

Current Concepts in Pain Management of Total Knee Replacement Surgeries: A Narrative Review

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Abstract

Total knee replacement/arthroplasty (TKR/TKA) is considered a life-changing surgery as it not only corrects the pathology and associated joint deformity but also renders the patient pain-free allowing them to perform activities of daily living as before. Such favorable outcomes depend entirely on the perioperative pain management strategies. Structuring such strategies requires background knowledge of the goals set, the process of pain generation before and after the surgery, and innervations of the pain-generating components involved in each surgical step.

The multifactorial origin of TKR pain requires a multidimensional pain management strategy such as multimodal analgesia (MMA). It should incorporate all the essential ingredients that target each step of the pain generation process. Apart from pharmacological agents and nonpharmacological techniques, regional analgesia (RA) plays a very important role as an adjunct to MMA to provide quality analgesia that promotes enhanced recovery and mobility. However, the choice of RA technique remains dependent on its motor-sparing effect, procedure-specific analgesic coverage, opioid-sparing effect, and suitability for enhanced recovery after surgery (ERAS). Psychological analgesia is also an important aspect of MMA, aiding in resolving psychological concerns and postoperative pain management and empowering patients in their own pain management process by encouraging active participation. In addition to providing appropriate pain management services, assessing expected outcomes in the postoperative period is also important to close loopholes and provide rescue analgesics when needed.

This narrative review article highlights important aspects of pain management strategies and the essential requirements for implementing them to achieve desired outcomes. We believe this article will help readers design or modify their pain management strategy to meet all of their goals.

Keywords: Total knee replacement, Total knee arthroplasty, Pain management, Motor-sparing regional anesthetic technique, Multimodal analgesia, Procedure-specific analgesia.

Introduction

Total knee replacement (TKR) is considered an ultimate surgical treatment option for end-stage knee osteoarthritis (OA) to regain complete functional recovery of the knee joint and eliminate severe pain associated with the pathology. It involves extensive surgical dissection and manipulation of the soft tissues

leading to severe pain in the early postoperative period. Despite the increasing interest in developing effective pain management strategies that incorporate multiple pain control modalities, most (approximately half) TKR patients experience extreme postoperative pain [1, 2, 3, 4]. It can be a major concern for the patient, surgical team, and anesthesiologists. Not being treated

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appropriately can affect postoperative recovery with physiological, psychological, and economic consequences.

Over the decades, advances in various pain management strategies have led to more effective and targeted outcomes with fewer complications. Previously, many patients were denied the right to remain pain-free (oligoanalgesia) as the pain was underrated and undertreated due to the fear of narcotic side effects (opioid phobia) [5]. Then came the era of a sudden surge of opioid use due to aggressive marketing of narcotics by pharmaceutical companies, when pain was declared the fifth vital sign by the American Pain Society [6, 7]. Subsequently, the decade of pain control and research (2000-2010) [8] gave rise to concepts such as patient-controlled analgesia (PCA), preemptive analgesia, and multimodal analgesia (MMA) that have become a cornerstone of the current pain management strategies. Regional analgesia (RA), as an essential component of MMA, has helped significantly reduce perioperative opioid consumption, encouraging the transition from opioid-sparing to opioid-free pain management protocols. In the future, researchers will focus on describing the innervations in more detail and achieving more procedure-specific protocols that may replace existing conventional strategies. We always strive for pain control, and the global burden of pain has indeed increased over the past century, despite a growing trend in postoperative pain management strategies. Identifying and treating the patients receiving inadequate analgesia remain a significant health care problem. Pain often remains unconquered due to ineffective and underdosed analgesic regimens. However, the solution to such problems lies in developing an effective strategy to deliver target-specific regimens to the patients through the introduction of postoperative pain management services. This narrative review focuses on the current concepts of pain management strategies in TKR. It also highlights the process of pain generation before and after the surgery, which is necessary for focused planning and determining strategies considering all causative factors, pathways, set goals, and, most importantly, patient satisfaction.

Setting the goals

The first and most important step in determining the pain management protocol for a TKR surgery is to understand the goals of everyone involved (the surgical team, the anesthesiologist, and the patient). The main focus should be on the common goals (Figure 1) that include a painless perioperative period and enhanced recovery after surgery (ERAS) suitability.

ERAS is an example of pathway-based perioperative care (Figure 2). It incorporates structured mechanisms that help

to optimize the patient, control perioperative physiology, minimize surgery and anesthesia-related stress response, reduce surgical care variability and associated complications, and finally improve the quality of care and surgical outcomes [9, 10, 11]. Key elements of the ERAS protocol include patient education, anticipation, aggressive optimization of comorbidities, standardized anesthetic and surgical techniques, effective pain management, and early oral feeding, mobilization, and discharge. ERAS reduces postoperative complications and costs, shortens hospital stays, and increases patient satisfaction. Rapid recovery from knee surgery is possible through less invasive surgical procedures, more selective soft tissue repair, improved patient education, careful instrumentation, selection of an appropriate implant design, and improved analgesia options. Achieving such goals requires a holistic approach. For this, understanding the patient profile is very important. Also, knowing the operating surgeons and their skills makes a big difference in being consistent with their goals. Optimal and effective analgesia is the ultimate goal of TKR surgery, which helps fulfill all other goals. For that, it is essential to understand the mechanism of pain generation, the innervation of the pain generators involved in each surgical step, the types of postoperative pain, and the available analgesic options or techniques.

Understanding patient and the surgery

Most patients undergoing TKR are from the geriatric age group with multiple comorbid conditions leading to reduced functional reserve. Due to their chronic OA problem and subsequent limited or restricted joint mobility, they can not carry out their routine activities independently. It leads to physical disability resulting from pain and loss of function, reducing the quality of life and increasing risk factors for further morbidity. Such a population should receive the best possible perioperative care, including the most appropriate analgesic options to improve quality of life. Surgical correction of deformity resulting in a well-functioning knee joint to perform the activity of daily living independently further adds to the quality of life. For this reason, TKR is also considered one of the most successful and life-changing surgeries [12, 13]. It is the best surgical solution for end-stage OA of the knee joint to restore full joint function by replacing damaged cartilage with an implant.

The surgical steps involve various approaches or incisions, extraarticular dissection, and intra-articular resection. An incision is the first iatrogenic injury where tissue insult begins. Of the various approaches, the medial parapatellar approach is the most common, known as the workhorse of the varus knee. The midline approach is mainly suitable for



Figure 1: Goals and priorities of total knee replacement surgery ERAS: Enhanced recovery after surgery.

