Narcotics and Pain Management

OTA Core Curriculum

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Objectives

- **Review pain pathways within the human body**
- **Review means by which pain transmission is mitigated**
- **Review variety of different classes of pain medications and their mechanism of action**
- **Review benefits and rationale for multi-modal pain relief in orthopedic surgery**

Introduction: Pain

Definition:

Unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage

International Association for the Study of Pain

Introduction: Pain

- Difficult to define!!
- Pain is a unique subjective experience of an individual
- Physiological protective system
  - Essential to warn, detect, and minimize contact with damaging stimuli

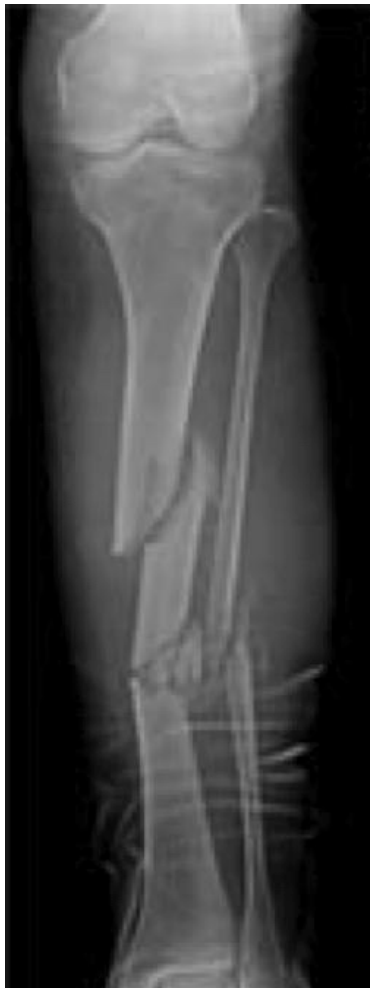
Introduction: Pain

- Dimensions of pain:
  - Sensory/discriminative→Intensity
    - Perception of sensory input
    - Quality, quantity and geographic area
  - Affective/motivational→Unpleasantness
    - Emotional/behavioral aspects of the pain experience
  - Cognitive/evaluative→Thoughts
    - How much pain an individual feels can depend upon past experiences
    - Modulation by central and peripheral nervous system can dampen or augment pain perception

Introduction: Pain

- Pain Threshold – the point at which any stimulus is felt as pain
  - Similar pain threshold among healthy people
  - Remains the same in the same person over time
  - Adults have a higher pain threshold than children b/w 15-18 y/o
  - Aging increases the pain threshold and may be due to changes in the skin thickness or the presence of peripheral neuropathies

- Perceptual dominance – the increase in the pain threshold at one point (part of the body) due to severe pain in another point (part of body)



Introduction: Pain

- Pain Tolerance – the intensity of pain that an individual will tolerate before any visible responses
  - Varies amongst people and in the same person over time
  - Affected by cultural background, physical and mental health, expectations and role behaviors
  - Tolerance is decreased with repeated pain, anger, fatigue, fear and sleep deprivation
  - Tolerance is increased by drugs, alcohol consumption, distraction, hypnosis and strong beliefs or faith

Introduction: Pain

Pain Classification

- Nociceptive pain
  - Sensing of noxious stimuli
  - Protective role requiring immediate attention and responses
- Inflammatory pain
  - Important to promote healing and protection of injured tissues.
  - Increases sensory sensitivity through pain hypersensitivity and tenderness.
  - Caused by activation of the immune system that causes inflammation after tissue injury or infection
- Pathological pain
  - Maladaptive response - results from abnormal functioning of the nervous system
  - Amplified sensory signals in the central nervous system
    - Fibromyalgia, irritable bowel syndrome, tension-type headache, temporomandibular joint disease

Introduction: Pain

Pain Classification

- Acute pain
  - Caused by noxious stimuli and is mediated by nociception
  - Early onset and serves to prevent tissue damage

- Chronic pain
  - Pain continuing beyond 3 months, or after healing is complete
  - May arise as a consequence of tissue damage or inflammation or have no identified cause
  - Complex condition embracing physical, social and psychological factors

General Pain Pathway

4 major processes for pain to be perceived

1. Transduction – tissue damaging stimuli activate nociceptor (pain receptor) nerve endings
2. Transmission – relay function carrying the impulse to the brain regions
3. Modulation – neural process to reduce activity of the transmission system
4. Perception – subjective awareness of the sensory signals

