5

Role of Anesthesiologist in Pain Management in the Preoperative Period

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A directed pain history, a directed physical examination, and a pain control plan be included in the anesthetic preoperative evaluation.

Patient preparation for perioperative pain management should include appropriate adjustments or continuation of medications to avert an abstinence syndrome, treatment of pre-existent pain, or preoperative initiation of therapy for postoperative pain management.

Anesthesiologists should provide patient and family education regarding their important roles in achieving comfort, reporting pain, and in proper use of the recommended analgesic methods, removing the misconceptions that overestimate the risk of adverse effects and addiction. Patient education for optimal use of patient-controlled analgesia (PCA) and other sophisticated methods, such as patient-controlled epidural analgesia, might include discussion of these analgesic methods at the time of the preanesthetic evaluation, brochures and video-tapes to educate patients about therapeutic options, and discussion at the bedside during postoperative visits. Such education may also include instruction in behavioral modalities for control of pain and anxiety.

1. Describe multimodal approach to perioperative pain management.

Ans. A multimodal approach to analgesia includes a combination of interventional analgesic techniques (epidural catheter or peripheral nerve catheter analgesia) and a combination of systemic pharmacologic therapies [nonsteroidal anti-inflammatory agents (NSAIDs), α-adrenergic agonists, NMDA receptor antagonists, membrane stabilizers, and opioid administration].

The essential elements of multimodal analgesia are the following:

- Neuronal blockade by local anesthetics that may be administered via epidural anesthesia, spinal anesthesia, peripheral nerve blockade, skin infiltration before surgical incision, or wound infiltration before surgical closure.
- Infusion of opioids via the IV, intrathecal, or epidural route before surgical incision and throughout the perioperative period.
- Administration of NSAIDs before surgical incision, throughout the intraoperative period, and postoperatively.
- Administration of other adjuvant medication.

The principles of a multimodal strategy include a sufficient diminution of the patient's pain to instill a sense of control over their pain, enable early mobilization, allow early enteral nutrition, and attenuate the perioperative stress response. The secondary goal of this approach is to maximize the benefit (analgesia) while minimizing the risk (side effects of the medication being used). These goals are often achieved through regional anesthetic techniques and a combination of analgesic drugs. The utilization of epidural anesthesia and analgesia is an integral part of the multimodal strategy because of the superior analgesia and physiologic benefits conferred by epidural analgesia.

Patients undergoing major abdominal or thoracic procedures and managed with a multimodal strategy have a reduction in hormonal and metabolic stress, preservation of total-body protein, shorter times to tracheal extubation, lower pain scores, earlier return of bowel function, and earlier achievement of criteria for discharge from the intensive care unit.

By integrating the most recent data and techniques for surgery, anesthesiology, and pain treatment, the multimodal approach is an extension of clinical pathways or fast track protocols by revamping traditional care programs into effective postoperative rehabilitation pathways. This approach may potentially decrease perioperative morbidity, decrease the length of hospital stay, and improve patient satisfaction without compromising safety. However, the widespread implementation of these programs requires multidisciplinary collaboration, changes in the traditional principles of postoperative care, additional resources, and expansion of the traditional acute pain service, all of which may be difficult in the current medical-economic climate.

ASA recommendation is for the use multimodal pain management therapy. Central regional blockade with local anesthetics should be considered. Unless contraindicated, patients should receive an around-the-clock regimen of Coxibs, NSAIDs, or acetaminophen. Dosing regimens should be administered to optimize efficacy while minimizing the risk of adverse events. The choice of medication, dose, route, and duration of therapy should be individualized.

2. Define pre-emptive and preventive analgesia. Describe the measures useful for pre-emptive and preventive analgesia.

Ans. Pre-emptive analgesia is the administration of an analgesic agent before the surgical incision to decreases or modulates the perioperative pain and also helps in minimizing central sensitization.

Some analgesic interventions have an effect on postoperative pain and/or analgesic consumption that exceeds the expected duration of action of the drug, defined as preventive analgesia.

Protective analgesia describes a technique that reduces measures of sensitization such as hyperalgesia.

Pre-emptive epidural analgesia results in lowering of pain intensity scores, supplemental analgesic consumption, time to first analgesic. While wound infiltration of local anesthetics and NSAIDs administration has also provided some benefit. Where systemic NMDA antagonist administration is of equivocal effects, and no clear evidence of pre-emptive opioids.

For preventive effects, NMDA antagonist, gabapentin, epidural has shown some benefit. Perioperative epidural analgesia combined with IV ketamine decreases the pain up to 1 year following colonic resection.

3. Outline some practical important measures to reduce pain.

Ans. In surgery, subsequent postoperative pain can be decreased with gentle intubation, careful positioning and transfer of the patient, adequate muscle relaxation, and minimization of surgical trauma.

4. What are the physiological and psychological effects of acute pain?

Ans. Acute pain activates the complex neurohumoral and immune response to injury, and both peripheral and central injury responses have a major influence on acute pain mechanisms. Thus acute pain and injury of various types are inevitably inter-related and if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome.

ADVERSE PHYSIOLOGICAL EFFECTS

Metabolic and endocrine responses to injury are shown in Table 1.

Table 1 | Metabolic and endocrine responses to injury

Endocrine	↑ Catabolic hormones	↑ ACTH, cortisol, ADH, growth hormone, catecholamines, angiotensin II, aldosterone, glucagons, IL-1, TNF, IL-6
	↓ Anabolic hormones	↓ Insulin, testosterone
Metabolic		
Carbohydrate	Hyperglycemia, glucose intolerance, insulin resistance	↑ Glycogenolysis, gluconeogenesis (cortisol, glucagon, growth hormone, adrenaline, free fatty acids) ↓ Insulin secretion/activation
Protein	Muscle protein catabolism, ↑ synthesis of acute phase proteins	↑ Cortisol, adrenaline, glucagons, IL-1, IL-6, TNF
Lipid	↑ Lipolysis and oxidation	↑ Catecholamines, cortisol, glucagon, growth hormone
Water and electrolyte	Retention of water and sodium, ↑ excretion of potassium and ↓ functional ECF with shifts to ICF	↑ Catecholamine, aldosterone, ADH, cortisol, angiotensin II, prostaglandins and other factors

Hyperglycemia

Hyperglycemia is proportional to injury response.

Circulating glucose enters cells that do not require insulin for uptake, resulting in cellular glucose overload and diverse toxic effects. Excess intracellular glucose nonenzymatically glycosylates proteins such as immunoglobulins, rendering them dysfunctional. Alternatively, excess glucose enters glycolysis and oxidative phosphorylation pathways, leading to excess superoxide molecules that bind to nitric oxide (NO), with formation of peroxynitrate, ultimately resulting in mitochondrial dysfunction and death of cells.

Even modest increases in blood glucose can be associated with poor outcome. Tight glycemic control is associated with improved outcomes with coronary artery bypass surgery (CABG), whereas in intensive care the tight glycemic control is still debatable.

Lipotoxicity

High levels of free fatty acids can depress myocardial contractility, increase myocardial oxygen consumption, and impair calcium homeostasis and increase free radical production leading to electrical instability and ventricular arrhythmias.

Protein Catabolism

After injury there is increase in protein catabolism to amino acids and amino acid oxidation, with decreased protein synthesis, this leads to loss of lean tissue. This leads to increased in length of time for normal return of physical function and increased hospital stay.

Protein loss may lead to delayed wound healing, reduced immune function (Chandra, 1983) and diminished muscle strength.

Pain and Analgesia: Effects on Organ Dysfunction

Pain activates the sympathetic nervous system leads to the following:
- Increased heart rate, blood pressure, inotropy
- Increased myocardial oxygen demand, reduced myocardial oxygen demand leading to ischemia, and arrhythmias
- Reduced gastrointestinal motility and ileus.

Pain from upper abdominal and thoracic surgeries leads to decreased cough, reduction of functional capacity, leading to atelectasis, hypoxemia, and pulmonary complications.

The injury response also contributes to suppression of cellular and humoral immune response, and leads to a hypercoagulable state.

Adverse Psychological Effects

Pain leads increasing anxiety, inability to sleep, demoralization, a feeling of helplessness, loss of control, inability to think and interact with others.

5. Describe the tools of pain assessment. Describe each tool in details.

Ans. Pain is a subjective experience modulated by physiological, psychological and environmental factors such as previous events, culture, prognosis, coping strategies, fear and anxiety. Therefore, most measures of pain are based on self-report. These results are influenced by mood, sleep disturbance and medications.

There are some instances when it may not be possible to obtain reliable self-reports of pain (e.g. patients with impaired consciousness or cognitive impairment, young children, elderly patients, or where there are failures of communication due to language difficulties, inability to understand the measures, unwillingness to cooperate or severe anxiety). For them other methods of pain assessment are used.

There are no objective measures of 'pain'. But associated factors such as hyperalgesia, the stress response (e.g. plasma cortisol concentrations), behavioral responses (e.g. facial expression), functional impairment (e.g. coughing, ambulation) or physiological responses (e.g. changes in heart rate) may provide additional information.

Analgesic requirements (e.g. patient-controlled opioid doses delivered) are commonly used as posthoc measures of pain experienced.

Pain intensity should be recorded as a fifth vital sign. Regular and repeated measurement leads to assessment of analgesic efficacy. Both static and dynamic assessment of pain should be made.

Pain can be measured by both unidimensional or multidimensional tools, but unidimensional ones are more useful in the perioperative setting.

UNIDIMENSIONAL TOOLS

Visual Analog Scale

The visual analog scale (VAS) is a straight 100-mm line, without demarcation, that has the words 'no pain' at the left-most end and 'worst pain imaginable' (or something similar) at the right-most end. Patients are instructed to place a mark on the line that indicates the amount of pain that they feel at the time of the evaluation. The distance of this mark from the left end is then measured, and this number is used as a numeric representation of the severity of the patient's pain.

