Chapter

Acute Post-operative Pain Management

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Abstract

Despite major advances in the field of anesthesia and medicine, postoperative pain continues to be undermanaged in a significant proportion of patients. The consequences of undermanaged pain are deleterious for both patients and the healthcare system. This review aims to give the readers a practical and updated approach to acute postoperative pain management. This chapter deals with the definition of pain, the physiology and pathophysiology of pain, and various approaches to the management of acute pain. A review of the literature was done to understand the methods of pain management with a major focus on the literature of the last decade (2010–2022). A literature search was done on PubMed and Google Scholar using keywords "acute postoperative pain" and "pain physiology." The research papers on the basics of pain physiology, the prevalence of acute post-operative pain and methods of acute postoperative pain management were reviewed. A brief practical approach for acute postoperative pain using pharmacological and non-pharmacological approaches and a brief discussion have been done on the approach for special group of patients. The management of acute postoperative pain can be done using various pharmacological and non-pharmacological methods. The approach for each patient has to be tailored depending on the individual patient's needs.

Keywords: acute postoperative pain, nociception, opioids

1. Introduction

Anesthesia as a specialty has primarily originated from the human endeavor to control pain. In the evolution of medicine and surgery, complex surgeries have been made possible due to the pain relief given by the science of anesthesia. As modern anesthesiology evolved, the role of anesthesiologists is not confined only to operating and recovery rooms but extends to surgical wards also. Pain management in the postoperative period is one of the most essential components of postsurgical care.

1.1 What is pain?

The International Association for Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with or resembling that associated with

actual or potential tissue damage" [1]. Pain is a multidimensional experience with the following components: objective, subjective, physiological, emotional, and psychological [1]. Differences in pain experience are influenced by the biological response, psychological state, personality traits, and social traits [2]. A large systemic review of literature pooled from 165 studies showed that in the first 24 hours after major surgery (abdominal, thoracic, orthopedic, and gynecological), the mean incidence of moderate to severe pain was 30% and 11%, respectively [3]. The incidence of these pain levels varied by analgesic technique, with lower incidence with patient-controlled analgesia and epidural analgesia. A questionnaire survey of Asian countries by Vijayan et al. showed that only 30% of patients in India receive adequate pain management [4]. These and a large number of other surveys and studies show an unacceptable level of acute postoperative pain [5–11].

1.2 Pain can also be classified as physiological pain or pathological pain

Physiological pain is a "normal" sensation and includes a range of transient sensations we experience in response to stimuli that are of sufficient intensity to threaten to damage the tissue or produce small localized areas of injury, but which neither provoke an extensive inflammatory response nor damage the nervous system. Pathological pain is a sensation that arises as a consequence of either the inflammatory response that accompanies tissue injury or as a result of damage to the nervous system [12]. Pathological pain involves the disruption of the normal selectivity or specialization of the somatosensory system [12].

1.3 Physiological pain

The term "nociception" is a process by which information about tissue damage is conveyed to the central nervous system. Nociceptors are specialized, free, unmyelinated nerve endings that convey a variety of stimuli into nerve endings that the brain interprets as pain. Many patients can experience pain in the absence of a noxious stimulus.

The process of pain transmission is illustrated in the **Figure 1** and involves four steps [12]:

1. Transduction: The conversion of energy from a noxious thermal, mechanical, or chemical stimulus into electrical energy by nociception.

2. Transmission: It is the process of transfer of these signals from the periphery to the spinal cord and brain.

3. Perception: The appreciation of these signals in higher structures as pain.

4. Modulation: It is the descending inhibitory/facilitator input from the brain that influences the nociceptive transmission at the level of the spinal cord.

1.4 Pain pathways and neurobiology of nociception

The etiology of acute postoperative pain is multifactorial. Surgical tissue injury releases histamine and inflammatory mediators (bradykinin, prostaglandins, serotonin, and nerve growth factor), which in turn activate peripheral nociceptors. These

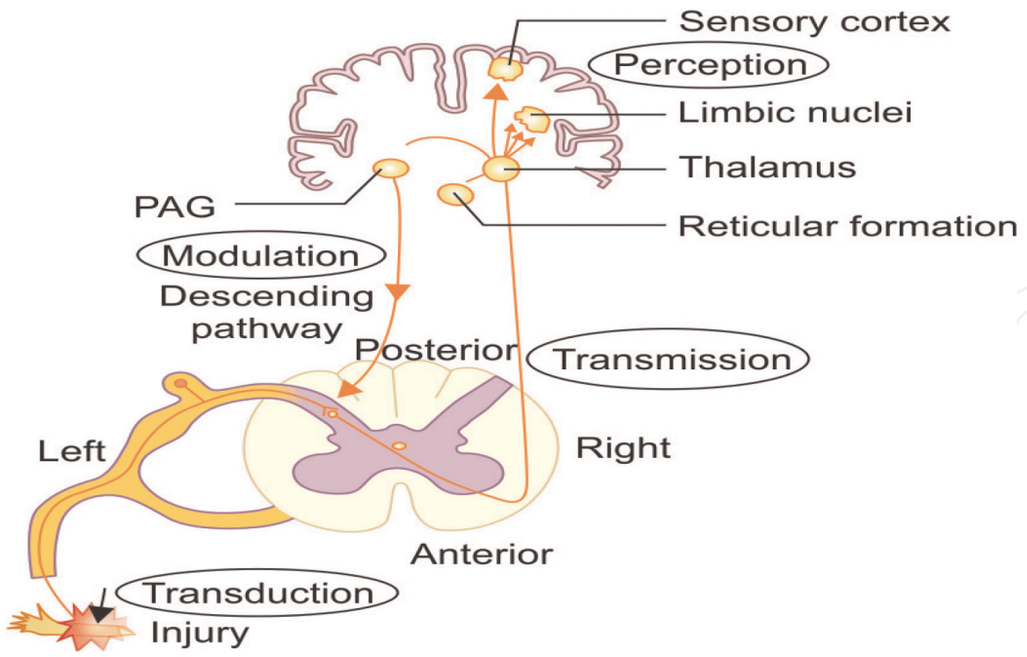

Figure 1.
Pain pathway [13].

nociceptors transmit the nociceptive information to the central nervous system by transduction and transmission [12].

Noxious stimuli are transduced by peripheral nociceptors and transmitted by A-delta and C nerve fibers to the dorsal horn of the spinal cord, where integration of peripheral nociceptive and descending modulatory input (i.e., serotonin, norepinephrine, GABA, enkephalin) occurs. After complex modulation, this information is passed on through the spinothalamic tract and spinoreticular tracts to higher centers where the pain is perceived. Some inputs pass to ventral and ventrolateral horns to initiate segmental spinal reflexes, which are associated with increased skeletal muscle tone, inhibition of phrenic nerve function, or decreased gastointestinal motility. The constant release of inflammatory mediators in the periphery sensitizes functional nociceptors and activates dormant ones (enlisted in **Table 1**). Further, it leads to a decreased threshold for activation and an increased rate of discharges. The surgical injury besides causing sensitization of primary and central pathways also leads to feelings of fear, anxiety, and frustration [2]. Intense noxious input from the periphery may lead to central sensitization and hyperexcitability causing a persistent post-injury change in central nervous system in addition to functional changes in the dorsal horn (spinal sensitization). This may lead to acute pain progression to chronic pain [12].The International Association for the Study of Pain defines chronic pain as persistent or recurrent pain lasting longer than 3 months [12].

The systemic response to surgery may contribute to perioperative morbidity and mortality. There are several systemic responses to surgery, including sympathetic nervous system activation, the neuroendocrine stress response, and inflammatory immunologic changes. Commonly observed pathophysiologic changes [14, 15] include:

1. Neurohumoral alteration (peripheral sensitization) occurring at the site and in regions immediately adjacent to the injury

2. Alternations in synaptic function and nociceptive processing within the spinal cord and limbic cortex

1. Bradykinin
2. Histamine
3. Substance P
4. Leukotriene
5. Prostaglandins
6. Arachidonic acid metabolites
7. Prostaglandin E2
8. Nerve Growth factor
9. Interleukin-1
10. Interleukin-4
11. Interleukin-6
12. Interleukin-8
13. interleukin-10
14. Tumor necrosis factor

Table 1.
List of cytokines/inflammatory mediators that contribute to acute effects of postoperative pain.

3. Sympatho-adrenal activation resulting in an elevation of heart rate and blood pressure and diminution in regional blood flow

4. Neuroendocrine response leads to hyperglycemia and a negative nitrogen balance and alternation in synaptic function.

The neurohumoral responses (peripheral sensitization) and central sensitization have already been explained in the physiology of pain.

Following extensive tissue injury (following surgery), nociceptive impulses stimulate sympathetic cells in the hypothalamus and preganglionic neurons in the anterior lateral horn. Surgical trauma results in increased plasma concentrations of epinephrine and norepinephrine. The magnitude and duration of catecholamine release are directly related to patient factors such as the type of surgery, inherent sympathetic response, patient age, and genetic polymorphisms. Pathophysiological changes associated with increased sympathetic tone and altered regional perfusion are illustrated in **Figure 2** [15].

1. Increased incidence of postsurgical hypertension that ranges from 5 to 50%

2. Increased peripheral vascular resistance associated with increased contractility and myocardial oxygen consumption. This can precipitate myocardial ischemic episodes

3. Due to the redistribution of blood to high-priority organs, microcirculation to injured tissue, viscera, and adjacent musculature may be reduced. This may lead to impaired wound healing, enhanced sensitization of nociceptors, muscle spasm, visceral/somatic ischemia, and acidosis

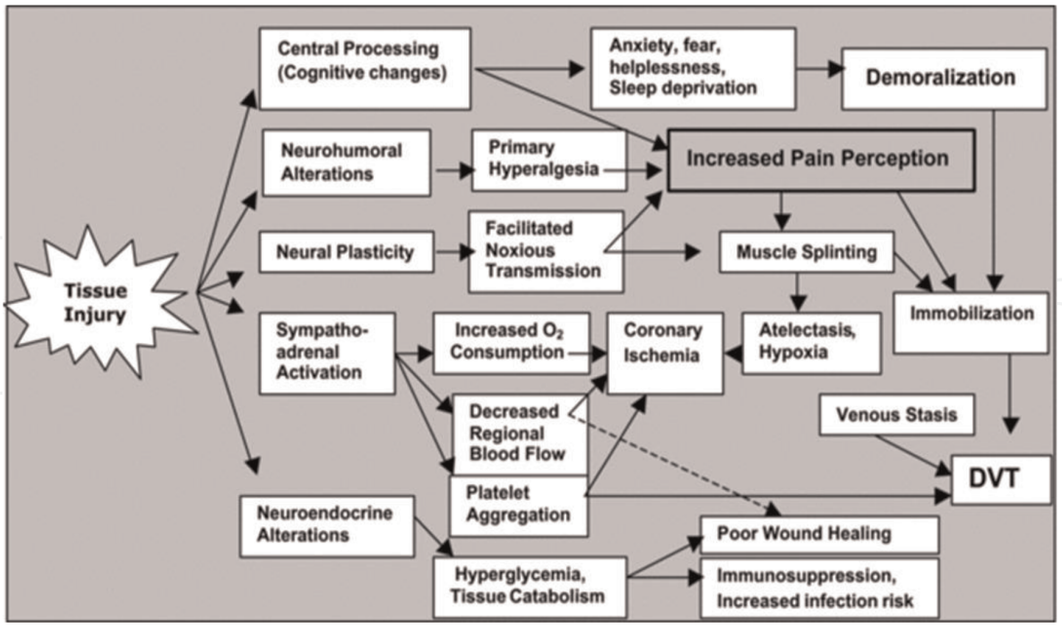

Figure 2.
Pathophysiology of postoperative pain [15].

4. Renal hypo-perfusion may occur, leading to activation of renin angiotensin aldosterone axis. Angiotensin released may further accentuate the redistribution by causing vasoconstriction and further hypoperfusion to injured tissue, skin, and visceral organs

5. Catecholamines, angiotensin, and other surgical-stress-related factors may release platelet fibrinogen activation and accelerate coagulation. In a patient with atherosclerosis, this may further reduce blood flow in critically stenosed vessels.

