A Multimodal Analgesia Protocol for Total Knee Arthroplasty. A Randomized, Controlled Study

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A Multimodal Analgesia Protocol for Total Knee Arthroplasty

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Background: Although numerous methods of postoperative analgesia have been investigated in an attempt to improve pain control after total knee arthroplasty, parenteral narcotics still play a major role in postoperative pain management. Local anesthetics have the advantage of blocking pain conduction at its origin and minimizing the systemic side effects associated with postoperative narcotic use. This study was performed to evaluate the benefits and safety of a multimodal analgesia protocol that included periarticular injection of large doses of local anesthetics in patients undergoing total knee arthroplasty.

Methods: We compared morphine consumption during the first twenty-four hours after unilateral total knee arthroplasty in forty-two patients who had been randomized to receive either (1) a perioperative infiltration mixture, consisting principally of local anesthetic, and self-administered morphine or (2) self-administered morphine only. Narcotics consumption, pain control, medication-related side effects, plasma levels of the local anesthetic (ropivacaine), and postoperative rehabilitation were monitored.

Results: Although there was high satisfaction and good pain control in both groups, morphine consumption was significantly lower in the local analgesia group than it was in the control group (28.8 ± 17.4 mg compared with 50.3 ± 25.4 mg twenty-four hours after surgery, and 46.7 ± 19.4 mg compared with 68.6 ± 38.6 mg forty hours after surgery). Both groups achieved a similar amount of knee flexion on the fifth postoperative day. Over the five-day period after the procedure, the patients in the local analgesia group reported a total of 2.6 ± 3.9 hours of nausea compared with 7.1 ± 12.2 hours in the control group. No complications related to the infiltration of the local anesthetic were observed, and all plasma concentrations of the local anesthetic were below the toxic range.

Conclusions: This multimodal perioperative analgesia protocol that included infiltration of a local anesthetic offered improved pain control and minimal side effects to patients undergoing total knee arthroplasty. Our study also confirmed the safety of the protocol.

Level of Evidence: Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

Although total knee arthroplasty is a successful procedure for the treatment of degeneration of the knee joint[1], perioperative pain control is suboptimal[2-6]. Parenteral narcotics play a major role in postoperative pain control strategies, despite notable side effects such as nausea, vomiting, confusion, constipation, urinary retention, dizziness, sedation, respiratory depression, and pruritus[2,4,6,7].

Continuous epidural, lumbar plexus, and femoral and/or sciatic nerve blocks improve postoperative pain control and reduce consumption of narcotics[6,8] at the cost of other potential problems, such as epidural bleeding (with prophylactic anticoagulation therapy), diminished muscle control, urinary retention, and nerve damage[6,9-12].

To reduce the occurrence of side effects or complications, an analgesia protocol should preferably be multimodal and should block pain at its origin. Furthermore, it should maintain maximum muscle control to optimize postoperative mobilization, allow active physical therapy, and reduce venous stasis. Periarticular injection of local anesthetics is a possible option to achieve these goals. The objective of this study was to assess the benefits and safety of a multimodal analgesia protocol that included periarticular soft-tissue in-

jection of large doses of a local anesthetic for pain relief after total knee arthroplasty.

Materials and Methods

Participants

Subjects with degenerative or rheumatoid arthritis of the knee who were candidates for total knee arthroplasty were recruited bvy four orthopaedic surgeons. The exclusion criteria were simultaneous bilateral total knee arthroplasty, previous patellectomy, acute or chronic knee infection, regular narcotic use, psychiatric illness, neuromuscular deficit, major systemic illness (heart failure, renal insufficiency, or coagulopathy), and known allergy or intolerance to one of the study drugs. The study protocol was approved by an ethics and a scientific committee, and all subjects gave written informed consent to participate in the study.

Study Design

Participants were randomly assigned to the two treatment groups: local anesthetic and control. A randomization table was created with SPSS 10.04 software (SPSS, Chicago, Illinois). The patients and the postoperative team (an internist, the nurses, and a physiotherapist) were kept blind to the treatment group.

