Review article

Perioperative pain management following total joint arthroplasty: A review and update to an institutional pain protocol

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ARTICLE INFO

Article history:

Received 31 August 2017

Accepted 26 September 2017

Available online 28 September 2017

ABSTRACT

As the rate of total joint arthroplasty increases with the aging population of the United States, new focus on decreasing opioid use through the development of multimodal pain regimens (MPRs) is becoming an important area of research. MPRs use different agents and modes of delivery in order to synergistically address pain at many levels of the pain pathway. MPRs include a combination of acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, opioids (short- and long-acting), spinal/epidural analgesia, regional nerve blocks, and local anesthetics. This review summarizes the available literature on major components of MPRs shown to be effective in the total joint arthroplasty population. Finally, the authors' preferred method for pain control in the TJA population is reviewed.

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1. Introduction

With the aging population of the United States, total hip (THA) and knee arthroplasty (TKA) volume is expected to increase significantly to reach an estimated 3.48 million per year by 2030.¹ As documentation of patient reported outcomes becomes routine and inpatient cost containment continues to be a priority, peri-operative analgesia has become a major focus for recent research. Furthermore, the opioid epidemic across the United States has led to the development of synergistic multimodal pain regimens aimed at achieving optimal analgesia and minimizing the risk of opioid abuse and addiction.

Multimodal approaches to pain control include the use of pre-operative spinal and epidural anesthesia, local nerve blocks, and peri-operative anti-inflammatories, narcotic based medications, as well as antiepileptic and neuropathic agents. This review will focus on the current trends in peri-operative pain control in the setting of THA and TKA, as well as the authors' preferred approach to this complex clinical challenge.

2. Multimodal pain regimen

In the past, peri-operative pain control was largely opioid-based. This model for pain control resulted in cognitive,

gastrointestinal (GI), and urinary (GU) complications and more profoundly, a potential long-term dependence on chronic opioids for pain control.² Elderly patients (>65 years of age) are at increased risk for these potentially devastating side effects, and since total joint arthroplasty (TJA) patients are exhibiting increased longevity, it has become increasingly important to minimize the use of opioid analgesics to limit long-term adverse outcomes. Multimodal pain regimens (MPRs) have been introduced in an effort to decrease opioid use with the hope of also decreasing complications in the TJA population.

An MPR utilizes multiple classes and administrations of medications in order to achieve a synergistic response to treat varying etiologies of pain.³ Pain pathways can be intercepted at multiple levels, from the local tissue inflammatory response to the central nervous system (CNS) via neurotransmission. An MPR attempts to address each of these pathways simultaneously with the primary aim being decrease in the overall use of narcotic medications.

Several key studies have shown the efficacy of MPRs in the TJA population.^{4–10} The majority of MPRs include a combination of acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, opioids (short- and long-acting), spinal/epidural analgesia, regional nerve blocks, and local anesthetics. The use of an MPR has been shown to decrease opioid consumption, improve peri-operative outcomes, and decrease length of stay in the TJA population.^{4,5,7,8} Administration of NSAIDs both pre- and post-operatively has been shown to have the most profound effect on

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outcomes.⁴ MPRs, with a special emphasis on NSAID use, are currently recommended as the standard of care by the American Society of Anesthesiologists Task Force on Acute Pain Management.¹¹

3. Opioid analgesia

Opioids have classically been the workhorse of for the treatment of surgical pain. Opioids are effective through the binding of mu, kappa, and delta receptors at the dorsal root ganglion and CNS levels of the pain reception pathway.³ Opioids are the pinnacle of the “Pain Relief Ladder” outlined by the World Health Organization that was created for the treatment of cancer pain.^{12–14} In this model, non-opioids are the first-line drugs for post-operative pain, and opioids are added with the development of moderate to severe pain.

Opiates are extremely effective both in short- and long-acting formulations, but the efficacy of opiates may only be enhanced through route of delivery and higher doses of medication. Unfortunately, the administration of higher doses of opioid medications amplifies the side effect profile disproportionately to the degree of pain control. These unwanted side effects with high-dose narcotics led to the development of patient-controlled analgesia (PCA), in which patients self-administer frequent, small-dose demand doses of medication.

