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# Pain Management

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## Abstract

Postoperative pain is caused by neuronal damage that occurs during the surgical procedure and the stimulation of the nociceptors. In postoperative period, total knee arthroplasty (TKA) is painful, and pain management is quite difficult. The main purpose of postoperative pain relief is to reduce the pain of the patient, to contribute to the healing process, to shorten the length of hospital stay, and to reduce hospital costs. Techniques such as intravenous analgesia, epidural analgesia, and peripheral nerve blocks are used to prevent postoperative pain. In addition, oral and parenteral analgesics, patient-controlled analgesia (PCA), nerve blocks, and periarticular injection methods are used as multimodal analgesia methods. Pain scales such as visual analogue scale (VAS), verbal descriptive scale (VDS), and numerical rating scale (NRS) are used as the standard methods in the evaluation of pain of patients. Systemic opioids, nonsteroidal anti-inflammatory drugs, and local anesthetics are used for postoperative analgesia. Preemptive analgesia, defined as analgesia initiated prior to surgical incision, and multimodal analgesia have been shown to reduce opioid consumption associated with high complication rates. Postoperative pain management should be planned considering the clinical characteristics of the patient, experience of the anesthetist, and clinical facilities. Early postoperative analgesia reduces systemic complication rates and improves early rehabilitation, patient satisfaction, and quality of life.

**Keywords:** pain management, analgesia, preemptive analgesia, multimodal analgesia, regional analgesia techniques, drug therapy

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## 1. Introduction

According to the definition made by the International Organization for Research on Aging (IASP), pain is a sensorial, emotional, unpleasant sensation about someone's past experiences, whether they are connected to an organic gown or not, starting from anywhere in the body.

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## 2. Classification of pain

1. Acute pain: it is a type of pain that starts suddenly, has a nociceptive nature, has tissue damage, shows a close relationship with the cause of the lesion in terms of location, time, and intensity, and gradually disappears as the healing progresses [1, 2]. The most common types of acute pain are posttraumatic, postoperative, and obstetric pain [3].
2. Superficial (cutaneous) pain: it is type of a pain that occurs against nociceptive stimuli that occur in skin, subcutaneous tissue, and mucous membranes.
3. Deep somatic pain: it is a pain that is usually caused by muscle, tendon, joint receptors or bones, which is blunt and cannot be localized.
4. Visceral pain: it is a pain originated from the deterioration of functions of their tissue (parietal pleura, pericardium, and peritoneum).
5. Chronic pain: it is defined as acute pain that begins as acute pain and lasts for 1–6 months [4].

## 3. Pain pathways

In order for a stimulus to be perceived as pain, it is necessary to go through four different physiological processes:

- a. Transduction; at the end of the nerve is the stage where the stimulus is converted into electrical activity.
- b. Transmission; it is the spread of electrical activity throughout the nervous system.
- c. Modulation; changes in nociceptive transmission.
- d. Perception; interaction with the individual's psychology and subjective emotional experiences.

## 4. Postoperative pain in total knee arthroplasty

Postoperative pain is caused by neuronal damage that occurs during the surgical procedure and the stimulation of the nociceptors. In postoperative period, total knee arthroplasty (TKA) is painful and pain management is quite difficult. The main purpose of postoperative pain relief is to reduce the pain of the patient, to contribute to the healing process, to shorten the length of hospital stay, and to reduce hospital costs.

Techniques such as intravenous analgesia, epidural analgesia, and peripheral nerve blocks are used to prevent postoperative pain. In addition, oral and parenteral analgesics, patient-controlled analgesia, nerve blocks, and periarticular injection methods are used as multimodal analgesia method. Systemic opioids, nonsteroidal anti-inflammatory drugs, and local anesthetics are frequently used for postoperative analgesia.

Pain scales such as visual analogue scale (VAS), verbal descriptive scale (VDS), numerical rating scale (NRS) are used as standard methods in the evaluation of pain of patients.

