Postoperative pain management

This article provides an overview of current methods used in acute pain management and explains why effective analgesia is crucial in the early postoperative period. It describes the pharmacology of both common and specialist analgesics, as well as explaining the role and uses of regional and neuraxial analgesia, for the non-anaesthetist.

Pain following surgery is usually acute and easily managed. However, it can be severe, under-treated and more persistent than expected with a high incidence of associated morbidity and mortality from cardiovascular, respiratory, gastrointestinal and metabolic complications. The prevalence of acute postoperative pain can be as high as 80% (Apfelbaum et al, 2003) with evidence suggesting that 50% and 35% of patients experience it at 30 minutes and 48 hours respectively (Couceiro et al, 2009). The intensity of postoperative pain is also significant; up to 65% of patients experience moderate and 40% severe pain (Couceiro et al, 2009). More worryingly, only one in four postoperative patients is being prescribed adequate pain relief (Phillips, 2000).

Acute pain mechanisms

Classic somatic and visceral pain mechanisms and pathways dictate the physiological processes in postoperative pain. Specialized nociceptors distributed particularly in the skin, viscera, muscles, joints and meninges are stimulated by noxious stimuli such as inflammatory mediators (e.g. bradykinin, serotonin, prostaglandins and cytokines) released following tissue damage. This is transduced and transmitted as electrical signals to the CNS via primary afferent Aδ and C nerve fibres which synapse with secondary afferent neurones within the dorsal horn of the spinal cord. Transmission ascends via the spinothalamic or spinoreticular tracts into higher centres of the brain including the pain matrix and parts of the somatosensory cortex. Sharp and localized somatic pain is transmitted via fast, myelinated Aδ nerve fibres while dull and diffuse visceral pain is transmitted via slow, unmyelinated C pain fibres. Of note, the phenomenon of persistent postoperative pain, a chronic pain state where symptoms continue beyond 2 months past the expected post-surgical healing process (Kehlet et al, 2006), differs from somatic and visceral pain transmission in that nociception is prolonged through inflammatory, ischaemic and neuropathic causes (Kehlet et al, 2006).

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Why is pain management poor?

The reasons given for poor postoperative pain management are multifactorial. Although protocols and guidelines have been produced for individual surgeries and the general surgical population, lack of adherence to these leads to inadequacies in postoperative pain management (Block et al, 2003; Benhamou et al, 2008). Other factors include known predictors such as extremes of age, female sex and the comorbidities of complex preoperative pain, catastrophizing, anxiety and obesity (Ip et al, 2009). The type of surgery is also significant with operations of the nose and pharynx, abdomen, plastic surgery of the breasts, and orthopaedics associated with prolonged and increased pain during the first 48 hours. Deficiencies in pain education and underuse of effective analgesic pharmacology and techniques also play important roles (Benhamou et al, 2008).

Interestingly, evidence does not suggest that poorly managed or severe post-surgical pain are contributing factors towards persistent postoperative pain (Eisenach, 2006). However, specific surgeries are associated with persistent pain occurring in up to 60% of patients after limb amputation, breast tumour excision or mastectomy and after thoracotomy (Haroutiunian et al, 2013). Persistent postoperative pain may last for many years in 5–10% of these patients and can be severe (Haroutiunian et al, 2013).

Finally, the lack of pain assessment by physicians and nurses is one of the biggest barriers to achieving good pain control. The American Society of Anesthesiologists has recommended that health-care professionals ensure that standardized assessment tools for acute pain management are used in the perioperative setting (American Society of Anesthesiologists Task Force on Acute Pain Management, 2012). These tools are based on pain intensity through use of validated and simple scales of numbers or words (e.g. visual analogue scale, numeric rating scale or through diagrams for children, the elderly and the cognitively impaired (e.g, the Wong-Baker FACES scale, the PAIN-AD)). The key is that assessments must be performed regularly so that comparisons

can be made and changes in pain intensity managed effectively (American Society of Anesthesiologists Task Force on Acute Pain Management, 2012).