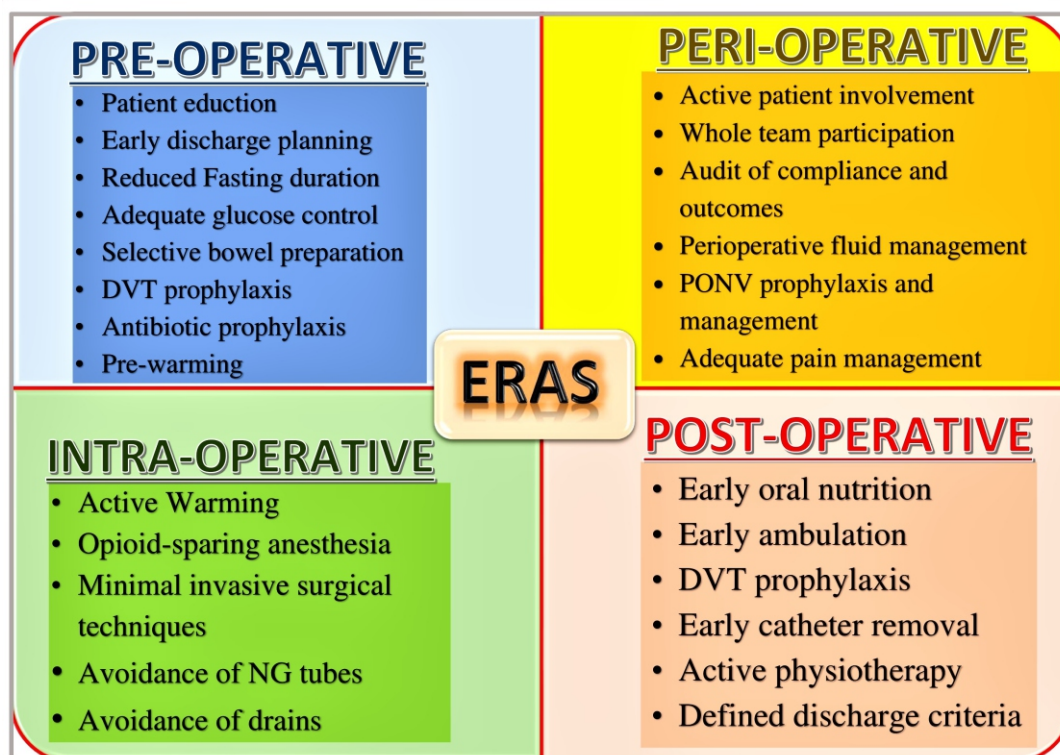


Figure 2: Enhanced recovery after surgery protocol

DVT: Deep venous thrombosis, PONV: Postoperative nausea and vomiting, NG: Nasogastric. (Adapted from Sonawane, K., Dixit, H. . Regional Analgesia for Knee Surgeries: Thinking beyond Borders. In: Whizar-Lugo, V. M., Saucillo-Osuna, J. R., Castorena-Arellano, G., editors. Topics in Regional Anesthesia [Internet]. London: IntechOpen; 2021 [cited 2022 Jul 12]. Available from: <https://www.intechopen.com/chapters/77934> doi: 10.5772/intechopen.99282).

revision TKR surgeries. Lateral approaches are sometimes required to correct the severe valgus deformity. Correction of such deformity can be associated with a high likelihood of common peroneal nerve injury during surgery, resulting in foot drop postoperatively. For this reason, RA techniques involving sciatic nerve (SCN) components should be avoided in such conditions. Therefore, it is always better to look for x-rays to confirm if the knee is varus or valgus. It is also essential to know the choice of the surgical approach, whether medial or lateral, as most of the RA techniques described for knee analgesia may not work with other approaches.

An incision follows the extraarticular dissection through the medial retinacular complex (deep fascia + retinacular ligament and fibrous capsule) along the medial border of the quadriceps tendon, patella, and patellar ligament. The knee joint is accessed by performing the synovectomy to allow the removal of menisci, cruciates, transverse ligaments, infrapatellar fat pads, and osteophytes [14, 15, 16, 17, 18, 19, 20]. Subsequently, the affected joint cartilage of the femoral and tibial condyles along with the back of the patella is resected. The final step includes shaping the articular surfaces of the femur and tibia to match the metal components of knee prostheses. The total duration of the operation is 1-2 hours. The majority of patients begin physical therapy within 24 hours of surgery. Patients are usually discharged within 3-5 days after surgery.

Postoperative complications include infection, nerve damage, increased risk of falls, fractures, persistent/chronic pain, deep vein thrombosis, joint stiffness, prosthetic-related complications (loosening/fracture of prosthetic components, joint instability/dislocation, component misalignment), and breakdown. In addition to various surgical modifications, rapid recovery is possible due to improved analgesia options that should address each process or step of the postoperative pain generation.

Pain generation process

Pain is the central level perception of the signals that are generated by the interaction of noxious stimuli with the nociceptors and transmitted through the spinal and supraspinal regions (Figure 3).

Noxious stimuli include mechanical (pressure, pinching), thermal, and chemical stimuli [21]. The mechanical and thermal stimuli are shorter (fast pain) than the chemical stimuli (slow pain). Pain-producing chemicals that primarily activate/sensitize afferent nociceptors are either released from damaged tissue or circulating blood cells (potassium, histamine, and serotonin) or synthesized by enzymes activated by tissue damage (bradykinin, prostaglandins, and

leukotrienes) [21, 22].

Nociceptors are sensory receptors that detect noxious/harmful stimuli and transmit electrical signals to the nervous system. Knee joint nociceptors commonly include slow conducting/responsive C fibers and fast conducting A-delta fibers that transmit sharp and transient pain. They are distributed everywhere extraarticular (in the skin, subcutaneous tissue, muscles, infrapatellar fat pad, and retinacular ligament) and intraarticular (in the joint capsule, menisci, cruciate ligaments, and bone periosteum) [23, 24, 25]. They are absent over the cartilages of the knee joint and adjacent cortical and trabecular bone. These nociceptors can have a variety of voltage-gated channels responsible for generating action potentials that initiate electrical pain signaling in the nervous system [26].

Nociception is the normal protective response of nociceptors to subliminal noxious stimuli. In comparison, pain is the central level perception of the transmitted signal in the form of an action potential generated by nociceptors. Transduction is the conversion of supraliminal noxious stimuli into an action potential by the nociceptors [27]. Transmission is the propagation of the action potential by nociceptive specific neurons (lamina I, II) and second-order wide dynamic range neurons (lamina III-VI) [28]. It involves relaying of message from the site of tissue damage to the area of the brain where it is perceived. Modulation is a specifically designed process by spinal and supraspinal centers to augment or attenuate the afferent pain transmission [29]. Perception is the subjective awareness generated by integrating inputs into the somatosensory cortex and third-order neurons of the limbic system. It is a complex function of multiple processes, that include attention, expectation, and interpretation.

The pain generation is a continuous process owing to nonadaptive nociceptors. It involves converting continuous noxious stimuli from the inflammatory process into pain signals, transmitting the pain signals along pain pathways, and perceiving the actual pain at a central level. Therefore, pain management strategies should target all levels of the pain pathway. It should reduce noxious stimuli by addressing causative factors like inflammations and nerve injuries, interrupt pain transmission by creating a conduction block using RA techniques, and modify central level pain perception using various centrally acting analgesics. Controlling multifactorial pain generation requires consideration of various pharmacological/nonpharmacological modalities, which constitute MMA (Table 1). The RA plays an important role as an adjunct to MMA by blocking the pain pathways and significantly reducing pain signal trafficking. Thus, MMA

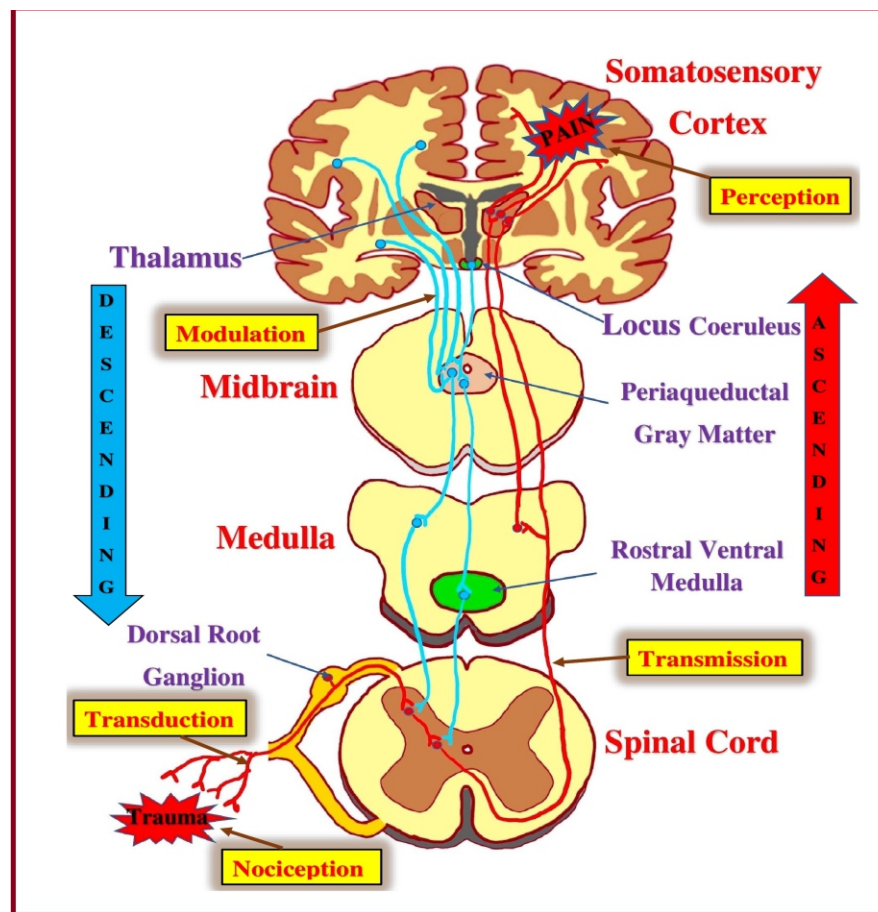


Figure 3: Various steps and components of the pain pathways

Pain process	Pharmacological agents	Non-pharmacological intervention
❖ Nociception	Local anesthetics, Capsaicin, COX-2 selective inhibitors, NSAIDs, opioids	<ul style="list-style-type: none"> • Touch therapy • Cryotherapy • Continuous passive motion • Heat therapy
❖ Transduction	Local anesthetics, COX-2 selective inhibitors, NSAIDs, opioids	
❖ Transmission	Local anesthetics, anticonvulsants, alpha-2 agonists, COX-2 selective inhibitors, opioids	<ul style="list-style-type: none"> • Transcutaneous electrical nerve stimulation • Acupuncture • Massage
❖ Perception	Opioids, alpha-2 agonists, COX-2 selective inhibitors, NSAIDs, centrally acting analgesics, NMDA antagonists	<ul style="list-style-type: none"> • Hypnosis • Massage • Acupuncture
❖ Modulation	Acetaminophen, anticonvulsants, antidepressants, Neuraxial opioids, alpha-2 agonists, NMDA antagonists, Opioids	

