Multimodal Pain Management in Orthopedics: Implications for Joint Arthroplasty Surgery

JAVAD PARVIZI, MD, FRCS; MICHAEL R. BLOOMFIELD, MD

Multimodal pain management has become an important part of the perioperative care of patients undergoing total joint replacement. The principle of multimodal therapy is to use interventions that target several different steps of the pain pathway, allowing more effective pain control with fewer side effects. Many different protocols have shown clinical benefit. The goal of this review is to provide a concise overview of the principles and results of multimodal pain management regimens as a practical guide for the management of joint arthroplasty patients.

Total joint arthroplasty (TJA) of the lower extremity is one of the most common operations in orthopedics, with an estimated 1 million cases being performed in the United States annually.1 Despite the success of TJA procedures in ultimately reducing pain and improving function, many patients are reluctant to consider surgery because of fear of uncontrolled postoperative pain. Historically, pain after joint replacement surgery has often been inadequately managed.2 In addition to patient discomfort, uncontrolled pain has numerous deleterious effects after orthopedic surgery, including slowed rehabilitation and perioperative medical complications.3,4 These issues can contribute to an increased length of hospital stay, unplanned readmissions, and higher cost of care.3,5,6 Poor participation in physical therapy as a result of pain can also compromise the ultimate function of the joint. The cumulative result of pain and these related factors is patient dissatisfaction,7 which negatively influences the choice of physician and willingness to undergo future treatment.8,9

High-dose intravenous opioids in the form of patient-controlled analgesia have traditionally been used to manage postoperative pain after joint reconstruction.10 Opioids are associated with numerous dose-dependent systemic side effects (Table 1), which can also impair postoperative recovery and lead to serious medical complications,11,12 resulting in increased length of stay and treatment costs.3,13,14 In addition, patients taking chronic narcotics preoperatively can become desensitized and tolerant, resulting in difficulty controlling surgical pain.

Multimodal methods for controlling postoperative pain were introduced and refined by Kehlet and Dahan9 and Wall.15 Advances in perioperative pain management and rehabilitation have evolved with newer surgical techniques and are likely responsible for many of the benefits seen with less invasive surgery.16 The principle of multimodal therapy is to use interventions that target several different steps of the pain pathway, allowing agents to act synergistically while requiring lower total doses of each drug (Table 2). This promotes more effective pain control with fewer associated side effects.14 A comprehensive pain management strategy combines pre-emptive analgesia using...
medications given preoperatively, neuraxial anesthesia, regional nerve blocks or periarticular injections, and postoperative oral and intravenous medications. The goal of this review is to provide a concise overview of the principles of multimodal pain management regimens as a practical guide for the management of joint arthroplasty patients.

**INDIVIDUAL COMPONENTS OF A MULTIMODAL STRATEGY**

**Neuraxial Anesthesia**

Spinal anesthesia is induced by injection of a local anesthetic into the intrathecal space. The addition of intrathecal morphine has been shown to improve postoperative pain control and decrease parenteral narcotic usage, but also has been associated with postoperative pruritus, nausea, and respiratory depression. Epidural anesthesia used intraoperatively can be maintained to provide effective analgesia during the postoperative period. This typically consists of a local anesthetic with epinephrine, which causes local vasoconstriction and leads to a higher local concentration of the local anesthetic. An extended-release liposomal morphine formulation has been used with epidural anesthesia to provide postoperative analgesia without requiring a continuous infusion.

A study from our institution showed improved pain scores on postoperative day 1 compared with a matched cohort receiving spinal anesthesia. However, this product was associated with an increased incidence of nausea, vomiting, and pruritus, as well as a slightly higher rate of supraventricular tachycardia and pulmonary embolism. Adjunctive agents such as ketamine (NMDA receptor antagonist) and clonidine ($\alpha$-agonist) have been described with epidural analgesia but are currently used infrequently.

