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EFFICACY OF PERIARTICULAR MULTIMODAL DRUG INJECTION IN TOTAL KNEE ARTHROPLASTY

A RANDOMIZED TRIAL

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Background: Postoperative analgesia with the use of parenteral opioids or epidural analgesia can be associated with troublesome side effects. Good perioperative analgesia facilitates rehabilitation, improves patient satisfaction, and may reduce the hospital stay. We investigated the analgesic effect of locally injected drugs around a total knee prosthesis.

Methods: Sixty-four patients undergoing total knee arthroplasty were randomized either to receive a periarticular intraoperative injection containing ropivacaine, ketorolac, epimorphine, and epinephrine or to receive no injection. The perioperative analgesic regimen was standardized. All patients in both groups received patient-controlled analgesia for twenty-four hours after the surgery, and this was followed by standard analgesia. Visual analog scores for pain, during activity and at rest, and for patient satisfaction were recorded preoperatively and postoperatively and at the six-week follow-up examination. The consumption of patient-controlled analgesia at specific postoperative time-points and the overall analgesic requirement were measured.

Results: The patients who had received the injection used significantly less patient-controlled analgesia at six hours, at twelve hours, and over the first twenty-four hours after the surgery. In addition, they had higher visual analog scores for patient satisfaction and lower visual analog scores for pain during activity in the post-anesthetic-care unit and four hours after the operation. No cardiac or central nervous system toxicity was observed.

Conclusions: Intraoperative periarticular injection with multimodal drugs can significantly reduce the requirements for patient-controlled analgesia and improve patient satisfaction, with no apparent risks, following total knee arthroplasty.

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

Total knee arthroplasty is associated with considerable postoperative pain^{1,2}. Good pain relief is important for postoperative knee rehabilitation, and it may influence the overall outcome³. Many modes of preoperative, perioperative, and postoperative analgesia have been reported for patients undergoing total knee arthroplasty. Epidural analgesia is of proven benefit but is associated with side effects such as spinal headache, neurogenic bladder, hypotension, respiratory depression, pulmonary hypertension, cardiac decompensation, and a risk of spinal infection^{4,5}. Continuous infusion of opioids and bupivacaine into the knee has provided good postoperative pain control but may be associated with prolonged wound drainage⁶.

The use of opioid drugs, administered by means of either patient-controlled analgesia or other methods, deals with postoperative pain efficiently but is often associated with side effects, including nausea and vomiting, respiratory depression, drowsi-

ness, pruritus, reduced gut motility, and urinary retention.

Providing analgesia locally in the area of surgical trauma, with minimal systemic side effects, is an attractive option. Intra-articular injections of different analgesics following knee surgery have been shown to reduce requirements for postoperative analgesia and may lead to an earlier discharge from the hospital⁷⁻⁹. Kalso et al. reviewed a number of randomized, controlled trials and found that intra-articular morphine provided good pain relief following knee surgery¹⁰. In contrast, a number of studies have shown that intra-articular injection of analgesics during total knee arthroplasty has been of equivocal benefit^{6,11,12}.

We performed a prospective, blinded, randomized study to investigate the use of a periarticular injection of multimodal drugs, consisting of an opioid (epimorphine), a nonsteroidal anti-inflammatory drug (ketorolac), a long-acting local anesthetic (ropivacaine), and epinephrine, to provide analgesia following total knee arthroplasty.

Materials and Methods

Following approval by our local ethics committee, sixty-four patients (Table I) undergoing unilateral total knee arthroplasty were randomized with the use of randomization tables. Thirty-two patients received an intraoperative periarticular injection of analgesic drugs, and thirty-two patients did not. Inclusion criteria consisted of an age of less than eighty years, a weight of 50 to 120 kg, and an ability to provide informed consent for, and cooperate with, the study. Exclusion criteria were major psychological problems, previous drug dependency, allergies to any of the ingredients of the injection, renal insufficiency, abnormal liver enzymes, a history of stroke or a major neurological deficit, or uncontrolled angina and bifascicular blocks with prolonged QT intervals. The knee arthroplasty was performed through a standard medial parapatellar approach.