Table 1: Adjuncts of multimodal analgesia acting on various steps of pain generation
(COX: Cyclooxygenase, NSAIDs: Nonsteroidal anti-inflammatory drugs, NMDA: N-methyl-D-aspartate)



Figure 4: Various components of multimodal analgesia

(Adapted from Sonawane, K., Dixit, H. . Regional Analgesia for Knee Surgeries: Thinking beyond Borders. In: Whizar-Lugo, V. M., Saucillo-Osuna, J. R., Castorena-Arellano, G., editors. Topics in Regional Anesthesia [Internet]. London: IntechOpen; 2021 [cited 2022 Jul 12]. Available from: <https://www.intechopen.com/chapters/77934> doi: 10.5772/intechopen.99282).

protocol control pain by acting on transduction, modulation, and perception processes of the pain pathway through pharmacological agents and on the transmission process of the pain pathway through RA techniques.

Concept of “multimodal analgesia”

The concept of MMA has been around since the 1990s and essentially refers to using more than one pain control modality to achieve effective analgesia [30]. MMA uses combinations of active ingredients to achieve a synergistic effect on pain control. It constitutes different types of modalities with different routes of administration and mechanisms of action, acting on different target sites in the peripheral and central nervous systems. Such combinations target different receptors and pathways, which help improve pain control by creating additive or synergistic effects and also minimize side effects associated with a single remedy. MMA includes pharmacological agents, nonpharmacological techniques, and RA as an important component (Figure 4). Pharmacological agents include opioids and nonopioids systemic analgesics (acetaminophen and nonsteroidal anti-inflammatory drugs). Other adjuvants

include N-methyl-D-aspartate (NMDA) receptor antagonists (ketamine, magnesium, or dextromethorphan), antiepileptic drugs (gabapentin and pregabalin), alpha-2 adrenergic agents (clonidine), glucocorticoids (dexamethasone), and others (antidepressants, calcitonin, nicotine, capsaicin, cannabinoids, and lidocaine) [31, 32]. Since post-TKR pain has both acute and chronic components, MMA with low-dose opioids is preferred to address already well-established central and peripheral sensitization. Low-dose opioids can be administered through transdermal patches or PCA [33, 34]. PCA has become increasingly popular in TKR patients to deal with moderate to severe postoperative pain [35, 36]. However, it is also associated with opioid-related side effects like nausea, vomiting, respiratory depression, and urinary retention [37]. It provides simple, fast, and adequate pain relief without a specialized anesthetist using a PCA electronic pump programmed according to the analgesic needs taking into account the initial pain and the patient's physical characteristics. Patients can dispense the opioids from the PCA as needed by pressing the button. Commonly administered opioids through PCA include oxycodone,

Table 2: Perioperative multimodal pain management protocol for total knee replacement surgery

Level I: Good evidence (high quality randomized trial or systematic review), Level II/III: Fair evidence (prospective or retrospective comparative study, case control study, or systematic review of level II or III study), Level IV/V: Poor quality evidence (case series or expert opinion).

COX: Cyclooxygenase, GA: General anesthesia, i-PACK: Infiltration between the popliteal artery and capsule of knee joint, PONV: Postoperative nausea and vomiting, LIA: Local infiltration analgesia.

Recommendations		Level of Evidence	Purpose
Preoperative	❖ Patient education: Focusing on surgical procedure, rehabilitation protocol, expected benefits, postoperative pain pattern, and pain management methods.	I, V	<ul style="list-style-type: none"> To reassure the patient and address concerns. Increase patient satisfaction. Shorten hospitalization and rehabilitation period.
	❖ Preemptive use oral multimodal analgesics: Like oral opioids (oxycodone), COX-2 inhibitors (celecoxib), gabapentin/ pregabalin	I, II, III I I, V	<ul style="list-style-type: none"> Provide synergistic effect with other analgesic drugs. Facilitate enhanced recovery and optimal analgesia with an opioid-sparing effect. Reduce the number of rehabilitation sessions.
Intraoperative	❖ Regional anesthesia (Neuraxial > General anesthesia)	I	<ul style="list-style-type: none"> Reduce intraoperative hemorrhage. Avoid PONV and pulmonary/cardiovascular complications. Provide excellent pain relief. Improve patient satisfaction.
	❖ Regional analgesia techniques: As an adjunct to GA (femoral nerve block, sciatic nerve block, femoral triangle block, adductor canal block, i-PACK, and LIA)	I, II, III	<ul style="list-style-type: none"> Single shot or continuous infusion via a catheter. Stable hemodynamics and clear surgical field. Motor-sparing preferred. Reduce intraop opioid consumption/drug requirements.
Postoperative	❖ Intravenous patient-controlled analgesia (IV-PCA):	I, II, III	<ul style="list-style-type: none"> Offer excellent analgesia with reduced rescue analgesia. Improve patient satisfaction. It should be used with extreme care in patients with advanced age (risk of opioid-related side effects).
	❖ Oral multimodal analgesics: Like acetaminophen, COX-2 inhibitors, tramadol, and oxycontin.	I	<ul style="list-style-type: none"> Consistent and optimal pain relief. Reduce opioid consumption and related complications. Higher patient satisfaction.

morphine, fentanyl, and hydromorphone [38, 39, 40, 41]. Nonpharmacological adjuncts include immersive virtual reality, acupuncture, trigger point injections, epidural steroid injections, cryotherapy, and transcutaneous electrical nerve stimulation. The choice of the RA techniques (neuraxial or single-shot/continuous nerve blocks) depends on understanding the nature and types of pain and the difference between the pain generators before and after surgeries.

As preemptive analgesia, MMA plays an important role in perioperative pain management by inhibiting central and peripheral sensitization. Preemptive analgesia is an antinociceptive intervention that should be started in the preoperative period. It significantly reduces the intensity of the postoperative pain and decreases the incidence of hyperalgesia [42, 43]. It also helps to avoid an increased need for postoperative analgesics by lowering the pain threshold. Based on the MMA concept, institutional perioperative

