# Multimodal Analgesia Without Parenteral Narcotics for Total Knee Arthroplasty

Lawrence D. Dorr, MD, Julio Raya, MD, William T. Long, MD, Myriam Boutary, BS, and Leigh Ellen Sirianni, OPAC

**Abstract:** Use of parenteral narcotics after total knee arthroplasty is considered by most orthopedic surgeons to be the standard of care. This study tested the hypothesis that a multimodal oral pain medication protocol could control pain and minimize complications of parenteral narcotics. Postoperative oral analgesia was augmented with either continuous epidural infusion or continuous femoral infusion using ropivacaine only. Seventy patients had total knee arthroplasty with a protocol that included preemptive oral analgesics, epidural anesthesia, pericapsular analgesic injection, and postoperative analgesia without parenteral opioids. The average daily pain score was less than 4 out of 10, nausea occurred in 15 patients (21%), emesis in 1 patient (1.4%), and there were no severe complications. This study proved the hypothesis that pain after total knee arthroplasty could be effectively managed without routine use of parenteral opioids. **Key words:** pain, pain medications, narcotics, total knee arthroplasty, multimodal treatment.


Parental opioids are often given to total knee arthroplasty patients by spinal or epidural anesthesia, and postoperatively by intramuscular injection or patient-controlled analgesia (PCA). These medications cause complications including nausea, reported in 37% to 73% of patients, cognitive impairment (somnolence, dizziness) in 34%, and pruritus in 15% to 43% of patients receiving opioids by PCA or epidural analgesia [1-11]. Potentially more severe complications are urinary retention in 60%, hypotension in 30%, and respiratory depression in 2% with PCA and 4% with epidural DepoDur (Endo Pharmaceuticals, Chadds Ford, Pa) [1-11].

The multimodal pain management program is designed to control postoperative pain by affecting the transmission of painful stimuli at multiple sites. The protocol addresses painful stimuli preoperatively, intraoperatively, and postoperatively. The inflammatory effect of released cytokines and prostaglandins [12] is reduced by oral and injected anti-inflammatory medications [12]. The establishment of central sensitization, and the amplification of painful stimuli, is prevented by blocking both central and peripheral cyclooxygenase-2 (Cox-2), cyclooxygenase-3 (Cox-3), and mu receptors [13]. Gastrointestinal side effects are avoided by prophylactically treating the patient with anti-emetic medications, eliminating inhaled anesthetics, and avoiding parenteral narcotics. The hypothesis of this study was that the use of a preemptive multimodal oral pain program, in combination with ropivacaine only infusion analgesia, would effectively control pain and avoid the use of parenteral narcotics, along with the associated complications.

*From The Arthritis Institute, Inglewood, California.*
Submitted August 3, 2006; accepted October 4, 2007.
Grant support provided by Zimmer Orthopedics.
Reprint requests: Lawrence D. Dorr, MD, The Arthritis Institute, 501 E. Harding Street, 3rd Floor, Inglewood, CA 90301.

0883-5403/08/2304-0003$34.00/0
doi:10.1016/j.arth.2007.10.004

## Materials and Methods

The premise of the pain management methodology was to avoid the use of parenteral narcotics for

patients who have primary total knee arthroplasty. The end points measured would be the avoidance of parenteral narcotics and the complications associated with their use. Nausea, vomiting, pruritus, and cognitive impairment were considered mild complications of parenteral opioids. Urinary retention, hypotension, ileus, respiratory depression, and emesis leading to dehydration were classified as severe complications. The study was conducted as a randomized comparison of continuous epidural vs continuous femoral nerve infusion using ropivacaine (Naropin, Astra Zeneca LP, Wilmington, Del). The continuous infusion analgesia was augmented by oral analgesics and intravenous ketorolac (Toradol, Roche Pharmaceuticals, Nutley, NJ). The necessity to use parenteral opioids to control postoperative pain was recorded as a complication of our protocol.

