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Review

Perioperative Pain Management in Total Knee Arthroplasty: A Narrative Review of Current Multimodal Analgesia Protocols

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Abstract: Since there is no consensus on the optimal perioperative analgesic method, the present article provides a brief and practical synthesis on current multimodal pre–postsurgery analgesia protocols for primary TKA (excluding intraoperative anesthetic techniques) reported especially in recent meta-analyses and reviews. The focus is not only on the traditional aims (pain scores and opioid sparing), but also the functional recovery and patient-reported outcomes. Multimodal analgesia (pre-emptive analgesia, local infiltration analgesia, peripheral nerve blocks, and specific systemic drugs) is considered the optimal regimen for perioperative pain management of TKA.

Keywords: perioperative pain management; total knee arthroplasty; analgesia; opioid; NSAID; multimodal

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1. Background

Total knee primary arthroplasty (TKA) is a common orthopedic operation to eliminate pain due to arthrosis or other severe knee pathology, allowing for better mobility and improvement of the quality of life [1–3]. Joint replacement surgery is considered one of the most painful orthopedic procedures. After TKA, the control of pain with effective analgesic treatment allows early functional recovery and patient satisfaction. Moreover, adequate treatment of postoperative pain significantly reduces the incidence of postoperative complications, the length of stay, and the consequent costs [4].

The postoperative period is often uncomfortable due to inadequate pain treatment, despite the fact that pain after surgery is controllable, predictable, and almost totally preventable [4]. However, the therapy is complex and linked to patient-specific factors: psychologic conditions, previous and concomitant medications, substance abuse disorders, and history of pain central sensitization. Acute postoperative pain is classified as moderate (30%) to severe (60%) and consists of nociceptive, neuropathic, and psychogenic pathways that are differently combined according to preoperative pain, orthopedic diagnosis, surgery (approach and intraoperative anesthetic treatment), and the pain threshold of the patient (psychological status) [5].

The complexity of postoperative pain needs a comprehensive assessment of the patient including psychologic conditions, concomitant medications, substance abuse disorders, and previous postoperative treatment regimens in case of history of chronic pain [5]. The pain caused by TKA surgery is often acute over chronic because many patients have chronic joint pain and have already performed unsuccessful analgesic treatments. When the surgery patients are on chronic opioid treatment, postoperative analgesic treatment is more complex. These data help to define a tailored and individualized pain management plan, according to the "around the clock concept" and not just "as required" ("pro re nata",

PRN) [6]. A validated pain assessment tool to define the intensity of pain is essential to track responses to analgesic treatments (e.g., Visual Analogic Scale, Numeric Rating Scale). Education of the patient and the caregivers (information on treatment options for managing postoperative pain) is useful to improve patient satisfaction [5,7]. A possible solution to the inadequate treatment of postoperative pain lies in better organization and utilization of the existing techniques. A multidisciplinary approach (surgeons, anesthesiologists, internists, nurses, physiotherapists), not yet widespread, seems fundamental to apply and coordinate all categories of pain medications to obtain a better outcome [8,9].

Historically, opioids have been widely used for perioperative pain management of surgery patients [10]. The exponential rise of synthetic opioid-related overdose deaths in recent years has forced a review of the opioid-only postoperative analgesic protocols, already in question for related adverse effects (drowsiness, fatigue, confusion, delirium, nausea, vomiting, ileus, urinary retention) that obstruct a rapid functional recovery after surgery [10]. Monotherapy with opioids is not enough to provide satisfactory postoperative pain relief after TKA, but it is widespread in the management of postoperative pain [11].

