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MULTIMODAL PAIN MANAGEMENT TECHNIQUES IN HIP AND KNEE ARTHROPLASTY

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Adequate control of postoperative pain following hip and knee arthroplasty can be a challenging task[1,2]. Previous studies have shown that over 50% of patients undergoing surgery report postoperative pain as a major concern[3]. Consequences of uncontrolled pain can lead to myocardial ischemia and infarctions, pulmonary infections, paralytic ileus, urinary retention, thrombo-embolisms, impaired immune functions, as well as anxiety. In addition, inadequate control of pain may result in patient dissatisfaction, impaired patient rehabilitation, and prolonged hospitalizations[3]. The negative influence of postoperative pain on rehabilitation is particularly concerning for patients undergoing joint replacement. Functional recovery and return of muscle strength is dependant on the ability of these patients to comply with rehabilitation. The drawbacks of inadequate rehabilitation are especially cumbersome in hip and knee surgeries, since faster mobilization leads to quicker discharge from the hospital. Furthermore, studies have shown that recovery from knee arthroplasty is prolonged up to 50 days postoperatively, far greater than recovery from hip replacement[4]. Pain control is especially important for knee arthroplasty patients to allow recovery of range of motion and muscle strength for ambulation[5].*The Journal of NYSORA; 13: 1-8.*

MULTIMODAL PAIN MANAGEMENT TECHNIQUES

INTRODUCTION

The current modalities for pain control often rely on single drug strategies for pain control after hip and knee arthroplasty. This may lead to significant patient dissatisfaction. Using opioids alone intensifies their familiar side-effect profile that includes respiratory depression, postoperative nausea and vomiting (PONV), over-sedation, and puritus. In addition patients may be concerned with the potential addiction to the opioids. In one study 72% of post-operative patients preferred non-narcotic drugs because of concern regarding addition potential of opioids[1]. On the other hand the administration of non-steroidal anti-inflammatory medications (NSAIDS), particularly at higher doses, may be associated with gastrointestinal side effects such as gastritis, gastric ulcers, increased bleeding, and renal impairments. Local anesthetics have been used in peripheral nerve block prior to or after surgical procedures. However, their use is sometimes limited due to their short duration of action. Excess dosage of local anesthetics in the blood can cause cardiovascular collapse and central nervous system side effects including seizures.

Multimodal Analgesia

The value of multimodal analgesia is understated in literature[6]. Most reports on control of postoperative pain consist of unimodal therapies. Most reports in the literature are based on studies that employ bimodal therapy (such as a combination of ketorolac and morphine) as a means to control pain. Bimodal therapy may be misunderstood as a true multimodal approach to analgesia. The vast majority of studies with combination therapies are in this category. Few studies provide evidence for true multimodal therapy. The combination of multiple analgesic drugs with different

mechanisms and pathways of action is the best way to achieve maximal control of pain after hip and knee arthroplasty[7]. Kehlet and Dahl first described the concept of combining multiple analgesic techniques in 1993 as a method of improving outcome following colon surgery[6].

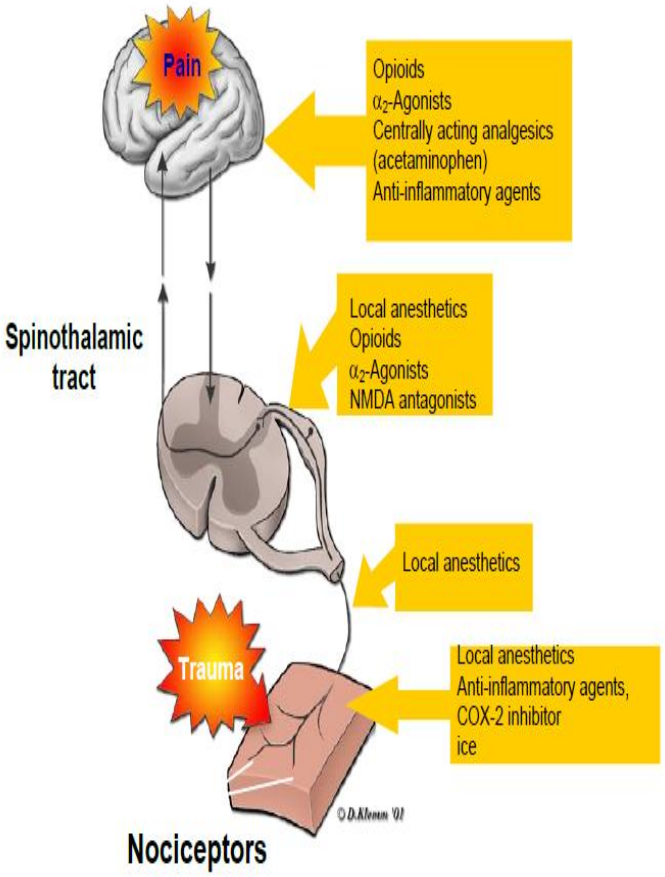

Figure 1. Pain Pathways and Multimodal Analgesic Therapy (Adapted from Gottschalk A, Smith DS. *Am Fam Physician)*

Multimodal analgesia requires an understanding of the molecular mechanisms of pain pathways. Postoperative pain is a consequence of tissue injury, nerve irritation and the resulting cascade of neurohumeral events that follow. After a painful stimulus, chemical mediators such as prostaglandins (PGE2) and bradykinin are released at the site of tissue injury. These chemical mediators stimulate nociceptors, peripheral pain receptors that respond to trauma and high temperatures. These nociceptors form pain fibers that enter the spinal cord via the dorsal root ganglion. Pain receptors that are principally responsible for noxious stimulation in the dorsal horn of the spinal cord are N-methyl D-aspartate (NMDA) receptors. Painful stimulus is propagated by central NMDA receptors in the spinal cord by way of the spinothalamic tract to the brain. Through this complex pathway, the brain experiences pain after trauma inflicted to the site of tissue injury caused by surgery. The concept of multimodal analgesia relies on understanding these complex neurohumeral interactions. Analgesia after surgery can be achieved by using a combination of drugs that inhibit this complex pathway at multiple sites (Figure 1).

