Management of postoperative pain

Wels D
Department of Anaesthesia, Chris Hani Baragwanath Academic Hospital, University of Witwatersrand
Correspondence to: David Wels, e-mail: dpwels@gmail.com
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Introduction

Postoperative pain is the most undesired consequence of surgery, and if not managed adequately, can lead to delayed recovery and increased hospital stay.[1] Surveys continue to reveal that postoperative pain is insufficiently managed throughout the first world, let alone in the Third World.[2] An American survey over 20 years showed that only one in four patients had adequate relief of postoperative pain. This has led recovery room protocols to include pain as a fifth vital sign that needs to be addressed before patients are discharged to the ward.[3] Opioid-sparing techniques are becoming more popular as they decrease the undesired side-effects from narcotic analgesics, especially since data now suggest that some patients who are treated with opioids may have paradoxical reactions, resulting in hyperalgesia, rather than analgesia.[4,5] Treatment of pain has also moved to the preventive realm, and aims to block the afferent nociceptive bombardment of the central nervous system, before and during surgery. This prevents neurochemical changes that could lead to central sensitisation and chronic pain.[6]

The importance of an acute pain service in hospitals has been shown to be invaluable. These teams practise in the recovery room, as well as the wards, to ensure continued analgesia services after discharge from theatre. They also provide valuable information to medical staff on the use of patient controlled analgesia (PCA) systems, epidurals, indwelling nerve catheters, and optimal drug dosing and administration.[7]

Pathophysiology

The pathophysiology of postoperative pain is multifactorial, and predominantly of inflammatory nature from skin incision and tissue damage. Inflammatory cytokines, interleukins and prostaglandins produced from the arachidonic acid pathway induce a neuro-inflammatory soup, which sensitises peripheral Aδ and C fibres. Ischaemia from retraction of tissue, as well as disrupted blood supplies, contributes to pain significantly, and is characterised by low tissue pH and high lactate levels at the site of incision.[8,9]

Persistent postoperative pain

The phenomenon of pain that persists beyond the time of expected tissue healing after surgery is termed persistent postoperative pain. The incidence varies depending on the type of surgery.[10] Procedures such as a mastectomy, thoracotomy, and hernia repair, have an incidence of persistent postoperative pain of 30-50%.[11] Preoperative risk factors for developing persistent postoperative pain include anxiety, depression, sleep disturbances, and genetic susceptibility. Intraoperatively, the amount of tissue damage and ischaemia are good predictors of persistent postoperative pain. Repeated surgery, as well as chemotherapy and radiotherapy, can contribute to persistent postoperative pain. Prevention of persistent postoperative pain appears to be possible by adequate pre-emptive and perioperative analgesia.[12] The most effective regimens are multimodal, and combine regional techniques together with opioid and non-opioid drugs, including gabapentanoids, ketamine and alpha-2 agonists.[13]

Opioids

Despite their undesirable side-effects, such as respiratory depression, nausea, vomiting, sedation and pruritus, as well as the possibility of paradoxical hyperalgesia, opioids still remain the treatment of choice for moderate-to-severe postoperative pain.[2] Their short onset of action, multiple parenteral routes of administration, and lack of ceiling effects (not all of them) makes them very useful in titration doses against pain.

Intraoperatively, nociception under anaesthesia is adequately controllable with potent synthetic opioids, such as sufentanil and remifentanil. It is the conversion to longer-acting and less potent opioids in recovery and the ward which requires a little skill and pharmacological expertise. This often involves administration of a bolus dose

intraoperatively, followed by small intravenous titrations in recovery.