Total knee arthroplasty (TKA) is known to be a very painful orthopedic procedure [5]. For this reason, effective pain control is important to optimize the rehabilitation process in order to ensure patient satisfaction, hospital stay, and cost reduction [6]. However, the difficulty of postoperative pain management after TKA is to maintain adequate motor function with adequate analgesia. The patient is informed about the surgery to be performed before the operation, and a training program and the physical preparation are recommended. Patients undergoing preoperative exercise and training showed significant improvements in function, quadriceps strength, and duration of stay. After the surgical intervention is performed, the patient can continue the rehabilitation program to speed up the healing process in the home under the supervision of a physiotherapist. Rehabilitation therapy depends on many factors such as patient characteristics, prosthesis characteristics, and postoperative complications.

More than 1.1 million joint arthroplasty (TJA) are performed annually in the USA, and more than 700,000 of them are primary TKA [7, 8].

## **5. Pathophysiological changes caused by postoperative pain in the organism**

Acute postoperative pain that is poorly treated is associated with both physiological and psychological functions in the body [2, 9–11], which are as follows:

- Cardiovascular system: coronary ischemia, myocardial infarction
- Pulmonary system: hypoventilation, decreased vital capacity, pulmonary infection
- Gastrointestinal system: reduced motility, ileus, nausea, vomiting
- Renal system: increases in urinary retention and sphincter tone, oliguria

There are negative effects on the muscular system, on the coagulation system, on the wound healing, and on the immune system. Finally, poorly controlled pain after surgery may impair sleep and have negative psychological effects, such as demoralization and anxiety.

## **6. Postoperative pain treatment/management methods**

1. Regional analgesia techniques and multimodal analgesia
2. Drug therapy
3. Nonpharmacological techniques
4. Preemptive analgesia
5. Patient education

### 6.1. Regional analgesia techniques and multimodal analgesia

Despite improvements in pain management, approximately half of TKA (total knee arthroplasty) patients develop severe pain in the early postoperative period. Excessive tissue damage and complex innervation in TKA make pain control difficult. Femoral nerve, sciatic nerve, and obturator nerve are involved in the innervation of the knee joint. In major surgeries, such as TKA, changes occur in the endocrine system and central, peripheral, and sympathetic nervous systems. If postoperative analgesia is not achieved adequately, systemic responses induced by the surgery increase and serious risks may occur to the patients.

Conventional methods such as parenteral opioids, epidural analgesia, and femur blocks have been widely used to remove the pain associated with TKA [12]. In addition, the fascia iliaca block has recently been used more frequently to reduce the pain associated with TKA [13]. Comparing general anesthesia with neuraxial anesthesia in the patients with TKA, the risk of perioperative complications was significantly reduced in patients undergoing neuraxial anesthesia [14]. In another study, the risk of short-term complications in patients with TKA was higher in patients receiving general anesthesia than in patients receiving neuraxial anesthesia [15]. Neuraxial anesthesia was associated with the reduction of major complications. A recent meta-analysis has shown that there is a significant decrease in the incidence of postoperative surgical site infection in neuraxial anesthesia when compared to general anesthesia and neuraxial anesthesia in the patients with TKA and total hip arthroplasty (THA) [16]. The use of peripheral nerve block (PNB) also reduced the need for postsurgical critical care services [17].

Multimodal analgesia techniques are often used in the “fast-track” recovery protocols to improve pain relief. Mixture of local anesthetics and anti-inflammatory and opioid analgesics for periarticular infiltration has been used in the multimodal protocols. It can improve the pain score, reduce the total perioperative opioid consumption, enhance the early mobilization, and increase the patient satisfaction [18]. Several multimodal analgesics have been developed in clinical practice [19, 20] and paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, ketamine [21], alpha-2 adrenergic agonists [22], and corticosteroids have been used [23].

