< 0.001
BMI (mean, SD)	32.2 (4.9)	< 0.001	32.4 (4.8)	0.012	32.5 (5.2)	< 0.001
Male (n, %)	2,110 (96.8)	< 0.001	101 (91.8)	0.679	255 (95.9)	0.059
Race (n, %)		< 0.001		0.767		0.389
African American	169 (7.8)		9 (8.2)		29 (10.9)	
Other	45 (2.1)		2 (1.8)		4 (1.5)	
Unknown	164 (7.5)		8 (7.3)		16 (6.0)	
White	1,801 (82.7)		91 (82.7)		217 (81.6)	
General Anesthesia (n, %)	1,376 (63.1)	0.974	60 (54.5)	0.065	173 (65.0)	0.522
Inpatient Adjunct (n, %)	1,886 (86.6)	0.280	98 (89.1)	0.602	230 (86.5)	0.641
CKD (n, %)	273 (12.5)	< 0.001	15 (13.6)	0.013	51 (19.2)	< 0.001
COPD (n, %)	262 (12.0)	< 0.001	9 (8.2)	0.905	37 (13.9)	0.002
CVD (n, %)	162 (7.4)	< 0.001	4 (3.6)	0.897	22 (8.3)	< 0.001
Depression (n, %)	831 (38.1)	0.398	70 (63.6)	< 0.001	112 (42.1)	0.331
DM (n, %)	793 (36.4)	< 0.001	31 (28.2)	0.654	113 (42.5)	< 0.001
Dysrhythmia (n, %)	953 (43.7)	< 0.001	51 (46.4)	< 0.001	125 (47.0)	< 0.001
HF (n, %)	469 (21.5)	< 0.001	26 (23.6)	< 0.001	134 (50.4)	< 0.001
HTN (n, %)	2,140 (98.2)	< 0.001	100 (90.9)	0.001	256 (96.2)	< 0.001
IHD (n, %)	669 (30.7)	< 0.001	19 (17.3)	0.021	104 (39.1)	< 0.001
OSA (n, %)	803 (36.9)	< 0.001	49 (44.5)	< 0.001	111 (41.7)	< 0.001
PTSD (n, %)	467 (21.4)	0.163	33 (30.0)	< 0.001	65 (24.4)	0.547
Tobacco Use (n, %)	296 (13.6)	0.010	11 (10.0)	0.095	32 (12.0)	0.093

**P*-values were obtained by comparing each medication use group against patients not taking any β-blocker. Student's t-test, Pearson's chi-squared test, and Fisher's exact test were used as appropriate.

Abbreviations: BMI – body mass index, CKD – chronic kidney disease, COPD – chronic obstructive pulmonary disease, CVD – cerebrovascular disease, DM – diabetes mellitus, HF – heart failure, HTN – hypertension, IHD – ischemic heart disease, OSA – obstructive sleep apnea, PTSD – post-traumatic stress disorder.

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