Observational Study

The Effect of Preoperative Opioid Dosage on Postoperative Outcomes in Patients Undergoing Knee Surgery

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Background: Opioid prescription before knee replacement surgery is associated with longer hospital stays, more postsurgical pain, and a higher rate of complications. Despite the growing evidence against opioids, they remain popular preoperative pain management prescriptions.

Objectives: The purpose of this study was to examine the effects of dosage of preoperative opioid use on orthopedic knee surgery pain control and postoperative outcomes and complications.

Study Design: Observational, retrospective evaluation.

Setting: University of Wisconsin Madison hospitals.

Methods: The patients underwent orthopedic knee surgery between May 1, 2014 and April 30, 2015. We randomly selected 197 patients and divided them into 2 groups that had preoperative opioid dosages of either low dose ≤ 120 mEq morphine (MME) or high dose >120 MME. Of 197 patients, 100 were in the low dose morphine group, whereas 97 were high dose. The cutoff at 120 MME was calculated to be the median dosage across all patients. The primary outcomes were compared, differences in postoperative pain control, and range of motion (ROM). Secondary outcomes included anesthetic complications, length of hospital stay, postoperative opioid dose, and postoperative complications.

Results: There were no statistically significant differences between the groups with regard to postoperative pain control, ROM, and immediate postoperative complications. Both groups showed similar length of hospitalization (2.199 to 2.304 days; $P = 0.374$), rate of postoperative infection, and joint intervention. The high dose group was more likely to have postoperative hemarthrosis and emergency department (ED) visits. However, the low dose group was more likely to have hypertension concurrently.

Limitations: Because the study length was restricted to one year, the lack of data on longer term prognosis may limit extrapolation of data. Subjectivity of pain is difficult to measure and compare objectively. This study was not randomized prospectively, which may bias certain results due to unobserved differences.

Conclusions: Preoperative opioid dose did not affect postoperative pain control or ROM in patients who received knee surgeries. Higher preoperative opioid doses were associated with more hemarthrosis and ED visits. Further exploration into quality of life indices and surgical complications such as need for revision may be a fruitful avenue.

Key words: Opioids, analgesic, knee pain, total knee replacement, knee surgery, pre-operative opioids, knee outcomes

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Osteoarthritis (OA) is the leading joint disorder in the United States, and millions of patients suffer from pain, stiffness, and decreased quality of life (1). Currently, the only definitive treatment of OA of the knee is total knee arthroplasty (TKA). Although TKA is an effective operation to relieve pain and recover function, it is often considered for cases refractory to nonsurgical treatments such as physical therapy, steroid or hyaluronic acid injections, nonopioid and opioid prescriptions. Guidelines for opioid prescription for knee OA prior to TKA are still inconsistent, but the Centers for Disease Control and Prevention (CDC) recommendations from 2016 seeks to offer a starting point for primary providers (2). Historical data from 2003 to 2009 showed that opioids were an increasingly used modality for the treatment of knee OA (3). A more recent study (4) demonstrated a stable prescription rate over 2007 to 2014. If the rates were to remain stable, absolute prescriptions will dramatically increase in the face of increasing prevalence of doctor-diagnosed arthritis, numbered from 54.4 million for 2013 to 2015 (5), including 30.8 million OA (6), to a projected 78.4 million by 2040 (7). Unfortunately, opioid usage may also be complicated with nausea, somnolence, constipation, cardiovascular events, respiratory depression, and mortality (8). Furthermore, the costs of OA management and treatment are quite substantial, with costs related to primary and revision TKA constituting 69% of total direct medical costs attributable to OA (9). Therefore, investigating factors to improve post-TKA outcomes will not only physically benefit the patient but also help reduce costs.

TKA postoperative outcomes are negatively impacted by chronic preoperative opioid use. High-risk opioid use is associated with even more postoperative morbidity and resource use after elective orthopedic surgery (10). In regard to orthopedics surgery, recent studies have found an association between opioid prescription before knee replacement surgery with longer hospital stays, more postsurgical pain, a higher need for additional procedures, and a higher rate of complications (11-15). These data were compared with a set of patients who were not opioid-dependent or at lower opioid doses. Comparable results have been found in patients undergoing spinal surgery: a larger dose of preoperative opioid is significantly associated with an increase in postoperative patient-reported adverse outcomes (outcomes were calculated based on patient-reported questionnaires and included items related to quality of life, complications, etc.) (16). This correlation between opioid dosage and patient outcome has also been shown in reverse shoulder arthroplasty (17), and even in nonsurgical functional restoration programs for musculoskeletal disorders (18). Most significantly, opioids do not appear to be cost-effective in OA patients without comorbidities (16). Pain catastrophizing scale has been shown to be higher for opioid users, as well as a 6-month reduction in pain relief after TKA (11). In addition, opioid usage was associated with increased TKA revisions (19-21). Given that preoperative opioid use has adverse effect on postoperative outcomes, proper opioid prescription management becomes very important.