The benefits of spinal and epidural anesthesia compared with general anesthesia in TJA patients have been established by many randomized controlled trials and synthesized in several meta-analyses. Neuraxial anesthesia is associated with reduced operative time and intraoperative blood loss and a lower incidence of postoperative venous thromboembolism and blood transfusions. After total hip arthroplasty (THA), neuraxial anesthesia can reduce pain, narcotic requirements, and nausea and vomiting. A study by Neuman et al comparing outcomes of hip fracture surgery in a large cohort of more than 18,000 patients treated at 126 New York hospitals found lower rates of inpatient mortality and respiratory complications when regional instead of general anesthesia was performed.

**Peripheral Nerve Blockade**

Peripheral nerve blockade is a commonly used technique to control postoperative pain after TJA. Local anesthetic is injected, typically under ultrasound guidance or nerve stimulation, around peripheral nerves that relay sensation from the operative site. Common targets for relief of postoperative total knee arthroplasty (TKA) pain are the femoral and sciatic nerves. Lumbar plexus blocks have been described following THA; however, they are infrequently performed because these patients are typically comfortable with use of other modalities. Regional blocks can be administered as a 1-time injection, or a catheter can be left in place for sustained pain relief. Single-shot blocks typically consist of a long-acting local anesthetic (bupivacaine or ropivacaine), with adjuvants such as epinephrine or corticosteroid to prolong the effect of the block. A short-acting narcotic may be administered along with a local anesthetic for a continuous infusion via catheter.

Many studies have established the effectiveness of these techniques for postoperative analgesia, and a large meta-analysis found significantly improved pain control, lower narcotic consumption,
and fewer side effects with continuous regional anesthesia when compared with treatment with narcotics.\textsuperscript{25} A randomized controlled trial of single-shot femoral nerve block vs continuous femoral nerve catheter after TKA found significantly better pain control in the catheter group, particularly on postoperative day 2 after the single block resolved.\textsuperscript{26}

When compared with continuous epidural analgesia, peripheral nerve blocks provide a similar level of pain relief without the side effects of urinary retention and hypotension common with epidurals.\textsuperscript{27}

Complications are rare after regional anesthetic techniques but are possible. The infection risk for single-shot blocks is small,\textsuperscript{24} but for indwelling catheters, it has been estimated at between 0% and 3% of cases.\textsuperscript{29} Catheters rarely may become incarcerated or break during attempted removal.\textsuperscript{30} Nerve injury after a block is also rare, with an estimated rate of 0.2% after catheter placement.\textsuperscript{28} Transient neurologic symptoms (typically mild paresthesias) are more common but are still infrequent.\textsuperscript{30}

**Periarticular Injections**

Injections given locally into and around the joint intraoperatively have been extensively studied in arthroplasty patients. Different protocols have been reported based on the composition and dose of the injection, its location, and the presence of a catheter for continuous postoperative infusion; and results of well-designed studies have been conflicting. Given this significant heterogeneity, the literature should be critically assessed before the surgeon implements a change in clinical practice.

**Local Anesthetics Alone.** Two double-blinded randomized trials compared single periarticular injections of local anesthetic (ropivacaine and bupivacaine, respectively) with saline placebo in primary THA.\textsuperscript{31,32} No benefit was seen in pain scores or opioid consumption from ropivacaine with epinephrine injection in combination with a multimodal oral regimen.\textsuperscript{31} No improvement in pain scores was seen with bupivacaine injection; however, narcotic requirements were significantly lower in the first 12 hours postoperatively in the treatment group of one study.\textsuperscript{32}

Similarly, a randomized trial comparing single ropivacaine injection to placebo in TKA found significantly lower morphine consumption in the injection group but no significant differences in pain level.\textsuperscript{33} Lower rates of nausea were reported in the local injection group, presumably related to decreased narcotic consumption.

