NON OPIOID MANAGEMENT OF ACUTE POSTOPERATIVE PAIN

Essay

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By

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List of Abbreviations

Abbr.	Full-term
BP	: Blood pressure
CGRP	: Calcitonin gene-related peptide
COX	: Cyclo-oxeginase
CPSP	: Chronic postsurgical pain
DVPRS	: Defense and Veterans Pain Rating Scale
FPS	: Faces Pain Scale
GABA	: Gamma-aminobutyric acid
HR	: Heart rate
INR	: International normalized ratio
nAChRs	: Nicotinic acetylcholine receptors
NMDA	: N -methyl- d-aspartate
NRS	: Numeric Rating Scale
NSAIDs	: Non-steroidal anti-inflammatory drugs
PACU	: Post-Anesthetic Care Unit
PCA	: Patient-controlled analgesia
PGE	: Prostaglandin E
PONV	: Postoperative nausea and vomting
PPP	: Persistent postsurgical pain
SNRI	: Serotonin–norepinephrine reuptake inhibitors

List of Abbreviations (Cont.)

Abbr.	Full-term
SSRI	: Selective serotinine reuptake inhibitors
SPI	: Surgical Pleth Index
TCA	: Tricyclic antidepressants
TCM	: Traditional Chinese medicine
TENS	: Transcutaneous electrical nerve stimulation
USFDA	: United States Food and Drugs Association
VAS	: Visual Analog Scale
VRS	: Verbal Rating Scale

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Introduction

Despite recent advances in our understanding of the physiology of acute pain, the development of new opioid and nonopioid analgesics and novel methods of drug delivery, and more widespread use of pain-reducing minimally invasive surgical techniques, pain after surgical procedures remains a challenge for many practitioner and still 86–89% of patients experience moderate to severe pain after surgery ***(Pommergaard et al., 2014)***.

Postoperative pain is the result of activation of different pain mechanisms, including nociceptive, neuropathic and inflammatory pains. Likewise, periphral and central sensitization further contributes to development of hyperalgesia with increased pain as a result ***(Mathiesen et al., 2013)***.

Progress in our neurobiological understanding of postoperative pain includes scientific discoveries of 'vulnerability factors', which substantially impact on the spinal cord, augmenting pain amplification mechanisms, perhaps to levels of no-return ***(Deumens et al., 2013).***

The use of opioid medications after surgery can lead to incomplete analgesia and may cause undesired side effects such as respiratory depression, somnolence, urinary retention, and nausea. Multimodal (opioid and nonopioid combination) analgesia may be an effective alternative to

morphine administration leading to improved postoperative analgesia with diminished side effects ***(Ryan et al., 2013).***

Various drugs and techniques have been used as part of multimodal analgesia with the aim of improving pain management and decreasing opioid consumption and opioid-related side-effects. Of these, the benefits of paracetamol, non-steroidal anti-inflammatory agents, and regional anesthesia techniques and because of poorly controlled pain at the time of surgery predisposes to chronic postsurgical pain (CPSP), drugs traditionally used for chronic neuropathic pain are being used more commonly in the perioperative period ***(Ramaswamy et al., 2013).***

There is increasing evidence that less invasive regional analgesic techniques are as effective as epidural analgesia. These include paravertebral block for thoracotomy, femoral block for total hip and knee arthroplasty, wound catheter infusions for cesarean delivery, and local infiltration analgesia techniques for lower limb joint arthroplasty ***(Narinder, 2012).***

Therefore we need to increase our knowledge about the recent advances of non-opioid drugs, regional analgesia and pain-reducing minimally invasive surgical techniques to improve the quality of pain management of postoperative pain aiming to reduce opioid side effects and decrease the perioperative complication.

Aim of the Essay

To highlight the appropriate way to manage the postoperative pain by sparing opioid use and minimizing the incidence of systemic opioid-related side effects and accelerate postoperative convalescence and decreasing occurrence of perioperative complications.

Chapter (1)
Pathophysiology of Pain

What is pain?

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." This definition recognizes the interplay between the objective, physiological sensory aspects of pain and its subjective, emotional, and psychological components (***Macintyre et al., 2010).***

Optimal management of postoperative pain requires an understanding of the pathophysiology of pain, methods used for assessment of pain in individual patients, and awareness of the various options available for pain control ***(Jessica, et al., 2015)***

Pain may be classified according to pathophysiology (e.g., nociceptive or neuropathic pain), etiology (e.g., arthritis or cancer pain), or the affected area (eg, headache or low back pain). Table 1. Such classifications are useful in the selection of treatment modalities and drug therapy ***(Richard and Bruce, 2013).***

Preoperative pain may be amplified or accelerated by surgical incision, subsequent tissue injury, pathophysiological responses and local inflammatory processes. Surgical factors contribute to the genesis of pain: intraoperative nerve damage

may contribute to the severity, character and chronicity of postoperative pain ***(Gerbershagen et al., 2010).***