General Pain Pathway

- Types of tissue damage perceived as stimuli
  - Thermal
  - Mechanical
  - Chemical

General Pain Pathway - Transduction

- Tissue injury releases potassium, serotonin, histamine, prostaglandins, substance P and bradykinin from damaged vessels
- These activate the sensory afferent nociceptor fibers which release prostaglandins which sensitizes nociceptors and leads to primary hyperalgesia
- Orthodromic transmission in sensitized afferents result in the release of substance P (sP) in and around the site of injury. Substance P is responsible for further release of bradykinin.
- Substance P also stimulates release of histamine from mast cells and serotonin from platelets, which in turn activates additional nociceptors and exacerbates the inflammatory response.
- Reflexes mediated by sympathetic efferents may sensitize nociceptors directly through secretions of norepinephrine (NE), indirectly through further release of bradykinin and prostaglandin, or by localized vasoconstriction.

Fields HL: Pain. New York: McGraw-Hill, 1987, p 36.

General Pain Pathway - Transmission

- Nociceptors are the first order sensory pain fibers synapsing with the secondary nerve fibers at the Dorsal Root ganglion

- First order neuron has cell body in dorsal root ganglion and long axon to periphery and short one to spinal column

- A second order fibers transmit the impulse through the anterolateral quadrant of the spinal cord to the brain stem, thalamus and somatosensory cortex

General Pain Pathway - Transmission

- The dorsal horn is divided into discrete laminae based upon the tendency of different types of afferent fibers to synapse at specific laminae or depths.

- Descending input from higher centers (higher spinal cord, midbrain, and cerebral cortex) can modulate this transmission

General Pain Pathway - Transmission

Pain Transmission

- The delta fibers and C fibers – innervate both skin and internal organs, including the periosteum, joints, viscera and muscles
- Terminate as free peripheral nerve endings = nociceptors
- Delta fibers are myelinated, typically transmit more quickly and give sensation of immediate pain and are well localized
- C fibers are unmyelinated, have a slower conduction velocity and could be termed polymodal because a single C fiber may respond to a variety of noxious stimuli and mediate the perception of “after pain”
- These nociceptive afferent fibers synapse at the spinal cord dorsal horn, where processing and modulation take place before further transmission

Processes that Enhance Pain

- Sensitization – repeated stimuli threshold for afferent nociceptors decrease leading to lower pain threshold
- Hyperactivity – Sympathetic Nervous System
- Muscle contraction – a result of nociceptor activity as primitive withdrawal effect
- Self- sustaining Painful processes – Livingston “Vicious Circle” – painful processes set in motion secondary processes not associated with tissue damage that cause a spread of the nociceptive input leading to chronic pain
- Neuropathic pain – pain from nerve damage e.g. causalgia

General Pain Pathway - Modulation

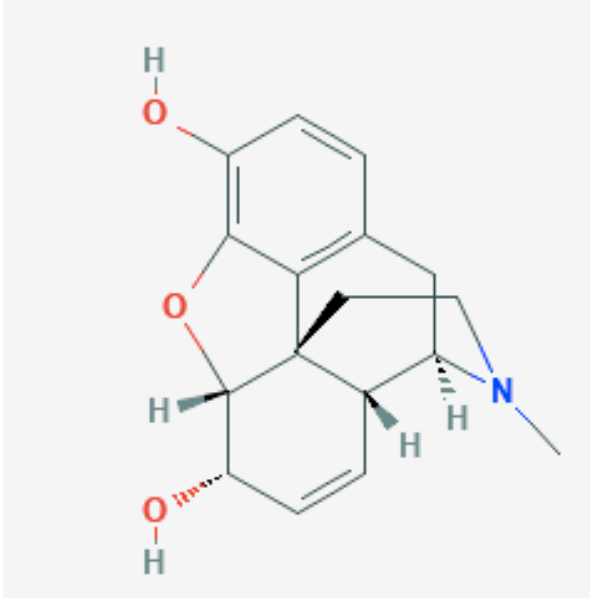
- Can occur by stimulation produced analgesia – electrical stimulation from various brain regions can block pain (midbrain to medulla)
- Analgesia –
  - Endogenous opioid peptides in brain stem will suppress pain (endorphins)
  - Exogenous opioids also act here

