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Intraosseous Morphine Decreases Postoperative Pain and Pain Medication Use in Total Knee Arthroplasty: A Double-Blind, Randomized Controlled Trial

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ABSTRACT

Background: Intraosseous (IO) infusion of medication is a novel technique for total knee arthroplasty (TKA) antibiotic prophylaxis. To decrease postoperative pain in TKA patients, we investigated addition of morphine to a standard IO antibiotic injection.
Methods: A double-blind, randomized controlled trial was performed on 48 (24 each) consecutive patients undergoing primary TKA. The control group received an IO injection of antibiotics as per the standard protocol. The experimental group received an IO antibiotic injection with 10 mg of morphine. Pain, nausea, and opioid use were assessed up to 14 days postoperatively. Morphine and interleukin-6 serum levels were obtained 10 hours postoperatively in a subgroup of 20 patients.
Results: The experimental group had lower Visual Analog Scale pain score at 1, 2, 3, and 5 hours postoperatively ($P = .0032$, $P = .005$, $P = .020$, $P = .010$). This trend continued for postoperative day 1, 2, 8, and 9 (40% reduction, $P = .001$; 49% reduction, $P = .036$; 38% reduction, $P = .025$; 33% reduction, $P = .041$). The experimental group had lower opioid consumption than the control group for the first 48 hours and second week postsurgery ($P < .05$). Knee Injury and Osteoarthritis Outcome Score for Joint Replacement scores for the experimental group showed significant improvement at 2 and 8 weeks postsurgery ($P < .05$). Serum morphine levels in the experimental group were significantly less than the control group 10 hours after IO injection ($P = .049$).
Conclusion: IO morphine combined with a standard antibiotic solution demonstrates superior postoperative pain relief immediately and up to 2 weeks. IO morphine is a safe and effective method to lessen postoperative pain in TKA patients.
Level of Evidence: Therapeutic, Level 1.

Pain management after total knee arthroplasty (TKA) is an important consideration to improve patient outcomes and reduce length of stay. This has led to the development of multimodal pain management protocols [1,2]. Currently, many institutions have incorporated cyclooxygenase-2-specific anti-inflammatory agents, neurogenic agents, intra-articular injections, and opioid pain medication for patients undergoing TKA [1,3–6]. Many studies have demonstrated that patients receiving multimodal pain management regimen had significantly better pain control and required less narcotics [7–10]. No clear consensus exists of the optimal perioperative regimen to alleviate pain [11,12].

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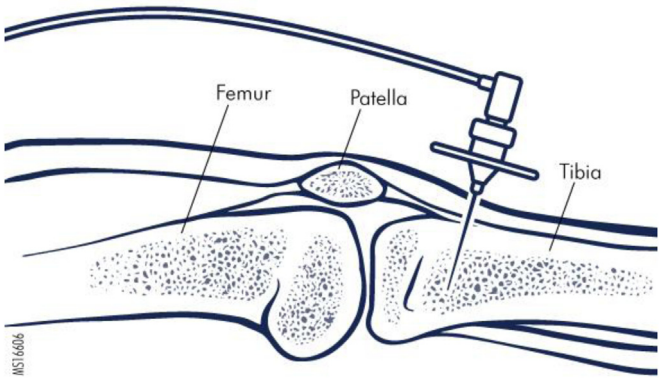


Fig. 1. Our technique for intraosseous administration of medications. Five hundred milligram of vancomycin powder in 150 mL normal saline (±10 mg morphine) was injected into the tibial tubercle after tourniquet inflation using IO vascular access system (Arrow EZ-IO; Teleflex) inserted with power driver into the tibial tubercle region. IO, intraosseous.

Intraosseous (IO) infusion of medication is a novel technique, and this delivery method has been shown to increase local tissue concentration of antibiotics [13,14]. Additionally, IO vancomycin delivery has an adequate safety profile in primary and revision TKA, eliminating the logistical challenge of timely prophylactic antibiotic administration [13]. Prior studies have supported the bioequivalence of intravenous and IO morphine in adults [15].

In this study, we sought to determine if a single dosing of IO morphine could decrease postoperative pain in TKA patients and display safety efficacy with decreased systemic morphine levels postoperatively. We hypothesized that adding morphine to the standard IO injection would result in less postoperative pain, decreased postoperative opioid consumption, and lower systemic morphine levels postoperatively.

Materials and Methods

Institutional review board approval (Pro000023481) was obtained for this double-blind, randomized controlled trial (trial registry: NCT04388111) and all patients provided informed consent prior to participating. Patients were eligible if they were undergoing a primary TKA and over 18 years of age. Patients were excluded for weight <100 pounds, body mass index >35, past medical history of opioid addiction, established hypersensitivity to morphine, acute or chronic liver disease, narcotic use within 5 days of surgery, or same-day discharge. Three fellowship-trained surgeons performed cemented primary TKA surgeries.

