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A Simple Method Associated With Reduced Opioid Consumption After Total Knee Arthroplasty

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ABSTRACT

Background: Most patients experience moderate to severe pain after total knee arthroplasty (TKA). We hypothesized that intraoperative treatment of cut bone surfaces with local anesthetic (preimplantation immersion anesthesia, PIA) would lead to decreased postoperative pain and opioid consumption.
Methods: Records of 76 patients who underwent unilateral, cemented TKA were retrospectively reviewed. For PIA patients, surgical wounds were immersed in local anesthetic solution immediately prior to component implantation. Both PIA ($n = 43$) and control ($n = 33$) groups received multimodal pain management, including intra-articular local anesthetic injections. Endpoints were opioid consumption and mean pain scores for postoperative day (POD) 0, 1, and 2. Demographic, medical, and social factors were included in multivariate analyses.
Results: PIA patients reported significantly lower mean pain scores than controls on PODs 0 and 1 (both $P < .005$). Pain scores on POD 2 were similar. PIA patients used 45%-33% less opioids on PODs 0, 1, and 2 (all $P < .005$). POD 0 pain scores showed a significant interaction between PIA treatment and preoperative opioid use ($P = .013$). On POD 1, PIA was the only factor associated with lower mean pain scores ($P < .001$). No factors were significant for POD 2. PIA was the only factor associated with lower postoperative opioid consumption on PODs 0 and 2 (both $P < .005$). For POD 1, PIA and increasing age (both $P \leq .005$) were associated with lower postoperative opioid consumption.
Conclusion: PIA was associated with significant reductions in opioid use and mean pain scores after TKA.
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Despite advances in perioperative protocols, pain management after total knee arthroplasty (TKA) remains suboptimal for many patients [1]. For example, from September 2015 to September 2016, the TKA patients of 7 different surgeons at our Veterans Affairs (VA) Medical Center used on average over 200 mg of opioids (oral morphine equivalents) postoperatively during the first 2 days of hospitalization. Opioid use and abuse is a special concern of the Veterans Health Administration. In fiscal year 2005, Veterans Health Administration patients had nearly twice the rate of fatal accidental poisonings as the general US adult population, with opioids accounting for the most deaths [2].

Skeletal pain after cemented TKA may arise due to bone damage from (1) bone resection and instrumentation, (2) impaction injury during implant seating, and/or (3) thermal injury from the exothermic polymerization of polymethylmethacrylate. Because bone has a rich nerve supply, with innervation of periosteum, marrow, and mineralized tissues [3], intraoperative treatment of cut bone surfaces with local anesthetic may be capable of decreasing transmission of pain signals and preventing central sensitization to pain [4]. Current anesthetic techniques do not directly target intraosseous nerves. We therefore began immersing TKA wounds with a ropivacaine solution immediately prior to implantation of components (preimplantation immersion anesthesia, PIA). We hypothesized that patients who received PIA during surgery would have lower pain scores and lower postoperative opioid consumption on postoperative day (POD) 0, 1, and 2 than patients who did not. We report the mean pain scores and postoperative opioid consumption of patients who did and did not (controls) receive PIA as part of a multimodal pain management protocol. In

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addition, we performed multivariate analyses to identify factors associated with lower mean pain scores and opioid use on PODs 0, 1, and 2.

Methods

This study is a retrospective review of the medical records of patients who underwent unilateral, primary, cemented TKA by a single surgeon at a single VA Medical Center. Data were obtained under a protocol approved by our Institutional Review Board. Surgeries for the PIA group were performed between August 2015 and September 2016. Surgeries for the control group were performed between August 2014 and August 2015, and in October 2016. We included TKA patients who received spinal anesthesia, an adductor canal nerve block, and an intra-articular injection of a local anesthetic solution after capsular closure (Table 1). Patients were excluded if they received other anesthetic techniques.

