Pain 1

Treatment of acute postoperative pain

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Although postoperative pain remains incompletely controlled in some settings, increased understanding of its mechanisms and the development of several therapeutic approaches have substantially improved pain control in past years. Advances in our understanding of the process of nociception have led to insight into gene-based pain therapy, the development of acute opioid-induced hyperalgesia, and persistent postsurgical pain. Use of specific analgesic techniques such as regional analgesia could improve patient outcomes. We also examine the development of new analgesic agents and treatment modalities and regimens for acute postoperative pain.

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This is the first in a **Series** of three papers about pain

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Introduction

The treatment of acute postoperative pain is an important health-care issue. Many advances have been made in our understanding of the process of nociception and innovations in both analgesic agents and techniques for provision of analgesia since the last *Lancet* review of the topic.[1] Although there have been many developments in acute postoperative pain during the past decade, we provide the latest perspective on several key areas in the treatment of this form of pain.

Search strategy and selection criteria

We searched Medline (between 2000, and July, 2010) and Embase (2000–11) using the search terms "acute pain" or "postoperative pain", and limiting the field to "title/abstract". Although we largely focused on reports published within the past 3 years, we did not exclude commonly referenced and highly regarded older publications. The reference lists of articles identified by this search strategy, several book chapters, and the authors' personal reference lists were also included. The reference list was subsequently modified during the peer-review process on the basis of comments from reviewers.

Key messages

- Despite the introduction of new standards, guidelines, and educational efforts, data from around the world suggest that postoperative pain continues to be managed inadequately, although the reasons why are not clear.
- Basic science and clinical data suggest that a paradoxical response to opioids might exist such that patients who receive opioids can actually become more sensitive to painful stimuli, thus resulting in hyperalgesia rather than analgesia (opioid-induced hyperalgesia). The implications of this response for routine postoperative pain management are, however, unclear.
- The issue of individualised genotype-based pain therapy is complex and far from being realised for routine clinical practice. Although there is clearly some genetic component to the perception of pain, the overall clinical effects of common polymorphisms in most patients are small, unlike the large genotype effects seen in rare variants.
- The development of a chronic pain state after surgery, termed persistent postsurgical pain, is being increasingly recognised as a not uncommon occurrence. Several risk determinants for persistent pain have been identified, but no one factor seems to have a dominant role.
- Data suggest that use of specific analgesic agents or techniques, particularly regional analgesia (eg, epidural or peripheral nerve analgesia) with a local anaesthetic-based regimen, can affect major postoperative morbidity. Use of regional analgesic techniques is associated with lower pain scores than are seen with systemic opioids.
- Research into multimodal analgesia does not reveal a consistent level of success in part because of the large number of variables (eg, different doses or analgesic agents or techniques, type of surgery) present in available studies; however, some multimodal analgesia trials have shown improved outcomes (eg, improved analgesia) or even possibly a reduced incidence of chronic postsurgical pain.

Treatment of acute postoperative pain: how are we doing?

During the past two decades, the undertreatment of acute pain has been widely recognised as an important issue in health care. Researchers have estimated that only one in four surgical patients in the USA received adequate relief of acute pain.[2] Acknowledgment of the widespread nature of acute postoperative pain led to the development of many medical societal guidelines and more notably of new regulatory standards (eg, Joint Commission on Accreditation of Healthcare Organizations) for the assessment and management of acute pain. One of the main emphases of these new standards has been the routine assessment of pain as the so-called fifth vital sign.[2]

Despite the introduction of new standards, guidelines, and educational efforts, data from around the world suggest that postoperative pain continues to be undermanaged. An assessment of 1490 surgical inpatients in the Netherlands revealed that, despite the presence of an acute pain protocol, 41% of patients had moderate-to-severe pain on the day of surgery, with almost 15% of patients noting the presence of moderate-to-severe pain on the fourth postoperative day.[3] A random sample of 250 US adults who had undergone surgical procedures showed that 80% of patients had acute pain postoperatively and, of these patients, 86% had moderate-to-severe pain, with more patients reporting pain after than before hospital discharge.[4] The continued undertreatment of pain is not limited to adult patients. A study of 261 children undergoing routine tonsillectomy and adenoidectomy noted that on the first day at home,

parents rated 86% of children as having significant overall pain.[5]