The control group (CONTROL) received an IO injection of antibiotics as per the standard protocol for primary TKA patients used at the senior author's institution just after inflation of pneumatic tourniquet [16]. The experimental group (MORPHINE) received 10 mg of morphine added to the IO antibiotic injection without the surgeon's or patient's knowledge. The IO medication was administered with a hand-held IO infusion device inserted into the tibial tubercle region (Arrow EZ-IO; Teleflex, Morrisville, NC; Fig. 1). All patients received spinal and adductor canal blocks, combined with total intravenous general anesthesia.

Spinal and adductor canal blocks were performed by 3 dedicated, experienced anesthesiologists who perform more than 450 blocks each. The spinal blocks are performed in the preoperative area using 0.75% hyperbaric bupivacaine 6-9 mg, and the adductor canal block was performed using 0.5% ropivacaine 15-20 mL + clonidine 75-100 mcg under ultrasound guidance.

The preoperative and intraoperative medication regimen and soft tissue intra-articular injection (50 mL 0.5% Naropin + 0.5 mL of epinephrine) were standardized. The tourniquet pressure was standardized to 275 mm Hg.

Randomization

Enrolled participants were randomly allocated with use of a randomization sequence by SAS 9.1 statistical software (SAS Institute, Cary, NC) on a 1:1 ratio, to receive either IO morphine or IO antibiotics. The outcome assessor and participants were blinded to the group assignment.

Pain Management Protocol

Postoperatively, a standardized oral pain regimen was adopted: acetaminophen 500 mg as needed (PRN) every 6 hours for mild pain (Visual Analog Score, VAS 1-3), hydrocodone 10/325 mg every 4 hours PRN for moderate pain (VAS 4-6), and oxycodone 5 mg every 6 hours PRN for severe pain (VAS 7-10). Ketorolac was not administered in the post anesthesia care unit or postoperatively. Intravenous narcotics (2 mg intravenous morphine) were given for breakthrough pain (>7 out of 10 only after oral pain medication). Postoperative narcotic medication was reported as daily intake of morphine milligram equivalents (MME) using established Center for Disease Control and Prevention guidelines [17]. All patients were discharged with 40 tablets of hydrocodone 10/325 mg. Some patients were either given a refill of hydrocodone or provided a prescription for acetaminophen-codeine 300/30 mg prior to their 2-week appointment.

VAS pain scores were recorded hourly for 5 hours postoperatively in the electronic medical record. Patients recorded VAS pain and nausea scores 3 times per day (morning/afternoon/evening) for 14 days in a journal (returned at the 2-week follow-up appointment). Opioid pain medication usage was recorded for 14 days postoperatively. MMEs were quantified [18].

Patient-reported outcome measures (PROMs) were recorded preoperative, 2 and 8 weeks after surgery using the Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10 and Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS JR) surveys [19,20].

Measurement of Serum Morphine and Interleukin-6 Concentrations

Blood draws were obtained from a subset of 20 patients (10 patients in each group) to determine systemic levels of morphine

Table 1
Patient Demographics.

	Control	Morphine	Significance/*P*-Value
Demographics			
Males (n)	13 (56.17%)	9 (37.50%)	.247, NS
Females (n)	11 (45.83%)	15 (62.50%)	
Age (y)	65.06 ± 6.37	65.20 ± 8.01	.947, NS
Weight (kg)	96.03 ± 21.74	88.13 ± 15.99	.158, NS
BMI (kg/m^2)	30.58 ± 3.89	31.36 ± 5.09	.549, NS
Blood sampling subgroup			
Males (n)	60.00%	50.00%	.653, NS
Females (n)	40.00%	50.00%	
Age (y)	67.03 ± 6.81	66.17 ± 9.05	.813, NS
Weight (kg)	97.59 ± 19.23	94.49 ± 17.95	.714, NS
BMI (kg/m^2)	30.17 ± 3.73	32.06 ± 3.16	.237, NS

Values are presented as means ± SD for age (y), weight (kg), and body mass index (kg/m^2) as well as the proportion of males and females in each group. Type I error set at $\alpha = 0.05$.
BMI, body mass index; NS, not significantly different between groups; SD, standard deviation.

