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Prospective Analysis of a Novel Long-acting Oral Opioid Analgesic Regimen for Pain Control After Total Hip and Knee Arthroplasty

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Abstract: Parenteral opioid use after total knee (TKA) and hip (THA) arthroplasty often results in substantial functional interference and side effects. This prospective study compared use of traditional intravenous patient-controlled analgesia (IV PCA) with a novel oral regimen after TKA and THA. Sixty-two patients received IV PCA and 62 received scheduled long-acting and, as needed, short-acting oral opioids postoperatively. Surveys and chart audits documented functional interference, pain scores, opioid-related side effects, and opioid consumption. Patients who received the oral regimen had significantly less opioid consumption ($P < .05$) and experienced less functional interference ($P < .05$) than the IV PCA group. Both groups had similar pain scores and incidence of opioid side effects. This study demonstrates some significant advantages of an oral analgesic regimen compared with IV PCA after TKA and THA. **Key words:** total hip arthroplasty, total knee arthroplasty, pain control, patient controlled analgesia, outcome analysis.

Postoperative pain control after total knee (TKA) or hip (THA) arthroplasty is a major concern. Inadequate postoperative analgesia can negatively influence surgical outcome and duration of rehabilitation [1,2]. Unrelieved postoperative pain has adverse physiological effects including delayed return of normal respiratory and gastrointestinal function [3]. In addition, unrelieved pain increases the stress response, which can effect the immune system and lead to delayed healing [4]. Adequate acute postoperative pain management is associated with lower cardiopulmonary and vascular complications, lower mortality, and reduced costs [5, 6]. Severe, uncontrolled acute pain is a risk factor for the development of postoperative delirium [7] and chronic pain [8]. Thus, there is a clear rationale for the need to develop postoperative pain management regimens that allow for early ambulation, techniques to reduce nausea and sedation, and early resumption of feeding [9]. These prior studies serve to emphasize the importance of optimal pain management in the postoperative period after total hip and knee arthroplasty.

Although use of intravenous patient-controlled analgesia (IV PCA) represents a popular method for pain control in postoperative settings, metaanalysis of 15 randomized controlled studies of IV PCA showed no statistically significant reductions in side effects, analgesic use, surgical morbidity, or hospital stay than conventional "as-needed" intramuscular injections [10]. The use of IV PCA after TKA and

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THA can be unsatisfactory because of inadequate pain control and undesirable side effects including nausea, vomiting, and pruritus. Although rare, hypoxemia and bradycardia have also been reported with IV PCA [11].

One approach to improve perioperative pain control after TKA and THA includes adopting the use of an opioid dosing schedule during the first several days after major operation to proactively control moderate to severe acute pain [12,13]. Oral administration may provide a better route of analgesia over IV PCA because of convenience and more steady plasma levels of the medication, avoiding the peaks and troughs of intravenous (IV) bolus dosing and the resultant gaps in pain control during periods of sleep. However, reliance on "as-needed" oral analgesia used alone has been a common source of inadequate pain management. Immediate release oral opioids must be given every 3 to 4 hours, and delays in administration are often noted. Controlled-release (CR) oxycodone is well suited for postoperative pain because the median time to onset of relief in clinical trials is just 46 minutes with a duration of action of 10 to 12 hours [14]. A randomized controlled trial of CR oxycodone during inpatient rehabilitation after unilateral TKA indicated that patients who receive preemptive treatment recover knee strength at an accelerated rate and use fewer resources [15].