1.5 Neuroendocrine responses

Following tissue injury (the nociceptive impulses reach via the spinal cord and midbrain reticular formation), the neurogenic stimuli affect the hypothalamus, secretory target organs, or both and cause a neuroendocrine response [15, 16]. This is also called the stress response to injury and is characterized by increased secretion of catabolic hormones such as cortisol, glucagon, growth hormone, and catecholamines and a decreased release of anabolic hormones such as insulin and testosterone. This results in substrate mobilization, followed by hyperglycemia and a negative nitrogen balance. Associated changes include gluconeogenesis, glycogenolysis, proteolysis, and breakdown of lipid stores. These changes have short-term benefits of enhanced energy production; however, if this response is amplified or prolonged, catabolic aspects of stress response ensue, which can have a negative impact on the postsurgical outcome. The effects may be the following:

1. Protein loss leads to muscle wasting and fatigue.

2. Impaired immunity secondary to diminished immunoglobulin synthesis and impaired phagocytosis. The activated cells (secondary to nociception) in the preoptic region secrete pro-opiomelanocortin, which in turn facilities the release of ACTH, β-endorphin, and other anterior pituitary hormones. The trauma-related

release of IL-6 and IL-1 β can also increase ACTH and cortisol secretion. The relation between plasma IL-6 and cortisol levels is linear in postsurgical patients. The prolonged nitrogen balance and sustained secretion of glucocorticoids result in impaired wound healing, decreased immunity, and diminution in protein synthesis, which may inhibit cell division, production of collagen, and acute convalescence; in already debilitated individuals, this can cause postoperative infections.

3. The levels of β endorphin increase threefold, and this can lead to immunosuppression, complement release, decreased peripheral vascular resistance, and initiation of shock. Also, plasma levels of posterior pituitary-derived octapeptide and arginine vasopressin (AVP) rise and remain elevated for up to 5 days after surgery. AVP may cause postsurgical fluid retention, plasma hyperosmolarity, and oliguria. Pain transmission from the periphery to CNS produces complex neuroendocrine stress response involving hypothalamic, pituitary, adrenocortical, and sympathoadrenal interactions apart from the localized release of inflammatory mediators (leukotriene, cytokines, prostaglandins, TNF).

4. Endocrine response: There occurs increased secretion of ACTH, cortisol, glucagon, aldosterone, renin, and angiotensin-II, leading to increased levels of blood glucose, free fatty acids, ketone bodies, and lactate as part of the stress response. There occurs sodium and water retention. A hypermetabolic, catabolic state follows leading to negative nitrogen balance and protein catabolism leading to delayed convalescence and wound healing.

5. Coagulation: The stress response leads to a hypercoagulable state due to decreased levels of anticoagulants and increased levels of procoagulants, inhibition of fibrinolysis, increased platelet reactivity and increased plasma viscosity. This leads to hypercoagulable events such as deep vein thrombosis, vascular graft failure, and myocardial ischemia [17].

6. Immunological: There occurs immunosuppression due to stress response. Hyperglycemia contributes to depression of immune function and poor wound healing.

7. Cardiovascular: The activation of the sympathetic nervous system leads to increased myocardial oxygen consumption, coronary vasoconstriction, and decreased coronary vasodilatation leading to tachycardia, raised blood pressure, and contributing to myocardial ischemia, and infarction.

8. Gastrointestinal: The sympathetic overactivity may decrease gastrointestinal motility and contribute to the development of paralytic ileus.

9. Respiratory: The postoperative respiratory function is markedly decreased especially after upper abdominal and thoracic surgery. There is a spinal reflex-mediated inhibition of phrenic nerve activity leading to decreased postoperative pulmonary function. Patients with postoperative pain have shallow breathing and inadequate cough and are therefore susceptible to the development of postoperative pulmonary complications.

2. Preemptive analgesia and enhanced recovery after surgery

Surgery produces a biphasic insult on the human body. First of all, during surgery, there is trauma to the tissue followed by an inflammatory process at the site, which is also responsible for noxious input. Both these processes sensitize the pain pathways. They occur at a peripheral level where there is a reduction in the threshold of nociceptive afferents at a central level with increased excitation of spinal neurons involved in pain transmission. This concept has implications in acute postoperative pain management and has led to the concept of preemptive analgesia [18]. This concept states that the analgesic intervention preceding surgical injury is more effective in relieving acute postoperative pain than the same treatment following surgery. It works by preventing central sensitization in central nervous system to intense noxious stimuli, thus preventing pain hypersensitivity and hyperexcitability [18].

Enhanced recovery after surgery (ERAS) protocols are multimodal perioperative care plans intended to accelerate the recovery process after surgical procedures by maintaining preoperative organ function and reducing the intense stress response following surgery [19]. Initiated by Professor Henrik Kehlet in the 1990s, ERAS, enhanced recovery programs (ERPs) or "fast-track" programs have become an important focus of perioperative management. These programs are designed to curtail the physiological and psychological responses to major surgery leading to a reduction in postoperative complications and hospital stays, improvements in cardiopulmonary function, earlier restoration of bowel activity, and earlier recommencement of normal activities. The ERAS protocols help to improve the quality of perioperative care with aim of alleviating the loss of functional capacity and speeding up the recovery process [20].

For ERAS programs, optimal pain management plays a key role. The complex nature of nociception and mixed mechanisms of generating surgical pain is responsible for the failure of unimodal analgesia to adequately address postoperative pain, hence the need for multimodal analgesia. Multimodal analgesia includes using multiple strategies and analgesics acting at various points of the pain pathway to manage postoperative pain. These strategies include patient education; local anesthetics-based infiltration, peripheral nerve blocks, neuraxial analgesia, and a combination of analgesic drugs that act via different mechanisms on different receptors within the pain transmission pathway to provide synergistic effects, superior analgesia, and physiological benefits [11]. The multimodal, evidence-based, and procedure-specific analgesic regimens should be the standard of care to achieve optimal analgesia with minimal side effects and facilitate the achievement of important ERAS milestones such as early mobilization and oral feeding [20]. Thoracic epidural analgesia (T6–T11) remains the gold standard for postoperative pain control in patients undergoing open abdominal surgery. Initiation of neural blockade before surgery and its maintenance throughout the surgery decreases the need for anesthetic agents, opioids, and muscle relaxants [20]. Epidural analgesia provides better postoperative static as well as dynamic analgesia for the first 72 hours to accelerate the recovery of gastrointestinal functions, decrease insulin resistance, and impact positively cardiovascular and respiratory functions. Intra-thecal analgesia is a valuable analgesic technique to improve early postoperative analgesia and facilitate surgical recovery [20]. Opioid side effects are dose-dependent and can cause a delayed recovery. Opioid-sparing analgesic strategies such as regional anesthetic techniques should be implemented in a context of a multimodal analgesic regimen.

Continuous wound infusion of local anesthetics leads to improved postoperative analgesia and reduces opioid consumption; however, the effect on the recovery of

bowel function is unclear. The use of intravenous lidocaine infusion, abdominal truncal blocks, intra-peritoneal anesthetic, and multimodal approach using NSAID, COX2 inhibitors, and paracetamol decreases opioid consumption by 30% and dose-dependent side effects [20].

In ERAS, the attenuation and treatment of postoperative ileus are also important [20]. The prolonged ileus can be prevented by the use of opioid-sparing strategies, thoracic epidural analgesia, intravenous lidocaine, NSAIDs/COX-2inhibitors, ketamine, etc. The use of opioid antagonists such as alvimopan and metitrexone, the use of laxatives, and gum-chewing are useful strategies to reduce side effects related to opioids [20].

3. Assessment of pain

This step is vital for effective pain management. Pain assessment should be done during rest as well as during movement. The assessment should be done before and after every treatment to evaluate the effectiveness of the treatment. In conditions where the pain is intense or in the intensive care units, and surgical wards, pain assessment, treatment, and re-evaluation should be done frequently or at regular intervals. Documentation of pain and response to treatment and adverse effects on a vital sign sheet is very much essential for proper treatment. It facilitates proper communication between staff and also facilitates auditing and quality control. Special attention should be paid to patients who cannot communicate their pain, e.g., those who are cognitively impaired, pediatric patients, unconscious patients, etc.

3.1 Self-assessment tools

Patient self-report is the most useful tool and the gold standard, and one should always listen to the patients and believe what they say. Several patient self-assessment tools are available:

1. Facial expression (Faces scale): A pictogram of six faces with different facial expressions from a happy smiling face to a teary-eyed face is used to assess pain. This scale is useful where there is a communication problem such as pediatric patients, the elderly, or those patients who do not understand the local language.

2. Verbal Rating Scale (VRS): Patients are asked to rate their pain on a five-point scale as none, moderate, severe, and very severe.

3. Numerical rating scale (NRS): It consists of a 0–10 scale where 0 correlates to no pain and 10 to the worst possible pain.

4. Visual analog scale (VAS) consists of a graduated straight 100 mm line marked at one end with the term “no pain and the other end “worst possible pain.”

The VRS and NRS are used most frequently while VAS is used mainly as a research tool.

Postoperative pain control is often not isolated to the surgical site but includes other locations such as sore throat following intubation and also injection sites [21]. One approach is preparing a body map and marking the sites with pain and individual

Sub-scale	Description	Score
Facial expression	Relaxed	1
	Partially tightened	2
	Fully tightened	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Figure 3.
Behaviorial pain scale [24].

pain scores, but this is a tedious and impractical approach for the postoperative period. The multidimensional tools are under validation such as the Clinically Aligned Pain Assessment (CAPA) tool that measures five dimensions of pain including comfort, change in pain, pain control, functioning, and sleep [22]. It may improve assessment of pain in the postoperative period and leads to increased communication between patient and healthcare professionals and increases patient satisfaction levels [22].

For patients who are unable to self-report, e.g., dementia or patients who are unable to verbalize due to different reasons, standardized objective assessment tools have been designed and validated. One is the "Pain assessment in Advanced Dementia" (PAINAD) scale, the electronic pain assessment tool (e-PAT), Abbey pain scale, Dolopus-2, ADD Protocol, Observation Pain Behavioral tool, are some of the recommended tools for individuals with severe cognitive impairment [23]. Also Critical Care Pain Observation Tool and Behavioral Pain Scale are useful for pain assessment in patients who are unable to verbalize in critical care [23]. The surrogate measures such as opiate consumption may also be useful. The cardio-respiratory parameters are unreliable for pain assessment. The trends in pain assessment scores are more helpful than isolated pain scales [23]. An example of an assessment tool in non-verbal patients is illustrated in **Figure 3** [24]. This is the behavioral pain scale for assessing pain in critically ill patients on a ventilator [24]. A score of 0 indicates no pain, mild pain is indicated by a score of 0–3, moderate pain by a score of 3–6, and severe pain by a score of 6–8.

4. Goals of postoperative pain management

Effective pain management not only decreases patient suffering but also reduces morbidity. It also facilitates early recovery and discharge from the hospital and reduces treatment costs. The goals of proper pain management are to improve the quality of life, facilitate postoperative recovery, reduce morbidity and improve functional outcomes, reduce hospital stay, prevent chronic pain, and promote patient satisfaction [21].

4.1 Principles for acute perioperative pain management

Optimal perioperative pain management should done by charting out a pain management plan based on individual patient's needs. For this, one needs to evaluate every patient preoperatively to assess the medical history, presence of coexisting diseases, psychological conditions, history of chronic pain, substance abuse, and other concomitant medications [21]. A multimodal pain management plan, which includes pharmacological and non-pharmacological techniques, needs to be formulated based on the patient history. The patients and their families as well as the healthcare personnel need to be informed and educated regarding the pain management plan and its goals. In the postoperative period, tracking and documentation of pain are of utmost importance using an appropriate pain assessment tool. The medication and treatment technique should be altered based on the patient's response and the presence of any adverse events. Education of healthcare workers about proper storage, disposal, and record-keeping of opioids and tapering the doses after hospital discharge are important steps. Pain specialists may be consulted for patients with special needs and those with uncontrolled pain.

5. Treatment of acute postoperative pain

Several options are available for treating postoperative pain including systemic (opioid and non-opioid) analgesics, regional analgesic techniques, and non-pharmacological methods. By taking into account each patient's preferences and making an individualized assessment of the risk and benefits of each treatment modality, the clinician can optimize the postoperative analgesic regimen for each patient.

6. Opioid medications

The action of opioids is mediated through three types of opioid receptors, namely MOR (mu), DOR (delta), and KOR (kappa), with varying levels of affinity to each type of opioid receptor and also varying interactions with these receptors (agonists, partial agonists, antagonists). They exert analgesic effects, influence mood, and behavior, and affect respiratory, cardiovascular, gastrointestinal, neuroendocrine, and immune systems [25]. The analgesic efficacy of opioids is limited by the development of tolerance or due to side effects such as nausea, vomiting, pruritis, sedation, or respiratory depression. Opioids may be administered by subcutaneous, transcutaneous, transmucosal, or intramuscular routes, but the most important routes commonly employed are intravenous and oral. Opioids may also be delivered at specific anatomic sites such as intrathecal or epidural space. Long-acting opioids should be avoided in the immediate postoperative period except in patients who are already taking them before surgery [26]. When treating opioid-naïve adults, clinicians should avoid basal infusions with intravenous PCA, as it does not provide additional analgesia and is associated with nausea, vomiting, and respiratory depression [26].