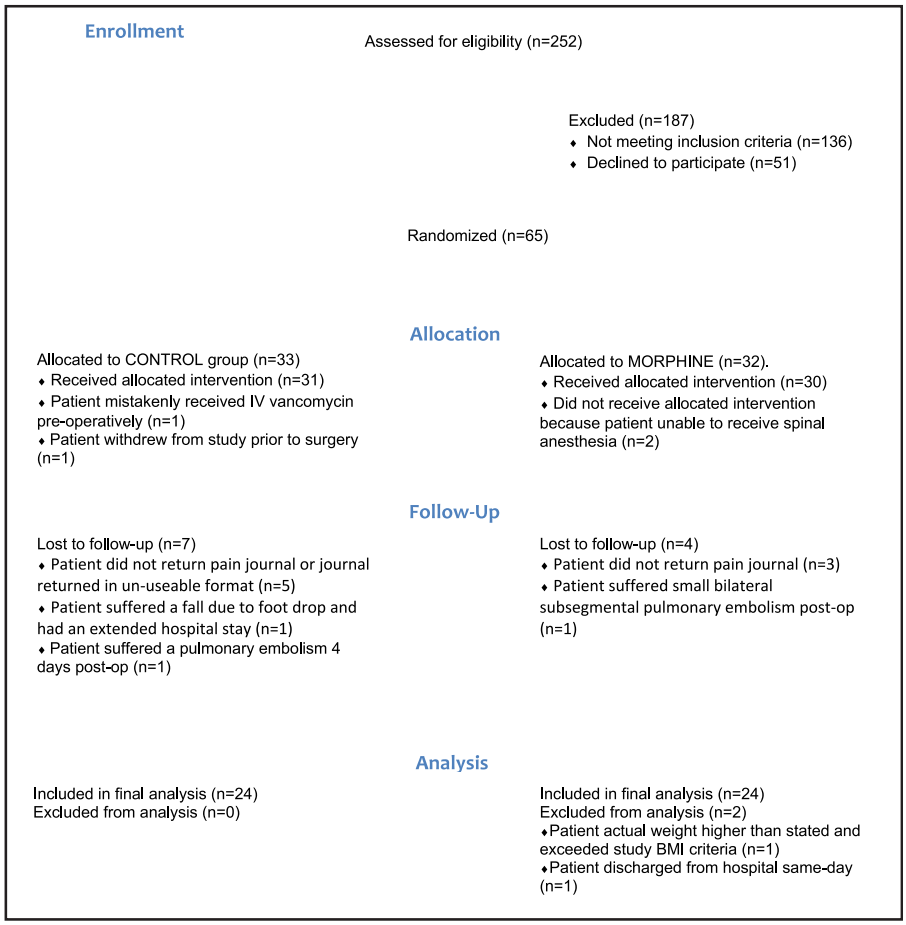


Fig. 2. CONSORT diagram for trial. CONSORT flow diagram showing participant flow through each stage of the randomized controlled trial (enrollment, intervention allocation, follow-up, and data analysis). BMI, body mass index; CONSORT, Consolidated Standards of Reporting Trials; IV, intravenous.

and interleukin-6 (IL-6). IL-6 is a marker of chronic inflammation, acute stress, and acute metabolic signaling. Blood samples were collected after anesthesia induction, 15 minutes after tourniquet release, and 10 hours after the IO injection. Blood was collected in an ethylenediaminetetraacetic acid glass tube. Following 30 minutes of centrifugation at 1,000 × g, serum was removed and stored at −80°C with Halt Protease Inhibitor Cocktail (Thermo Fisher Scientific, Waltham, MA) for further analysis. Following collection of all study samples, serum concentrations of IL-6 and morphine were quantified using established enzyme-linked immunoassay analysis techniques [21] via Quantikine high-sensitivity human immunoassay kits (R&D Systems, Minneapolis, MN and Creative Diagnostics, Shirley, NY for IL-6 and morphine, respectively). All samples were analyzed in triplicate and randomized by plate by an experienced technician. Serum concentration values were normalized to internal standards provided in each kit by the manufacturer.

Sample Size, Power, and Statistical Analysis

For our primary outcome variable of VAS recorded pain, a power analysis was performed using JMP statistics software (v.16; SAS Institute), utilizing data extracted from prior reporting of postoperative VAS Pain in TKA patients [11]. Based on preliminary data and previous pilot investigations, for a power of 0.8 at $\alpha = 0.05$ to detect a minimum clinically important VAS difference of 1.4 points [22–24] between groups at a given measurement timepoint, it was determined that a minimum of 48 total patients (24 patients per group) would be required.

Postoperative Pain, Nausea, and Medication Use

A treatment group × timepoint mixed model analysis of variance was used to detect differences in VAS ratings of average daily pain, nausea, and opioid pain medication use (MME) between groups at the same postoperative timepoints for the 14-day postoperative period. The same test was used to compare these measures averaged across the first 48 hours, as well as the first-week and second-week postsurgery. Significant interactions indicated by type III tests of fixed effects were followed by a Tukey's post hoc test for pairwise comparisons. Next, a similar Friedman test for nonparametric data followed by a Wilcoxon signed rank test with a Bonferroni post hoc adjustment was used to compare PROMs (PROMIS Global-10 and KOOS JR) within and between groups at the preoperative, 2-week postoperative, and 8-week postoperative timepoints.

