Cluster-Randomized Trial of Opiate-Sparing Analgesia after Discharge from Elective Hip Surgery

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BACKGROUND: Surgeons have traditionally relied on opiates after hip replacement, despite a growing epidemic of abuse. This study assessed the efficacy of multimodal analgesia and impact of conservative opiate prescribing after discharge from hip surgery.

STUDY DESIGN: In this cluster-randomized trial, 235 patients undergoing hip replacement (5 surgeons) received 1 of 3 discharge pain regimens: scheduled-dose multimodal analgesia with a minimal opiate supply (group A), scheduled-dose multimodal analgesia with a traditional opiate supply (group B), or a traditional pro re nata (as needed) opiate regimen alone (group C). Each of the surgeons comprised a distinct cluster and alternated in a randomized sequence between interventions. The multimodal regimen comprised fixed-schedule doses of acetaminophen, meloxicam, and gabapentin. Primary outcomes were daily visual analogue scale pain and opiate use for 30 days. Secondary outcomes included satisfaction, sleep quality, opiate-related symptoms, hip function, and adverse events. The primary intent-to-treat analysis was performed using linear mixed models.

RESULTS: Daily pain was significantly lower in group A (coefficient [Coeff] −0.81; $p = 0.003$) and group B (Coeff −0.61; $p = 0.021$) relative to group C. Although daily opiate use in group A (Coeff −0.77; $p < 0.001$) and group B (Coeff −0.30; $p = 0.04$) was lower than group C, opiate use for group A was also lower than group B (Coeff −0.46; $p = 0.002$). Duration of opiate use was significantly shorter for group A (1.14 weeks) and group B (1.39 weeks) compared with group C (2.57 weeks). There were fewer opiate-related symptoms, most commonly fatigue, in group A compared with C, but groups B and C were not significantly different. Both multimodal regimens improved satisfaction and sleep, and there were no differences in hip function or adverse events.

CONCLUSIONS: Multimodal analgesia with minimal opiates improved pain control while significantly decreasing opiate use and opiate-related adverse effects. It is time to rethink our reliance on opiates after elective operations. (J Am Coll Surg 2019;229:335−345. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Investigators in the Opioid Prescription in Orthopedic Surgery after Discharge Research Group who collaborated on this article are listed in the Appendix.

International Committee of Medical Journal Editors data sharing statement available online as eTable 1.

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Abbreviations and Acronyms

Coeff = coefficient
ED = emergency department
GI = gastrointestinal
HOOS = Hip Disability and Osteoarthritis Outcome Score
ORSDS = Opioid-Related Symptom Distress Scale
POD = postoperative day
PRN = pro re nata (as needed)
THR = total hip replacement
VAS = visual analogue scale
VTE = venous thromboembolism

Opiate abuse has become a national epidemic and one of the most rapidly growing public health concerns in the US. The incidence of opiate abuse increased 5-fold from 2010 to 2016, and 33,000 deaths were reported from overdoses in 2015 alone.[1,2] Traditional post-discharge analgesic regimens after total hip replacement (THR), one of the most common orthopaedic procedures, have relied heavily on opiates, and patients typically have been discharged with up to 100 tablets.[3-5] It is not uncommon for patients to misuse these medications after hip operation, with nearly 5% of previously opiate-naïve patients becoming chronic abusers.[6,7] A CDC study found that opiate prescriptions with medication supplies lasting more than 8 days increased the likelihood of long-term abuse at 1 year from 6.0% to 13.5%, and prescriptions beyond 31 days increased risk to 29.9%.[8] Even when used appropriately, opiates can cause significant adverse effects, which sometimes require emergency services.[9] Patients can also be at risk for injury if operating a vehicle or returning to work while still experiencing the sedative effects of opiates.

Multimodal analgesia targeting multiple distinct pain pathways is a potentially safer and more effective alternative to traditional opiate-predominant strategies. Unlike traditional as needed (pro re nata [PRN]) prescription of opiates, multimodal pain regimens typically rely on fixed dosing schedules of non-opiate medications to maintain analgesia upstream from potential symptom triggers. The goals of multimodal analgesia are to reduce opiate consumption and therefore opioid-related side effects and risk for chronic abuse, as well as improve functional recovery and patient satisfaction.[10,11] Although scheduled-dose multimodal strategies have been shown to be more effective during acute inpatient hospitalization, no randomized trial has assessed analgesia after hospital discharge.[12-14] Even with multimodal analgesia, the expectation remains that patients will require opiate pain medications, and large opiate supplies are still prescribed routinely at discharge. The goals of this cluster-randomized trial were to compare the efficacy of multimodal and traditional opiate analgesia after elective hip operations, and also to determine whether minimizing opiate oversupply can further reduce opiate consumption and opiate-related adverse effects.

METHODS

Study Design and Oversight

The Opioid Prescription in Orthopedic Surgery after Discharge (OPIOID) trial was a prospective, 3-arm, parallel-group, cluster-randomized trial. As medication blinding was deemed both impractical and unethical, the use of authorized deception was approved by our IRB. Authorized deception was necessary to avoid response expectancy for subjective outcomes and to prevent recruitment bias. Each surgeon acted as a "guardian" and allowed each of the low-risk study interventions to be implemented as standard of care for the allotted time period. Informed consent was obtained from patients for prospective data collection. This study was performed without any external sources of funding or relevant conflicts of interest among the authors and registered at ClinicalTrials.gov (NCT03358888).

Study population

Eligible participants were aged older than 18 years, undergoing primary, unilateral THR performed by 1 of 5 surgeons at 4 surgical sites. Key exclusions were chronic opiate use within 3 months of operation, contraindication to COX-2 inhibitors (ie history of major bleeding or "potent" venous thromboembolism [VTE] prophylaxis) or other protocol medications, and no access to a computer for electronic questionnaires (a complete list of study exclusions can be found in eDocument 1). Patients contraindicated from receiving tramadol (ie those on serotonin reuptake inhibitors) were permitted. Pain tolerance was assessed preoperatively using the Pain Catastrophizing Scale, a validated 13-item instrument that predicts postoperative pain and disability.[15,16]

Randomization, recruitment, and treatment allocation

Randomization was implemented in "clusters," with each of the 5 surgeons comprising a distinct cluster. At commencement, each surgeon was initially allocated at random (using a random number generator) to begin the study with a particular study intervention for a fixed 4-week interval. Subsequently, surgeon clusters

alternated between study arms every 4 weeks in a fixed sequence (ie group A→group B, group B→group C, group C→group A) until the necessary sample size was achieved for all groups. A fixed sequence of alternation after initial randomization simplified the protocol for mid-level providers administering discharge medications so as to not predispose to errors that could cause patient harm. Study enrollment was halted once all 3 study arms had enrolled a minimum of 76 patients, as determined at the end of each week. During each 4-week interval, a surgeon's allocated study intervention was considered "standard of care" for all opiate-naïve patients undergoing THR, not just those enrolled in the study. Patients were initially recruited and screened for participation by phone before hospital admission; however, consent was obtained on admission to the hospital for the procedure. Patients were allocated to the study intervention assigned to the operating surgeon on the date of discharge.