7. Side effects of opioid medications

The side effects of opioids are depicted in **Table 2**. The commonly used opioids and their routes of administration, side effects, and management are described briefly

Common	Occasional	Rare
Gastrointestinal		
Nausea	Delayed gastric emptying	Biliary colic
Vomiting		
Constipation		
Neurological		
Sedation	Hallucination	Delirium
Drowsiness	Mood disturbance	Seizure
Cognitive dysfunction	Anxiety	Addiction
	Myoclonus	
Respiratory		
Cough reflex inhibition	Dry mouth	Respiratory depression
	Bronchospasm	Non cardiac pulmonary edema
Others		
Miosis	Pruritus	Hyperalgesia
	Muscle rigidity	Allodynia
		Tolerance
		Physical dependence

Table 2.
Side effects of opioids [27].

in **Table 3**. The incidence of life-threatening adverse events, such as respiratory depression, is rare and occurs within 24 hours. A systematic review of observational studies reported the incidence of postoperative opioid-induced respiratory depression as five in 1000 [27]. Also, those with preexisting cardiac disease, pulmonary disease, and obstructive sleep apnea are at increased risk of opioid-induced respiratory depression [27]. Other common side effects of opioid administration are sedation, dizziness, nausea, vomiting, constipation, physical dependence, and tolerance. Physical dependence and addiction are important concerns that can act as a barrier to pain management. Less common side effects are delayed gastric emptying, hyperalgesia, immunologic and hormonal dysfunction, muscle rigidity, and myoclonus. The most common side effects of opioids are constipation and nausea, which are difficult to manage. Mostly tolerance does not develop in them, especially to constipation. This may lead to discontinuation or under-dosing and inadequate analgesia.

8. Non-opioid medications

These have been enlisted and described briefly in **Table 4** and are discussed as follows.

a. **Acetaminophen (Paracetamol):** It is used most often in conjunction with other medications as a part of multimodal analgesia protocol [16]. When used as a part of multimodal analgesia, it leads to faster recovery, higher levels of

Opioid	Route of administration with sample dosing	Side effects (Adverse reactions)	Cautions/ contraindications
Morphine	• IV 2–5 mg prn every 1–2 hours • IM/SC 5-10 mg every 4 hours or prn every 2 hours • Epidural: 2–4 mg (preservative free) • Spinal: 0.1–0.3 mg (preservative free)	• Hypotension • Bronchospasm • Pruritus • Nausea/vomiting • Confusion, agitation	Side effects also with neuraxial administration
Codeine Available alone or in combination with acetaminophen	PO 30–60 mg every 4 hours maximum 240 mg/day	• Nausea and vomiting • Drowsiness • Confusion, agitation • Constipation	To be avoided in renal and hepatic dysfunction
Fentanyl	• IV bolus: 0.001–0.005 mg/kg (can be titrated up to 0.05 mg/kg) • Epidural: 0.025–0.1 mg (diluted in local anesthetics or saline) • Spinal: 0.005–0.2 mg	• Respiratory depression • Epidural/spinal administration: pruritus and delayed respiratory depression	Muscle rigidity with high doses, Smaller doses needed in elderly
Tramadol	• PO 50–100 mg every 4 hours • IV/IM slowly 50–100 mg every 4 hours • Do not exceed 400 mg /day	Nausea, dizziness, dry mouth	• 30% of effect reversible with naloxone • Should not be used with drugs that increase serotonin
Tapentadol	PO 50–100 mg every 4–6 hours (short acting preparations) or every 12 hours (long-acting preparations)		• Should not be used along with drugs that increase serotonin • To be avoided in renal dysfunction
Hydrocodone	• P.O 5–10 mg every 6 hours (short-acting) • P.O 20 mg once daily(long-acting) • Intravenous/subcutaneous		• QTc interval prolongation in higher doses • (>160 mg/day) • Caution in renal dysfunction
Oxycodone Available alone or in combination acetaminophen	• P.O 5 mg every 4 hours (short-acting) • P.O 10 mg every 12 hours (long –acting)		Caution in renal dysfunction
Oxymorphone	• P.O 5 mg every 4 hours (short-acting) • P.O 5 mg every 12 hours (long –acting)		• To be taken on empty stomach for increasing bioavailability • Cautious use in renal dysfunction
Hydromorphone	• P.O 5 mg every 4 hours (short-acting) • P.O 8 mg every 24 hours (long –acting) • IV/SC: 0.5–1 mg every 4 hours		Caution in renal dysfunction

Table 3.
Commonly used opioids for acute pain: Routes of administration, side effects, and contraindications [28, 29].

Drug	Routes of Administration and Sample Adult dosage	Side effects/Adverse reactions	Cautions/ contraindications
Paracetamol/ Acetaminophen. Centrally acting Non-opioid analgesic	PO 0.5–1 gm./4 hours i.v, maximum dose 4gm./ 24 hours	Potential for hepatotoxicity when exceeding recommended dose	Neonates. History of G6-PD deficiency
Nefopam: Non-opioid, non-steroid, centrally acting	IV slow 20 mg every 4–6 hours not exceeding 120 mg/day	Nausea, vomiting, tachycardia, pain at the injection site, rare-hallucinations, convulsions, pruritis, etc.	In patients receiving medications which increase serotonin (MAOIs, SNRIs, SSRIs, TCAs, Pethedine and tramadol)
Diclofenac (NSAID)	PO-25–50 mg/8 hours, Deep I.M 75 mg/day, 25–50 mg IV infusion in 15–60 minutes, 6 mg/hour, maximum of 150 mg/day	Inhibits platelet function, causes gastric ulcers or upper GI bleeding, bronchospasm, tinnitus, water retention, acute renal failure in patients with pre-existing renal impairment	Contraindicated in aspirin allergy, asthma, severe renal impairment, gastric ulcers
Ketorolac (NSAID)	Normal adult dosage 30 mg IV once daily or 30 mg iv every 6 hours (not exceeding 120	Same as Diclofenac	Similar to other NSAIDs, Concurrent anticoagulants, antiplatelet or any other condition. Not to be used intraoperative in cases with expected massive bleeding
Naproxen (NSAID)	Po 250 m–500 mg	Same as Diclofenac	Same as other NSAIDs
Parecoxib (NSAID-selective COX-2 inhibitor)	IV/IM initial dose of 40 mg followed by 20–40 mg every 12 hours (not exceeding 80 mg /day)	Water retention. Acute renal failure in patients with pre-existing renal impairment or dehydration	Same as other NSAIDs. Allergies to sulphonamide or aspirin, heart failure, coronary artery disease cerebrovascular disease. Previous CABG or coronary stent pregnant or lactating women. Uncontrolled hypertension
Etrocoxib (NSAID selective COX-2 inhibitor)	PO 60–120 mg/day, 120 mg for acute pain - not to be continued for more than 8 days	Water retention. Acute renal failure or previous renal impairment	Same as parecoxib
Gabapentinoids	Gabapentin:300–1200 mg preoperatively an hour before surgery. Pre-gablin 75–300 mg	Dizziness, Visual disturbances, Ataxia	Caution in elderly patients and in those with co-morbidities.
Ketamine NMDA antagonist	0.3–0.5 mg /kg/hour bolus. 0.1–0.2 mg/kg/hour infusion	Hyper salivation, nausea and vomiting, and psychotomimetic effects - vivid dreams, blurred vision, hallucinations, nightmares and delirium. Prevents CPSP	Not to be used as part of ERAS regime. Caution in liver disease, coronary – artery disease, psychiatric conditions

Table 4.
Non-opioid group of drugs for postoperative pain management [28].

satisfaction, fewer opioid adverse effects, and a decrease in the length of hospital stay. A statistically significant decreased mean consumption in mean cumulative 24-hour morphine consumption is observed with paracetamol compared with placebo after major surgery. When given prophylactically, it is associated with lesser postoperative nausea and vomittimg, and this is postulated to be due to superior pain control.

b. **Nefopam**: It is a non-opioid, centrally acting analgesic drug [30]. It acts through centrally mediated nociceptive activation of triple monoamine descending inhibitory pathways. Its anti-hyperalgesic properties are due to its modulatory effect on glutaminergic transmission. Because of this property, it can be used for neuropathic pain besides treatment of acute nociceptive pain. When used as a part of a multimodal regime, it has opioid-sparing effects. It has no adverse effects on respiratory and hemostatic functions and has no antipyretic properties. It can cause sweating, nausea, vomiting, malaise, hallucinations, convulsions, pruritis, erythema, urticaria, etc. [30] Cautious use is needed in patients receiving medications that increase the serotonin levels [30].

c. **Non-steroidal Anti-inflammatory Drugs (NSAIDs):** The primary mechanism of action of NSAIDs is the inhibition of cyclooxygenase (COX) and inhibition of the synthesis of prostaglandins, which are the primary mediators of peripheral sensitization and hyperalgesia. They can also exert their effect through inhibition of spinal COX [11]. There are two isoforms of COX, i.e., COX 1 and COX 2. Recently, COX 3 variant has been described, which may have a role in the central action of NSAID'S. There are two types of NSAIDs: non-selective inhibitors and selective COX-2 inhibitors. Selective COX-2 inhibitors provide anti-inflammatory relief without compromising gastric mucosa integrity. The commonly used non-selective NSAIDs are diclofenac, naproxen, ketorolac, ibuprofen, sulindac, etc. The commonly used selective COX-2 inhibitors are celecoxib, etoricoxib, parecoxib, etc.

Used as sole agents, NSAIDs generally provide effective analgesia for mild to moderate pain. NSAIDs are also traditionally considered useful adjuvants to opioids for the treatment of moderate to severe pain. NSAIDs may be given orally or parenterally and are particularly useful as a component of a multimodal analgesia regimen.

a. **Gabapentinoids:** Gabapentin and pregabalin are antiepileptic drugs, also used in the treatment of neuropathic pain. These drugs cause depressed neuronal excitability due to the interaction with the α2δ calcium channel subunit. Also, there is enhanced descending inhibition and diminished descending serotonergic facilitation and modulation of the affective component of pain [25]. While prior studies [31] showed that there was a reduction in postoperative narcotic requirements with the benefits of decrease in the risk of postoperative nausea and vomiting. Recent meta-analysis however, showed no clinically significant improvement in pain relief with gabapentinoids [27]. However, there was a greater risk of dizziness and visual disturbance. A large range of the doses have been reported, ranging from 300 to 1200 mg for gabapentin and from 75 to 300 mg for pregabalin, given either preoperatively or postoperatively [31].

b. **Ketamine:** Ketamine is generally used as an intraoperative anesthetic agent. But, in subanaesthestic doses, it is a useful analgesic.The NMDA antagonistic properties of ketamine are responsible for attenuating central sensitization and opioid tolerance. The subanaesthetic dose of ketamine reduces the rescue analgesia requirement and pain intensity. In addition, perioperative ketamine reduces 24-hour patient-controlled analgesia (PCA) morphine consumption and postoperative nausea and vomiting and has minimal adverse effects. The side effects of ketamine are: hypersalivation, nausea, and vomiting, psychotomimetic effects such as vivid dreams, blurred vision, hallucinations, nightmares, and delirium. These act as deterrent to its routine use as an analgesic. Ketamine also reduces the likelihood of transition to chronic postsurgical pain. Although ketamine can be used effectively as part of a multimodal pain management regime currently, it is not recommended as a routine part of most ERAS postoperative pain strategies [2].

Patient-controlled analgesia (PCA): It is based on the idea that whenever the patient has pain, the patient can self-administer the analgesic drug, without having to request and wait for the healthcare staff [32]. PCA is useful in the acute pain setting where there is inadequate pain control from the initial opioid administration in the emergency department, and continued opioid dosing has been proven to improve patient outcomes [32]. Postoperative patients, especially those with indwelling nerve or epidural catheters, are ideal candidates for PCA. The ability of postsurgical patients to titrate and administer their pain medication allows for superior pain control compared to scheduled nurse dosing. Patients in labor pain are also well-established candidates for epidural PCA [32]. The pain associated with contractions, when exacerbated by induction agents such as oxytocin, can be adequately reduced and controlled by the patient [32]. A PCA device can be programmed for several variables such as demand dose (bolus), lockout interval, and background infusion. Compared to traditional analgesic regimens, PCA provides superior postoperative analgesia and improves patient satisfaction. Local anesthetics and opioids are commonly used medications for PCA. For intravenous PCA, opioids can be used as the sole analgesic. For epidural PCA, they are used or in combination with local anesthetics.