Blood Sampling

Histograms were used to visualize the distribution of the 2 outcomes: serum morphine and IL-6 concentration. It was shown that the distribution for both morphine and IL-6 was skewed, making the normality assumption invalid. Therefore, log-transformation was applied to address the skewness. A treatment

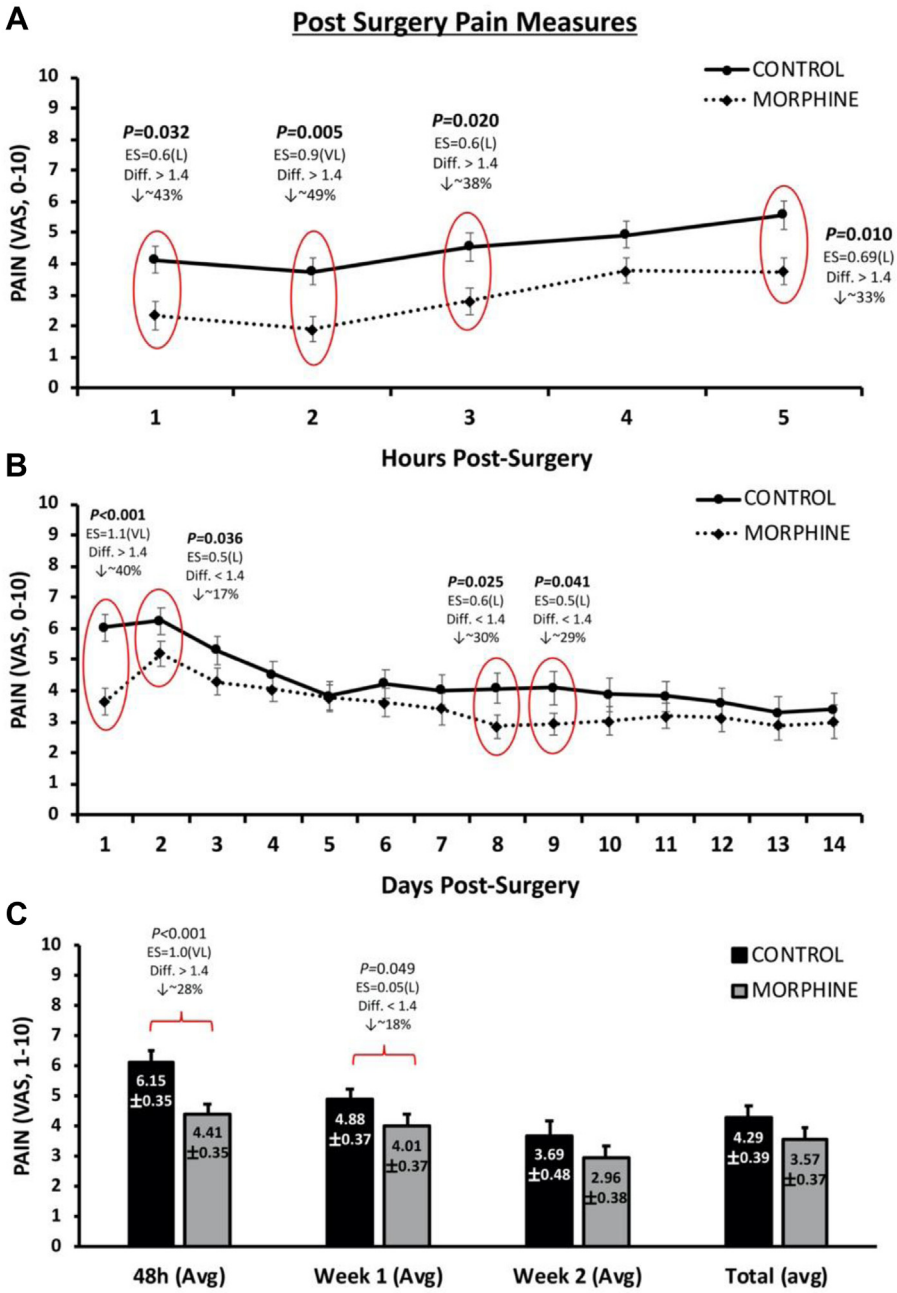


Fig. 3. Postoperative pain. Values are presented as means ± SEM for patient-recorded pain using a Visual Analog Scale (VAS, 0-10) within the first 5 hours postsurgery (A); averaged for each day for 14 days postsurgery (B); and averaged (avg) over the first 48 hours, week 1, week 2, and total 14-day postsurgery time intervals (C). Circles (A, B) or brackets (C) indicate significant differences between groups at the same measurement timepoint at $P < .05$. For all significant pairwise comparisons, effect size (ES) is provided as a Cohen's *d* statistic and interpreted as follows: <0.1 (Negligible, N); 0.1-0.3 (Small, S); 0.3-0.5 (Moderate, M); 0.5-0.7 (Large, L); and >0.7 (Very Large, VL). Significant differences exceeding the minimum clinically important difference (Diff. > 1.4) are also indicated. SEM, standard error of the mean.