Periarticular drug injection is an attempt to apply a low-concentration, high-volume local anesthetic solution to the joint capsule and periarticular surrounding tissues to provide postoperative analgesia [24]. When used as a part of a multimodal analgesic protocol in patients undergoing TKA, femoral nerve blockade has been shown to reduce narcotic consumption and improve postoperative pain scores [25]. However, periarticular infiltration is usually insufficient to provide adequate analgesia in the anterior direction of the knee [26]. Periarticular infiltration analgesic protocols that infiltrate anterior, posterior, and medial compartments of the knee are reported to only last between 6 and 12 h [27]. Prolonged motor blockade, quadriceps muscle weakness, difficulty ambulating, and postoperative falls limit the utility of femoral nerve block (FNB) in the “fast track” rehabilitation protocols [28, 29]. In a study, Fascia iliaca block effectively reduced the amount of morphine used after TKA in the first 24 h. This study shows that the fascia iliaca block provides the same level of analgesia with the use of less morphine compared with the periarticular injection [30]. However, the fascia iliaca block requires as much as 40–50 mL of volume to achieve an effective result [31]. In another study, the analgesic efficacy of the fascia iliaca block was compared to the femur nerve block in the guideline

of ultrasonography and no difference was found in VAS scores and opioid consumption [32]. The sciatic nerve block (SNB) is used in addition to FNB for complete analgesia after TKA. In a systematic review, SNB administered as a supplement to FNB has shown that it does not provide adequate analgesic activity [33]. Studies with larger patient groups showed a significant reduction in postoperative opioid consumption, less opioid-induced adverse effects, and significantly lower resting and dynamic pain scores [34–38]. Adductor channel block was also studied. In the meta-analysis study performed, there was no significant difference in pain control and morphine consumption between the adductor canal block (ACB) and the femoral nerve block (FNB) group. However, it was observed that ACB provided faster postoperative mobilization ability without reduction of analgesia in patients undergoing TKA [39]. Another study conducted after TKA to compare the efficacy of single-shot adductor canal block (SACB) and postoperative continuous adductor canal block (CACB) placement and showed that CACB was superior to SACB for analgesia control but ambulation ability, success rate, early functional recovery, and treatment-related side effects were similar [40]. Different studies have shown that ACB and FNB have similar motor function recovery, strength ratings, and quadriceps muscle strength at postoperative 24 and 48 h in TKA patients [41, 42].

## 6.2. Drug therapy

TKA operation is one of the most painful orthopedic procedures [43]. For this reason, it is difficult to provide adequate analgesia with a single drug or method. Multimodal analgesia methods will be more appropriate to reduce side effects and provide pain control. Multimodal analgesia is defined as providing more effective pain control by the combined use of various analgesic drugs and techniques that may have additive or synergistic effects targeting different pain mechanisms in the peripheral and/or central nervous system [44].

In multimodal pain management, patient education, preemptive oral medications, regional anesthesia methods, peripheral nerve blocks, local infiltrations, and postoperative rehabilitation are included. Most of the side effects seen in analgesia treatment are due to the parenteral opioid. One of the main goals of multimodal analgesia is to reduce the need for opioids.

### 6.2.1. Nonsteroidal anti-inflammatory drugs

Tissue inflammation in TKA surgery triggers the production of PGs that play a role in acute postoperative pain. NSAIDs reduce central sensitization by inhibiting central and peripheral prostaglandin synthesis. It may be effective for 2 weeks when inflammation continues in the postoperative period. Ketorolac is a nonselective COX inhibitor and has oral, parenteral, ophthalmic, and nasal forms. It is used in moderate and severe postoperative pain management after major surgeries [45]. It reduces opioid consumption when used as a part of multimodal pain management [46]. The use of NSAIDs can cause gastritis or peptic ulcer formation and impair platelet aggregation, renal function, and wound healing. For this reason, there are concerns about their use in the perioperative period. Preemptive use of selective COX-2 (cyclooxygenase) inhibitors (celecoxib and rofecoxib) has been shown to reduce postoperative pain scores in the knee surgeries [47]. The use of selective COX2 inhibitors in TKA surgeries has been shown to reduce opioid consumption, provide early onset of physical rehabilitation, and reduce



nausea and vomiting [48]. Similarly, diclofenac or ketorolac administered in a single dose in joint arthroplasty patients reduced morphine consumption by 29% compared to placebo [49].

