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Efficacy of Multimodal Perioperative Analgesia Protocol With Periarticular Medication Injection in Total Knee Arthroplasty: A Randomized, Double-Blinded Study

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ABSTRACT

Pain control is necessary for successful rehabilitation and outcome after total knee arthroplasty. Our goal was to compare the clinical efficacy of periarticular injections consisting of a long-acting local anesthetic (ropivacaine) and epinephrine with and without combinations of an α2-adrenergic agonist (clonidine) and/or a nonsteroidal anti-inflammatory agent (ketorolac). In a double-blinded controlled study, we randomized 160 patients undergoing total knee arthroplasty to receive 1 of 4 intraoperative periarticular injections: Group A, ropivacaine, epinephrine, ketorolac, and clonidine; Group B, ropivacaine, epinephrine, and ketorolac; Group C, ropivacaine, epinephrine, and clonidine; Group D (control), ropivacaine and epinephrine. Compared with Group D, Group A and B patients had significantly lower postoperative visual analog pain scores and nurse pain assessment and Group C patients had a significantly greater reduction in physical therapist pain assessment. We found no differences in other parameters analyzed.

According to the National Institutes of Health Consensus Statement on total knee arthroplasty (TKA), the success of TKA is supported by more than 20 years of follow-up data [1]. After TKA, 90% of patients experience rapid and substantial improvement in pain, functional status, and overall health-related quality of life, and 85% are satisfied with their results [1]. Importantly, there is overall consensus that aggressive postoperative pain management improves TKA outcomes [1].

Adequate postoperative pain control is 1 of the most important concerns for patients considering a TKA [2]. The Joint Commission on Accreditation of Healthcare Organizations [3] emphasizes that pain be assessed and treated. Pain control is necessary for successful postoperative rehabilitation and outcome. Severe pain leads to prolonged hospital stays and increased opioid use, with potential side effects of nausea and vomiting [4]. Severe pain may lead to restricted postoperative knee range of motion (ROM), arthrofibrosis, and an overall poor patient satisfaction [5].

There are many approaches to perioperative analgesia for patients undergoing TKA. Epidural analgesia, intravenous-patient-controlled analgesia (which allows a patient to self-administer a prescribed amount of opioid when pain is felt [6]), and femoral nerve blockade all have proven benefits. However, these methods also have potential side effects. Epidural analgesia may produce spinal headache, neurogenic bladder, hypotension, and contralateral leg numbness [7]. Femoral nerve blockade secondary to motor block may lead to falls or postoperative femoral neuritis [8]. Although morphine remains the standard and most widely administered intravenous patient-controlled analgesic agent, its drawbacks include somnolence, nausea and vomiting, ileus, constipation, pruritis, urinary retention, hypotension and respiratory depression [4,9], which can also affect the patient's ability to effectively participate in physical therapy.

Our current protocol uses a multimodal approach with an intraoperative periarticular injection containing clonidine (off label use), ketorolac (off label use), ropivacaine, and epinephrine. However, the advantage of each medication and the additive or synergistic effect of each medication are unknown. To our knowledge, no randomized study has been performed to assess the efficacy of these injections (single medication or in combination) in terms of postoperative pain control and early postoperative functional outcome. Therefore, our goal was to compare the clinical efficacy of these periarticular injections. Our hypothesis was that the group receiving the combination of all 4 medications (ropivacaine, epinephrine, clonidine, and ketorolac) would have a synergistic effect of those medications and show improved pain scores, improved early ROM, improved Knee Society Score (KSS) in the early postoperative period, and decreased postoperative narcotic usage, with no increased risk of complications.