Several studies have compared postoperative local anesthetic infusions via catheter following TJA. Dobrydnjov et al\textsuperscript{34} conducted a randomized trial comparing the location of continuous ropivacaine infusion after THA and found that intra-articular ropivacaine injection was superior to intravenous ropivacaine, ketorolac, and epinephrine injection with placebo after TKA, significant improvements in pain scores, narcotic consumption, and patient satisfaction were observed.\textsuperscript{40} Two trials have evaluated multidrug injection in patients undergoing bilateral TKA, where 1 knee was treated with ropivacaine, ketorolac, and epinephrine with intra-articular ropivacaine injection and with a multimodal oral analgesic regimen.\textsuperscript{36} Goyal et al\textsuperscript{37} found benefit to using a continuous ropivacaine infusion after TKA, noting significantly lower pain scores and narcotic consumption on postoperative days 2 and 3.

**Multimodal Injections.** Several randomized controlled trials have evaluated differing multimodal injections compared with placebo after TJA. Busch et al\textsuperscript{38} found that a periarticular injection of ropivacaine, epinephrine, and morphine resulted in lower 24-hour patient-controlled analgesia requirements and pain levels; however, no effect on patient satisfaction was seen. Ropivacaine blood levels were also measured and found to be significantly below toxic levels. In another study, a continuous postoperative ropivacaine and ketorolac infusion resulted in better pain control and satisfaction after THA.\textsuperscript{39} In a trial comparing ropivacaine, ketorolac, and epinephrine injection with placebo after TKA, significant improvements in pain scores, narcotic consumption, and patient satisfaction were observed.\textsuperscript{40} Two trials have evaluated multidrug injection in patients undergoing bilateral TKA, where 1 knee was treated and the other was administered saline placebo.\textsuperscript{41,42} One of these studies found only an early benefit on postoperative day 1 on the treated side when injected around the joint,\textsuperscript{43} whereas the other trial found no benefit to the injection when given intra-articularly.\textsuperscript{41}

Several randomized studies have compared periarticular multidrug injections to other pain management modalities. Parvataneni et al\textsuperscript{43} compared bupivacaine and morphine local injection with femoral nerve block in patients undergoing TKA and found no significant differences in pain scores. Two trials compared an injection of ropivacaine, ketorolac, and epinephrine with intrathecal morphine and epidural infusion, respectively, and both found improved pain control and length of stay in the injection groups.\textsuperscript{44,45}

**Oral and Intravenous Medications**

*Ropivacaine.* Ropivacaine is a centrally acting antipyretic and analgesic agent. Oral formulations are commonly used alone and in combination with opioids for the treatment of postsurgical pain. Widely available in Europe for many years, an intravenous form of acetaminophen (paracetamol) was recently approved for use by the US Food and
Drug Administration. Sinatra et al\textsuperscript{46} conducted a 3-arm randomized controlled trial comparing intravenous acetaminophen and propacetamol (its prodrug) with placebo after major orthopedic surgery. They found that both treatment groups provided significant pain relief compared with placebo, and significantly reduced morphine rescue consumption by approximately 30%. Reported rates of adverse events in the acetaminophen were similar to placebo. In a subsequent expanded analysis, these authors reported significantly longer times to morphine rescue dose requirement in the intravenous acetaminophen group compared with placebo after THA and TKA (3.9 and 2.1 hours, respectively, vs 0.8 hours in the placebo group).\textsuperscript{47} Differences in rates of nausea and vomiting were attributed to prerandomization factors by stepwise regression analysis.

**NSAIDs and COX-2 Inhibitors.** Nonsteroidal anti-inflammatory drugs (NSAIDs) have anti-inflammatory, antipyretic, and analgesic effects and work by inhibiting cyclooxygenase production of prostaglandins in the peripheral tissues. Traditional NSAIDs are nonspecific and inhibit both COX-1 and COX-2 enzymes, whereas COX-2 inhibitors are specific for COX-2 isoforms and have diminished gastrointestinal side effects as a result of less prostaglandin inhibition in the gastric mucosa. Recent cardiovascular warnings have been issued regarding long-term treatment with both classes of drugs,\textsuperscript{48} and celecoxib is currently the only COX-2 inhibitor on the market after others were withdrawn due to cardiovascular risks.

