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Post-Operative Pain: Mechanisms and Management

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ABSTRACT

Background: Proper postoperative pain management, which can be advanced using a multimodal approach, results in pain relief with minimal side effects. Newer recovery protocols, along with minimally invasive surgeries add to the better management of post-operative complication. Many factors play a role in failure of proper postoperative pain management, which mainly include insufficient education, fear of complications associated with analgesic drugs, poor pain assessment and inadequate staffing.

Methodology: we conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE fromJanuary 1987 toMarch 2017. The following search terms were used: post-operative pain mechanism, post-operative pain management, non-opioid pain management

Aim of the work: In this study we aimed to understand the mechanism and the management of post-operative pain, along with shining some light upon the recent advances.

Conclusion: Various combinations and modalities of pain management exist, and their use depends largely on the case, the patients, and their perception of pain. Enhanced recovery protocols have significantly improved perioperative and postoperative pain management, making the decrease in opioids need a priority**.**

Keywords: post-operative pain, complication after surgery, post-operative pain mechanism, post-operative pain management, non-opioid pain management.

INTRODUCTION

The American Society of Anesthesiologist defined acute pain as pain in a surgical patient after a procedure. Long-term rehabilitation, and other complications like chronic pain with decreased quality of life can result from poor management of postoperative pain. Whereas, satisfactory pain relief will result in reduced hospital costs, and improved quality of life. Therefore, pain relief is considered as a human right by the World Health Organization 'WHO', and the management of postoperative pain is measured continuously to assure quality and patients' satisfaction. Patients' satisfaction with in-hospital pain management can be estimated using the Hospital Consumer Assessment of Health Providers and Systems (HCAHPS) questionnaire[1].

Proper postoperative pain management, which can be improved using a multimodal approach, results in pain relief with minimal side effects. Enhanced recovery protocols, along with minimally invasive surgeries. Many factors play a role in failure of proper postoperative pain management. These factors include: insufficient education, fear of complications associated with analgesic drugs, poor pain assessment and inadequate staffing.In this paper, we reviewed the mechanisms of acute postoperative pain and its management, and discuss enhanced recovery protocols that addressed pain management[2].

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASEfrom January 1987 to March 2017. The following search terms were used:post-operative pain mechanism, post-operative pain management, non-opioid pain management

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data and disagreements were resolved by consensus. Studies were evaluated for

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quality and a review protocol was followed throughout.

The study was done after approval of ethical board of King Faisal university.

Molecular Mechanisms of Post-Operative Pain

In most cases, pain that occurs following surgery is nociceptive, but there are cases where normal sensations (as light touching) are perceived as painful. This occur due to neural sensitization and causes cases of hyperalgesia or allodynia, which can be the result of the release of prostaglandins, leukotrienes, bradykinin, histamine, serotonin, and other sensitizers that cause the secretion of calcitonin gene-related protein (CGRP), substance P, and cholecystokinin and other peptides. On the other hand, peripheral nociceptors sensitization causes primary hyperalgesia and CNS sensitization causes secondary hyperalgesia. Some processes involved in peripheral sensitization include nerve growth factor release, reflex sympathetic efferent release of norepinephrine, and histamine-induced vasodilatation. All these mechanisms stimulate impulses to transmit through A delta and C fibers to synapse in the lamina II and lamina V (and Lamina I in case of C fibers) of the spinal cord[3].

'Lamina I' is the first type of the second order neurons, and transmits signals from C fibers. The second type is 'lamina V' which transmits noxious and non-noxious stimuli, and uses glutamate and aspartate to achieve fast transmission through synapses. The later mentioned neurotransmitters activate amino-3-hydroxyl-5-methyl-4-proprionic acid (AMPA) and Kainate (KAR) receptors causing Na+ and K+ ion influx regulation, but stopping Ca++ ions. Voltage mediated priming of NMDA occurs following AMPA and KAR receptors activation[1].

Central sensitization and NMDA receptor

NMDA is a membrane-associated protein that is responsible for flow regulation sodium and calcium ions into the cell and the potassium out of the cell by an ion channel present intrinsically. The NMDA receptor consists of four subunits: two NR1, one NR2A, and one NR2B, each has a cytoplasmic portion outside the cytoplasm that responds allosterically to zinc ions[4].

NMDA receptors needs glutamate and aspartate ligand binding, membrane depolarization by AMPA, and a voltage change into positive, which cause NMDA receptors to be ligand dependent and voltage gated. Depolarization (that results from the activation of AMPA receptors) removes a magnesium plug from the NMDA receptor. Then more sensitization occurs as a direct action of glutamate. This causes intracellular accumulation of calcium, which in turn causes a fast and independent firing of spinal neurons in absence of stimulation, following some other neurochemical and physiological alterations. This whole process is sometimes referred to as 'wind up' which also refers to the transcription-independent excitation of neurons of specific genes[5].