Surgery

All patients received spinal anesthesia with 2 to 3 mL of 0.5% bupivacaine without a narcotic. (Spinal anesthesia was not possible in only two patients, one in each group, and both patients were excluded from the study.) Neither intravenous narcotics nor ketamine were administered during the surgery, according to the protocol, and no bladder catheter was inserted. The operations were performed with use of a tourniquet, which was inflated during draping and was released before or after skin closure according to the surgeon's preference. A standard medial parapatellar arthrotomy was used, and posterior stabilized components were fixed with cement (Simplex-P Bone Cement with tobramycin; Stryker, Kalamazoo, Michigan). A vacuum drain was inserted before joint closure and was removed on the first postoperative day. All patients received a COX-2 inhibitor (Celebrex [celecoxib], 200 mg twice a day) and acetaminophen (500 mg four times a day) preoperatively (on the morning of the surgery) and regularly postoperatively. Low-molecular-weight heparin (Fragmin [dalteparin], 5000 units subcutaneously daily for ten days) was administered beginning on the first day. A patient-controlled anesthesia pump with morphine was available for additional analgesia. The decision to discontinue use of the pump was determined by the anesthetist, with no standardized criteria in the study. Afterward, oral narcotics (hydromorphone, codeine, or oxycodone) were administered as needed.

Patients were allowed to become mobile as tolerated beginning on the day of the surgery. The morning after the surgery, isometric, passive, and active exercises were supervised by a senior physiotherapist. A continuous-passive-motion machine was used twice a day, with increases in the range of motion as tolerated.

Group Treated with Local Analgesia

The local infiltration mixture was prepared by adding 7.5 mL of a 10-mL Naropin (ropivacaine) 10.0 mg/mL sterile pack, 30 mg of ketorolac, and 0.5 mL of adrenaline (1:1000) to a 100-mL Naropin 0.2 mg/mL sterile pack (total of 275 mg of ropivacaine). Before the prosthesis was implanted, two 60-mL syringes, each with a 22-gauge needle, loaded with a total of 107.5 mL of the solution, were used to infiltrate the deep tissues (collateral ligaments, posterior aspect of the capsule, quadriceps tendon, patellar tendon, fat pad, periosteum, and synovium) with the mixture. Before wound closure, the subcutaneous tissues were infiltrated with 125 mg of ropivacaine (the rest of the Naropin 10.0 mg/mL sterile pack [2.5 mL] plus 50 mL of another 100-mL Naropin 0.2 mg/mL sterile pack [a total of 52.5 mL in a 60-mL syringe]). A 16-gauge catheter that passed through the vastus lateralis muscle was inserted into the joint (for intra-articular injection on the day after the surgery). A negative-pressure vacuum drain was also placed in all knees.

For the pharmacokinetics study, 7 mL of blood was collected into heparinized tubes preoperatively and every ten minutes after tourniquet release, until ninety minutes had elapsed. Blood samples were kept in an ice-water bath before centrifugation. Plasma was frozen at –70°C pending high-performance liquid chromatography analysis.

On the first postoperative day (between sixteen and twenty-four hours after the surgery), the vacuum drain was clamped and 150 mg of ropivacaine (15 mL of 10 mg/mL Naropin) was injected into the knee through the 16-gauge catheter, and then the catheter was removed. To avoid ropivacaine drainage through the skin hole, the clamped drain was removed three to six hours after injection.

Outcome Measures

The primary outcome measure was morphine consumption by means of the patient-controlled anesthesia pump over the first twenty-four hours after the surgery. With an alpha error of 0.05, a power of 80%, and a standard deviation of 25 (milligrams of morphine consumption per twenty-four hours)[13,14], thirty-two patients (sixteen in each group) were required for the study to detect a difference of 25 mg of morphine between the two groups. Morphine consumption was recorded every

TABLE I Conversion of Narcotics Use into Morphine Equivalents After Discontinuation of Patient-Controlled Analgesia at Forty-Eight Hours Postoperatively

Narcotics	Dose in Morphine Equivalents *(mg)*
Morphine, subcutan. or intramusc.	10
Hydromorphone, subcutan. or intramusc.	1.5
Hydromorphone, oral	7.5
Codeine, subcutan. or intramusc.	120
Codeine, oral	200
Oxycodone, oral	20