General Pain Pathway - Modulation

- Natural occurring OPIOID RECEPTORS
  - Mu – morphine receptors
    - Houde/Wallenstein 1956, Lasagna/Beecher 1954
  - Delta – based upon enkephalins
    - proposed by Kosterlitz (Lord et al. 1977)
  - Kappa – pharmacology of ketocyclazocine
    - Martin et al . 1976
  - Cannabinoid receptors in brain and spinal cord
  - Each of these receptors are G_1 protein coupled receptors and their activation leads to a reduction in neurotransmitter release through inhibition of AC/cAMP and cell hyperpolarization reducing cell excitability

Pain Mitigation

- Exogenous OPIOIDS
  - Morphine and its many derivative
- Cannabinoids – modulates neurotransmiter release
- Endogenous Opioid peptides
  - μ - opioids
  - B-endorphins
  - Dynorphins
  - Enkephalins
- Opioids regulate pain at spinal cord, brain stem, and cerebral cortex by reducing neuro transmitter from first order neurons



Morphine C17H19NO3

Pain Mitigation: Analgesic Classes: Non-endogenous Opioids

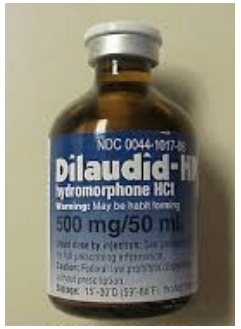
Two types of non endogenous opioids

- Natural Opioids – those derived from the poppy plant;
  - Parent compound = OPIUM
  - Morphine, codeine, thebaine

- Semi-Synthetic and Synthetic Opioids
  - Create an altered chemical structure to have morphine like analgesia with potential far greater potency but with decreased the number and degree of untoward side effects
    - Respiratory depression, constipation, drowsiness, etc…

Pain Mitigation: Analgesic Classes: Non-endogenous Opioids

- Semi-Synthetic Opioids – synthesized using chemical methods with natural opiate as a substrate;
  - Heroin and hydromorphone (dilaudid)
  - Hydrocodone from codeine
  - Oxycodone from thebaine



- Synthetic Opioids – synthesized completely in the lab with a natural opioid substrate;
  - Fentanyl, tramadol

Pain Mitigation: Analgesic Classes: Non-endogenous Opioids

Opioid	Type	Characteristics
Morphine	natural	Analgesic, metabolically active, neuroexcitable, metabolites can cause seizures
Codeine	Natural	Metabolized by liver to morphine, 7% Caucasians cannot do this, no effect
Hydrocodone	Semisynthetic	Metabolized to hydromorphone
Oxycodone	Semisynthetic	Metabolized to oxymorphone, may effect potency of fluoxetine, atorvastatin, erythromycin
Hydromorphone	Semisynthetic	Metabolically active. neuroexcitatory
Fentanyl	Synthetic	Metabolized by liver, , may effect potency of fluoxetine, atorvastatin, erythromycin
Tramadol	Synthetic	Metabolized to O-desmethyltramadol(M1), inhibits serotonin and norepinephrine reuptake to cause analgesia

Hagedorn JC, Danilevich M, Gary JL. JAAOS, 2019;27:e831-e837.

Opioid Receptors

- G protein-coupled receptors with opioids as ligands in brain and spinal cord and peripheral neurons
- Mu opioid receptors induce relaxation, trust and strong analgesia
- Kappa suppress mu-opioid effect while deltoid induce impulsivity
- The up and down regulation of the 3 receptors may account for psychiatric disorder fluctuations

Opioid Receptors: Physiological Effects

- Mu (μ) - supraspinal and spinal analgesia; sedation; inhibition of respiration; slowed GI transit; modulation of hormones and neurotransmitter release; euphoria

- Delta (δ) – supraspinal and spinal analgesia; modulation of hormone and neuro transmitter release

- Kappa (κ) - supraspinal and spinal psychomimetic effects; slowed GI transit; dysphoria

Opioid Antagonist and Partial Agonists

- Naloxone (Narcan) – antagonist of MOR, KOR, and DOR
  - Competitor inhibitor of opioids, reverses opioids by blocking MOR and preventing the euphoria associated with opioids
  - Pure MOR antagonist