## Patient Selection

Institutional review board approval was obtained for a prospective randomized study of the pain control for patients undergoing unilateral total knee arthroplasty. These patients would have the same pain management program except for randomized assignment to either continuous epidural or continuous femoral nerve catheter infusion analgesia for 36 hours after total knee arthroplasty. Eighty patients were enrolled in the study from January 2004 to August 2005 from 208 eligible patients.

The demographics of the 2 groups of patients are displayed in Table 1, and there were no differences between the 2 groups. Ten of the 80 enrolled patients were disenrolled because of catheter failures. Six patients had failure of the femoral nerve catheter including 4 that failed in the recovery room and 2 that failed on return to the floor. These patients were then treated by an epidural infusion, in addition to the oral medications, but could not continue in the study. There were 4 patients in whom an epidural could not be placed in the operating room and therefore they were removed from the epidural arm of the study. Postoperative pain was treated in one of these patients with a femoral catheter and 3 patients were treated with the addition of a PCA infusion with parenteral narcotics.

**Table 1.** Demographics

| Demographics | FNC (n = 35) | EPI (n = 35) |
|---|---|---|
| Mean age | 68 ± 10.44 | 70 ± 10.31 |
| Mean BMI | 29 ± 5.7 | 28 ± 5.1 |
| Men | 17 | 13 |
| Women | 18 | 22 |

FNC indicates patients with femoral nerve catheter infusion; EPI, patients with epidural infusion.

Before surgery, each patient attended a preoperative class that reviewed the operation, the preoperative and postoperative care, and the postoperative recovery and rehabilitation. Our preoperative class is conducted by a person who is experienced and knowledgeable in all aspects of care. Special emphasis is given to the pain management aspect, especially the scaling of pain scores. Patients are taught to report pain using a visual analog pain score from 0 to 10 (10 being the worst pain). Patients are educated regarding the type of pain medications given on the floor to prepare the patient to interact in a coordinated manner with the nurses. These factors are believed to ultimately enhance recovery. Educating patients in the preoperative class is considered a significant part of the protocol because this can influence the cerebral cortex response to painful stimuli [14].

One to 2 hours before the operation, each patient received oxycodone 10 mg (Oxycontin, Purdue Pharmaceuticals, LP, Stamford, Conn), acetaminophen 1000 mg (Tylenol, McNeil PPC, Inc, Fort Washington, Pa), and a Cox-2 inhibitor (valdecoxib, Pfizer, New York, NY, and Celecoxib, New York, NY). Oxycodone affects mu receptors in both the peripheral and central nervous system. Acetaminophen blocks the Cox-3 enzyme in the thalamus and raises the threshold for pain. Cyclooxygenase 2 drugs modify the central nerve system transmission in the dorsal horn of the spinal cord and in the thalamus by affecting the Cox-2 enzyme. By preoperatively blocking both the neurogenic and inflammatory sources and pathways of pain, the central nervous system excitability is diminished and pain medication can be more effective and administered in small amounts [15,16].

The epidural anesthesia was given in the operating room and consisted of ropivacaine 1% (Astra Zeneca) 60 to 80 mg and 1.5% to 2% lidocaine with epinephrine at 80 mg. After a successful epidural anesthetic was established, each patient was given intravenous sedation with a continuous infusion of propofol 10 mg/kg per hour (Baxter Health Care Corp Anesthesia and Critical Care, New Providence, NJ). The patient was not intubated and the airway was controlled with a laryngeal mask anesthesia. No intravenous narcotics were given during the operation. Zofran 4 mg (ondansetron hydrochloride, Glaxo Smith Kline Research, Triangle Park, NC) or Reglan 10 mg (metoclopramide Schwarz Pharmacy, Milwaukee, Wis) was given during the operation. A pericapsular injection (with emphasis on the posterior

capsule and injection into the extensor mechanism) was done with a mixture of morphine 4 mg (Astra Zeneca), ropivacaine 100 mg, Solu-Medrol 40 mg (methylprednisolone sodium succinate, Pharmacia and Upjohn, New York, NY) diluted in a total volume of 60 mL of normal saline. This mixture provided blockade to the peripheral mechanical and inflammatory receptors.