VAS can also be used to measure other aspects of the pain experience (e.g. affective components, patient satisfaction, side effects).

Advantage: Validated, easy to use.

Disadvantage: It attempts to assign a single value to the multidimensional experience of pain, there is no concept of worst imaginable pain as pain experience later may be more worse than present ones but the patient cannot at a later date change his previous score.
Pain assessment after surgery may be difficult due to transient anesthetic-related cognitive impairment and decreases in visual acuity.

Numeric Rating Scale

The numeric rating scale is consists of numbers written from 0–10 from left to right, 0 for 'no pain' and 10 for 'worst pain imaginable'. Patients are instructed to circle the number that represents the amount of pain that they are experiencing at the time of the evaluation. A variation of this scale is the verbal numeric scale (VNS), in which patients are asked to verbally state a number between 0 and 10 that corresponds to their present pain intensity.

Pain relief may be measured in the reverse direction with 0 representing 'no relief' to 10 representing 'complete relief'.

VAS ratings of greater than 70 mm are indicative of 'severe pain' and 0–5 mm 'no pain', 5–44 mm 'mild pain' and 45–74 'moderate pain'. A reduction in pain intensity by 30–35% has been rated as clinically meaningful by patients with postoperative pain, acute pain in the emergency department.

Advantage: Quick, easy to use, validated pain measure.

Disadvantage: It assigns single number to pain, has also a ceiling effect, i.e. if a value of '10' is chosen and the pain worsens, the patient officially has no way to express this change, also, with the VNS, patients often rate their pain as some number higher than 10 (e.g. '15 out of 10') in an attempt to express their extreme level of pain intensity.

Verbal Descriptor Scale

A verbal descriptor scale (VDS) is a list of words, ordered in terms of severity from least to most, that describe the amount of pain that a patient may be experiencing. Patients are asked to either circle or state the word that best describes their pain intensity at that moment in time. These terms can then be converted to numeric scores for charting and easy comparison over time.

Advantage: It is validated, simple and quick. May be useful in the elderly or visually impaired patient and in some children.

Disadvantage: It assigns only one objective to the pain experience, limited choice of 4 to 6 values, forces patient to choose from 4–6 values.

Pain relief may also be graded as none, mild, moderate or complete using a VDS.

Multidimensional Measures of Pain

Multidimensional tools provide information about the characteristics of the pain and its impact on the individual. Among them, most commonly used scales are Brief Pain Inventory, which assesses pain intensity and associated disability and the McGill Pain Questionnaire, which assesses the sensory, affective and evaluative dimensions of pain.

Also for measurement of neuropathic pain, there is DN4, pain detect tools.

FUNCTIONAL MEASUREMENT OF ACUTE PAIN

Most of the unidimensional pain measures only evaluates the pain intensity at rest. The measure of the ability to undertake functional activity measures the functional aspect of pain. This helps to titrate analgesia for optimized recovery.

Measurement of pain intensity scores on movement or with coughing is a useful guide.

The Functional Activity Scale score (FAS score) is a simple three-level ranked categorical score. Its fundamental purpose is to assess whether the patient can undertake appropriate activity at their current level of pain control and to act as a trigger for intervention should this not be the case. The patient is asked to perform the activity, or is taken through the activity in the case of structured physiotherapy (joint mobilization) or nurse-assisted care (e.g. ambulation, turned in bed).

The ability to complete the activity is then assessed using the FAS as:
A—no limitation the patient is able to undertake the activity without limitation due to pain (pain intensity score is typically 0 – 3);
B—mild limitation the patient is able to undertake the activity but experiences moderate to severe pain (pain intensity score is typically 4 – 10); and
C—significant limitation the patient is unable to complete the activity due to pain, or pain treatment-related side effects, independent of pain intensity scores.

This score is then used to track effectiveness of analgesia on function and trigger interventions if required.

Disadvantages of the FAS score are that it has not been independently validated and clinical staff need to be educated in its application.

Outcome Measures of Pain

Pain:
The degree of analgesic effect:
- Difference between the baseline and postintervention score of pain intensity or pain relief (Summed pain intensity difference [SPID]).
- The area under the time-analgesic effect curve for a given time (total pain relief [TOTPAR]).
- Dose of rescue analgesic consumption required in a given time period (e.g. PCA use).

The time to analgesic effect:
- The time to onset of analgesic effect.
- Mean time to maximum reduction in pain intensity or to peak relief.

The duration of effect:
- Time for pain to return to at least 50% of baseline.
- Time for pain intensity to return to baseline or for pain relief to fall to zero.
- Time to remedication/rescue analgesia.

Emotional Functioning

The unpleasantness of the experience and its meaning for the individual may have short-term (anxiety, depression, irritability) and long-term consequences (lost confidence or self-efficacy or post-traumatic stress disorder) for the individual's emotional functioning.

Adverse symptoms and events: If adverse events are sufficiently common (e.g. nausea with opioids) they may be quantifiable in trials of efficacy and specifically measured using dichotomous (present or absent), categorical (none, mild, moderate, severe) or interval (analog or Likert) scales. Analogous to NNTs, the number-needed-to-harm (NNH) may be used to describe the incidence of adverse effects.

PAIN ASSESSMENT IN PEDIATRIC POPULATION

Children's self-report of their pain, where possible, is the preferred approach.

For children who are unable to self-report, an appropriate behavioral or composite tool should be used. If pain is suspected or anticipated, use a validated pain assessment tool is recommended. Assessment, recording, and re-evaluation of pain at regular intervals to be done; the frequency of assessment should be determined according to the individual needs of the child and setting.

The tools useful for assessment of pain in neonates are Comfort scale, Cries scale, Neonatal facial coding system, neonatal infant pain scale, objective pain scale, premature infant pain profile (PIPP), all of them except Comfort scale can be used for premature neonates also.

For children between 3 and 12 years, the tools that can be used are Chedoke-McMaster Pediatric Pain Management Sheet, Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), Faces Pain Scale, Oucher, etc.

For children with cognitive impairment the tools that cab used are Face, Legs, Activity, Cry, Consolability (FLACC) tool (including a revised version of the FLACC tool), Pediatric Pain Profile (PPP), Noncommunicating Children's Pain Checklist, etc.

Pain Assessment in Intubated Postoperative Patients

6. What are the different tools of pain assessment in elderly patients with dementia? Describe one of them.

Ans. Many patients with moderate to severe dementia can report pain reliably at the moment or when prompted, however, pain recall and integration of pain experience over a period of time may be less reliable. Also, the number of pain complaints decreases as dementia progresses.

In older adults with dementia, pain expression sometimes takes on less obvious forms, such as confusion, social withdrawal, aggression, or subtle changes in behavior. So for measurement of pain in these group of patients, various observational scales have been described. These scales are based on the six of the following behavioral patterns:

1. Facial expressions
2. Verbalizations, vocalizations
3. Body movements
4. Changes in interpersonal interactions
5. Changes in activity patterns or routines
6. Mental status changes.

The Abbey tool, the ADD protocol, CNPI, DS-DAT, Doloplus 2, PAINAD, FLACC scale, etc.

The PAINAD Scale75 was developed to provide a clinically relevant and easy to use pain assessment tool for individuals with advanced dementia. It includes five items: breathing, negative vocalization, facial expression, body language, and consolability. Each item is leveled on a 3-point scale from 0 to 2 for intensity.

Pain assessment to be done by using behavioral pain scale (BPS) and the critical-care pain observation tool (CPOT) in postoperative patients who are unable to report pain. In them, using only the vital signs alone is not acceptable.

7. Describe the routes of administration of analgesics.

Ans. *Routes of administration and their uses:*

Oral route: Oral route may not be useful for immediate postoperative patients as most of the patients are not orally allowed. However, they can be used once the pain intensity is decreased. They are also used to decrease opioid requirement and postoperative pain.

The use of an opioid or nonopioid analgesic orally for postoperative pain is governed by the severity of the pain, patient-related factors (comorbidities, allergies, prior experience with

analgesics), the risk of postoperative bleeding (for aspirin or NSAIDs), and the plan for home analgesia. If an analgesic has already been chosen as a discharge medication, transition to that medication in the postoperative period is appropriate.

While using oral agents it is advisable to give single agents, rather than the combination to allow more flexibility. The NSAIDs were usually given as standing order, with opioids are used as an rescue analgesics.

Intramuscular Route

Used for moderate to severe pain, produces rapid analgesic effect. But nowadays are replaced by IV or subcutaneous injection. Disadvantages of this route include pain on administration, variable and sometimes slow onset of effect, and peaks and valleys of analgesic effect.

Intravenous Route

Used to treat acute and severe pain and produces rapid relief. Can be used as an continuous infusion or PCA or intermittent boluses.

Disadvantages of bolus IV injection include more pronounced peaks and valleys of analgesic effect and side effects and a relatively short duration of analgesic.

Continuous infusion results in better analgesia by eliminating peaks and valleys, and also provides a good patient satisfaction with less side effects. Continuous infusion results delay in analgesia if a bolus is not given. Also needs more vigilant monitoring.

Subcutaneous Route

Useful for patients without an intravenous access. Used in patients requiring long-term care, e.g. in oncology patients.

Transdermal/Iontophoretic Administration

Transdermal fentanyl is not ideal for acute perioperative pain. However, iontophoretic delivery of fentanyl provides sufficient analgesia in the perioperative period.

Transmucosal Administration

Used by oncology patients for control of breakthrough pain.