Considering the various postoperative pain mechanisms, it seems reasonable to use a multimodal analgesic approach [12]. Multimodal analgesia was first introduced by Kehlet in 1999, referring to a combination of several types of medications and delivery routes [12]. Multimodal treatment is based on the synergism of submaximal doses of painkillers, with different mechanisms of action, to increase therapeutic power and reduce adverse effects [12]. In the literature, there are many multimodal analgesic protocols for postoperative pain in TKA, based on different combinations (type and dosage) of preintra- and postprocedural interventions: systemic drugs (nonsteroidal anti-inflammatory drugs, NSAIDs, or cyclooxygenase-2 inhibitors, opioids, gabapentins), local infiltration analgesia, neuraxial anesthesia, peripheral nerve blocks, and other nonpharmacological strategies. This approach reduces the dependence on a single medication and may reduce or eliminate the need for opioids. Compared with monotherapy, multimodal analgesia in TKA patients provides superior postoperative pain relief. A postdischarge multimodal pain regimen significantly reduces the level of opioid used without compromising pain control [13].

To determine which are the most effective analgesic interventions, it is necessary to take into account the control of the pain, the effect on function, the length of stay, the costs, the patient satisfaction, the risk of addiction, and the complications [14]. Since there is no consensus on the optimal perioperative analgesic method, the present article provides a brief and practical synthesis on current multimodal pre–postsurgery analgesia protocols for primary TKA (excluding intraoperative anesthetic techniques) reported especially in recent meta-analyses and reviews [15]. The focus is not only on the traditional aims (pain scores and opioid sparing), but also the functional recovery and patient-reported outcomes. For this narrative review, a comprehensive search of PubMed, MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews was performed.

2. Search Strategy

For this narrative review, a comprehensive search of PubMed, MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews was conducted for English articles on the application of perioperative pain management using various combinations of keywords (perioperative pain management; total knee arthroplasty pain, analgesia in TKA, opioid TKA, NSAID TKA, multimodal analgesia TKA) from the inception of the database to 31 December 2022.

3. Pre-Emptive Analgesia

The pain therapy of surgical patients is most effective if it starts before the tissue insult [16,17]. Adequate pre-emptive analgesia reduces the production of inflammatory chemicals associated with surgery and so prevents hyperalgesia (activation of the peripheral nociceptors) and the development of a pain memory (central sensitization). The first is mediated by the local production of prostaglandins and other factors with a pronociceptive

action by lowering the threshold of stimulation of the nerve endings in the damaged area (peripheral sensitization). This signal is sensitive to peripheral NSAIDs and COX-2 inhibitors and nerve blockade with local anesthetics. The second signal is humoral: surgical site inflammation releases blood-borne prostaglandins and interleukins, which reach the central nervous system and are responsible for the induction of COX-2 and the overproduction of prostaglandins centrally [18]. Pain perception may persist long after trauma due to biochemical–structural adjustment in the central nervous system, mediated by cellular calcium channels or other secondary messengers (central sensitization). This signal is modulated by inhibitors that can cross the blood–brain barrier [19].

The preoperative use of acetaminophen, NSAIDs, or COX-2 inhibitors 1 h before surgery significantly reduces the VAS in the immediate postoperative period, as well as reduces opioid requirements and opioid-related adverse effects. COX-2-specific inhibitors have comparable analgesic efficacy to NSAIDs, but with no effects on platelet function, and thus could be safely administered preoperatively [16,18].

The preoperative use of gabapentins significantly decreases opioid consumption at 24 h postoperatively and pain scores were significantly lower in gabapentin-treated patients. Particular attention is needed when administering gabapentin to the elderly and to patients with chronic renal failure [20].

The combination of acetaminophen (1000 mg), celecoxib (200 mg), and pregabalin (75 mg) per os 1 h before surgery represents a widespread pre-emptive analgesic improvement. Another effective pre-emptive combination of the same drugs is their use three days before surgery [21].

Opioids are not included in the pre-emptive protocol and the reduction of their preoperative chronic use optimizes the benefits of TKA (postoperative pain relief, hyperalgesia, complications, and opioid consumption). If the patient is already on opioids, they should be continued and then weaned postoperatively. This is probably best achieved through a pain service that includes a clinical pharmacist [22].

