A multimodal approach to managing postoperative pain

STEPHAN SCHUG MD, FANZCA, FFPMANZCA, EDPM

Postoperative pain is the most common acute pain state. Management should be based on a multimodal approach, using a combination of analgesic drugs and techniques that have different modes or sites of action. This has the potential to improve recovery and reduce postoperative complications.

Key points

- **Postoperative pain is the most common acute pain condition. It requires management for humane reasons, but also because management will improve recovery, facilitate rehabilitation and reduce complications.**
- **Postoperative pain should be controlled by multimodal analgesia – the combination of multiple analgesic medications and techniques to improve pain relief and reduce opioid requirements and, thereby, related complications.**
- **Important components of multimodal analgesia are nonopioids (paracetamol and NSAIDs), adjuvants that reduce central sensitisation (e.g. gabapentinoids, alpha-2 agonists, N-methyl-D-aspartate receptor antagonists) and techniques of regional anaesthesia (peripheral and neuraxial approaches).**
- **An underestimated complication of acute postoperative pain is the development of chronic postsurgical pain, which is often neuropathic and requires prevention and early treatment.**
- **Care needs to be taken with regard to opioids prescribed to patients at discharge as these can result in long-term use, misuse and abuse. Limited prescribing and good communication between the specialist and the GP are important components of 'opioid stewardship'.**

Postoperative pain is the most common acute pain condition. Over 250 million operations were performed worldwide in 2004, with most of them leading to postoperative pain.[1] Relief of postoperative pain is not only a humane requirement of modern medicine, but may also result in improved recovery and reduced postoperative complications. It also has the potential to reduce the incidence and severity of chronic postsurgical pain, which is an underestimated problem.[2] There is a large body of evidence to support the management of acute postoperative pain, and general evidence-based guidelines and procedure-specific pain management guidelines have been published recently.[3-5] Despite this, postoperative pain remains often poorly managed. In large surveys, many patients describe severe postoperative pain, and poor pain management continues to hamper recovery and rehabilitation and contributes to chronic pain states and overuse of opioids.[6,7]

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Emeritus Professor Schug was Chair of Anaesthesiology and Pain Medicine in the Medical School of the University of Western Australia, Perth, WA.

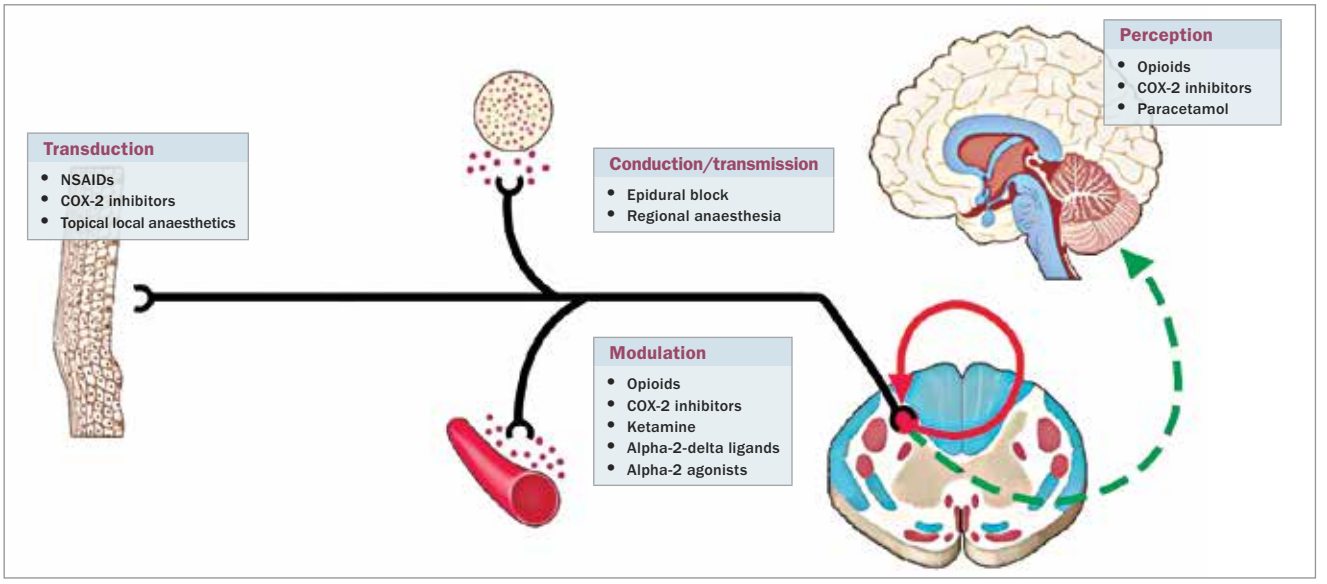

Figure. Site of action of different medications along the pain pathway, illustrating potential components of multimodal analgesia.
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Multimodal analgesia