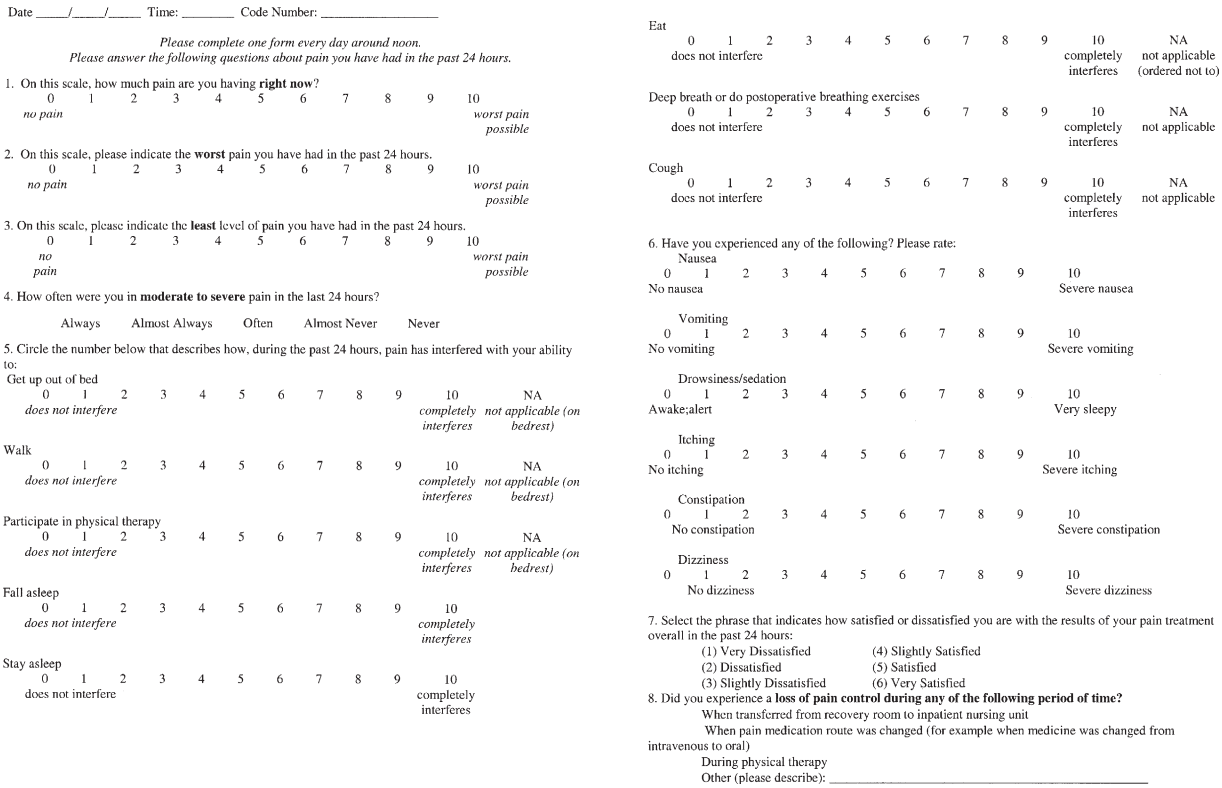
At our institution, IV PCA was used routinely for postoperative pain control after TKA and THA before July 2003. Based on the limitations of IV PCA noted historically [10] and in practice at our own institution, a pain management team was assembled to review our postoperative pain management protocols after TKA and THA. Based on this review, we discontinued using IV PCA after July 2003 and adopted a new long-acting oral opioid regimen for postoperative pain control after THA and TKA. The purpose of this study was to prospectively compare this new oral long-acting opioid regimen to our traditional IV PCA protocol. We hypothesized that this new oral regimen would provide improved pain control compared with IV PCA after primary THA and TKA based on quantified outcome measures including visual analog pain scores, total opioid consumption, functional interference measures, and rates of opioid-related side effects.

Materials and Methods

This study was approved through the institutional review board at our institution as part of our pain management improvement protocol. A preintervention and postintervention design was used to examine a total of 124 patients. The preintervention group included a sample of 62 patients who received IV PCA for postoperative pain management after TKA or THA between March 2001 and June 2003. Patients received a patient-controlled analgesia (PCA) either with morphine sulfate (MS) 1 to 2 mg or hydromorphone 0.2 to 0.4 mg with a 6-minute lockout. The postintervention group included a consecutive series of 62 patients who received oral opioids using a new set of standardized postoperative orders between July and October 2003. Patients in the postintervention group received a long-acting oral opioid (OxyContin C-II-oxycodone HCl CR [20 mg]) starting preoperatively the morning of surgery and continued BID through postoperative day 3 (6 doses total). Patients were also allowed a short-acting oral opioid (oxycodone 5 to 20 mg every 3 hours) as needed. Intravenous opioids were given only if the patient did not obtain satisfactory pain control or if they developed nausea or vomiting using the oral regimen.

