Original Article

Update of Multimodal Pain Management Strategies for Total Knee Arthroplasty

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Total knee arthroplasty [TKA] has traditionally been one of the most painful orthopedic procedures. Postoperative pain control in the past depended on high doses of opioids, resulting in dizziness and nausea, delayed ambulation, and prolonged hospital stays.

Over the last decade, multimodal pain control has been developed that provides excellent pain control and reduces opioid consumption. The key principle is the use of a variety of interventions that affect different sites in the pain pathway. Multimodal pain management for TKA includes preemptive analgesia, regional anesthesia, and local infiltrative anesthesia (periarticular injection) as well as various oral and intravenous pain medications such as NSAIDs, COX-2 inhibitors, and gabapentinoids. The goal of this review is to provide an update of current knowledge of multimodal pain management for TKA.

Keywords: Multimodal analgesia; Periarticular infiltration; Total knee arthroplasty

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Total knee arthroplasty [TKA] has long been one of the most painful surgeries, with high-dose intravenous opioids commonly used for pain control after TKA[1], medications that result in a high incidence of opioid side effects such as dizziness, nausea, and vomiting[2,3]. More recently, continuous epidural anesthesia and femoral nerve block were introduced for TKA pain control. Those techniques, however, were still associated with opioid side effects as well as weak weakened quadriceps resulting in delayed patient ambulation[4,5]. Moreover, inadequate postoperative pain control can lead to patient dissatisfaction, impaired range of motion, as well as a higher incidence of chronic and/or neuropathic pain[2,3,6,7].

Multimodal pain management (multimodal analgesia) involves the combined administration of various anesthetic and analgesic modalities to provide effective postoperative pain control with minimal side effects[2,7,8]. Each modality has different mechanisms of action and affects different sites of the pain pathway, which, acting together, result in a cumulative pain control effect. This method of pain management helps reduce opioid consumption and its accompanying side effects, shortens hospital stays, and enhances functional recovery[2,8].

Multimodal pain management for TKA includes preemptive analgesia, regional anesthesia, local infiltration of anesthetic agents (periarticular injection), and intravenous or oral pain medications[2,8]. This review focuses on current trends in multimodal perioperative pain management for TKA, e.g., peripheral nerve block, periarticular infiltration, and other new pain medications.

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The ideal pain management for TKA

The main goal of multimodal pain control for TKA is to reduce opioid consumption and its side effects in order to allow early ambulation and rehabilitation[2,3,6-8]. Total knee arthroplasty is a common procedure for elderly patients, a group at greater risk of increased opioid side effects than younger patients[9]. High doses of opioids for postoperative pain control in older patients can also result in over sedation, respiratory depression, nausea, vomiting, bowel ileus,

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urinary retention, and pruritus[2,3,6,7]. Significant opioid side effects can delay post-operative ambulation and rehabilitation in addition to increasing the length of hospital stay.

With the growing number of TKA operations worldwide and more restricted healthcare budgets, there is a trend toward accelerated patient rehabilitation and earlier hospital discharge[10]. Those objectives will be possible only if TKA patients do not experience severe pain or side effects which can prevent delay ambulation such as dizziness and nausea, and loss of quadriceps muscle power[2,7,8].

Multimodal analgesia can provide improved pain control while reducing the amount of postoperative opioids used and their concomitant side effects[2,3,6-8]. For example, motor-sparing nerve blocks and periarticular infiltration, both of which can provide adequate pain control and allow maintenance of strong muscle power, are preferable for TKA[5]. The use of other additional pain medications and NSAIDs can also be helpful[2,3,6-8]. Taken together, these factors justify multimodal analgesia being considered the most appropriate TKA pain control method.

Preemptive analgesia

Preemptive analgesia refers to administration of pain medications to prevent stimulation of peripheral and/or central nociceptors prior to the onset of tissue trauma, i.e., prior to surgery[2,6-8]. Preemptive medications, with their different mechanisms of action and their affects on different pain pathways (peripheral and central), can provide a synergistic effect[7]. A recent systematic review of post-operative pain guidelines recommended preemptive analgesia for TKA (Evidence level I, II)[2].