In the past, postoperative pain management was primarily based on the use of opioids. Although there is no doubt that opioids are highly effective and necessary to control severe acute pain, their use is intrinsically linked to adverse effects. These range from potentially life-threatening opioid-induced ventilatory impairment (OIVI) to classic gastrointestinal effects, such as nausea, vomiting and constipation, which can impair recovery and early postoperative oral nutrition.[8] These and CNS adverse effects, such as drowsiness, sedation and confusion, can also impair active rehabilitation with further negative impact on recovery and early discharge.[9] As the adverse effects of opioids are dose dependent, interest in the concept of 'opioid-sparing' techniques has developed. In the 1990s this led to the development of the concept of 'balanced' or now more commonly called 'multimodal' analgesia, initially pioneered by Henrik Kehlet.[10]

In principle, multimodal analgesia relies, instead of on one medication (opioid), on a combination of analgesic approaches (drugs or techniques), which have different modes or sites of action. If chosen appropriately, the combinations of medications and techniques should act synergistically (or at least additively) and achieve a triad of benefits, namely:

- improved pain relief
- reduced opioid consumption (opioid sparing)
- thereby reduced adverse effects of opioids.

The selection of medications and techniques is driven by an understanding of the pathophysiology of postoperative pain.[11] Postoperative pain is initially primarily nociceptive pain, but due to the rapid development of an inflammatory response after the operation, peripheral sensitisation processes increase the localised pain and lead to local hyperalgesia. Subsequently, central sensitisation develops and contributes further to the overall pain amplification in the early postoperative period.[12] Medications that reduce peripheral sensitisation (e.g. NSAIDs and COX-2 selective NSAIDs [coxibs]) or central sensitisation (e.g. gabapentinoids, N-methyl-D-aspartate receptor antagonists, alpha-2 agonists) are 'antihyperalgesic', reducing the pain amplification and, thereby, pain and analgesic requirements. It is possible to select medications and analgesic techniques by considering their effects on nociceptive/pain pathways as illustrated in the Figure.[13]

Nonopioid analgesics

Classic systemic nonopioid analgesics are paracetamol and NSAIDs. Paracetamol is the universal nonopioid with limited efficacy (number needed to treat of 3.6) but it also has a low rate of relevant adverse effects.[14] Therefore, it forms the basis of most multimodal strategies. Paracetamol should be combined with NSAIDs whenever possible as it enhances their efficacy.[15] In addition, paracetamol has preventive effects on postoperative nausea and vomiting, in particular if administered preoperatively.[16]

NSAIDs reduce peripheral sensitisation because of their anti-inflammatory effects and should be used whenever possible. They are a very effective component of multimodal analgesia (number needed to treat of 1.5 to 2.5) and are useful in controlling pain on movement, facilitating rehabilitation.[14] In contrast to most other analgesics, NSAIDs have a pre-emptive effect (i.e. they are more effective when used before the injury).[17] From an efficacy point of view, there is no difference between nonselective NSAIDs and coxibs.[18] With regard to adverse effects, however, there are important differences.[3] The COX-2 selectivity reduces the risk of gastrointestinal ulcerations, blood loss due to lack of platelet inhibition, induction of bronchospasm in aspirin-sensitive asthmatics and possibly acute kidney injury compared with nonselective NSAIDs. The risk of

cardiovascular events is not increased with use of COX-2 inhibitors, with a recent meta-analysis comparing parecoxib with placebo for postoperative analgesia showing similar incidences for all serious safety events with parecoxib and placebo.[19] As outlined above, the combination of NSAIDs with paracetamol achieves the best effects with regard to pain relief and opioid sparing.[15]

Adjuvant medications

A range of medications are available that can positively interact with the modulation of the nociceptive signal at the level of the dorsal horn of the spinal cord, as shown in the Figure. These medications are not classic analgesic drugs, but reduce central sensitisation by reducing excitatory mechanisms (e.g. gabapentinoids or ketamine) or by strengthening inhibitory mechanisms (e.g. alpha-2 agonists or antidepressants).