Controlled-release oxycodone was chosen in favor of extended release morphine formulations because it has a more rapid onset and time to peak analgesia. The 20-mg starting dose was selected based on previous reports of CR oxycodone use in orthopedic populations [15,16] and an examination of doses of opioids used by postoperative THA and TKA patients treated with IV PCA at our institution [17].

All surgeries were performed by 2 surgeons at 1 institution. All patients were surveyed each day at approximately the same time for 3 days about their experiences in the past 24 hours, and a medical record audit was completed for the same periods. The patient survey instrument (Fig. 1) was adapted from the American Pain Society's Patient Outcome Questionnaire [18] and the Brief Pain Inventory [19] and included items about pain intensity (worst, least, or now), side effects (nausea, vomiting, itching, or drowsiness), and interference with function (general activity, walking, physical therapy, falling and staying asleep, eating, or coughing). Inventory items are anchored with a 0-to-10 numeric rating scale to measure severity with higher numbers meaning more pain, side effects, or interference with function. Information was collected from patients' charts regarding the total amount of opioid administered, side effect management, and physical therapy tolerance. The amount of opioids administered was converted to equivalents of parenteral milligrams (mg) of MS for comparisons using the following approximate equianalgesic



Date _____/_____/_____ Time: _____ Code Number: _____

Please complete one form every day around noon.
Please answer the following questions about pain you have had in the past 24 hours.

1. On this scale, how much pain are you having **right now**?
0 1 2 3 4 5 6 7 8 9 10
no pain *worst pain possible*

2. On this scale, please indicate the **worst** pain you have had in the past 24 hours.
0 1 2 3 4 5 6 7 8 9 10
no pain *worst pain possible*

3. On this scale, please indicate the **least** level of pain you have had in the past 24 hours.
0 1 2 3 4 5 6 7 8 9 10
no pain *worst pain possible*

4. How often were you in **moderate to severe** pain in the last 24 hours?
Always Almost Always Often Almost Never Never

5. Circle the number below that describes how, during the past 24 hours, pain has interfered with your ability to:

Get up out of bed
0 1 2 3 4 5 6 7 8 9 10 NA
does not interfere *completely interferes* *not applicable (on bedrest)*

Walk
0 1 2 3 4 5 6 7 8 9 10 NA
does not interfere *completely interferes* *not applicable (on bedrest)*

Participate in physical therapy
0 1 2 3 4 5 6 7 8 9 10 NA
does not interfere *completely interferes* *not applicable (on bedrest)*

Fall asleep
0 1 2 3 4 5 6 7 8 9 10
does not interfere *completely interferes*

Stay asleep
0 1 2 3 4 5 6 7 8 9 10
does not interfere completely interferes

Eat
0 1 2 3 4 5 6 7 8 9 10 NA
does not interfere completely interferes not applicable (ordered not to)

Deep breath or do postoperative breathing exercises
0 1 2 3 4 5 6 7 8 9 10 NA
does not interfere completely interferes not applicable

Cough
0 1 2 3 4 5 6 7 8 9 10 NA
does not interfere completely interferes not applicable