## Postoperative Pain Management Protocol

In a prospective randomized fashion, one group of the patients had a femoral nerve catheter placed immediately at the conclusion of the operation in the operating room. The catheter was placed using a sheath needle and in conjunction with a nerve stimulator. Obvious muscle twitch of the quadriceps muscle which occurred at less than 0.4 mA was considered indicative of accurate needle placement. The femoral nerve analgesia was activated with a bolus of ropivacaine 0.2% using 100 mg and 20 mL of normal saline and maintained by continuous infusion at 5 mL/h for 36 hours. The second group of patients had continuous epidural infusion with ropivacaine 0.2% at 5 mL/h for 36 hours. The femoral nerve catheter and epidural catheter were discontinued after 2 nights, at 6 AM on postoperative day 2. Patients with the epidural infusion required a Foley catheter. Patients with incontinence or enlarged prostate in the femoral nerve catheter group also had a Foley catheter.

In the recovery room, OxyIR 5 mg (oxycodone hydrochloride immediate release, Purdue Pharm), which is a rapid-acting oral oxycodone, was given. Intravenous ketorolac 15 mg (Toradol, Roche Pharmaceuticals) was used for breakthrough pain. Only if these medications were not sufficient was intravenous Dilaudid 2 to 5 mg (hydromorphone, Abbott Laboratories, North Chicago, Ill) administered. Either Zofran 4 mg, Reglan 10 mg, or Anzemet 12.5 mg (dolasetron mesylate, Aventis Pharmaceuticals Inc, Bridgewater, NJ) was given intravenously if needed for nausea.

On the orthopedic ward, oral analgesics were given preemptively at night for the first and second postoperative nights. Afterwards, oral analgesics were given on request. During the day pain medications were available to the patient every 4 hours. Opiate analgesics used were Vicodin 5 mg/500 mg (hydrocodone and acetaminophen, Abbott Laboratories) or Norco 10 mg (hydrocodone and acetaminophen, Watson Laboratories, Inc, Corona, Calif). If these were not tolerated because of stomach discomfort or nausea, Darvocet 100 mg/650 mg (propoxyphene and acetaminophen, Xanodyne, Florence, Ky), Ultram 500 mg (tramadol hydrochloride, Ortho-McNeil, Raritan, NJ), or acetaminophen was used. Oxycodone 10 mg was given at 6 PM the day of surgery unless the patient was comfortable. Oxycodone was not used routinely thereafter. Ketorolac 30 mg intravenously was given every 6 hours for 24 hours. For the second 24 hours, ketorolac was given only as needed for breakthrough pain. Valdecoxib 20 mg was given each morning in 54 patients and Celebrex 200 mg was given twice a day in 16 patients. Aspirin 325 mg each day with intermittent pneumatic compression boots was used for deep venous thrombosis prophylaxis.

If the patient was 70 years or older the protocol substituted Darvocet, tramadol, or acetaminophen for the opiate analgesics. No postoperative oxycodone was used. Intravenous ketorolac was given as 15 mg every 6 hours.

Pain was scored by the patient on a scale of 0 to 10 (10 being the worst pain) before the administration of pain medications and scored on the same scale by patients 30 minutes after the administration of pain medication. The daily pain score reported for each patient was the average of the premedication and postmedication scores.

Patients were discharged home with the Cox-2 inhibitor to be taken each day, as was done in the hospital and with the oral pain medication that was used for them during the hospitalization. Aspirin 325 mg daily with thromboembolic disease hose (Kendall, Mansfield, Mass) was used for a total of 4 weeks. Patients were instructed to gradually increase their walking distance every day with a goal of 1 mile.