Why there has been little progress in the treatment of acute postoperative pain is unclear, but the causes might be multifactorial, including the continued paucity of pain assessment and documentation, heightened awareness and increased number of audits or surveys leading to increased identification of undertreatment of pain, absence of specific written postoperative pain protocols, deficiencies in educational pain management programmes for health-care workers, underuse of effective analgesic techniques (eg, epidural analgesia and peripheral nerve catheters), and poor adherence to available guidelines.[6–8] The inconsistent progress in the overall treatment of acute postoperative pain has occurred despite a possible increase in the overall use of opioids in an attempt to treat acute and chronic pain.[9–12] This increased opioid use could be associated with an increased incidence of opioid-related adverse drug events, including oversedation and respiratory depression,[13,14] although further studies examining the incidence and risk factors associated with opioid-related side-effects and complications are needed to elucidate possible trends. Further study and vigilance are needed because opioid-related adverse drug events have been associated with an increase in overall cost, length of stay, and even decreased survival during in-hospital resuscitation.[15,16]

Pathophysiology of postoperative pain

Mechanisms

Although a comprehensive overview of the nociceptive processing of acute postoperative pain is beyond the scope of this report, there have been several recent developments in the study of the nociception of acute postoperative pain.[17] Neurophysiological and pharmacological studies in recently developed animal models for postoperative pain have advanced our knowledge of the mechanisms of pain resulting from surgical incision and associated tissue injury.[18–21] These studies suggest that incisional pain differs in its mechanism from other inflammatory or neuropathic pain states. Hyperalgesia in the region of the incision is thought to be mediated by sensitisation of Aδ-fibre and C-fibre nociceptors and the conversion of mechanically insensitive or silent Aδ nociceptors to mechanically sensitive fibres after incision.[22] Additional studies show an important role of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA)/kainate ionotropic excitatory aminoacid receptors for incision-induced pain, hyperalgesia, and spinal sensitisation.[23] Increased lactate concentrations and low pH occur in skin and muscle wounds after incision and suggest that an ischaemic pain mechanism might contribute to postsurgical pain.[24] Central neuronal sensitisation probably contributes to postoperative pain and hyperalgesia. Neurophysiological studies in animal models have shown an increase in the prevalence and rate of spontaneous activity of spinal dorsal horn neurons after skin and deep muscle incision.[17] However, the precise role of central sensitisation in the development of persistent postoperative pain is uncertain.[25,26]

Predictors of postoperative pain

In an attempt to improve postoperative pain management, studies have focused on identification of predictors of postoperative pain resulting from various surgical procedures. 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.[27,28] Type of surgery, age, and psychological distress also predicted postoperative analgesic consumption. The postulate, which needs to be confirmed with future studies, is that early identification of predictive risk factors for postoperative pain will allow development of effective pain management programmes.

Acute opioid-induced hyperalgesia in the perioperative period

Recent basic science and clinical data suggest that a paradoxical response to opioids might exist such that patients who receive opioids could actually become more sensitive to painful stimuli, thus resulting in hyperalgesia rather than analgesia.[29] This event, known as opioid-induced hyperalgesia (OIH), presumably results from the upregulation of pronociceptive pathways within the central and peripheral nervous systems.[30] Although hyperalgesia has traditionally been associated with chronic pain, acute OIH can occur after intraoperative or postoperative administration of high doses of potent opioids, which can lead to increased postoperative pain despite a concurrent increase in postoperative opioid use.[29–32] OIH is distinctly different pharmacologically from analgesic tolerance to opioids (resulting from the desensitisation of antinociceptive pathways), although both will ultimately result in an increase in opioid requirements.[29] Clinically, differentiation between tolerance and OIH might be difficult.