What does a multimodal approach look like?

Multimodal approach to pain control involves administration of combination and often multiple analgesics or modalities at various time points during the course of surgery that includes preoperative period. Pain control after knee and hip arthroplasty can be achieved with a combination of drugs used during the preoperative (NSAIDS, COX-2 inhibitors, anticonvulsants), intra-operative (opioids, local anesthetics), and the postoperative periods (opioids, NSAIDS, COX-2 inhibitors, α2-Agonists, NMDA antagonists, anticonvulsants, and centrally acting analgesics as acetaminophen).

Pre-operative Period:

The pre-emptive strategy behind multimodal analgesia must begin in advance of the surgical incision.

NSAIDs and COX-2 Inhibitors

Use of non-opioid drugs during the preoperative period can reduce excess intra-operative opioid usage and the possible subsequent effect of opioid-induced hyperalgesia seen after surgery[8]. Opioid induced hyperalgesia is a complex phenomenon that can follow rapid escalation in opioids during or following surgical procedure which can paradoxically lower the pain threshold and result in greater opioid requirements. Research has shown that activation of NMDA receptors in the central nervous system results in hyperalgesia associated with opioids. This phenomenon may be minimized by limiting opioids and maximizing non-opioid drugs. The use of NSAIDs is recommended as a multimodal approach to management of pain as part of most acute pain management guidelines[9].

The use of preoperative NSAIDs and COX-2 inhibitors also has a significant effect on opioid requirements following surgery. This has been referred to as an "opioid sparing effect." The clinical significance of this may be the

reduction of opioid related side effects, improved analgesia, and better patient satisfaction. The primary site of action of NSAIDs and COX-2 inhibitors are in the periphery where they inhibit prostaglandin synthesis and stimulation of nociceptors (Figure 1). Through this inhibition, they target peripheral pain pathways (peripheral sensitization). Recent findings show elevation of prostaglandins in the central nervous system which may also play a role in central sensitization syndrome[10]. Furthermore, the hypersensitivity of injured tissue may also produce a secondary hyperalgesic effect on the uninjured tissue[11]. Prostaglandins have been demonstrated to lower pain thresholds in both the central and peripheral nervous system. NSAIDS or COX-2 inhibitors can be used preoperatively to effectively reduce the occurrences of central and peripheral sensitization syndrome after surgery.

Preemptive treatments with the NSAIDs such as ketorolac and ibuprofen are shown to have the advantage of decreasing postoperative pain scores, opioid requirements, and postoperative nausea after surgery[12]. Some surgeons are concerned about the use of NSAIDS prior to surgery due to a decrease in platelet aggregation and potential increase in bleeding time[13]. Consequently NSAIDs are commonly discontinued 7-10 days before surgery to reduce perioperative bleeding, particularly with hip arthroplasty[14]. Other concerns associated with NSAIDS include gastritis and peptic ulcer disease, renal impairment, and poor wound and bone healing. Because of these concerns, COX-2 selective inhibitors may have advantages over NSAIDS in the acute postoperative setting.

COX-2 selective inhibition provides selective inhibition of prostaglandins thereby reducing bleeding and gastric side effects seen with NSAIDS. COX-2 selective inhibitors allow for dosage on an empty stomach prior to surgery with low risk of bleeding during surgery. Recently, COX-2 inhibitors have fallen out of favor because of concerns for potential increased risk of cardiovascular side effects with long term usage. Rofecoxib has been withdrawn from the market because of its cardiovascular side effects. However, the COX-2 selective inhibitors have not been implicated for cardiovascular side effects with short term use such as in postoperative analgesia. Many studies have demonstrated benefits of employing these agents in the perioperative setting.

One study using pre-surgical dosing of COX-2 inhibitors one hour before arthroscopic knee surgery showed significant reduction in pain scores as compared to placebo at 1 hr., 2 hr., and 24 hours after surgery[15]. These patients had a significantly longer duration postoperatively before requiring analgesics and the 24 hour consumption of opioids was significantly lower than patients who were offered the same drug post-operatively. Another study using rofecoxib 24 hours and 1 hour before surgery with continued postoperative drug administration for 14 days had better outcomes in total knee arthroplasty[16]. These patients showed reduced opioid requirements, faster time to physical rehabilitation, reduced nausea and vomiting, better sleep patterns and greater patient satisfaction after surgery. In addition, an opioid sparing effect has also been demonstrated with the preoperative use of celecoxib and rofecoxib after spinal fusion surgery[17]. In this study, rofecoxib 50 mg showed an extended benefit for 24 hours after surgery. Both NSAIDs and COX-2 inhibitors may also be continued after the patient is discharged from the hospital for optimal management of pain. Dosage recommendations for preoperative treatments are given in Table 1.