Managing opioid prescriptions appropriately and accurately is a vital public health measure in the growing prevalence of opioid abuse and dependence (11). Although dependence and hyperalgesia are established opioid complications that interfere with pain relief, low dose preoperative opioids can induce hyperalgesia as well (22). It is important to understand the effect of preoperative opioid dosage on postoperative outcomes that have clinical implications for treatment strategies. Although there are ample manuscripts detailing the adverse effects of preoperative opioid use on surgical outcomes, there are fewer published on the effect of preoperative opioid dose on postoperative adverse outcomes. The goal of this study was to gain a better understanding between preoperative opioid management and postoperative outcomes, which can aid in preoperative anesthesia protocols. We hypothesized that patients with higher preoperative opioid treatment will have worse postoperative outcomes and complications as compared with a control group of similar patients with lower preoperative opioid treatment undergoing orthopedic knee surgery. To test our hypothesis, we reviewed 197 patients who underwent orthopedic knee surgery and assessed the effect of chronic preoperative opioid dosage on TKA surgical pain control and postoperative outcomes and complications.

Methods

Study Design

This was a retrospective study in which we reviewed 197 patients who underwent knee surgery at University of Wisconsin (UW) hospitals between May 1, 2014 and April 30, 2015. The study received an institutional review board exemption (protocol number: 2015-0522). Patients were divided into 2 groups that had preoperative opioid dosages of either ≤120 mEq morphine (MME) (low dose)

or >120 MME (high dose). Although this comparative number was higher than the 90 MME limit that the CDC recommended, the CDC value only applied to opioid naive patients, which many patients of this study were not. Moreover, the Overutilization Monitoring System continues to employ 120 MME over the previous 12 months or 90 consecutive days to determine opioid users (23). The 120 MME cutoff can also be seen in studies stratifying opioid levels (15,18). Therefore, we chose 120 MME as this was the median dose of opioids used before surgery in study subjects. Of the 197 patients, 100 were in the low dose group, whereas 97 were in the high dose group.

Outcomes

The primary outcomes were compared differences in postoperative pain control and range of motion (ROM). Secondary outcomes included anesthetic complications and morbidities, length of hospital stay, postoperative opioid dose, and postoperative complications.

Statistical Analysis

Data were collected from electronic medical records and entered in an Excel spreadsheet (Microsoft Corporation, Redmond, WA). Data were analyzed using Statistical Package for the Social Sciences (IBM Corporation, Armonk, NY), using 2-tailed t tests for numerical data, and the chi-squared tests for categorical data. Data are expressed in means with standard errors. *P* value was considered significant if ≤ 0.05.

Results

Patient Demographics

Patients ages were between 50 and 85 years, and all of them underwent a knee surgery. There were no significant differences in patient characteristics including gender, race, body mass index, and tobacco usage (Table 1). The only significant difference was that patients on lower dose opioids tended to be younger than the higher dose group, 62.28 versus 68.27 ($P < 0.05$). Despite lack of prospective randomization, the patient populations had similar characteristics to approximate randomization. There were variations of knee surgeries performed (primary replacements, knee reimplantation, debridement, unicompartment Mako, etc.), but there was no statistically significant difference in types of principle knee surgery used across both groups. In addition, there was no statistically significant difference in the mode of anesthesia (general, spinal, monitored anesthesia care, regional or combined) used between both groups (Pearson chi-square, $P = 0.545$). Every patient also received appropriate femoral or saphenous blocks for postoperative pain control and epidural for intraoperative management. These were done in equal percentages between the 2 groups (Pearson chi-square, $P = 0.362$). Blocks are done by a single regional anesthesia team in the preoperative area with standard single-shot protocol.

Table 1. *Comparison between both groups in regard to sex, race and tobacco use.*

	Low dose opioid	High dose opioids	**P* value
Male	65	54	
Female	35	43	0.181
White	92	96	
African American	4	1	
Asian	3	0	
American Indian	1	0	0.12
No tobacco use	52	58	
Current smoker	3	6	
Former smoker	45	33	0.209

P* < 0.05 denotes a significant difference compared to controls **(bold)

With regard to comorbidities, there were no statistically significant differences between individual conditions between the 2 groups (Table 2). There was also no statistically significant difference in diabetic status between both groups ($P = 0.514$).

Mood disorders have been linked to opioid usage (24). The psychiatric conditions charted, such as depression (24-25), anxiety (26), panic disorder (27), and posttraumatic stress disorder (28), have all been associated with higher chronic opioid usage and preoperative opioid requirements. In one example, the prospective cohort study by Stark et al (26) compared factors contributing to persistent postsurgical opioid use and discovered that anxiety presented an odds ratio of 2.1 ($P < 0.05$). Therefore, to control for mood factor, we compared the umbrella "psychiatric" group, and they were comparable between the 2 groups. We subsequently compared the number of patients in each group for the individual psychiatric conditions and found no significant differences (Table 3).

Of all the comorbid conditions collected, there were statistically significant differences in hypertension, history of colonic polyps, and vitamin D defi-

ciency. Interestingly, the lower dosage group had more patients with hypertension (71 to 47; $P = 0.001$), colonic polyps (5 to 0; $P = 0.026$), and vitamin D deficiency (8 to 1; $P = 0.019$). Overall, the comorbidity comparisons indicated that both groups were well matched for baseline characteristics.