The injection contained 400 mg of ropivacaine, 30 mg of Toradol (ketorolac), 5 mg of epimorphine, and 0.6 mL of epinephrine (1:1000). These were mixed with sterile normal saline solution to make up a combined volume of 100 mL in the operating room. The first aliquot of 20 mL of the mixture was injected, just prior to implantation of the component, into the posterior aspect of the capsule and the medial and lateral collateral ligaments. Care was taken to avoid excessive infiltration in the area of the common peroneal nerve. Then, while the cement was curing, the quadriceps mechanism and the retinacular tissues were infiltrated with an additional 20 mL of the mixture. Finally, the remaining 60 mL was used to infiltrate the fat and subcuticular tissues.

Operative anesthesia was either general or regional. The anesthetic regimen was standardized. No long-acting analgesics were used, and spinal anesthesia was administered with 10 to 15 mg of Marcaine (bupivacaine). Five patients had blood samples taken at thirty minutes, one hour, and four hours postoperatively to measure venous blood (protein-bound) ropivacaine levels. All patients received patient-

controlled analgesia (a morphine bolus of 1.5 mg, a lock-out of six minutes, and a maximum of 15 mg/hr) for twenty-four hours after the surgery.

The consumption of patient-controlled analgesia was measured at different time-points during the twenty-four-hour postoperative period and the patient's overall analgesic consumption was measured and converted to morphine equivalents to allow for comparison of the two treatment groups. Patients used a visual analog scale to assess pain, both at rest and during activity, as well as their satisfaction in the preoperative-assessment clinic (two to three weeks prior to the surgery), on the day of the surgery, in the post-anesthetic-care unit, during the inpatient stay, and finally at the six-week follow-up examination. The visual analog scales for pain and satisfaction ranged from 0 mm (indicating no pain or completely dissatisfied) to 100 mm (indicating extreme pain or completely satisfied) in 10-mm increments. Specific note was made of any signs of cardiac or central nervous system toxicity or wound complications. Knee Society clinical rating scores¹³ and scores according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)¹⁴ were collected prospectively for all patients. All patients had an ultrasound study of the lower limb to screen for deep vein thrombosis at five days after the surgery. Statistical analysis of the data set was performed with use of the Kolmogorov-Smirnov test ($p < 0.05$) for normality and subsequently a normal t test. The analyses were performed with SPSS software (version 11.5; SPSS, Chicago, Illinois).

Results

Patients who had received the multimodal drug infiltration used significantly less patient-controlled analgesia at six hours ($p < 0.01$) and at twelve hours ($p = 0.016$) and had a significantly lower overall requirement for patient-controlled analgesia over the first twenty-four hours after surgery ($p < 0.001$) compared with the patients who had received no infil-

TABLE I Demographic Data for Patients in the Study

	Group 1 (Infiltration)	Group 2 (No Infiltration)
Average age (range) (yr)	66 (51-78)	70 (51-80)
Gender	16 F, 16 M	19 F, 13 M
Average body mass index (and stand. dev.)	32.6 ± 6.1	32.2 ± 7.2
Average hospital stay (hr)	125.3	123.1
Deep vein thrombosis (at day 5) (no.)	1	0
Wound complications (no.)	4	5
Average Knee Society clinical rating (points)		
Preop.	86.5	88.6
3 mo	166.45	160.84
Average WOMAC score (points)		
Preop.	17.15	15.9
3 mo	9.39	8.73

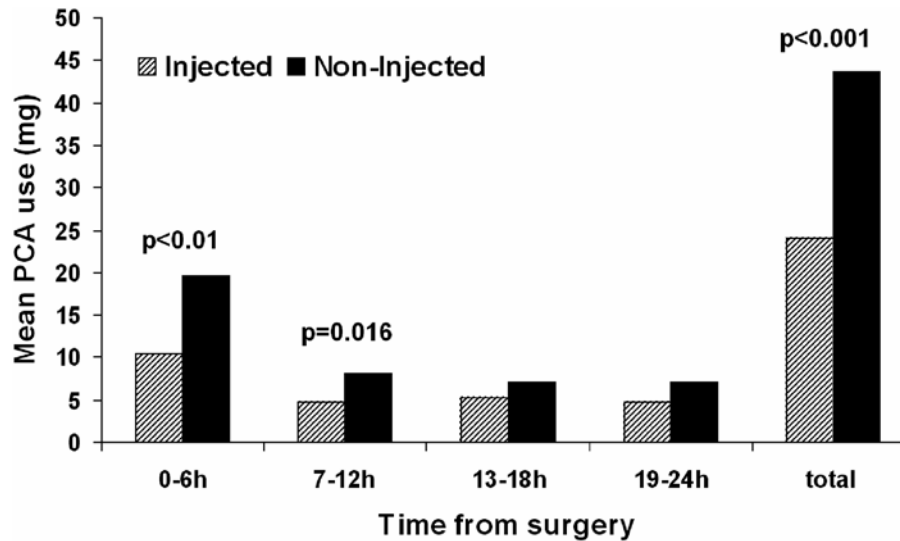


Fig. 1

Twenty-four-hour consumption of patient-controlled analgesia (PCA) in milligrams.

tration (Fig. 1). With the numbers available, there was no difference in the overall analgesic consumption in morphine equivalents between the two patient groups.