- Buprenorphine – partial agonist, activates the opioid receptors to a lesser degree than morphine, outcompetes morphine for the MOR receptor causes decreased overall opioid stimulus leading to a lower peak effect

Pain Mitigation: Analgesic Classes: Non – Opioids Medications

- NSAIDs – Block formation of thromoboxane and prostaglandins by blocking Cox-1 and Cox-2 enzymes (cyclooxygenase-1)
  - By doing so NSAIDs mitigate surgical and traumatic pain by directly blocking pain transmission and reducing local inflammation and additional tissue damage –decreases the nociceptive stimulus
  - Celecoxib – only selective COX-2 inhibitor
    - Increased risk of thrombosis, stroke and heart attack

Pain Mitigation: Analgesic Classes: Non – Opioids Medications

- Acetaminophen
  - Acts on COX-2 enzyme centrally with little anti-inflammatory effect
  - May block COX-3 found in CNS
  - Activates the serotonergic pathways potentiating pain modulation
  - Affects endogenous cannabinoid and vanilloid system through AM404 to decrease pain transmission and decrease body temperature

Oral Morphine Equivalents (OME)

Narcotic	OME
Codeine	0.15
Hydrocodone	1
Hydromorphone (Dilaudid)	4
Morphine	1
Oxycodone	1.5
Tramadol	0.1
Fentanyl transdermal (mcg/hr)	2.4

Pain Mitigation: Analgesic Classes: Non-endogenous Opioids

- Gabapentinoids (gabapentin/pregabalin)
  - Analog of neurotransmitter (GABA)
  - Affects a voltage-gated calcium channel that reduces neurotransmitter release and decreases post-synaptic excitability and therefore decrease neuropathic pain
  - Predominant effect in the dorsal horn of spinal cord
  - Not capable of being sole modality for acute surgical pain
  - Controversial use to decrease pain in acute postoperative setting

Multi-Modal Pain Relief

- Pain has many dimensions and so no single drug or technique is sufficient to provide complete/near complete pain relief without side effects

- Therefore, drugs and techniques should be used in combination to maximize the beneficial effects of combination therapy while minimizing the side effects of an individual approach.

- Multimodal analgesia is a combination of two or more analgesics with a different mode of action, designed to improve analgesia and decrease side effects through reduction in analgesic dose, particularly opioids.

American Pain Society Multi-Modal Pain Relief

- >80% of patients who undergo surgical procedures experience acute postoperative pain,
- ~ 75% of those with postoperative pain report the severity as either moderate, severe or extreme!
- <50% of the patients who undergo surgery report adequate postoperative pain relief,
- Inadequately controlled pain negatively affects quality-of-life, function and functional recovery, the risk of postsurgical complications and the risks of persistent postsurgical pain,

American Pain Society Multi-Modal Pain Relief

The American Pain Society (APS), with input from the American Society of Anesthesiologists (ASA), commissioned a guideline on management of postoperative pain to promote evidence based, effective, and safe postoperative pain management in adults

American Pain Society Multi-Modal Pain Relief

- The panel recommends that clinicians offer multi-modal analgesia, or the use of a variety of analgesic medications and techniques combined with non-pharmacological interventions for the treatment of postoperative pain in children and adults, (strong recommendation, high quality evidence)

- Multi-modal analgesia, defined as the use of a variety of analgesic medication techniques that target different mechanisms of action in the peripheral and/or central nervous system have an additive or synergistic effect and are more effective pain relief compared with single drug interventions

- Clinicians might offer local anesthetic base regional analgesic techniques, systemic opioids and other analgesics

Long term analgesic use after low risk surgery

- If get opioid prescription within 7 days of surgery had 44% chance of on long term opioids over those with no prescription

- If started taking NSAIDs within 7 days of surgery were 4 times more likely to become long term NSAID users compared to those with prescription

Alam A, Arch intern Med 2012; 172(5): 425 - 430

American Pain Society Multi-Modal Pain Relief

- Selection of multi-modal therapies is a challenge because for each surgical procedure, many potential multi-modal therapy combinations are possible

- When using multimodal analgesia, clinicians should be aware of the different side effect profile for each analgesic medication or technique used, and provide appropriate monitoring to identify and manage adverse events,

- Examples of Recommended multi-modal therapies:

Chou R, Gordon DB, de Leon-Casasola OA, et al. Guidelines on the Management of Postoperative Pain. The Journal of Pain, Vol. 17, No. 2 (February) 2016: pp 131-157.