#### 6.2.2. *Paracetamol*

It is nonopioid and non-NSAID analgesic. It inhibits prostaglandin synthesis in the CNS and plays a role in preventing central sensitization. There is a minimal effect on peripheral PG synthesis. Unlike NSAIDs, the anti-inflammatory effect is poor, and there are no negative effects on platelet function and gastric mucosa. It has been shown that 1 g intravenous paracetamol provides rapid and effective analgesia in major orthopedic surgeons [50]. Paracetamol can be administered 1 g/day four times. When combined with paracetamol and NSAIDs, better analgesia is achieved when both drugs are used alone [51].

#### 6.2.3. *Glucocorticoids*

Glucocorticoids have strong anti-inflammatory effects. Corticosteroids are thought to be an important component because of their local anti-inflammatory effects and their ability to reduce the local stress response in the operation [52]. There have been many studies on corticosteroids, and conflicting evidence has been obtained about their benefits [53–58]. Some studies have shown that postoperative pain is improved with corticosteroids [53–56] but other studies do not benefit [57, 58]. In another study, postoperative pain level was lower in the corticosteroid group than that in the noncorticosteroid group in first 24 h [59]. In a meta-analysis, dexamethasone, a long-acting glucocorticoid, has been shown to reduce postoperative pain and opioid consumption [60]. In one study, it was shown that preoperative single dose iv 40 mg dexamethasone reduced dynamic pain scores [61]. Another study showed that dexamethasone administered as a part of multimodal analgesia in 269 patients undergoing TKA reduced postoperative pain and bulimia and did not increase wound complications [62]. In contrast to these studies, patients with a periarticular injection with high- and low-dose corticosteroids were compared and found no improvement in postoperative pain level [58]. Surgical techniques such as the surgical approach and the use of pneumatic tourniquet may be effective on early postoperative pain [63, 64]. One of the most commonly used corticosteroids for periarticular injection is methylprednisolone [52, 57, 65–67].

#### 6.2.4. *Opioids*

Opioids have been used to provide analgesia and relieve anxiety for centuries. Opioid receptors are found in many regions of the CNS. These receptors are located in the central nervous system, cerebral cortex, hypothalamus, thalamus, midbrain extrapyramidal area, substantia gelatinosa, and sympathetic preganglionic nerves. Places with the highest concentration of these receptors are structures and pathways associated with pain [68].

The first opioid receptors were found in 1973. Later, endogenous opioids were found. There are four types of receptors. These include mu ( $\mu$ ), kappa ( $\kappa$ ), sigma ( $\sigma$ ), and delta ( $\delta$ ) receptors. Opioids show their effect by linking their receptors.

1. Mu ( $\mu$ ) receptors: specific morphine agonist. It is stimulated by morphine and is responsible for supraspinal analgesia.
2. Kappa ( $\kappa$ ) receptors: they are responsible for spinal analgesia and sedation.
3. Sigma ( $\sigma$ ) receptors: responsible for dysphoria and hallucinations.
4. Delta ( $\delta$ ) receptors: beta-endorphin and enkephalin are specific agonists. It is influential on motor integration and urine function.

Classification of opioids:

1. Natural opioids: phenanthrene derivatives: codeine, morphine, and thebaine. Benzylisoquinoline derivatives: papaverine.
2. Synthetic opioids: phenylpiperidine derivatives (fentanyl, sufentanil, and meperidine), benzomorphan derivatives (pentazocine and phenazocine), diphenylpropyl or methadone derivatives (methadone and d-propoxyphene), and morphinan derivatives (levorphanol).
3. Semisynthetic opioids: dihydromorphone/morphinone, heroin, and thebaine derivatives (etorphine).

Morphine contains the basic properties of the majority of the structures of the opioids. The effects of morphine in the central nervous system, analgesia, euphoria and sedation. The most important effect of morphine on the central nervous system therapeutically is analgesia.