Long-term potentiation of pain

NMDA activation wind up, and sensitization cause clinical hyperalgesia. Central sensitization happens in the spinal cord or the supra spinal regions of the CNS, like the anterior cingulate gyrus, amygdale, and rostroventral medulla. This activation of NMDA along with calcium influx increase, all cause wind up and early LTP of transcription-independent pain. Long-term potentiation of this pain causes an increase in the excitatory postsynaptic potentials (EPSP) involved in chronic pain[6].

Transcription-independent and transcription-dependent central sensitization

As we have mentioned earlier, both transcription-independent and transcription-dependent processes can occur with central sensitization. Transcription-independent processes include NMDA activation, wind up, and early LTP of pain, and continuous stimulation results in increasing pain. These processes are heterosynaptic central sensitization, meaning that low threshold A Beta input causes responses after C fiber conditioning. Moreover, wind up and early LTP are reversible processes[7].

Prolonged noxious facilitation, on the other hand, stimulates transcription-dependent processes, by activating mRNA transcription and translation into amino acids. Increased amount of calcium influx results in toxicity with a subsequent increase in prostaglandins, nitric oxide, and superoxides. Transcription- dependent sensitization may be associated with inflammation of the dorsal root ganglion, dorsal horn, and irreversible changes in CNS, and it has to forms: activity independent localized form, which includes the late phase of LTP, and the activity independent widespread form. Late phase LTP has been studied mainly in the hippocampus and other cortical areas[8].

Management of Post-Operative Pain

Preoperative Assessment

To achieve successful, sufficient postoperative pain management, it is essential to have proper planning and evaluation that include a full pain history and physical examination. However, there is no sufficient solid evidence to support this. Other important steps of planning include well-adjustment of preoperative medications to prevent withdrawal symptoms, reduction of preoperative anxiety and pain, and the application of a multimodal plan for pain management. Some evidence suggests that preoperative pain may be an indicator for the level of postoperative pain. Age, anxiety levels, depression, and quality of care are also among variables that also have an effect and can predict postsurgical pain. Interventions as patient and family education are recommended despite the absence of solid evidence to support their effect on postoperative pain[1].

A single essential step in effective pain treatment is well quantification, which can be achieved by routine postoperative administration of the patient's self-assessment tool. Of the several available pain assessment tools, the 10-point pain assessment scale, in which 1 means no pain and 10 means the worst possible pain imaginable, has been mostly used. Adequate pain control also depends on continuous reassessment of pain and satisfaction of patient, so satisfaction score is also crucial and should be routinely measured to eliminate the chances of unnoticed inadequate treatment. A successful treatment plan ideally will include good patient communication and responsive analgesia management[2].

Pre-emptive Analgesia

One method that may potentially prevent or decrease postoperative pain, is the administration of analgesics before the painful stimulus through via local wound infiltration, epidural or systemic administration prior to surgical incision. The use of multiple pharmacological agents that decrease or block receptors activation, is the main key to achieve effective pre-emptive analgesia.These drugs may also work by the inhibition of pain neurotransmitters, or the reduction of their production. Although this method has been hypothesized in several trials, no solid evidence about its efficacy is present in the literature. According to a meta-analysis, a reduction of analgesics consumption was observed in patients who got pre-emptive local anesthetic wound infiltration and nonsteroidal anti-inflammatory drugs. However, these patients did not show less postoperative pain scores. On the contrary, Pre-emptive epidural analgesia caused improvements in both pain scores and analgesics consumption. The administration of local anesthetics near laparoscopic port incision sites did not result in improved postoperative visceral pain. In conclusion, this method may have some short-term advantages especially in ambulatory surgery patients[9].

Pharmacological Agents and Routes

Opioid Analgesia

Although there has been several advances in pain management and pain medications over the last years, opioids are still the most important drugs in postoperative pain management. Opioids work in the both central and peripheral nervous system, and bind to receptors causing modulation in the effect of nociceptors. The most common way of postoperative opioid administration is intravenously, though they can be also administrated via oral, transdermal, parenteral, neuraxial, and rectal routes. Morphine is the standard prototype opioid that is mostly used. It has a quick onset of action, and peaks within 2 hours. Fentanyl and hydromorphone(dilaudid), are more potent opioids that are synthesized from morphine, work faster, and have shorter half-lives[10].

