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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.