PIA was performed as follows: prior to implantation of components, the wound was irrigated and dried. All bony surfaces were then immersed in a local anesthetic solution (Table 1) for 5 minutes. This solution was then removed, the cut surfaces of bone were dried but not further irrigated, and the implants were cemented in place. Postoperatively, patients received the same multimodal pain regimen, including acetaminophen, celecoxib, gabapentin, and opioids. Opioids included hydromorphone patient controlled analgesia, which was started on POD 0 and discontinued on POD 1. After discontinuation of the patient controlled analgesia, intravenous (IV) hydromorphone was available for severe pain not controlled by oral medications. Oral oxycodone was started on POD 0, and provided on a scheduled and as-needed basis. All patients received the same aftercare, including 24 hours of IV antibiotics (cefazolin, vancomycin, or clindamycin depending on allergies), 2 weeks of antithrombotic agents (enoxaparin), and physiotherapy starting on POD 1.

Information obtained from the medical record of the 76 patients included age, weight, gender, race, American Society of Anesthesiologists (ASA) score, body mass index (BMI), preoperative opioids dispensed by VA pharmacies up to 120 days prior to surgery, history of mental health disorders (including post-traumatic stress disorder, anxiety, depression, and bipolar disorder), history of substance abuse, operative time, and hospital length of stay. The primary endpoints were mean daily pain scores and amounts of opioids consumed postoperatively on the hospital ward during the first 3 days of hospitalization (PODs 0, 1, and 2). Pain scores were assessed using a 0-10 numeric rating scale. Opioid consumption in milligrams of oral morphine equivalents was calculated based on the following conversion factors: 1 mg IV hydromorphone = 20 mg oral morphine; 1 mg IV morphine = 3 mg oral morphine; and 1 mg oral oxycodone = 1.5 mg oral morphine [5]. Because patients spent variable amounts of time in the hospital on PODs 0 and 2, opioid consumption was normalized to a 24-hour period, and is reported as "mg opioid."

T-tests were performed to test for differences between the PIA and control groups for continuous variables and chi-square likelihood ratios were calculated to detect differences between the PIA and control groups for categorical variables. Tukey's post hoc multiple comparisons were performed for pain scores and postoperative opioid consumption over time (PODs 0, 1, and 2) to evaluate trends in pain and opioid use over time during hospitalization. Multivariate stepwise (mixed forward and backward) regression was used to identify factors that were associated with lower mean pain scores and opioid consumption. Factors examined in the multivariate analyses were treatment (PIA vs control), age, race, recent preoperative opioid prescriptions, operative time, weight, BMI, ASA, history of substance abuse, and mental health disorder (anxiety, depression, bipolar disorder, or post-traumatic stress disorder), as well as all second-order interactions. Mental health disorders and substance abuse are associated with opioid abuse and dependence among Veterans [6]. Gender was not included in the model because there were only 4 women, all of whom were in the PIA group. We used the Bayesian information criterion for more parsimonious models to avoid overfitting the dataset. Analysis of variance was performed on the final models selected. $P < .05$ was considered significant. All values are reported as means ± standard deviation. JMP 12.1 (SAS Institute, Cary, NC) was used for data analyses. Odds ratios (ORs) and their confidence intervals (CIs) were calculated with the package "compute.es" [7] in the R software package [8].

Table 1
Components of Solutions.

Solution	Medication	Amount
Intra-articular injection	30 mg/mL Ketorolac	1 mL
	1 g/mL Tranexamic acid	1 mL
	0.5% Ropivacaine[a]	30 mL
	Vancomycin	1 g
PIA solution	30 mg/mL Ketorolac	1 mL
	1 g/mL Tranexamic acid	1 mL
	0.5% Ropivacaine	30 mL
	Normal saline[b]	

[a] Volume adjusted based on patient weight and amount provided in spinal and adductor canal blocks.
[b] Volume to completely immerse bony surfaces.

Results

All eligible patients were included in this study (43 patients in the PIA group and 33 patients in the control group). The period of study was the inpatient hospitalization for each patient, and no patient was lost to follow-up. The patients in the PIA and control groups were very similar (Table 2). No significant differences existed for age, weight, BMI, ASA, race, percentage of patients with preoperative opioid prescriptions, percentage of patients with mental health disorders, and percentage of patients with histories

Table 2
Patient and Hospitalization Characteristics as Means (SD) or Percentage.