group × timepoint linear mixed model analysis of variance was utilized to evaluate within-group changes and between-group differences in serum morphine and IL-6 concentration across the postoperative sampling period. To account for postoperative voluntary opioid consumption, postoperative MMEs were also included in the model. Morphine or IL-6 concentrations were included as the dependent variables. All the analyses were done in SAS (v.9.4; SAS Institute). The statistical significance level is set at 0.05.

Type I error was set at $\alpha = 0.05$ for all analyses. For all significant pairwise comparisons between groups, the effect size (ES) was calculated using Cohen's *d* statistic [25] whereby ESs were interpreted as follows: 0.0-0.1 Negligible (N); 0.1-0.3 Small (S); 0.3-0.5 Moderate (M); 0.5-0.7 Large (L); and >0.7 Very Large (VL) [26–28].

Results

From May 2020 to April 2021, 48 (24 in the CONTROL group and 24 in MORPHINE group) consecutive patients underwent TKA. Patient enrollment and randomization is shown in Figure 2. Patient demographics are presented in Table 1. No differences were observed between groups for both the total patient population and

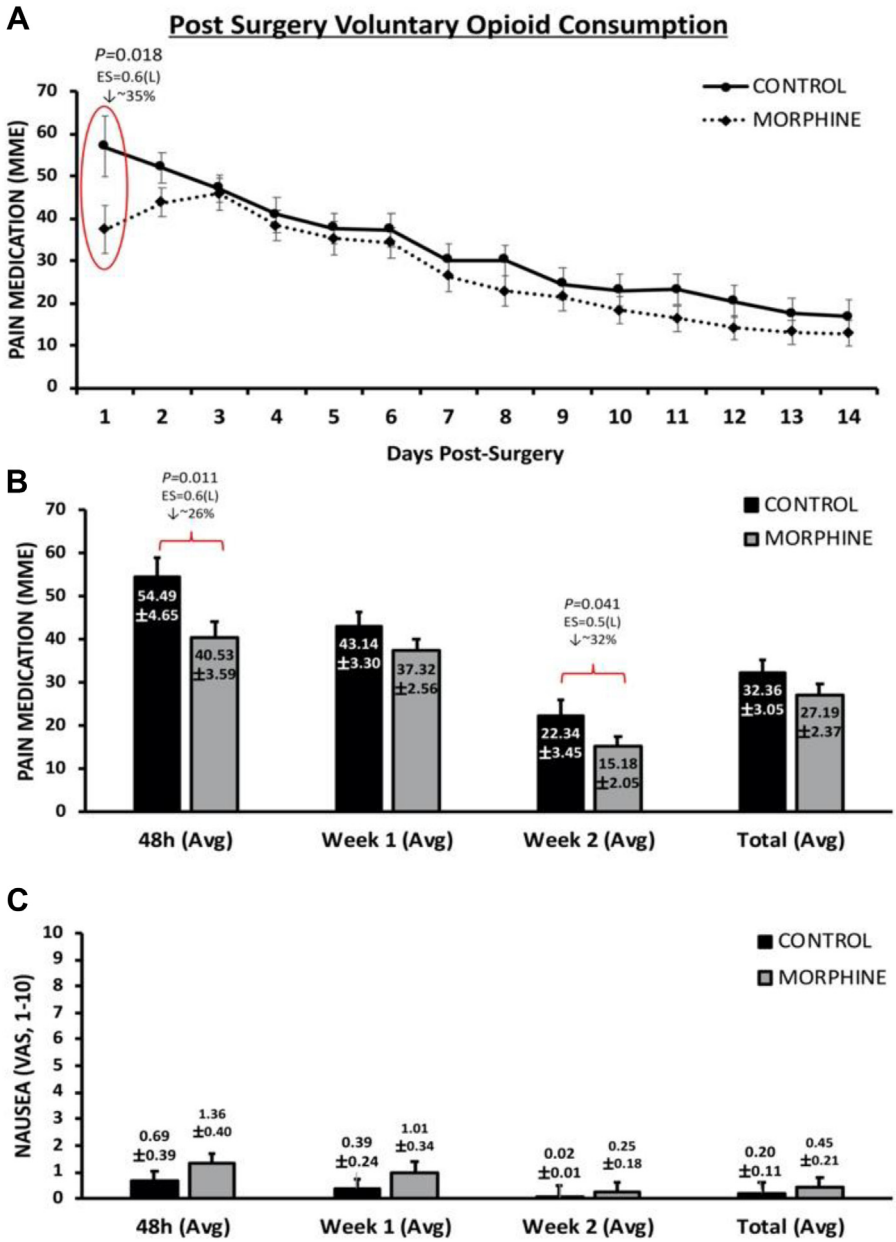


Fig. 4. Postoperative opioid consumption and nausea. Values are presented as means ± SEM for patient-recorded voluntary opioid usage (A, B—MME) and ratings of nausea (C—VAS, 0-10) across the postoperative period with opioid consumption compared between groups for each day for 14 days postsurgery (A); and both opioid consumption (B) and nausea (C) averaged (avg) over the first 48 hours, week 1, week 2, and total 14-day postsurgery time intervals. Circles (A) or brackets (B) indicate significant differences between groups at the same measurement timepoint at $P < .05$. For all significant pairwise comparisons, effect size (ES) is provided as a Cohen's d statistic and interpreted as follows: <0.1 (Negligible, N); 0.1-0.3 (Small, S); 0.3-0.5 (Moderate, M); 0.5-0.7 (Large, L); and >0.7 (Very Large, VL). MME, morphine milligram equivalents; SEM, standard error of the mean; VAS, Visual Analog Scale.

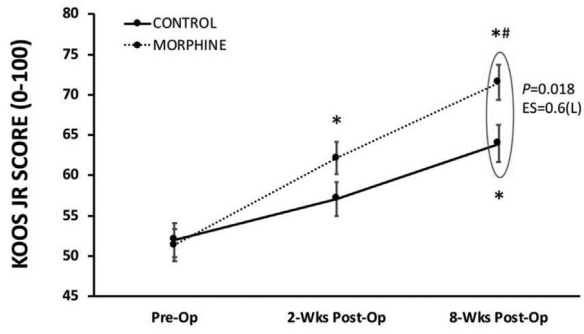
for the subgroup of patients where blood sampling was performed. All patients were discharged home within 23 hours of surgical procedure.