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Materials and Methods

Patient Population

From January 2010 through June 2011, after receiving institutional review board approval, we conducted a prospective, randomized double-blinded study of all eligible men and nonpregnant women scheduled to undergo primary TKA for osteoarthritis who were at least 30 and no more than 85 years old. Those who elected to participate provided informed consent. Patients were excluded if they had an allergy to any of the medications, contraindication to or failure of spinal anesthesia, known drug or alcohol abuse, a diagnosis of inflammatory arthritis, or previous major surgery on the operative knee. Based on a power analysis, we estimated a sample size of 40 patients in each group to detect a 1.5-point difference in the visual analog scale (VAS) score at each recording with a standard deviation of 2.0 points, a P value of .05, and a power of 80% or higher. A software program was used to determine 160 sets of 4 unique numbers per set with the range of 1 to 4 unsorted.

Patients were randomized to 1 of 4 periarticular injection groups (40 patients each) (Table 1); Group D served as the control. Normal saline was added to the medications to make a total of 100 mL. Blinding remained unbroken for all patients. Of the 160 patients enrolled, 10 were excluded from the analysis (5 patients failed spinal anesthetic, 1 patient underwent unicompartmental knee arthroplasty, 1 patient had simultaneous bilateral TKAs, 1 patient cancelled surgery, and 2 patients did not receive the injection [1 dropped from the study, 1 had an allergy]). The final analysis included 150 patients (A, 38; B, 38; C, 38; and D, 36). No significant differences were found among these groups in baseline demographics [gender ($P = .651$), side of surgery ($P = .077$), surgical approach ($P = .544$), body mass index ($P = .343$), or age ($P = .370$)] or in preoperative assessment of pain (pain KSS, $P = .319$), ROM (extension, $P = .260$; flexion, $P = .412$), alignment ($P = .291$) or functional score (function KSS, $P = .975$). With post-hoc analysis, there was a significant difference ($P = .044$) in preoperative total KSS scores, with patients in Group A having a higher mean score than patients in Group C.

Procedures

The hospital pharmacy prepared and labeled medication according to the randomization schedule (which had had peel-off labels that were removed sequentially 1 by 1 as each subject was enrolled) and maintained the documentation. The pharmacy department delivered the injections to the operating room unmarked, so that the surgeons were blinded to the group assignment. The surgeons, patients, nurses, physical therapists, and research personnel remained blinded throughout the study.

Table 1
Injection Regimens for the Four Study Groups.

Group	Medication[a]	Amount[b]
A	Ropivacaine	5 mg/mL (49.25 mL)
	Epinephrine	1 mg/mL (0.5 mL)
	Ketorolac	30 mg/mL (1 mL)
	Clonidine	1 mg/mL (0.08 mg to 0.8 mL)
B	Ropivacaine	5 mg/mL (49.25 mL)
	Epinephrine	1 mg/mL (0.5 mL)
	Ketorolac	30 mg/mL (1 mL)
C	Ropivacaine	5 mg/mL (49.25 mL)
	Epinephrine	1 mg/mL (0.5 mL)
	Clonidine	1 mg/mL (0.08 mg to 0.8 mL)
D (control)	Ropivacaine	5 mg/mL (49.25 mL)
	Epinephrine	1 mg/mL (0.5 mL)

[a] Ropivacaine is a long-acting local analgesic. Epinephrine was added for local vasoconstriction to prolong the action of the local anesthetic. Ketorolac is a nonsteroidal anti-inflammatory medication. Clonidine is thought to produce analgesia at presynaptic and postjunctional α2-adrenoceptors.

[b] Normal saline was added to medications to make a total of 100 mL.

One hour before the start of surgery, patients 70 or more years old received a preoperative 400-mg oral dose of celecoxib and a 10-mg oral dose of sustained-release oxycodone. Patients less than 70 years old received a preoperative 400-mg oral dose of celecoxib and a 20-mg oral dose of sustained-release oxycodone. All surgeries were done using a spinal anesthetic with 10 to 15 mg of bupivacaine. Intraoperative conscious sedation was not restricted by the protocol. Patients did not have any preoperative or postoperative femoral or sciatic nerve blocks.

A medial trivector approach was used for all patients. All implants were cemented cruciate retaining components (DePuy PFC Sigma, Warsaw, Ind) and included patellar resurfacing. The tourniquet was released before closure and electrocautery was used for hemostasis. A Hemovac drain was placed for drainage. Postoperative cryotherapy was used for all patients.