## Function Assessment

Patients were treated twice daily by physical therapy and the function of the patient in the hospital was graded by the physical therapist on a daily basis. The distance ambulated; quadriceps strength as measured by the ability to do an independent straight leg raise; the assistive device required for safety and balance at discharge; and the range of motion of the knee were recorded. The assessment of ambulation [20] according to the postoperative day had to be adjusted depending on the first time of ambulation because the patient was ambulated the day of surgery only if the patient returned to the floor before 2:00 PM.

## Safety

Safety was judged by absence of severe complications of respiratory depression, hypotension, ileus, and urinary retention and dehydration secondary to emesis.

### Statistics

The data were statistically analyzed using SPSS software (SPSS Inc, Chicago, Ill). A 95% confidence interval was used for each statistical analysis. Activity level and straight leg raise were analyzed using the Pearson's $\chi^2$ test. For statistical comparison of the amount of medication used for each patient and for comparison between the 2 groups of patients (epidural infusion and femoral nerve catheter infusion), the pain medications were all converted to equianalgesic milligrams of morphine. When we assume $a = 0.05$, $B = 0.20$ and compare the pain medication (equianalgesic milligrams of morphine sulfate), the sample size needed is 27 knees for each group. In this study, we had 35 knees in each group and provided a statistical power of 0.90. The conversion rates for morphine were obtained from conversion tables [17-20]. These tables gave conversion to morphine milligrams by percentage (ie, 50-67% of estimated oral equianalgesic dose), so that there is some approximation of the conversion doses for these medications. However, this is the most precise, and the recommended method, for expression of the comparative medicine usage. Student 2-tailed *t* tests were used to compare pain score, equianalgesic morphine, extension, flexion, and walking distance for normally distributed data. Otherwise, the Mann-Whitney test was applied. To more precisely compare femoral catheter group pain scores with epidural group pain scores, univariate analysis of variance was used. This test adjusts for the effect pain medication intake has on pain scored in each group.

## Results

Parenteral narcotics were used by 3 patients in the recovery room (Dilaudid; mean dose, 9.6 mg of equianalgesic morphine). No other parenteral narcotics were used by any patient. Three patients used oral medications every 4 hours for the first 24 hours. On the first postoperative night, 59 of 70 patients refused oral preemptive medications at least once; the second night 60 patients refused at least once. By postoperative day 2, the infusion (epidural or femoral nerve catheter) was completed and all patients used oral medications only.

### Pain Scores and Pain Management

The pain scores for the patients are listed in Table 2. The amount of pain medication used by patients is listed in Table 3. The pain scores were statistically better on postoperative days 0 and 1 (when the infusion was active) for patients with the femoral nerve catheter. On postoperative day 1, patients with femoral nerve catheter used less oral medication than those with the epidural. Twelve of 70 knees did not receive local wound injections at the operation and the pain scores were not statistically different.

**Table 2.** Pain Scores

| Day | 70 Patients | Epidural | FNC | *P* |
|---|---|---|---|---|
| 0 | 2.3 ± 1.9 | 2.9 ± 2.0 | 1.7 ± 1.7 | .002 |
| 1 | 3.2 ± 1.7 | 3.9 ± 1.4 | 2.5 ± 1.7 | .02 |
| 2 | 3.6 ± 1.4 | 3.7 ± 1.4 | 3.6 ± 1.5 | NS |
| 3 | 3.5 ± 1.4 | 3.7 ± 1.3 | 3.4 ± 1.6 | NS |
| Discharge | 3.3 ± 1.0 | 3.6 ± 0.8 | 3.1 ± 1.2 | NS |

Epidural indicates epidural infusion catheter; FNC, femoral nerve catheter infusion; NS, not significant.