Intrathecal Analgesia

Intrathecal opioids provides short or intermediate term analgesia, which can be increased with hydrophilic opioids like morphine providing analgesia up to 12–36 hours. Useful for lower abdominal surgeries with spinal anesthesia.

For hip and knee arthroplasty, cesarean section, intrathecal morphine provided excellent analgesia for 24 hours after surgery with no difference in side effects; with significant reduction in postoperative patient-controlled (PCA) morphine requirements. Intrathecal fentanyl, sufentanil are also used, but they provides shorter analgesia.

Continuous intrathecal administration is not done due to previous reports of cauda equina from intrathecal administration of high concentration of local anesthetics.

Disadvantage: Cannot be repeated.

Intra-articular Administration

Intra-articular injection of opioids may provide analgesia for up to 24 hours postoperatively and prevent the development of chronic postsurgical pain. The analgesic benefit of intra-articular opioids over systemic administration has not been demonstrated, and the systemic analgesic effect of these injections has not been excluded. Glenohumeral intra-articular continuous catheters have been associated with chondrolysis when bupivacaine is used.

Intrapleural Regional Analgesia

Intrapleural regional analgesia is produced by the injection of a local anesthetic solution through a catheter inserted percutaneously into the intrapleural space. The local anesthetic diffuses across the parietal pleura to the intercostal neurovascular bundle and produces a unilateral intercostal nerve block at multiple levels. Effective postoperative pain relief requires intermittent intrapleural injections approximately every 6 hours of large volumes of local anesthetic (20 mL of 0.25 – 0.5% bupivacaine). This large bolus of local anesthetic into the intrapleural space produces significant side effects while providing minimal analgesia. Pleural drainage tubes also causes loss of the local anesthetic solution and, consequently, poor analgesia. This technique is recommended only if all other options have been exhausted.

Paravertebral Blocks

This block is effective for controlling acute pain associated with breast surgery, but has also demonstrated benefit in decreasing the development of chronic postsurgical pain over other analgesic regimens. This technique can be performed as a single-shot technique or as a continuous catheter infusion to provide ongoing perioperative analgesia.

PERIPHERAL NERVE BLOCK

Intermediate-term pain relief (<24 hours) can be achieved with a combination of a local anesthetic and adjuvant drugs in a single injection. Longer-acting pain control may be indicated by the surgical technique, rehabilitation needs, and patient comorbidities; and can be achieved by utilizing perineural catheters for continuous local anesthetic infusions.

Techniques

Nerve blocks can be inserted using anatomic landmarks, nerve stimulation, and ultrasound guidance. The efficacy between ultrasound-guided techniques and nerve stimulation vary, depending on the skill of the provider, primarily resulting in differences in comfort during placement and procedural time of the blockade.

Adjuvant Drugs

Commonly used adjuvant drugs include epinephrine, clonidine, and opioids. Epinephrine for peripheral nerve blockade significantly increases the duration of the blockade, with minimal side effects. Epinephrine can also increase the sensitivity of intravascular injection; concentrations of 2.5 to 5 mg/mL are generally used. Opioid should not be added to a peripheral nerve blockade. Clonidine is beneficial in extending the duration of preoperative blockade, but hypotension, bradycardia, and sedation, are less likely to occur in doses less than 1.5 mg/kg.

Catheter versus Single-shot Techniques

Upper Extremity

Continuous interscalene blockade allows for longer duration of action compared with single-shot techniques, with better pain relief, with minimal opioid supplementation and increased patient satisfaction and sleep quality.

Lower Extremity

Lower extremity perineural catheters are utilized for major joint surgery of the hip, knee, ankle, and foot. Lumbar plexus catheters have been utilized as part of a multimodal regimen that include PCA with or without femoral catheters for unilateral hip repairs.

8. Epidural analgesia, its advantage over other routes. Advantages of thoracic over lumbar epidural. Drugs used and complications. What are adjuvant medication that can be used epidurally?

Ans. Epidural analgesia can be provided with local anesthetics alone or with opioids. It provides superior analgesia in upper abdominal surgeries, thoracotomies, joint replacement surgeries.

As compared to systemic opioids via PCA, epidural analgesia provides better pain relief at rest and with movement after all types of surgery and lower incidence of nausea/vomiting and sedation, pulmonary infections and pulmonary complications but a higher incidence of pruritus, urinary retention and motor block.

Addition of epidural analgesia in addition to general anesthesia resulted in a reduced rate of arrhythmias, earlier extubation, reduced intensive care unit (ICU) stay, reduced stress hormone, cortisol and glucose concentrations as well as reduced incidence of renal failure, when local anesthetics were used.

Usually a continuous infusion is used.

LEVEL OF ADMINISTRATION—THORACIC VS LUMBAR

Thoracic epidural analgesia (TEA) for the treatment of pain after major abdominal and thoracic surgery, resulted in improved bowel recovery after abdominal surgery and also postoperative myocardial infarction, while these benefits were not consistent with lumbar administration.

In patients undergoing gynecological surgery showed that TEA provided better pain relief only when the incision extended above the umbilicus.

Drug used for Epidural Analgesia

Local anesthetics: Infusions of bupivacaine or levobupivacaine at 0.1% or 0.125% with ropivacaine 0.2% are used. Local anesthetics alone results in more motor or sensory blockade, mostly employed to avoid opioid related adverse effects.

Opioids: The actions of epidural opioids is also governed largely by their lipid solubility. Lipophilic opioids (e.g. fentanyl) have a faster onset but shorter duration of action compared with hydrophilic drugs (e.g. morphine).

Morphine has a prolonged analgesic effect and it can be given by intermittent bolus dose or infusion; the risk of respiratory depression may be higher and analgesia less effective with bolus dose regimens. An infusion of epidural fentanyl appears to produce analgesia by uptake into the systemic circulation, whereas a bolus dose of fentanyl produces analgesia by a selective spinal

mechanism. There is no evidence of benefit of epidural versus systemic administration of alfentanil or sufentanil.

The addition of butorphanol to epidural bupivacaine resulted in more rapid and prolonged pain relief compared with butorphanol alone.

Neuraxial Drugs and their Doses (Table 2)

Table 2 | Neuraxial drugs and doses

Drugs	*Intrathecal single dose*	*Epidural single dose*	*Epidural infusion*
Fentanyl	5–25 mcg	50–100 mcg	25–100 mcg/hour
Sufentanil	2–10 mcg	10–50 mcg	10–20 mcg/hour
Morphine	0.1–0.3 mg	1–5 mg	0.1–1 mg/hour
Methadone		4–8 mg	0.3–0.5 mg/hour
Alfentanil	0.5–1 mg	0.1–1 mg	
Bupivacaine	5–15 mg	25–150 mg	1–25 mg/hour
Ropivacaine	—	25–200 mg	1–25 mg/hour
Clonidine	—	100–900 mcg	10–50 mcg/hour

Local Anesthetic Agents and Opioids

Combinations of low concentrations of local anesthetic agents and opioids have been shown to provide consistently superior pain relief compared with either of the drugs alone. Addition of fentanyl to a continuous epidural infusion of ropivacaine reduced the rate of regression of sensory block and decreased the discontinuation of postoperative epidural infusion due to lack of efficacy.

Adjuvant Drugs

The efficacy of adding of adjuvant drugs such as adrenaline (epinephrine), clonidine, ketamine, midazolam, neostigmine and magnesium to solutions used for epidural analgesia.

Complications

Permanant neurological injury, epidural hematoma, epidural abscess, respiratory depression, hypotension, postdural puncture headache.

9. What is patient-controlled analgesia? Described the route, drugs and doses used, advantages of PCA. Setting of PCA. Need for background infusion. What are the Complications?

Ans. PCA can be delivered via oral, intravenous, subcutaneous, epidural, and intrathecal routes, as well as by peripheral nerve catheter. There is limitation of the number of doses per unit time and also the time interval between two successive doses. A background continuous infusion is not indicated unless a opioid tolerant patient.

PCA provide better patient satisfaction, safety, better pain relief, less total drug use, less sleep disturbance, less sedation, more rapid return of physical function.

PCA may lead to sedation, so monitoring of respiratory rate and capnography (in critical cases) to be done.

IV PCA Drugs and Dose and Settings (Table 3)

Table 3 | IV PCA drugs and doses

Drug	*Bolus dose*	*Lock out*	*Continuous infusion*
Morphine	0.5–2.5 mg	5–10 min	1–2 mg/hour
Fentanyl	25–50 mcg	5–10 min	10–100 mcg/hour
Alfentanil	0.1–0.2 mg	5–10 min	
Oxymorphone	0.2–0.4 mg	8–10 min	
Sufentanil	2–10 mcg	4–10 min	2–8 mcg/hour
Methadone	0.5–1.5 mg	10–30 min	

While the optimal sized bolus dose should provide good pain relief with minimal side effects. Initial orders for bolus doses should take into account factors such as a history of prior opioid use and patient age. While adjust bolus dose the number of both successful and unsuccessful attempts should be taken into account. The routine use of a background infusion is not recommended, except for opioid-tolerant patients. Patient's pain should be controlled before PCA is started by administration of individually titrated loading doses.

Adjuvent Medications

Adjuvent medications like droperidol, ondansetron reduces nausea, vomitting. Concurrent ketamine infusion leads to decrease in opioid dose. Addition of clonidine, dexmedetomidine, magnesium to PCA leads to better pain relief and less adverse effects.

Equipment

- *Programmable PCA pumps:* Adjustments can be made to the dose delivered and lockout intervals, background infusions can be added, and accurate assessments can be made of the total dose of drug delivered. In addition, access to the syringe (or other drug reservoir) and the microprocessor program is only possible using a key or access code.
- *Disposable PCA devices:* No adjustments can be made and of single use.
- *Parenteral PCA devices:* Advantages include small size and weight, freedom from an external power source, elimination of programming errors, and simplicity of use.