The use of a PCA results in a uniform plasma opioid concentration over time which differs for each individual patient. Variations in patient's pre-operative pain medicine use, pain tolerance, lag between perception of pain and medication administration, and variable absorption of medications due to kinetics and body habitus all contribute to poor pain control with one uniform approach for all patients.¹⁵ Albert et al. showed that PCA is effective in the TJA population with 80% of patients reporting to be pain-free, comfortable, or in mild pain in the first 48 h after surgery.¹⁶ While overall PCA has a favorable safety profile, side effects such as nausea, respiratory depression, and over-sedation can still be seen.^{16–17} The side-effect profile can be accentuated when patient family members administer additional doses of the medication when they feel that the patient may be in pain.¹⁸

Wheeler et al. performed a comprehensive literature review focused on identifying adverse effects of narcotics when used in the post-operative setting.¹⁹ Adverse effects were broken down into respiratory, GI, GU, dermatologic, and CNS side effects. While respiratory depression is the most severe complication of narcotic administration (2.8% of patients), GI complications (nausea, vomiting) are the most common (30% of patients). Urinary retention is another common side effect with post-operative opioids affecting over 17% of patients, especially patients receiving intrathecal opioids intra-operatively. Interestingly, urinary retention varies widely with form of administration of narcotics with retention occurring in 36% of patients receiving intrathecal opioids but only 16% of patients receiving systemic narcotics.¹⁹

Unfortunately, CNS side effects of opioid medications in the post-operative period are as common as GI side effects (above 30% of patients), yet the morbidity and mortality of these effects can be much more devastating. The effects of opioids alone on mental status is difficult to determine as many factors affect mental status, but many studies have shown the correlation between the administration of opioids and the development of hallucinations, nightmares, and delirium.¹⁹ In a study aiming to predict post-operative delirium in the TJA population, Williams-Russo et al. found that 41% of elderly patients experience acute post-operative delirium.²⁰

The review by Wheeler et al. in 2002 posited that the effects of opioids on mental status are idiosyncratic and not dose-related.¹⁹

Nevertheless, the goal of post-operative pain control is to abate the negative effects of narcotics, and the authors maintain that the adverse sequelae of these medications can be minimized or eliminated through individualized pain regimens.

4. Non-opioid analgesia

4.1. Acetaminophen

Acetaminophen has widespread use as an antipyretic and analgesic agent. It is a non-opioid, non-NSAID agent that acts centrally as an analgesic.²¹ Acetaminophen is available as an oral and recently as an intravenous agent, and it is commonly used in combination with opioid analgesics as part of an MPR. Efficacy of oral acetaminophen on pain control alone has not been studied in a controlled manner, likely due to its widespread use and over-the-counter availability. However, the efficacy of oral acetaminophen as part of an MPR was demonstrated by a study by Imasogie et al., which showed that the use of tramadol HCl/acetaminophen decreased opioid use in a small sample of total shoulder arthroplasty patients.²²

A water-soluble prodrug of acetaminophen (propacetamol) has been shown to have similar analgesic efficacy to that of intravenous ketorolac in TJA patients.²³ The success of intravenous propacetamol as an analgesic agent lies in its ability to enter the cerebrospinal fluid within fifteen minutes of administration.²⁴ In non-orthopaedic populations, the use of intravenous acetaminophen was shown to decrease opioid use and lead to shorter time to extubation in the post-operative period.²⁵ Sinatra et al. demonstrated similar efficacy in the TJA population.²⁶ Furthermore, intravenous acetaminophen has been shown to be safe and effective in elderly patients for pain control following major orthopaedic procedures, which is particularly important in with the rising average age of patients with TJA.^{27–29} Given the established safety profile and efficacy of acetaminophen, the addition of acetaminophen to an MPR is certainly warranted.