Although intramuscular administration avoids the first-pass metabolism, and provides a fairly rapid onset, they often result in plasma level peaks and troughs that lead to breakthrough pain between dosing intervals. Increased labour and staffing often contribute to delayed administration of prescribed doses.[14,15] Therefore, PCA is far superior in the management of postoperative pain, especially in the ward.[16] Several disposable PCA pumps are available in South Africa currently, and they are becoming the standard of care in procedures where moderate-to-severe postoperative pain is expected. Usually, opioids are employed in PCAs. However, cocktails with ketamine and antiemetics are often used. This decreases the dose of opioid required, and is particularly useful in obese patients with obstructive sleep apnoea, where opioids precipitate upper airway obstruction.[17] In these patients, PCAs with short-acting opioids, such as fentanyl, are more appropriate than longer-acting drugs, such as morphine, as well as postoperative observation in a high-care environment.[18]

Neuraxial morphine provides excellent postoperative analgesia for up to 24 hours. Morphine is considered to be the gold standard, single-dose neuraxial opioid. Delayed respiratory depression remains a concern, and these patients need to be monitored in a high-care environment postoperatively. It is also important to note that additional opioids are to be administered cautiously after neuraxial morphine has been given. The optimal single-shot dose to be used is 0.075-0.15 mg for intrathecal use, and 2.5-3.75 mg for epidural use.[19]

An extended release epidural morphine, consisting of encapsulated lipid particles, has recently become available in the USA, and provides analgesia for up to 48 hours after a single dose. Therefore, no catheter need be placed, and patients can be fully anticoagulated postoperatively. However, respiratory depression still remains a concern.[20]

A new technology for the transdermal delivery of fentanyl allows for rapid absorbtion from a skin patch. The patch uses a low-intensity direct current (iontophoresis) for transfer from the skin to the systemic circulation. The device is patient controlled, and activates a demand dose of 40 µg of fentanyl, with a lockout time of 10 minutes.[21] Technical problems have resulted in its voluntary withdrawal from the US Food and Drug Administration, but the technology is under review, and a similar product may emerge on the market soon.

One of the problematic side-effects of opioids remains ileus and constipation. Peripherally acting µ receptor antagonists do not cross the blood brain barrier. Therefore, they have no effect on analgesia. However, they antagonise the peripheral effects, and promote a return of bowel movements after surgery. Methylnaltexone and alvimopan are both peripheral µ antagonists, but are not yet available in South Africa.[22]Adding a very low dose of naloxone to a PCA cocktail has similar effects, by preventing peripheral µ effects, and has little effect on analgesia.

A phenomenon in which opioids have a paradoxical effect, and cause painful stimuli to be more sensitive, is called opioid-induced hyperalgesia. Usually, this phenomenon was only observed in patients on chronic opioid treatment, but has been identified perioperatively in patients who received potent or high-dose opioids. The mechanism is different to that of opioid tolerance, but appears to involve activation of the N-methyl-D-aspartate (NMDA) receptor by the excitatory neurotransmitter, glutamate. Drugs antagonising the NMDA receptor appear to play a role in the management of opioid-induced hyperalgesia.[5]

Ketamine

Perioperative intravenous ketamine has been used as an adjuvant to treat postoperative pain for decades. A recent review of 70 studies with 4 701 patients, confirmed that perioperative opioid consumption was lower, postoperative nausea and vomiting was decreased, and that ketamine was especially useful in very painful procedures such as thoracic and major orthopedic surgery. The analgesic effect of ketamine was independent of the type of intra-operative opioid, timing of ketamine administration, and ketamine dose.[23]

Anti-inflammatory drugs

Currently, the American Society of Anesthesiologists recommends a multimodal approach to postoperative analgesia which specifically states "unless contraindicated, all patients should receive an around-the-clock regimen of nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 inhibitors (coxibs) or paracetamol".[24]

NSAIDs, coxibs and paracetamol are indicated for the relief of mild-to-moderate pain, but given in combination with opioids reduces the opioid consumption, and the adverse effects associated with opioid use.[25]

NSAIDs, coxibs and paracetamol are antipyretic, and analgesic, while NSAIDs and coxibs are anti-inflammatory. They work by inhibiting the products of the cyco-oxygenase pathway, both peripherally and centrally. The mechanism of paracetamol is less clearly understood, and seems to work via inhibition of central cyco-oxygenase enzymes, augmenting descending serotonergic pathways,

activation of cannabinoid receptors, and inhibiting nitric oxide pathways.[26-29]

Dexamethasone, given as a single intravenous dose at the induction of surgery, decreases acute postoperative pain.[30] This is due to its inhibition of the cyclooxygenase and lipogygenase pathways, as well as the inhibition of expression of genes and release of proinflammatory enzymes.[31] The ideal dose has not been established, but appears to be 0.1mg/kg.