TABLE II Demographic and Perioperative Data

	Local Analgesia Group	Control Group	P Value
Sex (M/F)*	6/16	6/14	0.845
Side (R/L)*	13/9	9/11	0.361
Diagnosis*			0.157
Osteoarthritis	20	20	
Rheumatoid arthritis	2	0	
Weight† *(kg)*	87.7 ± 14.5	88.7 ± 14.9	0.834
Body mass index† *(kg/m^2)*	33 ± 5.3	34 ± 5.7	0.539
Preoperative hemoglobin level† *(g/L)*	137 ± 15.9	138 ± 10.8	0.897
Surgical time† *(min)*	106 ± 18.3	108 ± 17.8	0.731
Blood loss† *(mL)*			
Intraop.	58 ± 229	37 ± 88	0.711
Postop.	538 ± 346	372 ± 316	0.132
Total	596 ± 441	409 ± 320	0.148
Wound discharge† *(days)*	1.15 ± 1.2	1.63 ± 2.0	0.354

*The values are given as the number of patients. †The values are given as the mean and standard deviation.

eight hours for the first forty-eight hours. After forty-eight hours, narcotics consumption was noted every twenty-four hours and transformed into morphine equivalents according to a conversion table (Table I)[15].

The postoperative pain level was estimated by the patient on a visual analogue scale three times daily (at 8:00 a.m., 4:00 p.m., and 10:00 p.m.) at rest and once or twice a day during physiotherapy exercises. The patients were told that the left end of a 10-cm line represented the absence of pain and the right end represented the most extreme pain that they had ever felt, and then they were asked to put an X on the line in the place that best estimated their pain level at that moment. Four times daily, the patients were asked about the number of hours during the last six-hour period that they had had nausea. Every fifteen minutes in the recovery room and every four hours for the first forty-eight postoperative hours on the ward, nurses and anesthetists observed the patient closely foFr medication side effects, especially those associated with the use of ropivacaine, which include blurred vision, hearing problems, peripheral paresthesias, dizziness, uncontrolled muscle contraction, con-

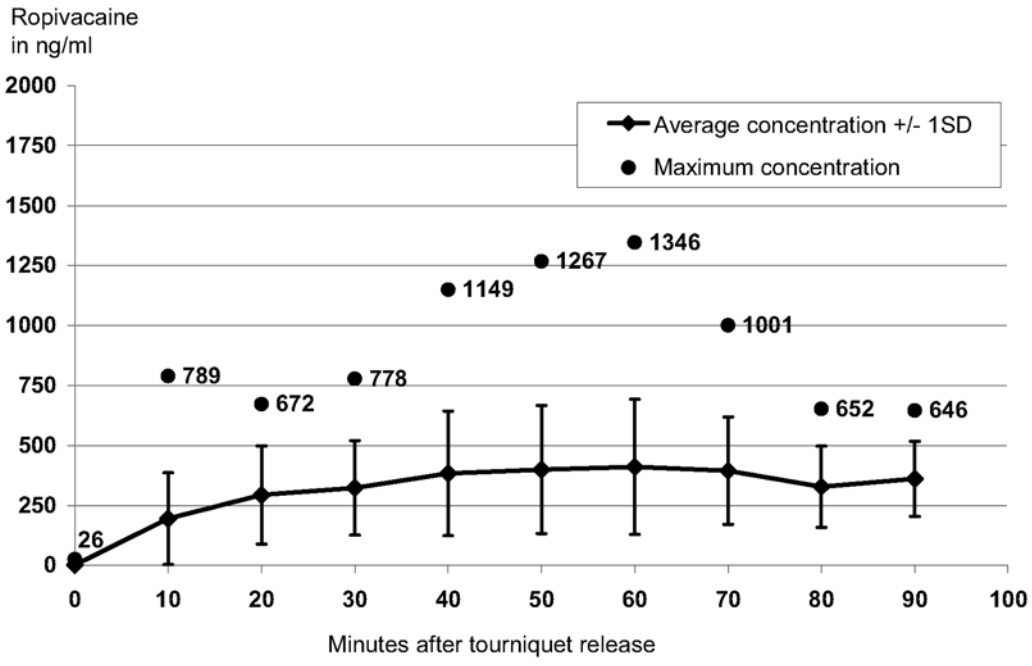

Fig. 1

Plasma concentrations of ropivacaine after the surgery.