Study interventions

Three post-discharge oral analgesic regimens were evaluated (Fig. 1). The primary investigational group (group A, "minimal opiate supply policy") was prescribed a fixed-schedule dose multimodal analgesic regimen with a minimal 2-day opiate supply (10 tablets each of oxycodone and tramadol). Patients were instructed to take non-opiate analgesic medications on a fixed daily schedule, and reserve opiates for emergency pain relief only. The secondary investigational group (group B, "multimodal with traditional opiate supply policy") was also prescribed the same scheduled-dose multimodal analgesic regimen, but with a conventional 2-week supply of opiates (60 tablets each of oxycodone and tramadol). Patients were again instructed to take non-opiate medications on a fixed daily schedule, and opioid medications were to be taken PRN for residual pain. Finally, the control group (group C, "traditional opiate supply policy without multimodal") was prescribed acetaminophen in addition to a 2-week supply of opiates. Patients in group C were instructed to take all medications on a PRN basis, starting with acetaminophen for mild pain and opioid medications for moderate or severe pain.

Patients taking serotonin reuptake inhibitors were not prescribed tramadol, given the risk for serotonin syndrome. All patients were contacted once after discharge to promote proper use of medications per protocol. Physician-directed analgesia was maintained for 4 weeks postoperatively unless continued intervention was deemed necessary. Clinical assistants were instructed to provide medication refills as needed based on their own clinical judgment.

Perioperative procedures

Preoperatively, all patients received oral acetaminophen, celecoxib (or meloxicam if allergic), and gabapentin within 2 hours of the procedure. Intraoperative spinal anesthesia was achieved with 3 mL 0.5% bupivacaine. Postoperatively, scheduled doses of oral acetaminophen, gabapentin, celecoxib (or meloxicam), and IV ketorolac were administered until discharge. Oral oxycodone and tramadol and, less commonly, hydromorphone or fentanyl, were administered as needed for breakthrough pain, and inpatient IV morphine-equivalent doses were recorded. Aspirin (81 mg or 325 mg, twice daily) was administered as VTE prophylaxis for the first month postoperatively. All patients were mobilized on the day of operation, irrespective of treatment allocation.

Outcomes measures

The primary outcomes were visual analogue scale (VAS) pain and daily IV morphine equivalents for each of the first 30 days after operation, excluding full inpatient days before discharge. Secondary outcomes, including VAS satisfaction and sleep quality, and opioid-related symptoms using the Opioid-Related Symptom Distress Scale (ORSDS), were also recorded for the first 30 days. The ORSDS is a validated measure of 10 common adverse opiate effects based on symptom severity.[17] Functional outcomes were assessed preoperatively and after 1 month using the short-form Hip Disability and Osteoarthritis Outcome Score (HOOS), Joint Replacement, and complications were assessed after 90 days.[18]

Sample size

This study was powered as a superiority trial contingent on a power to detect group differences in VAS pain with a 2-tailed α level of 0.05 set as the probability of type I error, 90% power level, and a correlation of 0.5 among repeated outcomes measures within patient (detailed statistical analysis methods can be found in eDocument 2). Despite the 3-arm design, the study was powered to test an interaction effect between 2 groups (differences in group by time interaction), which was then extrapolated for 3 groups. Assuming a small to moderate effect size ($d = 0.4$), the necessary sample size was 76 patients per group with an expected 10% attrition rate.[19-21]

Group A	Group B	Group C
• Multimodal pain regimen • Narcotic medications for emergency pain relief only • Oxycodone 5 mg q 4 hours PRN (10 tablets)[1] • Tramadol 50 mg q 6 hours PRN (10 tablets)[2]	• Multimodal pain regimen • Narcotic medications as needed • Oxycodone 5 mg q 4 hours PRN (60 tablets)[1] • Tramadol 50 mg q 6 hours PRN (60 tablets)[2]	• No standing dose regimen • Acetaminophen 500 mg q 6 hours PRN for 4 weeks • Oxycodone 5 mg q 4 hours PRN (60 tablets)[1] • Tramadol 50 mg q 6 hours PRN (60 tablets)[2]

Multimodal Medications	Dosing[3]	Duration
Acetaminophen	1000 mg q8h	4 weeks
Gabapentin	200 mg q12h	4 weeks
Meloxicam	15 mg q AM	2 weeks
Omeprazole[4]	20 mg q AM	2 weeks

Figure 1. Intervention groups and multimodal analgesic regimen. [1]All oxycodone prescriptions were for immediate-release tablets only (no extended-release tablets). [2]Tramadol was not prescribed to patients taking serotonin reuptake inhibitors or other medications with toxic drug interactions. [3]Multimodal pain medications were prescribed as scheduled doses. [4]Alternate proton pump inhibitor or H_2 histamine receptor blocker was acceptable if already prescribed. PRN, pro re nata (as needed).

Statistical analysis

Baseline characteristics of the 3 treatment groups were compared with chi-square tests for categorical variables and ANOVA or Kruskal-Wallis tests for continuous variables, depending on whether data were normally distributed. Based on an intent-to-treat approach, the primary analysis was performed using linear mixed models specifying random intercepts and slopes and adjusting for significant confounding variables ($p < 0.2$), which provided a coefficient that is to be interpreted in the same way as a β-coefficient in a traditional linear regression. Based on an analysis of intra-class correlation, the proportion of variance in outcomes accounted for by clustering within surgeon was essentially nil (intra-class correlation for surgeon was 0.018 for daily pain and 0.038 for daily opiate use), and therefore clustering by surgeon was not considered in the statistical model. In addition, although treatment was assigned at the level of surgeon, it was not possible to model random slopes for surgeon, as is typically done in a 3-level randomized cluster trial design, given the small number of those surgeon clusters. ANOVAs, followed by post-hoc test for the 3 group comparisons, were also performed to compare intervention groups on each individual postoperative day. Analysis of covariance was used for a comparison of time to discontinuation of opiate medications. Analyses were performed using SPSS, version 23 (IBM Corp).

RESULTS

Patients

From June 2017 to January 2018, six hundred and fifteen of 705 consecutive THR patients met eligibility criteria, of which 235 were enrolled (Fig. 2). Baseline patient characteristics are described in Table 1. There were no significant between-group differences ($p < 0.05$) except BMI ($p = 0.03$), for which post-hoc pairwise comparisons demonstrated that group B was significantly lower than group A ($p = 0.01$) and group C ($p = 0.046$). Scheduled-dose multimodal analgesia with a policy of prescribing a minimal opiate supply (group A), scheduled-dose multimodal analgesia with a traditional opiate supply (group B), or traditional PRN opiate regimen without multimodal analgesia (group C). There was no significant difference in pain catastrophizing scale, preoperative pain scores, or inpatient morphine equivalents use among the 3 groups. There was a mean of 28.6 daily responses per patient during the first 30 postoperative days (95.4% daily response rate).