  Disadvantages include an inability to alter the volume of the bolus dose delivered or add a background infusion, difficulties determining the amount of drug the patient has received accurately, the possibility of inaccurate flow rates, and long-term costs
- *Transmucosal PCA devices:* Metered-dose PCINA devices are available. The drugs must be administered in small volumes to avoid significant run-off into the pharynx.
- *Transdermal PCA devices:* The fentanyl PCTS uses a low-intensity electric current to drive the drug from the reservoir through the skin and into the systemic circulation. The Ionsys device, which is applied to the chest or upper outer arm, delivers a fixed dose of 40 mcg fentanyl over a 10 minutes period following a patient demand and allows delivery of up to 6 doses each hour, up to a maximum of 80 doses in 24 hours, to be replaced every 24 hours.

Complications Related to PCA

Complications related to the use of PCA can be divided into:
- Operator or patient-related errors
- Due to the equipment
- The opioid used.

Equipment-related Complications

There may be 'run-away' pumps, where the PCA pump unexpectedly delivers an unprescribed dose of drug due to spontaneous triggering and also uncontrolled syphoning of syringe contents when the PCA machine was above patient level.

Patient and Staff Factors

Education: Education of the patient about the opioid and PCA helps in removing worries about addiction and safety of PCA.

Inappropriate use of PCA occurs when some unauthorized person or family pressing the PCA, patient pressing PCA thinking it to a doorbell.

Nursing and Medical Staff

Wrong concentration of drug. Avoided by standard drug concentration in PCA. Also errors in programming bolus, and other setting can be avoided by using a present standard settings without a continuous infusion.

Other Types of PCA

- Patient-controlled regional analgesia via:
  - Incision (incisional PCRA) with local anesthetics
  - Intra-articular (IA) tissue (IAPCRA) with local anesthetics and opioids
  - Perineural site (perineural PCRA) with local anesthetics.
- Patient-controlled intranasal analgesia (PCINA) with fentanyl
- Patient-controlled transpulmonary analgesia.

It is a novel, proprietary inhalation formulation of free and liposome-encapsulated fentanyl intended to provide rapid, extended, and personalized analgesia for patients experiencing acute pain episodes.

Using this patients can identify and select a personalized dose for each pain episode, achieving both rapid onset and extended duration of analgesia.

10. Describe the various adjuvant medications used in perioperatve pain management.
Ans. *Alpha-2 agonists (Clonidine, Dexmedetomidine)*
The addition of clonidine to epidural, intrathecal, peripheral nerve blocks lead to prolonged analgesia and decreased opioid consumption. But intrathecal clonidine leads to sedation and hypotension.

With IVRA, dexmedetomidine prolongs increased duration and quality of analgesia, whereas clonidine delays the tourniquet pain. Intra-articular use has also resulted in improved pain relief.

Systemic administration (oral, IM, IV) of single doses of the alpha-2 agonists clonidine and dexmedetomidine decreased perioperative opioid requirements in surgical patients.

Additon of clonidine or dexmedetomidine to morphine PCA resulted better pain relief and lesser nausea, but lead to hypotension and sedation. Dexmedetomidine infusion in ventilated patients resulted in 50% decrease of morphine requirement.

Glucocorticoids: Systemic dexamethasone reduces postoperative pain, nausea and vomiting, and fatigue. It also reduces dynamic pain in breast and hip surgeries, reduces radicular pain in lumbar disectomy. Perioperative methylprednisolone resulted in less hyperesthesia.

Adrenaline: In postoperative thoracic epidural infusions, the addition of adrenaline (epinephrine) to fentanyl and ropivacaine or bupivacaine improved analgesia. The addition of adrenaline to intrathecal bupivacaine prolonged motor and sensory block.

NMDA receptor antagonists: The NMDA-receptor antagonists are ketamine, dextromethorphan, amantadine, memantine.

Ketamine: Perioperative low-dose ketamine used in conjunction with patient-controlled analgesia morphine is opioid-sparing and reduces the incidence of nausea and vomiting, but does not produce a clinically significant reduction in pain scores. Ketamine is a safe and effective analgesic for painful procedures in children. Ketamine may improve analgesia in patients with severe acute pain that is poorly responsive to opioids. Ketamine reduces postoperative pain in opioid-tolerant patients.

Amantadine and memantine: Oral amantadine and memantine lead to decreased opioid consumption. Oral amantadine has also reduced the incidence of phantom limb pain.

Neuraxial: Preservative free ketamine when added to intrathecal opioid analgesia results in improved pain relief, less opioid requirements, and less adverse effects. Ketamine and midazolam when added together to the intrathecal local anesthetics leads to better pain relief as compared to local anesthetic (LA) or LA and ketamine. Caudal epidural ketamine (0.25–0.5 mg/kg) resulted in prolonged pain relief with minimal adverse effects. There is no advantage of using ketamine in peripheral blocks, wound infiltration, intra-articular, etc.

A transdermal ketamine patch (delivering 25 mg over 24 hours) reduced analgesic consumption after gynecological surgery, but topical ketamine applied to tonsils has no advantage.

Midazolam

Preservative free midazolam has been proposed as a potential spinal analgesic due to its action on GABA A receptors. Intrathecal midazolam leads to increase in duration of analgesia and less nausea and vomitting. Caudal epidural midazolam in children prolongs the bupivacaine analgesia.

Neostigmine

Neostigmine acts as a spinal analgesic by potentiation of muscarinic cholinergic activity.

Intrathecal neostigmine resulted in higher nausea and vomiting, bradycardia requiring atropine and anxiety, agitation and restlessness; and also the pain relief is minimal.

Epidural neostigmine and resulted in improved analgesia, lesser opioid requirement.

Magnesium

Magnesium acts as an NMDA receptor antagonist. The benefits of using magnesium are:

- Combined intrathecal and epidural in orthopedic surgery leading to decreased opioid requirement

- With lignocaine in IVRA prolongs analgesia and improves tolerance to tourniquet
- Intra-articularly leads to better pain relief
- Magnesium added to morphine for PCA was opioid-sparing and led to better pain relief; added to tramadol, it was opioid-sparing but only provided better.

Membrane Stabilizers

Perioperative IV lignocaine (lidocaine) infusion was opioid-sparing and significantly reduced pain scores, nausea, vomiting and duration of ileus up to 72 hours after abdominal surgery and also reduced length of hospital stay. However addition of lignocaine to morphine PCA has no benefit.

Gabapentin and Pregabalin

Perioperative gabapentinoids improved analgesia (at rest and with movement) and reduced postoperative opioid consumption, decreased opioid induced adverse effects like nausea, vomiting, pruritus, urinary retention, but increased the incidence of sedation. The effects of gabapentin were not dose-dependent in the range of 300–1200 mg. They also reduce the epidural opioid requirement.

Pregabalin reduces opioid requirements, prevents and reduces of opioid tolerance, improves the quality of opioid analgesia, decreases incidence of respiratory depression and relieves anxiety.

Antidepressant Drugs

Amitriptyline is effective in the treatment of neuropathic pain following breast surgery.

Capsaicin

Injectable capsaicin is used for the control of postoperative pain, such as after total knee replacement, total hip replacement, hernia repair, shoulder arthroscopy, and bunionectomy. Preadministration of neural blockade before injection of capsaicin may greatly decrease the burning discomfort.

11. Describe the usefulness of paracetamol in postoperative pain.

Ans. Paracetamol (acetaminophen) is an effective analgesic and antipyretic.

Mechanism of action is still elusive. Suggested mechanisms include the activation of the endocannabinoid system and spinal serotonergic pathways, prevention of prostaglandin production at the cellular transcriptional level, independent of cyclo-oxygenase activity.

Single doses of paracetamol are effective in the treatment of postoperative pain. Paracetamol is also an effective adjunct to opioid analgesia, opioid requirements being reduced by 20–30% when combined with a regular regimen of oral or rectal paracetamol. In the same doses, orally administered paracetamol was less effective and of slower onset than paracetamol given by IV injection, but more effective and of faster onset than paracetamol administered by the rectal route. IV paracetamol was as effective as ketorolac, diclofenac and was equivalent to morphine and better tolerated after dental surgery.

It should be used with caution or in reduced doses in patients with active liver disease, history of heavy alcohol intake and glucose-6-phosphate dehydrogenase deficiency. But there is no evidence that therapeutic doses will lead to hepatic dysfunction in these groups of patients.

NONSELECTIVE NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (nsNSAIDs)

These are of the following classes:

- *Proprionic acid derivatives:* Ibuprofen and naproxen
- *Salicylates:* Aspirin and choline salicylate
- *Anthranilic acid derivatives:* Indomethacin and ketorolac
- *Oxicams:* Piroxicam
- *Cyclo-oxygenase-2 inhibitors:* Celecoxib.

Single doses of nsNSAIDs are effective in the treatment of pain after surgery. nsNSAIDs are integral components of multimodal analgesia. When given in combination with opioids after surgery, nsNSAIDs resulted in better analgesia, reduced opioid consumption and a lower incidence of PONV and sedation, however there was no effect on pruritus, urinary retention and respiratory depression. The combination of paracetamol and nsNSAID was more effective than paracetamol alone.

Guide for Choosing NSAIDs

- Assess patient's renal, cardiac, and gastrointestinal status before starting drug treatment.
- Determine best route of administration.
- Identify drugs that are appropriate for route of administration desired.
- Select familiar agent among the drugs whose time between onset of activity and peak effect is appropriate for pain syndrome being treated.