6. Have you experienced any of the following? Please rate:

Nausea
0 1 2 3 4 5 6 7 8 9 10
No nausea Severe nausea

Vomiting
0 1 2 3 4 5 6 7 8 9 10
No vomiting Severe vomiting

Drowsiness/sedation
0 1 2 3 4 5 6 7 8 9 10
Awake;alert Very sleepy

Itching
0 1 2 3 4 5 6 7 8 9 10
No itching Severe itching

Constipation
0 1 2 3 4 5 6 7 8 9 10
No constipation Severe constipation

Dizziness
0 1 2 3 4 5 6 7 8 9 10
No dizziness Severe dizziness

7. Select the phrase that indicates how satisfied or dissatisfied you are with the results of your pain treatment overall in the past 24 hours:
(1) Very Dissatisfied (4) Slightly Satisfied
(2) Dissatisfied (5) Satisfied
(3) Slightly Dissatisfied (6) Very Satisfied

8. Did you experience a **loss of pain control during any of the following period of time?**
When transferred from recovery room to inpatient nursing unit
When pain medication route was changed (for example when medicine was changed from intravenous to oral)
During physical therapy
Other (please describe): _____

Fig. 1. Patient survey instrument.

doses: 1.5 mg of IV hydromorphone is equal to 10 mg IV morphine or 20 mg of oral oxycodone.

Statistical Methods

A power analysis was performed using opioid use (parenteral mg MS equivalency) as the outcome variable. We predicted that the mean for opioid use would decrease by 30% in the oral opioid group, as compared with the IV PCA group. A mean of 57.04 mg and SD of 25.60 were assumed for the IV PCA group (these were the mean and SD for total hip and knee arthroplasty patients for the first 24 hours postoperatively in a previous study [17] and a projected mean of 39.90 and SD of 25.60 for the oral opioid group. Using an α level of .05 and 1-sided analysis, 28 patients in each group would yield a power of .80 [20].

Independent t tests were used to detect differences between IV PCA and oral opioid groups for age, pain intensity (worst, least), opioid use, side effects, interference with function, satisfaction, and length of stay. χ^2 analysis was used to test between group differences for sex, type of surgery, and amount of time in moderate to severe pain.

Results

No significant differences were noted between the IV PCA and oral opioid treatment groups with respect to age, sex, and type of surgery (See Table 1). There were no statistically significant differences comparing the oral narcotic and IV PCA groups with regard to the preoperative diagnoses before either total hip or total knee arthroplasty (85% osteoarthritis, 10% rheumatoid arthritis/inflammatory arthritis, and 5% other diagnoses). There were also no significant differences noted

Table 1. Demographics and Procedures

	IV PCA (n = 62)	Long-acting oral opioids (n = 62)
Age (mean ± SD)	61.84 ± 11.21	62.44 ± 13.86
Sex	29 men 33 women	28 men 34 women
Type of procedure	25 THA 37 TKA	28 THA 34 TKA
Use of nonsteroid anti-inflammatories	4 patients received cyclooxygenase-II inhibitors; 2 received toradol	8 patients received cyclooxygenase-II inhibitors

Table 2. Interference with Function by Group (Scale: 0 = no interference, 10 = complete interference, *$P < .05$)

		IV PCA group (n = 62)	Oral opioid group (n = 62)
	Interference with:	Mean (SD)	Mean (SD)
0-24 h postoperative	Getting out of bed	7.77 (3.09)	6.62 (2.73)
	Walking*	7.26 (3.47)	5.56 (2.59)
	Physical therapy	5.90 (3.11)	5.07 (3.00)
	Falling asleep	4.16 (3.29)	3.24 (3.23)
	Staying asleep	4.41 (3.08)	3.48 (3.41)
	Eating	2.28 (2.96)	1.55 (2.78)
	Deep breathing	1.33 (2.11)	0.65 (1.79)
	Coughing*	1.62 (2.27)	0.73 (1.70)
24-48 h postoperative	Getting out of bed	5.64 (3.40)	4.47 (3.24)
	Walking	5.18 (3.12)	4.30 (3.09)
	Physical therapy	3.93 (2.99)	4.10 (3.28)
	Falling asleep*	3.51 (2.91)	1.67 (2.75)
	Staying asleep*	3.23 (2.63)	1.96 (2.75)
	Eating	2.35 (2.79)	1.58 (2.75)
	Deep breathing*	1.68 (2.12)	0.60 (1.61)
	Coughing*	1.80 (2.07)	0.84 (1.76)
48-72 h postoperative	Getting out of bed*	4.24 (3.06)	3.01 (2.87)
	Walking*	4.22 (3.06)	2.86 (2.99)
	Physical therapy	3.61 (2.52)	3.06 (3.23)
	Falling asleep	2.15 (2.22)	1.42 (2.42)
	Staying asleep*	2.98 (2.48)	1.25 (2.02)
	Eating	1.35 (1.76)	0.79 (2.26)
	Deep breathing*	1.44 (2.08)	0.32 (1.44)
	Coughing*	1.40 (2.13)	0.37 (1.03)