Ganga Hospital's (India) Multimodal Analgesia Protocol for TKR surgeries			
1.	Night before Surgery	<ul style="list-style-type: none"> • T. paracetamol 1g, • T. Aceclofenac 100 mg, • T. Pantocid 40 mg, • T. Pregabalin 75 mg, • T. Alprazolam 0.5 mg 	<ul style="list-style-type: none"> • Psychological Counselling, • Sanitary Kit for an antiseptic bath before Surgery.
2.	Preoperative holding area	<ul style="list-style-type: none"> • Inj. Tranexamic acid 1 g, • Inj. Ramosetron 0.3 mg, • Inj. Cefuroxime 1.5 g, • Inj. Amikacin 1 g 	<ul style="list-style-type: none"> • Reassurance. • Reassessment.
3.	Intraoperative	<ul style="list-style-type: none"> • Neuraxial anesthesia>General anesthesia • Sedation SOS (Midazolam/Fentanyl) • Inj. Paracetamol 1g, • Inj. Dexamethasone 8 mg, • Inj. Ketorolac 30 mg, • Dual Subartoral Block (immediately after Surgery) 	<ul style="list-style-type: none"> • Fluid replacement. • Maintaining Vitals. • Intraoperative body warming.
4.	Postoperative (POD 0-first 24 hours) In PACU	<ul style="list-style-type: none"> • Inj. Cefuroxime 750 mg x 8 hourly 2 doses • Inj. Paracetamol 1g QID, • Inj. Dexamethasone 8 mg after 6 hr after the first dose, • Inj. Ketorolac 30 mg BD, • Inj. Pantocid 40 mg OD, • T. Ecosprin 150 mg OD, • Night sedation (Inj. Butadol 1 mg+Phenargan 12.5mg), • Buprenorphine 5/10 mg transdermal patch x 7 days 	<ul style="list-style-type: none"> • Regular pain assessment. • Passive joint physiotherapy by a trained physiotherapist. • Active leg movements after wearing off neuraxial effect. • A pneumatic compression device for DVT prophylaxis. • Standing/walking with support. • Rescue analgesia as per pain mapping.
5.	Postoperative (>24 hours)	<ul style="list-style-type: none"> • T. Paracetamol 1g QID x 5 days, • T. Aceclofenac 100 mg BD x 3 days, • T. Pantocid 40 mg OD x 5 days, • T. Ecosprin 150 mg OD x till discharge • T. Pregabalin 75 mg HS x 7 days, • T. Alprazolam 0.5 mg (SOS) HS, • Laxative HS x 5 days 	<ul style="list-style-type: none"> • Regular pain assessment. • Deep breathing exercises. • Rescue analgesia as per pain mapping. • Physiotherapy. • Walking with or without support.
6.	On discharge	<ul style="list-style-type: none"> • T. Paracetamol 1g QID (SOS), • T. Pantocid 40 mg OD (SOS), • T. Ecosprin 150 mg OD x 15 days, • T. Pregabalin 75 mg HS x 15 days 	<ul style="list-style-type: none"> • Walking exercises. • Joint exercises. • Quadriceps strengthening exercises.

Table 3: Ganga Hospital's perioperative multimodal pain management protocol for total knee replacement surgery

guidelines [44] (Table 2, 3) can be structured or modified according to available resources, facilities, and patient populations.

Pain before and after surgery (perioperative)

The pathology for which the patient decides to undergo TKR surgery is end-stage chronic OA, which leads to pain and deformity in the joint to such an extent that it causes loss of mobility. Therefore, due to the prolonged duration of pathology and symptoms, preoperative knee pain is considered a chronic type of pain with well-established peripheral and central sensitization. Before surgery, intraarticular knee joint pain predominates extraarticular pain due to pathology inside the joint. After surgery, the extraarticular pain predominates the intraarticular pain owing to the correction of the existing intraarticular pathology and the creation of an iatrogenic pathology

(surgical dissection) leading to tissue damage [5,45].

Postoperative knee pain can be categorized into joint-related and non-joint-related [46]. The joint-related causes include infections/inflammation (osteoarthritis), instability (ligament injury or malalignment/loosening of the implant), fractures, femoropatellar problems, and damage to the structures responsible for knee stability. In comparison, non-joint-related causes include soft tissue irritation (impingement owing to oversize implants and overuse of muscles/tendons during aggressive physiotherapy) and neuropathies. Therefore, post-TKR pain can be viewed as acute on chronic pain resulting from fresh tissue damage involved in surgical dissection over a relatively healthy area.

Postoperative pain can be a combination of musculoskeletal and neuropathic pain. Musculoskeletal pain is an aching, dull, and throbbing type that can occur due to damage to the soft tissues and muscles. Tourniquet pain is a type of

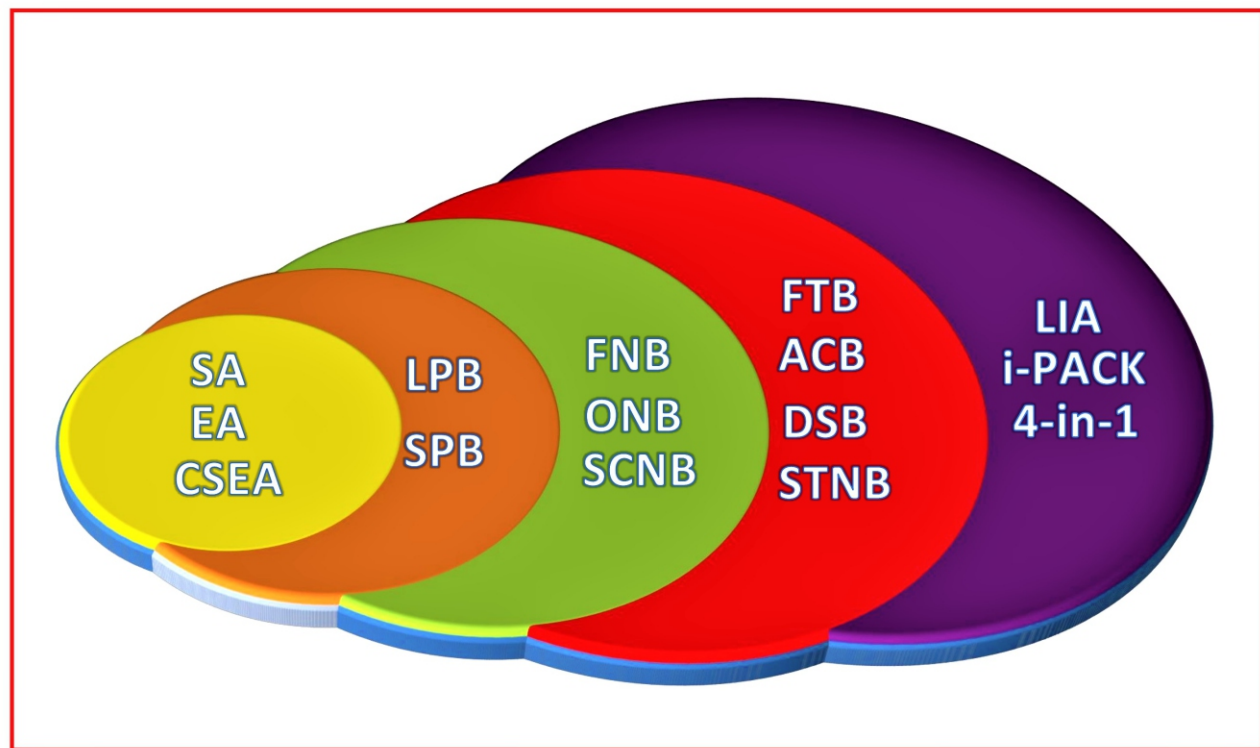


Figure 5: Regional analgesia options from 'center-to-periphery' for knee surgery

SA: Spinal analgesia, EA: Epidural analgesia, CSEA: Combined spinal-epidural analgesia, LPB: Lumbar plexus block, SPB: Sacral plexus block, FNB: Femoral nerve block, ONB: Obturator nerve block, SCNB: Sciatic nerve block, FTB: Femoral triangle block, ACB: Adductor canal block, DSB: Dual subsartorial block, STNB: Selective tibial nerve block, LIA: Local infiltration analgesia, i-PACK: Infiltration between the popliteal artery and capsule of knee joint. (Adapted from Sonawane, K., Dixit, H. Regional Analgesia for Knee Surgeries: Thinking beyond Borders. In: Whizar-Lugo, V. M., Saucillo-Osuna, J. R., Castorena-Arellano, G., editors. Topics in Regional Anesthesia [Internet]. London: IntechOpen; 2021 [cited 2022 Jul 12]. Available from: <https://www.intechopen.com/chapters/77934> doi: 10.5772/intechopen.99282).

Regional analgesia options for total knee replacement surgeries					
Neuraxial blocks	Plexus blocks	Peripheral nerve block	Motor-sparing block		
			Subsartorial blocks	High-volume blocks	Infiltration techniques
<ul style="list-style-type: none"> Subarachnoid block (SAB) Epidural analgesia (EA) Combined spinal + epidural analgesia (CSEA) 	<ul style="list-style-type: none"> Lumbar plexus block (LPB) Sacral plexus block (SPB) 	<ul style="list-style-type: none"> Femoral nerve block (FNB) Sciatic nerve block (SCNB) Obturator nerve block (ONB) Selective tibial nerve block (STNB) 	<ul style="list-style-type: none"> Femoral triangle block (FTB) Adductor canal block (ACB) Dual subsartorial block (DSB) 	<ul style="list-style-type: none"> Hi-Volume Proximal Adductor Canal (Hi-PAC) block 4-in-1 block Modified 4-in-1 block 	<ul style="list-style-type: none"> Infiltration between Popliteal Artery and Capsule of Knee (IPACK) block Local Infiltration Analgesia (LIA) Ultrasound-guided LIA or Ring block

Table 4: Available regional analgesia options for total knee replacement surgeries

musculoskeletal pain caused due to irritation of nociceptors by inflammatory mediators released during muscle ischemia. Neuropathic pain is usually a sharp, electric shooting and stabbing type with a complex mechanism involving nerve injury, which can alter pain processing [47, 48, 49]. The resulting hypersensitivity and hyperexcitability of the neurons can lead to dysesthesia, allodynia, and hyperalgesia.