Guide for Administering NSAIDs

- Review properties of agent selected
- Start at low end of dosing range
- Use loading dose when appropriate
- Do not exceed ceiling dose
- Ensure that equianalgesic doses are given if route of administration is changed.

Adverse Effects

NSAID side effects are more common with long-term use.

Renal function: The risk of adverse renal effects of NSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolemia, hypotension, use of other nephrotoxic agents and angiotensin-converting enzyme (ACE) inhibitors. With proper selection and monitoring, the incidence of NSAID-induced perioperative renal impairment is low and NSAIDs need not be withheld in patients with normal preoperative renal function.

Platelet function: NSAIDs inhibit platelet function. NSAIDs were found to increase the risk of reoperation for bleeding in tonsillectomy. NSAIDS results in increased bleeding in many surgeries including hip replacement, gynecological, breast surgeries, etc.

Peptic ulceration: Risks were shown to be significantly increased for patients using naproxen, diclofenac, ibuprofen, aspirin and rofecoxib, but not those taking celecoxib. Risk is increased with higher doses, a history of peptic ulceration, use for more than 5 days and in elderly people. Risk is very low with COX 2 inhibitors. Concurrent use of a proton-pump inhibitor (PPI) significantly reduced the incidence of NSAID-related peptic ulcer disease.

Aspirin-exacerbated respiratory disease: Aspirin-exacerbated respiratory disease (AERD) affects 10–15% of people with asthma, can be severe and there is a cross-sensitivity with nsNSAIDs but not coxibs. So, nsNSAIDS are contraindicated in these group of patients.

Cardiovascular events: Adverse cardiovascular events is higher with NSAIDS. Coxibs also causes CV events and are contraindicated in patients after CABG. Risks were significantly increased for patients using rofecoxib, diclofenac and ibuprofen. Naproxen as the preferred NSAID for long-term use in patients with or at high-risk for cardiovascular disease. Ibuprofen abolishes the protective effect of aspirin, and a gap of 8 hours should be there between ibuprofen intake and aspirin dosing.

Cyclo-oxygenase-2 Selective Inhibitors (Coxibs)

The coxibs available at present include celecoxib, etoricoxib and parecoxib.

Coxibs were as effective as NSAIDs in the management of postoperative pain. Preoperative coxibs reduced postoperative pain and opioid consumption and increased patient satisfaction. When given in combination with opioids after surgery, coxibs were opioid-sparing, but both a decrease in the incidence of opioid-related side effects or pain scores were not observed.

Opioids

All full opioid agonists given in appropriate doses produce the same analgesic effect and therapeutic index, although accurate determination of equianalgesic doses is difficult due to interindividual variability in kinetics and dynamics. Equianalgesic conversion dose tables are often used to assist in the change from one opioid to another. However, such tables should be used as a guide only as they are based largely on single-dose studies in opioid-naive subjects and may not be as relevant when conversions are made after repeated doses of an opioid have been given.

Buprenorphine

Buprenorphine is a semisynthetic derivative of thebaine, an alkaloid of opium, and a partial mu-opioid receptor agonist and kappa-opioid receptor antagonist with high receptor affinity and slow dissociation from the mu-receptor. Mean half life is 2–3 hours after parenteral injection; two-thirds of the drug is excreted unchanged, mainly in feces, while the remaining one-third is metabolized predominantly in the liver and gut wall via glucuronidation. There was a ceiling effect found for respiratory depression but not for analgesia. The risk of respiratory depression is low compared with morphine, methadone, hydromorphone and fentanyl. To reverse buprenorphine induced respiratory depression, higher dose and prolong infusion of naloxane is needed. Withdrawal symptoms, which may be seen if the drug is ceased after long-term treatment, are milder and more delayed in onset (72 hours or more) than other opioids. Preoperatively patient may be on buprenorphine for opioid addiction.

Codeine

It is a very weak mu-receptor agonist and its analgesic action depends on the metabolism of about 10% of the dose given to morphine.

In Caucasian populations, 8–10% of people are poor metabolizers; however 3 – 5% are ultrarapid metabolizers. Those who are ultrarapid metabolizers (carriers of the *CYP2D6* gene duplication) have significantly higher levels of morphine and morphine metabolites after the same dose of codeine.

Fentanyl

Fentanyl is a highly potent phenylpiperidine derivative. It is metabolized almost exclusively in the liver to minimally active metabolites. Fentanyl is commonly used in the treatment of acute pain, especially when its lack of active metabolites and fast onset of action may be of clinical benefit.

Hydromorphone

Hydromorphone is a derivative of morphine that is approximately five times as potent as morphine. The main metabolite of hydromorphone is hydromorphone-3-glucuronide (H3G), a structural analog of morphine-3-glucuronide (M3G). Like M3G H3G is dependent on the kidney for excretion, has no analgesic action and can lead to dose-dependent neurotoxic effects.

Methadone

Methadone is a synthetic opioid commonly used for the maintenance treatment of patients with an addiction to opioids and in patients with chronic pain. It is commercially available as a racemic mixture of R- and L-enantiomers, but it is the R-enantiomer that is responsible for most, if not all, its mu-opioid receptor mediated analgesic effects.

It has good oral bioavailability (70–80%), high potency and long duration of action, and a lack of active metabolites. It is also a weak NMDA receptor antagonist and monoamine (serotonin and norepinephrine) reuptake inhibitor and has a long and unpredictable half-life (mean of 22 hours; range 4–190 hours) leading to an increased risk of accumulation. Therefore, it is of limited use for acute pain treatment. Dose conversion is complex and depends on many factors including absolute doses of other opioids and duration of treatment.

High dose methadone has been associated with prolonged QT intervals.

Morphine

Morphine is a naturally occurring opioid with poor lipid solubility. After oral administration, plasma levels of morphine peak at 30–90 minutes. Bioavailiability is low via oral route, usually 20–30%. Protein binding is 45%. Mean elimination half life is 1.5–3.5 hours. Morphine is rapidly distributed to highly perfused tissues like kidney, lungs, liver, spleen. It is metabolized in liver to morphine-3-glucoronide, morphine-6-glucoronide and morphine-3, 6-glucoronide. Morphine-3-glucoronide is inactive and responsible for the development of tolerence. Morphine-6-glucoronide is active and accumulates in renal failure leading to toxixcity.

12. Describe the changes in drugs metabolism in hepatic and renal failure, and the dose adjustments of the drugs.

Ans. *Hepatic impairment*

- While there are limited data, dose adjustments are usually not required for alfentanil, buprenorphine, fentanyl, morphine, oxycodone and sufentanil
- Tramadol may need to be given at lower doses
- Methadone should be used with caution in the presence of severe liver disease because of the potential for greatly prolonged clearance
- The clearance of local anesthetics may be significantly impaired; doses may need to be decreased if use is prolonged
- Carbamazepine and valproate should be avoided in patients with severe hepatic impairment

- It may be wise to reduce the dose of paracetamol in patients with significant degrees of hepatic impairment.

Renal impairment:

- Analgesics that exhibit the safest pharmacological profile in patients with renal impairment are alfentanil, buprenorphine, fentanyl, ketamine, paracetamol (except with compound analgesics) and sufentanil. None of these drugs delivers a high active metabolite load or has a significantly prolonged clearance
- Oxycodone can usually be used without any dose adjustment in patients with renal impairment. Its metabolites do not appear to contribute to any clinical effect in patients with normal renal function
- Amitriptyline, bupivacaine, levobupivacaine, lignocaine, ropivacaine, clonidine, gabapentin, codeine, hydromorphone, methadone, morphine and tramadol have been used in patients with renal disease but depending on the degree of impairment and, in the case of local anesthetics, whether or not administration is prolonged, may require a reduction in dose
- Levobupivacaine, with similar clearance mechanisms, and ropivacaine may be safer than bupivacaine because of a higher therapeutic ratio
- NSAIDs (both nsNSAIDs and coxibs), dextropropoxyphene and pethidine should not be used in the presence of significant renal impairment.

Analgesic Drugs in Patients with Renal Impairment (Tables 4 and 5)

Table 4 | Analgesic drugs with renal impairment

Drug	*Pharmacokinetics and pharmacodynamics*	*Recommendations*
Alfentanil	• No active metabolites • 92% protein bound; increases in free fraction may result from alterations in protein binding	No dose adjustment required unless renal failure is severe
Buprenorphine	• Pharmacokinetics unchanged; predominantly biliary excretion of metabolites • Pharmacokinetics also unchanged with dialysis	No dose adjustment required
Codeine	• Accumulation of active metabolites can occur; prolonged sedation and respiratory arrest have been reported in patients with renal impairment • No good data on removal by dialysis	Dose adjustment recommended or use an alternative opioid
Dihydrocodeine	• Metabolic pathway probably similar to codeine	*Insufficient evidence:* Use not recommended
Fentanyl	• No active metabolites • Not removed to any significant degree by dialysis	No dose adjustment required; may be used in patients with severe renal impairment
Hydromorphone	• Neurotoxicity from accumulation of H3G possible • H3G is effectively removed during dialysis	Dose adjustment recommended or use alternative opioid

Contd...

Contd...