comparing the type of anesthesia used for either total hip or knee arthroplasty with either the oral or IV PCA groups (80% general anesthesia and 20% regional anesthesia).

We initially analyzed the THA and TKA groups separately regarding pain severity and opioid use. Independent *t* tests were run to detect differences in the opioid use of THA and TKA patients. Although the SDs tended to be smaller in the THA patients, mean opioid use did not differ significantly between the THA and TKA. Specifically, mean opioid use differed by 3.4 mg in the IV PCA group (THA mean, 57.42 ± 41.17 mg vs TKA mean, 60.74 ± 34.44 mg, $P > .05$) and by a mean of 6.1 mg in the oral opioid group (THA mean, 34.60 ± 13.41 mg and TKA mean, 40.85 ± 30.18 mg, $P > .05$). We were not able to detect any significant differences between the THA and TKA comparing any of the outcomes measures tested in this study. Based on these findings, we chose to present all of our data combining the THA and TKA groups (Tables 1 and 2, Figs. 2 and 3).

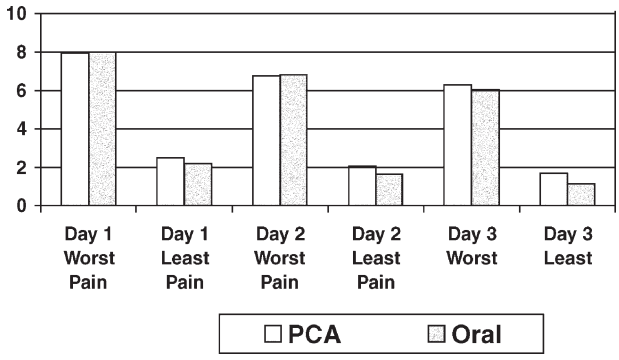


Fig. 2. Patient-reported pain intensity ratings.

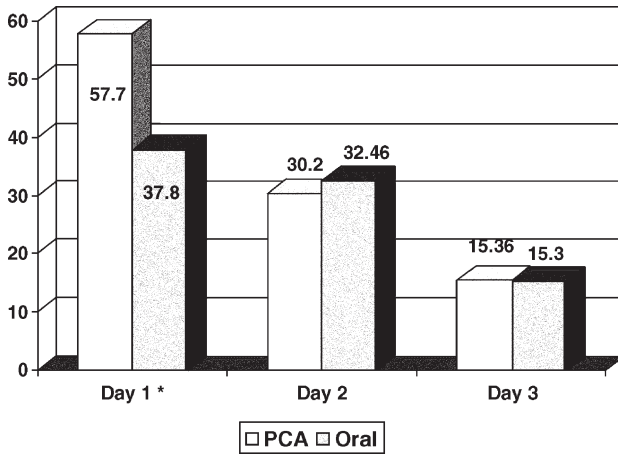


Fig. 3. Mean amount (mg) of opioid consumed in parenteral morphine equivalents.

Pain Ratings

Patients in both the oral and IV PCA groups had similar pain ratings for all 3 days (Fig. 2). Mean worst pain ratings were approximately 8 (range, 2-10) on postoperative day 1 and gradually declined to a mean of 6 by day 3 in both groups (range, 0-10). Least pain ratings also declined daily in a similar fashion in both groups (Fig. 2), and there was no difference in the amount of moderate to severe pain in either group.