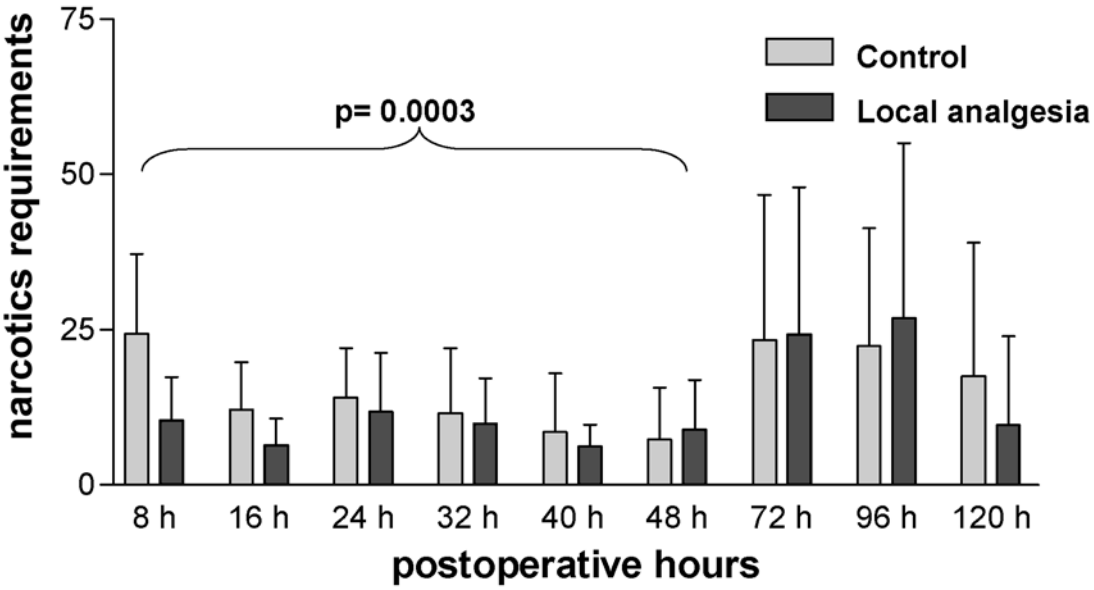

Fig. 2

Postoperative narcotics requirements (mean and standard deviation). For the first forty-eight hours, the overall requirements were higher in the control group than they were in the local analgesia group ($p = 0.0003$). The narcotics consumption is reported for each eight-hour period between zero and forty-eight hours and for each twenty-four-hour period after forty-eight hours.

vulsion, hypotension, bradycardia, headache, and pruritus. Postoperative knee flexion was measured with a goniometer by the physiotherapist every postoperative day. Intraoperative blood loss was estimated by weighing the used sponges and adding that weight to the blood volume collected by suction. Postoperative blood loss was estimated by measuring the drain output until removal of the drain at twenty-four hours. Wounds were evaluated every day to determine if there were any zones of skin ischemia or cellulitis and to ascertain the number of days before wound discharge stopped. The criteria for discharge from the hospital included active knee flexion of >80°, an extension lag of <10°, walking >30 m without help, and a dry surgical wound. Details regarding the measurement of the plasma concentration of ropivacaine are available in the Appendix.

Statistical Analysis

The Student t test and the chi-square test were used to compare continuous and categorical variables, respectively, between the two groups. Continuous variables are presented as a mean and standard deviation, and categorical variables are given as the frequency and percentage. To evaluate narcotics consumption, pain, and knee flexion over time, two-way repeated-measures analysis of variance was used, when appropriate, by Bonferroni post tests. Analyses were performed with Prism 3.0 software (GraphPad Software, San Diego, California). Significance was defined as $p < 0.05$.