Opioids commonly used for PCA are: The pure Mu opioid receptor agonists (morphine, fentanyl, hydromorphone, meperidine, sufentanil, alfentanil, and remifentanil), Mu opioid receptor agonist-antagonists (butorphanol, nalbuphine, and pentazocine), and partial Mu opioid receptor agonists (buprenorphine, dezocine) [32]. Despite the availability of several analgesics, morphine is still considered the gold standard for PCA. The local anesthetics used for epidural analgesia and indwelling nerve catheter PCA are: bupivacaine, levobupivacaine, and ropivacaine [32]. Other medications added to intravenous PCA in order to reduce side effects and improve pain control include: ketamine, naloxone, clonidine, magnesium, ketorolac, lidocaine, and droperidol [32].

The opioid dosing is depicted in **Table 5**. However, the medication dose, which is given in PCA, must be tailored according to individual patients' analgesic needs. The patients should be oriented, alert, and demonstrate the ability to administer the demand dose for pain. The basal or continuous infusion is started if the patients are using frequent demand doses or if the pain is severe. The suggested basal dose is 30–50% of the average hourly dose [29]. For opioid-tolerant patients, one should consider the patient's current opioid regimen, clinical condition (cause and its severity), side effects from opioids, baseline sedation, and need for opioid rotation. First,

Opioid	Demand(PCA) dose	Lock-out interval (minutes)	1-hour dose limit	Continuous dose	Nurse bolus prn	Nurse bolus interval (hours)
Morphine	1 mg (0.5–2.5 mg)	10–30 minutes	4 mg	30–50% of hourly dose	2–4 mg	2
Hydromorphone	0.2 mg (0.1–0.5)	10–30	0.8 mg		0.5–1 mg	2
Fentanyl	10mcg (5–25)	10–30	40mcg		25mcg	2

Table 5.
Intravenous patient-controlled analgesia for opioid-naïve patients [29].

the total opioid dose used in the previous 24 hours is estimated, and then an equianalgesic opioid conversion table is used for calculating the IV dose of opioid intended for use in PCA. The hourly dose is the new IV dose from this step divided by 24 hours to obtain the basal/hourly dose. The PCA demand dose is 10–20% of this new opioid dose as PRN every hour [29].

9. Neuraxial analgesia

The analgesia provided by epidural is site-specific and superior to that with systemic opioids. The use of this technique may even reduce morbidity and mortality [10].

1. **Single-dose neuraxial opioids:** Administration of a single dose of opioid may be efficacious as a sole analgesic or as an adjuvant, when administered intrathecally or epidurally. The hydrophilic opioids: morphine and hydromorphone tend to remain in CSF and produce delayed analgesia with a longer duration of effect. However, they cause more frequent side effects because of the cephalic or supraspinal spread. Neuraxial administration of lipophilic opioids such as fentanyl and sufentanil provides quick onset of analgesia. Their rapid clearance from CSF leads to less incidence of side effects such as respiratory depression.

2. **Continuous epidural analgesia:** Analgesia delivered through an indwelling epidural catheter is a safe and effective method for management of acute postoperative pain. Analgesia through the epidural route can provide analgesia superior than the systemic opioids. Intraoperative use of epidural with general anesthesia results in less pain and faster recovery than general anesthesia followed by systemic opioids [15, 18].

9.1 Analgesic drug for epidural

1. **Local anesthetics:** Epidural infusion of local anesthetics alone may be used for postoperative analgesia, but provides better analgesia when given in combination with opioids.

2. **Opioids:** Opioids used alone for postoperative epidural infusion do not cause motor block or hypotension from the sympathetic blockade [18]. Analgesic site of action for continuous hydrophilic opioids is primarily spinal. It is useful when the epidural insertion is not congruent with the surgical site. Continuous epidural

infusion of morphine may provide superior analgesia with fewer side effects compared to intermittent doses.

Local anesthetic and opioid combinations: The epidural infusion of LA-opioid combination is advantageous than the infusion of LA or opioid alone. This combination provides superior postoperative analgesia, limits time for regression of sensory blockade, and decreases the dose of local anesthetic. Continuous epidural analgesia of LA-opioid combination provides superior analgesia than the intravenous patient-controlled analgesia with opioids [14].

Patient-controlled epidural analgesia (PCEA): Like intravenous PCA, PCEA allows individualization of postoperative analgesia requirements and may have several advantages over continuous epidural infusion, including lower drug use and better patient satisfaction. PCEA may also provide analgesia superior to than intravenous PCA [15]. PCEA is a relatively safe and effective technique for postoperative analgesia.

The drug doses for continuous epidural infusion and PCEA drug doses are given in **Table 6**.

Adjuvant drugs: A variety of adjuvants may be added to epidural infusion to enhance analgesia while minimizing side effects. Clonidine acts centrally as an agonist on alpha-2a adrenergic receptors [33]. Clonidine also mediates its effects through the spinal dorsal horn alpha-2 receptors via the primary afferents, interneurons, and through the descending noradrenergic pathways. Clonidine enhances the analgesic activity of opioids and local anesthetics and prolongs the duration of blocks [33, 34]. Two proposed mechanisms for the analgesic effects produced by clonidine include the reduction of glutamate and excitatory neuropeptide release from central afferent terminals, as well as the hyperpolarization of dorsal horn neurons [33]. Epidural dose of clonidine is 5–20 micrograms/hour. Its side effects are hypotension and bradycardia [1].

Location of epidural catheter: The insertion of an epidural catheter congruent to incision dermatome results in optimal postoperative analgesia with lesser side effects (lower extremity block, urinary retention) and a decrease in morbidity [10, 18]. There is a summary of neuraxial opioids, their adverse effects, and management of same in **Table 7**.

	Epidural Analgesia	**Dose for continuous infusion (lumbar/thoracic)**	**Patient controlled analgesia (lumbar/thoracic)**	**Continuous peripheral nerve analgesia**
Ropivacaine OR	0.2% (2 mg/ml)	6–12 ml/hour	Background 4–6 ml/hour Bolus dose 2 ml (2–4 ml) Minimum lockout interval – 10 minute Recommended max. Hourly dose (bolus + background) = 12 ml	0.2%
Bupivacaine OR	0.1–0.2% (1–2 mg/ml)			0.1 to 0.125%)
Levobupivacaine	0.1 to 0.2% (1–2 mg/ml)			0.1 to 0.2%
			Type of block	
			Interscalene /Infraclavicular	5–9 ml/hr.
			Axillary	5–10 ml/hr.
			Femoral	7–10 ml/hr.
			Popliteal	3–7 ml/hr.

Table 6.
Local anesthetics dose for postoperative patient controlled anaesthesia [28].

Adverse reactions	Risk factors	Evaluation	Treatment
Respiratory depression/ Sedation	• Opioid naïve Extremes of age, Obesity, Preexisting respiratory disease • Obstructive sleep apnoea • Concurrent use of sedatives	Respiratory route < 10 min. Sedation score > 2	Supplemental oxygen, open airway. Naloxone IV 0.4–0.2 mg every 2–3 minutes (till awake or normal respiration) Followed by infusion in patients on long acting opioids –dose- 2-5 mcg/ kg/hour titrate as per response
Hallucination/ delirium/ cognitive failure	High dose, depression, drug abuse, elderly, preexisting cognitive impairment Impaired liver/ renal function	Rule out other causes and side effects of other drugs	• Decrease dosage • Opioid rotation • -Major or minor tranquilisers • Haloperidol 2–5 mg IM every 4–8 hours
Rigidity/ myoclonus/ seizures	• High dose • Preexisting epilepsy • Neurotoxity from M3G norpethidine or tramadol		• Opioid rotation to opioids with inactive metabolites • Lorazepam PO 0.5–1 mg BID • Clonazepam PO 0.5-1 mg • Baclofen 10mgBID-TID
Nausea/ vomiting	Female, history of nausea/ vomiting	Rule out other causes	• Pre-emptive anti-emetics, • Opioid rotation • Anti-emetics
Pruritus			• Diphenhaydramine 25 mg i.v OR • Nalbuphine 1-5 mg i.v OR • Naloxone 0.25–2 mcg/kg/ hour
Urinary retention	Common with neuraxial opioid	Evaluate for full bladder and urinary voiding every 1–2 hours postoperatively	Cold pack, catheterization, Naloxone 0.001–0.002 mg/kg IV titrate according to clinical response
Constipation			• Stool softeners, stimulants like • Bisacodyl 1–2 tablets HS • Lactulose 30 ml HS • Milk of magnesia 30 ml HS TID

Table 7.
Adverse reactions from neuraxial opioids and treatment.

10. Regional analgesia

The use of peripheral nerve blocks (PNBs) as a single injection or as continuous infusion can provide site-specific analgesia superior to the systemic opioids and may even result in improvement in various outcomes [14]. The PNBs may have several advantages over systemic opioids (i.e., good analgesia and lesser opioid-related side effects) and neuraxial techniques (i.e., less risk of spinal hematoma, better hemodynamic instability). All this can lead to faster recovery, reduced stay in the hospital, decreased incidence of nausea and vomiting, early rehabilitation, and greater patient satisfaction [34]. Absolute contraindications to the use of peripheral nerve blocks

include allergy to local anesthetics, inability to cooperate due to dementia or similar conditions, or patient refusal. PNBs should not be given if there is an active infection at the injection site, or if there are preexisting neural deficits in area of distribution of the block, and in patients with coagulopathies or on antithrombotic drugs [35].

11. Upper extremity blocks

The regional blocks can be given using a nerve stimulator or ultrasound visualization for locating the nerves. The nerve stimulator causes muscle contractions when the corresponding nerve is stimulated. Commonly used local anesthetics include bupivacaine and ropivacaine. Once the local anesthetic is placed, the patient can expect pain relief and limb heaviness for the duration of the local anesthetic action and adjuncts used [36].

- **Interscalene block**: The interscalene block covers most of the brachial plexus; however, the ulnar (C8-T1) nerve is spared [36]. It is useful for patients undergoing surgery of the shoulder, upper arm, and elbow. It is not an effective block for hand surgery as the inferior trunk is spared. This block is contraindicated in patients who have respiratory disorders because of higher possibility of ipsilateral phrenic nerve block resulting in diaphragmatic hemiparesis. This can lead to a 25% reduction in pulmonary function. Furthermore, the recurrent laryngeal nerve may be blocked, which could result in incomplete airway obstruction if there is already an existing vocal cord palsy.

- **Supraclavicular block:** The indications for supraclavicular block are: the surgeries of the distal two-thirds of the upper extremity, and surgeries from the mid-humerus to the fingertips [37]. Sparing of distal branches, especially the ulnar nerve, can occur. Besides the general contraindications applicable to PNBs, caution is advised for patients with severe pulmonary disease as local anesthesia spread can cause diaphragmatic paresis or pneumothorax [37].

- **Infraclavicular block**: It is indicated for postoperative pain control for upper extremity surgeries such as the elbow, forearm, wrist, and hand, and when positioning is restricted due to limited abduction at the shoulder [38].The shoulder area may be spared since the superficial cervical plexus C1–C4 innervates it. The skin of the axilla and proximal medial arm requires an additional intercostobrachial nerve block to provide full anesthesia. There may also be an incomplete radial nerve sensory block [38]. The infraclavicular block has the advantages that pneumothorax can be avoided and that it is suitable for catheter usage. The disadvantage is that the brachial plexus is located deeper and the angle of approach is more acute making it challenging unless the anesthesiologist is experienced in performing it [38]. The procedure is also challenging in patients with obesity for the same reasons.

- **Axillary block**: provides surgical anesthesia for elbow, forearm, and hand procedures, cutaneous anesthesia for superficial procedures of the inner part of the arm.The block anesthetizes the nerves of the brachial plexus at the level of the individual nerves [39]. The axillary approach is the safest of the four approaches, as it does not cause the blockade of the phrenic nerve. Also, it does not have the

potential to cause pneumothorax, making it an ideal option for day -case surgery [39]. However, the general risks of accidental intravascular and intraneural injection still exist.

- **Intercostobrachial block:** The intercostobrachial nerve arises from the second thoracic nerve root. It is not a component of the brachial plexus and therefore, cannot be given by any brachial plexus approach [40]. For this block, the patient is positioned supine with the arm abducted to expose the axillary fossa. The intercostobrachial nerve is located in the subcutaneous tissue of the medial portion of upper arm. For this block, the needle is advanced subcutaneously, across the medial aspect of the arm while injecting 5–10 cc of local anesthetic [40].