The group that had had the infiltration had significantly greater mean visual analog scores for patient satisfaction in the post-anesthetic-care unit ($p = 0.016$) and four hours postoperatively ($p = 0.013$) (Fig. 2) and significantly lower visual analog scores for pain during activity in the post-anesthetic-care unit ($p = 0.04$) and at four hours after the surgery ($p = 0.007$) (Fig. 3).

The average operating time (and standard deviation) from the skin incision until the dressing application and the average tourniquet time were 75.1 ± 13.5 and 77.5 ± 12.6 minutes, respectively, in the group treated with the injection and 77.2 ± 16.9 and 81.8 ± 15.7 minutes in the group that did not receive the injection.

General anesthesia was used in twenty patients who were treated with the injection and in seventeen patients who did not receive the injection. Spinal anesthesia was used in twelve patients who were treated with the injection and in fifteen who did not receive the injection. With these small numbers, there was no difference between treatment groups with regard to the numbers of patients receiving general or spinal anesthesia ($p = 0.446$).

At six weeks, no significant difference in the range of motion could be detected between the two groups. In addition, with the numbers available, there was no significant difference in the average hospital stay or the rate of wound complications between the two groups. One patient who had received the infiltration had a deep vein thrombosis postoperatively.

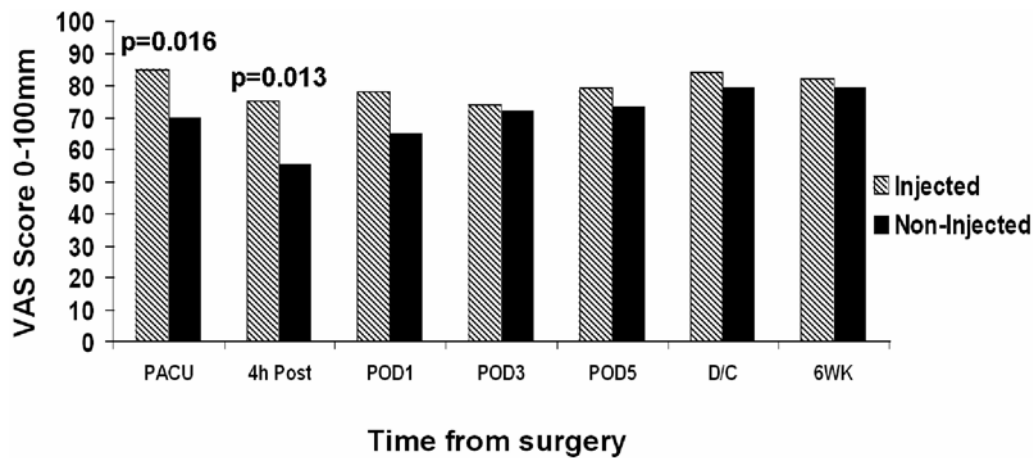


Fig. 2

Summary of visual analog scores (VAS) for patient satisfaction. PACU = post-anesthetic-care unit; 4h Post = four hours postoperatively; POD1, POD3, and POD5 = one, three, and five days postoperatively; D/C = discharge; and 6WK = six weeks postoperatively.