Table 2. *Comparison of baseline comorbidities between both groups.*

Comorbidities	Low dose opioid	High dose opioids	*P value
Had Cardiac conditions	24	21	0.970
Had Dyslipidemia conditions	56	48	0.145
Had Respiratory conditions	25	22	0.655
Had GI conditions	39	36	0.953
Had Psychiatric conditions	27	30	0.295
Hypertension	71	47	0.001
Vitamin D deficiency	8	1	0.019
Colonic polyps	5	0	0.026

*$P < 0.05$ denotes a significant difference compared to controls **(bold)**

Table 3. *Comparison of psychiatric conditions between both groups.*

Comorbidities	Low dose opioid	High dose opioids	*P value
Depression	21	21	0.881
Anxiety	12	15	0.462
Panic disorder	0	1	0.306
PTSD	0	3	0.075

*$P < 0.05$ denotes a significant difference compared to controls **(bold)**

ROM Pre- and Postoperation

Generally, the difference in opioid dosage did not significantly affect ROM. Both groups showed a gradual improvement in maximum ROM from postoperative discharge to the one-year follow-up. Both groups were closely matched with most patients demonstrating ROM from 0 to 120 at one year. This suggested the different opioid dosages did not hinder the gain in function in either patient pool. Notably, the only significant difference was in preoperative minimum ROM, which favored the lower dosage group (1.760 vs. 3.010 degrees; $P = 0.029$) (Fig. 1).

Pain Scores Pre- and Postoperation

Overall Pain Scores

In general, there was no statistically significant difference in pre- or postoperative pain scores and control between both groups. The only point that differed in pain score was at the one-hour postoperative timeframe (1.80 vs. 1.06; $P < 0.05$). Time points used were taken in the preoperative phase, immediately postoperative to discharge (specifically postoperative 0 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 6 hours, day 1, and day 2), one week, 6 weeks, and one-year follow-up (Fig. 2). Over time, we can appreciate an overall decrease in pain levels to below a score of one in both groups at one year (0.910 low dose to 0.8333 high dose; $P = 0.976$). In fact, most patients reported little to no pain.

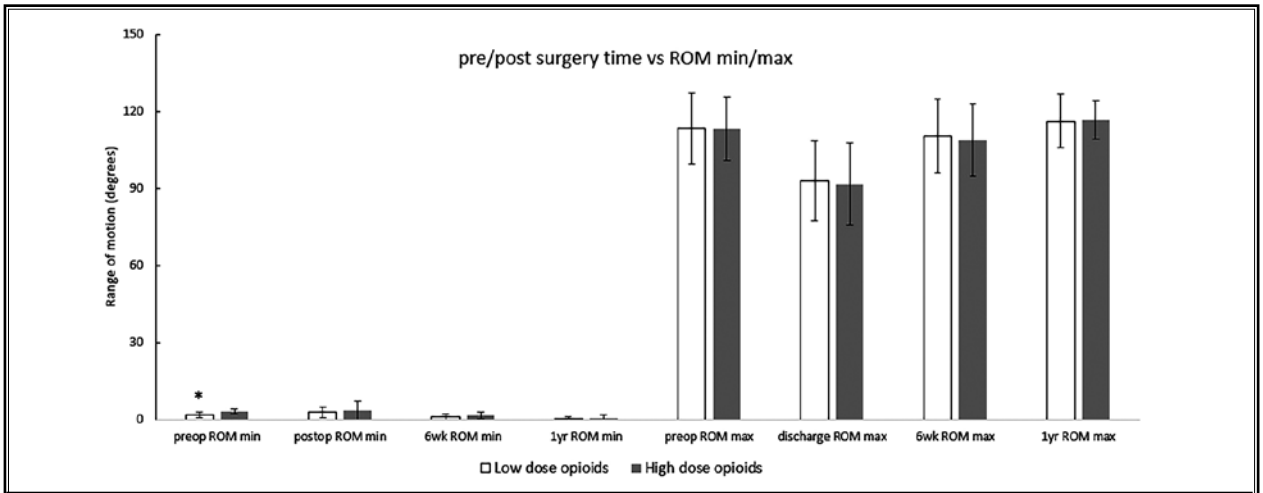

Fig. 1. Pre- and postknee surgery comparing ROM. White bars represent low-dose group, whereas gray bars represent high dose group. Values are expressed in means with standard errors. $P \leq 0.05$ denotes a significant difference compared with the other group (*).