Direct evidence for the acute development of OIH comes from several volunteer studies in which amplification of experimentally induced hyperalgesia was noted after infusion of remifentanil, a short-acting potent opioid.[29] Acute OIH can occur in various settings including low-dose, high-dose, and maintenance-dose regimens of opioids.[29,30] Although the exact mechanisms of OIH are unclear, available data suggest that glutaminergic system interaction and N-methyl-D-aspartate (NMDA) receptor activation might be important in the development of OIH. Modulation of acute OIH has been reported with α_2 agonists, cyclo-oxygenase (COX)-2 inhibitors, and NMDA receptor antagonists, with most studies examining the use of clinically available NMDA receptor antagonists (ie, ketamine, dextromethorphan, and methadone) in attenuating OIH.[29]

Genetics-based pain therapy

With advances in identification of all the genes in human DNA and understanding of the neurobiology of nociception, there has been hope that genetics-based personalised pain therapy would be feasible, in which preoperative determination of a patient's genotype could guide the choice of analgesic agent and dosage postoperatively.[33,44] There are examples of potential genotyping-tailored treatments in other areas of medicine.[35,36] Furthermore, reports of individuals with a complete inability to sense pain and identification of the mutation (α subunit of the voltage-gated sodium channel Nav1.7, SCN9A)[37] have raised hopes of a clinically relevant genotyping-based pain therapy.

Available studies suggest that several gene candidates could be important in the development of an individualised genetics-based pain therapy. The cytochrome P450 2D6 (*CYP2D6*) gene might affect codeine analgesia, because the CYP2D6 enzyme is needed for prodrug activation (ie, codeine is transformed to morphine). CYP2D6 is a polymorphic enzyme, and genotyping can predict reduced enzyme function.[34] Conversely, *CYP2D6* gene amplification can result in accelerated metabolism of tramadol[38] and morphine (ie, ultrarapid metaboliser), which in rare instances can result in significant toxicity.[39] Another gene candidate that could be influential in treatment of acute pain is the human μ-opioid receptor gene (*OPRM1*) 118A→G variant. Although there are more than 100 identified variants in *OPRM1*,[40] the single nucleotide polymorphism 118A→G is present in up to 17% of the white population and 49% of the Asian population, and might be associated with a reduction in μ-opioid receptor expression or signalling.[41] Other possibilities include genes encoding enzymes related to prostaglandin production (*PTGS2* for the COX-2 gene), which might in part account for the interindividual differences in analgesic responses to COX-2 inhibitors, and to production of ABCB1 (P-glycoprotein) encoding a polymorphic transporter, which might have clinical relevance in identification of patients susceptible to respiratory depression induced by opioids.[42,43]

Despite the promise and potential, the reality of individualised genotype-based pain therapy is far from being realised for routine clinical practice. Although there is clearly some genetic component to the perception of pain, the overall clinical effects of common polymorphisms in most patients are small, unlike the large genotype effects seen in rare variants (eg, *SCN9A*).[34] Another obstacle is that not all variants have been identified and the clinical effects of the currently commonly studied genes have generally been negligible such that routine genotyping would not be able to reliably predict an individual's response to a particular analgesic agent.[33,34] For instance, a meta-analysis of studies examining *OPRM1* 118A→G found no effect of the presence of this variant on pain levels.[41] Ultimately, common gene variants, many of which probably have not been identified, might account for only a small clinical effect.[33,34]

Persistent postsurgical pain

The development of a chronic pain state, termed persistent postsurgical pain (PPP), is increasingly being recognised as a not uncommon sequel of surgery. PPP should be diagnosed when pain persists beyond the expected healing period associated with tissue injury and inflammation (2 months or longer after most surgical procedures) and other causes for the pain have been excluded.[44,45] Although incidence can vary depending on the nature of the surgery, many common operations (eg, mastectomy, thoracotomy, hernia repair, coronary artery bypass surgery, amputation) are associated with an incidence of PPP of up to 30–50%.[44,45] Ongoing inflammation or injury to peripheral nerves during the surgery have been postulated as primary causal factors leading to persistent pain. Much research has focused on understanding of the mechanisms of the transition from acute to chronic pain and predictors of chronic pain, in an attempt to prevent development of PPP (figure 1).[46]