### Function

There was no statistical difference between the 2 groups in the preoperative activity level of patients. The walking distance on postoperative day 0 and day 1 was statistically better for patients with epidural infusion ($P = .02$). The patients with the femoral nerve catheter infusion had to walk with a knee immobilizer on postoperative day 0 and day 1 to avoid buckling of the knee from quadriceps weakness. After the discontinuance of the infusion analgesia, there was no difference in the walking distance and all patients did walk 250 to 275 ft at the time of discharge.

There was no difference on any postoperative day in the assistive devices used. Forty patients were discharged with a single assistive device (1 crutch or cane) and 30 patients were discharged with a bilateral assistive device (2 crutches or walker). The postoperative day of discharge for all 70 patients was a mean 4 ± 0.9 days. Patients with epidural infusion had a mean discharge of 4.0 ± 0.8 days, and those with femoral nerve catheter infusion had 4.05 ± 0.9 days. Sixty-four of 70 patients were discharged home and 6 went to a rehabilitation center. These 6 patients were 3 from the epidural group and 3 from the femoral nerve catheter group.

On the day of surgery, 8 (23.5%) of 35 patients with the epidural infusion could straight leg raise whereas only 1 (2.8%) of 35 femoral nerve catheter infusion patients could do this ($P < .006$). Patients with the epidural infusion continued to have statistically better extension on days 2 ($P = .009$) and 3 ($P = .011$), and at discharge the extension was 6° ± 3.5° for the epidural patients and 12° ± 8.8° for the femoral nerve catheter patients ($P = .01$). At the time of discharge, 35 (100%) of 35 epidural patients

**Table 3.** Opioid Consumption Equianalgesic Milligrams of Morphine Sulfate

| Study day | All patients (n = 70) | Epidural (n = 35) | FNC (n = 35) | *P* |
|---|---|---|---|---|
| Day of surgery | 24.3 ± 21.8 | 27.4 ± 24.5 | 21.2 ± 18.4 | NS |
| 1 POD 1 | 41.3 ± 25.9 | 50.7 ± 22.8 | 31.9 ± 25.7 | .0002 |
| 2 POD 2 | 38.3 ± 23.4 | 43 ± 22.1 | 33.9 ± 24 | NS |
| 3 POD 3 | 35.2 ± 21.2 | 34.7 ± 20.8 | 35.8 ± 22.1 | NS |

Epidural indicates epidural infusion; FNC, femoral nerve catheter infusion; POD, postoperative day.

could straight leg raise vs 30 (95%) of 35 femoral nerve catheter patients ($P$ = .02). At discharge, epidural patients had 84° ± 10.9° flexion whereas the femoral nerve patients had 80° ± 13.3° ($P$ = .01).

At 6 months postoperative, 70 patients scored their results as 21 excellent, 39 very good, 7 good, and 3 fair. Sixty-seven patients used no assistive device, one used 2 crutches (back disease), one a walker for ataxia, and one a wheelchair (multiple medical comorbidities). Strength against manual resistance was grade 5 in 67 patients, 4 in 7 patients, and 3 in the patient with ataxia [11]. The flexion range of motion did not differ between epidural patients (114° ± 13.7°) or femoral nerve catheter patients (111° ± 12.2°) nor did extension (1.7° ± 4.0° versus 1.8 ° ± 4.2°).

### Complications

One patient in the epidural group had bladder inflammation caused by a reaction to latex of the Foley catheter. Two patients had successful closed manipulation at 6 weeks postoperative. One patient fell at home with traumatic dehiscence of the surgical wound which was surgically repaired without occurrence of infection. One patient (1.4%) had a deep infection which was successfully treated with 2-stage reimplantation.

### Safety

No patient had respiratory depression or ileus. One (1.4%) of 70 patients had hypotension secondary to parenteral narcotics in the recovery room which resolved with Narcan (Endopharmaceuticals, Chaddsford, Pa). Seven (10%) of 70 patients had hypotension from low hemoglobin on day 0 which resolved in all 7 patients with transfusion of 1 U of their autologous blood; 3 (4.3%) of 70 patients had orthostatic hypotension with physical therapy which also resolved with transfusion of their 1 U of autologous blood. Two patients (3%) had urinary retention after the Foley was discontinued which was resolved with the use of an in-and-out catheter.

