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CURRENT AND INNOVATIVE PAIN MANAGEMENT
TECHNIQUES IN TOTAL KNEE ARTHROPLASTY

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Current and Innovative Pain Management Techniques in Total Knee Arthroplasty

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Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage."[1] It is of considerable concern to patients undergoing total knee replacement because the procedure has the reputation of being extremely painful, and fear of this pain is frequently cited as a reason for delaying the decision to undergo surgery[2]. Postoperative pain is intensified by movement and has a circadian rhythm with increasing pain at night[3]. Failure to adequately control pain following total knee replacement induces pathophysiologic responses, which increase postoperative morbidity, hinder physiotherapy, increase anxiety, disrupt sleep patterns, and, in general, decrease patient satisfaction and recovery. Patients believe that physicians do not fully appreciate the need for perioperative pain management, and this adds to patient anxiety. Surgeons need to recognize the importance of managing pain. In addition, the Joint Commission on Accreditation of Healthcare Organizations has declared pain to be the "fifth vital sign" and acknowledged that patients have a "right" to adequate pain management[4].

Mechanism of Surgical Pain

The trauma of surgery activates the nociceptor system, including the nociceptors in peripheral nerves and in the central nervous system. There are two types of nociceptors that transmit information. A-delta fibers are myelinated nociceptors that are activated by mechanical and thermal stimulation and provide rapid information to the central nervous system. C fibers are unmyelinated nociceptors that are activated by mechanical, chemical, and cold stimulation and are involved in the inflammatory process.

Total knee arthroplasty produces a peripheral noxious stimulus. Action potentials are propagated from the nerve endings in the peripheral nerves to the spinal cord and then to the central nervous system, which generates a secondary inflammatory response. These signals induce prolonged changes in both the peripheral and central nervous systems that can amplify and prolong postoperative pain. The surgery also leads to cell injury and inflammation, which promote the release of various substances and cytokines including hydrogen and potassium, histamine, serotonin, prostaglandins, leukotrienes, thromboxane, and substance P. This leads to a reduction in pain threshold of the nociceptor afferent terminals at the surgical site, a condition called primary hyperalgesia. The reduction in the pain threshold of the nociceptor afferent terminals in the surrounding

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"Multimodal Pain Management with Peripheral Nerve Blocks for Total Knee Arthroplasty," by Michael R. Pagnotto, MD, and Mark W. Pagnano, MD

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noninjured tissue is called secondary hyperalgesia. Peripheral and central sensitization also leads to primary and secondary hyperalgesia. Peripheral sensitization occurs when there is inflammation of the site of surgical trauma, which leads to a reduction in the threshold of nociceptors of afferent terminals. Central sensitization occurs when there is excitability of the spinal neurons secondary to persistent exposure to nociceptor afferent input from peripheral neurons. If the pain is prolonged, it may become chronic in nature.

To control surgery-associated pain, multimodal pain management can minimize these stimuli and limit activation of the central nervous system during and after a total knee arthroplasty.

Patient responses are variable, and there is not a direct correlation between noxious stimuli and perceived pain. Effective pain control takes this into consideration. Psychological status influences a patient's perception of pain. Patients with higher depression and anxiety scores experience more pain, and patients with poor coping skills have increased pain perception. In 2010, Riddle et al. found that pain catastrophizing was a consistent predictor of poorer pain outcome after total knee replacement[5].

Racial and ethnic groups have different pain responses to noxious stimuli, concerns of drug addiction vary, and some patients prefer to rely on prayer to deal with their pain[6-8]. To make matters worse, as a group black Americans have more advanced disease and pain compared with white Americans by the time they have surgery[8].

Biologic differences explain some of the variability. Tseng et al. showed that 10% of whites do not have an enzyme needed to convert codeine to its active state, while only 0.5% of patients of African or Asian descent do not have the enzyme[9]. The bioavailability of drugs is likely another biologic cause because of individual differences in drug metabolization.

Conventional Pain Management

The most common means of controlling pain associated with surgery is to start treating the pain by administering opioids postoperatively. Although parenteral opioids work quickly, there are more side effects with parenterally administered pain medications compared with orally administered opioids[10]. Whether the medication is given orally or parenterally, the patient waits for the nurse to administer the pain medication, which reduces the effect of the pain medication[11]. Patient-controlled analgesia is an alternative method for the administration of pain medication that is attractive to patients as they are able to administer medications when and how they may need them. The sense of self-control is appealing; however, adverse reactions (excessive somnolence and sedation, respiratory depression, pruritus, nausea or vomiting, constipation, and urinary retention) associated with narcotic usage are common[12].