4.2. Non-steroidal anti-inflammatory drugs (NSAIDs)

Like acetaminophen, NSAIDs are widely prescribed and used for pre-operative pain control in patients with osteoarthritis. Non-selective NSAIDs and cyclooxygenase (COX) –2 inhibitors have antipyretic and analgesic effects similar to acetaminophen, but they also exert an anti-inflammatory effect at the tissue level acting against prostaglandin production through COX inhibition. However, NSAIDs have classically been held in the peri-operative period due to concern for increased bleeding. Traditional NSAIDs (such as ketorolac) act through COX-1 and COX-2 inhibition. Ketorolac can be given through many routes and does not have associated respiratory or CNS depressive effects seen with opioids.³⁰ A meta-analysis focusing on efficacy of ketorolac in the post-operative period showed that a single dose of ketorolac in the immediate post-operative period had opiate-sparing effects.³¹ Another study showed a decrease in morphine consumption by 29% compared to placebo when ketorolac was used as part of an MPR. A decrease in post-operative nausea, vomiting and pruritis were observed as secondary outcomes.³²

COX-1 is expressed systemically throughout the body whereas COX-2 is selectively expressed in inflammatory tissue. Selective COX-2 inhibitors (such as celecoxib) have grown in favor due to the dampening of effects seen with COX-1 inhibition, most notably GI effects.^{4,33} Additionally, selective COX-2 inhibitors have minimal effect on the coagulation cascade and therefore are potentially valuable in this population where peri-operative bleeding is ideally minimized.

A randomized, placebo-controlled, double-blinded trial by Buvanendran et al. demonstrated that the use of rofecoxib, a selective COX-2 inhibitor, decreased opioid consumption in patients undergoing TKA⁸. Decreases in pain and sleep disturbances and increases in post-operative range of motion and overall satisfaction were observed as secondary outcomes.⁸ These findings were supported by further studies that found that pre-operative administration of rofecoxib as part of an MPR decreased pain scores and opioid consumption and increased patient satisfaction compared to placebo.^{34–35} Finally, while there have long been concerns regarding the effect of NSAIDs on osseointegration and bleeding, selective COX-2 inhibitors do not seem to be associated with these side effects.⁴

4.3. Gabapentinoids

Pregabalin and its predecessor gabapentin have been classically prescribed as anticonvulsant medications. Gabapentin has also been prescribed for neuropathic pain. Both medications act on the $\alpha_2\text{-}\delta$ (alpha₂-delta) subunit of voltage gated calcium channels in the central nervous system, thereby modulating pain perception by decreasing the release of neurotransmitters in excitatory pathways at those levels.^{4,36} While early use of this class of medications in the TJA population showed mixed results, more recent prospective trials randomizing patients to receive pre- and post-operative pregabalin or gabapentin have been promising.³⁷

Buvanendran et al. used pregabalin as part of an MPR in patients undergoing TKA, and they found that pre- and post-operative use of pregabalin reduced pain, decreased opioid consumption, decreased sleep disturbance, decreased time to discharge, and increased range of motion at 30 days post-operatively.³⁸ However, there was increased risk of post-operative sedation and confusion in the group that received pregabalin³⁸. Clarke et al. had similar findings in their 2009 study focusing on post-operative gabapentin use in patients undergoing TKA. Interestingly, no difference in pain scores was found in patients undergoing THA.^{39–40}

5. Regional nerve blocks

Peripheral nerve blocks with single or continuous infusions of local anesthetic have been commonly used in the field of TJA. The use of a peripheral nerve block is more commonly used in TKA in the form of a femoral, sciatic nerve, or adductor canal block. Psoas nerve blocks can be administered for THA patients.⁴ Complications that dissuade surgeon preference against the use of regional nerve blocks include nerve damage and muscle weakness in the immediate post-operative period, possibly limiting early ambulation or physical therapy participation.⁴¹ Despite these concerns, there is evidence that patients receiving a peripheral nerve block were able to undergo faster rehabilitation compared to patients using a PCA.¹⁰ There has been additional evidence that patients with a peripheral nerve block had less restricted movement than patients receiving an epidural.⁴² This may lead to an additional benefit of early return to ambulation and rehabilitation.