Four (5.7%) of 70 patients had pruritus on the first postoperative day treated with 25 mg of Benadryl (diphenhydramine, Pfizer). One patient (1.4%) had an allergic reaction to Norco with tongue swelling which resolved with 25 mg of Benadryl. Fifteen (21%) of 70 patients had nausea in the recovery room treated with intravenous antiemetics and none had emesis. On postoperative day 1, 8 patients (11%) had nausea after physical therapy treated successfully with an intravenous antiemetic (Reglan 10 mg). One patient (1.4%) had emesis on both day 1 and day 2.

## Discussion

The results of this study proved the hypothesis that the postoperative pain of total knee arthroplasty could be effectively controlled without routine use of parenteral narcotics. The importance of this finding is that severe complications caused by parenteral opioids were nearly eliminated, yet pain was well controlled with daily pain scores below 4 out of 10 on an analog scale. No patient had respiratory depression compared to 9 (5.4%) of 168 patients who were treated with DepoDur (Endo Pharmaceuticals) intrathecal morphine [23] in a study by Hartrick et al [23]. Furthermore, our patients had 1 (1.4%) of 70 with emesis compared to 43% with the intrathecal morphine. Patients who received PCA morphine, in a study by Weller et al [21], had 5 (33%) of 15 with emesis, and their comparative group with epidural morphine also had 5 (33%) of 15 with emesis. Herrick et al [22] reported 26 (25%) of 96 patients with patient-controlled analgesic opioids had nausea and vomiting. Nausea in our patients occurred in 21% in the recovery room and 11% on postoperative day 1.

Urinary retention was also more common in patients with PCA morphine with 6 (40%) of 15 in one study [21] and 19 (18%) of 96 in another study [22]. Nausea and vomiting, in addition to postoperative pain, are the factors most commonly associated with patient dissatisfaction in the hospital [1-11]. Patient comfort, early rehabilitation, and early discharge home are the consequences of improved control of pain, nausea, and vomiting [11].

The limitations of this study are the exclusion of some patient groups with comorbid medical conditions. Secondly, not testing this protocol in combination with chemical prophylaxis for deep venous thrombosis (which is used by many surgeons) does not prove its safety when used with these drugs. Because we use only aspirin, intermittent compression devices, and thromboembolic disease hose for

deep venous thrombosis prophylaxis, we were able to study continuous epidural infusion. Unfortunately, the use of low molecular weight heparin for prevention of venous thromboembolic embolism has been shown to increase the risk of epidural hematoma and irreversible nerve damage by as much as 50 times [30-32]. Therefore, continuous epidural infusion is contraindicated when low molecular weight heparin is used for postoperative deep venous thrombosis prophylaxis. Thirdly, some patients were disenrolled from the randomized study because the femoral nerve catheter or epidural catheter did not function. Any study which involves invasive techniques will have some failures of the technique, so this is unavoidable.

The use of preemptive oral analgesics was effective in replacing parenteral narcotics, such as by a PCA. Animal studies have shown that preemptive opioids and local anesthetics can prevent prolonged behavioral psychological sequelae following brief noxious stimuli [24-26]. Our preemptive medications combined oral opioids with Cox-1 to Cox-3 enzyme antagonists. We did not observe any increase in perioperative or postoperative bleeding with the use of Cox antagonists, including intravenous ketorolac, which had been reported to cause increased perioperative bleeding during arthroscopic surgery by Lee et al [27].