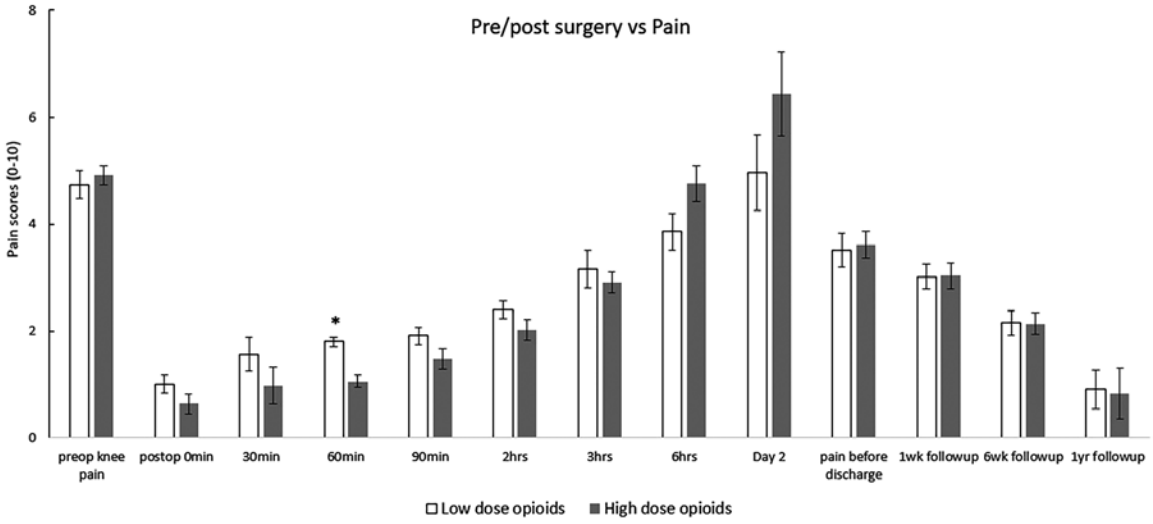

Fig. 2. Pre- and postknee surgery comparing pain scores. White bars represent low-dose group, whereas gray bars represent high dose group. Values are expressed in means with standard errors. $P \leq 0.05$ denotes a significant difference compared with the other group (*).

Intraoperative and Total Hospital Stay Dosage of Opioid

Patients in both low and high dose groups received the comparable amounts of intraoperative midazolam (1.020 to 1.155 mg; $P = 0.448$) and total hospital stay to discharge dosage of opioid (224.376 to 234.743 MME; $P = 0.753$) (Fig. 3). Patients in the lower dose group received similar amounts of intraoperative opioids (13.116 to 12.208 MME; $P = 0.491$) (Fig. 4).

Other Intraoperative Medications

In addition to intraoperative opioids and midazolam, all patients received bupivacaine for nerve block and propofol. In select patients, intravenous ketamine and lidocaine were used as well. Comparison of all the intraoperative medications did not show any significantly increased usage in either group (Table 4).

Postoperative Morbidities

Data points were gathered for presence of postoperative complications including nausea, vomiting, hypotension, chills, respiratory depression, and constipation. There were no statistically significant differences in the earlier mentioned morbidities between the 2 groups up to postoperative day 2.

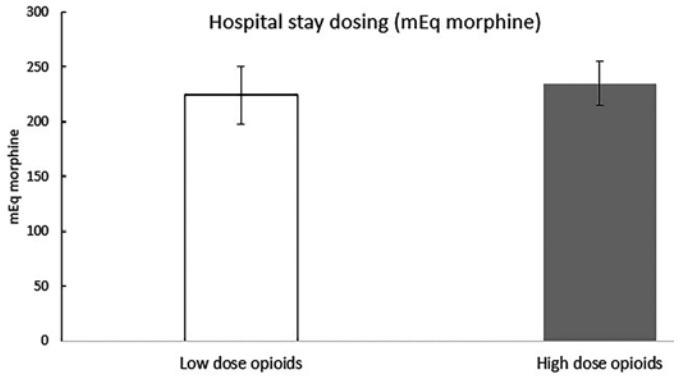

Fig. 3. Low and high dose opioid group and total hospital stay opioid usage. Values are expressed in means with standard deviation errors. $P \leq 0.05$ denotes a significant difference compared with the other group (*)

Length of Hospital Stay

Hospital stay length was defined as the time between the end of anesthesia to discharge. There were no differences in the number of hours spent in the hospital between the low and high dose groups (2.199 to 2.304 days; $P = 0.374$).

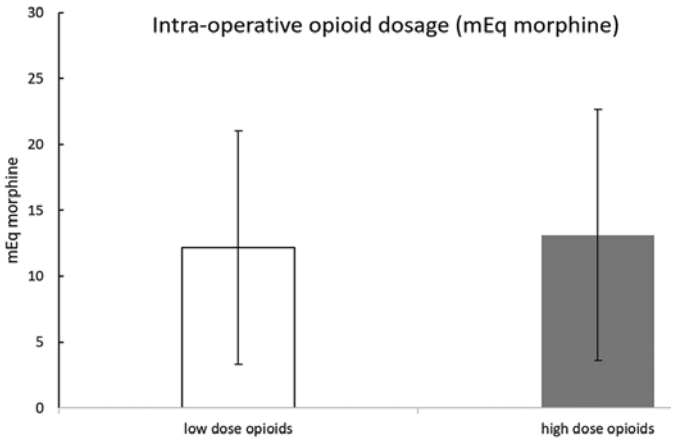

Fig. 4. *Low and high dose opioid group and intraoperative opioid usage. Values are expressed in means with standard deviation errors. $P \leq 0.05$ denotes a significant difference compared with the other group (*).*

Table 4. *Comparison of intra-operative medications.*

Intra-op Medications	Low dose opioid	High dose opioids	*P value
Ketamine (mg)	15.970 ± 26.279	14.938 ± 26.169	0.783
Propofol (mg)	725.780 ± 422.527	685.604 ± 456.008	0.523
Lidocaine 2% (mg)	32.400 ± 41.566	24.354 ± 30.986	0.127
Bupivacaine 0.5% (mg)	19.840 ± 5.846	19.255 ± 8.341	0.569

*$P < 0.05$ denotes a significant difference compared to controls **(bold)**

Postoperative Opioid Dosage

There were no significant differences in opioid dosages at the 6- and 10-week follow-ups (Fig. 5). At the 6-week follow-up, 62% of the low dose opioid group still received prescriptions versus 68.357% of the high dose group ($P = 0.295$). The average of the oral morphine equivalent (OME) in those with prescriptions was 71.808 (5 to 180) MME in the low dose group to 82.447 (10 to 240) MME in the high dose group ($P = 0.524$). At the one-year follow-up, 20% of the low dose opioid group were receiving prescriptions versus 26.237% of the high dose opioid group ($P = 0.354$). The average postoperative OME was 23.891 (5 to 260) MME for the low dose group to 45.375 (5 to 220) MME for the high dose group ($P = 0.103$) (Fig. 5). The patients at this time point had a large range in their prescription MME, thus there was a wide standard deviation to account for a few patients needing more opioids.