- **Radial nerve block**: The radial nerve comes out between the brachioradialis tendon and the radius, just proximal to the styloid process [41]. The needle is inserted subcutaneously, just proximal to the styloid process of the radius, aiming medially, and 3–5 cc of local anesthetic is injected. A radial nerve block will provide anesthesia and/or analgesia to the dorsal radial side of the hand. This includes anesthesia dorsally to the thumb, index and middle fingers, and the lateral aspect of the ring finger [41]. It is used as a sole or adjunctive therapy for interventions of the hands and fingers, for the management of acute pain in the radial nerve's distribution, for the diagnosis and treatment of radial tunnel syndrome, and for the diagnostic prognostication procedure in injury to the radial nerve [41].

- **Median nerve block:** The median nerve is located between the tendons of the flexor palmaris longus and the flexor carpi radialis [42]. The needle should be inserted between the two tendons until it passes through the fascia, and it is to be moved further until it touches the bone. The needle direction should then be changed in a way that the local anesthetic is injected in lateral and medial directions. A median nerve block is a simple, safe, and effective procedure. It provides analgesia to the palmar aspect of the thumb, index finger, middle finger, the radial portion of the palm, and ring finger [42].

- **Ulnar nerve block**: The ulnar nerve runs between the ulnar artery and flexor carpi ulnaris tendon, which is just superficial to the ulnar nerve [43]. The block is administered by placing the needle under this tendon close to its attachment, just above the styloid process of the ulna, and by moving further for 5 mm to 10 mm. A total of 3–5 cc of local anesthetic is injected at this location. It is used for surgical procedures in the distribution of the ulnar nerve either as a sole block or combined with ulnar or radial nerve blocks for a complete hand block. It can act as a rescue for inadequate brachial plexus blocks. An ulnar nerve block is used as an alternative to sedation for painful procedures such as fracture reduction and to provide pain relief in burns [43].

12. Lower extremity blocks

- **Lumbar plexus block:** The lumbar plexus (LP) is formed within the body of the psoas major muscle by the four spinal nerves of L1–L4. In 60% of people, the lumbar plexus receives a contribution from the nerve root of T12 as well [44].

The LPB is used to provide analgesia following injuries or surgeries of the hip or thigh (e.g., acetabular fractures, femoral neck or mid-shaft fractures, hip replacement, hip arthroscopy, knee replacement). It has also been used for chronic pain conditions such as herpes zoster. It is important to note that the LPB is unlikely by itself to produce complete anesthesia for hip replacement surgery due to the innervation of the posteromedial hip capsule deriving from branches of the sacral plexus and sciatic nerve [44].

- **Femoral nerve block:** The femoral nerve is one of the largest branches of the lumbar plexus. The femoral nerve arises from the ventral rami of the L2, L3, and L4 spinal nerves and is located in the femoral triangle inferior to the inguinal ligament. The femoral nerve is the most lateral of the structures within the triangle, which also contains the femoral artery and femoral vein at its medial end [45]. The femoral nerve block is useful for anterior thigh and knee procedures [45].

- **Fascia iliaca compartment block:** This block is considered an anterior approach to the lumbar plexus where local anesthetic (LA) is injected proximally beneath the fascia iliaca. In this, there occurs blockade of the femoral nerve (FN), obturator nerve (ON), and lateral cutaneous nerve of the thigh (LCNT) simultaneously [46]. Unlike the FN block, the needle is not placed adjacent to the FN, thus reducing the risk of neuropraxia. Indications for FICB include perioperative analgesia for fractured neck of femur, hip and knee surgery, above knee amputation, and application of plaster cast to femoral fracture in pediatric patients. Complications include block failure, hematoma, neuropraxia, local anesthetic systemic toxicity (LAST), quadriceps weakness, perforation of peritoneal cavity contents, and bladder puncture [46].

- **Obturator nerve block:** An ONB is performed commonly to prevent thigh adductor jerk during transurethral resection of bladder tumor, to provide analgesia for knee surgery, to treat hip pain, and to improve persistent hip adductor spasticity [47].The proximal approach comprises a single injection of local anesthetic into the interfascial plane between the pectineus and obturator externus muscles. The proximal approach may be superior for reducing the dose of local anesthetic and providing successful blockade of the obturator nerve, including the hip articular branch, when compared with the distal approach.

- **Sciatic nerve block:** The sciatic nerve originates from the sacral plexus (L4-S3) and provides most of the motor and sensory innervation to the leg: [48] The sciatic nerve is an important major nerve of the lower extremity, supplying the vast majority of the motor and sensory function to the lower limb. It is the motor nerve for the posterior thigh and all muscles below the knee. Sensory function is provided to the posterior thigh, posterior knee joint, and everything below the knee, except a narrow band on the medial lower leg, supplied by the saphenous nerve. The long course of the sciatic nerve, from the sciatic notch in the gluteal region to the popliteal fossa, allows for multiple possible sites for an anesthetic blockade.

- **Popliteal nerve block:** The popliteal nerve block is a block of the sciatic nerve in the popliteal fossa with the patient lying in a prone position. The block is useful for surgeries of the lower leg, particularly the foot and ankle. It anesthetizes the same dermatomes as both the anterior and lateral approaches to the sciatic nerve [48].

- **Saphenous nerve block**: The saphenous nerve block is indicated for procedures related to the lower leg or foot along its neural distribution [49]. It is most commonly used in conjunction with a popliteal sciatic nerve block to provide complete anesthesia of the lower leg for various surgical and nonsurgical procedures.

- **Pericapsular nerve group block**: The pericapsular nerve group (PENG) block is an interfascial plane block used for blocking the articular branches supplied by femoral, obturator, and accessory obturator nerves. PENG block is useful in anterior and lateral hip arthroplasties and hip fractures. It is performed with the patient in a supine position by depositing 15–20 ml of local anesthetic in the plane between the psoas tendon and the pubic ramus under direct ultrasound visualization [50]. The main advantage of PENG block is that it provides better analgesia of the hip without causing any motor block. As there6is no muscle weakness so the patient can participate in physical therapy early [50].

- **Femoral nerve block, fascia iliaca compartment block or lumbar plexus block** has been used to manage postoperative analgesia in hip surgeries. These blocks cause the weakness of quadriceps muscles, and hence, the patients are predisposed to falling. These blocks also result in incomplete analgesia to the hip as there is a sparing of few articular branches to the hip [44, 45].

- **iPACK block**: IPACK block is an acronym for infiltration of local anesthetic into the interspace between the popliteal artery and the posterior capsule of the knee and was first introduced in 2012 [51].The iPACK block is used for postoperative analgesia in total knee arthroplasties and cruciate ligament repair. Posterior knee sensory supply is through the articular branches of the tibial nerve with contributions from the obturator nerve. In the iPACK block, 15–20 ml of local anesthetic is injected under ultrasound guidance in the tissue plane popliteal artery and posterior aspect of the capsule of the knee joint. The main advantage of the iPACK block is that it is a motor-sparing block and does not result in foot drop or loss of sensorimotor function of the leg and foot [51].

13. Truncal blocks

Several non-epidural/truncal regional analgesia techniques can be used for management of postoperative thoracic and abdominal pain. Truncal blocks include the blocks of chest wall and anterior abdominal wall. The chest wall blocks are thoracic paravertebral, intercostal blocks, pectoral blocks, serratus anterior plane block, suprascapular, interpleural analgesia, and cryoanalgesia. The blocks of anterior abdominal wall are transverses abdominis plane block (TAP), rectus sheath block, quadrates lumborum blocks, erector spinae blocks, ilioinguinal, iliohypogastric nerve [52]. The ultrasound-guided regional blocks have revolutionized the management of perioperative pain. The unique feature of this is that no nerve or plexus needs to be identified. The local anesthetic is injected into a particular muscle plane, which spreads and reaches the intended nerves. The current research is leading us to an era where ultrasound will become a basic necessity for practice of regional anesthesia [52].

13.1 Chest wall blocks

- **Thoracic paravertebral blocks**: have been used for thoracic, breast, upper abdominal surgery and treatment of rib fracture pain. The paravertebral space lies on either side of the vertebral column. The thoracic paravertebral space (TPVS) is continuous with the intercostal space laterally, epidural space medially, and contralateral paravertebral space via the prevertebral and epidural space [53].The classical technique involves contacting the tranverse process of the vertebra, walking the needle above it, and gradually advancing it till there is a loss of resistance. A pressure measurement technique can also be used. Pressure in the erector spinae muscle is higher in inspiratory phase than expiration. Once the superior costotranseverse ligament is traversed and TPVS is entered, the pressure inversion occurs and expiratory pressure is higher [53]. Other approaches are medial approach and paravertebral-peridural block technique [53]. The local anesthetics can be administered as a single injection or as a continuous infusion through a catheter. This block may provide analgesia equal or superior to that of thoracic epidural and is a valuable alternative to thoracic epidural [18, 19].

- **Intercostal blocks:** These are used for pain management in the chest wall for conditions such as incisional pain, thoracotomy, herpes zoster, rib fracture, breast surgery, and upper abdominal surgery [54]. The block is given by walking off the needle along the inferior border of the rib and advancing 1–3 mm anteriorly where a give way or "pop" is felt as it advances through the fascia of internal intercostal muscle, and then 3–5 ml of local anesthetic is injected after negative aspiration [54]. Ultrsound-guided block decreases the possibility of pneumothorax, allows administration of LA before the division of lateral branch, which is necessary to achieve anesthesia of the entire dermatome [54]. The block is simple, but one needs to be careful to avoid pneumothorax and intravascular injections of LA [54]. If multiple blocks are to be given, the concentration should be reduced and total dose of LA should be calculated to avoid toxicity.

- **Serratus anterior plane block:** It is indicated in pain management of thoracoscopy, thoracotomy, and breast surgery and in rib fractures (effective in lateral rib fractures and ineffective in anterior and posterior rib fractures) [55]. Superficial serratus anterior plane block is given under ultrasound guidance by injecting LA anterior to the serratus anterior muscle and for the deep SAPB, the local anesthetic is injected anteriorly to the rib and deep to the serratus anterior muscle [55].The SAPB targets the lateral cutaneous branches of the thoracic intercostal nerves, which run inferior to each rib at mid-axillary line, they run through the intercostal muscles and serratus anterior muscle, innervating the musculature of lateral thorax [55].

- **Pectoralis nerve block**: The pectoral nerve blocks: PEC 1 block and PEC2 block, are novel techniques to block the pectoral nerves, intercostal nerves 3–6, intercostobrachial nerves, and the long thoracic nerves. These blocks are useful for surgeries such as insertion of breast expanders, submuscular prostheses, ports, pacemakers, implantable cardiac defibrillators, anterior thoracotomies, sentinel node biopsy, and axillary dissection [56].The PEC1 block is given under ultrasound guidance in the fascial plane between pectoralis major and minor muscle, while PEC2 is an extension of PEC1 with second injection being given in

the plane between pectoralis minor and serratus anterior muscles often at the level of third rib [56].

13.2 Blocks of anterior abdominal wall

- **Transversus abdominis plane block** is an approach for blocking the abdominal wall neural afferents to provide postoperative analgesia to the parietal peritoneum, skin and muscles of the anterior abdominal wall. The transversus abdominis plane compartment can be sited with landmarks or ultrasound guidance or identified intraoperatively by surgeons. The landmark technique can be used exclusively for posterior approach and involves identification of lumbar triangle of Petit and the plane between the internal oblique and transversus abdominis muscles with tactile pops [57]. However, these may be difficult to locate in obese patients and absent or variable in other patients. Ultrasound-guided posterior approach involves placing the probe in mid-axillary line superior to the iliac crest (over the triangle of Petit) and identifying the target fascial plane. Another TAP block for upper abdominal surgery is by oblique subcostal approach. Another four-point, single-shot approach technique is recently described that combines the posterior and oblique subcostal techniques [58]. There can be needle-related complications such as breach of the peritoneum and injury to viscera and those related to LA toxicity [58].

- **Rectus Sheath Block:** It is an anterior abdominal block that reduces postoperative pain associated with midline incisions around the umbilicus and laparoscopic surgery. Ultrasound-guided rectus sheath block will block the ventral rami of 7th–12th thoracolumbar nerve by injecting the LA into the space between the rectus muscle and posterior sheath [59]. Potential complications are related to LA toxicity and needle injury, namely injury to epigastric vessels and wound infections. These are rare with ultrasound-guided blocks [59]. A study showed that rectus sheath block provided analgesia equivalent to epidural analgesia in colorectal surgery with advantage of lesser incidence of hypotension [60].