In a randomized controlled trial, the administration of celecoxib both pre- and postoperatively was found to decrease pain and narcotic requirements after TKA.\textsuperscript{49} Similar results were seen in a study evaluating the now-withdrawn rofecoxib.\textsuperscript{50} In a meta-analysis of randomized trials evaluating preoperative dosing of a COX-2 inhibitor compared with placebo, active preoperative treatment was found to significantly reduce postoperative pain parameters in the majority of studies.\textsuperscript{51} Although concerns exist regarding treatment with NSAIDs during fusion and fracture surgeries, no reliable evidence suggests diminished bony ingrowth or impaired component fixation in arthroplasty surgery with these classes of medications.

**Gabapentinoids.** Gabapentinoids were initially developed as anticonvulsants. However, they have gained considerable popularity for the treatment of neuropathic pain.\textsuperscript{52} They exert their mechanism of action via inhibition of the presynaptic voltage-gated sodium channels present in the dorsal horn of the spinal cord, reducing afferent excitatory signaling. Side effects include sedation, and caution should be used in patients with renal insufficiency due to drug accumulation.

Two prospective randomized trials have evaluated these medications after TJA. Clarke et al\textsuperscript{53} evaluated several dosing regimens of gabapentin in 40 patients undergoing TKA. They found that although reported pain scores were similar, patients treated with gabapentin used significantly less patient-controlled analgesia morphine up to 2 days postoperatively, and had less opioid-related side effects (eg, itching). Buvanendran et al\textsuperscript{54} randomized 240 patients undergoing TKA to a regimen of pregabalin (given preoperatively and for 14 days postoperatively) or placebo. They found that significantly fewer epidural and oral narcotics were used in the pregabalin group, and these patients also had greater knee flexion at 30 days postoperative and significantly less neuropathic pain at 3 and 6 months postoperatively. However, sedation and confusion were both significantly more common in patients receiving pregabalin compared with controls.

**Opioids.** Opioids have been the mainstays of treatment for acute surgical pain by which all other interventions are judged. Analgesic effects are produced by binding to specific receptors in the brain and spinal cord. Numerous systemic side-effects associated with narcotic treatment are detailed in Table 1. Although tolerance and addiction can result when using opioids to treat chronic pain, these are generally not factors when narcotics are used to treat acute postsurgical pain for a short duration.

As previously discussed, opioids are best used for breakthrough pain in conjunction with a comprehensive pain management strategy. Many dosing options exist for postsurgical pain—from oral combination products to parenteral patient-controlled analgesia pumps. Recently, oral sustained-release formulations given preoperatively and continued for a short duration postoperatively have become popular. The goal of this strategy is to provide a steady baseline concentration without the serum fluctuations of repeated dosing intervals. However, caution should be used when prescribing these powerful narcotics to elderly patients and those who are susceptible to the concomitant adverse effects.

**Multimodal Analgesic Regimens in Total Joint Arthroplasty**

Several comparative studies have compared various multimodal medication strategies to traditional methods in patients undergoing joint replacement arthroplasty.

Peters et al\textsuperscript{55} retrospectively compared 2 cohorts of 50 consecutive TJA patients before and after implementing a multimodal protocol of scheduled oral narcotics, COX-2 inhibitors, femoral nerve catheters, and percutaneous injections. They found significant improvements in postoperative pain and walking distance and decreased narcotic consumption and length of stay in the multimodal cohort. Complications were similar in both groups.

Fu et al\textsuperscript{56} conducted a randomized controlled trial involving 100 TKA pa-
patients. Half were assigned to a multimodal protocol consisting of oral celecoxib and tramadol before and after surgery with an intra-articular injection of morphine, ropivacaine, epinephrine, and betamethasone. Oral and intra-articular placebo was given to the control group. Narcotic use was significantly lower in the treatment group, as were visual analog pain scale (VAS) scores at rest and during activity. The treatment group patients met physical therapy milestones sooner, including the ability to perform an active straight leg raise and flexion past 90°. Nausea and vomiting were also significantly diminished in the multimodal group, but other complication rates were similar.