Therefore, the modalities included in the MMA protocol for TKR surgery should be selected considering both pain components (acute and chronic) and both pain types (musculoskeletal and neuropathic).

RA as an adjunct to MMA

RA techniques for knee surgery have evolved to improve

patient outcomes, reduce complications, and improve patient satisfaction [50]. With the addition of ultrasound into RA practice, the perioperative analgesic strategies for knee surgery have undergone a conceptual revolution in the last decade. In addition to providing optimal analgesia and a clear surgical field intraoperatively, RA also helps reduce serious postoperative complications such as deep vein thrombosis, pulmonary embolism, need for blood transfusion, pneumonia, and respiratory depression [51, 52, 53].

TKR surgeries are commonly done under neuraxial anesthesia, the safety profile of which is time- tested compared to general anesthesia (GA). The intraoperative analgesic demands may also differ as per the type of anesthesia. Neuraxial anesthesia can act as preemptive analgesia by blocking the pain transmission at the spinal level before surgical dissection. GA can lead to increased analgesic demands during and after surgery due to the lack of provision to block the pain signals before their generation, like in neuraxial. Such demands can be controlled or reduced by

providing a supplemental procedure-specific RA technique with the GA prior to the surgical incision. Thus, the severity and analgesic requirement of the postoperative pain depends on the prior control of the firing of nociceptive impulses. The required analgesic coverage of the RA technique can also differ when used for either intraoperative or postoperative analgesia. For intraoperative analgesia, the RA technique should target all innervations of the pain generators involved in surgical dissection. In comparison, RA for postoperative analgesia should focus only on the innervation of the retained pain generators after the surgery. Various RA options are available for knee surgeries from center to periphery (Figure 5) (Table 4).

Before planning any particular RA technique, it is important to understand the purpose of each block and whether they are effective for anterior knee pain, posterior knee pain, or both (Figure 6). Neuraxial blocks were once considered the gold standard but lost their popularity due to undesirable side effects such as urinary retention, delayed mobility, blockage of other limbs, and the likelihood of epidural

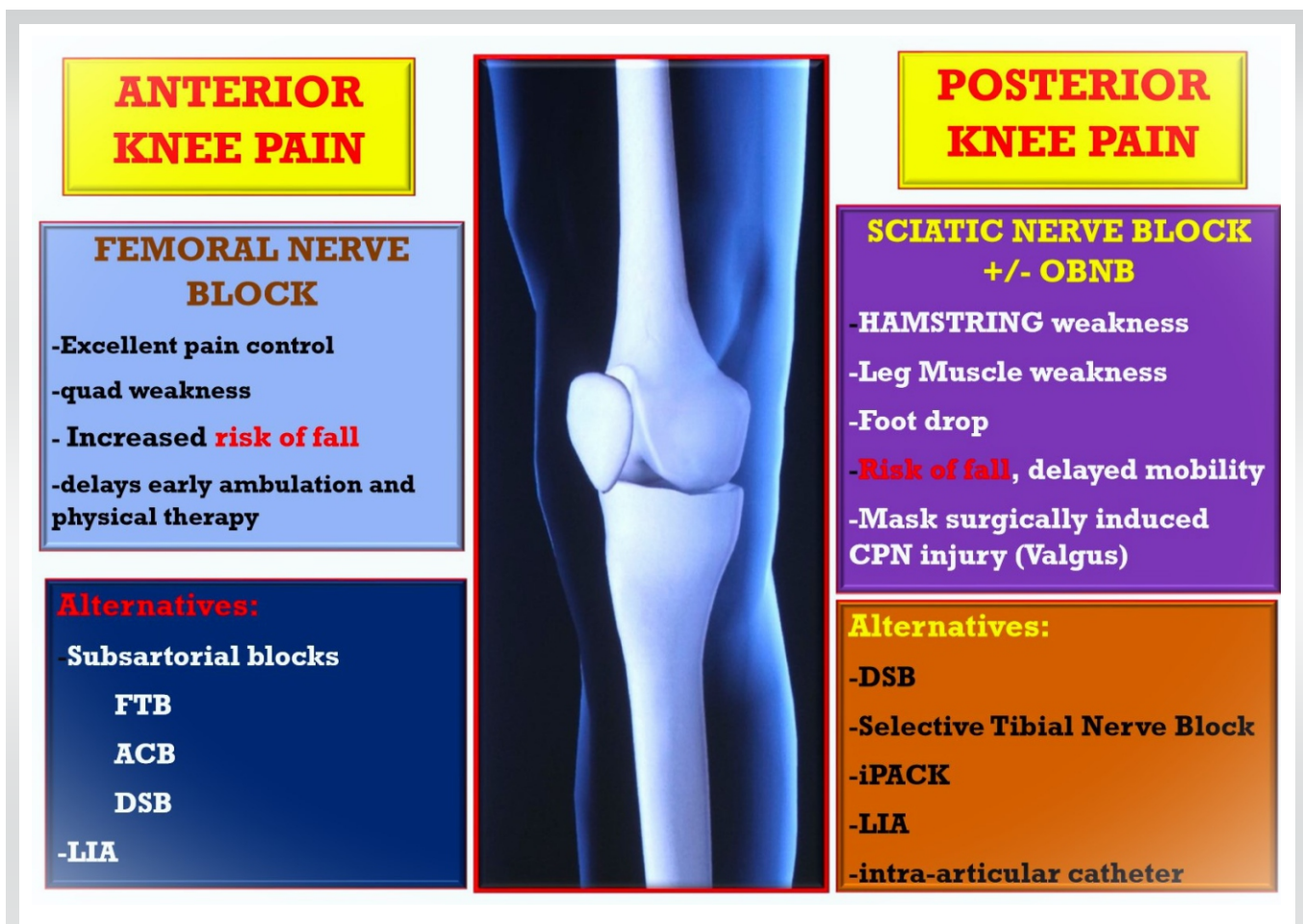


Figure 6: Regional analgesia option for anterior and posterior knee pain

FTB: Femoral triangle block, ACB: Adductor canal block, DSB: Dual subsartorial block, LIA: Local infiltration analgesia, iPACK: Infiltration between the popliteal artery and capsule of knee joint. (Adapted from Sonawane, K., Dixit, H. . Regional Analgesia for Knee Surgeries: Thinking beyond Borders. In: Whizar-Lugo, V. M., Saucillo-Osuna, J. R., Castorena-Arellano, G., editors. Topics in Regional Anesthesia [Internet]. London: IntechOpen; 2021 [cited 2022 Jul 12]. Available from: <https://www.intechopen.com/chapters/77934> doi:10.5772/intechopen.99282)



Figure 7: Identify-Select-Combine approach to procedure-specific regional analgesia techniques