Medications recommended for preemptive analgesia include acetaminophen, COX-2 inhibitors, gabapentinoids, and corticosteroids[2,3,6-8]. On the other hand, preoperative use of opioids in total knee arthroplasty was never popular because it was associated with worse clinical outcomes and many side effects[11,12].

Acetaminophen

Acetaminophen or paracetamol is commonly used as part of pain control regimens for TKA. Its action predominantly inhibits prostaglandin production in the central nervous system via serotonin, opioid, eicosanoid, and nitric oxide pathways[2,7]. Acetaminophen has been shown in a randomized study to be superior to placebo in pain control for TKA[13]. Another study found no difference in efficacy between intravenous and oral acetaminophen[8]. Although acetaminophen is relatively safe, hepatotoxicity can occur with doses exceeding 4 gm/day[8].

COX-2 inhibitor

Several studies, including randomized controlled trials [RCT] and meta-analysis, have shown that perioperative administration of selective COX-2 inhibitors significantly reduces opioid consumption, improves outcomes, and decreases post-operative nausea and vomiting, especially during the first week after TKA[7,14-16]. Preemptive COX-2 inhibitors can also improve active knee ROM significantly during the first three days after TKA[16]. Moreover, perioperative use of COX-2 inhibitors does not appear to increase the incidence of bleeding complications[17-19].

Gabapentinoids

Pregabalin and its predecessor, gabapentin, are primarily used for neuropathic pain. Gabapentin acts by binding to alpha subunits of voltage calcium channels in the central nervous system, thus decreasing neurotransmitter release[8]. A previous study related that chronic pain was reported in as high as 12.7% of patients 6 months after total knee arthroplasty[8]. The aim of gabapentinoid in the perioperative period is to minimize opioid consumption, reduce pain-related sleep disturbance, and prevent late neuropathic pain[7,8,20-22]. A pregabalin dose of 300 mg started preoperatively has been reported to improve pain scores, lessen postoperative nausea and vomiting, and increase patient satisfaction[21]. However, gabapentin, with its lower sedative properties, may be preferable to pregabalin for elderly patients, who are at increased risk of dizziness and confusion[23].

In conclusion, many studies have demonstrated the efficacy of preemptive analgesia in TKA in significantly reducing opioid consumption, decreasing post-operative pain, shortening hospital stays, and improving clinical outcomes[11,12,16-19,23-25].

Neuraxial anesthesia

Currently there are two types of neuraxial anesthesia used in TKA: spinal (subarachnoid) block and epidural block. The advantage of the epidural block over the spinal block is less pronounced motor blockage and the possibility of retaining an epidural catheter for continuous administration of medication. Knowledge of the duration of the neuraxial anesthetic effect of each modality is important so that initiation of other

modalities can be appropriately scheduled to provide uninterrupted pain control[7]. Moreover, a combination of neuraxial and regional anesthesia has been recommended because of several advantages including excellent pain relief, maintenance of systolic pressure, reduced nausea and vomiting, decreased incidence of pulmonary and cardiovascular complications, and improved patient satisfaction[2,7].

Peripheral nerve block

Peripheral nerve blocks have recently become a popular anesthetic technique for TKA, especially the adductor canal block [ACB]. The target nerve of ACB is the sensory branch of the femoral nerve in the adductor canal[26]. ACB has been proven to be an effective TKA postoperative pain modality which provides better quadriceps muscle strength, greater mobilization ability, and less disturbance for early rehabilitation[4,5,27,28]. A randomized controlled trial of a continuous adductor canal catheter vs. a single-shot adductor canal block after TKA found significantly better pain control in the continuous catheter group, particularly on postoperative day two[29].

Recent meta-analysis studies comparing the efficacy of ACB with femoral nerve block [FNB] reported that their efficacy in pain control and levels of opioid consumption were similar. However, ACB provided earlier ambulation, less post-operative nausea, and no quadriceps weakness. A side effect of FNB, prolonged quadriceps weakness, can lead to falls after TKA[4,5,27,28].