Results

Forty-four patients were recruited into the study between March 2003 and March 2004, and two were excluded because the spinal anesthesia was unsuccessful. Twenty-two knees in twenty-two patients were assigned to the local analgesia group, and twenty knees in twenty patients were assigned to the control group. The demographic data were comparable between the two groups (Table II). The total blood loss (intraoperative plus drain output) was higher in the local analgesia group (596 mL compared with 409 mL), but the difference did not reach significance ($p = 0.148$). Most of the difference was attributable to the increased drain output (+166 mL) in the local analgesia group (Table II).

No complications related to the ropivacaine infiltration were reported. The infiltrated doses were all greater than the manufacturer's recommended maximum dosage of 3 mg/kg (average in our study, 4.7 ± 0.8 mg/kg; range, 3.3 to 6.9 mg/kg), but all of the plasma levels were lower than the toxicity threshold concentration of 1.5 μg/mL[16] (range of maximum serum levels in our study, 0.646 to 1.346 μg/mL; standard deviation, 0.28 μg/mL; Fig. 1).

The patient-controlled anesthesia pump with morphine was maintained for more than forty-eight hours for twelve patients: it was maintained for up to seventy-two hours for three patients in the control group and for two patients in the local analgesia group, and it was maintained for up to ninety-six hours for three patients in the control group and for four patients in the local analgesia group. Narcotics consumption was significantly lower in the local analgesia group during the first forty-eight hours postoperatively (Fig. 2, $p = 0.0003$). It was also significantly lower during the first eight hours after surgery (10.4 ± 7.0 mg compared with 24.4 ± 12.7 mg in the control group; $p < 0.001$), from eight to sixteen hours postoperatively (6.4 ± 4.3 mg compared with 12.2 ± 7.7 mg; $p = 0.006$), at twenty-four hours (28.8 ± 17.4 mg compared with 50.3 ± 25.4

mg; p = 0.004), and up to forty hours postoperatively (46.7 ± 19.4 mg compared with 68.6 ± 38.6 mg; p = 0.044). The local analgesia group had a significantly lower mean visual analogue score for pain during exercise than did the control group (4.7 compared with 6.6) on the first postoperative day (p = 0.008) as well as a significantly lower score for pain at rest (p = 0.01, Fig. 3) and during exercise (p = 0.02) for the first forty-eight hours after surgery. The local analgesia group and the control group achieved similar amounts of active knee flexion (72° compared with 63° on day 2 [p = 0.182] and 85° compared with 86° on day 5 [p = 0.815]) and passive assisted knee flexion (80° compared with 75° on day 2 [p = 0.420] and 90° compared with 94° on day 5 [p = 0.377]) during the first five postoperative days.

The mean duration of nausea was significantly shorter in the local analgesia group than in the control group (2.6 ± 3.9 hours compared with 7.1 ± 12.2 hours, p = 0.011). Urinary catheterization was needed once for three of the twenty patients in the control group compared with four of the twenty-two patients in the local analgesia group. One symptomatic deep vein thrombosis was diagnosed in the local analgesia group. Two were diagnosed in the control group, and one of them progressed to a pulmonary embolism. There were no superficial or deep infections. The average time to discharge was 4.8 ± 2.1 days in the local analgesia group and 5.2 ± 2.5 days in the control group (p = 0.672).

Discussion

Although many analgesia protocols for total knee arthroplasty have been evaluated, none is optimal and narcotics still play a major role[2-6]. The addition of local anesthetics through continuous epidural infiltration has been demonstrated to be more effective than parenteral analgesia alone[11]. However, epidural infiltration can be associated with side effects (nausea, pruritus, hypotension, urinary retention, poor muscle control, and delayed mobilization)[6,11,12], and it has also been associated with peroneal nerve palsy[9] and gluteal compartment syndrome[17]. Moreover, the risk of epidural hematoma with concomitant thromboprophylaxis is still a concern[10,11].

Other possible pain-control modalities include single, multiple, or continuous peripheral nerve blocks[18,19]. Nerve blocks reduce the occurrence of side effects and complications related to epidural or self-administered analgesia[20]. However, to effectively control pain, it may be necessary to block the sciatic, femoral, and obturator nerves[21]. In one study, 15% (nine) of sixty nerve blocks were unsuccessful, and 13% (six) of forty-eight successful blocks had to be combined with parenteral analgesia[21].