Several risk determinants for PPP have been identified, but no one factor seems to play a dominant part. For example, the intensity of perioperative pain has been suggested as a key risk factor; however, less than 20% of

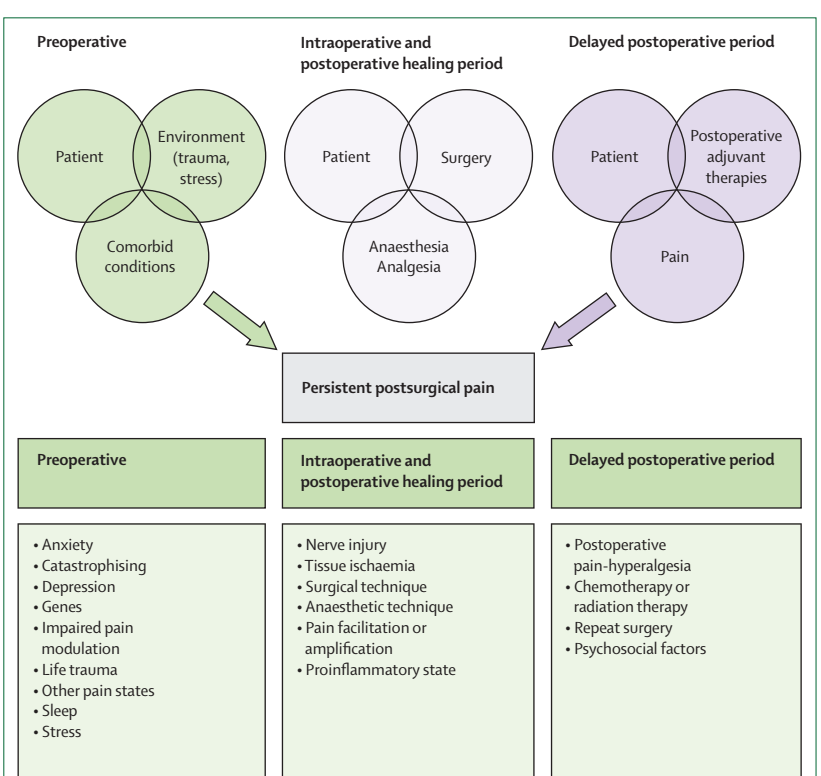

Figure 1: **Potential risk determinants of persistent postsurgical pain**
Multiple inputs (preoperative, intraoperative, and postoperative) can contribute to the development of persistent postsurgical pain.

the overall risk of chronic pain can be predicted by the severity of postoperative pain.[47] Several other surgical, psychosocial, and patient-related genetic and environmental risk factors have been identified.[48] For instance, old age, female sex, obesity, and depression were independent predictors of patient-related pain and function as well as use of pain treatment, 2 and 5 years after revision total hip arthroplasty.[49] Depression, psychological vulnerability, stress, and duration of disability (time to return to work) are the best psychosocial predictors of PPP.

Many analgesic agents and techniques, most notably peripheral nerve blocks and epidural analgesia, can provide preventive analgesia, which is broadly defined as any perioperative regimen used to control pain-induced sensitisation.[25] Preventive measures have focused on aggressive multimodal perioperative analgesic regimens, adjuvant non-opioid therapies such as COX antagonists, α_2-adrenergic agonists, gabapentin, and pregabalin, NMDA antagonists, steroids, and extended regional analgesia with local anaesthetics.[48,49] However, despite some encouraging results, there is no established and definitive evidence for the role of any intervention for the prevention of PPP.