Drugs	Dose	Route of administration	Time before surgery	Time after Surgery
NSAIDs				
Ketorolac	15-30 mg	PO/IV	1-2 hour	15-30 mg q6hrs
Ibuprofen	800mg	PO	1-2 hour	800 mg q6hrs
COX-2 Inhibitors				
Celecoxib	400mg	PO	1 hour	200 mg X 1 2hrs after surgery
Valdecoxib	40mg	PO	1 hour	Bid
Anti-neuropathic				
Gabapentin	1200mg	PO	1-2 hours	1200mg X 1 (24 hrs after surgery)
Pregabalin	150 mg	PO	1 hour	150 mg X1 (12 hrs after surgery)
Propacetamol	2 g	PO/IV	15 minutes	2 g every 4 hours
Acetaminophen	1 g	PO/IV	15 minutes	1 g every 4 hours

Table 1. Dosage recommendations for individual non-opioid agents that may be administered as part of multimodal analgesia

Gabapentin and pregabalin

In addition to NSAIDs and COX-2 inhibitors, anti-neuropathic drugs are playing a role in treatment of post-operative pain. Such drugs as gabapentin and pregabalin, intended for seizures and neuropathic pain syndromes, can inhibit central neuronal sensitization[18]. Studies have shown that preoperative administration of gabapentin leads to reduction in post-operative pain and morphine consumption[19-21]. Gabapentin administered one hour before surgery in patients undergoing knee surgery had significantly improved post-operative analgesia and better range of knee motion[22]. Synergistic benefits are seen up to 72 hours when COX-2 inhibitors and gabapentin are used together prior to surgery for lower abdominal and spinal fusion surgeries[19,25] Pregabalin was also found to have a synergistic effect with COX-2 inhibitors in clinical studies involving patient undergoing spinal fusion[26]. The combination of the two drugs reduced postoperative pain, morphine consumption at 24 hours, and opioid induced side effects. Improvements in outcome were greater when these drugs were used in combination than either of the drugs used alone.

Primary Intraoperative Period:

Spinal and Epidural Analgesia

Regional anesthesia is generally preferred over general anesthesia in the US. The merits of regional anesthesia are many. Regional anesthesia provides optimal surgical conditions and analgesia extending into the postoperative period. The motor block achieved by spinal anesthesia is unsurpassed by any other technique. The modest reduction in arterial blood pressure contributes to reduced surgical blood loss. Regional analgesia may also result in reduced postoperative nausea and vomiting, less respiratory and cardiac depression, and decreased risks of thrombo-embolisms[27-29]. Regional anesthesia has the advantage of blunting stress response in surgery and decreasing morbidity and mortality in high risk surgical patients[30-31]. Regional analgesia utilizes local anesthetics (such as bupivicaine, ropivicaine or tetracaine) as the primary agent for blockade of central sensory and motor receptors. The onset of analgesia is dependent on characteristics of the local anesthetic (lipid solubility, pK_a, dosage and volume of anesthetic used), patient anatomy (age, weight, height, and gender), and technique used (site of injection, type of needle used, and the direction of the needle). Local anesthetics in regional anesthesia block nociceptive transmission in the peripheral (via peripheral nerve block) and central nervous system (via spinal/ epidural blocks) (Figure 1). Some agents may be co-administered with local anesthetics in an attempt to enhance the quality of neural blockade. Agents commonly used include vasoconstrictors (epinephrine), opioids (morphine or fentanyl), α-2 receptor agonists (clonidine), NSAIDs (ketorolac), or COX-2 inhibitors[32]. While many studies have demonstrated a benefit to this practice, the use of some agents is equivocal. Also, the addition of some agents introduces other side effects. Hence the risk-benefit ratio must always be individualized to the specific patient.

Regional analgesia during the perioperative period involves the uses of spinal analgesia, combined spinal-epidural analgesia, or peripheral nerve blockade for pain control during and after surgery. Spinal anesthesia commonly used for total joint arthroplasty utilizes a spinal needle (Quincke, Sprotte, and Whitacre) to place drugs (local anesthetics) into the intrathecal (subarachnoid) space. The onset of spinal anesthesia is rapid since the cerebrospinal fluid (CSF) rapidly carries the drug to various sites in the spinal cord. The intensity and height of spinal blockade depends on the baricity (compared to spinal fluid) and the volume of the local anesthetic used. Opioids such as morphine and fentanyl may be added to the intrathecal mixture to prolong postoperative pain control. Fentanyl, because of its lipophilic properties, produces rapid onset (10-15 minutes) but short duration (2-4 hours) of analgesia, while morphine with it's hydrophilic properties has a longer duration (18-24 hours) of action into the postoperative period[32]. Relatively small doses of intrathecal morphine (0.2 mg) are very effective for providing prolonged analgesia after hip arthroplasty. For optimal post-operative pain relief as part of multimodal analgesia, morphine has a higher degree of patient satisfaction due to prolonged analgesic effect. Randomized controlled studies with patients undergoing total hip replacement show significant reduction in postoperative intravenous morphine requirements for patients who received 0.1-0.3 mg of intrathecal morphine[33]. The same dose of morphine with total knee replacement did not significantly reduce the need for supplemental IV morphine in the postoperative period. The most common side effects of intrathecal morphine reported after the surgery was puritus, nausea/vomiting, and oxygen desaturation. Older patients undergoing hip arthroplasty may benefit from a more conservative dose of 100ug of morphine added to the spinal anesthetic, since serious side effects as oversedation and

delayed respiratory depression are minimized[34]. Nonetheless, intrathecal morphine has a long track record of safety when moderate doses are employed and tailored to the specific patient.