The observed pain reduction with continuous intra-articular infusions of analgesics supports the hypothesis that there are opioid receptors in the synovial membrane[22,23]. This method of analgesia may have reduced the consumption of pain medications in some studies[24-27]; however, continuous intra-articular injections are associated with larger effusions of the surgical wound and may provide direct access for infectious agents.

A few authors have investigated the benefits of intra-articular injections of local anesthetics after total knee arthroplasty[28-30]. Some did not find a reduction in narcotics consumption after surgery[22,29-31]; however, Badner et al. reported

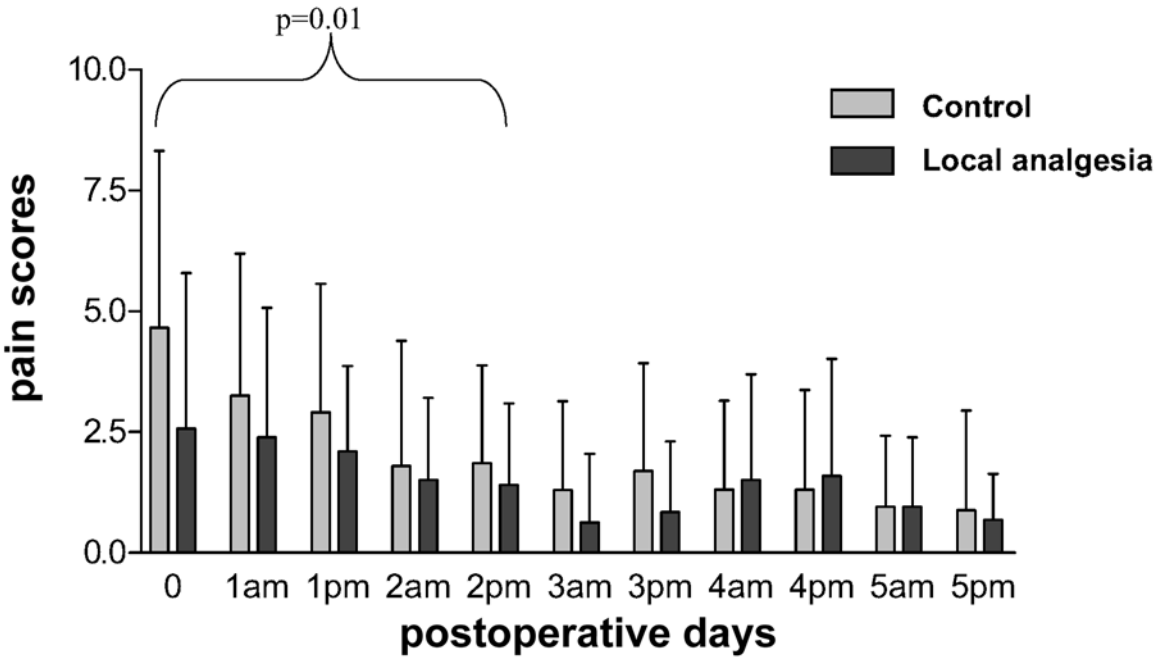

Fig. 3

Postoperative pain at rest (mean and standard deviation). The mean visual analogue pain score is higher in the control group than in the local analgesia group for the first two postoperative days (p = 0.01). 1am = postoperative day 1, in the a.m.; 2pm = postoperative day 2, in the p.m.; and so on.

that a single injection of 150 mg (30 mL) of bupivacaine after skin closure significantly decreased narcotics use during the first twenty-four postoperative hours compared with that following injection of a placebo and also significantly improved the range of motion at the time of discharge[28]. In a similar study, Browne et al.[31] did not find a significant reduction in narcotics consumption following a single injection of 100 mg of bupivacaine before skin closure.

We are aware of only one retrospective study of the benefits of a local anesthetic injection into soft tissues after total knee arthroplasty[32]. One dose of local anesthetics (200 mg of bupivacaine, 10 mg of morphine, and 0.40 mg of epinephrine in 80 mL) was infiltrated into the soft tissues and the joint. Postoperative pain was reduced in the recovery room, but the group treated with the local anesthetics had a higher pain level (a rebound effect) on the first and second postoperative days.