Characteristic	Control ($n = 33$)	PIA ($n = 43$)	*P* Value
Mean age (y)	67.9 (8.4)	66.9 (6.8)	.575
Mean weight (US pounds)	217.2 (35.0)	208.1 (44.7)	.338
Mean BMI (kg/m^2)	31.5 (4.9)	29.7 (5.0)	.136
Mean ASA	2.7 (0.6)	2.7 (0.6)	.822
Gender: %male	100%	90.7%	.030
Race			.472
White	75.8%	74.4%	
Black	18.2%	14.0%	
Hispanic	6.1%	7.0%	
Asian	0.0%	4.7%	
Percent with preoperative opioid prescriptions	33.3%	41.9%	.447
Percent with mental health disorder	30.3%	37.2%	.528
PTSD	18.2%	18.6%	
Depression	15.2%	25.6%	
Anxiety	12.1%	9.3%	
Bipolar	9.1%	4.7%	
Percent with substance abuse history	18.2%	18.6%	.962
Operative time (h)	2.11 (0.33)	1.98 (0.31)	.088
LOS (d)	3.6 (1.4)	2.7 (1.4)	.008

PTSD, post-traumatic stress disorder; LOS, length of stay; SD, standard deviation.

of substance abuse. Gender, however, was significantly different between the 2 groups ($P = .030$). There were very few women in the study and by chance they were all in the PIA group. Operative time was similar for patients in both groups ($P = .080$). Patients in the PIA group had a shorter length of stay, on average, than those in the control group ($P = .008$). Complications were rare in each group. Postoperatively, 1 patient in the control group developed atrial flutter that reverted to normal sinus rhythm. Otherwise, there were no medical or surgical complications in either group. There were no incidents of local anesthetic toxicity.

Pain Scores

Patients receiving PIA reported significantly lower mean pain scores (mean ± standard deviation) on POD 0 (PIA 2.3 ± 2.1 vs control 3.9 ± 2.5, $P = .003$, OR 3.64, 95% CI 1.54-8.63) and POD 1 (PIA 3.1 ± 1.9 vs control 4.6 ± 1.7, $P < .001$, OR 4.52, 95% CI 1.89-10.80). Pain scores were not significantly different between the 2 groups on POD 2 (PIA 3.6 ± 2.1 vs control 3.9 ± 1.9, $P = .444$, OR 1.38, 95% CI 0.6-3.19; Table 3). Averaged over the entire time period examined (POD 0 to POD 2), patients in the PIA group reported 25% less pain than patients in the control group (PIA 3.0 ± 1.5, control 4.1 ± 1.4, $P < .001$, OR 4.24, 95% CI 1.78-10.10).

Opioid Use

Patients in the PIA group used significantly less opioids on POD 0 (PIA 116 ± 137 mg opioid, control 213 ± 150 mg opioid, $P = .004$, OR 3.42, 95% CI 1.45-8.08), POD 1 (PIA 86 ± 48 mg opioid, control 128 ± 68 mg opioid, $P = .002$, OR 3.79, 95% CI 1.60-9.00), and POD 2 (PIA 57 ± 32 mg opioid, control 84 ± 40 mg opioid, $P = .002$, OR 3.97, 95% CI 1.67-9.43; Table 3). From POD 0 to POD 2, patients in the PIA group used 34% less postoperative opioids normalized to a 24-hour period than patients in the control group (PIA 80 ± 41 mg opioid, control 122 ± 48 mg opioid, $P < .001$, OR 5.57, 95% CI 2.31-13.44).

Factors Associated With Lower Mean Pain Scores on PODs 0, 1, and 2

On POD 0, there was a significant interaction between treatment (PIA vs control) and history of preoperative opioid prescription on average pain scores ($F_{1, 72} = 6.43$, $P = .013$; Table 4). For the patients without preoperative opioid prescriptions ($n = 47$), the patients in the PIA group had significantly lower reported pain scores than those in the control group (PIA 1.8 ± 1.6, $n = 25$ vs control 4.4 ± 2.8, $n = 22$; OR 5.48, 95% CI 2.27-13.21). For the patients with preoperative opioid prescriptions ($n = 29$), no difference in POD 0 pain scores was observed between the PIA and control groups (PIA 2.9 ± 2.5, $n = 18$ vs control 2.8 ± 1.5, $n = 11$; OR 1.04, 95% CI 0.45-2.40). On POD 1, PIA was the only factor associated with lower mean pain scores ($F_{1, 74} = 12.91$, $P < .001$; PIA 3.1 ± 1.9 vs control 4.6 ± 1.7, $P < .001$, OR 4.52, 95% CI 1.89-10.80; Table 4). On POD 2, none of the evaluated factors were significantly associated with lower mean pain scores.