In addition to the uses of morphine, the administration of clonidine with spinal local analgesics can also decrease the need for post-operative morphine consumption. Clonidine is a α_2-adrenergic agonist which potentiates the sensory and motor blocks of local anesthetics in the spinal cord. The combination of clonidine and morphine to an intrathecal regimen has significant improvements in post-operative pain and decreased morphine requirements for 12 hours after total knee arthroplasty[35]. However, hypotension was reported in some of these patients.

Epidural anesthesia is preferred by some clinicians. Epidural anesthesia and analgesia requires placing a specially designed needle (Hustead, Tuohy, or Crawford) into the epidural space. Drugs may be injected directly through the needle or an epidural catheter may be inserted. Subsequent postoperative analgesia may utilize continuous drug infusion or injection of a single drug. A variety of other agents have been added to epidural infusions Epinephrine can induce a synergistic analgesic on the spinal cord as well as elicit vasoconstriction on the blood vessels for decreased absorption of local anesthetic[36]. Other multimodal approaches have utilized small doses of ketamine, an NMDA antagonist in the spinal cord, for sensory blockade and prevention of central sensitization of nociceptors[37].

The benefits of epidural analgesia and surgical outcomes have been well documented in the literature[38]. Compared with parenteral opioid use after surgery, the utilization of continuous infusion with epidural analgesia provides superior relief in post-operative pain with few adverse outcomes. The limitations of epidural analgesia often involve failed or dislodged catheters, unilateral blocks, and incompatibility in patients who are anti-coagulated. There is a risk of spinal hematomas with patients who are receiving anti-coagulation with an indwelling epidural catheter. Other limitations related to local anesthetics include hypotension and motor impairment in these patients.

Some of these issues related to epidural catheters or the local anesthetics themselves may be addressed by utilizing an extended-release epidural morphine formulation[38]. DepoDur, recently approved by the FDA in the U.S., utilizes microscopic multivesicular liposomal spherical particles with internal aqueous chambers containing morphine. Patients given a single epidural injection of extended-release epidural morphine (EREM) have demonstrated a 48 hour period of analgesia[39]. Patients given EREM in clinical trials after hip replacement had significant less supplemental opioid requirement after surgery than placebo[39]. Furthermore, the needs for rescue medications were minimal with less instances of hypotension. Other potential advantages of EREM include no epidural catheter or pump related issues which can create gaps in analgesia postoperatively. The absence of epidural and patient controlled analgesia pump technology theoretically reduces opportunities for medication errors and pump programming errors as well. The side effects of EREM are similar to other opioids including nausea, vomiting, constipation, and respiratory depressions. Ideally, the use of EREM in a multimodal analgesic approach and with appropriate patient selection may result in analgesia without the need for any tethering pump technology

	Dose	Onset
Spinal Block		
Epinephrine	0.1-0.6 mg	rapid
Meperidine	1.2-1.5 mg/kg	rapid
Morphine	100-300 ug	20-30 min
Fentanyl	5-25 ug	45-75 min
Clonidine	75 ug	5-10 min
Intravenous		
Ketamine	5-6 ug/kg/min	rapid

Table 2. Dose recommendations for agents that may be used as adjuncts perioperatively.

Peripheral Nerve Blocks

Peripheral nerve blocks (PNB) are an increasingly popular technique for anesthesia and pain management for total joint arthroplasty. Some clinicians prefer PNB in patients who will be anti-coagulated because of concerns for epidural hematomas. PNB may also reduce the incidence of arterial hypotension or urinary retention compared to spinal or epidural techniques. The psoas compartment block of the lumbar plexus is an effective analgesic block for total hip arthroplasty. Anesthesia for total knee arthroplasty requires block of both the lumbar plexus (femoral or psoas compartment) and the lumbosacral plexus (sciatic nerve).

However, adequate postoperative analgesia is usually achieved with block of the lumbar plexus alone. Peripheral nerve blocks can be achieved with single injection of a local anesthetic or with the use of a catheter that utilizes continuous infusion of a local anesthetic.

Some studies show that a continuous femoral nerve block has efficacy equal to epidural analgesia in patients undergoing total hip arthroplasty[40]. Although there were no significant differences between the two, some of the side-effects seen with epidural blocks as hypotension and spinal hematomas may be avoided with femoral nerve blocks. The authors concluded that peripheral blocks may be superior to epidural blocks due to decreased systemic side effects seen with these blocks.

In studies involving total knee arthroplasty, both epidural analgesia and continuous femoral nerve block had better pain relief and faster knee rehabilitation compared to IV PCA usage after surgery[41]. The efficacy of femoral nerve blocks alone is questioned by some since the sciatic nerve innervates the posterior and lateral aspect of the knee. While it is necessary to combine both femoral and sciatic nerve blocks for total knee arthroplasty anesthesia, adequate postoperative analgesia is usually achieved with femoral nerve block. Some studies have utilized a combination of continuous sciatic nerve block and femoral nerve block in patients undergoing total knee arthroplasty[42]. In one study, adding sciatic nerve block significantly decreased morphine requirements up to 36 hours. However one randomized study found minimal benefits of adding a sciatic nerve blocks to femoral nerve block[43]. There were no differences in morphine consumption with femoral blocks and the combined sciatic-femoral block. The authors concluded that sciatic innervation of the posterior knee may be a minor contributor of post-operative pain following total knee arthroplasty. Furthermore, the value of blocking the obturator nerve in a psoas block may also give limited benefit[44]. There was limited benefit in analgesic requirements in a psoas block and no difference in functional outcome when compared to femoral and sciatic blocks. No block is without risk, hence clinicians must carefully evaluate the individual risk/ benefit ratio of adding the sciatic block solely for postoperative analgesia.