Cumulative One-Year Follow-Up Complications

Cumulative one-year postoperative infections and joint interventions were similar between the low and high dose groups, whereas the high dose group showed significantly more hemarthrosis and emergency department (ED) or urgent care visits (Table 5). The low dose group was complicated by cellulitis (2 cases) and suture abscess (2 cases), whereas the high dose group had cellulitis (2 cases), postoperative aspiration pneumonia with sepsis (one case), and community-acquired pneumonia (one case). The number of joint interventions was not significantly different and was a complication grouping that included irrigation and debridement (one case), manipulation under anesthesia (2 cases), and revision open reduction internal fixations for periprosthetic fractures (2 cases). However, the number of patients with hemarthrosis and prolonged wound drainage was significantly higher for the high dose opioid group (10 to 2; $P = 0.033$). This was mostly an early postsurgical complication that occurred before 6 weeks and resolved 2 to 3 weeks after the initial encounter with appropriate discontinuation of blood thinning medication. One case in the high dose group required an incision and debridement due to a possible complication with infection at the same time.

The high dose group also demonstrated a higher number of ED or urgent care visits (10 to 2; $P = 0.033$) up to the one-year follow-up. The visit complaints were limited to those that were related to or a complication of surgery and opioids. Patients with multiple ED visits were noted but charted once, this was mostly seen with the high dose group. As shown in Table 5, visit complaints for the low dose group were for falls (one case), lower extremity edema (one case), and acute knee pain (one case). The complains for the high dose group were for falls (one case), lower extremity edema (one case), acute knee pain (2 cases), dyspnea without clear diagnosis (2 cases), community-acquired pneumonia (one case), aspiration pneumonia (one case), deep venous thrombosis (one case), pulmonary embolisms (2 cases), and drug-seeking behavior (one case).

Loss to Follow-Up

Most patients do not receive primary care at UW clinics and hospitals, merely arriving for surgeries and appropriate follow-up.

Table 5. *Comparison of cumulative 1-year post-operative complications.*

Post-operative complications	Low dose opioid	High dose opioids	*P value
Infections	Cellulitis (2) Suture abscess (2) Total: 4	Cellulitis (2) Post-op aspiration pneumonia (1) CAP** (1) Total :4	0.272
Hemarthrosis	2	10	0.033
Joint interventions	Irrigation and debridement (1) Manipulation under anesthesia (1) Revision ORIF periprosthetic fracture (2) Total: 4	Revision w/ re-implantation due to infection (1) Manipulation under anesthesia (1) Total: 2	0.438
ED/Urgent Care visits***	Fall (1) Lower extremity edema (1) Acute knee pain (1) Total patients: 2	Fall (1) Lower extremity edema (1) Acute knee pain (2) Dyspnea (2) CAP** (1) Post-op aspiration pneumonia (1) Deep venous thrombosis (1) Pulmonary embolism (2) Drug seeking behavior (1) Total patients: 10	0.033

*$P < 0.05$ denotes a significant difference compared to controls (bold)
**CAP – community acquired pneumonia
***For ED/Urgent Care visits, some patients presented with multiple complaints and each complaint is charted separately. The total number listed towards the end represents the total number of patients for each group.

As a result, many follow-ups after one year, and some even before were missing from our database. The patients lost to follow-up at one year were comparable between the 2 groups (12.000% to 13.402%; $P = 0.088$). After one year, the next time point for follow-up would be 3 to 4 years, at which time we anticipate many more patients to be lost to follow-up.

Correlations

When we performed the Pearson correlation, we found positive correlation between preoperative opioid dose and postoperative opioid consumption in the hospital and pain scores on discharge, which was statistically insignificant for both (data not shown).