Management of acute pain and patient outcomes

Pathophysiological responses

Acute pain causes a wide range of pathophysiological responses, which are initiated when nociceptors are activated after tissue injury, resulting in a local inflammatory response and subsequent behavioural and physiological responses.[1] After tissue injury, sympathoneural and neuroendocrine activation (along with uncontrolled pain) can ultimately lead to various potentially detrimental responses such as tachycardia, hypertension, hyperglycaemia, immunosuppression, decreased regional blood flow or venous stasis, and platelet aggregation.[1] In high-risk patients (eg, presence of multiple comorbidities, decreased physiological reserves) or those undergoing high-risk procedures, these pathophysiological responses can result in increased morbidity. Some analgesic agents or techniques, such as regional anaesthesia–analgesia with local anaesthetics, used for the treatment of acute postoperative pain can attenuate these pathophysiological responses to a greater extent than that seen with systemic analgesics[50] and result in improvement of some patient outcomes.

Panel: **Potential benefits of regional anaesthesia–analgesia on patient outcomes**

Epidural analgesia[51–56]

- Analgesia: lower pain scores with epidural analgesia than with systemic opioids
- Cardiovascular: reduced risk of myocardial infarction and dysrhythmias (thoracic epidural analgesia in high-risk patients)
- Gastrointestinal: earlier return of bowel function (thoracic epidural analgesia in abdominal surgical procedures)
- Pulmonary: reduced risk of postoperative pulmonary complications (thoracic epidural analgesia in high-risk patients)

Peripheral nerve analgesia[57]

- Analgesia: lower pain scores with peripheral nerve analgesia than with systemic opioids
- Rehabilitation: facilitates earlier rehabilitation goals and reduced length of stay (most studies done in orthopaedic patients)

Paravertebral analgesia[58]

- Analgesia: lower pain scores with paravertebral analgesia compared with systemic opioids
- Pulmonary: reduced risk of postoperative pneumonia in patients undergoing thoracotomy

Conventional outcomes

Whether the treatment of acute pain might globally affect patient outcomes after surgery is not entirely clear, but data suggest that use of specific analgesic agents or techniques can affect major postoperative morbidity (panel).[51–58] For instance, two large database analyses suggest that postoperative epidural analgesia might be associated with a small but significant reduction in 30-day mortality for patients undergoing major non-cardiac surgery, although this effect should be interpreted cautiously and the absolute magnitude was also small (corresponding to a number needed to treat of 477 in one study).[59,60] For other major morbidities, the data are slightly more compelling. Results of several meta-analyses suggest that use of epidural analgesia or continuous paravertebral blockade is associated with decreased risk of postoperative pulmonary complications in patients undergoing upper abdominal and thoracic surgical procedures.[58,61] The perioperative use of epidural analgesia is also associated with a reduction in respiratory complications after major abdominal surgery, although the effect of epidural analgesia might not be as prominent as it was previously, partly because the incidence of respiratory complication has progressively decreased during past years.[51] Meta-analyses in patients undergoing high-risk cardiothoracic and vascular procedures suggest that use of perioperative thoracic epidural analgesia might decrease pulmonary complications, cardiac dysrhythmias, and overall cardiac complications.[52,53] Finally, perioperative use of either thoracic epidural analgesia or intravenous local anaesthetics are associated with faster resolution of postoperative ileus after major abdominal surgery.[54,61,62] Specific evidence-based recommendations, based on systematic reviews, for postoperative pain management have been made for different surgical procedures.[63]

Patient-centred outcomes

Data suggest that use of one analgesic regimen might have a different effect when compared with another with respect to patient-centred outcomes (eg, analgesia, satisfaction). For instance, use of intravenous patient-controlled analgesia with opioids versus conventional opioid analgesia (eg, a nurse administering an analgesic