Multi – Modal for Common Orthopaedic Surgical Procedures

Type of Surgery	Systemic Pharmacologic	Local, Intraarticular	Regional	Neuraxial Anesthetic	Nonpharmacologic
Total hip	Opioids, NSAIDs and or acetaminophen, gabapentin, pregabalin, i.v. ketamine	Intra articular local and/or opioid	Site specific with local	Epidural with local with/or with opioid or intrathecal opioid	Cognitive modalities, TENS
Total Knee	Opioids, NSAIDs and or acetaminophen, gabapentin, pregabalin, i.v. ketamine	Intra articular local and/or opioid	Site specific with local	Epidural with local with/or with opioid or intrathecal opioid	Cognitive modalities, TENS
Spinal Fusion	Opioids, NSAIDs and or acetaminophen, gabapentin, pregabalin, i.v. ketamine	Intra articular local and/or opioid		Epidural with local with/or with opioid or intrathecal opioid	Cognitive modalities, TENS

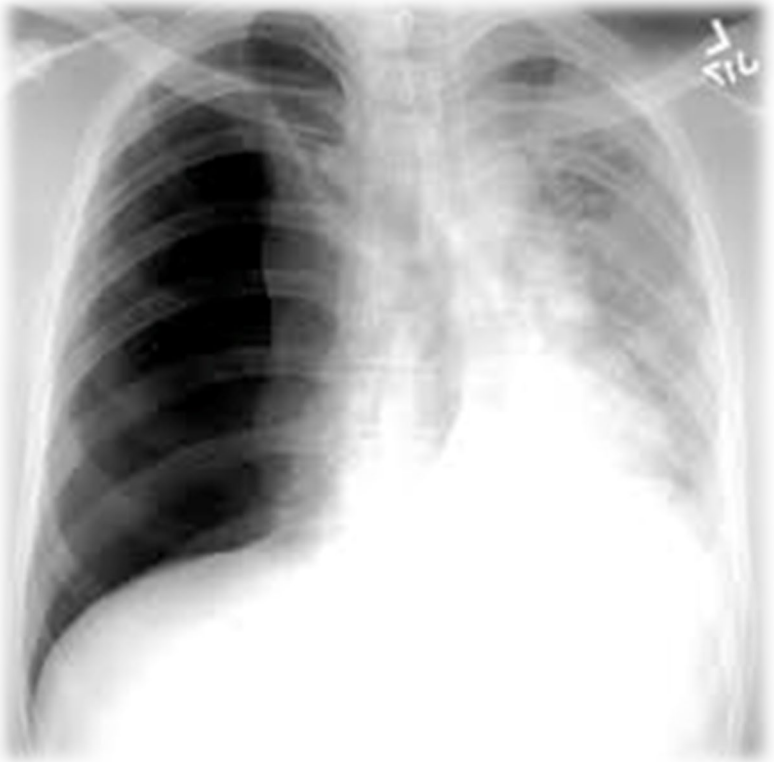
Regional Anesthetic Techniques

- From 11 randomized and quasi randomized trials with 1062 patients showed the fascia iliaca compartment block was superior to opioids for preoperative analgesia for hip fracture patients
  - High block success rate with few adverse effects
- Faster the block is administered from the time of presentation the less opioids consumed
- Femoral nerve and Adductor canal nerve blocks are effective in knee surgery
  - Adductor canal block will spare the quadriceps

JBJS 2020,00:1-7
Anesthesia, 2014; 120: 540 - 550
J Pain Research 2017.10 2833-41
British Journal of Anaesthesia, 120 (6): 1368-1380 (2018) doi: 10.1016/j.bja.2017.12.042

Regional Anesthetic Techniques

- Upper Extremity Block Coverage: Complications
  - Systemic
  - Phrenic Nerve
  - Nerve Injury
  - Pneumothorax
  - Vascular puncture
  - Horner syndrome
  - Brachial plexus neuritis
  - CRPS
  - Bronchospasm (hiccups)



Locoregional Analgesia for Post-op Pain

- Local Wound Infiltration (LIA) – infiltration of a large volume dilute solution of a long-acting local anesthetic agent at the end of surgery