Drug	*Pharmacokinetics and pharmacodynamics*	*Recommendations*
Methadone	• Methadone and its metabolites are excreted in urine and feces; in anuric patients it may be mostly in feces • High protein binding, high volume of distribution and moderate water solubility would suggest that it is likely to be poorly removed by dialysis	Dose adjustment may be required in severe renal impairment
Morphine	• Major metabolites M3G and M6G excreted via kidney and accumulate in renal impairment • M6G is an opioid agonist that crosses the blood-brain barrier slowly; delayed sedation from M6G has been reported in renal failure • Neurotoxicity from accumulation of M3G possible • Oral administration results in proportionally higher metabolite load • Morphine and its metabolites are cleared by most hemodialysis procedures but may not be significantly affected by peritoneal dialysis • M6G also removed but slow diffusion from CNS delays response	Dose adjustment recommended or use alternative opioid
Oxycodone	• The metabolite oxymorphone is active but plasma levels are normally negligible and therefore it has an insignificant clinical effect in patients with normal renal function. • Higher blood concentrations of oxycodone and metabolites with moderate to severe renal impairment; half life significantly increased in endstage renal disease • Oxycodone and its metabolites are dialyzable	No dose adjustment required in most patients
Pethidine	• Norpethidine is the only active metabolite and is renally excreted; it is dialyzable • Accumulation of norpethidine can lead to neuroexcitation including seizures	Use of alternative agent recommended
Sufentanil	Minimally active metabolite	No dose adjustment required
Tramadol	• Increased tramadol-like effects from active metabolite • O-desmethyltramadol (M1) • Tramadol is removed by dialysis	Dose adjustment recommended Use of alternative agent recommended with significant renal impairment

Contd...

Contd...

Drug	*Pharmacokinetics and pharmacodynamics*	*Recommendations*
Local anesthetics	• There may be no significant difference in plasma concentration of levobupivacaine, bupivacaine or ropivacaine in patients with chronic renal failure unless renal failure is severe, continuous infusions are used or repeated doses are used • Risk of toxicity may be affected by abnormalities in acid-base balance and/or potassium levels	Doses may need to be reduced if prolonged or repeated administration, e.g. continuous infusions
Paracetamol	• Terminal elimination half-life may be prolonged and is dialysable	• May need to increase dose interval if renal impairment is severe • Weak evidence that it may increase the rate of progression to chronic renal failure
nsNSAIDs and coxibs	• Can affect renal function • Behavior during dialysis not clearly elucidated for most	• Use with caution in patients with mild renal impairment and avoid in patients with severe renal impairment
Clonidine	• Half-life is increased in severe renal failure 50% metabolized by the liver; remained excreted unchanged by the kidney	• Limited data; dose adjustment has been recommended
Tricyclic antidepressants	• Amitriptyline is metabolized in the liver to nortriptyline, the active agent • Not significantly removed by dialysis	• Limited data; metabolite accumulation may occur and increase the risk of side effects but little evidence to indicate need for dose reduction
Ketamine	• Dehydronorketamine levels are increased but it has only 1% of potency of ketamine • Ketamine is not removed well by dialysis	• Limited data; probable that no dose adjustment is required
Gabapentin	• Impaired renal function results in reduced clearance in direct proportion to creatinine clearance; about 35% cleared by dialysis	• Dose adjustment recommended on basis of creatinine clearance
Pregabalin	• Impaired renal function results in reduced clearance in direct proportion to creatinine clearance; highly cleared by dialysis	• Dose adjustment recommended on basis of creatinine clearance

Table 5 | Analgesic drugs in patients with hepatic impairment

Alfentanil	• No significant difference in half-life found in children undergoing liver transplant	*Limited data:* No dose adjustment required
Buprenorphine	• Buprenorphine • Lower blood concentrations of buprenorphine and norbuprenorphine • Limited	*Limited data:* No dose adjustment required
Fentanyl	• Disposition appears to be unaffected	*Limited data:* No dose adjustment required
Methadone	• Increased half-life but limited significance	*Limited data:* No dose adjustment required in chronic stable liver disease
Morphine	• Hepatic impairment does not appear to have a significant effect on morphine pharmacokinetics; even in patients with cirrhosis there is a large hepatic reserve for glucuronidation • Blood concentrations of morphine but not morphine metabolites higher after liver resection; blood concentrations also higher in patients with liver cancer Increased oral bioavailability of morphine due to its normal high first pass metabolism when given via this route	In most patients no dose adjustment required
Oxycodone	Decreased oxycodone clearance with mild to moderate hepatic impairment	*Limited data:* No dose adjustment required in most patients
Pethidine	Reduced clearance	*Limited data:* Dose adjustment may be required; use not recommended
Sufentanil	No difference in clearance or elimination	No dose adjustment required
Tramadol	Reduced clearance	*Limited data:* Dose adjustment may be required if impairment is severe
Local anesthetics	• Amide-type local anesthetics undergo hepatic metabolism and clearance may be reduced in hepatic disease • Increased plasma concentrations of ropivacaine after continuous infusion but not single dose	*Limited data:* Dose adjustment may be required with prolonged or repeated use
Paracetamol	• Metabolized in the liver; small proportion metabolized to the potentially hepatotoxic metabolite • N-acetyl-p-benzoquinone imine • This is normally inactivated by hepatic glutathione • Clearance is reduced	• Used with caution or in reduced doses or frequency with active liver disease, alcohol-related liver disease and glucose-6-phosphate dehydrogenase deficiency. However, others report that it can be used safely in patients with liver disease and is preferred to NSAIDs, and that therapeutic doses of paracetamol, at least for short-term use, are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol
Tricyclic antidepressants	Amitriptyline is metabolized in the liver to nortriptyline, the active agent	Reduce dose if hepatic impairment is severe

Pharmacogenetics and its Influence on Pain Sensitivity and Drug Metabolism

With time an increasing number of genetic variants modulating nociception, susceptibility to pain conditions, as well as response to pharmacotherapy have been discovered.

Pharmacogenomics deals with the influence of genetic variation on drug response in patients. By correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity, the aim is to develop rational means to optimize drug therapy with respect to the patient's genotype and ensure maximum efficacy with minimal adverse effects.

Loss of Pain Sensation

Loss of pain sensations occurs in some recognized hereditary syndromes that include:

- Channelopathy-associated insensitivity to pain'caused by variants in the *SCN9A* gene
- Hereditary sensory and autonomic neuropathy (HSAN) I-V syndromes.

Reduced Sensitivity to Pain

Reduced pain sensitivity has been associated with variants in genes encoding the mu-opioid receptor (OPRM1), catechol-O-methyltransferase (COMT), guanosine triphosphate cyclohydrolase 1/dopa-responsive dystonia (GCH1), transient receptor potential (TRPV 1), and the melanocortin-1 receptor (MC1R).

Drug Metabolism

Most of the drugs are metabolized by the polymorphic cytochrome P450 enzymes and they show interindividual variability in their catalytic activity.

Codeine

In children and adults receiving codeine for postoperative pain, very low or undetectable levels of plasma morphine have been noted in those with poor metabolizer or intermediate metabolizer genotypes, but with variable impact on analgesia.

With ultrarapid metabolizers, there is more than 50% increase in morphine concentration in the plasma, this along with concurrent renal failure may cause toxicity.

Tramadol

Poor metabolizers have low concentration of its metabolite and poor analgesic efficacy. Whereas ultrarapid metabolizers have higher concentration of the metabolite, and it may result in respiratory depression with concurrent renal failure.

Methadone

Genetic polymorphisms in genes coding for methadone-metabolizing enzymes, transporter proteins (p-glycoprotein), and mu-opioid receptors may explain part of the observed inter-individual variation in the pharmacokinetics and pharmacodynamics of methadone; blood concentrations may vary up to 20-fold for a given dose.

NSAIDs

NSAIDs like ibuprofen, naproxen and piroxicam are metabolized by CYP2C9. Between 1 and 3% of Caucasians are poor metabolizers. Homozygous carriers of the CYP2D9* 3 allele may accumulate celecoxib and ibuprofen in blood and tissues and be at risk of increased adverse effects.

13. Define tolerance, addiction, pseudoaddiction.

Ans. *Tolerance:* A predictable physiological decrease in the effect of a drug over time so that a progressive increase in the amount of that drug is required to achieve the same effect. Tolerance develops to desired (e.g. analgesia) and undesired (e.g. euphoria, opioid-related sedation, nausea or constipation) effects at different rates.

Physical dependence: A physiological adaptation to a drug whereby abrupt discontinuation or reversal of that drug, or a sudden reduction in its dose, leads to a withdrawal (abstinence) syndrome.

Withdrawal can be terminated by administration of the same or similar drug.

Addiction: A disease that is characterized by aberrant drug-seeking and maladaptive drug-taking behaviors that may include cravings, compulsive drug use and loss of control over drug use, despite the risk of physical, social and psychological harm.

While psychoactive drugs have an addiction liability, psychological, social, environmental and genetic factors play an important role in the development of addiction.

Unlike tolerance and physical dependence, addiction is not a predictable effect of a drug.

Pseudoaddiction: Behaviors that may seem inappropriately drug seeking but are a result of under treatment of pain and resolve when pain relief is adequate.

Clinical Implications of Opioid Tolerance and Opioid-induced Hyperalgesia and Plan of Acute Pain Management in these Groups of Patients

Both tolerance and opioid induced hyperalgesia (OIH) may contribute to increased pain.

If inadequate pain relief is due to OIH, a reduction in opioid dose may help; if it is due to opioid tolerance, increased doses may provide better pain relief.

Other reasons for increased pain and/or increased opioid requirements should also be considered. These include acute neuropathic pain, pain due to other causes including postoperative complications, major psychological distress, and aberrant drug-seeking behaviors.

Three main groups of opioid-tolerant patients/patients with OIH are encountered in acute pain settings:

1. Patients with chronic cancer or noncancer pain being treated with opioids, some of whom may exhibit features opioid addiction.
2. Patients with a substance abuse disorder either using illicit opioids or on an opioid maintenance treatment program.
3. Patients who have developed acute opioid tolerance or OIH due to perioperative opioid administration, particularly opioids of high potency.

MANAGEMENT OF ACUTE PAIN

Management of these patients should focus on:

- Effective analgesia
- Use of strategies that may help to attenuate tolerance or OIH
- Prevention of withdrawal
- Close liaison with other treating clinicians and specialist teams as required and appropriate discharge planning.