All nerve blocks discussed above may be performed with a single injection of local anesthetic or with a continuous infusion through an indwelling catheter. The benefits offered by a continuous infusion may include better analgesia through the second postoperative day, however one study did not demonstrate a difference in length of hospital stay and functional recovery[45]. The limitations of a continuous catheter include additional time, cost, and skills required to manage the catheter. There are also potential risks of infections and nerve injury with continuous catheters. External infusion pump technology also introduces the potential for technical failures and requires additional surveillance. For these reasons, some clinicians avoid this approach.

Postoperative Pain Control:

Intravenous Patient Controlled Analgesia (IV-PCA)

Intravenous PCA is the most widely utilized form of post-operative analgesia offered to patients after surgery[46]. PCA utilizes infusion pumps to deliver patient activated fixed and small doses of opioids based on demand and a lock out period with an hourly maximum dose. Opioids commonly utilized in PCA include morphine, hydormorphone, and fentanyl. For PCA to be successful, patients have to be willing to actively participate in their care. Patients must comprehend the operation of the devise and be able to give themselves bolus when needed. Effective PCA treatment involves initial clinician titration by bolus to establish analgesia. PCA is intended to maintain analgesia, not to achieve analgesia. Opioid related side effects are common. Elderly patients are particularly vulnerable to confusion and delirium after PCA use. Multimodal analgesia in combination with PCA may reduce opioid requirements resulting in better pain control and fewer side effects. The complexity of standard PCA pumps may consume valuable healthcare resources including nursing and pharmacist time and materials. PCA pumps have been implicated in medication errors and programming errors that may lead to patient harm. Hence, strict protocols need to be in place to prevent these harmful errors.

Transdermal PCA

Transdermal PCA is a novel approach to delivering opioids to the postoperative patient without venous access, external infusion pumps, or the potential for programming errors. Transdermal PCA utilizes iontophoresis technology to deliver drugs through the skin by use of an external electrical field[47]. The fentanyl iontophoretic transdermal system (fentanyl ITS) has recently been approved for treatment of post-operative pain[48-49]. This system consists of a preprogrammed, needle-free credit-card sized system

that is applied to the patient's upper outer arm or chest for 24 hours. The system utilizes an on-demand delivery dose of 40 mcg of fentanyl for 10 minutes up to six doses an hour with a maximum of 80 doses. The system shuts down after 80 doses or 24 hours, whichever comes first. Randomized placebo controlled trials demonstrated that the fentanyl iontophoretic transdermal system was superior to placebo for pain control in the first 24 hours following surgery. Patients who received the fentanyl ITS had lower pain scores and fewer drug discontinuations compared to placebo. The side effect profiles were also similar between controls and those that received fentanyl ITS. Another randomized study conducted on patients undergoing abdominal and orthopedic surgeries in Europe showed fentanyl ITS to be just as effective as morphine PCA[50]. However, the iontophoretic system had greater ease of use and was less time consuming than traditional PCA. The fentanyl iontophoretic transdermal system may be particularly attractive for total joint arthroplasty patients as it eliminates the need for a bulky infusion pump and tethering IV tubing that may impede patient activity and participation in physical therapy. Further studies will be needed to identify the benefits of less invasive technologies.

Acetaminophen (Paracetamol)

Acetaminophen is a popular adjuvant to opioids as part of multimodal analgesia in acute post-operative pain management. It also has opioid sparing effect especially when used in combination with NSAIDs. Acetaminophen has no associated post-operative bleeding and is a cost-effective centrally acting analgesic (Figure 1). An intravenous formulation of acetaminophen is available in many parts of the world and is currently under development in the US. The intravenous acetaminophen formulation has been demonstrated to have great efficacy in patients undergoing total joint arthroplasty[51]. The use of the drug also resulted in reduced morphine requirements and was better tolerated in the elderly and high risk patients.

An Institutional Approach to Multimodal Analgesia

We employ protocols and pathways to apply multimodal techniques for total joint arthroplasty (Figure 2). Our protocols utilize multiple modalities employed at different times prior and after surgery. These protocols are reduced to order sets with pre-selected options available for computer physician order entry (CPOE). Of course, the options are adjusted to the particular patients needs. However, the availability of standard pathways facilitates application to a large number of patients in our high volume orthopedic practice. Patient outcomes are tracked and these protocols are adjusted over time based on these findings and other emerging evidenced based techniques.