Pharmacology

Paracetamol

Paracetamol or acetaminophen is a weak base, first discovered in 1886. Around 70% of absorption occurs in the small intestine by passive diffusion. Once in the bloodstream, it easily crosses the blood–brain barrier and into tissues.

Paracetamol is metabolized predominantly by glucuronide conjugation and sulfone conjugation into non-toxic, water-soluble species excreted in the urine. A small proportion (4%) is oxidized via cytochrome p450 into N-acetyl-p-benzoquinone imine, a toxic substance normally neutralized by liver stores of glutathione. In cases of overdose greater than 4 g/day, glutathione stores became depleted and N-acetyl-p-benzoquinone imine reacts within hepatocytes causing cell death and acute liver failure (Zeilhofer and Brune, 2013).

Despite its prevalent use, the exact pharmacodynamics of paracetamol remain unclear. Suggested mechanisms of analgesic and antipyretic action include: inhibition of cyclooxygenase (COX) enzymes and prostaglandin synthesis, interaction via the central serotonergic pathways, activation of cannabinoid receptors, the opioidergic system and inhibition of nitric oxide synthase.

Paracetamol is a popular paediatric antipyretic and analgesic.

According to the 2008 Cochrane review, single dose oral paracetamol is an effective and safe analgesic in adults experiencing acute pain, 4–6 hours after surgery (Toms et al, 2008). Its efficacy is comparable to non-steroidal anti-inflammatory drugs (except in dental surgery)(Hyllested et al, 2002) and single dose intravenous paracetamol is associated with 30% less opiate use than placebo.

Paracetamol is more effective when combined with other classes of analgesics (*Table 1*). It enhances the effect of aspirin, non-steroidal anti-inflammatory drugs and opioids, and is opioid sparing, particularly in moderate to severe acute pain. However, this combined use has the potential for increased side effects, toxicity and cost.

Non-steroidal anti-inflammatory drugs are blockers of the COX enzyme, which converts arachidonic acid into prostaglandins. The COX-1 isoform is constitutively expressed and regulates homeostatic processes – renal vascular tone, gastric cytoprotection and platelet function, while COX-2 regulates acute processes and is induced in significant quantities by trauma, infection, inflammation and cancer.

With the exception of aspirin, most non-steroidal anti-inflammatory drugs are either reversible competitive inhibitors, variably blocking both COX-1 and COX-2 isoforms (ibuprofen, diclofenac, ketoralac, ketoprofen, mefenamic acid, piroxicam, meloxicam, indomethacin) or selective inhibitors of COX-2 (celecoxib, rofecoxib), known as coxibs.

Coxibs were introduced in 1999 and aimed to provide safe analgesia and anti-inflammation without causing gastrointestinal side effects. However, large trials such as APPROVe, VIGOR and APC demonstrated a higher risk of serious prothrombotic events.

Single dose non-steroidal anti-inflammatory drugs are effective in treating acute postoperative pain and in reducing the acute need for opiates. Their efficacy is summarized in *Table 2*. Some agents have a number needed to treat similar to 10 mg of intramuscular morphine (number needed to treat 2.9), which suggests they are equally effective interventions.

Although effective, non-steroidal anti-inflammatory drugs have more adverse effects than paracetamol in the postoperative period – gastrointestinal damage, acute kidney injury in patients with hypertension or pre-existing kidney impairment, impaired bone healing and poor haemostasis. Less common problems include asthma exacerbation (diversion of arachidonic substrates into the leukotriene pathway), disruption of sleep pattern and alteration of morphine metabolism (Hyllested et al, 2002).

Opioids

Opioids are used to treat moderate to severe perioperative pain. They can be administered via many routes and come in different preparations including modified release, extended release and iontophoretic transdermal systems.