New Approaches to Pain Management

Pain is probably easier to prevent than to eradicate and, on the basis of this concept, anesthesiologists originally termed this approach *preemptive analgesia*. The current understanding suggests that, when a noxious stimulus causes pain, there is a so-called recruitment of adjacent neural pathways, which makes the pain worse and difficult to control. Prevention of the initial postoperative pain should make subsequent pain management simpler[13,14].

The use of a variety of medications at relatively low doses is another new method, which is referred to as *multimodal analgesia* as it takes advantage of the multiple pain modulators. The use of a variety of medications, which affect different steps along the pain pathway, results in lower narcotic use and therefore fewer side effects.

Multimodal pain management combined with preemptive analgesia results in optimal pain control. The preoperative phase includes patient education and preemptive analgesia. Preoperative education includes a frank discussion with the patient concerning issues related to pain management, including realistic goals in the perioperative period.

Intraoperatively, both the narcotic (or other primary mediators) and the anti-inflammatory agents are injected directly at the surgical site. Postoperatively, patients are administered oral pain medications and anti-inflammatory agents. Liberal use of antiemetics helps the patients to avoid nausea and minimizes or eliminates the use of patient-controlled analgesia and parenteral narcotics.

Preemptive analgesia limits the sensitization of the nervous system to painful stimuli and blocks the transmission of noxious efferent information from the peripheral nervous system to the spinal cord and brain. Therefore, the analgesic agents must be given before the incision and must be of sufficient magnitude to limit sensitization of the nervous system. Opioids, nonsteroidal anti-inflammatory medication, acetaminophen, clonidine, and ketamine have all been shown to be effective agents in protocols designed to induce preemptive analgesia.

Prostaglandin E_2 (PGE_2) is upregulated in the central nervous system and peripheral tissue during and after surgery, and high levels of PGE_2 are associated with increased pain scores on a visual analog scale[15-17]. PGE_2 does not directly activate nociceptors but facilitates pain transmission by sensitizing nociceptors from mechanical and chemical stimuli, leading to central sensitization and lowering the pain threshold in the surrounding uninjured tissue. Patients with higher PGE_2 levels needed a longer time to achieve milestones in physical therapy, including the time to walk distances of 10 m and 25 m, the time needed to get out of bed, and the time needed to climb steps[15]. Perioperative multimodal analgesia can reduce the peripheral PGE_2 levels. A prostaglandin inhibitor (we prefer a cyclooxygenase-2 [COX-2] inhibitor) administered both preoperatively and postoperatively limits prostaglandin release, preventing the usual nervous system sensitization associated with surgical trauma. We treat our patients with 400 mg of

TABLE I Preoperative and Perioperative Medications

Medication	Dose	Administration	Frequency
Celecoxib*	400 mg	Oral	The day before surgery and then daily for 3 days postop.
Oxycodone controlled release	10 to 20 mg	Oral	Prior to surgery (10 mg if patient is >75 yr old or reports sensitivity to narcotics) and then every 12 h for 24 h postop
Oxycodone	5 to 10 mg	Oral	Every 4 h as needed
Acetaminophen	1000 mg	Oral	Three times a day
Ketorolac	30 mg	Intramuscular	Every 8 h as needed (3 doses maximum)
Tramadol	50 to 100 mg	Oral	Every 6 h as needed
Gabapentin	300 mg	Oral	At bedtime
Ondansetron	4 mg	Oral	As needed for nausea

*If the patient has a sulfa allergy, substitute 15 mg of meloxicam for the celecoxib.

celecoxib (or 15 mg of meloxicam if the patient has a sulfa allergy) for two days before surgery and with 20 mg of oxycodone extended release (10 mg for a patient over seventy-five years old or who has a narcotic sensitivity) one hour before surgery.

Buvanendran et al., in 2003, performed a randomized placebo-controlled double-blind trial of treatment with or without oral rofecoxib in patients undergoing primary total knee arthroplasty with spinal and epidural anesthesia[18]. Patients in the treatment arm were administered oral rofecoxib immediately prior to and for thirteen days after the surgery. All patients were evaluated for pain, nausea, sleep disturbance, and knee range of motion. Patients who received the COX-2 inhibitor had less opioid consumption, pain, vomiting, and sleep disturbance and had improved knee range of motion at one month after surgery. Increased plasma levels of the COX-2 inhibitor at the beginning of the surgery were associated with decreased analgesic consumption postoperatively.

During the postoperative recovery, we administer 400 mg of celecoxib daily for three days; 10 to 20 mg of oxycodone controlled release (depending on age) for the first twenty-four hours after surgery; 5 to 10 mg of oxycodone every four hours, as needed; 1000 mg of acetaminophen every eight hours, as needed; 30 mg of ketorolac given intramuscularly every eight hours (three doses maximum), 50 to 100 mg of tramadol every six hours, as needed; and ondansetron, as needed, for nausea (Table I).