	Common routes of administration	Probable mechanisms of analgesic action	Potential relevant side-effects
Local anaesthetics (bupivacaine, lidocaine)	EA/SA, PNB/C, SC, TR	Inhibition of sodium channel	Hypotension, motor block, myotoxicity, systemic toxicity (seizures, cardiac dysrhythmias, cardiac arrest) in high doses
Opioids (fentanyl, morphine)	EA/SA, IV, SC, TR	μ-receptor agonist	Sedation, nausea, vomiting, pruritus, respiratory depression, immunosuppression
Paracetamol	PO, IV	Uncertain	Hepatic toxicity and liver failure at high doses, hypersensitivity
Non-steroidal anti-inflammatory agents (celecoxib, ibuprofen, ketorolac)	PO, IV	Inhibition of cyclo-oxygenase	Gastrointestinal irritation, platelet inhibition, renal insufficiency or failure, cardiovascular, hypersensitivity
Gabapentinoids (gabapentin, pregabalin)	PO	Inhibition of voltage-gated sodium channels	Sedation, peripheral oedema, gastrointestinal; decrease dose for renal insufficiency
α_2 agonists (clonidine, dexmedetomidine)	PO, IV	α_2-receptor agonist	Sedation, hypotension, bradycardia

EA/SA=epidural/spinal. PNB/C=peripheral nerve block/catheter. SC=subcutaneous. TR=transdermal. IV=intravenous. PO=oral.

Table: **Analgesic agents commonly used for the treatment of acute pain**

agent at the patient's request) for postoperative pain control results in improved pain control and increased patient satisfaction.[64] Use of regional analgesic techniques (eg, epidural or peripheral nerve analgesia) with a local anaesthetic-based regimen is associated with significantly lower pain scores than is seen with systemic opioids.[55,57] Despite data suggesting that improved postoperative analgesia leads to improved conventional patient outcomes,[61] there is insufficient evidence to support subsequent improvements in some other patient-centred outcomes such as quality of life and quality of recovery.[56]

Multimodal analgesia and adjuvant agents

The use of multimodal analgesia, a strategy that concurrently uses more than one class of analgesic agent or technique (table), has been advocated as a means to improve analgesia through either additive or synergistic effects while reducing opioid-related side-effects.[65] Although there are many permutations by which analgesics can be combined, multimodal analgesia realistically can be defined as a combination of an opioid and non-opioid analgesic, with or without a regional anaesthetic block, typically resulting in improved analgesia with concurrent reduction in the incidence of some opioid-related side-effects (eg, a decrease in postoperative nausea, vomiting, and sedation), presumably through an opioid-sparing effect.[66,67] As a whole, research into multimodal analgesia does not reveal a consistent level of success, in part because of the large number of variables (eg, different doses or analgesic agents or techniques, type of surgery) present in available studies; however, some multimodal analgesia trials have shown improved outcomes or lowered incidence of chronic postsurgical pain.[68,69] Despite the recent high-profile case of academic fraud that resulted in the retraction of several multimodal analgesia studies, carefully performed systematic reviews seem to be robust against the effect of these reports.[70] In general, the benefits of the combination of non-opioid agents (apart from the combination of paracetamol with non-steroidal anti-inflammatory agents[71]) for multimodal analgesia in the postoperative period are unclear because high-quality, large-scale randomised controlled trials are scarce. Although many adjuvant agents have been used, we describe some of the more promising and novel agents.

Originally designed for the treatment of seizures, gabapentin and pregabalin have been used to treat neuropathic pain and, more recently, postoperative pain. Gabapentin and pregabalin bind to a subunit of the voltage-gated calcium channel, thus inhibiting calcium influx and preventing the release of excitatory neurotransmitters. Systematic reviews of randomised controlled trials suggest that use of gabapentin will decrease postoperative pain, opioid consumption, and opioid-related adverse effects, but might be associated with an increased incidence of sedation.[72,73] Few studies are available on pregabalin for the treatment of acute or postoperative pain. Although a recent systematic review suggested that evidence to support the use of pregabalin in acute pain scenarios might be lacking,[74] studies published subsequent to this review suggested otherwise.[75,76] Additional studies will be needed to elucidate the appropriate dosing regimen, analgesic efficacy (pregabalin), and any long-term benefits of the gabapentinoids on acute postoperative pain.