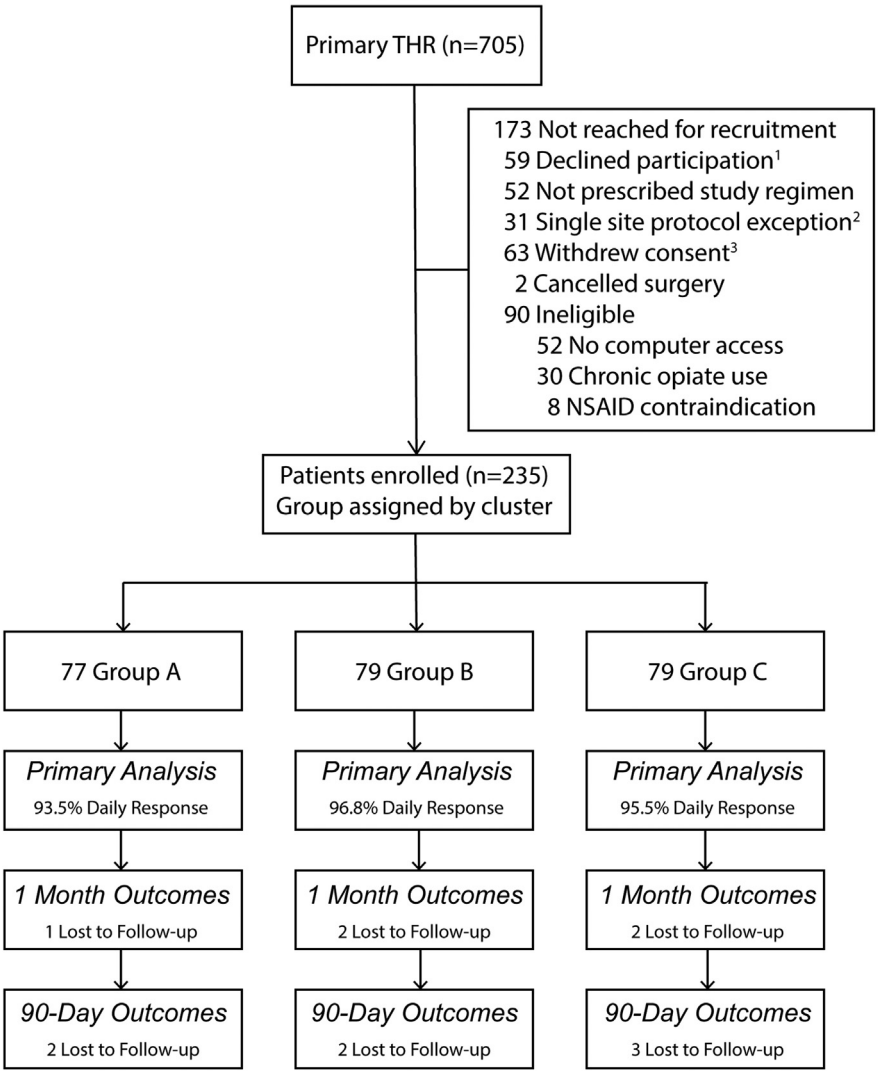

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study, including recruitment, enrollment, and follow-up. [1]Declined participation during initial recruitment. [2]Temporary halt of clinical trial protocol at single clinical site. [3]Withdrew consent for participation after initial recruitment but before hospital discharge. THR, total hip replacement.

Primary outcomes

Postoperative pain

There was no significant difference in pain among groups on postoperative day (POD) 1 ($p = 0.87$), and daily pain scores decreased significantly with time for all 3 groups (coefficient [Coeff] −0.10; 95% CI −0.12 to −0.09; $p < 0.001$) (Fig. 3A). The VAS pain scores during the first 30 days postoperatively were lower for group A (Coeff −0.81; 95% CI −1.33 to −0.29; $p = 0.003$) and group B (Coeff −0.61; 95% CI −1.13 to −0.09; $p = 0.021$) relative to group C. However, there was no significant difference between groups A and B (Coeff −0.20; 95% CI −0.72 to 0.33; $p = 0.46$). In post-hoc testing, group A reported significantly lower pain scores than group C on PODs 4 to 7 and 9 to 11. Similarly, group B reported significantly lower pain scores than group C on PODs 4, 5, 7, 10, and 11. However, there was no significant difference between groups A and B on any postoperative day. The impact of significant covariates can be found in eTable 2.

Postoperative opiate usage

There was no significant difference in morphine-equivalent use between groups on POD 1 ($p = 0.26$), and daily morphine equivalents decreased significantly with time

Table 1. Baseline Patient Characteristics

Characteristic	Group A (n = 77)	Group B (n = 79)	Croup C (n = 79)
Age, y, mean (SD)	62.6 (9.4)	64.3 (8.6)	63.0 (8.3)
Sex, n (%)			
Male	42 (54.5)	42 (53.2)	42 (53.2)
Female	35 (45.5)	37 (46.8)	37 (46.8)
BMI, kg/m^2, mean (SD)	29.5 (4.7)	27.7 (4.1)	29.1 (4.6)
ASA physical status classification, n (%)			
I	1 (1.3)	4 (5.1)	2 (2.5)
II	69 (89.6)	63 (79.7)	63 (79.7)
III	7 (9.1)	12 (15.2)	14 (17.7)
Length of stay, d, median (IQR)	1.24 (0.80)	1.22 (0.32)	1.27 (0.44)
Preoperative pain score,* mean (SD)	59.0 (20.9)	57.8 (24.1)	61.8 (19.9)
Pain catastrophizing score, mean (SD)	11.0 (10.6)	11.1 (9.5)	11.1 (9.5)
Pain expectation score,* mean (SD)	50.6 (24.5)	49.9 (23.2)	51.6 (25.0)
Inpatient morphine equivalent,† median (IQR)	14.1 (9.4)	12.0 (11.8)	12.8 (10.7)
Preoperative pain medicine, n (%)			
None	7 (9.1)	10 (12.7)	9 (11.4)
NSAID (Cox inhibitor)	60 (77.9)	56 (70.9)	58 (73.4)
Acetaminophen	24 (31.2)	26 (32.9)	26 (32.9)
Neuropathic‡	5 (6.5)	4 (5.1)	5 (6.3)
Opioid-like (tramadol)	8 (10.4)	9 (11.4)	10 (12.7)
Preoperative sleep aid, n (%)			
None	50 (64.9)	50 (63.3)	59 (74.7)
Benzodiazepine	4 (5.2)	6 (7.6)	3 (3.8)
Non-benzodiazepine GABA agonist§	6 (7.8)	5 (6.3)	5 (6.3)
Alternative agent‖	19 (24.7)	18 (22.8)	14 (17.7)
Tramadol contraindication,¶ n (%)	7 (9.1)	8 (10.1)	9 (11.4)

*A 100-mm visual analogue pain scale; patients asked were to rate the severity of their preoperative pain and, subsequently, expectations for postoperative pain using the analogous scale.
†Inpatient morphine equivalents defined as inpatient hospital IV morphine equivalent use per 24-h period.
‡Neuropathic drugs included gabapentin, carbamazepine, pregabalin, topiramate, serotonin and norepinephrine reuptake inhibitors, tricyclics, among others.
§Non-benzodiazepine GABA agonists included zolpidem, zaleplon, eszoplicone, among others.
‖Alternative sleep agents included Benadryl, muscle relaxant, cannabis, melatonin, trazadone, mirtazapine, and amitriptyline.
¶Tramadol contraindication included selected serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, monoamine oxidase inhibitor, tricyclics buproprion, mirtazapine, triptan, lithium, carbamazepine, among others.
ASA, American Society of Anesthesiologists; IQR, interquartile range.

for all 3 groups (Coeff −0.05; 95% CI −0.06 to −0.04; p < 0.001) (Fig. 3B). Daily morphine equivalents during the first 30 days were lower for group A (Coeff −0.77; 95% CI −1.06 to −0.47; p < 0.001) and group B (Coeff −0.30; 95% CI −0.60 to −0.01; p = 0.04) compared with group C. Daily morphine equivalents for group A were also significantly lower those of group B (Coeff −0.46; 95% CI −0.76 to −0.17; p = 0.002).