The gabapentinoids, gabapentin and pregabalin, have been used extensively as premedication and they have been shown to have analgesic and opioid-sparing effects with reduced adverse opioid effects, and also a desirable anxiolytic effect. This evidence has been recently weakened by more critical systematic reviews, but gabapentinoids show a specific benefit in patients undergoing operations that increase levels of central sensitisation.[20] However, they also have a sedative effect (absolute risk increase of 41 per 1000 patients) and can cause visual disturbances (absolute risk increase of 10 per 1000 patients) in some people which may impair rehabilitation[20] and may increase the risk of OIVI if combined with opioids.[21,22] Their use should therefore be targeted to patients after consideration of the potential side-effect profile and patient comorbidities, as well as the expected severity of postoperative pain.[23] Discontinuation on discharge in patients with no proven neuropathic pain is recommended as the risk of abuse has been reported.[24]

The N-methyl-D-aspartate antagonist ketamine has gone through a renaissance recently as a component of multimodal analgesia in low doses.[25] Here, ketamine provides advantages, in particular after major surgery in opioid-tolerant patients and in acute pain states with a neuropathic component.[3] With low-dose use, serious adverse effects are unlikely and psychomimetic effects such as nightmares or hallucinations are rare and easily treatable.

Alpha-2 agonists such as clonidine and increasingly the more selective compound dexmedetomidine are used as components of multimodal analgesia with good effect.[26,27] Their anxiolytic effects and reduced withdrawal reactions in opioid-dependent patients may be beneficial.

The evidence in favour of postoperative use of antidepressants remains weak, but for the serotonin and norepinephrine reuptake inhibitors (SNRIs), duloxetine and venlafaxine, some supportive data have been published.[28]

The local anaesthetic lignocaine has been used by systemic infusion perioperatively with some benefits for pain relief, opioid consumption and some other outcomes.[29] However, the potential risk of arrhythmias may require monitoring and most studies have limited the infusions to the operating room and the recovery room.

Corticosteroids, in particular dexamethasone, are extensively used perioperatively to reduce postoperative nausea and vomiting and may offer some benefits in enhancing recovery after some operations.[30] Dexamethasone also has some analgesic effects, but these are relatively weak.

Regional techniques

The use of peripheral regional anaesthetic regimens has significantly increased over the past years. This is because of increasing use of ultrasound to perform blocks with increased accuracy and safety, the use of catheter techniques for continuous blocks, the decreasing use of neuraxial techniques with increasing use of anticoagulation and the increasing evidence for the efficacy and safety of these peripheral techniques.[3]

The simplest peripheral regional techniques are wound infiltration and continuous wound infusion through catheters inserted by the surgeon on wound closure.[31] Depending on the type of operation this approach improves analgesia and reduces opioid requirements.

Blocking the conduction of nociceptive signals along the pain pathways can be achieved by blocking nerves with local anaesthetics. The effects of such blockade can be extended into the postoperative period by either using long-lasting local anaesthetics (bupivacaine, ropivacaine, levobupivacaine) or by inserting catheters perineurally and then infusing such local anaesthetics in lower concentrations either continuously or as automated bolus dose achieving a better spread.[32] Anatomical structures that can be blocked are either peripheral nerves (e.g. the femoral nerve after total knee joint replacement) or a nerve plexus (e.g. the brachial plexus for surgery on the arm or hand).

Finally, blocks can be performed near the spinal cord, which are then called neuraxial blocks. Intrathecal administration of local anaesthetics is classically used as spinal anaesthesia, but the block cannot be extended into the postoperative period due to a lack of catheters with an acceptable safety profile. However, the analgesic effect can be extended by adding small amounts of intrathecal opioids (such as morphine).[33] Although this route of administration may reduce the incidence of adverse effects of opioids, it introduces new adverse effects, including increased pruritus and the risk of delayed OIVI due to diffusion of the opioid in the CNS. Therefore, this technique requires extended monitoring.

Epidural techniques have been regarded as the 'gold standard' of postoperative analgesia, providing excellent analgesia, and can contribute to enhanced recovery and reduced perioperative complications, in particular respiratory ones.[34] However, their use has reduced over the past 20 years, in particular in Australia due to the increased monitoring requirements and the potential to cause very rare, but devastating, complications in the form of epidural haematoma and infection with the risk of neurological compromise. The risk of epidural haematoma has been highlighted by the increasing use of perioperative anticoagulation with low-molecular-weight heparin with long duration of effect, which makes careful timing of insertion and removal of epidural catheters necessary.[3]

Therefore, the use of epidural analgesic techniques requires an individualised risk/benefit analysis and will then only be beneficial for major surgery (e.g. upper abdominal and thoracic surgery) and more so in high-risk patients.