4. Local Anesthetics

(1) Periarticular injection

Local infiltration analgesia (LIA) is based on the injection of an anesthetic cocktail into periarticular regions (multiple punctures into posterior capsule, collateral ligaments, capsular incision, quadriceps tendon, and subcutaneous tissues), near the end of a surgical procedure, with the aim to prevent generation and conduction of pain signals from incision. LIA significantly reduces pain scores and opioid consumption and improves functional outcomes and range of motion in the early postoperative period after TKA [23–26]. Single femoral nerve block and LIA provide equally satisfying analgesia, but the well-known risk of motor blockade with block may render this method less attractive [26,27].

The composition of LIA includes a combination of local anesthetic (ropivacaine 150–400 mg or bupivacaine 20–400 mg), ketorolac (15–30 mg), morphine (4–10 mg), clonidine (80 mg), corticosteroid (methylprednisolone 40 mg or betamethasone 1–4 mg), and epinephrine (300–600 mg). However, the combination of medications is heterogeneous and varies according to the surgeon's habits. The lack of comparative studies makes it difficult to define the most effective analgesic dosages. The use of LIA with liposomal bupivacaine does not appear to improve the duration of pain control in patients undergoing TKA. If periarticular injection is performed in addition to peripheral nerve blockade, the total dose of LIA should be calculated to avoid excessive dosing and to minimize the risk of local and systemic anesthetic toxicity [28–30].

(2) Neuraxial anesthesia

Epidural analgesia was used as a postoperative analgesic regimen for patients after TKA, consisting of a local anesthetic agent and an opioid. Compared with parenteral opioids, epidural analgesia provides better postoperative analgesia with less nausea, vomiting, and pruritus [31]. However, some studies show that epidural anesthesia has many

adverse effects, such as urinary retention, hypotension, pruritus, and motor blockade, which preclude rapid functional recovery [32,33]. Epidural analgesia provides no additional analgesic benefit when compared with peripheral nerve blocks or LIA. Continuous epidural analgesia may be added to a multimodal analgesic regimen for patients who undergo complex TKA or are expected to have difficulty with pain control.

Intrathecal morphine injection reduces postoperative pain significantly early (first 12 to 24 h), but does not seem to provide superior control of pain to LIA. It is easier to perform and less time-consuming than the regional blocks. The side effects (such as epidural analgesia) could interfere with postoperative recovery, therefore this technique is indicated when TKA surgery is performed under spinal anesthesia and neither peripheral nerve blocks nor LIA is possible [34,35].

(3) Peripheral nerve blocks

The use of peripheral nerve blocks (PNBs) is a common practice in orthopedic surgery, but it is limited by availability of a trained regional anesthesia team. PNBs provide excellent pain management after TKA, promote early mobilization, and reduce the consumption of opioids, the incidence of opioid-related adverse effects, and the hospital stay [36,37].

Femoral nerve blocks (FNBs) have been widely accepted as the gold standard for TKA postoperative pain relief. Although FNBs may provide effective analgesia (anteromedial part of the knee, leaving the posterior knee untargeted), they reduce the muscle strength postoperatively, increasing the risk of falling. Adductor canal blocks (ACBs) reduce the same pain scores as FNBs (anteromedial part of the knee, leaving the lateral and posterior compartments uncovered), but preserve quadriceps strength, thus preventing falls and facilitating early mobilization in patients after TKA. A single-shot ACB results in a better early rehabilitation, a longer ambulatory distance, and a reduction in length of hospital stay compared with FNB. Continuous catheter ACBs are not recommended because of inconsistent benefits [19]. The combination of ACB and LIA has a synergistic effect with a significant decrease in pain and opioid consumption in patients after TKA. LIA is considered cost-effective, whereas nerve blocks are cost-effective only if administered by an experienced anesthesiologist [32].

An interspace between the popliteal artery and the capsule of the posterior knee (IPACK) block is effective according to preliminary data, but of short duration (less than 12 h) [38,39]. There are other types of peripheral blocks (e.g., sciatic and selective tibial nerve block) less widespread in practice due to lower efficacy and/or more operative difficulties. Femoral plus sciatic nerve blocks are indicated for patients who undergo complex revision (not candidates for fast-track recovery) or require complete analgesia of the knee because of opioid tolerance or chronic pain.