Lee et al57 randomized 60 patients undergoing THA to either a multimodal or conventional analgesia group. The multimodal group was given an intraoperative injection (morphine, methylprednisolone, and ropivacaine), and pre- and postoperative sustained release oxycodone and acetamphen. The treatment showed significantly lower VAS pain scores over the first 4 days postoperatively and ambulated comfortably with crutches sooner than the control groups. No differences were found in complication rates, length of stay, or narcotic consumption.

Certain complications and costs may also be less with a multimodal strategy after TJA. Lavernia et al58 retrospectively compared the rates of arthrofibrosis in a cohort of more than 1100 TKA patients. Patients receiving traditional pain control had a significantly higher rate of manipulation while under anesthesia (4.75% of 778 patients) compared with those receiving a multimodal regimen (2.24% of 357 patients). Duncan et al59 evaluated the economic impact of implementing a multimodal pain control regimen, comparing the costs of 100 patients treated with multimodal therapy with matched historical controls treated with traditional methods. They found significantly decreased mean direct hospital costs (nearly $2000 difference) in the multimodal group. They noted the greatest cost difference was seen in patients with significant comorbidities.

**CURRENT PROTOCOL AT OUR INSTITUTION**

A comprehensive multimodal analgesia protocol has evolved at our institution over several years. The net effect is a strategy that maximizes patient comfort while minimizing adverse effects from regional anesthesia and pain medications to promote accelerated postoperative rehabilitation.

Preoperative screening and evaluation are important parts of a comprehensive pain protocol. Frequently, patients are on narcotics for chronic musculoskeletal pain, making postoperative pain control exceptionally challenging. We make every effort to wean patients off these medications before planning surgery, and frequently consult a pain management specialist for assistance with both pre- and postoperative management. Realistic expectations for postoperative pain must be set for patients in these difficult situations. One provider should be responsible for managing all opioid medications, and this must be clearly communicated to the patient in advance of surgery. Unless contraindicated, patients receive spinal anesthesia with bupivicaine. Intrathecal morphine is used only in healthy, younger patients without cardiopulmonary disease or sleep apnea due to potential adverse effects including pruritus, nausea, hypotension, and respiratory depression. No regional nerve blocks are performed in patients undergoing THA. In TKA patients, femoral and sciatic nerve blocks are also infrequently performed at our institution. Although effective at providing pain relief, they can result in significant weakness of the major muscle groups, which interferes with physical therapy and independent mobilization, and predisposes the patient to falls.

We have found THA patients typically remain comfortable and do not require a periarticular injection of local anesthetic and associated medications. However, patients undergoing TKA usually have more pain. Current practice at our institution is to use a continuous intra-articular bupivicaine infusion delivered by an elastomeric device (On-Q; I-Flow Corp, Lake Forest, California) placed at the time of surgery and discontinued on the morning of postoperative day 2. A double-blinded, randomized trial performed at our hospital showed this device to be superior to placebo in patients undergoing TKA.37 Significant reductions in VAS pain scores during postoperative days 1 and 2 and significant decreases in narcotic requirements during days 2 and 3 were found in the treatment group. However, this device should not be used in patients with remaining native cartilage (ie, partial knee arthroplasty or unresurfaced patella) due to significant reports of chondrolysis when used in the knee and shoulder following arthroscopic surgery.60-62

Nonnarcotic medications are an integral part of our multimodal approach. Table 3 contains the dosing regimens of commonly used pre- and postoperative medications.