Table 1. Efficacy of single dose oral paracetamol *vs* combination analgesics in the early postoperative period

Analgesic (oral)	Number needed to treat for >50% pain relief, within 4–6 hours postoperatively (95% confidence interval)
Paracetamol 1000 mg	3.6 (3.2–4.1)
Paracetamol and ibuprofen	1.5 (1.4–1.7) (Derry et al, 2013)
Paracetamol 1000 mg and codeine 60 mg	2.2 (1.7–3.9) (Toms et al, 2009)
Paracetamol 975 mg and tramadol 112.5 mg	2.8 (2.1–4.4)
Paracetamol 650 mg and oxycodone 10 mg	2.7 (2.4–3.1)

Table 2. Efficacy of different types of single dose non-steroidal anti-inflammatory drugs in the early postoperative period

Analgesic (oral)	Number needed to treat for >50% pain relief, within 4–6 hours postoperatively (95% confidence interval)
Valdecoxib 40 mg	1.6 (1.4–1.8)
Diclofenac potassium 50 mg	2.1 (1.8–2.4)
Ibuprofen 400 mg	2.5 (2.4–2.6)
Celecoxib 400 mg	2.5 (2.2–2.9)
Naproxen 500/550 mg	2.7 (2.3–3.2)
Aspirin 600 mg	4.2 (3.9–4.8)

In theory opioids do not have a ceiling effect dose and can be titrated to effect. However, high doses lead to potentially fatal side effects, which limit their efficacy and administration in the management of both acute pain (side effects include sedation, suppression of respiratory drive, nausea, vomiting, pruritus, reduced bowel motility) and chronic pain (side effects include immunosuppression, opioid-induced hyperalgesia, tolerance and dependence).

Opioids exert their action via specific opioid receptors: mu, delta, kappa and ORL1. These are located in the central and peripheral nervous, endocrine and immune systems (Marvizon et al, 2010). Analgesia is primarily mediated via the mu receptor.

Most opioid receptors are inhibitory G-coupled proteins, which inhibit nerve depolarization by reducing intracellular cAMP, intracellular calcium and sodium, increasing potassium, causing nerve hyperpolarization (McDonald and Lambert, 2005) and reduced neurotransmitter release. In the peripheral nervous system, opioid receptors are formed in the dorsal root ganglion and transported anterograde and retrograde within the Aδ and C axons to reduce substance P release from the nerve terminals and inhibit presynaptic discharge of glutamate (McDonald and Lambert, 2005) at the dorsal horn. In the spinal cord, activated mu receptors in lamina 2 prevent relay of nociceptive impulses into the brain. In the periaqueductal gray, mu receptors stimulate descending inhibition by removing gamma-aminobutyric acid (GABA)-mediated tonic inhibition (McDonald and Lambert, 2005).

Intravenous patient-controlled analgesia is the most common mode of parenteral opioid administration because it has better pain control and greater patient satisfaction compared with nurse/physician administered parenteral opioids (Hudcova et al, 2006). The most popular opioid used in intravenous patient-controlled analgesia is morphine because of its optimal onset time (5–15 minutes) and half life (2 hours).

Opioids provide better quality analgesia and reduce perioperative mortality and morbidity in certain groups of patients when given via the neuraxial route (Pöpping et al, 2014).

Neuraxial opioids are equianalgesic at much lower doses than the intravenous route, and thus cause fewer systemic side effects. However, they are less popular than intravenous patient-controlled analgesia because the insertion techniques are more labour intensive and they pose more management difficulties and thromboprophylaxis safety issues.

Neuraxial opioids act predominantly via CNS receptors; however, they can easily pass into the systemic circulation and exert peripheral side effects depending on their lipophilicity. Diamorphine and fentanyl are commonly used in single dose intrathecal injections, while continuous epidural infusions contain mostly fentanyl. New formulations of extended release epidural morphine offer prolonged periods of analgesia (48 hours) in below-waist surgery, but are associated with delayed respiratory depression and a higher incidence of systemic side effects, comparable with that of intravenous opioids.

End tidal CO_2 monitoring must be used to monitor for signs of respiratory toxicity in patients receiving continuous or prolonged release epidural or spinal opioids.

Parenteral opioids are safer, faster and more efficient than oral formulations in the early postoperative period, especially in patients with inadequate tolerate oral intake, but are invasive and cannot be continued at home.