The primary objective of our study was to evaluate the safety and efficacy of a new perioperative intra-articular analgesia protocol. Ropivacaine[33] is a long-acting analgesic with efficacy similar to that of bupivacaine but with fewer cardiovascular and neurotoxic side effects[16,34]. We noted a significant reduction in the postoperative pain level at rest ($p = 0.01$) and during exercise ($p = 0.02$) during the first forty-eight hours after the surgery and a significant reduction of narcotics consumption that lasted for forty-eight hours ($p = 0.0003$). Many factors may explain the success of our protocol in comparison with that of the protocols used in other studies. Periarticular tissues were infiltrated under direct vision intraoperatively, providing a direct block of nerves that were injured or stretched at the time of the surgery. We also believe that entrapment of local anesthetics in the soft tissues improved the efficacy of the block and reduced the amount of medication discharged through the drain or the skin incision. Furthermore, injections of ropivacaine were given both during the surgery (400 mg) and on the first postoperative day (150 mg), and the anesthetic doses were much higher than those used in other studies, in which the patients received single injections ranging from 50 to 200 mg of bupivacaine[28,30-32]. The large dose of local anesthetic that we used appears to be safe, as no side effects were observed in our study group. However, our study included a small number of patients (twenty-two in the local analgesia group), and in some patients the maximum measured plasma level of ropivacaine (1346 ng/mL) almost reached the concentrations at which side effects can occur (1500 to 2000 ng/mL)[16,34].

The addition of a large dose of adrenaline (0.5 mg, 1:200,000 in 100 mL) to the local anesthetics probably slowed the release of the ropivacaine into the vascular system and prolonged its local action (ropivacaine has a half-life of 1.7 hours[35]). Since the patients who were treated with the infiltration used significantly less morphine in the second eight-hour postoperative period (6.4 ± 4.3 mg compared with 12.2 ± 7.7 mg in the control group, $p = 0.006$), our study suggests that the adrenaline had a beneficial effect. In addition, it helped to achieve a bloodless operating field after tourniquet release.

The advantages of this protocol include ease of use, low cost, and better operating-room efficiency. Operating time was not increased by the infiltration step, and this is a major advantage over peripheral nerve blocks, which may be time-consuming if they are performed in addition to spinal or general anesthesia in the same theater as the surgical procedure[36].

The benefits of the local infiltration protocol described in this study include lower narcotics consumption over the first forty postoperative hours (mean, 46.7 mg compared with 68.6 mg in the control group), improved pain scores during rest and exercise for the first forty-eight hours, and fewer nausea symptoms during the first five postoperative days.

The pharmacokinetics profile of ropivacaine in epidural infiltration has shown up to sixteen hours of efficacy[37]. The addition of an intra-articular bolus injection on the first postoperative day most likely prolonged pain control and delayed pain rebound in our study. The intra-articular catheter could have been used for additional injections, but it carried the risk of contaminating the joint. A possible improvement in our protocol would be the administration of another local anesthetic agent with a longer half-life.

A limitation of this study was the use of a COX-2 inhibitor (Celebrex) in the protocol, as that drug has been recently associated with increased cardiac risks[38]. Before this COX-2 inhibitor is used widely in a multimodal analgesia protocol, there must be further study to determine the exact cardiovascular risk when the drug is given for a short period of time for postoperative pain control[38,39]. Also, parenteral narcotics were used in both groups in our study. To optimize the reduction of narcotics-related side effects, the aim of multimodal pain control regimens should be to avoid the use of parenteral narcotics. In addition to the injection of local anesthetics, patients should be treated regularly with acetaminophen (1000 mg three times a day), anti-inflammatory drugs, and oral oxycodone (5 to 10 mg, on request) instead of with patient-controlled analgesia with morphine. If pain control becomes suboptimal, subcutaneous narcotics should then be given as needed.

Appendix

eA A description of the method of measuring the plasma concentration of ropivacaine is available with the electronic versions of this article, on our web site at jbjs.org (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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