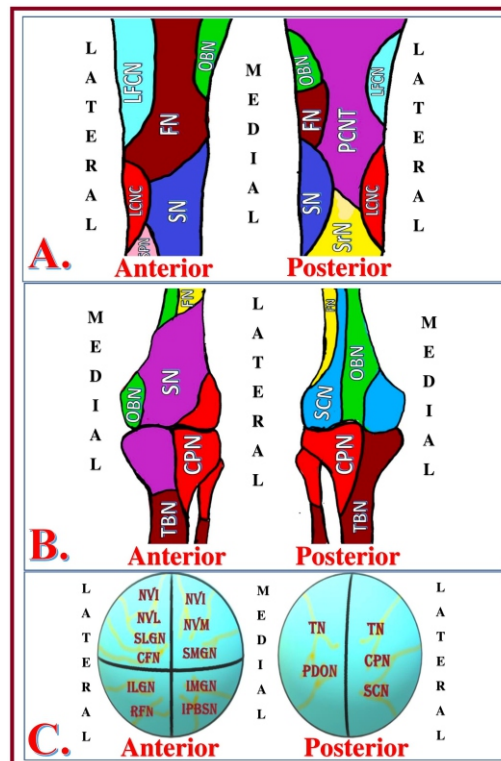


Figure 8: Dermatomal, osteotomal, and capsular innervation of the knee joint

A: Dermatomal innervations B: Osteotomal innervations C: Capsular innervations

NVI: Nerve to vastus intermedius, NVM: Nerve to vastus medialis, NVL: Nerve to vastus lateralis, SMGN: Superomedial genicular nerve, SLGN: Superolateral genicular nerve, IMGN: Inferomedial genicular nerve, ILGN: Inferolateral genicular nerve, IPBSN: Infrapatellar branch of the saphenous nerve, RFN: Recurrent fibular nerve, TN: Tibial nerve, CPN: Common peroneal nerve, SCN: Sciatic nerve, PDOBN: Posterior division of obturator nerve. (Adapted from Sonawane, K., Dixit, H. . Regional Analgesia for Knee Surgeries: Thinking beyond Borders. In: Whizar-Lugo, V. M. , Saucillo-Osuna, J. R. , Castorena-Arellano, G. , editors. Topics in Regional Anesthesia [Internet]. London: IntechOpen; 2021 [cited 2022 Jul 12]. Available from: <https://www.intechopen.com/chapters/77934> doi: 10.5772/intechopen.99282).

hematoma in patients on anticoagulants [54, 55]. The choice of lumbosacral plexus block is excluded from the ERAS protocol because it can cause muscle weakness, resulting in delayed mobility and discharge. Also, its deeper location and rich vascularity make it unsuitable for patients on anticoagulants. Femoral nerve block provides excellent pain control but is associated with quadriceps weakness, which delays ambulation and increases the risk of falls. Similarly, the SCN block is also associated with muscle weakness leading to postoperative foot drop, which can mask the outcome of the common peroneal nerve (CPN) injury during knee surgery,

especially in valgus deformity.

Motor-sparing and procedure-specific RA options can facilitate enhanced recovery and mobility. The motor-sparing effect of the block depends on the LA concentration used and the choice of target innervations. For procedure-specific RA techniques, an “identify-select-combine” algorithmic approach [56, 57] can be considered for complexly innervated knee joint surgeries (Figure 7). This approach includes identifying all target innervations, selecting target blocks involving all identified target nerves, and combining all selected target blocks covering

Plexus	Location	Contributing nerves	Innervations
Subsartorial plexus	Medial knee under the sartorius	<ul style="list-style-type: none"> Infrapatellar branch of saphenous nerve Anterior division of obturator nerve Medial femoral cutaneous nerve Nerve to vastus medialis 	<ul style="list-style-type: none"> Skin over the medial aspect of the knee Medial retinaculum Medial collateral ligaments Anterior capsule of the knee joint
Peripatellar plexus	Around the patella	<ul style="list-style-type: none"> Medial femoral cutaneous nerve Intermediate femoral cutaneous nerve Lateral femoral cutaneous nerve Infrapatellar branch of the saphenous nerve Nerve to vastus medialis (NVM) Medial retinacular nerve (terminal branch of NVM) Lateral retinacular nerve (terminal branch of the sciatic nerve) 	<ul style="list-style-type: none"> Skin over the anterior, superior, inferior, medial, and lateral to the patella Retinacula Collateral ligaments Anterior capsule of the knee joint
Popliteal plexus	Posterior aspect of the knee joint	<ul style="list-style-type: none"> Articular branches from the tibial nerve, common peroneal nerve, and sciatic nerve Posterior division of the obturator nerve 	<ul style="list-style-type: none"> Posterior capsule of the knee joint All intraarticular structures Retinacula Collateral ligaments

Table 5: Various plexuses innervating the knee joint

(Adapted from Sonawane, K., Dixit, H. . Regional Analgesia for Knee Surgeries: Thinking beyond Borders. In: Whizar-Lugo, V. M., Saucillo-Osuna, J. R., Castorena-Arellano, G., editors. Topics in Regional Anesthesia [Internet]. London: IntechOpen; 2021 [cited 2022 Jul 12]. Available from: <https://www.intechopen.com/chapters/77934> doi: 10.5772/intechopen.99282).

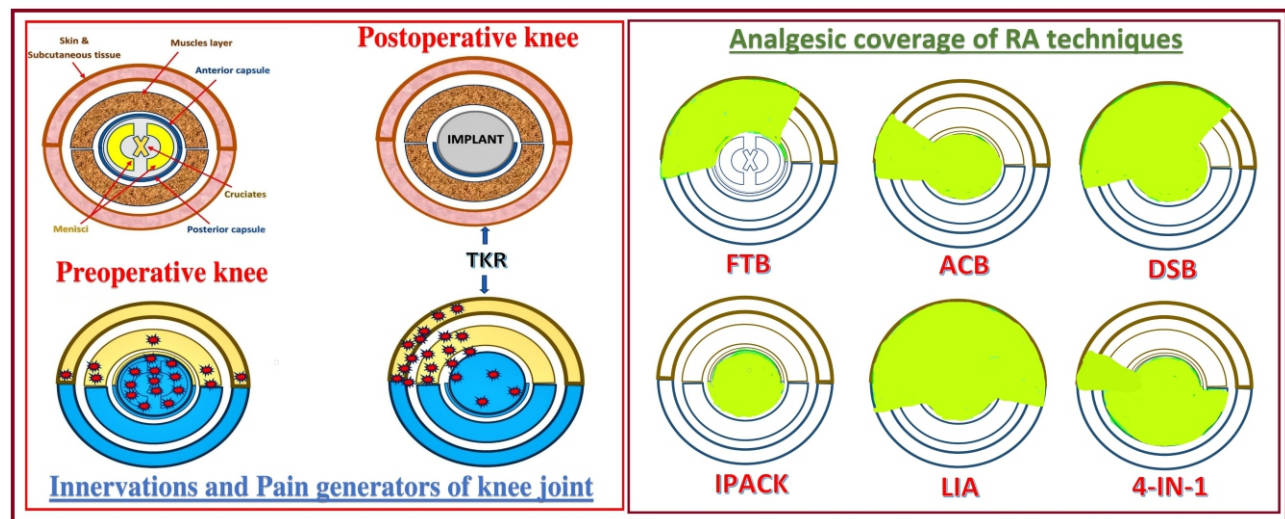


Figure 9: Pain generating structures and analgesic coverage of various regional techniques of total knee replacement

Yellow-colored area in circles: Anterior knee innervations, Blue-colored area in circles: Posterior knee innervations, Red star-like dots: Pain-generating area, TKR: Total knee replacement, Green-colored area in circles: Analgesia coverage, FTB: Femoral triangle block, ACB: Adductor canal block, DSB: Dual subsartorial block, IPACK: Infiltration between the popliteal artery and capsule of knee joint, LIA: Local infiltration analgesia. (Adapted from Sonawane, K., Dixit, H. . Regional Analgesia for Knee Surgeries: Thinking beyond Borders. In: Whizar-Lugo, V. M., Saucillo-Osuna, J. R., Castorena-Arellano, G., editors. Topics in Regional Anesthesia [Internet]. London: IntechOpen; 2021 [cited 2022 Jul 12]. Available from: <https://www.intechopen.com/chapters/77934> doi: 10.5772/intechopen.99282).

innervations of all the pain generators.

For the first step of this approach, the knowledge of the complex innervation of the knee joint (Figure 8) is essential to identify specific target innervations involved as per the surgical steps. The knee joint is innervated anteriorly by the lumbar plexus and posteriorly by the sacral plexus through their cutaneous branches supplying the skin, the muscular

branches supplying the muscles, and the osteotomal branches supplying the bone. These branches form 3 different plexuses before directly innervating the knee joint [58] (Table 5).

For the second step, the knowledge of the sonoanatomy of the subsartorial blocks is essential to select the exact location of the target block to involve identified target innervations.

Table 6: Procedure-specific regional analgesia options for total knee replacement surgeries

FNB: Femoral nerve block, LFCN: Lateral femoral cutaneous nerve, FTB: Femoral triangle block, ACB: Adductor canal block, DSB: Dual subsartorial block, SCN: Sciatic nerve, i-PACK: Infiltration between the popliteal artery and capsule of knee joint, LIA: Local infiltration analgesia. (Adapted from Sonawane, K., Dixit, H. . Regional Analgesia for Knee Surgeries: Thinking beyond Borders. In: Whizar-Lugo, V. M. , Saucillo-Osuna, J. R. , Castorena-Arellano, G., editors. Topics in Regional Anesthesia [Internet]. London: IntechOpen; 2021 [cited 2022 Jul 12]. Available from: <https://www.intechopen.com/chapters/77934> doi: 10.5772/intechopen.99282).