In conclusion, peripheral nerve blocks such as ACB, especially when combined with local infiltration, have shown excellent clinical results and faster recovery in patients undergoing TKA, especially during the early postoperative period.

The current anesthetic technique of choice at our institution is spinal anesthesia and continuous adductor canal block combined with periarticular infiltration. An additional single shot posterior tibial nerve block has recently come into use as well (Figure 1). Our patients can perform active motion of the knee within the first day after surgery. This protocol can provide effective pain control and improve patient satisfaction in total knee arthroplasty.

Periarticular soft tissue infiltration (anesthetic cocktails)

Periarticular soft tissue infiltration [PAI] is done by injecting periarticular tissue such as a capsule or synovium with a mixture of analgesic agents to reduce both peripheral and central pain sensitization

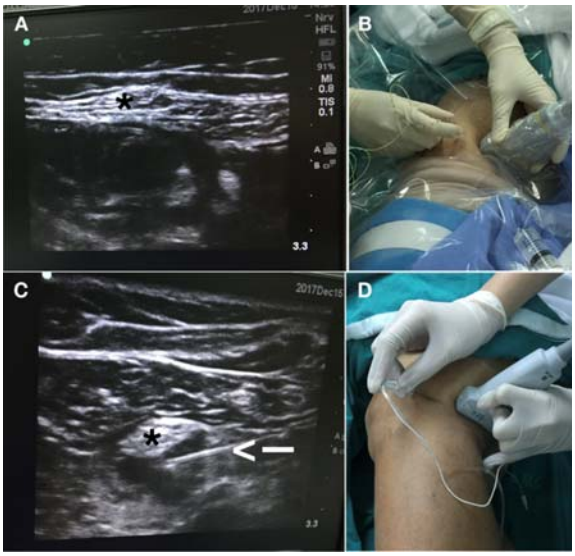

Figure 1. A) Cross-sectional ultrasonography image of the adductor canal. Bupivacaine (0.15%; 15 ml) was infiltrated around the saphenous nerve (asterisk). B) Continuous adductor canal block. C) Cross-sectional ultrasonography image of the posterior tibial fossa. Bupivacaine (0.25%; 15 ml) was infiltrated (arrow) around the tibial nerve (*). D) Posterior tibial nerve block.

caused by surgical trauma[30]. Thus PAI can be viewed as localized preemptive analgesia. There are no standard compositions of the mixture, but it usually contains bupivacaine, epinephrine, morphine, and NSAIDs or steroids. Details of each agent are discussed separately.

Bupivacaine

Bupivacaine is the most widely use ingredient in periarticular anesthetic mixtures. A prospective randomized controlled trial demonstrated that periarticular injection with bupivacaine alone can improve pain control and reduce post-operative morphine consumption after TKA when compared to a normal saline control[31]. Newer local anesthetics such as liposomal bupivacaine [LBUP] and ropivacaine are equally effective in terms of pain scores, but involve a lower risk of cardiac and nervous system complications[32,33].

Epinephrine

Epinephrine reduces local absorption and peak plasma concentration of anesthetic drugs such as bupivacaine, resulting in prolonged duration of

action[30,34]. Furthermore, some studies have shown that periarticular injections of bupivacaine and epinephrine also reduce blood loss after TKA[35,36]. However, intraarticular injection or lavage with a combination of epinephrine and bupivacaine does not help reduce post-operative blood loss[30,36,37].

Morphine

The presence of opioid receptors in inflamed peripheral tissue has been verified in two recent studies[30,38,39]. Nevertheless, a randomized controlled trial by Iwakiri et al did not demonstrate significant benefit of morphine in a multimodal cocktail in terms of pain relief, swelling, or range of motion[40].

Corticosteroids

Several studies have shown that corticosteroids have a potent local anti-inflammatory effect at the surgical site. A randomized controlled study by Kim et al demonstrated that the addition of methylprednisolone to a mixture of ropivacaine, morphine, and ketorolac resulted in better ROM and lower serum CRP during post-operative days 2 to 4[41-44]. Several other studies have shown that adding corticosteroids to a periarticular infiltration significantly improves the analgesic effect and results in no increase in the incidence of complications[45-48] (Table 1).