The interaction between group and time was significant for daily morphine equivalents (p = 0.04), with group A having a quicker reduction in opioid consumption in the first 9 days than both group B (Coeff −0.045; 95% CI −0.08 to −0.007; p = 0.02) and group C (Coeff −0.04; 95% CI −0.08 to −0.003; p = 0.035) (see detailed explanation of group and time interaction in eDocument 3). In post-hoc testing, morphine equivalent use for group A was significantly lower than group C on PODs 2 to 22 and 24 to 26. Additionally, group A reported significantly lower morphine-equivalent use than group B on PODs 3 to 11. However, morphine equivalents were only significantly reduced on POD 2 for group B compared with group C. Mean total morphine-equivalent use was 44.8 mg for group A, 79.9 mg for group B, and 109.8 mg for group C.

Mean time to discontinuation of opiate medications was significantly shorter for group A (1.14 weeks) and group B (1.39 weeks) compared with group C (2.57 weeks) (p < 0.001 and p = 0.001, respectively). After 90 days, no patients (0.0%) in group A, 1 patient (1.3%) in group B, and 2 patients (2.6%) in group C had not discontinued

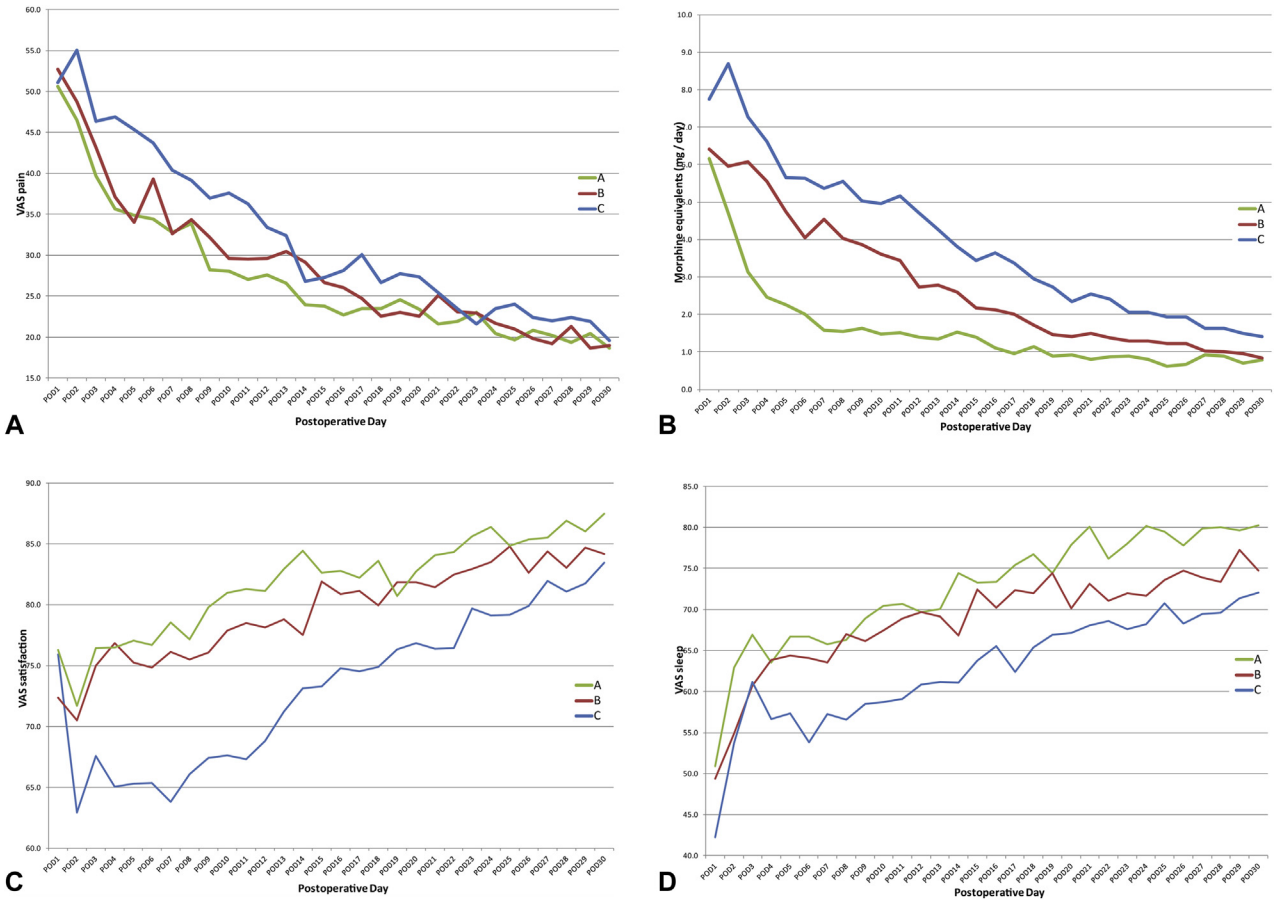

Figure 3. Thirty-day postoperative daily assessments. (A) Mean daily visual analogue scale (VAS) pain scores, 100-mm VAS ranging from 0 to 100 (higher scores indicating greater pain intensity). (B) Mean daily IV morphine-equivalent use. (C) Mean daily VAS satisfaction scores, 100-mm VAS ranging from 0 to 100 (higher scores indicating more satisfaction). (D) Mean daily VAS sleep scores, 100-mm VAS ranging from 0 to 100 (higher scores indicating more satisfaction). POD, postoperative day.

opiate use, and opiate refills were required for 10.5% of patients in group A, 6.5% of patients in group B, and 15.6% of patients in group C. In addition, mean time to discontinuation of tramadol was significantly shorter for group A (1.64 weeks) compared with group B (2.40 weeks) and group C (2.38 weeks) ($p = 0.04$ and $p = 0.02$, respectively). After 90 days, 2 patients (2.7%) in group A, 1 patient in group B (1.3%), and 4 patients (5.3%) in group C had not discontinued tramadol use, and tramadol refills were required for 11.8% of patients in group A, 5.2% of patients in group B, and 5.2% of patients in group C.