Postoperative Pain

In the immediate postoperative period, the MORPHINE group was observed to have significantly lower VAS at hours 1, 2, 3, and 5 postsurgery ($P = .0032$, $P = .005$, $P = .020$, $P = .010$) with all observed differences exceeding the minimally clinically important difference of 1.4 cm (Fig. 3A). In the 14-day postoperative period, the MORPHINE group recorded significantly lower pain scores at days 1, 2, 8, and 9 postsurgery ($P < .05$) with observed differences exceeding the minimally clinically important difference of 1.4 cm on day 1 (Fig. 3B). When averaged over time, the MORPHINE group recorded lower pain scores across the first 48 hours and week 1 postsurgery (on average) across the first 48 hours (Fig. 3C). ESs for all significant comparisons ranged from large ($d = 0.5$-7) to vary large ($d > 0.7$).

Voluntary Opioid Consumption and Nausea

When comparing groups at each day during the 14-day postoperative period, the MORPHINE group recorded significantly



CONTROL	52.0 ± 2.0	57.1 ± 2.0	64.0 ± 2.2
MORPHINE	51.4 ± 2.1	62.2 ± 2.1	71.5 ± 2.3

Fig. 5. Patient-reported outcomes KOOS JR. Values are presented as means ± SEM for patient-reported outcome scores for KOOS JR. Circles indicate significant differences between groups at the same measurement timepoint at $P < .05$. *Significantly different from Pre-Op time point within group ($P < .05$). #Significant difference between 2-Wks and 8-Wks Post-Op time points within group ($P < .05$). For all significant pairwise comparisons, effect size (ES) is provided as a Cohen's *d* statistic and interpreted as follows: <0.1 (Negligible, N); 0.1-0.3 (Small, S); 0.3-0.5 (Moderate, M); 0.5-0.7 (Large, L); and >0.7 (Very Large, VL). KOOS JR, Knee Injury and Osteoarthritis Outcome Score for Joint Replacement; SEM, standard error of the mean.

lower opioid consumption at day 1 postsurgery ($P = .018$; Fig. 4A). When averaged over time, the MORPHINE group recorded lower opioid consumption across the first 48 hours and week 2 postsurgery ($P < .05$; Fig. 4B). No differences between groups were observed with regards to nausea (Fig. 4C) for both groups across the entire 14-day postoperative period. ESs for all significant comparisons were large ($d = 0.5$-7).