Alpha-2 agonists

Clonidine and the more selective dexmedetomidine, have opioid-sparing, sedative and analgesic properties.[32] Unfortunately, the analgesic doses of these drugs cause significant side-effects in the form of sedation, hypotension and bradycardia. They are also very long-acting, and can cause delayed awakening after general anaesthesia. The analgesic properties are very alluring though! A dose of 0.4 µg/kg dexmedetomidine was comparable with 60 µg/kg oxycodone to treat postoperative pain after laparascopic sterilisation.[33]

Intramuscular dexmedetomidine (1-1.5 µg/kg), provides excellent premedication and causes minimal haemodynamic changes.[34] Peak plasma levels are reached 1.5 hours after administration, and analgesia effects persist beyond six hours.[35]

When supplemented to local anaesthetics, alpha-2 agonists provide analgesia which outlasts the effect of the local anaesthetic. This makes regional techniques much more effective postoperatively.[36] Dexmedetomidine and clonidine can be used epidurally and intrathecally with local anaesthetics, and have been shown to prolong and improve the quality of neuraxial blocks.[37,38]

Local anaesthetics

Peripheral regional anesthesia can be very effective in the treatment of postoperative pain, especially when catheters are left in situ for the continuous infusion of local anaesthetics. A significant decrease in opioid consumption leads to less nausea and vomiting, less sedation and early mobilisation.[2] Perineural catheters and epidural catheters can be attached to patient-controlled devices for self-administration of local anaesthetics. Interestingly, in a comparison exercise, patients preferred intravenous PCA analgesia to epidural PCA analgesia, even though the epidural group was associated with lower pain scores.[16]

Extended-release local anaesthetics, encapsulated in liposomes and other media, are now available in the USA, which provide a slow release of agent over 72 hours. Injections of these local anaesthetics into incisions after surgery or nerve blocks provide prolonged nerve block and analgesia. Epidural and intrathecal use for these drugs has not been studied. There are some concerns about myotoxicity and neurotoxicity.[39,40]

Intravenous lignocaine as an intravenous bolus of 1.5 mg/kg, followed by an infusion of up to 2 mg/kg/hour for 24 hours postoperatively reduces analgesic requirements significantly, and has an opioid-sparing effect.[41]

Gabapentanoids

Gabapentin and pregabalin, used extensively in the treatment of chronic neuropathic pain, reduce postoperative pain if given pre- and perioperatively. Pre-emptive pregabalin decreases postoperative pain scores, opioid consumption, as well as opioid-related adverse effects. However, postoperative sedation is increased. The recommended dose is 150-300 mg po as a premedication.[42-44]

Conclusion

Adequate treatment of postoperative pain remains challenging. Since postoperative pain has a multimodal aetiology, a multimodal treatment regimen makes sense. Opioids are still the mainstay of treatment for moderate-to-severe pain, but their adverse effects make them limiting. The combination of drugs with opioids, such as paracetamol and anti-inflammatory drugs, or ketamine and alpha-2 agonists, enables the use of less opioids. Premedication and perioperative administration of calcium anatagonists, such as pregabalin, also attenuate postoperative pain. Regional procedures are extremely effective in managing postoperative pain, and use of indwelling catheters enables continued nerve blockade postoperatively. The most effective management of postoperative pain is performed by acute pain teams who monitor patients in the immediate postoperative period, as well as in the ward later.

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