Side effects are the most important obstacles in opioid use. Respiratory depression is among the most important and serious side effects as it can lead to hypoxia and respiratory arrest. To minimize the risk of respiratory depression, respiration and oxygen saturation are advised to be monitored regularly. Other less serious events include nausea, vomiting, pruritus, and decreased bowel motility leading to ileus and constipation. Of long-term side effects, dependence is the most important. Patients should be converted from intravenous opioids to oral opioids as soon as they can receive oral intake, and this treatment will continue after discharge. Due to recent development in recovery protocols, especially in colorectal surgery, other non-opioid-based regimens have been used in postoperative pain management[1].

Intravenous Patient-Controlled Analgesia

In 1970s, patient-controlled analgesia (PCA) through intravenous pumps came into practice. Most common opioids that have been administrated through PCA pumps include morphine, hydromorphone, and fentanyl. Autonomy and control are among the advantages of this method, but it still needs special equipment. Training for proper use are crucial for both patients and physicians to achieve

better response. Pooling of 15 RCTs that compared PCA with IM opioid use, came into conclusion that PCA was preferred by patients and caused improved pain control, with no difference of side effects. Another Cochrane meta-analysis also showed that patients on PCA had higher satisfaction scores. However, pain scores and length of hospital stay, the amount of drugs used, and adverse events did not change. In conclusion, PCA is an effective way for the management of postoperative pain[11].

Epidural and Spinal Analgesia

In pelvic, thoracic, and abdominal surgeries, epidural and spinal analgesia are commonly used. Epidural analgesia is done by the insertion of a catheter into the epidural space in the thoracic or lumbar spine. This is followed by the infusion of anesthetics and opioids causing analgesia. IV PCA was compared with continuous epidural analgesia (CEA), and a published meta-analysis showed CEA to be associated with improved pain control especially within the first 72 hours following abdominal surgery. The rate of side effects, and the length of hospital stay did not change, except for pruritus that increased with patients on CEA. Another meta-analysis showed that postoperative pain, and ileus were significantly less with CEA following colorectal surgery. However, CEA was linked to an increase in hypotension, pruritus, and urinary retention. A patient-controlled epidural pump using a combination of opioids and anesthetics, can cause less dose requirements and thus less adverse events[1].However, another recent study showed that the combination of a single-dose intrathecal opioid followed by IV PCA achieved improved pain control, and shorter hospital stay than CEA following colorectal surgery. Another trial showed longer duration of nausea, loss of bowel function and hospital stay after laparoscopic colorectal surgery among the CEA group. However, pain was improved in the CEA group than the PCI group. Later study also confirmed the improved pain control with CEA following colorectal surgery[12].

The main problem in this method is the difficulty of inserting an epidural catheter, causing failure of analgesia in 27-32% of patients after lumbar and epidural techniques. Another problem is hypotension following successful CEA that will eventually need IV fluids to be controlled[1].

Paravertebral blockade

Paravertebral block is done by the injection of anesthetics in the vicinity of thoracic spinal nerves, and causes both somatic and sympathetic blockade at the side of injection. It can be performed both percutaneously and intraoperatively. Local anesthetic is injected 2.5 cm lateral to the midline (determined by the spinous processes) and 1 cm past the transverse process. Three to five mL of the local anesthetic is injected. The choice of the anesthetic determines the onset and duration of action; 0.5% ropivacaine, for example,works in 15-25 min and its effects last for 8-12 h, and 0.75%ropivacaine works in 10-15 minutes for 12-18 h. Another example is 0.5% bupivacaine that is injected with epinephrine and works in 15-25 minutes for 12-18 h[13].

This type causes anesthesia that is somehow similar to unilateral epidural anesthesia. However, it is safer than the later in cases of disturbed coagulation. Proper assessment in the postoperative pain help adjusting the range of anesthesia, and therefore the location of its dermatomal distribution. Paravertebral blockade is preferred to be done with direct visual control to prevent potential complications[14].

Peripheral Nerve Blocks

Another technique, which was first described in 2001, is transversus abdominis plane (TAP) block. This works by blocking peripheral nerves causing abdominal wall anesthesia. It can be done by unilateral/bilateral injection of the anesthetic into the plane between the transabdominal and internal oblique muscles. The exact site is changed in accordance with the surgical incision. This can be done blindly, laparoscopically, or with ultrasound guidance. TAP block is linked with a lower rate of adverse events and complications, and is more preferred by patients than CEA[15].However, the literatures still suffer lack of evidences on the efficacy of this method in pain relief, and also the exact localization, timing, doses, and volumes of drugs. Moreover, conducted studies are heterogeneous due to the easily affection of this method by the operator physicians and their skills. A Cochrane meta-analysis showed that patients who underwent TAP block required significantly less postoperative morphine, with no significant change of adverse events. Other studies on TAP block usage in colorectal surgery showed reduced morphine use, earlier restore of bowl function, and shorter hospital stays with TAP block. However, there is still no sufficient evidence to prove better pain scores with TAP block, and therefore, further studies are still required[16].