The evidence toward the efficacy of peripheral nerve blocks has been mixed. Kardash et al. found no difference in opioid consumption in patients receiving obturator or femoral nerve blocks compared to patients who did not receive a peripheral nerve block.⁴³ Another study by Ozen et al. showed decreased narcotic use (on PCA) and decreased pain scores in patients receiving a three-in-one femoral nerve block compared to patients without a block undergoing TKA.⁴⁴ However, a study by Siddiqui et al. demonstrated decreased narcotic use and improved pain scores in patients receiving lumbosacral plexus blocks following THA.⁴⁵

Despite mixed evidence, peripheral nerve blocks have a favorable safety profile and should be considered in any MPR.

Fowler et al. have demonstrated that peripheral nerve blocks have fewer side effects and a more favorable side effect profile to that of epidural anesthesia while maintaining comparable pain relief.⁴²

6. Local anesthetic injection

Intra- and peri-articular injection of local anesthetics has become common practice, particularly in patients undergoing TKA. Many studies have shown the advantages of local injection intra-operatively. Andersen et al. studied the efficacy of a single-shot intra-articular injection of ropivacaine, toradol, and epinephrine by comparing patients undergoing THA receiving the local injection to patients receiving an epidural alone.⁴⁶ Opioid consumption and length of stay were significantly decreased in the group receiving local and intra-articular injections compared to epidural alone.⁴⁶

Similar promising results have been found in patients receiving local and intra-articular injections during TKA. Essving et al. performed a double-blind trial randomizing patients to receiving intra- and post-operative boluses of ropivacaine, ketorolac, and epinephrine versus intrathecal morphine alone.⁴⁷ The local analgesic group had lower opioid consumption, decreased pain, increased satisfaction, and decreased time to discharge compared to the intrathecal morphine group.⁴⁷ Fu et al. supported these findings in a randomized study in 2010. Importantly, the study by Fu et al. demonstrated that there was no difference in infection rate or wound-healing in patients who received local injection versus those who did not.⁴⁸

Intra-operative injection of liposomal bupivacaine (EXPAREL) has been increasingly studied for its efficacy and safety in the TJA population. It is an attractive addition to any MPR as a single intra-operative injection releases local bupivacaine for 96 h post-operatively. Major concerns limiting the widespread use of EXPAREL have been cost and local wound healing complications.⁴⁹ However, a review of prospective controlled clinical studies focusing on administration of EXPAREL does not show a significant impact on wound or bone healing. Interestingly, there has been little evidence that a single liposomal bupivacaine injection offers significant improvement over benefit over local bupivacaine HCl injection intra-operatively.^{49–51}

A recent study by Smith et al. showed that EXPAREL did not have any superior efficacy over local extended bupivacaine delivery via an On-Q Pain Relief System when measuring post-operative opioid consumption.⁵¹ While an On-Q Pain Relief System costs less than a single EXPAREL injection (\$225 versus \$310 per patient, respectively), a limited number of patients with an On-Q Pain Relief System experienced leakage at the catheter site which would be avoided with EXPAREL. There were no significant differences in complications between groups, including infection.⁵¹ Clearly, further work is warranted to evaluate the ideal administration of local anesthetics in TJA. However, the efficacy of local anesthetics has been demonstrated by multiple recent randomized, controlled trials and therefore warrants consideration in any MPR.

7. Author's preferred pain control method for primary total joint arthroplasty

7.1. Pre-operative interventions

As part of our MPR, pain control begins in the initial pre-operative visit in the form of setting expectations for pain control in the immediate and long-term post-operative periods. At the time of the visit, the patients receive a personalized booklet on TJA compiled by the senior author that includes pre- and post-operative instructions including expected intra- and post-

operative course. Patients are counseled to continue strengthening exercises and physical therapy (if they are already enrolled in a program) up until the day of surgery. Patients are also given a prescription for a Lidoderm patch that will be applied on the morning of surgery. A diagram depicting proper placement of the Lidoderm patch is included in the booklet (Fig. 1).