Secondary outcomes

Patient satisfaction and sleep quality

There was no significant difference in satisfaction ($p = 0.67$) or sleep quality ($p = 0.21$) between groups on POD 1 (Figs. 3C, 3D). Daily satisfaction during the first 30 days postoperatively was higher for group A (Coeff 1.26; 95% CI 0.69 to 1.82; $p < 0.001$) and group B (Coeff 1.08; 95% CI 0.52 to 1.64; $p < 0.001$) relative to group C, and there was no significant difference between groups A and B (Coeff 0.18; 95% CI −0.39 to 0.74; $p = 0.53$). Similarly, sleep quality during the first 30 days postoperatively was better for group A (Coeff 0.67; 95% CI 0.18 to 1.15; $p = 0.008$) and group B (Coeff 0.56; 95% CI 0.08 to 1.05; $p = 0.02$) relative to group C, and again there was no significant difference between groups A and B (Coeff 0.10; 95% CI −0.39 to 0.59; $p = 0.68$). Post-hoc testing can be found in eTable 2 and eDocument 3.

Adverse effects and complications

Mean composite ORSDS scores for groups A, B, and C were 0.22, 0.31, and 0.33, respectively, for week one, 0.10, 0.12, and 0.15, respectively, for week two, 0.07, 0.08, and 0.12, respectively, for week three, and 0.05, 0.08, and 0.10, respectively, for week 4. Across all weeks, the composite

ORSDS score for group A was significantly lower than that for group C ($p = 0.005$), but group B and group C did not differ ($p = 0.13$). Although there was also no statistically significant difference in composite ORSDS score between groups A and B ($p = 0.19$), the composite ORSDS score for group A was marginally lower than that for group B in week 1 ($p = 0.05$). Additional comparisons of weekly composite ORSDS scores can be found in eFigure 1.

The most common opiate-related symptoms were fatigue, drowsiness, and difficulty with concentration (Fig. 4). In comparison with group C, group A patients reported significantly less fatigue ($p = 0.004$), difficulty with concentration ($p = 0.022$), nausea ($p = 0.006$), urinary retention ($p = 0.009$), and confusion ($p = 0.027$). Group A patients also reported significantly less difficulty with concentration ($p = 0.017$), urinary retention ($p = 0.008$), and confusion ($p = 0.009$) than group B patients. However, there was no significant difference in the severity of any one symptom between groups B and C. Symptom-specific ORSDS scores for each of weeks 1 through 4 can be found in eFigure 1.

Additionally, gastrointestinal (GI) upset was reported on 3.6% of patient-days for group A, 4.4% of patient-days for group B, and 7.2% of patient days for group C. Severe GI upset was reported on only 0.45% of patient-days for group A, 0.17% of patient-days for group B, and 0.45% of patient-days for group C. Daily compliance with non-opioid medications, such as non-steroidals, can be found in eFigure 2.

During the 90-day postoperative period, there were 2 emergency department (ED) visits (2.6%) in group A, 3 ED visits (3.8%) in group B, and 5 ED visits (6.3%) in group C ($p = 0.50$). Additionally, there were 3 hospital readmissions (3.9%) in group A, no readmissions (0.0%) in group B, and 4 readmissions (5.1%) in group C (p = NS). There were no ED visits specifically for pain or GI bleeding (a complete list of adverse events can be found in eTable 3).

Patient-reported function and quality of life

There was no difference in baseline HOOS between groups, with scores of 53.0 points, 52.3 points, and 50.5 points, for groups A, B, and C, respectively ($p = 0.54$). After 1 month, improvements in HOOS from baseline, 23.9 points for group A, 23.3 points for group B, and 24.6 points for group C, did not differ ($p = 0.86$).

DISCUSSION

Opiate abuse continues to be a growing national concern, and much of the blame can be levied on healthcare providers who have been slow to change practice standards. In the OPIOID trial, we found that a scheduled-dose multimodal analgesic regimen, even with a policy of prescribing only a 2-day supply of opiates, provided significantly better pain relief after THR than the traditional approach of prescribing opiates as needed. Although the scheduled-dose multimodal approach in and of itself reduced daily opiate use and duration of use and improved satisfaction and sleep, the benefits were augmented with a minimal opiate supply policy.

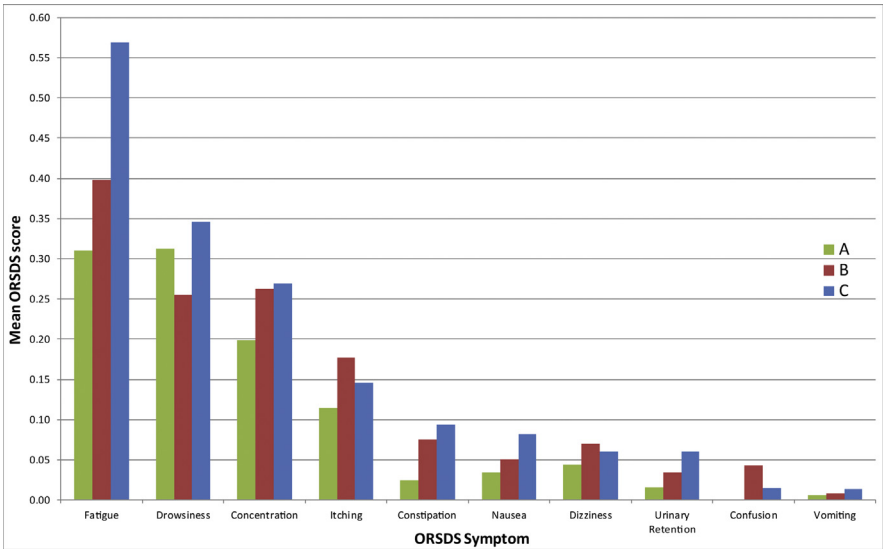

Figure 4. Opiate-Related Symptom Distress Scale (ORSDS) symptom-specific scores ranging from 0 to 4 (higher score indicates worse severity). Scores are provided as a daily mean during the 30 postoperative days.

Consequently, patients in the minimal opiate supply group reported significantly fewer adverse opiate-related effects, in particular fatigue and drowsiness. Clearly, opiate supply significantly impacts postoperative consumption habits, likely because it dramatically redefines patient expectations for pain. The role of establishing reasonable patient expectations for postoperative pain, which can be critically influenced by trusted providers, cannot be overemphasized. Importantly, a reduced opiate supply did not jeopardize pain control; no patients required ED visits for uncontrolled pain and few patients required prescription refills. Analgesic intervention also had no impact on return of hip function. Therefore, our results serve to controvert the conventional belief that opiates are a central, or even more so, an essential component of analgesia after discharge from elective hip operation. Based on our findings, it is now time to relinquish the unsubstantiated reliance on traditional opiate analgesia after elective surgical procedures.

It is evident that as much as 5% of opiate-naïve patients can become chronic abusers after hip operations, and duration of use is highly correlated with subsequent abuse.[6-8] Mean duration of opiate use for patients receiving multimodal analgesia was about half of that in the traditional opiate group without multimodal therapy. Accordingly, not a single patient in the minimal opiate policy group and 1.2% of patients in the traditional multimodal group continued opiate medications beyond 90 days, compared with 2.6% of patients in the traditional opiate without multimodal group. However, the relatively small size and short follow-up of this trial did not allow for a definitive comparison of risk for chronic abuse.