Commonly used oral opioids include immediate release (morphine, oxycodone, codeine, dihydrocodeine and tramadol) and modified release preparations (morphine sulphate MST, oxycodone (Oxycontin) and tramadol MR). A systematic review of single dose analgesics in the acute postoperative period showed they had relatively poor efficacy compared with non-opioid oral analgesics (Moore et al, 2011).

Tramadol is a synthetic analogue of codeine, used in both acute and chronic pain settings. It is a weak mu receptor agonist and noradrenaline and serotonin reuptake blocker. It is effective in mild to moderate postoperative pain, with a number needed to treat similar to oral paracetamol, but has a significantly higher side-effect profile, especially in patients post dental surgery.

Tapentadol is a synthetic mu receptor agonist and central noradrenaline reuptake inhibitor. Originally used in chronic somatic and neuropathic pain, it has similar efficacy to immediate release oxycodone, with fewer opioid-induced systemic side effects in the acute postoperative setting.

Transdermal opioids can be potentially used in the postoperative period as they are minimally invasive, improve patient mobility (no connection to an infusion pump) and have a better pharmacokinetic profile than oral, intramuscular or subcutaneous routes. Fentanyl, commonly used as patches in chronic pain, is ideal because of its high lipophilicity and small molecular size which allows steady delivery of drug into the systemic circulation over a period of 72 hours. Patient-controlled fentanyl hydrochloride iontophoretic transdermal systems (fentanyl ITS) have been as effective as intravenous patient-controlled analgesia in the postoperative setting. A localized, low density electrical current stimulates on-demand release of quantified fentanyl boluses (40 μg) across intact skin, to achieve peak efficacy within 10 minutes of self-administration.

GABA analogues

Gabapentin and pregabalin are GABA analogues which block voltage-gated calcium channels and prevent the release of excitatory neurotransmitters. Initially developed as antiepileptics and anxiolytics they are now routinely used in the management of chronic, predominantly neuropathic pain (Wiffen et al, 2013).

Pregabalin doses greater than 300 mg per day significantly reduce opioid consumption and opioid-related adverse effects in the acute postoperative period. Drug side effects include somnolence and visual disturbances.

Gabapentin has a similar opioid-sparing effect. Although small doses of 250 mg per day were more effective at reducing acute post-surgical pain than placebo, other non-opioids such as non-steroidal anti-inflammatory drugs and paracetamol were more efficacious. However, at higher pre-emptive doses of 300–600 mg and regular postoperative doses of 1.2 g per 24 hours, gabapentin showed significant opioid sparing and a low side-effect profile.

Perioperative gabapentin modulates both immediate acute perioperative pain and reduces the incidence of latent neuropathic and chronic post surgical pain.

Other drugs

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist used in a variety of settings – induction and maintenance of general anaesthesia, sedation, analgesia for acute, chronic and cancer pain. It modulates the monoaminergic descending pathways, and interacts with opioid and muscarinic receptors. In the first 24 postoperative hours ketamine is an effective opioid-sparing adjunct with mild side effects. It can be administered as boluses or an infusion. It is used in subanalgesic doses to manage opioid tolerance and hyperalgesia (Hirota and Lambert, 2011).

Alpha 2 agonists are used in the intensive care setting as anxiolytics, sedatives and hypotensive agents. Their role has now expanded into the multimodal treatment of acute and perioperative pain.

Clonidine and dexmedetomidine act in the supraspinal regions, reducing central sympathetic outflow and pre- and postsynaptic nociceptive transmission in the dorsal horn. They block transmission along peripheral nerve afferents (especially C fibres), reduce substance P release and induce cross-tolerance with mu opioid receptors.

Dexmedetomidine is more selective and causes fewer cardiovascular side effects, such as bradycardia and hypotension, than clonidine. A systematic review and meta-analysis in adults receiving clonidine and dexmedetomidine showed significant reduction in pain, opioid consumption and nausea compared to placebo at 24 hours post surgery (Schnabel et al, 2013).