Table 3
Mean (SD) Pain Scores and Postoperative Opioid Consumption (mg Opioid) of Patients.

Outcome	Control ($n = 33$)	PIA ($n = 43$)	P Value	Odds Ratio	95% CI
Pain score on POD 0	3.9 (2.5)	2.3 (2.1)	.003	3.64	1.54-8.63
Pain score on POD 1	4.6 (1.7)	3.1 (1.9)	.001	4.52	1.89-10.8
Pain score on POD 2	3.9 (1.9)	3.6 (2.1)	.444	1.38	0.60-3.19
24-h opioid consumption on POD 0	213.4 (150.4)	116.4 (137.2)	.005	3.42	1.45-8.08
24-h opioid consumption on POD 1	128.3 (68.0)	86.0 (48.1)	.002	3.79	1.60-9.00
24-h opioid consumption on POD 2	83.6 (40.3)	56.6 (31.5)	.002	3.97	1.67-9.43

SD, standard deviation.

Table 4
ANOVA Summary Statistics From Factors[a] Contributing to Pain on POD 0, 1, 2 and Contributing to Opioid Consumption on POD 0, 1, 2.

Variable	R^2	Factors	DF	F Ratio	P Value
Pain on POD 0	0.19	Treatment (PIA vs control)	1	5.68	.020
		Preoperative opioids	1	0.18	.670
		Treatment × preoperative opioids	1	6.43	.013
Pain on POD 1	0.15	Treatment	1	12.91	<.001
Pain on POD 2	–	None	–	–	–
Opioid consumption on POD 0	0.10	Treatment	1	8.59	.005
Opioid consumption on POD 1	0.21	Treatment	1	12.35	<.001
		Age	1	8.38	.005
Opioid consumption on POD 2	0.12	Treatment	1	10.77	.002

ANOVA, analysis of variance; DF, degrees of freedom.
[a] Factors examined included treatment (PIA or control), age, race, preoperative opioid prescription, operative time, weight, BMI, ASA, history of mental disorder, and history of substance abuse.

Factors Associated With Lower Opioid Consumption on PODs 0, 1, and 2

PIA was the only factor that was associated with lower postoperative opioid consumption on PODs 0 and 2 ($F_{1, 74} = 8.59$, $P = .004$, OR 3.42, 95% CI 1.45-8.08 and $F_{1, 74} = 10.77$, $P = .002$, OR 3.97, 95% CI 1.67-9.43, respectively; Table 4). For POD 1, both PIA ($F_{1, 72} = 12.35$, $P < .001$, OR 4.37, 95% CI 1.83-10.43) and increasing age ($F_{1, 72} = 8.38$, $P = .005$, OR 0.30, 95% CI 0.13-0.70) were significantly associated with lower postoperative opioid consumption, that is, older patients tended to use less opioids than younger patients.

Discussion

Local anesthetics are frequently used to decrease discomfort after TKA, and can block transmission of pain signals at many anatomic locations, including the spinal cord (spinal anesthesia), peripheral nerves (femoral, sciatic, and adductor canal blocks), and periarticular soft tissues (periarticular infiltration and intra-articular injection). Because bone is injured during TKA, we evaluated the effects of direct application of local anesthetic to damaged bone. Patients receiving this treatment (PIA) reported significantly lower pain scores and used significantly less opioid medication than patients who did not receive this treatment (controls) (Table 3).

The overall 25% reduction in pain scores and 34% reduction in opioid consumption associated with PIA is similar in magnitude to other analgesia techniques for TKA. A trial that evaluated periarticular infiltration showed a 24% lower median cumulative consumption of oxycodone compared to controls at 48 hours [9]. Celecoxib reduced visual analog pain scores by 38% at 48 hours and reduced opioid requirements by 40% [10]. Similarly, celecoxib reduced daily opioid consumption by 32% in another cohort [11]. Of note, both PIA and control patients in this study received celecoxib, indicating that the effect of PIA was additive to that of celecoxib.