Despite its efficacy, physicians might be concerned about the potential toxicity of prolonged use of COX-2 inhibitors and acetaminophen. COX-2 inhibitors can cause GI intolerance and bleeding, and surgical patients can be at increased risk from the stress of operation and VTE prophylaxis.[22-24] However, COX-2 inhibitors were well tolerated in this study, with no episodes of bleeding and no increase in GI upset. In our own internal audit of 3,018 cases performed from 2015 to 2016, the risk of postoperative GI bleeding was 0.07% after THR. The potential for GI morbidity was minimized by prescribing meloxicam, with its improved GI risk profile, for only 2 weeks and in conjunction with a proton pump inhibitor.[25] There is some evidence that co-therapy with a proton pump inhibitor can reduce the incidence of major GI side effects in high-risk patients.[26,27] Finally, 8 patients requiring VTE prophylaxis with an agent other than aspirin or a history of a GI bleed were not prescribed COX-2 inhibitors and were ineligible for this study. Although there have been reported cases of hepatotoxicity and even fulminant hepatitis with therapeutic doses of acetaminophen, acetaminophen is generally very safe and well tolerated.[28,29]

There are several reasons for our decision to undertake the pragmatic design of a cluster-randomized trial as opposed to a traditional randomized controlled trial. First and foremost, this study design was critical for maintaining the integrity and ethical foundation of authorized deception without risk for subject contamination.[30] Cluster randomization also simplified discharge prescriptions and refills to prevent medication errors, as all patients from each surgeon received the same regimen during the allotted period, even those declining study participation. Although one major pitfall of cluster randomization is the potential for recruitment bias, the implementation of cluster crossover served to mitigate this risk.[31]

Authorized deception was essential to avoid response expectancy and prevent selection bias based on regimen allocation, as medication blinding was not practical. A patient's preconception of the inadequacy of their allocated analgesic regimen would interfere with the impartiality of their judgments and alter consumption habits. Instead, establishing the prescribed analgesic regimen as the "standard of care" served to reinforce an expectation of efficacy. Additionally, we expect patients would elect not to participate after randomization if group assignment did not match their preference, resulting in dropout bias. However, the decision to enroll or decline participation in this study did not impact discharge analgesia, as patients declining participation still received the same standard of care regimen for that time interval (eliminating risk for dropout bias). In adopting the practice of authorized deception, the issue of informed consent and patient autonomy was considered carefully by study investigators and the IRB.[32] In current practice, patients do not have absolute autonomy in selecting a postoperative analgesic regimen, especially with regard to opiate prescription. In fact, by providing consent for operation, patients generally agree to standard of care practices implemented by their surgeon, who must act as a responsible surrogate. In this study, surgeons provided consent to implement each of the low-risk interventions as their own standard of care.

A major limitation is that the small number of surgeon clusters did not make it possible to model random slopes for surgeon, as would typically be done in a 3-level randomized cluster trial design. In addition to limitations inherent to study design, the major limitation of

this study was our reliance on patient report of daily opiate consumption. However, daily use was compared with pill counts at the end of the first month, and patients were contacted directly to resolve obvious discrepancies.

CONCLUSIONS

Scheduled-dose multimodal analgesia after discharge from elective hip operation provided superior pain control with less opiate use compared with a traditional PRN opiate regimen. In addition, a policy of prescribing a minimal opiate supply served to further curtail opiate use and, consequently, its adverse effects without compromising the net benefit on pain control. It is abundantly clear that it is now time for surgeons to forego the traditional reliance on opiates and embrace a more balanced, evidence-based approach to analgesia after elective surgical procedures. Based on evidence from this study, patients undergoing elective procedures should be provided a scheduled-dose multimodal analgesic regimen at discharge, which can be supplemented with a limited opiate supply if necessary for emergency pain relief in the immediate postoperative period.

Author Contributions

Study conception and design: Fleischman, Tarabichi, Foltz, Makar, Hozack, Austin, Chen

Acquisition of data: Fleischman, Tarabichi, Makar

Analysis and interpretation of data: Fleischman, Tarabichi, Foltz, Makar, Hozack, Austin, Chen

Drafting of manuscript: Fleischman

Critical revision: Fleischman, Tarabichi, Foltz, Makar, Hozack, Austin, Chen

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APPENDIX

Additional investigators in the Opioid Prescription in Orthopedic Surgery after Discharge Research Group who assume responsibility for the overall content and integrity of the article are as follows: Andrew M Star, MD, Rothman Institute, Philadelphia, PA; Max Greenky, MD, Rothman Institute, Philadelphia, PA; Brian Henstenburg, MD, Rothman Institute, Philadelphia, PA; Matteo Petrera, BS, Rothman Institute, Philadelphia, PA.

eDocument 1. COMPLETE EXCLUSION CRITERIA

Chronic opiate use other than tramadol within 3 months before surgery (tolerance)
Contraindication to COX-2 inhibitors, including history of clinically significant bleeding
Patients requiring "potent" anticoagulation with agents other than aspirin for venous thromboembolism prophylaxis
Other contraindications to protocol medications (tramadol contraindication permitted)
No access to computer for online daily questionnaires
Simultaneous, bilateral total hip replacement
Extended postoperative hospitalization (more than 4 days)
Discharge to a rehabilitation facility or other long-term care facility
Revision total hip replacement
Conversion total hip replacement with removal of previously implanted hardware
Sensory or motor function of operative limb

eDocument 2. DETAILED STATISTICAL MODEL AND ANALYTICAL METHODS

Descriptive statistics were presented for each of the 3 intervention groups. Mean and SD was provided for normally distributed characteristics and median and interquartile range were provided for skewed data. To determine whether there were any group baseline differences, comparisons of normally distributed continuous variables were analyzed by ANOVA and skewed variables (distribution of which cannot be normalized with data transformations) were analyzed with Kruskal-Wallis test. Chi-square test was used to compare the 3 groups on categorical variables. Any significant omnibus test was followed by focused post-hoc testing to distinguish significant group differences (eg *t*-test, Mann-Whitney U test, independent proportions). Any variable that proved to be significantly ($p < 0.05$) different between the groups at baseline was considered as a potential confounder in subsequent analyses.

This study was powered as a superiority trial contingent on a power to detect group differences in VAS pain with a 2-tailed α level of 0.05 denoting the probability of type I error, 90% power level, and a within-subject correlation of 0.5 among repeated outcomes measures for a single patient. Assuming a small to moderate effect size ($d = 0.4$), the necessary sample size was 76 patients per group, with an expected 10% attrition rate. Despite the 3-arm design, the study was powered to test an interaction effect between 2 groups, which was then extrapolated for 3 groups. As the number of surgeon clusters that could participate at our institution was fixed, and clustering within surgeon was not expected to explain variance among the primary outcomes, we did not attempt to consider patient clustering within surgeon in performing a power analysis.

Before executing the primary outcomes analyses, preliminary analyses were conducted to carefully screen all variables, including an examination of outliers and the application of transformations to normalize any variable with poor distributional properties. If transformations failed to achieve normality, any non-normal variable was broken down into categories and/or alternative nonparametric tests were used to examine outcomes for these variables.