Opioid Use

Patients in the oral opioid group used significantly less opioid (mean parenteral morphine equivalent) in the first 24 hours after surgery than patients using IV PCA (37.80 mg. + 23.45 vs 59.41 + 37.00 mg, respectively, $P < .001$; Fig. 3). Opioid use was similar in both groups on days 2 and 3 (Fig. 3). Twenty-six (42%) of patients in the oral group received at least 1 parenteral rescue dose in the first 24 hours. Twenty-seven (44%) of the IV PCA patients were started on oral opioids on postoperative day 2, and by day 3, 80% of patients in the IV group had been transitioned to oral opioids on an as needed basis.

Side Effects

There were no statistically significant differences between groups in the type side effects reported. Drowsiness was the most frequently reported side effect on all 3 days, followed by nausea, dizziness, and itching. Constipation became a frequent concern by day 3.

Interference From Pain with Function

Patients taking oral opioids reported statistically less interference from pain in walking (P = .024) and coughing (P =.022) on day 1 and falling and staying asleep (P = .001 and .013, respectively), coughing (P = .004), and deep breathing (P = .011) on day 2, and getting out of bed (P = .05), walking (P = .038), staying asleep (P = .001), coughing (P = .003), and deep breathing (P = .003) on day 3 (Table 2). Although not statistically significant, there was a trend toward less interference in eating on all 3 days in the oral group (P = .14-.19). No significant difference was noted comparing the knee range of motion in patients with total knee arthroplasty that received oral compared with IV PCA narcotic regimens. All total hip and knee patients ambulated on postoperative day no. 1 as part of our standard postoperative physical therapy protocol. Therefore, we did not demonstrate any significant differences in the date of ambulation for either THA or TKA patients with either the oral or IV PCA narcotic protocols.

Patient Satisfaction

Patients in the oral group reported slightly higher satisfaction ratings (scale 1, very dissatisfied, to 6, very satisfied) with a statistical difference by day 3 (5.48 oral group and 4.85 IV PCA group, t = −2.88, $P < .05$).

Length of Stay

No statistically significant difference was noted comparing the length of stay for the oral compared with the IV PCA groups (mean, 3.88 +2.77 vs 4.43 + 3.05 days, respectively; P = .37).

Cost

The average patient charge for the opioid was calculated using the mean amount of opioid consumed by each group in the first 24 hours. The charge included only drug cost plus pharmacy delivery fee and was similar for both groups ($74 for oral medications; $65 for IV PCA). The IV PCA cost did not include costs related to pump, tubing, or nursing time.

Discussion

Our study supports the hypothesis that use of a long-acting oral opioid regimen demonstrates improvement in measured outcomes compared with the traditional IV PCA protocol. Both groups had similar pain scores at all time points (Fig. 2), but the oral group consumed less opioid, suffered less functional interference, and had improved patient satisfaction scores compared with the IV PCA group. However, despite lower rates of opioid consumption in the oral opioid group, rates of opioid-related side effects were similar at all time points tested. It should be noted that 42% of patients in the oral group required 1 dose of "rescue" IV opioid during the first 24 hours. This may have resulted in increasing the rate of opioid related side effects during the first 24 hours in the oral opioid group. Efforts to reduce the reliance on IV opioids and opioid-related side effects further might include other pain management modalities (postoperative epidural analgesia, post operative selective regional nerve blocks, preemptive antiemetic therapy, and use of other nonopioid agents to reduce pain (ie, gabapentin).