Analgesia provided by systemic opioids often accompanies side effects such as sedation, nausea, pruritus, urinary retention, and constipation. However, they continue to be an important part of severe postoperative pain management [69]. They can be used intramuscularly, intravenously, orally, rectally, sublingually, subcutaneously, epidurally, or intrathecally. If patients are able to use the oral route, oral administration is recommended. Side effects of oral opioids are less frequent and are mostly related to the gastrointestinal system. Intravenous patient-controlled analgesia (PCA) should be preferred if the parenteral route is used. Intravenous opioid PCA is recommended for bolus application with appropriate lock interval without basal infusion. In the postoperative period, it is usually administered via intravenous PCA for the first 24–48 h and then is used as oral agents [44]. Oral opioids have immediate release and controlled release forms [70]. Rapid-release patients are effective in the treatment of moderate and severe postoperative pain, but are impractical because they need to be reapplied every 4 h. Since postoperative pain is continuous at the beginning, analgesics should be used regularly especially in the first 24 h. Long-acting oxycodone and oxycodone have been shown to be effective in postoperative analgesia in TKAs [71, 72]. Especially morphine and fentanyl are frequently used for postoperative analgesia in TKA cases. The application of intrathecal morphine and fentanyl is very effective in postoperative pain control. In a study conducted, 0.2 mg and 0.3 mg intrathecal morphine administration was shown to be effective for postoperative analgesia [73]. Other studies have been done to support this study. The use of 0.5 mg intrathecal morphine has been shown to be more reliable and more effective than injections of 0.2 mg [74].



Intrathecal morphine is less hydrophobic than other opioids, has a longer duration in the cerebrospinal fluid, and provides very good postoperative analgesia [75]. On the other hand, another study reported that morphine should not be used even in small doses due to these side effects [76]. Opioids are known to produce more effective and long-lasting anesthesia when used with local anesthetics. Opioids are known to produce more effective and long-lasting anesthesia when used with local anesthetics [77, 78]. In a study of TKA cases, we compared the use of intrathecal morphine and fentanyl for postoperative analgesia and found that fentanyl provided more effective postoperative analgesia [79]. Long-acting opioids (LAO) are often used for malignant, nonmalignant, and different pain treatments. A lot of work about LAO (oxycodone, morphine) has been done in this regard. In a study on LAO, there was a decrease in pain while there was an increase in vomiting and sedation [80]. After the use of LAO (oxycodone), the rehabilitation of patients was found to be better in TKA cases [81]. In the studies performed, intravenous PCA and oxycodone were compared and there was no difference in pain [82], and no difference in pain after LAO (oxycodone) used after total joint arthroplasty [83].

#### 6.2.5. Gabapentinoids (*gabapentin and pregabalin*)

Gabapentin has been shown to be effective in the treatment of herpetic neuralgia, neuropathic pain [84], and diabetic neuropathy [85]. These anticonvulsant drugs, which have been used for a long time in the management of chronic pain, have started to be used in acute postoperative analgesia in recent years. They may cause side effects such as sedation and dizziness. It has been shown that administration of pregabalin (300 mg preoperatively and 150–50 mg twice daily for the first 14 days postoperatively) reduces the incidence of opioid consumption and neuropathic pain development after TKA [86]. We also have studies showing that postoperative analgesia is reduced after the application of preoperative gabapentin and pregabalin in lower extremity surgeons [87, 88]. Another study has shown that gabapentin effectively reduces postoperative narcotics consumption and pruritus incidence [89]. In another meta-analysis trial, the use of pregabalin shows that it could improve pain control at 24 and 48 h with rest, reduce morphine consumption, and improve knee flexion level, as well as reduce nausea, vomiting, and pruritic event rate. However, pregabalin increased the incident rate of dizziness after total knee arthroplasty (TKA) and total hip arthroplasty (THA) but could not improve the pain control at 72 h with rest [90].