Nerve injury is much more likely to be related to surgery or to the use of a tourniquet than a nerve block. The most common neurologic complication after TKA is peroneal nerve palsy, particularly in patients with severe valgus alignment in combination with a flexion deformity. It may be wise to avoid sciatic nerve block in patients at high risk of peroneal nerve injury, since the peroneal nerve is a branch of the sciatic nerve. In bilateral simultaneous TKA, single-injection spinal anesthesia may not last long enough and a continuous neuraxial anesthetic (epidural) allows extension of the block as long as necessary [40].

5. Systemic Drugs

Acetaminophen reduces nociceptive pain through selective inhibition of COX enzyme activity in the central nervous system [41]. It is efficacious, inexpensive, and has a favorable safety profile with relatively few adverse effects. IV acetaminophen use should be reserved only for patients unable to swallow tablets as the efficacy of the IV and oral form is the same. However, IV administration does have more rapid and predictable onset of effect than oral administration (5–10 vs. 10–60 min, respectively) [41].

In the postoperative period, the recommended acetaminophen dose is 650 mg per os every 6 h or 1000 mg per os every 8 h (not to exceed 3000 mg per day). A reduced dose of

acetaminophen should be used in patients with body weight ≤ 50 kg, or mild–moderate hepatic insufficiency, or chronic alcoholism, malnutrition, or dehydration. If creatinine clearance is less than 30 mL/min, the dose is the same. Acetaminophen is contraindicated in patients with severe hepatic insufficiency [42].

Combination with NSAIDS or COX-2 inhibitors for postoperative pain is more effective than acetaminophen alone. This should be continued for another 2 weeks after discharge [41].

NSAIDs and COX-2 inhibitors are the main tools of multimodal analgesia in TKA; they reduce the inflammation from surgery, the postoperative pain (by approximately 30%), and the opioid consumption with relatively low adverse effects [43]. However, the individual patient risk should be assessed, including gastroduodenal ulcer history, cardiovascular morbidity, renal and hepatic dysfunction, and aspirin-induced asthma. Due to their side effect profile, judicious use and appropriate molecule selection are required. NSAIDs are unlikely to be the cause of postoperative bleeding complications in patients with adequate gastric acid inhibitor activity. The "black-box" warning about COX-2 inhibitors is related to cardiovascular risk, although this risk appears to be associated with long-term use [18,44]. For example, in the postoperative period, ketorolac should be administered 30 mg IV every 6 h for a maximum of 4 days. The dose of ketorolac should be reduced to 15 mg every 6 h if patients are over 65 years old or have mildly impaired renal function. It should not be used in patients with acute or chronic kidney disease or ulcerative gastrointestinal disease. After discharge, it is recommended to follow anti-inflammatory therapy with meloxicam 15 mg per os daily, or celecoxib 200 mg per os every 12 h. The use of these drugs beyond the hospital stay (for up to 6 weeks) alleviates pain and facilitates postoperative rehabilitation [44].

Opioids. Although opioids are effective in pain management after TKA, adverse effects such as nausea, vomiting, somnolence, sedation, respiratory depression, retention of urine, and constipation must be considered [10]. In addition, long-term use of opioid medications may lead to tolerance and dependence. According to enhanced recovery after surgery (ERAS) protocols, the use of opioids as first-line or primary analgesics for perioperative pain must be reconsidered and daily opioid dosage and duration must be limited (opioid sparing) [45]. Opioids should be prescribed carefully, starting with the minimum dose needed to alleviate pain and only after exhausting nonopioid analgesic options. Monitoring opioid use after discharge is designed to stop its use as soon as possible. This is accomplished by the surgeon, the anesthesiologist, and the general practitioner working together. More attention is needed in opioid-naïve patients where the prescription should be limited to a maximum of 7 days. Patients who receive an initial opioid prescription of 10 days have almost a 20% probability of still taking opioids 1 year later, and the probability increases to about 35% at 1 year with a 30-day supply [45,46].