Patient-Reported Outcomes

For the KOOS JR survey (Fig. 5), both groups were observed to have significant improvements by 8 weeks postsurgery compared to preoperative scores ($P < .001$) with only the MORPHINE group observed to have a significant improvement at 2 weeks postsurgery compared to preoperative scores ($P < .001$). Additionally, the MORPHINE group recorded a significantly higher score compared to the CONTROL group at 8 weeks postsurgery ($P = .003$; Fig. 5). For the PROMIS Global-10 survey, both groups had similar reductions in *T*-scores for the physical component at 2 weeks postoperative that remained constant by 8 weeks postoperative (CONTROL: preoperative [50.4 ± 1.0], 8 weeks postoperative [44.5 ± 1.1] | MORPHINE: preoperative [49.3 ± 1.1], 8 weeks postoperative [43.9 ± 1.2]; $P < .001$) with no differences observed between groups. For the mental component, no significant changes over time or differences between groups were detected.

Blood Sampling: Serum Morphine and Interleukin-6 Levels

An overall significant effect of group was observed for serum morphine concentration ($P = .0118$), and the MORPHINE group was observed to have lower concentrations at both the 15-minute ($P = .0147$) and 10-hour ($P = .049$) postoperative time points (Fig. 6A). An overall effect of time was observed for all patients with regards to IL-6 concentration which was observed to be elevated in both groups at the 10-hour postoperative timepoint ($P < .001$) with no pairwise differences observed between groups at any of the measurement timepoints.

Complications

There was one case of pulmonary embolism (PE) in each group. Neither patient was considered high risk for developing a PE, and both were treated with aspirin 81 mg twice daily postoperatively. Because both were hospitalized within 2 weeks of surgery, they were unable to complete the study. No complications associated with the use of vancomycin, such as Red Man syndrome, occurred during the IO vancomycin infusion. There were no side effects or complications at the injection site including needle breakage.

Discussion

This study demonstrates superior postoperative pain relief, averaging 2 VAS points lower, in patients receiving 10 mg of morphine added to the standard IO vancomycin infusion compared to IO antibiotics alone. This was effective up to 2 weeks. Serum morphine concentrations were significantly lower in the MORPHINE group in the immediate postoperative period suggesting that this mode of delivery is clinically safe. A decreased serum morphine concentration in the MORPHINE group suggests that IO morphine results in less immediate postoperative narcotic use. Furthermore, no change in nausea over time between the groups indicates similar tolerance between treatments. Finally, these acute findings were paired with improved knee-specific outcomes at both 2 and 8 weeks postsurgery. Cumulatively, these results

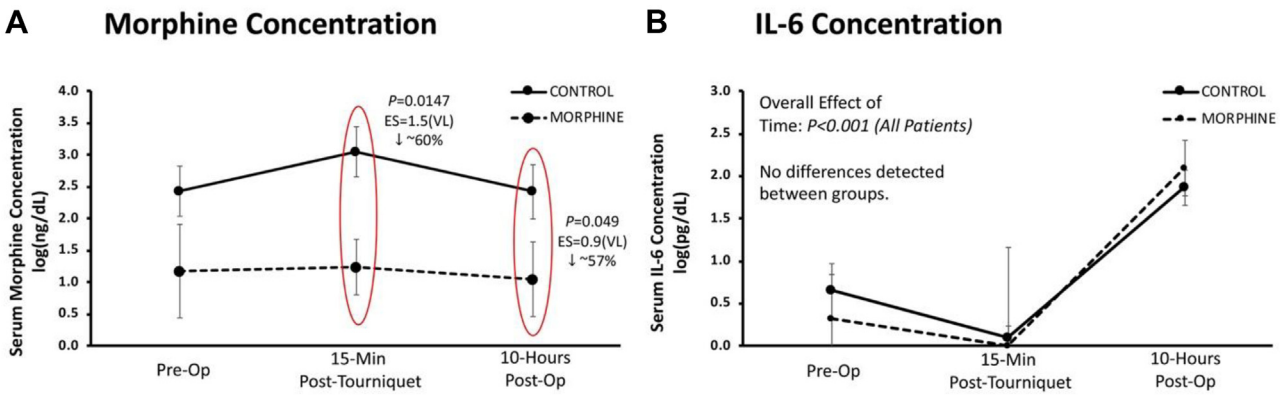


Fig. 6. Data are presented as adjusted means ± SEM for (A) serum morphine [log (ng/dL)] and (B) IL-6 [log (pg/dL)] concentrations measured preoperatively as well as at 15-minute post-tourniquet release and 10-hour postsurgery. Circles indicate significant differences between groups at the same measurement timepoint at $P < .05$. For all significant pairwise comparisons, effect size (ES) is provided as a Cohen's *d* statistic and interpreted as follows: <0.1 (Negligible, N); 0.1-0.3 (Small, S); 0.3-0.5 (Moderate, M); 0.5-0.7 (Large, L); and >0.7 (Very Large, VL). IL-6, interleukin-6; SEM, standard error of the mean.

suggest that this technique provides a clinically meaningful and safe method of pain management that results in a reduction in postoperative opioid use and possibly, greater improvements in patient-reported knee function over time.