Effective Analgesia

Opioid requirements are usually significantly higher in opioid-tolerant compared with opioid-naive patients. Opioid-tolerant patients using PCA or epidural analgesia may require approximately three times the dose than their opioid-naive counterparts. Opioid-tolerant patients with chronic pain also reported higher pain scores after surgery and their pain resolved more slowly compared with opioid-naive patients, which may even higher in patients with opioid tolerant noncancer chronic pain.

The incidence of opioid-induced nausea and vomiting may be lower in opioid-tolerant patients although the risk of excessive sedation/respiratory depression may be higher.

IV PCA is a useful modality for pain relief in opioid-tolerant patients provided that pain intensity and opioid consumption are carefully monitored and background requirements are provided if the patient cannot take their usual opioid; larger bolus doses will often be needed. Regardless of the initial dose prescribed, subsequent doses will need to be titrated to effect for each patient.

Neuraxial opioids have been used effectively in opioid-tolerant patients; although higher doses may be required and may not result in an increase in adverse effects. Effective analgesia using intrathecal or epidural opioids will not necessarily prevent symptoms of opioid withdrawal.

Attenuation of Tolerance and Opioid-induced Hyperalgesia

There are a number of strategies that may help attenuate opioid tolerance and OIH, at least to a certain degree. These include:

- Use of NMDA- or opioid-receptor antagonists
- Opioid rotation
- Other adjuvant drugs.

NMDA and opioid-receptor antagonists: In patients taking opioids on a long-term basis, the administration of ketamine has been reported to lead to improved pain relief and reduced opioid requirements.

Opioid rotation: Opioid rotation is commonly used in the treatment of chronic noncancer and cancer pain when a change to another opioid can improve analgesia and reduce side effects. Opioid rotation (e.g. using an opioid that is different from the preadmission opioid) may also be of use in the acute pain setting. The concept is based on the rationale that the different opioids do not act to the same degree on different opioid receptor subtypes and are metabolized differently, and also takes advantage of the fact that cross-tolerance is likely to be incomplete and that the degree of OIH and tolerance appears to vary between opioids.

Prevention of withdrawal: Withdrawal from opioids is characterized by excitatory and autonomic symptoms including abdominal cramping, muscle aches and pain, insomnia, dysphoria, anxiety, restlessness, nausea and vomiting, diarrhea, rhinorrhea and sneezing, trembling, yawning, runny eyes and piloerection or 'gooseflesh'. The time of onset of withdrawal symptoms after cessation of the drug will depend on the duration of action of the opioid.

It should be prevented by maintenance of normal preadmission opioid regimens where possible or appropriate substitutions with another opioid or the same opioid via another route.

While multimodal analgesic regimens (e.g. nsNSAIDs, paracetamol, ketamine, tramadol, regional analgesia) are of analgesic benefit, opioid-tolerant patients are at risk of opioid withdrawal if a purely nonopioid analgesic regimen or tramadol is used. For this reason opioid antagonists (naloxone, naltrexone) or mixed agonist-antagonists (e.g. buprenorphine, pentazocine) should be also avoided (unless the former are needed to treat respiratory depression) as their use may precipitate acute withdrawal reactions.

Use of intrathecal or epidural opioids will not necessarily prevent symptoms of opioid withdrawal and additional systemic opioids may be required.

Clonidine, administered orally or parenterally, will aid in the symptomatic management of opioid withdrawal symptoms.

14. Describe the pain management in patients with addiction disorder.

Ans. Effective management of perioperative pain in patients with an addiction disorder may be complex due to:

- Psychological and behavioral characteristics associated with that disorder
- Presence of the drug (or drugs) of abuse
- Medications used to assist with drug withdrawal and/or rehabilitation
- Complications related to drug abuse including organ impairment and infectious diseases
- Presence of tolerance, physical dependence and the risk of withdrawal.

Effective analgesia may be difficult, may be required for longer periods than in other patients and often requires significant deviations from 'standard' treatment protocols.

Management of pain in patients with an addiction disorder should focus on:

- Effective analgesia
- Use of strategies that may attenuate tolerance, and prevention of withdrawal
- Symptomatic treatment of affective disorders and behavioral disturbances
- The use of secure drug administration procedures.

Not all aberrant drug behaviors indicate opioid addiction. Those that may include unsanctioned dose escalations, 'lost' or 'stolen' medications, obtaining the drugs from a number of different prescribers, polysubstance abuse, use of opioids obtained illicitly, and forging prescriptions.

In general, when opioids are used in the short-term to treat acute pain, they are usually effective and the risk of abuse is considered to be very small. This may not be the case when these drugs are used in the management of chronic noncancer pain, where long-term use of opioids may not provide as effective pain relief and the risk of abuse of the drugs may be higher. Both patients with chronic pain and those with an addiction disorder have a high rate of psychiatric comorbidities (such as anxiety, depression and personality disorders) and patients with chronic pain may therefore be more at risk of developing behavioral problems associated with opioid use.

The prevalence of addiction in chronic pain patients prescribed opioids is reported to range from 0–50%.

Alcohol and benzodiazepines: There is no cross-tolerance between opioids and alcohol or benzodiazepines and there is therefore no pharmacological reason to use higher than 'standard' initial opioid doses in patients with an alcohol or benzodiazepine addiction.

Alcohol and/or benzodiazepine abuse is relatively common and prevention of withdrawal should be a clinical priority in all patients. If benzodiazepines are administered for the treatment of withdrawal signs and symptoms, patient sedation levels must be monitored, especially if they are receiving concurrent opioids. Excessive sedation will limit the amount of opioid than can safely be given.

Cannabinoids: Anecdotal reports suggest higher opioid doses may be required for the management of acute pain in patients who are heavy users of cannabinoids, there is no published information to support this.

Drugs used in the treatment of addiction disorders.

Methadone: Methadone is a long-acting opioid agonist used in the management of patients with an opioid addiction. It is usually given once a day, which is often enough to suppress symptoms of opioid withdrawal; the duration of any analgesic effect from the dose is likely to be much shorter. In

the acute pain setting methadone should be continued, where possible, as usual at the same dose. If the patient is unable to take methadone by mouth, substitution with parenteral methadone or other opioids will be required in the short-term. Parenteral methadone doses should be based on half to two-thirds of the oral maintenance dose by IM or SC in 2–4 times.

Buprenorphine: Buprenorphine is a partial opioid agonist used in the treatment of opioid addiction. It is usually given once everyday or two, which again is often enough to suppress symptoms of opioid withdrawal; like methadone the duration of any analgesic effect from the dose is likely to be much shorter. Preparations that combine buprenorphine and naloxone are available to reduce potential parenteral abuse of the drug.

If shorter-acting opioid agonists will be required, a decision needs be made whether or not to continue buprenorphine. Suggestions for management vary from withholding the buprenorphine and substituting an alternative opioid (e.g. methadone), to continuing the buprenorphine as usual. However, in practice, there appears to be little problem if the buprenorphine is continued and acute pain managed with the combination of a short-acting pure opioid agonist as well as other multimodal analgesic strategies. As with methadone, dividing the daily doses on a temporary basis may take advantage of the analgesic properties of the buprenorphine.

Naltrexone: Naltrexone is a pure opioid antagonist used in the management of patients with opioid or alcohol addiction. The usual oral maintenance dose is up to 25–50 mg daily. Orally administered, naltrexone has an apparent half-life of about 14 hours and binds to opioid receptors for over 24 hours following a single dose.

It has been recommended that, where possible, naltrexone be stopped for at least 24 hours before surgery. In these patients and in patients requiring surgery within this 24-hour period, multimodal analgesic regimens (e.g. NSAIDs, paracetamol, ketamine, tramadol and regional analgesia) should also be employed.

There is experimental evidence of μ (mu)-opioid receptor upregulation following antagonist withdrawal and abrupt discontinuation of naltrexone, leading to a period of increased opioid sensitivity, so the amount of opioid required to maintain analgesia may also need to be decreased in order to avoid signs of excessive opioid dose (in particular, respiratory depression).

Recovering Patients

Patients in drug treatment programs or in drug-free recovery may be concerned about the risk of relapse if they are given opioids for the management of their acute pain.

However, there is no evidence that the use of opioids to treat acute pain increases the rate of relapse. Effective communication and planning, the use of multimodal analgesic strategies, reassurance that the risk of reversion to an active addiction disorder is small, and information that ineffective analgesia can paradoxically lead to relapses in recovering patients, will help to prevent undertreatment.

15. Pain management in elderly patients. What are the clinical implications of the changes in the elderly population?

Ans. *Clinical implications:* Pain intensity after surgery may also be less. Older patients, matched for surgical procedure, reported less pain in the postoperative period: pain intensity decreased by 10–20% each decade after 60 years of age.

Nonselective nonsteroidal anti-inflammatory drugs, coxibs and paracetamol: Older patients are more likely to suffer adverse gastric and renal side effects following administration of nsNSAIDs and may also be more likely to develop cognitive dysfunction.

Coxibs have a significantly lower incidence of upper gastrointestinal complications and have no antiplatelet effects, which might be of some advantage in the older patient; the risk of other adverse effects, including effects on renal function and exacerbation of cardiac failure, are similar to nsNSAIDs.

Opioid Dose

Older patients require less opioid than younger patients to achieve the same degree of pain relief. In the clinical setting there is evidence of an age-related 2- to 4-fold decrease in morphine and fentanyl requirements. It has been suggested that doses of fentanyl, sufentanil and alfentanil should all be reduced by up to 50% in older patients; reductions in the doses of other opioids is also advised.