Opioids should be administered by continuous IV only in a monitored setting (intensive care unit) and with small bolus doses with a fixed lockout interval (patient-controlled analgesia—PCA). PCA is useful in conscious patients who cannot take oral medications and are capable of understanding instructions for use of the pump. Any opioid can be administered via PCA. Opioids administered as PCA cause less severe adverse effects than conventional opioid treatment. The pump can be discontinued when the patient is able to tolerate oral analgesics. When the patient can tolerate oral medication, the opioid regimen can be changed from IV to oral. The opioid dose (e.g., codeine, tramadol, oxycodone, hydromorphone, morphine) should be calculated based on 24 h opioid consumption and with the appropriate conversions [13]. In addition, patients on opioids should not take benzodiazepines. If discharged on opioids, patients should receive a co-prescription of nasal naloxone if MME is greater than 50 mg per day (Table 1).

Tramadol in combination with acetaminophen and/or NSAIDs after TKA significantly improves pain control and early ambulation. Tramadol has a lower affinity for the mu opioid receptor than full mu receptor agonists (e.g., morphine, oxicodone) which means less efficacy in pain control and lower opioid side effects. It can still be addictive. In the

postoperative period after TKA, tramadol should be limited to moderate pain and/or as needed (breakthrough pain); the recommended dose is 50 mg orally every 6 h and every 8 h after discharge from hospital [47] (Table 1).

Table 1. Calculating morphine milligram equivalent (mme).

Opioid (doses in mg/day)	Conversion Factor
Codeine	0.15
Fentanyl transdermal (mcg/h)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1–20 mg/day	4
21–40 mg/day	8
41–60 mg/day	10
>61–80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorhone	3

Oxycodone should be limited to severe pain and/or as needed (breakthrough pain); the recommended dose is 5–10 mg orally every 4–6 h both in the postoperative period and after hospital discharge [47] (Table 1).

Gabapentins control neuropathic pain. Opinions vary in the literature about the routine use of gabapentin due to the lack of certain clinical efficacy. Compared to the use of the basic analgesia regimen (acetaminophen, NSAIDs/COX-2-specific inhibitors, and LIA), gabapentins reduce the postoperative opioid consumption, but do not significantly reduce the pain score. Their potential side effects (e.g., sedation, dizziness, visual disturbances) are amplified when they are taken together with opioids.

Recently, Han et al. in a meta-analysis analyzed side effects of gabapentin. The authors concluded that although pruritus is a side effect during the administration of gabapentin, gabapentin can significantly decrease the incident rate of postoperative pruritus. Other side effects such as nausea, sedation, and dizziness in the gabapentin group shared the same incident rate with the placebo group [48]. It is useful to limit their use to patients younger than 75 years who are already taking them before surgery or have chronic neuropathic pain conditions. In the postoperative TKA period, the recommended dosage of pregabalin is 75 mg per os every 12 h and gabapentin 300 mg per os every 12 h, to be continued for 2 weeks after discharge [48,49].

Dexamethasone. Preoperative administration of dexamethasone (10 mg or >0.1 mg/kg IV) reduces postoperative pain scores, opioid consumption, nausea, and vomiting, and improves functional recovery and patient satisfaction after TKA. The risk of impaired healing and periprosthetic joint infection due to corticosteroids is clinically irrelevant. The efficacy and safety of repeated doses of glucocorticoids to improve postoperative recovery remain questionable. Transient hyperglycemia, especially in diabetic patients, can be controlled with an adequate dose of insulin [50,51].