Preoperative pain, anxiety, young age, obesity, surgical fear, catastrophising, and type of surgery (abdominal, orthopaedic, and thoracic surgery, long duration) have been identified as predictors of postoperative pain ***(Bruce et al., 2012).***

Inadequate treatment of postoperative pain continues to be an important clinical problem, not only leading to worse outcomes in the immediate postoperative period but also an increased risk for persistent postoperative pain ***(Jessica et al., 2015).***

Table (1): Types of pain ***(Jessica et al., 2015)***

Nociceptive Pain **Somatic** **Visceral**	Normal processing of stimuli that damages normal tissues Responds to opioids Pain arises from bone, joint, muscle, skin, or connective tissue Aching, throbbing Localized Arises from visceral organs Tumor: localized pain Obstruction of hollow viscus: poorly localized
Neuropathic Pain **Centrally generated** **Peripherally generated**	Abnormal processing of sensory input by PNS or CNS Deafferentation pain: injury to PNS or CNS (eg, phantom pain) Sympathetically maintained pain: dysregulation of autonomic nervous system (eg, complex regional pain syndrome I and II) Painful polyneuropathies: pain is felt along the distribution of many peripheral nerves (eg, diabetic neuropathy) Painful mononeuropathies: associated with a known peripheral nerve injury (eg, nerve root compression, trigeminal neuralgia)

Pathophysiology of postoperative pain

Tissue trauma releases local inflammatory mediators, which can produce hyperalgesia (increased sensitivity to stimuli in the area surrounding an injury) or allodynia (misperception of pain to nonnoxious stimuli). Other mechanisms contributing to hyperalgesia and allodynia include sensitization of the peripheral pain receptors (primary hyperalgesia) and increased excitability of central nervous system neurons (secondary hyperalgesia) ***(Jessica et al., 2015).***

How can pain signal be transduced?

I. Excitation of primary afferent neurons.

When the receptors that located in the peripheral terminals of primary nociceptive neurons encounter the appropriate specific stimulus (e.g., high heat, extreme cold, chemicals, or excessive pressure) that is of sufficient intensity, the receptor molecule undergoes a conformational change that transduces the noxious signal into an electrical current by triggering the opening of depolarizing cationic ion channels or the closing of outward potassium channels ***(Gold and Gebhart, 2010).***

Tissue trauma results in local release of inflammatory mediators such as bradykinins, 5-hydroxytryptamine, leukotrienes, prostaglandins (PGE2, PGG2 and PGH2), substance P and histamine which serve as activators of primary nociceptors. Several of these signaling molecules have been proposed as potential targets for pain management ***(Gandhi et al., 2011).***

If the initial signal reaches the threshold or activation potential, further conduction of the signal requires the generation of an action potential via opening of depolarizing voltage-gated calcium and sodium channels or closure of hyperpolarizing potassium channels ***(Gold and Gebhart, 2010).***

Endogenous and exogenous substances that modulate the function of these ion channels can amplify or dampen transmission of the pain signal. Table 2 ***(Babos et al., 2013).***

Table (2): Summary of voltage-gated ion channels and Drugs that modify their function ***(Babos et al., 2013).***

Ion channel	Function	Drugs that modify function
Calcium	Inward channel, primary driver for most intracellular responses to stimulation	Pregabalin Gabapentin Ziconotide
Sodium	Inward channel; influx of sodium through open channels makes membrane potential less negative, bringing it closer to the threshold potential necessary to initiate an action potential	Local anesthetics Carbamazepine Phenytoin
Chloride	Inward channel; influx of chloride makes the membrane potential more negative (hyperpolarized)	Benzodiazepines (amplify GABA type A induced opening of channel)
Potassium	Outward channel; efflux of potassium makes the membrane potential more negative (hyperpolarized)	Baclofen Clonidine Opioids

II. Dorsal root ganglion, dorsal horn, and modulation of secondary neurons

Signals reach the dorsal root ganglion via unmyelinated and myelinated noxious fibers and synapse in the dorsal horn of the spinal cord. The stimulus is then carried by second-order spinal neurons through the neospinothalamic and paleospino-thalamic tracts ***(Gandhi et al., 2011).***

When an excitatory action potential reaches the terminal end of the presynaptic afferent neuron, N-type voltage-gated calcium channels open. The influx of calcium leads to vesicle docking and exocytosis of the specific neurotransmitter contained within the vesicle. The neurotransmitter molecules diffuse across the synaptic cleft to convey the signal to the secondary neuron. The released neurotransmitter may interact with its specific receptor to evoke either excitatory or inhibitory responses ***(Babos et al., 2013)***.

Glutamate is a primary excitatory neurotransmitter; it interacts with one of three receptor subtypes.Substance P is another common excitatory mediator; it interacts with the G-protein-coupled NK1 (neurokinin1) receptor to produce a slightly slower response compared to ion channel-coupled signals. Gamma-aminobutyric acid (GABA) is a common inhibitory signaling transmitter. Likewise, endorphins interact with Gi-protein-coupled mu and delta opioid receptors to reduce the activity of pain signaling pathways ***(Griffin and Woolf, 2012).***