This is the only study of pain management, of which we are aware, that did not use PCA as the control against which the use of medications was measured. Mallory et al [15] found a reduction in the use of opiate requirements through the PCA after total knee arthroplasty with the use of Cox-2 inhibitors (they used the same drugs as did we). Lombardi et al [29] also measured opioid consumption by PCA and found reduced use of opioids with periarticular and intracapsular injections. Our use of these pain prevention modalities in combination enabled us to avoid parenteral opioids while providing good pain relief, as graded by self-assessment which showed mean pain scores below 4 on every postoperative day.

In our study, the infusion of ropivacaine gave better pain relief through a femoral nerve catheter than the epidural infusion. This finding confirmed the study of Chelly et al [28] who also found superior pain relief with the femoral nerve catheter as compared to the epidural infusion. Better analgesia with the femoral nerve catheter was offset by severe quadriceps weakness which was observed during the time of the femoral nerve infusion. This effect of the femoral nerve catheter was reflected in the reduced straight leg raising and compromised ambulatory function in the first 2 days postoperative in these patients. Ambulation on the day of surgery or on postoperative day 1 was not delayed in these patients; however, a bilateral assistive device and a knee immobilizer were required for safety during this ambulation period. Quadriceps paresis in our study did not delay discharge home because our protocol required each patient to remain in the hospital for 3 nights to be sure safety was achieved after the discontinuance of any infusion.

Currently, we continue to use the oral medication program and avoid parenteral narcotics. We use a femoral nerve catheter infusion with ropivacaine for invasive pain control for only the first postoperative night to avoid quadriceps weakness and increase the effectiveness of the postoperative physical therapy. If the patient received a physical therapy treatment on the day of surgery, the catheter is discontinued at 6:00 AM the morning after surgery. If the patient returned to the floor too late in the evening for physical therapy on the day of surgery, the catheter is retained until after the first physical therapy session and then discontinued. We maintain the catheter for the first physical therapy treatment so patients can do active flexion with protection from pain so there is less of a chance that they will be sensitized to severe pain with range of motion therapy. Early removal of the catheter permits discharge on postoperative day 2 rather than postoperative day 4. This protocol also avoids the Foley catheter necessary for epidural analgesia.

## References


1. Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA 2003;290:2455.
2. Horlocker TT, Kopp SL, Pagnano MW, et al. Analgesia for total hip and knee arthroplasty: a multimodal pathway featuring peripheral nerve block. J Am Acad Orthop Surg 2006;14:126.
3. Ilahi OA, Davidson JP, Tullos HS. Continuous epidural analgesia using fentanyl and bupivacaine after total knee arthroplasty. Clin Orthop Relat Res 1994;299:44.
4. Keita H, Geachan N, Dahmani S, Couderc E, et al. Comparison between patient-controlled analgesia and subcutaneous morphine in elderly patients after total hip replacement. Br J Anaesth 2003;90:53.
5. Rathmell JP, Pino CA, Taylor R, et al. Intrathecal morphine for postoperative analgesia: a randomized, controlled, dose-ranging study after hip and knee arthroplasty. Anesth Analg 2003;97:1452.
6. Sarvela J, Halonen P, Soikkeli A, et al. A double-blinded, randomized comparison of intrathecal and epidural morphine for elective cesarean delivery. Anesth Analg 2002;95:436.