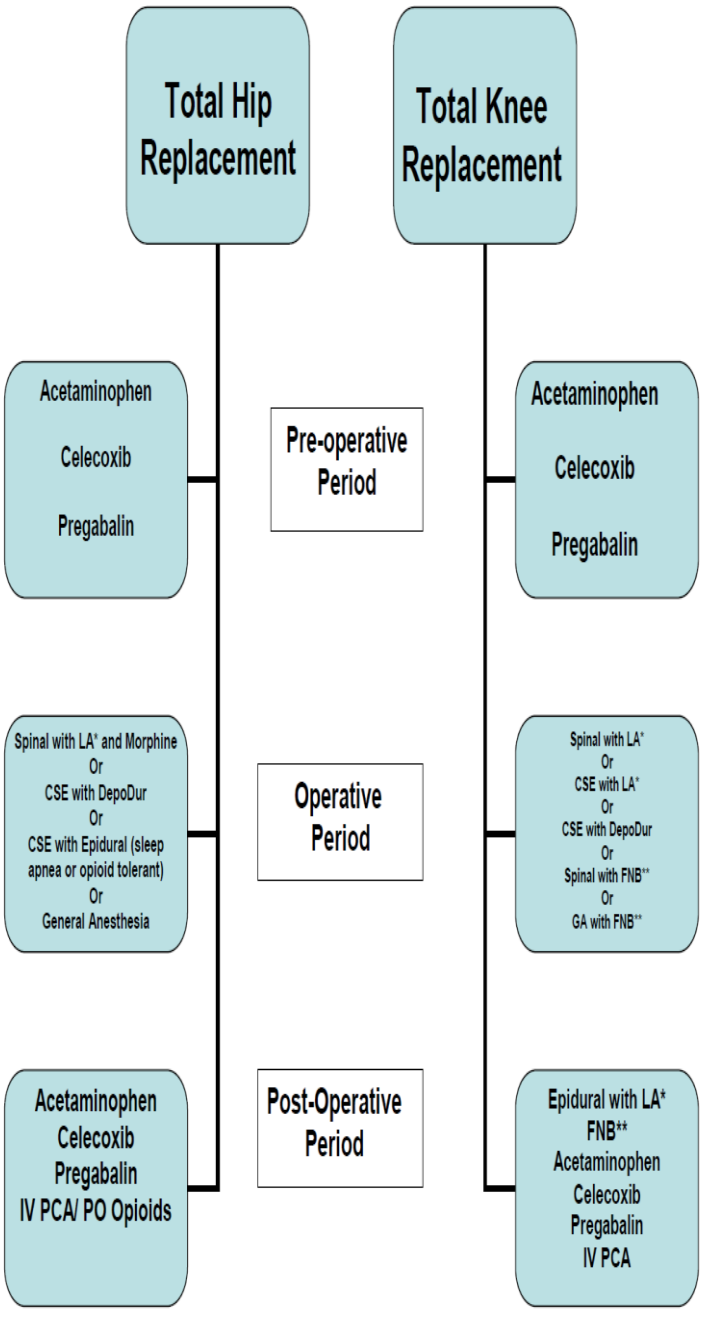

Figure 2: Multimodal Analgesia Algorithm for Hip and Knee Arthroplasty at Thomas Jefferson University Hospital and Rothman Institute for Orthopedics.
***LA**- Local Anesthetic, ****FNB**- Femoral Nerve Block

Conclusion:

Multimodal analgesia offers many benefits to patients undergoing total joint arthroplasty. Opioids remain an integral part of most analgesic plans but techniques that reduce opioid requirements typically improve pain control both at rest and with motion, reduce opioid related side effects, provide better patient satisfaction and according to a recent study, may reduce the incidence of long-term pain following surgery. Well designed pathways incorporating multimodal analgesia may impact length of hospital stay and functional outcome of these patients with prosthetic joints. Effective multimodal regimens require an understanding of the multiple pathways of pain. Optimal application of these techniques is often best served by developing institutional pathways for specific procedures.

REFERENCES:

1. Apfelbaum JL, Chen C, Mehta SS, Gan TJ., Postoperative Pain Experience: Results from a National Survey Suggest Postoperative Pain Continues to Be Undermanaged. Anesthesia & Analgesia, 2003. 97:534-40.
2. Warfield C, Kahn CH., Acute Pain Management: Programs in U.S. Hospitals and Experiences and Attitudes Among U.S. Adults. Anesthesiology, 1995. 83:1090-1094.
3. Joshi GP, Ogunnaike BO., Consequences of Inadequeate Postoperative Pain Relief and Chronic Persistent Postoperative Pain. Anesthesiology Clinics of North America, 2005. 23: p. 21-36.
4. Salmon P, Hall GH, Peerbhoy D, Shenkin A, Parker C., *Recovery from Hip and Knee Arthroplasty: Patients's Perspective on Pain, Function, Quality of Life, and Well-Being Up to 6 Months Postoperatively.* Ach Phys Med Rehabil, 2001. **82**: p. 360-366.
5. Shoji H, Solomonow M, Yoshino S, et al., *Factors affecting post-operative flexion in total knee arthroplasty.* Orthopedics, 1990. **13**: p. 643-9.
6. Kehlet H, Dahl JB., *The Value of "Multimodal" or "Balanced Analgesia" in Postoperative Pain Treatment.* Anesthesia & Analgesia, 1993. **77**: p. 1048-56.
7. White., *The Changing Role of Non-Opioid Analgesic Techniques in the management of Postoperative Pain.* Anesthesia and Analgesia, 2005. **101**: p. S5-S22.
8. Mercadante S, Ferrera P, Villari P, Arcuri E, *Hyperalgesia: an emerging iatrogenic syndrome.* Journal of Pain Symptom Management, 2003. **26** p. 769-775.
9. Task Force on Pain Management, A.P.S., *Practice guidelines for acute pain management in the perioperative setting.* Anesthesiology, 1995. **82**: p. 1071-81.
10. Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, Bounventre JV, Woolf CJ, *Interleukin-1 β-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity.* Nature, 2001. **410**: p. 471-475.
11. Woolf CJ, Chong MS, *Preemptive analgesia: treating postoperative pain by preventing the establishment of central sensitization.* Anesthesia and Analgesia, 1993. **77**: p. 362-379
12. Comfort VK, Code WF, Rooney ME, YIP RW. , *Naproxen premedication reduces postoperative tubal ligation pain.* Canadian Journal of Anesthesiology, 1992. **4**: p. 349-52.
13. Souter AJ, Fredman B, White PF, *Controversies in the perioperative use of nonsteroidal anatiinflammatory drugs.* Anesthesia and Analgesia, 1994. **79**(6): p. 1178-80.
14. Robinson CM, Christie J, Malcon-Smith N., *Nonsteroidal anti-inflammatory drugs, perioperative blood loss, and transfustion requirements in elective hip arthroplasty.* Journal of Arthroplasty, 1993. **8**: p. 607-610.
15. Reuben SS, Bhopatkar S., Maciolek H, Joshi W, Sklar J. *The Preemptive Analgesic Effect of Rofecoxib After Ambulatory Arthroscopic Knee Surgery.* Ambulatory Anesthesia, 2002. **94**: p. 55-9.
16. Buvanendran A, Kroin JS, Tuman KJ, Lubenow TR, Elmofty D, Moric M, Rosenberg AG. *Effects of Perioperative Administration of a Selective Cyclooxygenase 2 Inhibitor on Pain Management and Recovery of Function*