For all patients, the injections were given before component implantation as follows: 9 mL into the posterolateral soft tissues and lateral femoral periosteum; 1 mL into the posterior cruciate ligament; 10 mL into the posteromedial soft tissues and medial femoral periosteum. After component implantation, injections were given as follows: 25 mL into the medial meniscal remnant, inferomedial capsule; 25 mL into the superomedial capsule, starting at the meniscal remnant; 10 mL into the lateral capsule; 10 mL into the medial subcutaneous tissues; and 10 mL into the lateral subcutaneous tissues.

Data, including basic patient demographic information, were collected during hospitalization, and at office appointments. VAS pain scores were assessed in the preoperative area, in the recovery room and every 4 h thereafter for a total of 48 h, and at discharge. Nurses asked the patients to rate their pain (scale 0 [no pain] to 10 [most severe pain]) every 8 h shift as part of their standard assessment. Physical therapists also asked patients to rate their pain (same scale) during activity at each physical therapy session. Inpatient narcotic consumption and any side effects were documented. A variety of pain medications were used after surgery to keep patients comfortable. Patients were instructed to ask the nurse for pain medication after surgery as needed and were offered meloxicam (15 mg daily) or celecoxib (400 mg daily), oxycodone SR (10 to 20 mg every 12 h for 2 doses), oxycodone (5 to 10 mg every 4 h), acetaminophen (1000 mg every 8 h), hydrocodone and/or acetaminophen (5 to 500 mg, 1 to 2 doses every 4 h), tramadol (50 mg every 8 h), ketorolac (30 mg intravenously every 8 h, with a 4-dose maximum), and morphine or hydromorphone intravenously for supplementary pain control. Narcotic use was recorded as morphine equivalents.

Bilateral compression stockings, sequential compression devices, early ambulation, and 325 mg of aspirin twice a day was the standard for deep venous thrombosis prophylaxis. Patients at higher risk for deep venous thrombosis were treated with warfarin.

At morning and afternoon inpatient therapy sessions, physical therapists assessed and recorded pain, active and passive knee ROM (using goniometers), and ambulation distance (in feet). Scores were averaged for each day.

All patients remained hospitalized until postoperative day 3 when they were discharged home or to an inpatient rehabilitation facility. Physical therapy continued at home, or at outpatient centers once the patient was able to travel to outpatient physical therapy. KSSs, ROM, and complications were recorded at 6 weeks after surgery.

Statistical Analysis

There were 3 assessments of pain: patient-reported VAS pain score, nurse-reported score, and physical-therapist-reported score. Using a repeated measures linear equation, longitudinal changes in pain assessment across the 4 groups were modeled.

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VAS pain score was plotted over time for the 4 groups. The relationship between VAS pain score and time indicated a curvilinear relationship. An adjustment was made for preoperative pain score and a quadratic term for time to reflect this relationship.

Demographic and clinical characteristics were examined across the 4 treatment groups to test the randomization. Continuous measures (eg, age) were analyzed using analysis of variance. Categorical measures (eg, gender) were analyzed using χ^2 test of association.

Outcomes of interest were measures of pain severity (patient-assessed VAS pain score, physical-therapist-assessed pain score, and nurse-assessed pain score), ROM (inpatient and 6-week active and passive assessment), inpatient walking distance, and KSSs. In addition, inpatient narcotic use was calculated as morphine equivalent dose. For repeated measures (eg, repeated patient-reported VAS pain score during hospitalization), a generalized estimate equation was used to determine the influence of treatment group on pain severity [10]. Statistical interaction terms between treatment group and time were assessed to determine longitudinal effects of each treatment group on the outcome of interest.

Statistical significance was set at $P < .05$.

Results

With a repeated measures model, Group A and B patients had significantly lower VAS pain scores ($P < .001$ and $P = .023$, respectively) (Fig. 1) than did Group D patients. We found no significant difference in VAS pain scores between Group C and D patients ($P = .113$).