At discharge, the patient is advised to take 200 mg of celecoxib orally every day for six weeks and one or two 5/500-mg hydrocodone/acetaminophen tablets orally every four hours, as needed (Table II). Elevated interleukin (IL)-6 and IL-8 levels are associated with an increased frequency of sleep disturbance. Gabapentin has been added as it has been shown to improve sleep disturbances associated with pain[19,20].

All nonsteroidal anti-inflammatory medications can induce cardiac toxicity. Therefore, cox-inhibitors should be avoided in high-risk patients who have a history of cardiac ischemia, stroke, congestive heart failure, or recent coronary artery bypass surgery.

Other Medications

Acetaminophen is often used in perioperative pain protocols. The mechanism of action of this drug is poorly understood but leads to a decreased need for opioids.

Gabapentin was first developed as an anticonvulsant. When used preoperatively, it enhances the effect of morphine, nonsteroidal anti-inflammatory drugs, and COX-2 inhibitors. The side effects of gabapentin include dizziness and somnolence with long-term use.

Clonidine is an α2-adrenergic agonist. Its mechanism of action of analgesia is unknown. Theoretically, it potentiates the effects of local anesthetics. It is administered intravenously or locally. Clonidine is presently used in some multimodal pain management protocols.

Ketamine is a general analgesic and a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor and inhibitor. The NMDA receptors are associated with central sensitization. Ketamine has opioid-sparing effects but no reduction in opioid-related adverse effects. Intravenous ketamine can be used in

TABLE II Discharge Medications

Medication	Dose	Administration	Frequency
Celecoxib*	200 mg	Oral	Daily for 6 wk
Hydrocodone	5/500 mg (1-2 tablets)	Oral	Every 4 h as needed
Gabapentin	300 mg	Oral	At bedtime

*If the patient has a sulfa allergy, substitute 7.5 mg of meloxicam for the celecoxib.

conjunction with femoral nerve blocks or epidural analgesia after total knee arthroplasty. It can also be infiltrated into the wound.

Operative Anesthesia Options

Overall pain relief is better with a regional anesthesia, blocks, and local injections than with general anesthesia[21]. Epidural anesthesia is a popular method of anesthesia for total knee replacement, and a meta-analysis of studies on epidural anesthesia has suggested that, regardless of the analgesic agent or location of the catheter, epidural analgesia provided superior postoperative analgesia compared with parenteral opioids[22]. Risks associated with this modality include motor block, numbness in the contralateral lower extremity, ileus, pressure phenomenon, pruritus, epidural hematoma, nausea and vomiting, technical issues, and limitations on anticoagulation choices, all of which can prolong hospitalization and delay rehabilitation.

Peripheral nerve blocks may be better. Barrington et al. compared femoral nerve block with epidural analgesia after total knee replacement and found equivalent pain scores, knee range of motion, and rehabilitation outcomes among the groups, but significantly less nausea and vomiting in the femoral nerve block group[23]. On the other hand, a femoral nerve block may produce motor loss and a need for support (such as a knee immobilizer) or bed rest, is technically difficult, provides less predictable pain relief, and often needs to be combined with other blocks to achieve relief of posterior knee pain.

We prefer regional anesthesia. A spinal anesthetic, in general, is a more predictable regional anesthetic, should be used unless contraindicated, and is the preferred form of anesthesia for total knee replacement. Macfarlane et al., in 2009, performed a systematic review and found that, although a regional anesthetic did not decrease blood loss compared with general anesthesia, it did reduce postoperative pain and morphine consumption[24].

TABLE III Intraoperative Management

	Medication	Dose
1	Spinal anesthesia	
2	Pericapsular injection*	Total of 100 mL
	Ropivacaine	5 mg/mL (49.25 mL)
	Epinephrine	1 mg/mL (0.5 mL)
	Ketorolac	30 mg/mL (1 mL)
	Clonidine	0.1 mg/mL (0.08 mg = 0.8 mL)
	Normal saline solution	48.45 mL

*The combined medication is premixed by the pharmacy and remains stable for twenty-four hours. The injection is made behind the knee into posterior soft tissues (30 mL); into the medial and lateral gutters, which should include the periosteum of the femur (25 mL); and then into subcutaneous tissue (20 mL). The location of the injection is key.