After Knee Replacement: A Randomized Controlled Trial. JAMA, 2003. **290**(18): p. 2411-2418.
17. Reuben SS, Connelly NR. *Postoperative Analgesic Effects of Celecoxib or Rofecoxib After Spinal Fusion Surgery.* Anesthesia and Analgesia, 2000. **91**: p. 1221-5.
18. Rose MS, Kam PC. *Gabapentin: pharmacology and its use in pain management.* Anesthesia 2002. **57**: p. 451-462.
19. Turan A, Karamanlioglu B, Memis D, et al., *Analgesic effect of gabapentin after spinal surgery.* Anesthesiology, 2004. **100**: p. 935-938
20. Turan A, Karamanlioglu B, Memis D, et al., *The analgesic effects of gabapentin after total abdominal hysterectomy.* Anesthesia and Analgesia, 2004. **98**: p. 1370-1373.
21. Dierking G, Duedahl TH, Rasmussen ML, et al., *Effects of gabapentin on postoperative morphine consumption and pain after abdominal hysterectomy: a randomized, double-blind trial.* Acta Anaesthesiol Scand, 2004. **48**: p. 322-7.
22. Menigaux C, Adam F, Guignard B, Sessler DI, Chauvin M, *Preoperative Gabapentin Decreases Anxiety and Improves Early Functional Recovery from Knee Surgery.* Anesthesia and Analgesia, 2005. **100**: p. 1394-9.
23. Akeson WH, Amiel D, Abel MF, et al., *Effects of immobilization on joints.* Clinical Orthopedics, 1987. **219**: p. 28-37.
24. Colwell CW Jr, Morris BA, *The influence of continuous passive motion on the results of total knee arthroplasty.* Clinical Orthopedics, 1992. **276**: p. 225-8.
25. Turan A, White PF, Karamanlioglu B, Memis D, Tasdogan M, Pamukcu Z, Yavuz E, *Gabapentin: An Alternative to the Cyclooxygenase-2 Inhibitors for Perioperative Pain Management.* Pain Medicine, 2006. **102**: p. 175-81.
26. Reuben SS, Buvanendran A, Kroin JS, Raghunathan K, *The Analgesic Efficacy of Celecoxib, Pregabalin, and Their Combination for Spinal Fusion Surgery.* Pain Medicine, 2006. **103**(5): p. 1271-1277.
27. Modig J, Boreg T, Karlstrom G, Maripuu E, Sahlstedt B, *Thromboembolism after total hip replacement: Role of epidural and general anesthesia.* Anesthesia and Analgesia, 1983. **62**: p. 174.
28. Thornburn J, Louden J, Vallance R, *Spinal and general anesthesia in total hip replacement: Frequency of deep vein thrombosis.* British Journal of Anesthesiology, 1980. **52**: p. 1117.
29. Christopherson R, Beattie C, et al., *Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery.* Anesthesiology, 1993. **79**: p. 422.
30. Kehlet, *The stress response to surgery: Release mechanisms and teh modifying effect of pain relief.* Acta Chir Scand Suppl, 1988. **550**: p. 22.
31. Yeager M, GlassD, Neff R, Brinck-Johnsen T, *Epidural anesthesia and analgesia in high-risk surgical patients.* Anesthesiology, 1987. **66**: p. 729.
32. Rathmell JP, Lair TR, Nauman B, *The Role of Intrathecal Drugs in the Treatment of Acute Pain.* Anesthesia and Analgesia, 2005. **101**: p. S30-S43.
33. Rathmell JP, Pin CA, Taylor R, Patrin T, Viani BA, *Intrathecal Morphine for Postoperative Analgesia: A Randomized, Controlled, Dose-Range Study After Hip and Knee Arthroplasty.* Anesthesia and Analgesia, 2003. **97**: p. 1452-1457.
34. Murphy PM, Stack D, Kinirons B, Laffey JG, *Optimizing the Dose of Intrathecal Morphine in Older Patients Undergoing Hip Arthroplasty.* Pain Medicine, 2003. **97**: p. 1709-15.
35. Sites BD, Beach M, Biggs R, Rohan C, Wiley C, Rassias A, Gregory J, Fanciullo G, *Intrathecal Clonidine Added to a Bupivicaine-Morphine Spinal Anesthetic Improves Postoperative Analgesia for Total Knee Arthroplasty.* Anesthesia and Analgesia, 2003. **96**: p. 1083-8.
36. Huang KS, Tseng CH, Cheung KS, et al., *Influence of epinephrine as an adjuvant to epidural morphine for postoperative analgesia.* Acta Anaesthesiol Sin, 1993. **31**: p. 245-8.
37. Chia YT, Liu K, Wang JJ, Liu YC, Chang HC,Wong CS, *Adding Ketamine in a Multimodal Patinet-Controlled Epidural Regimen Reduces Postoperative Pain and Analgesic Consumption.* Anesthesia and Analgesia, 1998. **86**: p. 1245-9.
38. Viscusi, *Emerging Techniques in the Management of Acute Pain: Epidural Analgesia.* Anesthesia and Analgesia, 2005. **101**: p. S23-S29.
39. Viscusi ER, Martine G, Hartrick CT, et al., *48 Hours of postoperative pain relief following total* hip *arthroplasty with a novel, extended-release epidural morphine formulation.* Anesthesiology, 2005. **102**: p. 937-47.
40. Sigelyn FJ, Ferrant T, Malisse M, Joris D, *Effects of Intravenous Patient-Controlled Analgesia With Morphine, Continuous Epidural Analgesia, and Continuous Femoral Nerve Sheath Block on Rehabilitation After Unilateral Total-Hip Arthroplasty.* Regional Anesthesia and Pain Medicine, 2005. **30**(5): p. 452-457.
41. Singelyn FJ, Deyaert M, Jorist D, Pendeville E, Gouverneur JM, *Effetts of Intravenous Patient-Controlled Analgesia with Morphine, Continuous Epidural Analgesia, and Continuous Three-in-One Block on Postoperative Pain and Knee Rehabilitation After Unilateral Total Knee Arthroplasty.* Anesthesia and Analgesia, 1998. **87**: p. 88-92.