Patients are given a single dose of MSContin 15 mg two weeks prior to surgery and are asked to call the office the following day to discuss personal tolerance of the medication. This test dose allows us to gauge the patient's narcotic tolerance prior to admission and prior to the stress of surgery and subsequently alter our standard post-operative protocol tailored to the patient's predicted needs. Patients are asked to discontinue all NSAIDs and narcotic medications seven days prior to surgery in an effort to increase the efficacy of these medications intra- and post-operatively. Two days prior to surgery patients are asked to start taking daily senna to abate the constipating effects of opioid analgesics. Finally, the night before surgery the patients are called by the senior author and given the opportunity to ask questions or voice concerns prior to the procedure in an effort to minimize anxiety, which has been shown to be related to post-operative pain.⁵³

7.2. Perioperative interventions

On the morning of surgery, patients apply a Lidoderm patch on their lower back at the predicted point of spinal injection. In the pre-operative holding area, patients are given single doses of MSContin, ranitidine, intravenous ketorolac, metoclopramide, ondansetron, acetaminophen, gabapentin, and a scopolamine patch. Our preferred method of anesthesia is spinal anesthesia for a THA and spinal anesthesia with an adductor canal block for

TKA. These forms of anesthesia are administered in the pre-operative areas.

Intra-operatively, a mixture of 0.25% lidocaine with epinephrine (60cc) and 0.25% lidocaine without epinephrine (30cc) is prepared. A total of 80cc of this mixture is injected into the various locations. For TKA, the solution is injected into the posteromedial knee capsule, the plane between the capsule and synovium, and the surrounding subcutaneous tissues. The posterolateral corner is avoided to prevent injection into the peroneal nerve. For THA, the injection is focused at the inferior capsule and surrounding soft tissues due to the high density of nerve fibers in this location.

7.3. Post-operative interventions

Pain and rehabilitation expectations are discussed with the patient and their family in the immediate post-operative period and subsequent post-operative days. Through our protocol, post-operative and discharge plans/expectations are discussed at least four times: the office, the night before surgery, immediately post-operatively, and on subsequent post-operative days. We believe that the reiteration of the agreed upon post-operative course is beneficial to align patient's expectations with that of the surgeon, which has been shown to lead to favorable clinical outcomes.⁵²

Our MPR focuses on the use of acetaminophen, celecoxib, gabapentinoids, and opioid medications. The post-operative dose of MSContin is adjusted according to the pre-operative test dose. The patient is given a 10-day course of long-acting narcotics and a two-week course of short-acting opiates, and they are discharged with the regimen that resulted in adequate pain control while in the hospital. The patients are given instructions on how to appropriately wean off of their pain medications at the time of

Lidoderm Patch Information Sheet

What is the Lidoderm Patch?

It is a patch that contains a numbing agent to help numb your lower back. This may make your encounter with the anesthesiologist prior to surgery more comfortable.

Place the patch the morning of surgery:

Take a shower the morning of surgery prior to coming to the hospital. After you have dried off, place the Lidoderm patch on the center of your lower back as shown in the picture below. It should be placed just above the center of your buttocks and along the line of your spine. Do NOT place it on your hip or knee. Do NOT place it on your upper back or neck.

Fig. 1. Instructions and cartoon included in Pre-operative Patient Information Booklet indicating proper timing and location of Lidoderm patch application.

discharge. Celecoxib, acetaminophen, and gabapentin are started in the hospital and continued for two weeks after surgery. Celecoxib is not administered to any patient with history of kidney disease or any patient who develops an acute kidney injury while hospitalized. Importantly, acetaminophen is prescribed as a scheduled medication rather than a medication to be taken only as needed. Finally, the patient is directed to their booklet that includes instructions and reminders on the appropriate way to take their pain medications and a thorough review on what to expect after surgery.

8. Summary

Multimodal pain regimens have the potential to revolutionize pain control in the immediate and extended post-operative periods in patients undergoing TJA. MPRs have been shown to be effective in reducing total opioid consumption in this population, which will become increasingly important as the average age of patients with TJA increases in coming years. Our institution has successfully implemented an MPR that can be individualized for each patient and optimizes the synergistic effects of the different medications used. Future work should focus on individualizing MPRs for each patient based on age, comorbidities, unique pharmacokinetics, and cost.

Conflict of interest

None.

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