However, the clinical importance of the statistically significant decrease in pain scores for the PIA group compared to controls on

PODs 0 and 1 is unclear. To our knowledge, the minimal clinically important difference (MCID) in knee pain scores between 2 separate patient populations receiving 2 different therapies has not been established. MCID has been defined as "the smallest difference in score reported by patients that correlates with the patient stating that he or she is slightly better compared to his or her own state at an earlier point" [12]. MCID should therefore be used to compare different treatments within a single population, rather than the effects of different treatments in different populations. In patients with chronic musculoskeletal pain, a 15% reduction in pain was found to be an appropriate MCID ("slightly better"), with a 33% reduction corresponding to the highest degree of improvement ("much better"). In our study, the PIA group had a 41% lower average pain score on POD 0 and a 33% lower average pain score on POD 1 compared to controls.

Our findings regarding age and preoperative opioid consumption are consistent with previous reports. For example, lower pain levels have been reported in older TKA patients, with no significant differences based on race or BMI [13]. Other investigators have also found an inverse correlation between age and opioid consumption [11]. Preoperative opioid use has been associated with increased opioid consumption and pain after TKA [14,15]. Because all female patients in our cohort were in the PIA group, we could not evaluate the association between gender and pain/opioid consumption in this study. Female gender has been associated with higher pain scores in other investigations. In a retrospective evaluation of anesthetic technique, age, and gender, female patients reported higher pain ratings than male patients but did not use more opioids [16]. Female gender and younger age were also associated with higher analog pain scores in another cohort [13].

This study has several limitations, including its retrospective nature, which allows demonstration of correlation but not causation. Although surgical technique, anesthetic technique, patient demographic factors, rates of preoperative opioid use, and postoperative pain management were similar for the 2 groups, we cannot exclude confounding. The control patients could by chance have had inherently higher opioid requirements and pain perceptions. Although we attempted to include as many plausible factors as possible in the multivariable analysis, unrecognized variables may be significant. Another limitation is the homogenous nature of the Veteran population. The majority of our patients were white men, and we do not know whether similar associations will be found in other groups.

Caution should be used when introducing PIA into practice due to the potential for local anesthetic systemic toxicity. Although no episodes of toxicity occurred in either group, care must be taken to provide an appropriate weight-based dose of medication. We used a total of 3 mg/kg local anesthetic in the spinal anesthesia, the peripheral nerve block, and the intra-articular injection. This dose is within published guidelines [17]. A standard dose of 150 mg of ropivacaine was used for the adductor canal blocks in both patient groups. A total of 150 mg of ropivacaine was used for PIA, regardless of patient weight. Following incubation, this solution was removed with thorough suctioning of the wound, including all bony surfaces and the medullary canals. In addition, tourniquet was used during PIA to minimize systemic spread of anesthetic. Despite this, PIA almost certainly leads to local deposition of ropivacaine in the wound, but due to bony bleeding, we were unable to accurately quantify the amount of local anesthetic that remained in the knee. The effects of PIA on uncemented implant fixation are also unknown. Finally, we do not know the complication rate associated with PIA in larger cohorts. However, the medications used have been administered intra-articularly and periarticularly in thousands of patients with rare adverse effects.

Conclusion

In conclusion, in a patient population with high post-TKA opioid consumption despite multimodal pain control that included intra-articular local anesthetic, PIA was associated with significant reductions in opioid use and mean pain scores without an increase in complications. This novel, simple, inexpensive technique is compatible with other perioperative methods for pain management, including periarticular injections. Other local anesthetics and medications can be incorporated. A randomized controlled trial is required to prove that PIA decreases pain and opioid consumption. Such a trial should ideally be performed in a population with wider gender and racial diversity than the current cohort. Additional research is required to determine how best to combine PIA with other pain control modalities and the rate of complications in larger cohorts. Finally, this approach may be evaluated for other procedures in which bone is damaged.

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