Ongoing pain management throughout the postoperative period

Postoperative pain is usually worse in the first 24 hours after surgery and decreases in most patients with a typical declining pain trajectory.[35] Therefore, postoperative analgesia can often be reduced over the postoperative course.

Initially, many patients require parenteral administration of analgesia. This is usually achieved by using parenteral nonopioids and, if necessary, adjuvants and rescue opioids via a patient-controlled analgesia pump. This leaves the dosing of the opioid to the individual requirements of the patient with increased patient satisfaction and safety compared with continuous administration.[36] With the return to oral intake (increasingly earlier in fast-track programs) nonopioids and adjuvants are changed to oral administration with access to immediate-release oral opioids to control breakthrough pain. It is not advisable to use slow-release or transdermal opioid preparations in the postoperative period due to their long half-life making individualised titration difficult and slow and resulting in an increased risk of OIVI.[37] In selected cases slow-release opioids can be useful, but then atypical opioids such as transdermal buprenorphine, tramadol or tapentadol should be used due to their better safety profile.

If regional anaesthetic techniques are used as a single shot of a long-lasting local anaesthetic, the effects wear off 12 to 16 hours after the injection. Therefore, sufficient oral (and rarely parenteral) rescue analgesia needs to be prescribed to avoid severe breakthrough pain; nonopioids and adjuvants can be prescribed prophylactically to reduce opioid requirements. Regional anaesthesia catheter techniques and epidural analgesia can be maintained longer into the postoperative period, but on discontinuation similar plans should be in place.

As outlined above, usually postoperative pain declines rapidly in the postoperative period and therefore analgesia can be reduced accordingly, in particular with regard to opioid doses. However, in some patients severe pain persists or increases in the postoperative period.[35] In such cases, surgical complications (e.g. development of compartment syndrome after orthopaedic surgery) need to be excluded and, if identified, treated appropriately.

In other patients, postoperative pain persists or increases despite successful surgery. Here, acute neuropathic pain needs to be excluded and, if identified, treated with specific medications for this indication (pregabalin or gabapentin, ketamine, tapentadol or tramadol). This is particularly important as acute neuropathic pain increases the risk of chronic postsurgical pain; this is an underestimated complication of surgery.[2] Other risk factors for chronic postsurgical pain, which can also increase the acute postoperative pain experience, are psychological factors such as catastrophising personality and depression, chronic pain states such as fibromyalgia before the surgery and preoperative long-term opioid use. Patients identified by such a positive pain trajectory postoperatively are a concern and need more intense management to reduce the risk of chronic postsurgical pain and ongoing opioid use. A suggested approach is early involvement of chronic pain clinics or, ideally, care from a transitional pain service, as suggested in the international literature but not yet implemented in Australia.[38]

Discharge planning

Due to the current emphasis on fast-track surgery and employment of enhanced recovery after surgery pathways, postoperative patients are discharged earlier and earlier. This requires ongoing provision of analgesia after discharge and careful planning, with involvement of GPs and allied healthcare professionals such as physiotherapists.[7] This planning should include consideration of the risks associated with opioids prescribed at discharge (e.g. increased risks of falls, impairment of driving skills and the initiation of long-term opioid use). In addition, opioids prescribed at discharge form a pool for potential diversion and misuse and abuse. Therefore, rules of opioid stewardship with careful prescribing of appropriate small quantities of immediate-release opioids (ideally atypical opioids on top of multimodal analgesia) should be implemented and long-acting opioids should be avoided because they are linked to an increased risk of long-term use.[39]

Communication between the specialist and the GP in this phase is essential and should include advice on ongoing management, opioid weaning and early referral of the patient for pain management in case of problems. As stated previously, early identification of at-risk patients and early involvement of pain management services is desirable.

Conclusion

Multimodal analgesia has revolutionised the management of postoperative pain. Nonopioids, adjuvant medications and, in particular, regional techniques improve pain relief and reduce opioid requirements, and thereby their adverse effects. Improved postoperative analgesia offers the opportunity to improve postoperative recovery and rehabilitation and to reduce complications (such as OIVI). Postoperative pain decreases rapidly in the postoperative period and therefore pain management needs to be adjusted accordingly. Acute postoperative pain can develop into chronic postsurgical pain, which requires early recognition and treatment. With the increasing trend towards early discharge after surgery, patients often require opioids on discharge. This carries a risk of long-term use, misuse and abuse; therefore, cautious prescribing of opioids while maintaining the use of nonopioids and co-ordination with the GP after discharge are important precautions. **PMT**

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