Oral dosing appeared to produce an opioid-sparing effect compared with IV PCA. The difference in amount of opioid consumed was most notable in the first 24 hours when patients in the oral group used approximately one third less total opioid compared with the IV PCA group. The lack of differences in the amount of opioid consumed on day 2 and 3 between groups may be related to the natural progression of patients in the IV PCA group to oral analgesia on days 2 and 3. Patients may have required less total opioid in the oral group because the long acting oral opioid provided a more constant steady state of analgesia than may have been possible through the use of intermittent IV boluses obtained from PCA or PRN oral opioid dosing used alone. Although both groups were using oral analgesia by day 3, patients in the long-acting oral opioid group were more satisfied. This difference may represent better qualitative control of pain from more steady analgesia produced by scheduled long-acting opioid. One approach to reduce the peak and trough effect of intermittent IV PCA dosing is to add a continuous background or basal infusion. The results of studies examining the addition of a continuous opioid background infusion with PCA for postoperative pain, however,

have been equivocal [21,22]. The routine use of a continuous opioid infusion in combination with standard PCA has not been shown to improve pain management or decrease the amount of nocturnal awakenings secondary to pain and may be associated with an increased rate of hypoxemia [21,22].

Despite a reduction in the total amount of opioid used by the oral group, drug costs were relatively similar between groups. However, it is difficult to fully quantify the relative costs of oral drug administration with IV PCA. Cost drivers of IV PCA have been identified including direct medical costs (eg, IV tubing and pump purchase), nonmedical costs (eg, nursing and pharmacy labor, storage, pump maintenance), and intangible costs (eg, analgesia gaps from malfunctioning pumps and adverse events related to programming errors) [23]. The cost of the oral opioid regimen is also difficult to fully quantify, especially the nonmedical costs (nursing and pharmacy labor) and the intangible costs (delays in medication delivery with resulting suboptimal pain control). Future work is needed to better quantify the economics of various postoperative analgesia regimens.

There appeared to be no differences in the type or intensity of opioid-related side effects between the groups based on the opioid used (oxycodone, morphine, or hydromorphone) or the route of delivery (oral vs IV). Opioid side effects are often assumed to be dose-related, so we anticipated that the larger total daily dose of IV PCA opioid would have resulted in a worse side effect profile on day 1. Because opioid side effects are related to centrally mediated effects of the circulating drug (and an individual patient's tolerance to side effects from prior opioid exposure), it would be reasonable to expect the same side effects whether an opioid was administered orally or parenterally. Studies that have compared the incidence of side affects among the opioids during short-term administration have produced conflicting results, ranging from no differences, to morphine being the least emetogenic, to morphine being the most emetogenic [24]. In our study, approximately 71% of IV PCA and 67% of oral opioid patients reported some degree of nausea. Other studies have documented similar rates of nausea with the use of morphine IV PCA after orthopedic, abdominal, thoracic, or craniofacial surgery [25].

Interestingly, despite similar pain intensity ratings and side effects, patients with oral dosing reported significantly less functional interference. High pain intensity ratings, such as those reported in this study, have consistently been associated with high levels of functional interference in postoperative studies [26]. The decreased functional interference reported by patients in this study may reflect a more global measure of improvement in the quality of pain control obtained from long-acting oral analgesia. Future studies should examine functional interference and its relation to route and amount of opioid administration as well as the intensity of opioid-related side effects.

The use of oral long-acting opioids for the management of postoperative pain after THA and TKA appears to provide safe and relatively effective pain control with diminished functional interference compared with IV PCA. Patients on oral opioids demonstrated no less pain control than patients treated with IV PCA, despite receiving significantly less total opioid. Oral dosing was not associated with increased incidence of nausea and vomiting and was generally well tolerated. It should be noted that patients in both the oral narcotic and IV PCA groups were allowed to use nonsteroidal anti-inflammatory medications for breakthrough pain. Our study did not randomize the groups to isolate the effect of nonsteroidals on postoperative pain control.

Although significant advantages were noted comparing the oral opioid regimen to IV PCA, further improvements are needed. In our study, both the IV PCA and oral opioid treated groups demonstrated a suboptimal mean "worst pain" intensity of 8/10 on postoperative day no. 1. We believe that further improvements in pain control after THA and TKA may result from the use of a multimodal regimen such as regional anesthesia techniques and/or nonopioid analgesics such as gabapentin [2,27]. Further study is needed to determine if such modifications to the oral opioid regimen will demonstrate additional improvements compared with traditional IV PCA for postoperative pain control after THA and TKA.

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