We use direct intra-articular injection of a so-called cocktail of medications during the operation to improve immediate postoperative pain. We studied four different combinations of medications to establish which medications should be included in the injection. Four groups of twelve patients undergoing total knee replacement with similar anesthetics and the identical orally administered pain management and physiotherapy protocols were the test subjects. The pain score on a visual analog scale and pain assessments by the nursing staff were recorded every four hours for three days, and knee range of motion, pain scores, and walking distance were recorded by the physical therapists at each session. There was a trend for superior pain control in the group receiving all four medications, and their functional outcomes were significantly superior[25]. The most successful anesthetic cocktail contains 5 mg/mL of ropivacaine (49.25 mL), 30 mg/mL of ketorolac (1 mL), 1 mg/mL of epinephrine (0.5 mL), 0.1 mg/mL of clonidine (0.08 mg = 0.8 mL), and normal saline solution, which is added to the medications, for a total of 100 mL

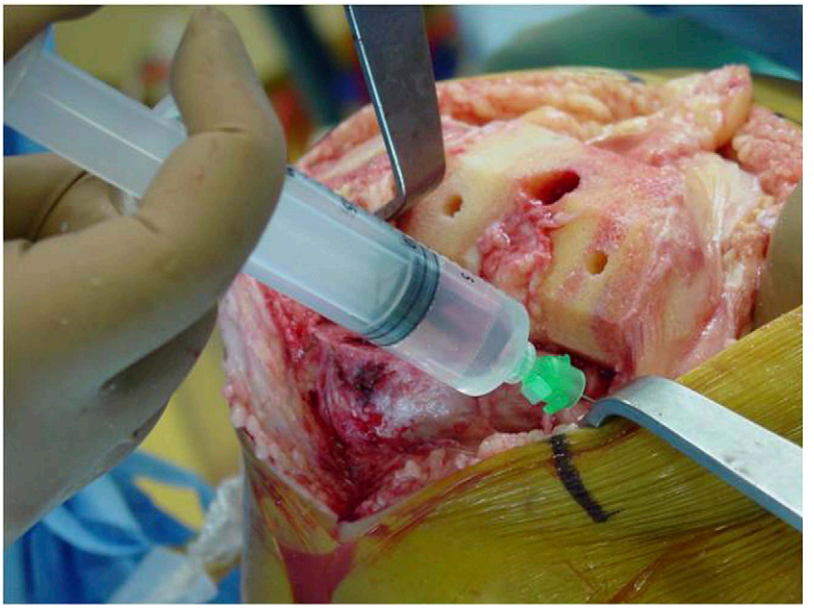

Fig. 1

Injection into the posterior capsule of the knee.

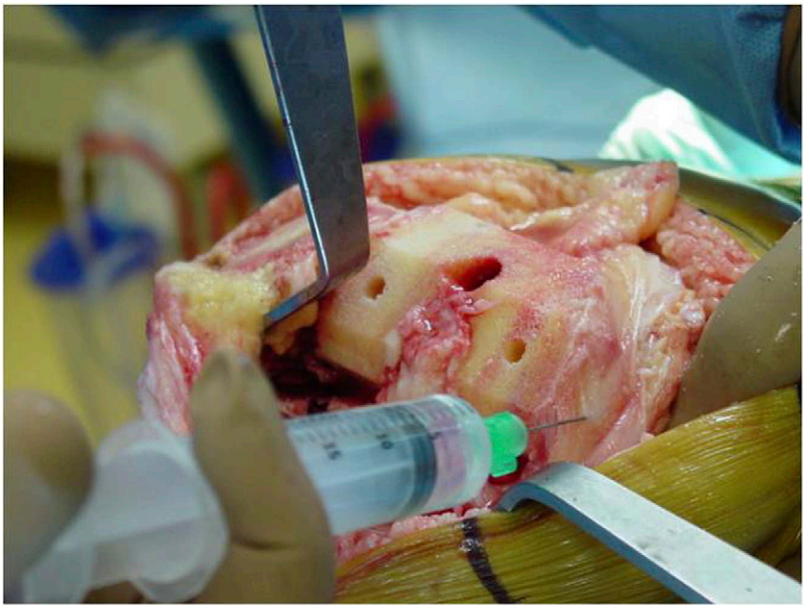

Fig. 2

Injection into the periosteum and gutters of the femur.

(Table III). This mixture is prepared by the pharmacy and is stored for up to twenty-four hours. The placement of the injections is important, and the total volume should be divided into quarters, with one-quarter injected into the posterior capsule, one-quarter into the medial periosteum and medial capsule, one-quarter into the lateral periosteum and lateral capsule, and one-quarter into the soft tissues around the skin incision (Figs. 1 and 2).

Establishing a New Protocol for Total Knee Replacement Pain Management

Introducing a new pain management protocol requires the commitment of the surgeon; however, it also takes a team of committed anesthesiologists, pharmacists, physical therapists, and nursing staff to be successful. Education and patience are required to change from the conventional pain management after a total knee replacement. We found that it is worth the effort, and we believe that the patients, the staff, and the surgeon will be rewarded with excellent perioperative and postoperative results.

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