Nursing pain assessments over time for the 4 groups showed a linear relationship. With a repeated measures model, Group A and B patients had significantly lower nurse pain assessment ($P < .001$ and $P = .030$, respectively) than did Group D patients. We found no significant difference in VAS pain score between Groups C and D ($P = .051$).

Physical therapist pain assessment over time indicated a linear relationship. With a repeated measures model, we found no significant differences in physical therapist pain assessment for Group A ($P = .227$) or B ($P = .481$) patients compared with Group D patients. Group C patients had a greater reduction in pain assessment ($P = .016$) than Group D patients.

In terms of physical-therapist-assessed ROM, we found no significant differences in active extension, active flexion, passive extension, or passive flexion for Group A, B, or C patients compared with Group D patients.

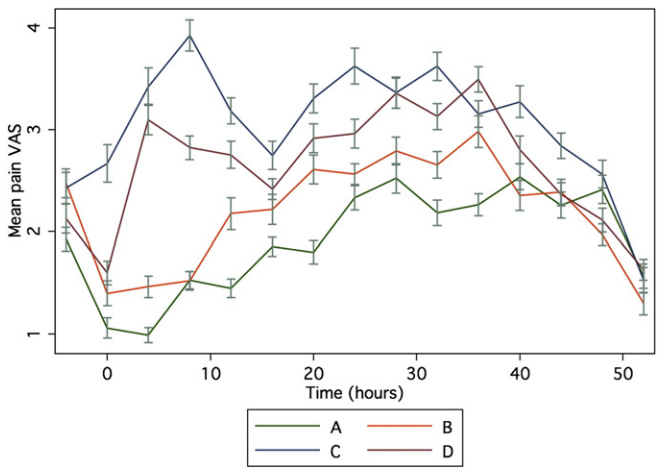

Fig. 1. The mean VAS pain score is shown for the preoperative assessment and for every fourth hour after surgery for each injection type.

In terms of physical-therapist-assessed ambulation, we found no significant differences for Group A ($P = .405$), B ($P = .478$), or C ($P = .078$) patients compared with Group D patients.

With respect to the morphine equivalence, the mean equivalence was examined on postoperative days 1, 2, and 3 and overall across the 4 groups. Narcotic conversion factors were used to convert various narcotics to morphine equivalents. Group C patients had a higher mean morphine equivalence at all time points; however, we found no significant differences among groups (postoperative day 1, $P = .129$; postoperative day 2, $P = .463$; postoperative day 3, $P = .593$; and overall, $P = .169$).

At the 6-week assessment, we found no significant differences among groups in pain (pain KSS, $P = .435$), ROM (extension, $P = .835$; flexion, $P = .540$), alignment ($P = .893$), functional KSS ($P = .627$), or total KSS ($P = .371$).

There were no complications that we could attribute to the injected medications. One patient in Group C had wound dehiscence within 2 weeks after surgery that was treated successfully with prophylactic antibiotics. Specifically, there were no infections or manipulations in any of the groups.

Discussion

The current physiologic understanding of pain suggests that stimuli that are perceived as painful cause a “recruitment” phenomenon, in which initial painful stimuli induce hyperpolarization of adjacent neural pathways, making subsequent pain more difficult to control. If a mechanism exists to prevent the initial postoperative pain from being experienced, subsequent pain management is achieved more reliably. This finding is the principle of “preemptive analgesia” [11,12].

The concept of multimodal pain control with periarticular injections is receiving increasing interest in the literature [13–16]. Recent publications have shown patient safety and are promising in terms of improved pain control, decreased narcotic use, and decreased associated side effects [13–15,17]. Although several different multimodal protocols exist, a gold standard has not been established. The primary goal of a multimodal strategy would be to decrease pain at the central and peripheral levels while minimizing side effects, facilitating patient participation in postoperative rehabilitation, allowing earlier discharge, and improving overall functional outcome [18].