- **Qudratus Lumboram block**: It is also called as interfascial plane block as the block is given by injecting LA into the thoracolumbar fascia, which is the extension of abdominal wall fascia posteriorly and embodies the back muscles: quadratus lumboram, psoas major, and erector spinae [61].The block provides analgesia for abdominal and pelvis surgeries: gynecologic, obstetric, and urologic surgeries. It is also useful in hip, femur, and lumbar vertebral surgeries. There are no reports of LA-related toxicity with this block and also no infectious complications. Variants of block have been described relative to the site of deposition of LA around quadratus lumboram: lateral, anterior, posterior, and intramuascular [61].

- **Erector Spinae block**: It is a newer regional technique and can be used for analgesia related to anterior, posterior, and lateral thoracic and abdominal areas. The ESP block is performed between the T5–T7 paraspinal levels and can be performed at lower levels as well. The block is given under ultrasound guidance with needle being advanced through trapezius muscle, rhomboid major muscle, and erector spinae muscle toward the transverse process and LA deposited below the erector spinae nuscle [62].

- **Ilioinguinal and iliohypogatric nerve blocks:** These blocks are used for postoperative analgesia in lower abdominal surgeries and cesarean section. The block involves the blocking of ilioinguinal and iliohypogastric nerves in the plane between the transversus abdomini and internal oblique muscles [63]. In the conventional blind method, this plane is reached by the "click" felt during needle insertion at this point. With this blind method, there are possibilities of missing the plane between the transversus abdominis and internal oblique. Also there are chances of complications such as bowel perforation, injury to blood vessels, urinary retention, and femoral nerve blockade [63]. Ultrasound-guided procedure avoids these complications and helps in accurate drug placement after identifying the nerves and thus lesser dose of LA [63].

14. Adjuncts to regional nerve blocks

The duration of action of local anesthetics in PNB varies but may last up to 24 hours. Patients who have had a single-shot PNB may complain of slightly greater postoperative discomfort between 16 and 24 h compared with those who have had only systemic analgesics [64]. Rebound pain may occur after single-shot PNBs, resulting in sleep disturbances, difficulties employing enhanced recovery and physiotherapy protocol, and increased consumption of opioids and related side effects [64]. Hence, strategies have been sought to extend the benefits of single-shot PNBs beyond the maximum of 8–16 h. A continuous PNB involves the percutaneous insertion of a catheter adjacent to a peripheral nerve, plexus, or fascial plane, followed by the administration of LA through the catheter [64]. Such a procedure may involve problems such as inaccurate catheter tip placement and secondary block failure; catheter-related mechanical nerve irritation, catheter knotting, migration, obstruction or shearing, fluid leakage or inflammation at the insertion site of the catheter; bacterial catheter colonization; infusion pump malfunction; myonecrosis with repeated large boluses of bupivacaine; and LA systemic toxicity [64]. The use of "perineural adjuncts" is technically simple and effective alternative to the continuous PNBs in order to extend the benefits of single-shot PNBs. The term perineural adjuncts refers to the co-administration of pharmacological agent(s) with LA(s) around a peripheral nerve, plexus or fascial plane with the aim of affecting the characteristics of the resulting block [64]. Over time, the number of potential perineural adjuncts has increased to a wide variety of drugs.

Several drugs have been used to improve the quality and duration of block.

1. **Dexamethasone**: It is a potent long-acting glucocorticoid with minimal mineralocorticoid activity. It stimulates the glucocorticoid receptors located on the cell membranes of neurons after perineural administration, increasing the expression of inhibitory K^+ channels and thereby decreasing the excitability of and neuronal transmission in nociceptive unmyelinated C-fibers. It may be that its actions are mediated via localized vasoconstriction or systemic anti-inflammatory effects after absorption through the vasculature. Dexamethasone must be administered as a preparation without preservatives such as benzyl alcohol and propylene, both of which can cause neurolytic effects [64]. Studies have demonstrated that perineural dexamethasone was associated with an increase in the mean duration of analgesia, decrease in pain scores at rest and on movement, and reduction of cumulative morphine consumption at 24 hour [64].

2. **Clonidine and dexmedetomidine:** These are also useful adjuncts for PNB. As α_2-adrenoceptors are not located on the axons of peripheral nerves, the mechanism of action of α_2-adrenoceptor agonists after perineural administration is not related to these receptors. In the refractory phase of an action potential, hyperpolarization-activated cation currents normally restore the resting potential of the neuron, allowing restoration of functional activity [64].Clonidine and dexmedetomidine block the hyperpolarization-activated, cyclic nucleotide-gated channels responsible for these currents, maintaining the neuron in a hyperpolarized, thereby inhibiting conduction in Aδ and C-nerve fibers and producing analgesia. Clonidine could also work partially through localized vasoconstriction mediated through the lesser selective activity at α_1-adrenoceptors. Perineural clonidine and dexmedetomidine cause an increase in the mean duration of analgesia, sensory and motor block irrespective of whether intermediate-acting (lidocaine, mepivacaine, or prilocaine) or long-acting (bupivacaine or ropivacaine) LAs were injected [64]. They also increase the occurrence of adverse effects such as bradycardia, arterial hypotension, fainting or orthostatic hypotension, and sedation [64]. Furthermore, perineural dexmedetomidine was related to a decrease in the mean time to onset of sensory block and motor block.

3. **Adrenaline** is one of the oldest perineural adjuncts to LAs. It acts by decreasing the time to onset, increasing the duration of block characteristics, and delaying the systemic uptake of local anesthetic, thereby reducing the risk of LA systemic toxicity. It can also serve as a marker of intravascular injection. Its mechanism of action after perineural administration is thought to be related to vasoconstriction secondary to α_1-adrenoceptor stimulation. In a meta-analysis of five RCTs, perineural adrenaline was associated with an increase in the mean duration of analgesia by approximately 1 h [65].However, adrenaline can lead to a significant decrease in blood flow to the peripheral nerve, particularly when administered in combination with LA, predisposing to neurotoxicity.

4. **Buprenorphine** is a partial MOP (μ) opioid receptor agonist and KOP (κ) opioid receptor antagonist, which has analgesic and antihyperalgesic properties [66]. Its mechanism of action after perineural administration is secondary to concentration-dependent block of voltage-gated sodium channels, inhibition of the generation of action potentials in a similar manner to LAs, and interaction with MOP opioid receptors on the axons of unmyelinated C fibers [64]. Perineural buprenorphine was associated with an increase in the mean duration of analgesia by approximately 8.5 h and a slightly longer duration of motor block of 13 min. Its main adverse effects were postoperative nausea and vomiting (PONV) and pruritus.

5. **Hyaluronidase** is an enzyme that can be administered in conjunction with LA to decrease the time to onset of ophthalmic blocks and provide improved akinesia and analgesia. It degrades hyaluronic acid, a glycosaminoglycan that attaches to proteoglycans in the orbital connective tissue and otherwise hinders the spread of LA [64].

6. **Sodium bicarbonate** can reduce the time to onset of neuronal block by alkalinization of the solution, increasing its pH closer to the p*K*a of the LA, and thus favoring the non-ionized form of the LA that is able to penetrate the peripheral nerve to reach its site of action [67].

7. **Magnesium** is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that has been found to increase the excitation threshold in peripheral nerves, more so in myelinated Aβ than unmyelinated C-fibers. Its mechanism of action after perineural administration could be secondary to the effects of its positive divalent charge on the neuronal membrane or its role as a physiological calcium antagonist [64]. Perineural magnesium was associated with an increase in the mean duration of analgesia by approximately 2 h, duration of sensory block by 1.75 h and duration of motor block by 1.5 h. Perineural magnesium did not increase the risk of PONV [64].

Drugs such as fentanyl, morphine, ketamine, tramadol, midazolam, and neostigmine are not used as perineural adjuncts in PNBs because of conflicting or limited evidence and worries about their potential for adverse effects or neurotoxicity [64].

15. Non-pharmacological methods for acute pain

The non-pharmacological methods of pain management can be divided into physical interventions and psychological interventions. Physical/sensory interventions are patient-specific, they inhibit nociceptive input and pain perception. They include methods such as massage, positioning, rest, ice/heat therapy, acupuncture, TENS, accupressure, etc. [68] The psychological interventions consist of therapies such as cognitive-behavioral therapy, mindfulness-based stress reduction, acceptance and commitment therapy, guided imagery, biofeedback, music therapy, and meditation etc. [69]. These can act as an important adjuvant for pain management. It has the advantage of being relatively inexpensive and safe. It helps decrease fear, distress, and anxiety and is convenient The non-pharmacological methods have significant and often enduring efficacy in pain management and can be employed alone or in combination with pharmacological methods [70]. A few of the common non-pharmacological techniques are discussed below.

1. **Massage:** It is manipulation applied on soft tissue with various techniques such as friction, percussion, vibration, and tapotement for recovery and supporting health [71]. It is done by pressing or kneading parts of the body especially joints and muscles with hands to reduce pain and decrease tension [71]. Massage can interrupt the patients' cycle of distress, it can increase the blood circulation as well as the lymphatic circulation, it can initiate an analgesic effect to the area being rubbed and decrease inflammation and edema. It can release spasm manually while increasing endogenous endorphin release and conflicting sensory stimuli that override pain signals. It can lead to relaxation of tense muscles and increase blood flow to the underlying tissues and decrease in pain.

2. Positioning: It is the most commonly employed non-pharmacological method of pain relief in postoperative period. It is the physical intervention that includes maintaining a proper body alignment to reduce stress and anxiety. Use of special beds, pillows and weight lifting are done. The benefits of positioning are prevention of bed ulcers, reduced risk of injuries, bed ulcers, relief of muscle pain, tension and discomfort, and improved blood circulation. Elevating extremities decreases pain and prevents edema [71].

3. Rest: It is useful for certain group of patients such as those with fractures, those receiving traction for back pain, etc. It should not be used as a sole method for pain management. It can decrease edema, when employed with proper positioning.

4. Hot and cold therapy: Hot and cold fomentation has the benefits of reduction in pain, anxiety, nausea, and heart rate in patients treated with active warming for pain related to mild trauma, cystitis, urolithiasis, and cholelithiasis. This is also indicated in muscle and joint pain, arthritis, back pain, etc. Hot therapy works by moving the reflex arcs that inhibits the pain by stimulating heat receptors in the skin and deeper tissues (gate control theory) and also reduces pain by vasodilatation effect [71]. It reduces striated muscle spasm by minimizing muscle spindle excitability and reducing tension in muscle trigger points. In painful joints, application of heat reduces the viscosity of synovial fluid, which alleviates painful stiffness and increases joint range [6]. Deep ultrasound therapy for tissues, which are 3–5 cm deep can increase the temperature of these areas and reduce pain by mechanism as explained before.

5. Benefits of hot application are it is inexpensive, easy-to-use with minimal side effects when used appropriately. Hot therapy is given by hot compresses, warm baths, paraphine usage, and surface application. Cold therapy: Can be done by application of cold temperature using cold gel package or ice package. Cold therapy works by increasing pain threshold, reduction of edema, and suppression of inflammatory process.

6. **Acupuncture**: The needle is put in specific region of the body, which stimulates the nerve [60].Each needle will cause little to no discomfort and produces a small injury, which will stimulate the body and the immune system to increase the circulation, wound healing, pain modulation, and pain analgesia.

7. **Trans-electrical nerve stimulation (TENS)**: T.EN.S is an electric device used to treat pain.It is defined as applying electricity to the skin to manage pain. It is an electro-analgesia method. It consists of battery-powered unit and has two to four leads connected to sticky pads, which are positioned on the skin to cover or surround the painful area [71].

Trans-electrical nerve stimulation (TENS) and acupuncture may provide postoperative analgesia, decreased postoperative opioid requirements, reduced opioid-related side effects, and attenuate activation of sympathoadrenal system. In general, all of these techniques are relatively safe, noninvasive, and devoid of systemic side effects seen with other analgesic options [68–71]. Cognitive therapy and behavioral therapy may be efficacious in reducing pain and alleviating psychological factors associated with pain.

16. Considerations for acute postoperative control in specific patient populations

Opioid tolerant patients: These patients are chronically on opioid for preexisting pain or may be taking opioids for recreational purposes. Opioid tolerance is characterized by a decreased responsiveness to an opioid agonist such as morphine and is

usually evident by the need to use increasing doses to achieve the desired effect [72]. Patients who are taking opioids for management of cancer pain or chronic non-cancer pain or who have an opioid addiction may become opioid-tolerant. Acute pain management in opioid-tolerant patients should ideally be done by a multidisciplinary team comprising pain specialists, physicians, psychologists, trained nursing staff, etc. A meticulous evaluation, proper coordination, and effective interdisciplinary communication are needed. So also, there should be effectual interaction between each discipline and the patient for a successful outcome. The aims of management in opioid-tolerant patients are to promote optimal perioperative analgesia, prevent withdrawal syndromes, and deal with any related social, psychiatric, and behavioral issues [73]. Patients with an opioid dependency have three challenges to effective pain management: : [i] opioid-induced hyperalgesia (OIH), resulting in increased pain sensitivity; [ii] opioid tolerance, leading to reduced efficacy of opioids used to treat pain; and [iii] opioid withdrawal, producing sympathetic stimulation and heightened stress responses if the usual opioids are not given [73]. There is a high prevalence of psychiatric disorders in those with drug dependence, with more than 50% of patients showing evidence of conditions such as anxiety disorders and affective disorders, including depression. Such comorbidities may further complicate patients' behavior and their interaction with staff while in the hospital [74].