The 2014 Cochrane systematic review showed similar results in children, where clonidine premedication reduced the need for postoperative pain relief compared to placebo, and caused minimal adverse cardiovascular effects (Lambert et al, 2014).

Capsaicin is a peripherally acting selective TRPV-1 agonist found in chillies. It stimulates peripheral release of substance P, causing its depletion, which reduces peripheral nociception. Predominantly used as a topical treatment in chronic neuropathic pain, studies where it was instilled directly into surgical wounds showed a reduction of postoperative pain and an opioid-sparing effect compared to placebo in patients undergoing total knee replacements (Hartrick et al, 2011) and open hernia mesh repairs.

Regional analgesia

Multimodal analgesia is defined as the use of a variety of interventions to address pain at various origins along the transmission pathway. Multimodal regimens provide enhanced analgesia and attempt to limit single agents (especially opioids) to decrease pharmacological side effects.

Enhanced recovery programmes advocate multimodal approaches to facilitate early discharge from hospital and resumption of normal activities after elective surgery. One of the main pillars of enhanced recovery is good postoperative pain management using various analgesic techniques including regional anaesthesia.

Regional analgesia can be divided into central and peripheral anaesthesia.

Central anaesthesia

Central or neuraxial regional blockade includes spinal, epidural and caudal anaesthesia. First performed in 1885, it is a common practice worldwide 2 decades later. In the UK the NHS carries out around 700 000 central or neuraxial regional blockade procedures per year (Cook et al, 2009).

In spinal anaesthesia, local anaesthetic is injected into the intrathecal space. The analgesia lasts for a few hours and is beneficial in the intraoperative setting. Addition of medium- to long-acting opioids prolongs the analgesic effect for up to 24 hours postoperatively. Side effects of intrathecal opioids include pruritus, nausea, respiratory depression, urinary retention, motor block, and sympathectomy-induced reduction in blood pressure.

Epidural anaesthesia involves injecting dilute local anaesthetic in the epidural space with an indwelling catheter left in situ. Anaesthetic infusions with or without opioids are administered as continuous infusions or boluses via a catheter to prolong the analgesic effect postoperatively. The spread of analgesia ranges from the thorax to the lower limbs depending on the vertebral level of epidural placement. Adverse events are similar to those of spinal anaesthesia. Epidural catheters are usually removed within 72 hours of insertion to reduce the risk of catheter site infection. The timing of epidural insertion and removal in relation to anticoagulation therapy is key in reducing the risk of neuraxial haematomas. Timings differ depending on types and doses of anticoagulation therapy.

Caudal anaesthesia involves local anaesthetic solution injected into the caudal canal to produce effective analgesia to the sacral and lumbar nerve roots. It is useful in surgical procedures below the umbilical region, and catheter placement is possible to prolong the analgesia. This is technique is commonly used in paediatrics.

The safety of regional analgesia was reviewed by the National Audit Project 3, a large audit carried out by the Royal College of Anaesthetists in 2009. It sought to determine the incidence of complications of central or neuraxial regional blockade resulting in patient harm (Cook et al, 2009). The audit indicated that the incidence of complications of central or neuraxial regional blockade in children, adult chronic pain and obstetric patients is extremely low. Permanent injury caused by central or neuraxial regional blockade was 2–4.2 per 100 000 cases and the incidence of paraplegia or death was 0.7–1.8 per 100 000.

Peripheral anaesthesia

Peripheral regional anaesthesia incorporates all varieties of neural blockade other than central anaesthesia blockade. The region of blockade relies on the site of surgery and the patient's anatomy (*Table 3*).

Peripheral regional anaesthesia can be carried out as local infiltration or as specific peripheral nerve blocks. The latter can be the sole surgical anaesthetic or an adjunct to other techniques such as general or neuraxial anaesthesia. Peripheral nerve block may last for up to 24 hours if a single shot technique is used. This prolonged analgesic effect is useful in enhancing early postoperative physical rehabilitation particularly after orthopaedic surgery.