To our knowledge, few studies have examined the efficacy of a multimodal pain control protocol with periarticular injections in terms of postoperative pain control in combination with functional outcome in the early postoperative period. Therefore, our goal was to assess, via a randomized, double-blinded study, the advantage or synergistic effect of an injection cocktail of clonidine, ketorolac, ropivacaine, and/or epinephrine on early postoperative pain control and functional outcome in patients undergoing TKA. Further, the benefits of these injections beyond the inpatient setting are unknown. We followed these patients in a continued blinded fashion through their 6-week postoperative period.

Our results showed that patients in Group A (ropivacaine, epinephrine, ketorolac, and clonidine) and Group B (ropivacaine, epinephrine, and ketorolac) had significantly lower VAS pain and nursing pain assessments during the early postoperative period than did patients in Group D (ropivacaine and epinephrine). No group showed differences in active or passive ROM while in inpatient physical therapy. Ambulation distance and narcotic usage were not statistically different among groups.

In a randomized trial of 64 patients, Busch et al [15] found that patients who received a periarticular injection containing ropivacaine, ketorolac, epimorphine, and epinephrine used less patient-controlled analgesia at 6, 12, and 24 h after surgery and had lower pain scores in the postanesthetic care unit and at 4 h after the operation. Mullaji

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et al [19] evaluated 40 patients undergoing concurrent bilateral TKAs in which a periarticular injection containing bupivacaine, fentanyl, methylprednisolone acetate, and cefuroxime was used only on 1 knee. Patients reported significantly lower pain scores for the injected knee up to 4 weeks after surgery. In contrast, Joo et al [20] evaluated 286 patients in a randomized, double-blinded study of concurrent bilateral TKA in which 1 knee was infiltrated with a periarticular injection containing bupivacaine, morphine, methylprednisolone acetate, and epinephrine. Their intraarticular injection did not improve pain scores at 12, 24, or 36 h or on postoperative day 7 or 14. In a study of 76 patients, Christensen et al [21] compared periarticular injections consisting of bupivacaine, morphine, epinephrine, clonidine, and cefuroxime with and without inclusion of a corticosteroid. They found that the addition of the steroid did not appear to improve pain in the postoperative period. In terms of pain, our randomized double-blinded study of 150 patients showed lower patient VAS pain scores for Groups A and B, but we did not find a statistical difference in narcotic consumption.

In terms of the effect of periarticular injections on ROM, Mullaji et al [19] found greater active flexion at discharge, 2 weeks, and 4 weeks after surgery in patients receiving their specific injection protocol. Once again in contrast, Joo et al [20] found no difference in terms of ROM at 2 weeks after surgery. In our study, we found no difference in postoperative ROM through 6 weeks of follow-up.

Christensen et al [21] found no additional benefit from the addition of the corticosteroid to their periarticular injection in terms of KSS at 6 or 12 weeks after surgery. Although our injection did not contain corticosteroid, in terms of KSS, we also found no differences among the groups at the 6-week postoperative visit.

Our study has several strengths. First, it is a well powered, randomized, double-blinded study. Second, we included follow-up beyond the initial hospitalization. Third, the injection medications we used are available through any hospital pharmacy and are easily administered during the surgical procedure, so our findings could be generalized for any joint reconstruction surgeon.

Our study also has limitations. First, 2 different surgeons were involved in the study; however, the surgical technique was similar and the injection locations were standardized. Second, the medication side effects may not have been entirely captured through the entire 6-week postoperative period; however, we could not identify any specific complication from the injections. Third, we did not account for patients' preoperative medications and therefore cannot adjust for patients' tolerances to narcotics in the perioperative period.

In conclusion, a multimodal pain control protocol, including an intraoperative periarticular injection with ropivacaine, epinephrine, clonidine, and ketorolac showed better early postoperative pain control compared with a control group. These early improvements in pain control did not persist at the 6-week follow-up, and we found no statistical differences in terms of postoperative functional improvements. More study is needed to determine if additional medications or changes in the medication concentrations in the injection could provide added benefit or long-term functional improvements beyond the perioperative period.

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