All hip and knee arthroplasty patients receive a cocktail of medications with a sip of water 1 hour prior to surgery for preemptive analgesia. Preoperative medication administration ensures therapeutic drug levels at the completion of surgery, which minimizes pain in the recovery room. Acetaminophen (1 g orally or intravenously) is given, unless the patient has a history of liver disease or elevated liver function tests. Celecoxib (400 mg orally) is also administered, unless the patient is taking this medication preoperatively, in which case a 200 mg dose is given. Celecoxib is contraindicated in patients with a sulfa allergy, and naproxen (500 mg orally) is substituted in this circumstance. Pregabalin (75 mg orally) is given unless the patient is at elevated risk of postoperative delirium,
such as elderly patients with preexisting mild dementia or cognitive decline.

Total hip arthroplasty patients are continued on this regimen throughout their postoperative hospital course. A prospective study at our institution compared this acetaminophen, pregabalin, and celecoxib protocol with supplemental fentanyl patient-controlled analgesia for breakthrough pain with the protocol of a fentanyl patient-controlled analgesia alone. The multimodal group showed significantly lower pain scores and reduced narcotic consumption during the first 24 hours postoperatively. There were also significantly fewer opioid-related adverse effects (e.g., itching, constipation, and dizziness) and significantly fewer interruptions to physical therapy in the multimodal group.

A slightly different postoperative protocol is used in patients undergoing TKA. Acetaminophen and pregabalin are given as previously discussed. Ketorolac, a potent intravenous NSAID, is typically substituted for celecoxib starting the evening of surgery and continuing through postoperative day 2. Nonsteroidal anti-inflammatory drugs are not given to patients with renal insufficiency and those with a history of gastrointestinal ulcers or bleeding. In addition, the usual 30 mg dose of ketorolac is reduced to 15 mg in elderly patients, who have decreased creatinine clearance. A proton pump inhibitor should be co-administered to minimize gastrointestinal complications.

Opioids are given as a second-line treatment for residual pain. Oral narcotics are sufficient in the vast majority of patients. Tramadol (50-100 mg every 6 hours) is used for mild to moderate pain and oxycodone (5-10 mg every 4 hours) for moderate to severe pain. Every effort is made to avoid strong narcotics in patients older than 80 years with an elevated risk of postoperative delirium. Attentive nursing care ensures that patients receive oral pain medication 1 hour prior to physical therapy to minimize discomfort and disruptions. Occasionally, parenteral narcotics are necessary for severe breakthrough pain. We prefer to start with 1-time injections of short-acting narcotics such as fentanyl. Rarely, a patient-controlled analgesia may be necessary to achieve adequate pain control; however, we prefer to institute these only for a short time period.

Techniques for controlling postoperative pain after lower extremity joint reconstruction have advanced significantly. A comprehensive, multimodal analgesia strategy provides effective pain control in the majority of patients, while limiting adverse effects and facilitating rapid rehabilitation. These protocols have demonstrated improvements in patient satisfaction and decreased costs when compared with traditional practices. New developments and innovations will further improve patient comfort and satisfaction after these common, elective procedures.

**Table 3**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Preoperative Dosing†</th>
<th>Postoperative Dosing</th>
<th>Common Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID</td>
<td></td>
<td>15-30 mg every 6h</td>
<td>Renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Intravenous</td>
<td>15-30 mg every 6h for 7 doses</td>
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<td></td>
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<tr>
<td>Ibuprofen</td>
<td>Oral</td>
<td>800 mg every 6h</td>
<td>Gastric ulcers</td>
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<td>COX-2 inhibitor</td>
<td>Oral</td>
<td>400 mg every 12h</td>
<td>Sulfuric acid allergy</td>
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<tr>
<td>Celecoxib</td>
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<td>300 mg every 12h</td>
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<td>Anti-neuropathic</td>
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<td>Acetaminophen</td>
<td>Oral/intravenous</td>
<td>1000 mg every 6h</td>
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</tbody>
</table>

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

†Preoperative doses of all medications should be given as 1 administration within 2 hours of the start of surgery.

**REFERENCES**

6. Parvizi J, Porat M, Gandhi K, Viscusi ER, Rothman RH. Postoperative pain management techniques in hip and knee arthro-