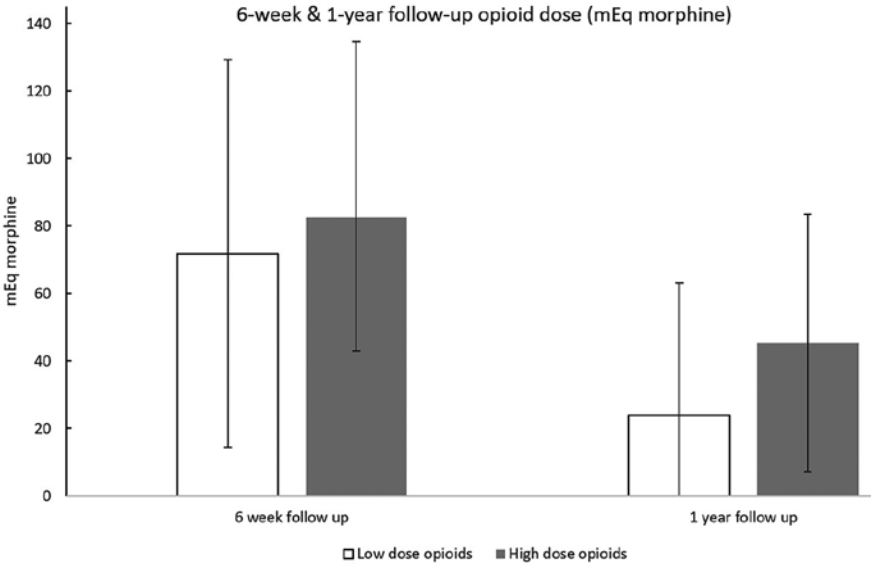

Fig. 5. *Low and high dose opioid group and 6-week and 1-year follow-up opioid usage. Values are expressed in means with standard deviation errors. $P \leq 0.05$ denotes a significant difference compared with the other group (*).*

Discussion

Primary Outcomes: ROM and Postoperative Pain

Our study was designed to investigate the effect of preoperative opioids dosage on pain control and outcomes after knee surgeries. The primary outcomes of this study were 2-fold. One was that high dose preoperative opioid usage did not affect postoperative and long-term follow-up ROM. The other was high dose preoperative opioid usage did not affect short-term and long-term postoperative pain control compared with lower dose preoperative usage.

Although ROM only represented a part of functional recovery, it was an important objective measure. Several studies have focused on the role of preoperative opioids on TKA outcomes, and not many specifically report the effect on ROM. Zywiel et al (12) reviewed 98 patients undergoing primary TKAs comparing patients with chronic opioid use (≥6 weeks) versus those who did not. They found no difference between the mean ROM at final follow-up for an average of 3 years, 107 to 111 (P = 0.223). This finding is reported with other studies that also found no difference in ROM between opioid and nonopioid patients (29). For many patients, refractory pain rather than the ROM was the primary issue. Normally, a full ROM for the knee is approximately 0 degrees of flexion to 130 degrees extension (30). Recovering ROM from TKA seemed to peak by 12 months (31), with some studies showing a plateau even earlier at 6 months (32). Preoperative ROM was also a factor in determining postoperative ROM recovery (33-34), and when preoperative ROM was high the postoperative gain in ROM is limited (32). For our cohort, the preoperative ROM was approximately 3 to 118 and was close to the normal ROM, thus the one-year ROM at 0 to 120 is not surprising. Although not statistically significant, there was an average of 2-degree gain in flexion and 3-degree gain in extension in both groups. Our data were similar to what has been previously reported in other studies in which the high ROM patients made less significant gains in ROM (32-34). Recovering that baseline ROM is expected but going beyond is less common.

Postoperative pain was a more commonly compared outcome, often a positive correlation with chronic opioid use. Zywiel et al (12) reported higher incidence of recalcitrant pain (8 to 0; $P < 0.001$) with referrals to pain management (10 to 1; $P < 0.001$). Smith et al (11) reviewed 156 patients comparing preoperative opioid use within 2 years of TKA. They found the nonopioid group had a lower 6-month Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain. These 2 studies were among the many that have found worse pain control with preoperative opioid use in TKA (13,17,29,35). In contrast, our study found no effect on postoperative short-term pain control by preoperative opioid dose. This result was similar to what has previously been reported (36). In this prospective observational study, Aasvang et al (36) found that preoperative opioid dose did not affect postoperative acute pain control use. Preoperative opioid did, however, increase the risk for postoperative pain at rest and walk and increased opioid consumption after TKA compared with preoperative opioid-free patients for the first 6 postoperative days. Except for one-hour postoperation, our study did not show a difference in pain scores for all time points including the one-year follow-up. Although not specifically orthopedic, Kelly et al (37) also reported lack of differences in opioid strength and postoperative outcomes. They compared patient populations on high, low, and no preoperative opioids undergoing anterior cervical decompressive surgery and found no change in pain scores (P = 0.355) and neck disability index scores (P= 0.181) at the 24-month follow-up. Our study did not stratify in opioid chronicity, but rather the preoperative daily dosage prescribed. With the exception of Kelly et al (37) and Nguyen et al (35), our results were different from previously mentioned studies (11-13,17,29,35) as all our patients were on opioids before surgery as our goal was to compare whether the dose of opioids will influence postoperative outcomes. This was different from aforementioned studies that compared opioid-dependent and opioid-naive patients before surgery. Although there are studies that have shown that higher preoperative opioid doses predict lower functional and qualitative outcomes (15,18), none specifically compare pain after TKA.

Secondary Outcomes: Length of Stay, Postoperative Opioid Use, and Morbidities

Our study was most similar to the studies done by Zywiel et al (12), Cozowicz et al (15), and Kim et al (14) that compared preoperative opioid use on postoperative outcomes. However, these articles all reported overall worse qualitative outcomes in preoperative opioid users such as length of stay (LOS), readmission, and infections. To our knowledge, our study was the only one showing no difference in length of hospitalization, postoperative OME, and some postoperative outcomes. Apart from Cozowicz et al (15), the other 2 explored opioid exposure rather than opioid dosage in their experimental groups (12,14).