- Local analgesics blocks the ion-gated Na channels on the A-delta and C-type nerves and therefore block nociceptive nerve endings to produce analgesia

- Pain relief usually lasts longer than the duration of the local anesthetic and the anti-inflammatory effect of the local anesthetic could be contributing factor for this prolonged effect,

Locoregional Analgesia for Post-op Pain

- Infiltration carried out at the conclusion of surgery is more effective than pre-incisional local wound infiltration
- Local anesthetics possess antimicrobial properties and do not influence wound healing,
- Drugs commonly used for LIA - Lidocaine 0.5%, bupivacaine 0.25%, levobupivacaine, 0.25%, ropivacaine 0.2%

Best Practice for Acute Pain Management

- 15 member panel – expertise in orthopedic surgery and/or management
- Literature review and panel review
- Recommendations for acute pain for musculoskeletal injury
- Approved by the OTA October 16, 2018

Hsu J. Mir Hassan, Wally Megan et al, J Orthop Trauma Volume 33, Number 5, May 2019

Best Practice for Acute Pain Management

Cognitive and Emotional Strategies

- Discussion with patient of expected course and patient experience
- Pain greater than expected or depression, anxiety PTSD, poor coping refer to psychosocial interventions
- Anxiety reducing strategies to increase self efficacy like aromatherapy, music therapy or cognitive behavior therapy

Best Practice for Acute Pain Management

Nociception and Pain

- Nociception – physiology of actual or potential tissue damage
- Pain – unpleasant thoughts emotions and behavior that accompany nociception
- Pain catastrophizing – ineffective coping strategy
- No association between pain intensity and degree of nociception
- Pain intensity variation accounted for by psychological aspects

Best Practice for Acute Pain Management

Psychosocial Interventions

- Improve overall mental health and decrease depression, anxiety and PTSD
- Cognitive behavior therapy, self management interventions and training, peer support and online social networking
- Difficult for many to access

Best Practice for Acute Pain Management

Physical Strategies

- TENS – adjunct, based on Gate Theory of pain, use strong sub painful frequencies

- Cryotherapy for acute and post op pain, variable results, beware of nerve palsies

Best Practice for Acute Pain Management

Opioids Safety and Effectiveness

- Use the lowest effective dose for shortest period of time
- No benzodiazepines with opioids
- Avoid long acting opioids in acute pain
- Prescribe precisely – no ranges of dose or time
- Combine with NSAIDs make more effective

Best Practice for Acute Pain Management

Combination Pharmaceutical Strategies

- Multimodal Analgesia
  - Recommended over monomodal opioid therapy
  - Periarticular local or regional anesthetic injections as adjunct
  - NSAID effective for musculoskeletal pain with no clinical evidence that fracture healing is effected
  - Tailored to patients injuries and comorbidities
  - Short term corticosteroids may be beneficial

Hsu J. Mir Hassan, Wally Megan et al, J Orthop Trauma Volume 33, Number 5, May 2019

Best Practice for Acute Pain Management

Patients on long term opioids

- Recommends multimodal analgesia
- Consultation with Acute Pain Service when patient on medication assisted therapy (e.g. methadone)
- Opioid tolerant patient must be identified early and pain controlled (review section in reference below)

Conclusions

- Opportunities exist to further improve pain management, with increased effectiveness, longevity and safety

- Nature and extent of surgery, anesthetic medications used, routes of administration and anesthetic techniques are important factors which determine the intensity of the post-op pain

- Therefore, to assure adequate control of postoperative pain these factors should be taken into account when establishing surgical pain treatment protocols

Conclusions

- **Multimodal Pain Management Regimens** are strongly encouraged, particularly following ORTHOPEDIC SURGERY, in order to maximize effectiveness and safety, decrease complications and long term addiction,
  - All patients should receive:
    - When possible, regional anesthesia +/- general
    - Round the clock regimen of NSAIDs, COXIBs, and/or acetaminophen,
    - Short term opioids or synthetic analgesics (Tramadol)
    - Adjuvants
      - Alpha-2 adrenergic agonist (clonidine, dexmedetomidine)
      - Gabapentin-type drugs (gabapentin, pregabalin)
      - Glucocorticoids (dexamethasone)
    - Local Infiltration Analgesia (LIA) – local wound infiltration

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