Surgical Steps	Approaches	Target innervations	Target Blocks	Procedure-specific RA options
Incision	Medial	<ul style="list-style-type: none"> Subsartorial plexus 	<ul style="list-style-type: none"> Subsartorial blocks 	<ul style="list-style-type: none"> ❖ Medial approach: <ul style="list-style-type: none"> FTB + ACB DSB FTB + i-PACK LIA ❖ Lateral approach: <ul style="list-style-type: none"> FNB + ACB infiltration over incision FNB + i-PACK + infiltration over incision LIA ❖ Anterior approach: <ul style="list-style-type: none"> FNB + ACB FNB + i-PACK LIA ❖ Posterior approach: <ul style="list-style-type: none"> ACB + infiltration over incision site Popliteal sciatic nerve block + infiltration over the incision site i-PACK + infiltration over incision site
	Lateral	<ul style="list-style-type: none"> Peripatellar plexus 	<ul style="list-style-type: none"> FNB LFCN block Lateral cutaneous nerve of the calf block 	
	Midline	<ul style="list-style-type: none"> Peripatellar Plexus 	<ul style="list-style-type: none"> FNB 	
	Posterior	<ul style="list-style-type: none"> PCNT 	<ul style="list-style-type: none"> Infiltration over the incision site 	
Superficial + Deep dissection	Medial	<ul style="list-style-type: none"> Subsartorial plexus 	<ul style="list-style-type: none"> Subsartorial blocks 	
	Lateral	<ul style="list-style-type: none"> Peripatellar plexus 	<ul style="list-style-type: none"> FNB 	
	Midline	<ul style="list-style-type: none"> Peripatellar plexus 	<ul style="list-style-type: none"> FNB 	
	Posterior	<ul style="list-style-type: none"> Popliteal plexus Sciatic nerve 	<ul style="list-style-type: none"> ACB i-PACK Popliteal SCN block LIA 	
Joint Access	Anterior capsule	<ul style="list-style-type: none"> Subsartorial plexus Peripatellar plexus 	<ul style="list-style-type: none"> Subsartorial blocks FNB 	
	Posterior capsule	<ul style="list-style-type: none"> Popliteal plexus 	<ul style="list-style-type: none"> ACB i-PACK LIA 	
Intraarticular dissection		<ul style="list-style-type: none"> Popliteal plexus 	<ul style="list-style-type: none"> ACB i-PACK LIA 	

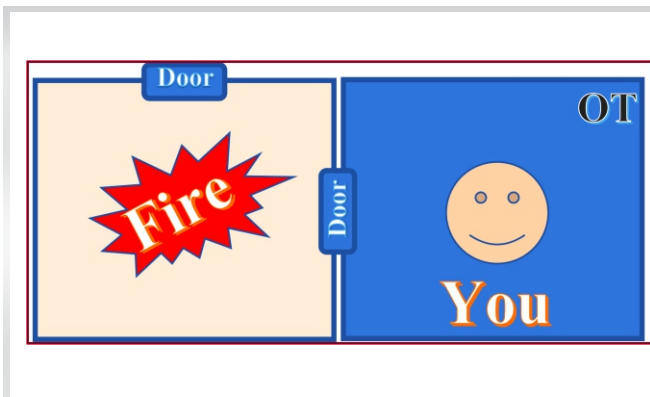


Figure 10: Scenario of "Fire outside the door" Theory OT: Operation theatre

The apex of the femoral triangle, which appears as a "sign of 3" or "kissing sign" under ultrasound [5], is an important identification landmark that demarcates the femoral triangle and adductor canal region. It is also important to know the drug spread pattern and involvement of the neural structures in various subsartorial blocks.

The third step is to combine all selected target blocks that will cover all important procedure- specific innervation of the pain generators retained after the surgery (Figure 9). Such a combination should provide effective and complete analgesia coverage. Knowledge of analgesic coverage for each commonly used RA technique in TKR surgeries is essential (Figure 9).

Post-TKR pain is contributed by the retained pain generators like skin/subcutaneous tissues over the incision area, medial retinaculum, periosteal rim of the cut bones, anterior joint capsule remnant, and damaged nerves, microfractures, and inflammation [5, 45]. After surgery, the extraarticular pain over the surgical dissection area contributes more than the intraarticular joint area due to the replacement of the affected joint surface with nonneural and nonvascular metal implants [5, 45]. Therefore, the innervations of these retained components are essential targets for any procedure-specific RA techniques to provide effective and complete postoperative analgesia (Table 6).

"Fire outside the door" theory:

The "Fire outside the door" theory best explains the need for MMA by creating a scenario where the person becomes trapped inside the room and notices a fire just outside the room door (Figure 10).

What steps must a person follow to protect from the fire?

1. The first step will be to call for help by shouting or making telephone calls.
2. The second step will focus on stopping the fire from spreading in the room by closing the door to avoid entering

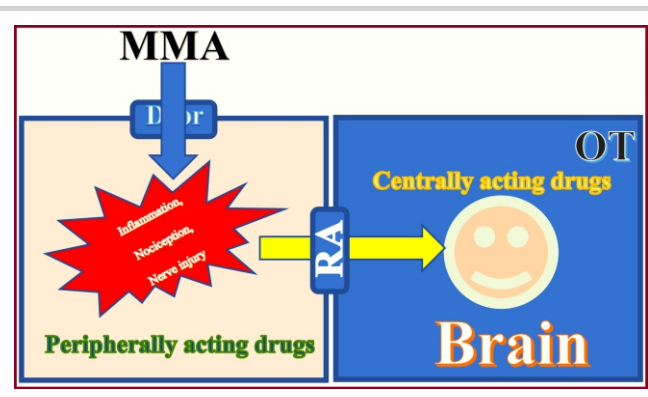


Figure 11: Correlation of "Fire outside the door" Theory scenario with pain management strategy
MMA: Multimodal analgesia, RA: Regional analgesia, OT: Operation theatre.

the heat or the smoke coming from the fire.

3. The third step may involve keeping the room and self moist with the available liquids in the room.

4. The final step is to wait and watch until the fire is completely extinguished and the exit is cleared.

In this scenario, the final step, "wait and watch," entirely depends on the first step, "call for help." Upon skipping the first step, the protection of the person will be completely dependent on closing the door. However, how long will this door endure fire damage? How long will this person remain protected? After some time, the door will also catch fire, and the fire will spread throughout the room, endangering the person's life. Damage to the person will be directly related to the time taken for the fire to get extinguished automatically, which can cause far more damage to surrounding regions.

On the other hand, skipping the second step (closing the door), the fire will spread inside the room. Until help arrives, it can cause significant harm to the occupant through suffocation from smoke or direct/indirect burn from fire and elevated temperature. Thus, the first two steps are very important in protecting the person and making arrangements for dealing with the fire. Including an additional step like taking prior precautions and anticipating a fire in advance will further reduce the expected damage.

If we correlate this scenario with pain management strategy (Figure 11)

1. The person getting trapped in the room is the brain.
2. Fire outside the room is the inflammation occurring due to surgical dissection.
3. The door of the room is nothing but the pain pathway connecting nociceptors to the CNS.
4. Call for help is the administration of MMA that deals directly with the fire or surgical inflammation and protects the brain by reducing impulse firing or modulating the pain pathway peripherally and centrally. These drugs include anti-inflammatory drugs (NSAIDs), antipyretics

Table 7: ABCDE of the pain management

ABCDE of the pain management	
A	<ul style="list-style-type: none"> Assess the pain using the pain scale Ask about the pain
B	<ul style="list-style-type: none"> Believe the patient's account of the pain description
C	<ul style="list-style-type: none"> Choose the most appropriate pain control options
D	<ul style="list-style-type: none"> Deliver possible therapeutic interventions in a timely, logical, and coordinated manner
E	<ul style="list-style-type: none"> Empower and enable the patient to have pain control

(acetaminophen), antineuropathics (gabapentinoids, antiepileptic), opioids, and steroids.