42. Dang CP, Gautheron E, Guilley J, Fernandez M, Waast D, Volteau C, Nguyen JM, Pinaud M, *The Value of Adding Sciatic Block to Continuous Femoral Block for Analgesia After Total Knee Replacement.* Regional Anesthesia and Pain Medicine, 2005. **30**(2): p. 128-133.
43. Allen HW, Liu SS, Ware PD, Nairn CS, Owens BD, *Peripheral Nerve Blocks Improve Analgesia After Total Knee Replacement Surgery.* Anesthesia and Analgesia, 1998. **87**: p. 93-97.
44. Morin AM, Kratz CD, Eberhart LH, Dinges G, Heider E, Schwartz N, Eisenhardt G, Geldner G, Wulf H., *Posoperative Analgesia and Functional Recovery After Total-Knee Replacement: Comparison of a Continuous Posterior Lumbar Plexus (Psoas Compartment) Block, a Continuous Femoral Nerve Block, and the Combination of a Continuous Femoral and Sciatic Nerve Block.* Regional Anesthesia and Pain Medicine, 2005. **30**(5): p. 434-445.
45. Salina FV, Liu SS, Mulroy MF, *The Effect of Single-Injection Femoral Nerve Block Versus Continuous Femoral Nerve Block After Total Knee Arthroplasty on Hospital Length of Stay and Long-Term Functional Recovery Within an Established* Clinical Pathway. Anesthesia and Analgesia, 2006. 102: p. 1234-9.
46. Grass, Patient-Controlled Analgesia. Anesthesia and Analgesia, 2005. 101: p. S44-S61.
47. *Ashburn MA, Strisand J, Zhang J, et al., The iontophoresis of fentanyl citrate in humans. Anesthesiology, 1995. 82: p. 1146-53.*
48. Viscusi ER, Reynolds L, Taint S, Melson T, Atkinson LE, *An Iontophoretic Fentanyl Patient-Activated Analgesic Delivery System for Postoperative Pain: A Double-Blind, Placebo-Controlled Trial.* Anesthesia and Analgesia, 2006. **102**: p. 188-94.
49. Viscusi ER, Reynolds L, Chung F, Atkinson LE, Khanna S., *Patient-Controlled Transdermal Fentanyl Hydrochloride vs Intravenous Morphine Pump for Postoperative Pain: A Randomized Controlled Trial.* JAMA, 2004. **291**(11): p. 1333-1341.
50. Ground S, Hall J, Spacek A, Hoppenbrouwers M, Richarz, Bonnet F., *Iontophoretic transdermal system using fentanyl compared with patient-controlled intravenous analgesia using morphine for postoperative pain management.* British Journal of Anesthesiology, 2007. **98**(6): p. 806-15.
51. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C., Efficacy and Safety of Single and Repeated Administration of 1 Gram Intravenous Acetaminophen Injection (Paracetamol) for Pain Management after Major Orthopedic Surgery. Anesthesiology, 2005. 102: p. 822-31.