7. Sinatra RS, Torres J, Bustos AM. Pain management after major orthopaedic surgery: current strategies and new concepts. J Am Acad Orthop Surg 2002; 10:117.
8. Singelyn FJ, Ferrant T, Malisse MF, et al. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous femoral nerve sheath block on rehabilitation after unilateral total-hip arthroplasty. Reg Anesth Pain Med 2005;30:452.
9. Souron V, Delaunay L, Schifrine P. Intrathecal morphine provides better postoperative analgesia than psoas compartment block after primary hip arthroplasty. Can J Anaesth 2003;50:574.
10. Viscusi ER, Martin G, Hartrick CT, et al. Forty-eight hours of postoperative pain relief after total hip arthroplasty with a novel, extended-release epidural morphine formulation. Anesthesiology 2005;102:1014.
11. Wheeler M, Oderda GM, Ashburn MA, et al. Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain 2002;3:159.
12. Kehlet H, Dahl JS. The value of "multimodal" or "balanced analgesia" in postoperative pain treatments. Anesth Analg 1993;77:1048.
13. Wall PD. The prevention of postoperative pain. Pain 1988;33:289.
14. Dorr LD. The new process of total hip replacement. In: Elyse O'Grady, editor. Hip arthroplasty. Minimally invasive techniques and computer navigation. Pennsylvania: Saunders Elsevier; 2006. p. 1.
15. Mallory TH, Lombardi Jr AV, Fada RA, et al. Pain management for joint arthroplasty: preemptive analgesia. J Arthroplasty 2002;17(Suppl 1):129.
16. Flory DA, Fankhauser RA, McShane MA. Postoperative pain control in total joint arthroplasty: a prospective, randomized study of a fixed-dose, around-the-clock, oral regimen. Orthopedics 2001;24:243.
17. Massachusetts General Hospital. Equianalgesic doses of opioid analgesics. Table adapted from Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 4th ed. Chicago: American Pain Society; 1999.
18. Kim MH, Hahm TS. Plasma levels of interleukin-6 and interleukin-10 are affected by ketorolac as an adjunct to patient-controlled morphine after abdominal hysterectomy. Clin J Pain 2001;17:72.
19. Quality Tools. Tool summary: Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain Medications Pocket Guide, pg. 2 (Veterans Affairs and Department of Defense). In: QualityTools [Web site]. Rockville (MD): [cited 2003 June]. Available: http://www.oqp.med.va.gov/cpg/cpg.htm.
20. Magee DJ. In: Magee DJ, editor. Muscle test grading: orthopedic physical assessment. 4th ed. Saunders; 2002. p. 30.
21. Weller R, Rosenblum M, Conrad P, et al. Comparison of epidural and patient controlled intravenous morphine following joint replacement surgery. An J Anesth 1991;38:582.
22. Herrick IA, Ganapathy S, Komar W, et al. Postoperative cognitive impairment in the elderly. Choice of patient-controlled analgesia opioid. Anesthesia 1996;51:356.
23. Hartrick CT, Martin G, Kantor G, et al. Evaluation of a single-dose, extended-release epidural morphine formulation for pain after knee arthroplasty. J Bone Joint Surg Am 2006;88:273.
24. Coderre TJ, Vaccarino AL, Melzack R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. Brain Res 1990;535:155.
25. Dickenson AH, Sullivan AF. Subcutaneous formalin-induced activity of dorsal horn neurones in the rat: differential response to an intrathecal opiate administered pre or post formalin. Pain 1987;30:349.
26. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. Neurosci Lett 1986;64:221.
27. Lee VC, Kendrick WD, Brown NW, et al. Ketorolac given prior to arthroscopic knee surgery decreases postop pain scores and narcotic doses. Anesth Analg 1992;74:351.
28. Chelly JE, Greger J, Gebhard R, et al. Continuous femoral blocks improve recovery and outcome of patients undergoing total knee arthroplasty. J Arthroplasty 2001;16:436.
29. Lombardi AV, Berend KR, Mallory TH, et al. Soft tissue and intra-articular injection of Bupivacaine, epinephrine, and morphine has a beneficial effect after total knee arthroplasty. Clin Orthop 2004;428: 125.
30. Schroeder DR. Statistics: detecting a rare adverse drug reaction using spontaneous reports. Reg Anesth Pain Med 1998;23S:183.
31. Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of venous thromboembolism after knee arthroplasty: a randomized, double-blind trial comparing enoxaparin with warfarin. Ann Intern Med 1996; 124:619.
32. Heit JA. Low-molecular-weight-heparin: biochemistry, pharmacology, and concurrent drug precautions. Reg Anesth Pain Med 1998;23S:135.