5. Closing the door means blocking the pain pathways, which can be achieved with the local anesthetics used in the planned RA techniques. The duration of the blockade can be prolonged by choosing some adjuvants such as dexamethasone or by choosing the continuous RA technique. Selective pain signals can be blocked without affecting other impulses by using a diluted concentration of LA.

6. The prior arrangement of things to take care of an anticipated fire is none other than preemptive analgesia, which helps reduce surgical inflammation and nociceptive firing and its CNS impact. Therefore, it plays an important role in preventing peripheral and central sensitization.

7. Relying entirely on the RA technique without actually addressing the source of the pain (surgical inflammation) results in increased production of inflammatory mediators and nociception. Continuous impulse firing can lead to hypersensitization of nociceptors and also cause upregulation of the sodium channels, making additional sodium channels available to reinitiate the blocked pain pathway [59, 60]. By reversing the blockade of the pain pathway, the overall duration of the RA technique will also get affected. This can result in hyperalgesia and severe breakthrough pain, further escalating the analgesic demands. It also leads to high opioid consumption and associated side effects, resulting in delayed mobility and discharge.

8. Protecting the brain from high-impulse firing can be accomplished with centrally acting drugs like opioids or NMDA antagonists that help modulate the pain process.

Psychological analgesia as an adjunct to MMA

The psychological components of the pain can change personality, disrupt the sleep cycle, interfere with work, reduce overall creativity or productivity, and interfere with existing relationships [61, 62]. On the other hand, emotional well-being can affect the overall experience of pain, helping to understand the cause of pain and learning effective ways to deal with it, ultimately improving quality of life. Psychological factors such as stress, anxiety, and fear can affect the experience and magnitude of pain. Such known modulating influences can prolong pain episodes in susceptible individuals. Pain perception results from the processing of electrical signals in different brain regions, which explains the different emotional reactions of people to pain. Psychological analgesia involves reducing high levels of psychological stress, which often aggravates the pain, and ameliorating the indirect consequences by helping patients learn how to manage many pain-related problems.

The first two components of the ABCDE of pain management [63] prioritize the psychological aspect of pain before moving on to the actual pain control options (Table 7). During periodic pain assessments, many associated psychological factors can be identified that can worsen symptoms, affect treatment outcomes, and delay recovery. Believing the patient's description of the pain also helps to see how much the existing pain has affected the patient's life and how it has changed their beliefs. Simultaneous rectification of the psychological concerns with existing postoperative pain management contributes to improved recovery and positive outcomes. It also empowers the patients in their own pain management process by encouraging active participation.

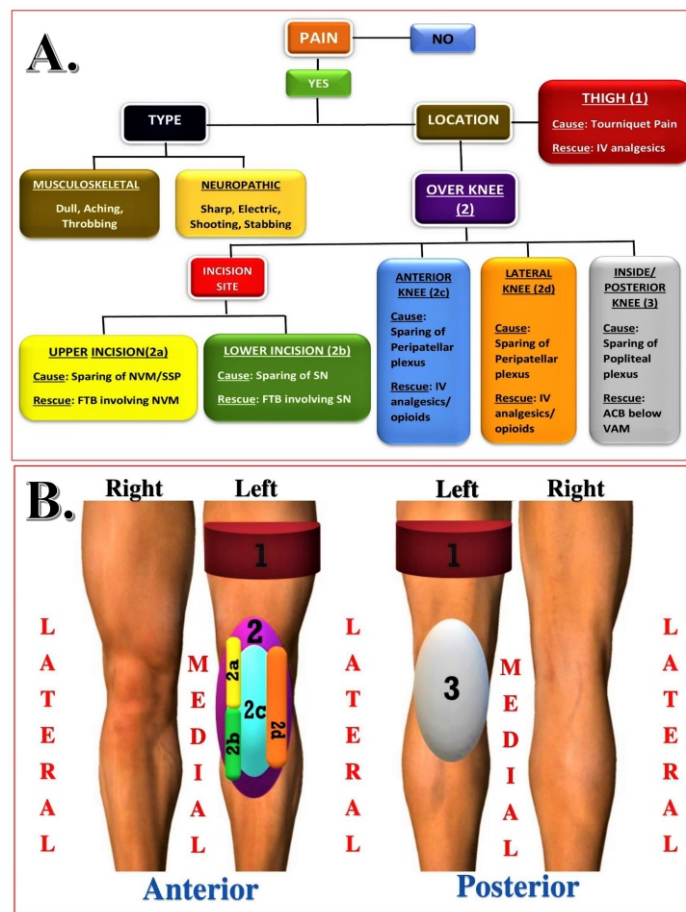


Figure 12: Postoperative pain assessment and rescue analgesia plan

A. Rescue analgesia as per the location of the pain, B. Pain location mapping of postoperative knee pain

IV: Intravenous, NVM: Nerve to vastus medialis, SSP: Subsartorial plexus, FTB: Femoral triangle block, SN: Saphenous nerve, ACB: Adductor canal block, VAM: Vasoadductor membrane. (Adapted from Sonawane K, Dixit H, Mistry T, Balavenkatasubramanian J. Comparing Analgesic Efficacy of a Novel Dual Subsartorial Block Using Two Different Volumes in Patients Undergoing Total Knee Arthroplasty: A Prospective, Double-Blind, Monocentric, Randomised Trial. *Cureus*. 2021 Dec 17;13(12):e20488. doi: 10.7759/cureus.20488. PMID: 34934599; PMCID: PMC8683700).

Consequences of oligoanalgesia

Extensive tissue damage associated with surgery can lead to the generation of noxious stimuli due to inflammatory changes that can cause severe pain. Untreated or partially treated pain can trigger multiple neuroendocrine stress responses, leading to the release of various stress hormones [64, 65] (cortisol, glucagon, growth hormone, and catecholamine) that can exacerbate surgical-induced reactions and put the patient at risk. Stress on the cardiovascular system can lead to increased oxygen demand, fatal hemodynamic fluctuations, ischemic cardiac events, and myocardial insufficiency. Immobilization due to severe pain can affect lung function, gastrointestinal function (ileus), and thrombus formation (deep vein thrombosis). Elevated stress hormones due to uncontrolled pain can also lead to disrupted sleep and reduced immunity, causing a higher risk of postoperative infections. It affects the mental state of the elderly population, resulting in delirium or anxiety disorders.

Continuous inflammatory changes and the nonadaptive nociceptors can cause sensitization of nerve systems, converting acute pain into chronic pain. These systemic manifestations of uncontrolled pain from surgical stress lead to prolonged hospital stays, increased hospital costs, decreased patient satisfaction, and a greater burden on the healthcare provider. Every effort should be made to avoid acute postoperative pain turning into chronic pain since acute pain can be well managed, but chronic pain is difficult to manage. Therefore, regular postoperative assessment with an emphasis on determining exacerbating factors plays an important role in avoiding all possible complications related to poor analgesic control.

Periodic postoperative assessment

Regular pain assessment in the postoperative period is an important aspect of monitoring outcomes of the pain management protocol. The severity of the pain, both resting and dynamic, can be noted using appropriate pain

scales. Also, the spared area of the RA technique can be identified, and the exact location of the pain can be noted during such assessments. The choice of the rescue analgesia strategy can be determined based on pain mapping of the spared areas and considering the severity and analgesic demands of the breakthrough pain [66] (Figure 12). Such postoperative follow-ups help rectify or modify RA techniques based on the spared area, provide complete and regular analgesic coverage, and increase the patient's active participation in pain management.

Conclusion

TKR is a life-changing surgery that can involve significant postoperative pain that impacts patients' mobility, recovery, and satisfaction scores. Managing the perioperative pain of such a patient requires careful

planning and a holistic approach, considering the patient profile, the surgical steps, the pain generation process, targeting each step of the pain pathway with MMA, and providing procedure-specific and motor-sparing RA techniques. Regular assessment of the analgesic strategy is very important to address patient concerns and to gain active patient involvement in their own pain management strategy. Apart from the scientific knowledge available, other contexts such as patient suitability and surgical compatibility play an important role in deciding the final individual pain management strategy considering all the goals set. Further clarity can be gained by researching and conducting comparative studies between different protocols to determine which protocol is most appropriate for the patient.

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Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his/her consent for his/her images and other clinical information to be reported in the Journal. The patient understands that his/her name and initials will not be published, and due efforts will be made to conceal his/her identity, but anonymity cannot be guaranteed.

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