Early identification through a careful assessment and history in patients with opioid tolerance is essential for adequate pain-management planning. Postoperative pain management should start at the time of preoperative assessment, even prior to admission, and should include appropriate discharge planning [72]. If opioid tolerance has not been identified preoperatively, it should be suspected if the following triad is present after surgery: 1) elevated pain scores, 2) high opioid use, and 3) low incidence of side effects (apart from sedation). A multimodal pain regimen with a combination of pharmacologic and non-pharmacologic approaches is ideal. Opioids are the drugs of choice for severe pain and are also useful to manage moderate pain. However, multimodal approach with acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and adjuvants such as ketamine also provides effective pain relief. Patients with opioid tolerance may require more opioids than opioid-naïve patients. The dose of opioids should be tailored as per the individual need of the patient so as to achieve adequate analgesia without causing harmful side effects, such as over-sedation or respiratory depression. "Opioid rotation" is the substitution with a different opioid when one opioid does not provide desired level of analgesia even with increasing doses. This may be employed as required in patients with opioid tolerance, as cross-tolerance is uncommon. The recommended approach for opioid rotation is to initially substitute with one-half to two-thirds equianalgesic opioid and then monitor for safety and effectiveness. One needs to exercise caution while switching from a long-acting opioid to a short-acting one as this may precipitate withdrawal symptoms in the patient [73].

Opioid-related side effects are less common in opioid-tolerant patients; however, if opioid therapy is selected as analgesia of choice in these patients, monitoring for side effects or complications related to opioid therapy is also important. The risk of adverse drug events is more if opioid dosage is increased rapidly, even if the patient is opioid-tolerant. In fact, opioid-tolerant patients are more susceptible to the sedative properties of opioids [73].

For opioid-tolerant patients, patient-controlled analgesia (PCA) offers a convenient method of delivery, as it minimizes the risk of under treatment, allows self-titration, and negates possible conflicts with nursing staff. Additionally, a

retrospective study found that opioid-tolerant patients who had PCA were less likely to report adverse effects—with the exception of sedation—compared with the opioid-naïve group [72]. In order to calculate the PCA bolus dose and background infusion rate, an individual preoperative "fentanyl challenge" is done to the point of respiratory depression followed by pharmacokinetic modeling to predict intra and postoperative opioid requirements [72]. An alternative and simple method is to calculate the PCA bolus dose on the basis of the dose of long-term opioid already being taken. The use of PCA background infusions is to be avoided in the opioid-naïve, because of the increased risk of respiratory depression. However, in opioid-tolerant patients, the PCA infusion is used to deliver the equivalent dose of long-term oral opioid if oral administration is not possible. Various studies have shown that gabapentin and pregabalin, paracetamol, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and alpha-2 agonists all lessened the opioid tolerance [73].

Opioid withdrawal can occur in opioid-dependent patients receiving a reduced amount of their usual opioid or if an opioid antagonist is given. The patients may exhibit at least three of these signs and symptoms: dysphonic mood, nausea, vomiting, diarrhea, muscle aches, rhinorrhoea, lacrimation, pupillary dilation, piloerection, sweating, yawning, fever, and insomnia. These may impair social, occupational, and other important areas of functioning [73]. The central principle of withdrawal management is to prevent its development, providing more stability for patients and reducing psychological and physiological stress. Clonidine has long been used to manage opioid withdrawal symptoms [74]. The most commonly used drugs for OST (opioid substitution therapy) are sublingual buprenorphine and oral methadone. These drugs reduce the level of drug abuse and related behavior and provide stability to the drug users and their families. The duration of withdrawal suppression is about 24 hours, so the dose can be continued once a day or may be given in two or three divided doses [73]. The drugs used for OST will not provide analgesia, and hence, withdrawal prevention and analgesia provision should be considered as separate entities. Methadone may predispose patients to the ventricular arrhythmia, the torsades de pointes as it can cause prolongation of the corrected electrocardiographic QT interval. So appropriate monitoring is needed. When buprenorphine, which is a partial agonist with a high-binding affinity at the mu-opioid receptor, is used as OST at higher doses of 16–32 mg, there is minimum free receptor availability. In such cases, the additional pure opioid agonists including drugs such as heroin would provide no analgesic effect. Hence, buprenorphine should be stopped during perioperative period to allow receptor accessibility for opioids used for analgesia [73].

Patients with pain taking long-term opioids, those abusing heroin, and those on methadone and buprenorphine substitution therapy may develop hyperalgesia. Multimodal analgesia should be optimized by adding opioid-sparing analgesics such as paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs, or cyclooxygenase-2 inhibitors, using local anesthetic regional techniques, whereas ketamine attenuates OIH in patients on long-term opioids. Studies have demonstrated that gabapentin and pregabalin reduce OIH in animal models, human volunteers, and patients [74]. Similarly, there is evidence that alpha-2 agonists—clonidine and dexmedetomidine—may also decrease OIH, whereas experimental results indicate that COX- 2 inhibitor can also impart this benefit [74].

Pediatric patients: Pediatric patients continue to be undertreated for acute pain. There is a common myth that pediatric patients do not feel pain or they do not remember the pain. Control of pain in pediatric patients is important because poor pain control may result in increased morbidity and mortality. Different treatment modalities have

evolved, and multimodal analgesia has become the treatment of choice not only involving a pharmacological approach but also non-pharmacological approaches (e.g., regional analgesia, rehabilitation, cognitive behavioral therapy, virtual reality).

Special scales are available for children to self-report their pain. One important scale is Children and Infants Postoperative Pain Scale (CHIPPS) where scores of 0–2 are assigned as indicators of level of pain for crying, facial expression, posture of the trunk, posture of the legs, motor restlessness, etc. [12] The other scales are Faces Pain Scale-Revised, pain word scale, Revised-Face Legs Activity Cry Consolability (r-FLACC), Premature Infant Pain Profile, Neonate Facial Coding system, Neonate Infant pain scale, Maximally Discriminative Facial Movement Coding System.

Oral and rectal route is preferred in children for administering analgesics [12]. Intramuscular injections are to be generally avoided for pain and fear associated with injection and unpredictable absorption of drug [12]. Regional nerve block, neuraxial blocks, peripheral nerve blocks, local infiltration analgesia with general anesthesia may improve postoperative pain management in pediatric patients. Intravenous patient controlled analgesia can be effectively used with prior education of patient about its use in children aged over 5–6 years [1].

Acetaminophen has antipyretic and anti-inflammatory properties. Its mechanism of action is through COX3 enzyme (inhibition of prostaglandin synthesis) inhibition, cannabinoid agonist, NMDA agonist, and activation of descending serotonergic pathways in CNS and via inhibition of prostaglandin synthesis [75]. NSAIDs are used commonly in pediatric population. Their use in pediatric population has demonstrated adequate pain control, opioid-sparing effect, and decrease in postoperative nausea vomiting [75, 76]. Use of ketorolac for pain control after tonsillectomy is associated with more risk of postoperative bleeding. However, that risk is counterbalanced with decreased PONV, sedation, and respiratory depression [75]. Gabapentinoids are not recommended in children for acute postoperative pain as per the current evidence [75]. Ketamine used in perioperative period in pediatric patients could have the potential of decreasing hyperalgesia, central sensitization, and reverse opioid tolerance [75]. The clinical scenarios where ketamine could be used are patients at high risk of developing postsurgical neuropathic pain, opioid-tolerant patients, patients who are more susceptible to develop opioid-related side effects, patients with chronic pain conditions, etc. Intravenous lidocaine should be avoided in patients weighing <40 kg [75]. Dexmedetomidine is useful adjunct to decrease postoperative pain with an opioid-sparing effect and decrease in emergence delirium [75].

Obese patients: These patients present various anatomic and pathophysiologic challenges in pain management. A major challenge is their altered pharmacokinetic profile, which accompanies physiologic changes in this population, which make obese patients more susceptible to respiratory depression and sleep apnea if opioids are used. The goal of pain management in such patients is provision of comfort, early mobilization, and improved respiratory function without causing respiratory compromise [26]. Recommendations are multimodal analgesic management, preference for regional techniques, avoidance of sedatives, noninvasive ventilation with supplemental oxygen, early mobilization, and elevation of the head.

17. Discussion

Optimal treatment of postoperative pain requires multidisciplinary approach and a dedicated team for providing a round-the-clock service [12]. Each surgical procedure

produces varying degrees of pain. A comprehensive and effective pain management plan includes the appropriate care of individual patients' needs during the various stages of perioperative period. The patients and the caregivers should be educated about the importance of postoperative pain management. The acute pain teams should assess patients preoperatively and plan a pain management protocol. There should be regular assessment, treatment, and documentation of pain. The staff should be given training and continued education about physiology of pain, pathophysiology, pharmacology, monitoring routines, etc. All this is possible if an acute pain service is set up, which is a dedicated organization for acute pain management. Before establishing the acute pain service, an audit should be conducted for studying the effectiveness of the current pain management protocols, and later comparisons must be done after the establishment of pain service. Daily pain ward rounds should be started, which provides an ideal opportunity to teach service providers, address misconceptions, discuss pain-related issues with patients, and adopt prescription charts to improve pain control as needed. Various studies have shown improved pain scores after establishment of APS. The studies have shown that not only the newer techniques that improved postoperative pain but also the systematic and planned application of already existing ones [77].

18. Conclusion

Untreated postoperative pain can have untoward consequences not only on individual patient health but also adversely affects the health care system. Optimal pain management improves the quality of life, facilitates recovery, and decreases morbidity. A multimodal, evidence-based, and procedure-specific, individualized analgesic regimen with minimum side effects should be the standard of care. Such a regime is an integral part of ERAS, which facilitates the important ERAS milestones such as early mobilization and oral feeding. Assessment, documentation of pain and response to its treatment are vital for effective postoperative pain management. Patient-controlled intravenous and epidural analgesias have the advantages of superior pain relief and improved patient satisfaction. The regional techniques have become an integral part of pain management programs. The use of ultrasound-guided techniques has made the regional techniques hassle-free with potent analgesia and lesser possibility of complications. Besides the pharmacological methods, which are routinely used, non-pharmacological methods should also be integrated into the postoperative pain management plan. These techniques are relatively inexpensive and safe and help decrease fear, distress, and anxiety and can be instituted by the nursing staff as well as the patients' caretakers. The patients with special needs such as the opioid-tolerant patients, patients in extremes of age, and obese patients, etc., need a well-planned approach under the care of experienced and expert healthcare staff. The institutionalized and dedicated team approach for acute pain management in the form of Acute Pain Service will go a long way in incorporating all the above said principles, thus improving postoperative pain management and patient satisfaction.