#### 6.2.6. *Ketamine*

Ketamine is used by anesthetists for sedation and general anesthesia. With the detection of the N-methyl-D-aspartate receptor's role in nociceptive pain transmission and central sensitization, ketamine has begun to be used as a potential antihyperalgesic agent. Subanesthetic low doses of ketamine provide significant analgesic efficacy without psychomimetic side effects [45]. Low-dose ketamine has no adverse effects on respiratory and cardiovascular system and does not cause nausea-vomiting, urinary retention and constipation or postoperative ileus. In patients receiving TKA, low-dose ketamine infusion has been shown to reduce morphine consumption postoperatively (3  $\mu\text{g}/\text{kg}$  per minute intraoperatively and 1.5  $\mu\text{g}/\text{kg}$  per minute for 48 h) [91].

### 6.3. Nonpharmacological techniques

There have been many studies on surgical techniques and equipment, but most have had no or limited effect on postoperative analgesia. These studies focused on drains, surgical approaches, tourniquet use, prosthetic types, and reshaping of the patellar surface. A comparison of cooling and compression techniques with the control group showed that postoperative pain and morphine consumption were reduced [92]. The efficacy of TENS administration in postoperative analgesia after TDP was not demonstrated [93]. The results of cryotherapy are contradictory. The potential benefits of cryotherapy in a meta-analysis are not clinically significant [94]. Routine use is therefore not recommended.

### 6.4. Preemptive analgesia

Analgesics are administered before painful stimulation to prevent peripheral and central sensitization. Preemptive analgesia inhibits peripheral sensitization and central sensitization. It should also prevent inflammatory and neuropathic pain types [95]. Local anesthetic infiltration, regional anesthesia methods, and drugs (NMDA receptor antagonists, opioids, COX-2 inhibitors, nonsteroidal anti-inflammatory drugs (NSAID), and local anesthetics) can be used for preemptive analgesia. According to a study, preemptive analgesia is statistically significant, although not clinically significant [96]. When preemptive analgesia is administered, it should be considered as a method of pathological pain as well as physiological conventional perioperative analgesia [97]. Preemptive analgesia is an effective method in clinical practice for the approach to postoperative pain involving incisional and inflammatory injury [98].

Drugs used in preemptive analgesia:

1. Local anesthetics
2. Nonsteroidal anti-inflammatory drugs (NSAIDs)
3. COX-2 inhibitors
4. Opioids
5. NMDA receptor antagonists

### 6.5. Patient education

There are two major components of pain perception: the sensory discriminative component and the motivational affective component [99]. Emotional component is targeted with patient education. Patients and their relatives are informed, and their anxiety is reduced by eliminating their fears about the unknown; the realistic goals are identified, and a relationship is established with patients and their relatives; the patient satisfaction increases, and the pain scores decrease [100].

## 7. Conclusion

In TKA, many methods are proposed and used for postoperative pain management. There are many factors that affect postoperative pain management. The age of the patient, the experience of the surgeon, the technical conditions, and the method used are some of these. Taking all these factors and literature into consideration, the use of multimodal analgesia techniques is recommended.

Systemic medications for postoperative analgesia after TKA:

1. Paracetamol
2. NSAIDs
  - a. Celecoxib
  - b. Ibuprofen
  - c. Naproxen
  - d. Ketorolac
3. Ketamine
4. Gabapentinoids
  - a. Gabapentin
  - b. Pregabalin
5. Glucocorticoids
6. Opioids
  - a. Morphine
  - b. Fentanyl
  - c. Hydromorphone
  - d. Hydrocodone
  - e. Tramadol
  - f. Extended-release oxycodone
  - g. Extended-release morphine

## 8. Key rules in knee rehabilitation

1. Bone-bond stability is a prerequisite for optimal knee function recovery [101, 102].
2. Postsurgery rehabilitation program should be started early.

3. During the rehabilitation program, unbalanced and full weight should not be allowed until a normal range of motion and walking pattern is achieved.
4. The development of reflex inhibition in the extensor or flexor mechanisms should be recognized early and must be struggled in the appropriate modalities.
5. The operated and unoperated extremities should be strengthened together.
6. For the success of the rehabilitation program, orthopedic surgeon, physical medicine and rehabilitation specialist, physiotherapist, occupational therapist, nurse, and the social team of service specialists need to communicate well.

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