LOS

There have been varying reports of preoperative opioid use on hospitalization LOS. Some studies discovered a difference (12,14,15), whereas others did not (24,33). Our study reported no difference in LOS for both groups as 2.199 to 2.304 days ($P = 0.374$). Zywiel et al (12) found that patients on chronic opioids had longer hospitalizations (4.3 vs. 3.4 days; $P = 0.013$), and a recent study by Kim et al (14) also demonstrated similar findings (2.6 vs. 2.90 days; $P = 0.017$). Cozowicz et al (15) compared preoperative opioid dosages among combinations of total hip arthroplasties (THA) and TKA (n = 1,035,578) in an observational study. They found LOS increased by 12% when comparing low to high dose opioids ($P < 0.001$). The difference in LOS between our study and Cosowiszce et al (15) may be owing to our limited power (n = 196 to n = 1,035,578). The latter study, however, combined data from TKA and THA, whereas our study focused solely on TKA. In contrast, our results were consistent with studies done by Manalo et al (29) and Zarling et al (38) in LOS, but both of which also compared chronic users to naive patients. Further clarifying the association between preoperative opioid dosage/chronic use and LOS is important as LOS is a predictor of persistent opioid use (39), as well as increased health care costs.

Postoperative Opioid Use

The postoperative opioid usage in our study was not significantly different during hospital stay and at subsequent follow-ups to the one-year mark. At 6 weeks, 62% of the low dose group and 68.357% of the high dose group still received prescriptions (71.808 to 82.447 MME, respectively). Most of our patients in both dosage groups gradually weaned off opioids by one year (80% for both), in correlation with gradual improvement in pain and ROM. At one year, both groups had similar OME at 23.891 to 45.375 MME, respectively. Regarding the persistence of opioid use, other studies have shown that chronic opioid use was associated with persistent use (14,38,40). At our current opioid dose comparison, there was no difference in prolonged opioid use postoperatively. The rate of opioid wean in our study is consistent with those of opioid-naive groups in other studies (14,38). Hansen et al (40) reported opioid cessation rates of 50% in occasional users and 30% of chronic users. The analgesic benefit of TKA played a large role, and although opioid cessation rates were insignificant between both groups, the low dose group had higher rates and lower OME requirement.

Postoperative dosages of OME generally decreased as postoperative time increased. When our results were compared with the 6-week follow-up in the study by Kim et al (14), the high dose group were similar to their chronic opioid group and discharge OME reported in Zywiel et al (12), 85 to 91 MME. The 1-year OME for the high dose group are also comparable to previous studies (14,38,40). The low dose group, however, consistently received higher dosages than nonchronic opioid users in the study done by Kim et al (14). The difference in the low dose group between the studies at one-year follow-up may be partly explained by outliers, as most patients in the low dose group received 10 to 20 MME, but there were 3 patients with >200 MME. In addition, the dose levels were likely exaggerated because we measured MME by assuming maximum use from the PRN prescription. This is a less accurate method of determining actual daily usage, and it is a limitation in our study. Kim et al (14) instead employed the statewide drug monitoring system to determine medications filled. Thus comparison of OME between the studies may be limited. Nevertheless, the general trend of opioid consumption was comparable to these studies. Although our study did not find significant differences among time points, the high dose group on average seemed to receive more OME than the low dose group.

Postoperative Infections

Previous studies revealed a possible link between opioid use and post-TKA infections (15,21). Opioids have even been postulated to cause cell-mediated and humoral immunosuppression (41-42). The large study by Cozowicz et al (15) showed increased adjusted odds for infection in a dose-dependent manner, but the direct causality was not shown. Our study likely has too low power to generate a significant difference in postoperative infections between the 2 preoperative opioid usage groups. In addition, reevaluating and performing a case-control at a different opioid dose level may yield different results.

Hemarthrosis

In the current study, we found a significantly higher incident rate of hemarthrosis postoperatively in the high dose group. To our knowledge, this is the first study to discuss hemarthrosis and opioid use after TKA. Some studies have shown the possible role of opioid receptors mediating antiangiogenic factors (43) and reduced wound healing (44). Yet others also found that morphine treatment decreased inflammation and

improved healing of ischemic wounds and improved angiogenesis in mice (43,45). Fewer articles are published on the role of opioids on postoperative bleeding. One study found that gastrointestinal tract bleeding risk was similar between nonselective nonsteroidal antiinflammatory drugs and opioid users (46). Although opioids are not classically associated with warfarin interaction, a study found an elevation of international normalized ratio shortly after starting tramadol and an appropriate decrease with reducing warfarin dose (47). In the current study, all patients with hemarthrosis were prescribed oxycodone and none were prescribed tramadol. As mentioned earlier, all cases occurred early and before the 6-week follow-up. Of note, none of the patients with prolonged wound drainage presented to the ED, and all but one case was managed by close monitoring and discontinuing thromboprophylaxis or other antiplatelet agents. The exact mechanism of opioid-associated hemarthrosis remains unclear. If there was an interaction with warfarin, the effect is small and manageable, and studies thus far have been controversial regarding wound healing and angiogenesis. There were no cases of lasting complications from early persistent drainage, however, consequences may be more dire in coagulopathic patients. We speculate the association of opioid and postoperative bleeding may be due to a possible interaction between opioids and warfarin as well as the role of peripheral opioid receptors in wound healing. Future studies are warranted to explore the relationship between opioids and hemarthrosis mechanistically.