Local Infiltration

The local infiltration of anesthetics has been used by colon and rectal surgeons for a very long time as this method can be effective in many cases. The use of old anesthetic agents (Xylocaine and bupivacaine) was limited because of their short duration. However, a recent formulation that can work for 72 hours received FDA approval for postsurgical analgesia; this approval happened after two studies on hemorrhoidectomy and bunionectomy patients. A recent multimodality protocol used local infiltration and was shown to have great outcomes[1].

Nonopioid Analgesia

Non-opioid-based regimens have been increasingly used in postoperative pain management. Of these drugs, NSAIDs are used to decrease the amount of administrated opioids in cases of mild to moderate pain. NSAIDs inhibit the cyclooxygenase (COX) enzyme causing reduction in prostaglandins production and release. The most important adverse event with NSAIDs is bleeding, this their use depends on the tolerability of the patient. The classification of NSAIDs is based on their COX isoenzymes selectivity; ibuprofen and other nonselective NSAIDs have increased risk of bleeding, though they are still preferred over celecoxib and other selective COX-2 inhibitors, as these have been associated with increased cardiovascular risks[17].

Ketorolac is a COX-1 inhibitor with analgesic effects that is commonly used in colorectal procedures. It is injected with other agents in pre-emptive analgesia.Ketorolac is usually given in a 30 mg IV dose, and can cause a reduction of other agents use up to 45%. An RCT on colorectal surgery patients concluded that ketorolac reduced the postoperative need of opioid use and the rate of postoperative ileus[18].

Acetaminophen is also an analgesic that acts centrally but it does not have the anti-inflammatory effects of NSAIDs. Despite its slow onset, acetaminophen is used widely for acute pain relief, and also common in combinations with many other medications. A high risk of hepatotoxicity is carried with a dose of 4000 mg or more. Although the efficacy of oral acetaminophen has been confirmed in many RCTs and reviews, its used in postoperative pain management has very limited value. The IV form of acetaminophen 'paracetamol' is preferred over NSAIDs as it does not have risk of bleeding, and it is safe in peptic ulcer and asthma. Paracetamol has been used postoperatively and found to cause a reduction in morphine need, and a reduction of opioids side effects. A systematic review pooling data from 21 studies found that paracetamol had increased efficacy when combined with other NSAIDs[19].

New Agents

Dexmedetomidine

Dexmedetomidine is a new drug that works by selectively activation of central active alpha- 2-adrenergic receptors, causing analgesia and sparing respiration. Studies on postoperative patients found dexmedetomidine to effectively maintain sedation and significantly reduce the need of morphine. This drug can be used intravenously safely, and may later be used as a mono-anesthetic for conscious sedation[20].

Remifentanil

Remifentanil is a potent drug that activates m-opioid receptors, and then rapidly metabolized and cleared by nonspecific esterases. The level of analgesia induced by remifentanil depends on the infusion rate. This drug carries a high risk of respiratory depression, as it is a very potent agonist. Moreover, its effects are shore due to rapid metabolism, causing analgesia to stop immediately after termination of infusion. Remifentanil can be used carefully in ICU settings, but should be used cautiously with extubated patients as it has a very narrow window, and has a significant risk of respiratory depression. Remifentanil has been proved to be effective in reducing postoperative pain following lung transplantation[2].

CONCLUSION

Different combinations and modalities of pain management exist, and their use will depend on the case, the patients and their perception of pain. Enhanced recovery protocols, mainly for colorectal surgery, have significantly improved perioperative and postoperative pain management, making the decrease in opioids need a priority. The use of patient-controlled analgesia with morphine is a suitable option following abdominal surgery. However, multimodal pain management protocols must always be used for postoperative pain management. Pre-emptive analgesia is another technique that provides regional block and may be used in ambulatory cases and in surgeries that need extensive incisions. NSAIDs and acetaminophen have been proved effective in improving the quality of anesthesia and lowering opioid use, and should

preferably be used unless there is an absolute contraindication. The use of TAP block is supported by limited evidence, but it is thought to improve pain scores and decrease opioid consumption following abdominal surgery.

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