The primary analysis was performed using an intention-to-treat design. The primary analyses compared changes in VAS pain scores and morphine-equivalent opiate use between groups during the entire 30-day period. The null hypothesis was that daily pain scores and opiate use would be equivalent for all 3 groups. To determine whether there was differential change over time across groups (accounting for daily repeated outcomes measurements), the primary analyses were performed using linear mixed models conducted separately for each outcomes measure, specifying fixed effects for group (A, B, C), random intercept and slopes for day (0 to 30 days after discharge), and their interaction. Only potentially confounding variables that had a significant association with the primary end point ($p < 0.2$) and/or were significantly different between the groups at baseline were included in the final model. As such, the model adjusted for covariates (BMI [$p = 0.03$] and length of stay [$p = 0.16$]), which distinguished groups at baseline at $p < 0.2$, used restricted maximum likelihood estimation and modeled an unstructured variance-covariance matrix, which fit the data best. The primary reported end point was the coefficient from the linear mixed model. Coefficients from linear mixed models (whether fixed and random) are interpreted in the same way as a β-coefficient from traditional linear multiple regression.

Each mixed model specified the main effects of treatment (protocols A, B and C), time (0 to 30 days), and their interaction to test for differential improvement/change by treatment. Preliminary linear mixed models were conducted to determine the best-fitting covariance matrix, as well as explore the fitting of random vs fixed intercepts and slopes. Based on an analysis of intra-class correlation, the proportion of variance in outcomes accounted for by clustering within surgeon was essentially nil, and therefore clustering by surgeon was not included in the statistical model. The intra-class correlation for surgeon per se was <0.1 (0.018 for pain and 0.038 for morphine equivalent utilization). In essence, almost none of the variance I outcomes could be accounted for by clustering within surgeon. In addition, the small, fixed number of surgeons did not allow for an estimate of the intra-class correlation for surgeon clusters, as model convergence was prohibited. Although treatment was assigned at the level of surgeon, it was not possible to model random slopes for surgeon or patient nested within surgeon, as is typically done in a 3-level randomized cluster trial design, given the small number of those surgeon clusters. As part of our pragmatic cluster randomized study design and in balancing the need for proper randomization while maintaining the integrity of authorized deception and simplifying the care process, we instead modeled clustering during the 30-day follow-up period within patient.

We also performed post-hoc ANOVA to compare intervention groups on each individual postoperative day, and an analysis of covariance was used for a comparison of time to discontinuation of opioid medications and tramadol, defined in weeks. For secondary outcomes that involve count or binary data, generalized linear mixed models, which include the same terms and covariates (including the key time by group interaction) were conducted. For example, reports of side effects were expected to be rare, and this secondary end point required a nonparametric approach. Linear mixed models and generalized linear mixed models have multiple advantages over traditional repeated measures, such as the ability to include patients with missing outcomes data and flexibility in specifying the covariance matrix. All analyses for this clinical trial were performed using SPSS, version 23 (IBM Corp).