N-methyl-D-aspartate receptor antagonists. Ketamine is a noncompetitive, reversible antagonist of the N-methyl-D-aspartate (NMDA) receptor, and acts as a mu opioid, monoaminergic, and gamma aminobutyric acid receptor. Ketamine administered intraoperatively and in subanesthetic doses in the postoperative period reduces pain and opioid consumption. The clinical use of ketamine is limited by side effects (e.g., hallucinations and a dissociative mental state). Data on the use of ketamine in multimodal pain therapy for TKA remain inconclusive. Watson et al., in an evidence-based review on

1284 patients, demonstrated the viability of ketamine as a safe and effective alternative to opioids in the perioperative setting with major total joint arthroplasty surgery [52]. Magnesium sulfate is an antagonist of the NMDA receptor. Intraoperative and perioperative IV magnesium has been found to be an effective adjuvant for reduction of opioid requirement. Both bolus and continuous infusion regimens are effective. The optimal dose has not been determined [53].

Alpha-2 receptor agonists. Clonidine produces analgesia in the perioperative period and especially in association with opioids. The mechanism by which alpha-2 agonists produce analgesia remains unknown (likely with the release of acetylcholine). Although not routinely used, preoperative oral 150–200 mcg clonidine reduces the requirement of postoperative opioids. Dexmedetomidine is not recommended because of limited and conflicting evidence and concerns of adverse effects, such as bradycardia and hypotension [50].

Serotonin–norepinephrine reuptake inhibitors. Few studies have demonstrated the use of the duloxetine in post-TKA patients. Pre-emptively and when added to a multimodal analgesia postoperative regimen, 60 mg/day duloxetine seems to reduce the opioids consumption in hospital stay [54,55].

6. Nonpharmacological Strategies

Cryotherapy reduces pain scores at 48 h postoperatively as well as blood loss. Simple cold packs or ice packs are equivalent to advanced equipment [56].

Some other techniques have been suggested for analgesia after TKA and particularly in persistent pain: cryoneurolysis (preoperative percutaneous freezing of sensory nerves causing Wallerian degeneration), radiofrequency ablation (genicular nerve), peripheral nerve stimulation (through subcutaneous electrical leads to stimulate either the femoral or sciatic nerve), virtual reality-based rehabilitation, and acupuncture. Further studies are required before recommending any of them for routine use [57].

7. Persistent Pain after TKA

The prevalence of chronic pain after TKA is nearly 20%. Different causes (surgical factors, prosthetic loosening, malalignment, and instability of the prosthesis; peripheral or central sensitization, complex regional pain syndrome, and localized nerve injury; psychological and psychiatric disorders) can simultaneously contribute to the development of chronic pain, making the care complex and difficult. People with ongoing pain at 3 months after surgery are often disappointed with a sense of abandonment, a low level of function, and an elevated risk of developing long-term opioid use (in general, 6–10% of patients still use opioids at 1 year after the procedure) [58].

Recalcitrant pain after TKA is sometimes treated with intra-articular steroid injections, but that is not a benign procedure and it may be associated with a significantly increased risk of periprosthetic joint infection [59].

Given the difficulty of preoperative identification of individuals at high risk of chronic pain after TKA (e.g., dose of postoperative plasma levels of specific cytokines), a support and treatment program that starts at 8–10 weeks postsurgery (time of transition from acute pain to chronic pain) is useful [60]. Support and treatment after replacement (STAR) is a clinically effective and cost-effective intervention. It is based on an assessment of pain characteristics, psychological status, knee examination, knee radiographs, and blood markers of infection. STAR recommends the most appropriate and personalized treatments (surgical, rehabilitative, pharmacological) and implements monthly follow-ups to monitor clinical progress. STAR allows achievement of good control and/or resolution of pain and should be considered in all instances of chronic post-TKA pain [61].

8. Conclusions

Optimal pain control after TKA is achievable in most patients. The postoperative pain treatment cannot disregard other postoperative outcomes (fast functional recovery, complications, patient satisfaction) and because of that, it is nearly impossible to find the

best "one size fits all" analgesic regimen. Multimodal analgesia is considered the optimal regimen for perioperative pain management of TKA and improves the clinical outcomes and the patient satisfaction, through a combination of several types of medications and delivery routes. Before every TKA, the optimal and the most suitable analgesic method should be selected based on the updated guidelines and meta-analyses, the pain team's experience, and specific patient conditions and characteristics.

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