In patients over 75 years the elimination half-life of tramadol was slightly prolonged. Lower daily doses have been suggested.

Side Effects of Opioids

The incidence of nausea/vomiting and pruritus in the postoperative period lessens with increasing age. In older people, fentanyl may cause less postoperative cognitive dysfunction than morphine and less confusion, although administration of an appropriate opioid medication is often associated with higher levels of cognitive function compared with cognitive function if postoperative pain is undertreated.

Local Anesthetics

Older patients are more sensitive to the effects of local anesthetic agents because of a slowing of conduction velocity in peripheral nerves and a decrease in the number of neurons in the spinal cord.

Ketamine

There are no good data on the need or otherwise to alter ketamine doses in the older patient.

Tricyclic Antidepressants

Clearance of tricyclic antidepressant (TCA) drugs may decrease with increasing patient age and lower initial doses are recommended in older people and are more prone to the adverse effects.

In addition, clinical conditions that may require TCAs to be administered with caution are more common in older people and include prostatic hypertrophy, narrow angle glaucoma, CV disease and impaired liver function.

Anticonvulsants

Initial doses of anticonvulsant agents should be lower than for younger patients and any increases in dose should be titrated slowly. The side effects such as somnolence and dizziness with pregabalin may be more common. However, other features of gabapentin and pregabalin, such as a lower risk of drug—drug interactions, lower (less than 3%) protein binding, no hepatic metabolism and the lack of any need to monitor liver function and blood count on a regular basis, means that these drugs may be well-suited to the older patient population.

Patient-controlled Analgesia

Patient-controlled analgesia (PCA) is an effective method of pain relief in older people. They require less opioid, but pain relief, adverse effects, risks of addiction is similar to young ones. Compared to IM morphine PCA morphine provides better analgesia with fewer pull complications.

Epidural Analgesia

Older patients given PCEA had lower pain scores at rest and movement, higher satisfaction scores, improved mental status and more rapid recovery of bowel function compared with those using IV PCA. Epidural morphine requirements decrease as patient age increases. Older patients require less volume and are more susceptible to adverse effects like hypotension.

Intrathecal Opioid Analgesia

Intrathecal morphine using a variety of doses provided more effective pain relief after major surgery compared with other opioid analgesia, although the risk of respiratory depression and pruritus was greater.

Intrathecal morphine 100 mcg dose provided the best balance between good pain relief and pruritus.

Other Regional Analgesia

Possible advantages include a reduction in the incidence of side effects compared with central neuraxial blockade. The duration of action of sciatic nerve and brachial plexus blocks is prolonged in the older patient. In older patients regional blocks like femoral, paravertebral are useful.

16. Implication of pregnancy in pain management (Describe the precautions in using the drugs and the analgesic techniques).

Ans. *Paracetamol:* Paracetamol is regarded as the analgesic of choice during pregnancy, although it has been suggested that prostaglandin actions may have adverse effects in women at high-risk of pre-eclampsia such as preterm birth, increase incidence of asthma in infants.

Nonselective nonsteroidal anti-inflammatory drugs: Use of nsNSAIDs during pregnancy was associated with increased risk of miscarriage. While relatively safe in early and mid pregnancy, they can precipitate fetal cardiac and renal complications in late pregnancy, as well as interfere with fetal brain development and the production of amniotic fluid; they should be discontinued in the 32nd gestational week. Fetal exposure to nsNSAIDs has been associated with persistent pulmonary hypertension in the neonate and an increased risk of premature closure of the ductus arteriosus.

Opioids: Much of the information about the effects of opioids on neonates comes from pregnant patients who abuse opioids or who are on maintenance programs for drug dependence. Maternal long term opioid use can have significant developmental effects in the fetus, although social and environmental factors may also have an impact.

Neonatal abstinence syndrome (NAS) requiring treatment occurs in over 60–90% of infants exposed to opioids *in utero*. Outcomes tend to be better in mothers on maintenance therapy rather than heroin, even better with mothers receiving it for pain than addiction.

Overall, the short-term use of opioids to treat pain in pregnancy appears safe.

Risk Factors for Progression from Acute Postoperative Pain to Chronic Pain

Risk factors for chronic postsurgical pain:

- Preoperative factors
  - Pain, moderate to severe, lasting more than 1 month
  - Repeat surgery
  - Psychological vulnerability (e.g. catastrophizing)
  - Preoperative anxiety
  - Female gender
  - Younger age (adults)
  - Workers' compensation
  - Genetic predisposition
  - Inefficient diffuse noxious inhibitory control (DNIC)
- Intraoperative factors: Surgical approach with risk of nerve damage.
- Postoperative factors
  - Pain (acute, moderate to severe) and radiation area pain
  - Neurotoxic chemotherapy pain
  - Depression
  - Anxiety.

17. Describe the preventive approaches for the chronic postsurgical pain syndromes.

Ans. *Acute postamputation pain syndromes:* Following amputation of a limb, and also breast, tongue, teeth, genitalia and even inner organs such as the rectum, or a deafferentation injury such as brachial plexus avulsion a number of phantom phenomena can develop.

Prevention: Perioperative (pre, intra and postoperative) epidural analgesia has reduced the incidence of severe phantom limb pain. Perioperative ketamine, preoperative gabapentin, local anesthetic infusion via peripheral nerve catheters are not effective in preventing phantom pain.

Treatment: Medications such as opioids, gabapentin, ketamine, TCA are effective in treatment of phantom pain. IV or locally injected local anesthetics are also useful. Nonpharmacological measures such as sensory discrimination training, mental imagery of limb movement and motor imagery, consisting of 2 weeks each of limb laterality recognition, imagined movements and mirror movements.

Post-thoracotomy Pain Syndrome

Post-thoracotomy pain syndrome is one of the most common chronic pain states. It is thought to be caused primarily by trauma to intercostal nerves and most patients relate their pain directly to the site of surgery.

The preventive measures includes:

- Epidural analgesia initiated prior to thoracotomy and continued into the postoperative period.
- The addition of low-dose IV ketamine to thoracic epidural analgesia
- Cryoanalgesia.

Postmastectomy Pain Syndrome

Measures to prevent it includes:

- Preincisional paravertebral block
- Perioperative use of gabapentin or mexiletine
- The use of a eutectic mixture of local anesthetics alone or in combination with gabapentin.

Posthysterectomy Pain Syndrome

Spinal anesthesia in comparison with general anesthesia reduced the risk of chronic postsurgical pain after hysterectomy.

18. What are the various nonopioid infusions that are used in perioperative period?
Ans. Infusions of ketamine, lidocaine, and naloxone and wound infusion of local anesthetics (Table 6).

Table 6 | Doses of ketamine and lignocanine

Drugs	*Bolus dose*	*Infusion dose*
Ketamine	0.5–1 mg/kg	40–100 mcg/hour
Lignocaine	1–1.5 mg/kg	2–3 mg/minute

Lignocaine and ketamine infusion is useful in abdominal and gynecological surgeries.

Ketamine is not useful when the total analgesia is given via the IV route.

IV ketamine may find its use as an adjunct in opioid-tolerant patients, or in patients with a higher incidence of chronic postsurgical pain such as thoracotomy, inguinal herniorrhaphies, limb amputation procedures, or even mastectomies. Most of the studies on perioperative IV lidocaine infusion showed salutary effects especially in abdominal surgery. The infusion appears to be less effective in total hip surgery and coronary artery bypass surgery.

The efficacy of perioperative IV lidocaine infusion may be related to the degree of trauma, it may not be as effective when the surgical trauma is greater.

IV naloxone infusion is used to control the side effects of neuraxial opioids.

A **local anesthetic wound infusion** is an effective and simple technique to decrease postoperative pain. Side effects are minimal and blood levels of the local anesthetic after 48–55 hours of infusion are below toxic levels. Infusion dose is 0.25–0.5% bupivacaine at rate of 2–10 mL per hour. Local anesthetic wound infiltration resulted in improved analgesia across a range of procedures, a very low technical failure rate, and zero reported toxicity, with no increase in wound infection. Found useful in cesarean section, hystectomy, laparotomy, thoracotomy, etc.

Nonpharmacological Techniques for Postoperative Pain

Accupunture: Perioperative accupuncture might be a useful adjunct for acute postoperative pain management.
TENS—may be useful in a few conditions like herniorrhaphy, thoracotomy.
Psychological interventions:

- Relaxation techniques are useful in management of postoperative pain, especially in cancer patients, in whom it also helped in improving nausea, blood pressure, pulse rate, and also helped in reducing anxiety and depression
- Hypnosis may be useful for the management, but evidence is limited
- Attention techniques may be useful, but limited evidence
- Listening to music leads to decreased postoperative pain and opioid requirement
- Distraction is useful in children for procedure related pain.

Physical Therapy

- *Massage therapy:* There is little inconsistent evidence in the use of massage therapy
- *Heat or cold therapy:* The evidence is mixed with few good results from orthopedic surgery, while few others reported no benefit.

Issues in the Pain Management in Children

Pain assessment in children is more difficult than in adults. Children are not malingerers; they are very open about expressing their feelings. But many a times it may not be easy to differentiate between pain and distress.

As the emotional component of pain is very strong in children, psychological support is very important. Minimal separation from parents, holding, nurturing, and distraction are all important modalities.

Nonopioid analgesics such as acetaminophen or nonsteroidal anti-inflammatory agents are useful for mild pain control and as an opiate-sparing measure. Oral, rectal, or intravenous routes are the preferred methods of administration of analgesics—and avoid intramuscular injections. Intravenous fentanyl, morphine are the most popular opiates. Patient-controlled analgesia has been used successfully even with very young children. Regional analgesia performed while the patient is under general anesthesia can provide excellent early postoperative pain relief.

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