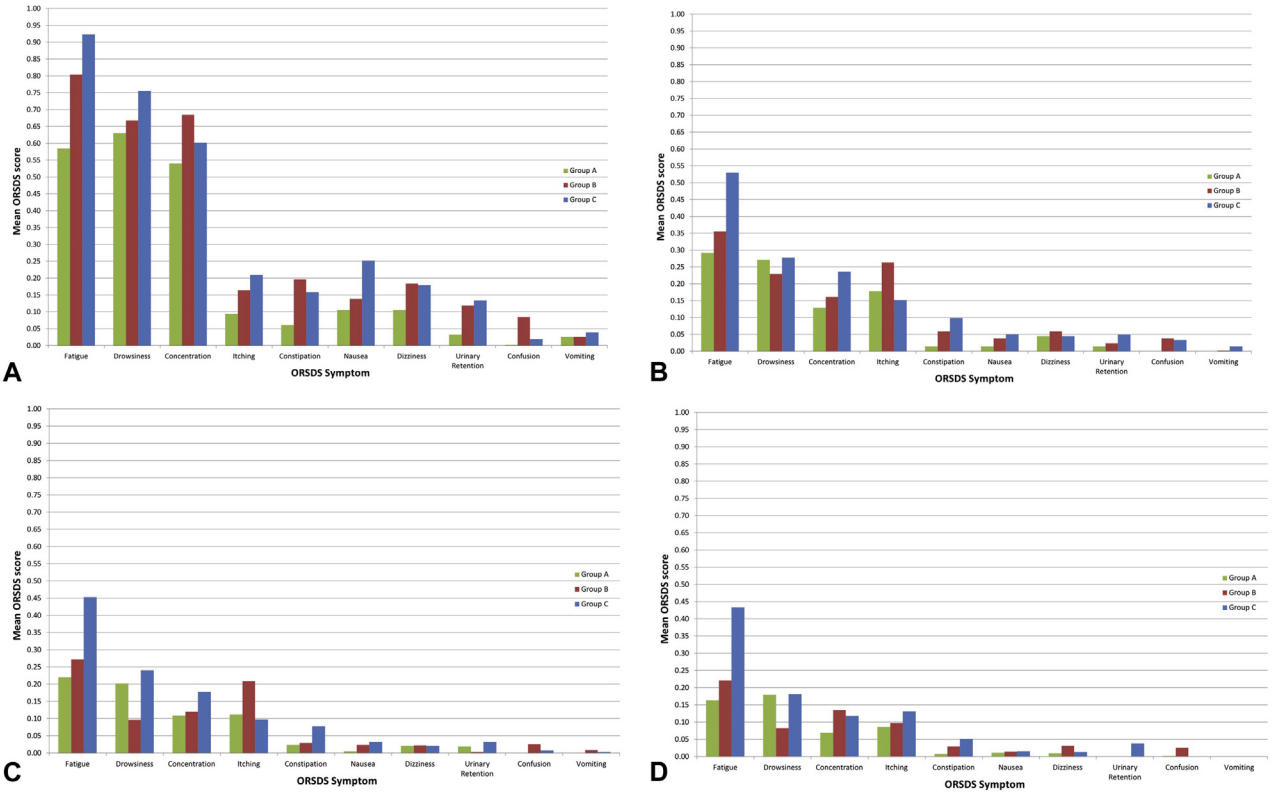
eDocument 3. SUPPLEMENTAL ANALYSES

Group and time interaction (rate of change) in mixed model analysis

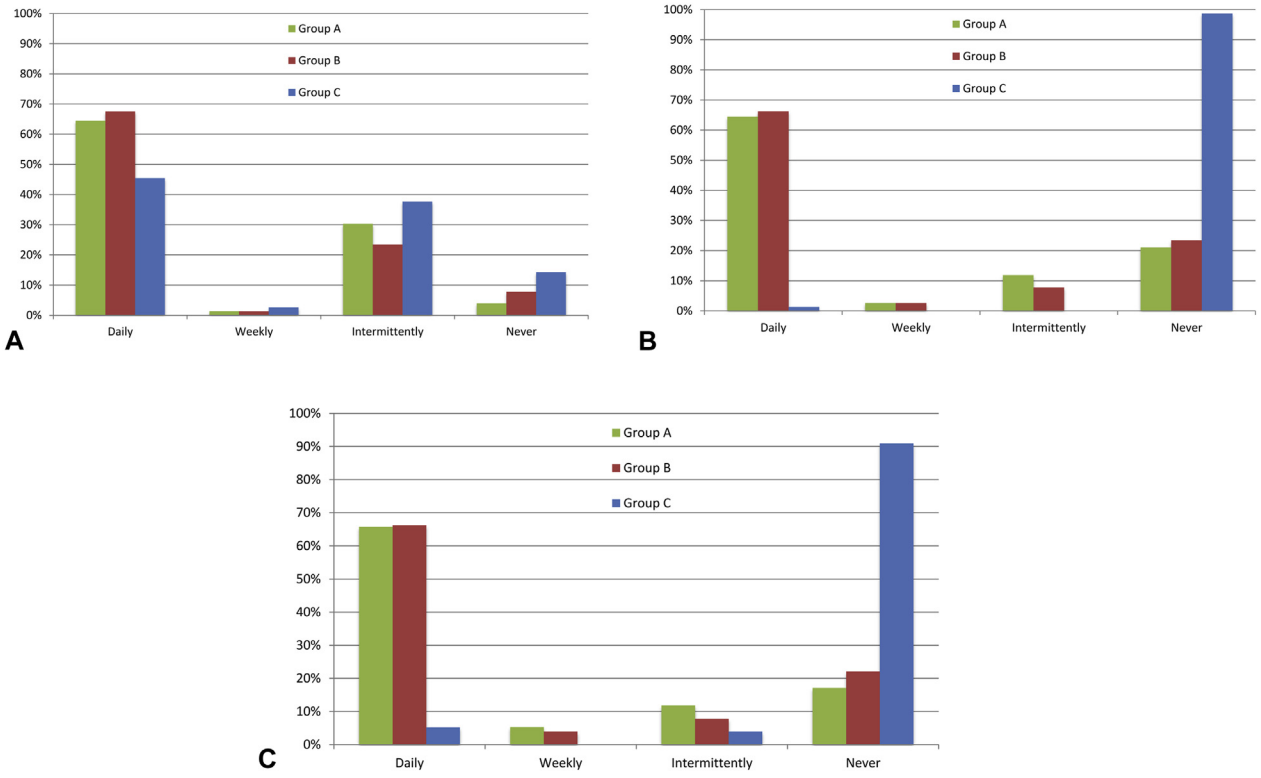
The interaction between group and time was not significant for VAS pain ($p = 0.19$), patient satisfaction ($p = 0.13$), or sleep quality ($p = 0.16$). However, the interaction between group and time was significant for daily morphine equivalents ($p = 0.04$), with group A having a quicker reduction in opioid consumption in the first 9 days than both group B (Coeff -0.04; $p = 0.02$) and group C (Coeff -0.04; $p = 0.035$).

Post-hoc testing of patient satisfaction and sleep quality

In post-hoc testing, group A reported significantly higher satisfaction than group C on PODs 3 to 26 and 28. Additionally, group B reported significantly higher satisfaction than group C on PODs 3 to 13, 15 to 22, and 25. However, there was no significant difference in satisfaction between groups A and B on any postoperative days. Additionally, group A reported significantly better sleep quality than group C on PODs 5 to 30. Group B reported significantly better sleep quality than group C on PODs 6, 8 to 12, 15, 17, and 19. Finally, group A reported significantly better sleep quality compared with group B on POD 14, 20, 21, and 24.



eFigure 1. Opioid-Related Symptom Distress Scale (ORSDS) score by postoperative week. (A) In week 1, there was a significant difference between the composite ORSDS scores between groups A and C ($p = 0.001$) and a marginal difference between groups A and B ($p = 0.05$), but no difference between groups B and C ($p = 0.30$). Composite ORSDS: group A, $p = 0.22$; group B, $p = 0.31$; and group, C $p = 0.33$. (B) In week 2, there were no significant between-group differences in composite ORSDS ($p = 0.06$). Composite ORSDS: group A, $p = 0.10$; group B, $p = 0.12$; and group C, $p = 0.15$. (C) In week 3, there were no significant between-group differences in composite ORSDS ($p = 0.35$). Composite ORSDS: group A, $p = 0.07$; group B, $p = 0.08$; and group C, $p = 0.12$. (D) In week 4, there were no significant between-group differences in composite ORSDS ($p = 0.20$). Composite ORSDS: group A, $p = 0.05$; group B, $p = 0.08$; and group C, $p = 0.10$.



eFigure 2. Frequency of use and compliance with non-narcotic medications. Compliance with non-narcotic medication regimens was tracked qualitatively for the first month postoperatively. For patients assigned to multimodal therapy in groups A and B, daily compliance with (A) acetaminophen was 64.5% and 67.5%, respectively, daily compliance with (B) meloxicam was 64.5% and 66.2%, respectively, and daily compliance with (C) gabapentin was 65.8% and 66.2%, respectively. Accordingly, a subset of patients had never use the prescribed non-narcotic medications (not including intermittent or weekly compliance); acetaminophen was not used by 3.9% and 7.8% of group A and B patients, respectively, meloxicam was not used by 21.1% and 23.4% of patients, respectively, and gabapentin was not used by 17.1% and 22.2% of patients, respectively. For patients in group C who were instructed to use acetaminophen as needed, daily use was 45.5%, and 14.3% did not to take any acetaminophen. Although meloxicam and gabapentin were not prescribed for group C, 1.3% and 5.2% of patients, respectively, used these medications, likely from earlier prescriptions.

eTable 1. International Committee of Medical Journal Editors Data Sharing Statement

Question	Answer
Will individual deidentified participant data (including data dictionaries) be shared?	Yes, for acceptable research meta-analyses
What data in particular will be shared?	All primary and secondary outcomes data
Will additional related documents be available (eg study protocol, statistical analysis plan)?	Study protocol and statistical analysis plan
When will the data become available and for how long?	Immediately after publication with no end date
Who will have access to the data?	Researchers with acceptable proposals
For what types of analyses will the data be available?	Meta-analyses only
By what mechanism will the data become available?	Proposals should be submitted to corresponding author

eTable 2. Supplemental Analysis: Additional Covariates Included in Mixed Model Analysis

	BMI		Length of hospital stay	
Outcomes	**Coefficient**	**p Value**	**Coefficient**	**p Value**
Daily pain	0.003	0.90	0.35	0.05
Daily morphine equivalent use	0.017	0.09	0.27	0.001
Daily satisfaction	−0.002	0.92	0.35	0.078
Daily sleep quality	0.002	0.91	0.18	0.30

Only BMI and length of hospital stay met criteria ($p < 0.2$ between groups) for inclusion in the mixed model.

eTable 3. Individual Adverse Events for Each Group

Adverse event, group
Hospital readmission
Group A
Periprosthetic joint infection
Periprosthetic fracture
Small bowel obstruction
Group B
None
Group C
Atrial fibrillation
Tibial plateau fracture
Acute renal failure
Periprosthetic fracture
Emergency department visit
Group A
Stomach pain
Foot burn
Group B
Chest pain
Influenza
Uncomplicated fall
Group C
Syncope
Pre-syncope
Sleeping aid overdose
Influenza
Fall/muscle tear