Pain control after TKA has been of great clinical interest in the last decade [29–35]. The length of hospitalization after primary TKA has been decreasing, and many patients are being discharged home on the same day of surgery [36,37]. Therefore, pain management in the immediate postoperative period is increasingly important to clinical outcomes and patient satisfaction. Here we observed that the use of IO morphine preemptively treats pain, requiring less opioid pain medication for up to 2 weeks postoperatively (Fig. 4). Importantly, we also observed a concomitant improvement in patient-reported knee-specific outcomes (Fig. 5), which may indicate not only improved pain management, but also improved recovery trajectories.

In the past decade, deaths in the United States due to opioid-related overdoses have tripled [38]. In addition, the opioid crisis has had a substantial cost to society in health care, criminal justice, and productivity, and the cost burden to society is estimated at $78.5 billion [39–41]. Because TKA procedures are one of the most common surgical interventions performed to treat arthritic pain in the United States, examining the utility of IO opiates could potentially allow a decrease in prescribed oral opioid medication. Although further investigation is needed, the present findings (Figs. 3 and 4) may be helpful to potentially decrease the incidence of opioid addiction.

IL-6 is a biomarker of the immune response to trauma and/or cell stress [42–44]. However, IL-6 is not a direct measure of inflammation. Following TKA, elevated levels of IL-6 occur [45]. Although there are elevated IL-6 levels due to cell stress, IL-6 is unrelated to pain. Patients in the MORPHINE group had more effective pain relief, while using less systemic morphine and continued to have a normal postoperative inflammatory (IL-6) response that is expected after surgery. The immune response following trauma and/or surgery is important in the postoperative healing period, and therefore ensuring that IO morphine does not affect this mechanism is vital. This is demonstrated by the MORPHINE group having similar IL-6 at 10 hours postoperatively, suggesting that IO morphine allowed for a retained immune response relative to the CONTROL group [29–31]. It is important to retain the inflammatory response after trauma, even with IO morphine, to allow for improved tissue healing and rapid recovery. Therefore, the present study suggests that IO morphine results in less postoperative pain, less opioid use, while also retaining the inflammatory response to achieve rapid and normal recovery and tissue healing.

Importantly, the present findings should not imply that postoperative pain management will not be required after a one-time administration of IO morphine. The half-life of morphine is 2-3 hours [46–48], so this technique may not substitute for oral medication after hospital discharge. However, these results do suggest that by blunting the initial pain and inflammatory response, IO morphine allows for patients to better manage postoperative pain with less medication and improved recovery trajectories. In addition, patients in the CONTROL group may be more apprehensive about movement and load-bearing activity compared to the MORPHINE group [49], who experience less pain in the early postoperative period.

In this study of 48 patients, we observed 2 cases of PE, 1 in each group. We have been using this technique for approximately 2 years and have not noted any increase in our deep vein thrombosis/PE rate. We plan on continuing our vigilance to postoperative deep vein thrombosis/PE moving forward.

Although we performed a controlled randomized investigation, the present study is not without limitations. For example, there can be patient variability in symptom journal and PROM completion [50]. However, it is unlikely that there would be a significant difference in variability between the 2 study groups due to patient randomization. In addition, the implant was not standardized, but all were done using cemented primary TKA implants. Also, although the postoperative pain medication was standardized as listed in the *Methods* section, the medications administered fluctuated based on the anesthesia staff in the post anesthesia care unit and nurses on the floor. Moreover, spinal and adductor blocks can have varying degrees of pain relief, which could influence postoperative pain levels, opioid use, and clinical outcomes.

The strength of this study is the double-blind, randomized controlled design. Finally, the inflammatory processes involved in the acute inflammatory response to surgical trauma are complex with a great deal of crosstalk between local and systemic effectors and their tissue-specific targets. Therefore, we caution the reader that the present findings on systemic IL-6 should be indicative of an indirect marker of acute inflammation and not a direct measure (eg, localized fluid accumulation/swelling).

In summary, IO morphine administration is an additional tool that can be used to improve postoperative pain following TKA. The benefits of IO morphine with standard antibiotic solution include less opioid medication use postoperatively, decreased pain, decreased inflammation, and improved early clinical outcomes compared to IO antibiotics alone. Moreover, we did not find any adverse events related to IO morphine or vancomycin, suggesting clinical safety.

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