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References

[1] Vrooman BM, Richard WR. Morgan & Mikhail's Clinical Anaesthesiology. 6th ed. United States: McGraw-Hill Education; 2018

[2] Small C, Laycock H. Acute post-operative pain management. British Journal of Surgery. 2020;**107**(2):e70-e80

[3] Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute-post-operative pain management. Evidence from published data. British Journal of Anesthesia. 2002;**89**(3):409-423

[4] Vijayan R. Managing acute pain in the developing world. PAIN: Clinical Updates. 2011;**19**:1-7

[5] Singh PK, Saikia P, Lahakar M. Prevalence of acute post-operative pain adults in patients in adult age-group undergoing inpatient abdominal surgery and correlation of intensity of pain and satisfaction with analgesic management: A cross-sectional single institute-based study. Indian Journal of Anaesthesia. 2016;**60**:737-743

[6] Warfield CA, Kahn CH. Acute pain management. Programs in U. S hospitals and experiences and attitudes among U. S. adults. Anesthesiology. 1995;**83**:1090-1094

[7] Mwashambwa MY, Isaya M, et al. Post-operative pain prevalence, predictors, management practices and satisfaction among operated cases at Regional Rferral Hospital in Dar es Salaam. Tanzania Tanzania Jourrnal of Health Rsearch. 2018;**v20i2**:10

[8] Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. Anesthesia and Analgesia. 2003;**97**:534-540

[9] Gramke HF, de Rijke JM, van Kleef M, Raps F, Kessels AG, Peters ML, et al. The prevalence of postoperative pain in a cross-sectional group of patients after day -case surgery in a university hospital. The Clinical Journal of Pain. 2007;**23**:543-548

[10] Sommer M, de Rijke JM, van Kleef M, Kessels AG, Peters ML, Geurts JW, et al. The prevalence of postoperative pain in a sample of 1490 surgical inpatients. European Journal of Anaesthesiology. 2008;**25**:267-274

[11] Couceiro TC, Valenca MM, Lima LC, de Menezes TC, Rapaso MC. Prevalence and influence of gender, age, and type of survey on postoperative pain. Revista Brasileira de Anestesiologia. 2009;**59**(3): 314-320

[12] Patel NB. Physiology of pain. In: Kopf A, Patel NB, editors. Guide to Pain Management in Low Resource Settings. e-book by International Association for the Study of Pain. 2010. pp. 13-18. Available from: www.iasp- pain.org/.../Guide_to_Pain_Management_in_Low-Resource_Settings.pdf

[13] Sharma RS, Das G. What is the minimum knowledge of pain medicine needed for other speciality. Journal on Recent Advances in Pain. 2018;**4**(1):32-35

[14] Brennan TJ. Acute pain: Pathophysiology and clinical implications. ASA Refresher Courses in Anesthesiology. 2010;**38**:8-15

[15] Ghori MK, Zhang Y, Sinatra RS. Pathophysiology of acute pain. In: Sinatra RS, de Leon Cassasola OA, editors. Acute Pain Management. 1st edn. New York: Cambridge University Press; 2009. pp. 21-32

[16] Rao M. Acute postoperative pain. Indian Journal of Anaesthesia. 2006;**50** (5):340-344

[17] Wu CL, Fleisher LA. Outcomes research in regional anesthesia and analgesia. Anesthesia and Analgesia. 2000;**91**(5):1232-1242

[18] Kissin I. Pre-emptive analgesia. Anaesthesiology. 2000;**93**(4):1138-1143

[19] Greenshields N, Mythen M. Enhanced recovery after surgery. Current Anesthesiology Reports. 2020; **10**:49-55. DOI: 10.1007/s40140-020-00372-y

[20] ERAS for Gastrointestinal Surgery Part 2: Consensus Statement for Anaesthesia Practice. Guidelines ERAS Society. Available from: http://erassociety.org [Accessed: July 22, 2022]

[21] Elzohry AAM, Foli AME. Basics of Acute Postoperative Pain. American International Journal of Multidisciplinary Scientific Research. 2018;**1**(2):19-23

[22] Twining J, Padula C. Pilot testing the clinically aligned pain assessment (CAPA) measure. Pain Management Nursing. 2019;**20**(5):462-467

[23] Breivik H, Borchgrevink PC, Allen SM. Assessment of pain. British Journal of Anaesthesia. 2008;**101**(1): 17-24

[24] Alderson S. Unrecognised, undertreated, pain in ICU—Causes, effects, and how to do better. Open Journal of Nursing. 2013;**03**:108-113. DOI: 10.4236/ojn.2013.31014

[25] Puntillo F, Giglio M, Varrassi G. The Routes of Administration for Acute Postoperative Pain Medication Pain Therapy. 2021;**10**(2):909-925

[26] De Andros J, Narachi P, Fischer HJB. General recmmendations for post-operative pain management. In: E-booklet Produced in Consulation with European Society of Regional Anaesthesia and Pain Therapy. Available from: www.anaesthesia-az.com. [Accessed: June 22, 2022]

[27] Horn R. Post-Operative Pain Control. Available from: https://www.statpearlSCom/Article Library/view article/27536

[28] Theinthong S, Niruthisard S, Ittichaikulthon W, et al. Clinical guidance for acute post-operative pain management 2019. The Royal College of Anasthesiologists of Thailand(RCAT) and the Thai Association for the study of Pain (TASP): Second edition. Thai Journal of Anesthesiology. 2020;**46**(1):47-70

[29] Perioperative Pain Management. Available from: https://www.mdanderson.org/documents/for-physicians/algorithms/clinical management/post-op-pain-web -algorithm.pdf

[30] Kim KH, Abdi S. Rediscovery of nefopam for the treatment of neuropathic pain. The Korean Journal of Pain. 2014;**27**(2):103-111

[31] Han C, Li X, Jiang H, et al. The use of gabapentin in the management of postoperative pain after total hip arthroplasty: A meta-analysis of randomised controlled trials. Journal of Orthopaedic Surgery and Research. 2016;**11**(1):79

[32] Pastino A, Lakra A. Patient controlled analgesia. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551610/

[33] Carr A, Ferguson M. What is the evidence to support clonidine as an

adjuvant analgesic? Practical Pain Management. 2019;**19**(5)

[34] Joshi G, Gandhi K, Shah N, Gadsden J, Corman SL. Peripheral nerve blocks in the management of postoperative pain: Challenges and opportunities. Journal of Clinical Anesthesia. 2016;**35**:524-529

[35] Chang A, Dua A, Singh K, et al. Peripheral nerve blocks. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459210/

[36] Zisquit J, Nedeff N. Interscalene block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519491/

[37] D'Souza RS, Johnson RL. Supraclavicular block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519056/

[38] Williams LM, Singh K, Dua A, et al. Infraclavicular nerve block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537016/

[39] Satapathy AR, Coventry DM. Axillary brachial plexus block. Anesthesiology Research and Practice. 2011;**2011**:5. DOI: 10.1155/2011/173796

[40] Neal J Gurkan Y. Cutaneous Blocks for the Upper Extremity –Landmarks and Nerve Stimulator Technique. Available from: https://www.nysora.com/techniques/upper-extremity/distal-nerves/cutaneous-blocks-upper-extremity/ [Accessed: July 30, 2022]

[41] Durrani MI, Dasgupta S. Radial nerve block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532951/

[42] Pester JM, Bechmann S, Varacallo M. Median nerve block techniques. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK

[43] Pester JM, Varacallo M. Ulnar nerve block techniques. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459208/

[44] Polania Gutierrez JJ, Ben-David B. Lumbar plexus block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556116/

[45] Sykes Z, Pak A. Femoral nerve block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK546704

[46] O'Reilly N, Desmet M, Kearns R. Fascia iliaca compartement block. British Journal of Anaesthesia and Education. 2019;**19**(6):191-197

[47] Yoshida T, Nakamoto T, Kamibayashi T. Ultrasound-guided obturator nerve block: A focused review on anatomy and updated techniques. BioMed Research International. 2017, 2017:9. DOI: 10.1155/2017/7023750

[48] Rodziewicz TL, Stevens JB, Ajib FA, et al. Sciatic nerve block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470391/

[49] Arnold C, Alvarado AC, Brady MF. Saphenous nerve block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK536967/

[50] Berlioz BE, Bojaxhi E. PENG regional block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK565870/. [Accessed: May 9, 2022]

[51] Feng W, Wenming M, Zhihui H. Analgesia effects of IPACK block added to multimodal analgesia regiments after total knee replacement: A systematic review of the literature and meta-analysis of 5 randomized controlled trials. Medicine. 2021;**100**(22):e25884

[52] Chakraborty A, Khemka R, Datta T. Ultrasound-guided truncal blocks: A new frontier in regional anaesthesia. Indian Journal of Anaesthesia. 2016;**60**(10): 703-711. DOI: 10.4103/0019-5049.191665

[53] Karmakar MK. Thoracic paravertebral block. Anesthesiology. 2001;**95**(3):771-780

[54] Baxter CS, Singh A, Ajib FA, et al. Intercostal nerve block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482273/. [Accessed: July 26, 2022]

[55] Southgate SJ, Herbst MK. Ultrasound guided serratus anterior blocks. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538476/. [Accessed: July 25, 2022]

[56] Battista C, Krishana S. Pectoralis nerve block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022

[57] Tran DQ, Bravo D, Leurcharusmee P, et al. Transversus Abdominis Plane Block. A narrative review. Anesthesiology. 2019; **131**(5):1166-1190

[58] Young MJ, Gorlin AW, Modest VE, et al. Clinical implications of the transvesus abdominis plane block in adults. Anesthesiology Research and Practice. 2012;**2012**:731645

[59] Kartalov A, Nn J, Kuzamanovsk B, et al. The effect of Rectus Sheath block as a supplement of general analgesia in adult patients undergoing umbilical hernia repair. Prilozi. 2017;**38**(3):135-142

[60] Tudor EC, Yang W, Brown R, Mackey PM. Rectus sheath catheters provide equivalent analgesia to epidurals following laparotomy for colorectal surgery. Annals of the Royal College of Surgeons of England. 2015 Oct;**97**(7): 530-533

[61] Dhanjal S, Tonder S. Quadtratus lumboram block. In: Statpearls. Treasure Island (FL): Statpearls Pblishing; 2022. Available from https://www.ncbi.nlm.nih.gov/books/NBK 537212/ [Accessed: August 22, 2022]

[62] Krishnan S, Cascella M. Erector spinae plane block. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545305/. [Accessed: April 30, 2022]

[63] Khedkar SM, Bhalerao PM, Yemul-Golhar SR, Kelkar KV. Ultrasound-guided ilioinguinal and iliohypogastric nerve block, a comparison with the conventional technique: An observational study. Saudi Journal of Anaesthesia. 2015;**9**(3):293-297

[64] Desai N, Albrecht E, El-Boghdadly K. Perineural adjuncts for peripheral

nerve block. BJA Education. 2019;**19**(9): 276-282

[65] Tschopp C, Tramèr MR, Schneider A, Zaarour M, Elia N. Benefit and harm of adding epinephrine to a local anesthetic for neuraxial and locoregional anesthesia: A meta-analysis of randomized controlled trials with trial sequential analyses. Anesthesia and Analgesia. 2018;**127**(1):228-239

[66] Schnabel A, Reichl SU, Zahn PK, et al. Efficacy and safety of buprenorphine in peripheral nerve blocks. A meta-analysis of RCTs. European Journal of Anaesthesiology. 2017;**34**(9):376-586

[67] Brummett CM, Brian W. Additives to local anaesthetics for peripheral nerve blocks. International Anesthesiology Clinics. 2011;**49**(4):104-116

[68] Geziry AE, Toble Y, Kadhi FA, Nobani MPMA. Non-pharmacological pain management. In: Shallik NA, editor. Pain Management in Special Circumstances. London: IntechOpen; 2018. DOI: 10.5772/intechopen.79689. Available from: https://www.intechopen.com/chapters/62969 [Accessed: August 03, 2022]

[69] Nasiri M, Le-Wendling L, Ihnatseka B Y. Emerging Techniques in Acute Pain Medicine. ASRA Pain Medicine Practice Management. Available from: https://www.asra.com/nes/-pubication/asranewsletter/feb2020 [Accessed: August 3, 2022]

[70] Bushnell MC, Frangos E, Madian N. Non –pharmacological treatment of pain. Grand challenge and future oppurtunities. Frontiers in Pain Research. 2021. DOI: 10.3389/fpain.2021.696783

[71] Demir Y. Non-pharmacological therapies in pain management. In: Racz GB, Noe CE, editors. Pain Management - Current Issues and Opinions. London: IntechOpen; 2012. DOI: 10.5772/30050. Available from: https://www.intechopen.com/chapters/26152 [Accessed: August 3, 2022]

[72] Morgan MM, Christie MJ. Analysis of opioid efficacy, tolerance, addiction and dependence from cell culture to human. British Journal of Pharmacology. 2011;**164**(4):1322-1334

[73] Adesoye A, Duncan N. Acute pain management in patients with opioid tolerance. US Pharm. 2017;**42**(3):28-322

[74] Quinlan J, Cox F. Acute pain management in patients with drug dependence syndrome. PAIN Reports. 2017;**2**(4):e611. DOI: 10.1097/PR9.0000000000000611

[75] Eduardo V, Rivera G, Gonzalez V. Current trends and new strategies in acute post-operative pain management in children. Medical Research Archives. 2021;**9**(9). DOI: 10.18103/mra.v9i9.2539

[76] Huxtable CA, Roberts LJ, Somogyl AA, et al. Acute pain management in opioid-tolerant patients: A growing challenge. Anaesthesia and Intensive Care. 2011;**39**(5):804-823

[77] Gould TH, Crosby DL, Harmer M, Lloyd SM, Lunn JN, Rees GA, et al. Policy for controlling pain after surgery: Effect of sequential changes in management. BMJ. 1992;**305**(6863): 1187-1193