NSAIDs

Ketorolac has been the only NSAID used in periarticular infiltration for TKA. It has been demonstrated that intra-articular ketorolac has a local rather than a systemic effect[51]. Currently, it is also being included in periarticular infiltration formulas. Andersen et al demonstrated that PAI with ropivacaine and epinephrine plus ketorolac is better than PAI with just ropivacaine and epinephrine, i.e., reduced morphine consumption, reduced pain intensity, and earlier readiness for hospital discharge[52]. There are concerns that the simultaneous use of NSAIDs and corticosteroids in PAI might cause interference between them because of their similar target pathway (arachidonic acid cascade). However, Kim et al showed that the combination of NSAIDs and corticosteroids can help reduce opioid consumption during the first 24 hours although it does not reduce total opioid consumption[42].

Recent studies have reported that an adductor canal block combined with periarticular infiltration significantly reduced post-operative pain and allow earlier ambulation when compared to either periarticular infiltration or adductor canal block alone although there were no significant differences in morphine consumption, length of hospital stays, or postoperative complications[28,53].

It can be concluded from the above mentioned studies that the combination of bupivacaine or ropivacaine with morphine, ketorolac and/or steroids in an analgesic mixture can create synergistic analgesic effects in periarticular infiltration in TKA.

The PAI mixture used at our institute consisted of bupivacaine (0.5%, 20 ml), epinephrine (0.3 mg, 0.3 ml), morphine (5 mg, 0.5 ml). One surgeon also add 40 mg of Triamcinolone Acetonide (1 ml). These

Table 1. Summary of periarticular steroid injection studies[41,43,45,49,50]

Study	Number of patients steroid: control (surgery)	Drug regimen	Outcome
Ikeuchi et al[41]	20: 20 TKA	Ropivacaine (150 mg) ±Dexamethasone (6.6 mg)	Pain: lower POD 1 and POD 3; opioid use: lower, but not statistically significant
Ng et al[43]	41: 42 UKA	Bupivacaine (150 mg) ±triamcinolone (40 mg)	Pain: lower at 6, 30 h; opioid use: lower, but not statistically significant
Pang et al[44]	45: 45 UKA	Bupivacaine (150 mg) ±triamcinolone (40 mg)	Pain: lower at 12, 18, 24 h; opioid use: less at 12, 18, 24 h
Sean et al[45]	50: 50 TKA	Bupivacaine (150 mg) ±triamcinolone (40 mg)	Pain: lower POD 2 and POD 3; opioid use: less at 18, 24, 36 h
Kwon et al[49]	76: 76 TKA	Triamcinolone acetonide (40 mg)	Increased immediate pain relief but not sustained after POD1; straight leg raise achieved earlier
Joo et al[50]	286: 286 TKA	Methylprednisolone (40 mg)	No difference in pain, satisfaction, ROM or blood loss

were mixed with sterile normal saline solution to make up a total volume of 100 ml. The mixture was then injected into the joint capsule and the soft tissue around the knee, e.g., the medial and lateral gutters, the supra patellar pouch, and the quadriceps tendon (Figure 2). Extra care must be taken to avoid injection into subcutaneous tissue to prevent skin ischemia. The process was performed after joint lavage and before cementing implants.

Dexamethasone

Corticosteroids have a potent anti-inflammatory effect. Immediate-acting steroids such as methylprednisolone and triamcinolone have become an integral part of periarticular anesthetic infiltration in TKA[7]. However, the benefits of parenteral administration of long-acting steroids such as dexamethasone for pain control in TKA have until recently not been definitively demonstrated. Apart from its effectiveness in reducing post-operative nausea and vomiting, high IV doses of dexamethasone (>10 mg) also have a potent analgesic effect[24,25,54]. Several randomized controlled trials have demonstrated that the addition of perioperative intravenous dexamethasone to a multimodal pain regimen in total hip and knee arthroplasty can improve pain control, reduce nausea, enhance mobility, and shorten hospital stays[6,8,24,25,54].