The additional placement of an indwelling catheter adjacent to a peripheral nerve is also used to prolong postoperative analgesia. It can be inserted at the surgical incision site or perineurally away from the surgical site, with an infusion of local anaesthetic continued postoperatively. The analgesia is prolonged beyond 24 hours and allows for opioid sparing.

Table 3. Most commonly used nerve blockade for specific types of surgeries

Surgery		Regional blocks used	Catheter option
Head and neck	Carotid endarterectomy	Superficial/deep cervical plexus	No
	Neurosurgery	Supraorbital nerve	
		Zygomaticotemporal nerve	No
Upper limb		Brachial plexus	Yes
		Distal peripheral nerve (i.e. radial, ulnar, median nerve)	
Lower limb		Spinal/epidural	Yes
		Femoral nerve	
		Saphenous nerve	
		Sciatic	
		Ankle	
Truncal (i.e. hernioraphy, laparotomy)		Spinal/epidural	Yes
		Ilioinguinal	
		Fascial plane blocks	
		Transversus abdominis block	
		Rectus sheath block	

The overall benefits of regional anaesthesia remain controversial. One reason is the small sample size of the various trials carried out to date. The incidence of complications is low and a very large trial size would be required to show a statistically significant difference in patient outcome.

There is strong evidence that central or neuraxial regional blockade provides superior analgesia compared with other alternatives (Carli et al, 2002; Rigg et al, 2002; Guay, 2006), but the outcome benefits are not as clear. Studies on neuraxial analgesia have shown better postoperative outcomes and reduction in overall complications following major surgery (Carli et al, 2002; Guay, 2006). Continuous neuraxial blockade leads to earlier restoration of gastrointestinal motility, favourable patient discharge criteria, reduced risk of postoperative pneumonia, prolonged ventilation, reintubation and respiratory failure (Rigg et al, 2002). The National Institute for Health and Care Excellence supports the use of regional analgesia to reduce thromboembolic disease.

Research in cancer recurrence and survival has been carried out in various surgical specialities (Exadaktylos et al, 2006; Biki et al, 2008). The perioperative period is physiologically pro-tumourigenic, immunosuppressive and angiogenic. The use of regional analgesia may have a potential benefit to attenuate the stress response, reduce opioid requirements (immunosuppressive) and decrease or abolish the need for volatile anaesthesia (which may enhance tumour growth).

Patient outcomes based on health-related quality of life and patient satisfaction have become a focal point in outcome assessment (Macario et al, 1999; Carli et al, 2002). In colonic surgery, neuraxial techniques showed favourable results in walking exercise capacity and health-related quality of life measures when compared to opioid-based analgesia regimens. This benefit continued at 6 weeks postoperatively (Carli et al, 2002). Patients ranked vomiting, gagging on the tracheal tube, incisional pain and nausea as the most undesirable postoperative outcomes when asked which clinical outcomes were most important to them (Macario et al, 1999). This study provides additional encouragement for clinicians to seek alternative methods of anaesthesia/analgesia other than the traditional general anaesthesia and opioid analgesia methods.

Conclusions

The take-home message is to note the importance of appropriate and effective analgesia for all patients, surgical and medical. Advances in our understanding of pain control and its implications in recovery, survival and related quality of life for patients should be the driving force for all clinicians to provide more comprehensive management to address pain control. The progress of

pain management for surgical patients is ever evolving and this article provides an insight into the options that could be sought for patients. **BJHM**

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KEY POINTS

- Effective pain management is vital in the postoperative period and a key part in the enhanced recovery programme.
- Good postoperative pain management improves patient outcomes including reduction in mortality and morbidity, earlier hospital discharge, reduced risk of chronic postoperative pain and greater patient satisfaction.
- Multimodal analgesia is key in providing effective pain relief while minimizing the associated side effects, especially those with opioid-based analgesia.
- Regional analgesia is an effective and safe mode of pain relief but requires additional specialist training to maximize its potential and prevent any possible adverse events.

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