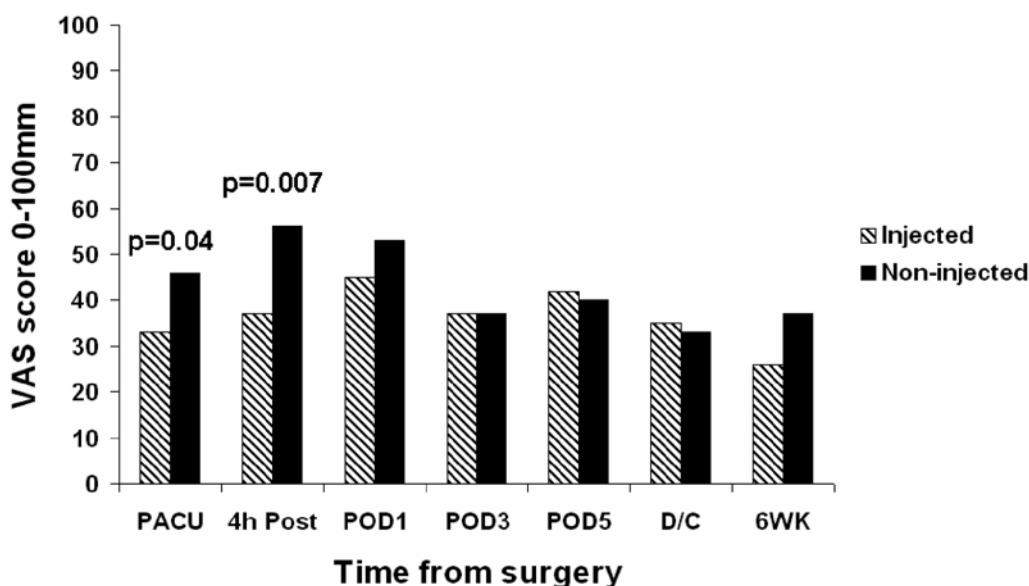


Fig. 3

Summary of visual analog scores (VAS) for pain during activity. PACU = post-anesthetic-care unit; 4h Post = four hours postoperatively; POD1, POD3, and POD5 = one, three, and five days postoperatively; D/C = discharge; and 6WK = six weeks postoperatively.

Of the five patients in whom we measured ropivacaine levels, three showed a small increase in the level four hours after the release of the tourniquet. The maximum level of unbound ropivacaine observed was 60 ng/mL, which is 2.5 times below the toxic level reported by Knudsen et al. (150 ng/mL)¹⁵.

No cardiac or central nervous system toxicity was observed (Table I).

Discussion

Pain following total knee arthroplasty is a problem that is severe in approximately 60% of patients and moderate in approximately 30%.¹ The pain may be a result of trauma to the bone or soft tissues or of hyperperfusion following tourniquet release¹⁶. The optimal form of pain relief is one that is applied preoperatively, perioperatively, and postoperatively to avoid the establishment of pain hypersensitivity¹⁷. Good pain relief allows effective postoperative rehabilitation³. Intra-articular injections following knee surgery have been shown to reduce requirements for postoperative analgesia and to allow earlier discharge from the hospital⁷⁻⁹.

The idea of administering preemptive analgesia directly to the operative site with minimal systemic side effects is an attractive option. Surgical trauma during total knee replacement modifies the responsiveness of the nervous system in two ways. It causes peripheral sensitization by reducing the threshold for afferent nociceptive neurons, and it causes central sensitization by increasing the excitability of spinal neurons. Together these changes contribute to postoperative pain hypersensitivity, which increases the response to noxious stimuli and decreases the pain threshold at the site of the injured tissue as well as the surrounding uninjured tissue. The preemptive use of analgesia has been shown to pre-

vent central sensitization and improve postoperative pain control¹⁸⁻²⁰. It may be that the window of opportunity for preempting central pain activation is limited. Two studies of the results of administration of morphine and bupivacaine after wound closure did not show effective postoperative pain relief^{21,22}.

The four active ingredients of the infiltration mixture that we used were epimorphine, ketorolac, ropivacaine, and epinephrine. Opioid receptors are present in peripheral inflamed tissues^{11,23}. These receptors are expressed within hours after surgical trauma and are thought to be responsible for afferent sensory input to the central nervous system^{24,25}. Non-steroidal anti-inflammatory drugs reduce peripheral sensitization and activation of nociceptors by inhibiting the eicosanoid pathway that leads to production of inflammatory mediators²⁶. Ropivacaine is pharmacokinetically similar to bupivacaine, but it is longer acting and is associated with less cardiac and central nervous system toxicity, which allows patients to tolerate a larger dose^{27,28}. The maximum circulating level is reached twenty to thirty minutes after injection. Although the main action of ropivacaine is to block afferent peripheral nociceptive activity, the drug has also been shown to have some anti-inflammatory properties in human mucosal cells²⁹. The addition of epinephrine helps to reduce the toxicity of the local anesthetic by keeping it localized to the area of injection³⁰. In conclusion, intraoperative periarticular injection of multimodal drugs can significantly reduce requirements for patient-controlled analgesia and improve patient satisfaction, with no apparent risks, following total knee arthroplasty. ■

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