Meta-analyses and systemic reviews have reported that short-term perioperative glucocorticoid use is safe in terms of infection risk, and that there is no difference in the incidence of wound complications, superficial infections, or deep infections[54,55].

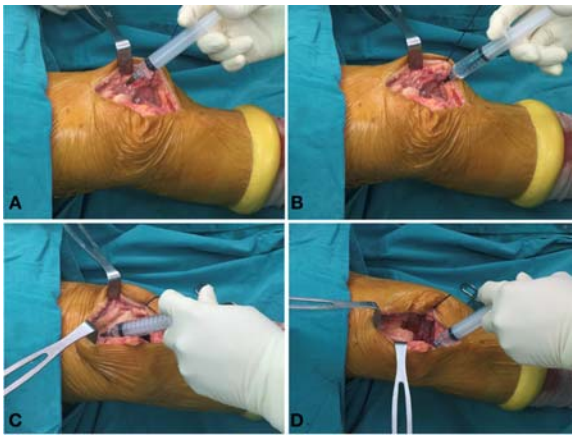

Figure 2. Intraarticular injection with an analgesic cocktail. (A) Supra patellar pouch, (B) medial gutter, (C) synovial tissue around the quadriceps tendon, (D) lateral gutter.

Summary of preferred multimodal pain management methods at the author's institution

The multimodal pain control methods for TKA used at our institute are summarized in Table 2. Results of three postoperative doses of Parecoxib have been satisfactory and without adverse effects on either cardiovascular or kidney function[56]. Oral medications are continued at least until the first follow-up visit or for 6 weeks in patients with persistent pain or poor range of motion due to prolonged joint inflammation[57].

Conclusion

Multimodal pain management or multimodal analgesia is an emerging technique for postoperative pain management in TKA. The most important advantages of multimodal analgesia are reduced opioid consumption and earlier ambulation. Multimodal pain control techniques are still evolving, e.g., peripheral nerve block and periarticular injection, but are already well accepted. The shortened stay and reduced cost of hospitalization for TKA patients achieved by multimodal pain control is highly beneficial both for the healthcare system and for the welfare of the patient.

What is already known on this topic?

There was no recent article which included all updated strategy in pain control management, local block anesthesia and periarticular infiltration.

What this study adds?

The aims of this review were to investigated and update current knowledge of multimodal pain management for TKA which focus on perioperative pain management and concluded the risk and benefit in peripheral nerve block, periarticular infiltration and newer pain medications.

Potential conflict of interests

The authors declare no conflict of interest.

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Table 2. Author's perioperative regimen

Medications	Dose	Route	Frequency
Day of surgery			
Regional Anesthesia (Spinal block + Adductor canal block + Posterior tibial nerve block)	Bupivacaine - single shot (0.25%, 15 ml) Bupivacaine - continuous, (0.15%, 15 ml) Bupivacaine - posterior tibial nerve block (0.25%, 15 ml)		
Periarticular injection (Bupivacaine + Epinephrine + Morphine ± Triamcinolone acetonide)	20 ml + 0.3 ml + 0.5 ml ±40 mg		
Parecoxib	20 to 40 mg*	IV	Every 12 hours, 3 doses
Tramadol	50 mg	IV	As needed or every 6 hours
Acetaminophen	650 to 1,000 mg*	Oral	Every 6 hours
Gabapentin or Pregabalin	300 mg, 75 mg	Oral	Once daily
Postoperative days 1 to 3			
Morphine	2 to 3 mg	IV	As needed every 3 hours
Diclofenac	75 mg	IM	Once daily (day 2)
Dexamethasone	5 mg	IM	Once daily (day 2)
Etoricoxib or Celecoxib	90 mg, 400 mg	Oral	Once daily
Gabapentin or Pregabalin	300 mg, 75 mg	Oral	Once daily
Acetaminophen + codeine	300 mg/15 mg	Oral	1 tablet every 8 hours

IV = intravenous; IM = intramuscular
*Adjusted based on renal or hepatic function

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