Joint Interventions

The current study did not find a difference in postoperative joint interventions including revisions between the 2 groups. In contrast, the Ben-Ari et al (19) Veterans Affairs study with 32,636 patients showed that with long-term opioids before TKA, patients were more likely to undergo revision within 12 months, with an odds ratio of 1.40 ($P < 0.005$). Zywiel et al (12) found an increased number of revisions for recalcitrant pain and/or stiffness 8 to 0 ($P < 0.001$) in the preoperative opioid use group compared with the nonopioid group. In addition, other studies found increased manipulations under anesthesia (20), aseptic revisions (n = 35,770) (21), and 12-month revisions (n = 324,154) (48) in the preoperative opioid use group than the opioid-naive group. Again, our lack of a significant finding in this category may be due to small sample size (n = 196), an insignificant comparison at the current cutoff, and comparing opioid dosing instead of opioid exposure.

ED and Urgent Care Visits

Our results showed increased ED visits for surgically related complications for the high dose opioid group (10 to 2; $P = 0.033$). Kim et al (14) found no difference in ED visits and admission, with 8 (2.8%) nonchronic users and 2 (3.7%) chronic users admitted. However, they explored all-cause readmissions, and 2 patients were admitted for chronic heart failure (one case) and coronary artery disease (2 cases). Cozowicz et al (15) reported an increase in thromboembolic events in high- versus low-dose opioid groups, with an increased odds ratio of > 50% for deep venous thrombosis and 30% for pulmonary embolism. This association can be seen in our population as well, with only the high dose group having 2 complications related to hypercoagulability. Furthermore, our findings of a higher rate of ED and urgent care visits in the high dose group were consistent with Cancienne et al (21) and Weick et al (48), both of which also found preoperative narcotic use was independently associated with increased ED visits and hospital readmissions. Together, chronic preoperative opioid use and high dose opioids have an association with increased ED visits, which may be attributed to opioid-associated increase in postoperative complications. Further investigation at a lower opioid dosage and modifying its use will have beneficial effects on postoperative health care expenditure.

Chronic opioids affecting clinical outcomes are often attributed to opioid dependence and opioid-induced hyperalgesia (OIH) (35,49). OIH would decrease the analgesic effect of opioids and paradoxically decrease pain threshold, not to mention the psychological effect of potential dependence. Although many studies have reported worse clinical outcomes and complications with chronic opioid use (11,12,19), others reported insignificant differences for various data points (36-37). Our study found mostly comparable data between the low and high dose opioid groups for nearly all the outcome measures and morbidities. This may be partially explained by the study from Nguyen et al (35), which reported substantially improved clinical outcomes comparable to control with patients who weaned off opioids preoperatively. Of course, it is unclear how much the natural course of TKA recovery and analgesic benefit of surgery is contributing to the measured outcomes. The extent to which opioids and OIH affect outcomes is not well understood. In addition, many previous studies

compared opioid-dependent and opioid-naive patients, limiting the comparison with the current study. Taken together, these findings and studies suggest that measuring the effect of preoperative opioid dosages on postoperational outcomes is promising but necessitates further investigation.

Although this study was a retrospective study, the patients in both dosage groups compared similarly to each other preoperatively. Both groups had comparable demographics (race, gender, smoking status), type of elective surgery, general preoperative comorbidities, and preoperative pain. The only data point that differed was preoperative ROM, which favored the low dose group. However, we found that the low dose preoperative opioid group were more likely to have hypertension concurrently and required a high dose of intraoperative opioid use. Hypertension has been associated with hypoalgesia, and untreated essential hypertension is associated with significantly reduced postoperative morphine requirement and pain intensity after major abdominal surgery (50). These data support our finding that patients with hypertension were more likely to have lower dose preoperative opioid treatment for TKA.

Limitations

One limitation in this study is the lack of data on longer term prognosis. Given the extent of data reaching the one-year follow-up period, we cannot accurately anticipate longer term outcomes. As with any retrospective study, the patients also lacked prospective randomization in our study. Although basic demographics were comparable, other factors besides opioid usage could have contributed to unobserved differences. Moreover, because pain is subjective and self-reported, it is difficult to compare pain scores objectively. Additionally, opioids are prescribed on a PRN basis, so there is no way to ascertain the exact dosage of opioids used over a period of time, and whether the patient pursued opioids outside of the system. This information is poorly reflected in office notes as well, so our method was to calculate the maximum daily dosage prescribed. Using the statewide prescription monitoring system may help decrease this inconsistency. Another limitation involved choosing the median dosage as a basis for comparison. Although the current dosage (120 MME) has been used in other studies to stratify patients, results may certainly be different if we decreased the dose of comparison, particularly if the dosage is moved to the CDC recommended 90 MME. Finally, we did not have immediate access to more standardized scoring indices such as the WOMAC, Short Form 12 item (version 2) Health Survey, and UCLA activity score. Exploring these in-depth questionnaires and performing a graded dose-dependent comparison will be our next step in data collection and analyses.

Conclusions

Our study showed that preoperative dose of opioids did not affect postoperative pain control, ROM, LOS, infections, and joint interventions following knee surgeries immediately postoperation up to the one-year follow-up. We did find a significant difference in the incidence of early hemarthrosis and ED visits for the high dose group. A randomized controlled trial is needed to confirm our results.

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