Dexmedetomidine is an intravenous α_2 agonist that had been used mainly as a sedative and analgesic agent in the intensive care unit setting and might be associated with reduced opioid consumption and improved analgesia when used perioperatively.[65] Prescription of buprenorphine, an opioid analgesic that has partial agonist activity at the μ_1 receptor and antagonist activity at the κ receptor, has increased substantially during the past few years, and patients taking buprenorphine can have severe postoperative pain that might not be easily treated with typical doses of opioids.[77,78] Dexmedetomidine can be useful in the treatment of acute postoperative pain in opioid-tolerant patients treated with buprenorphine;[79] however, additional studies are needed

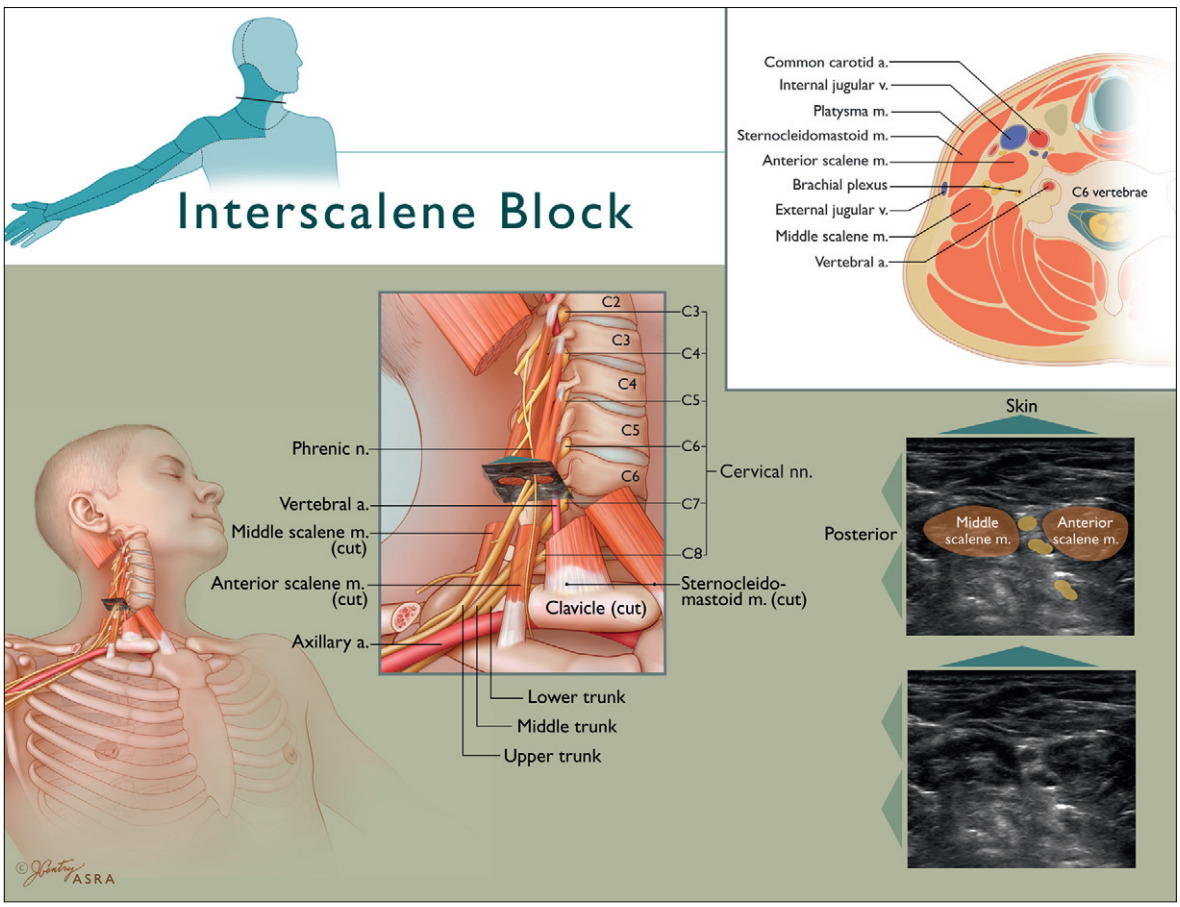

Figure 2: **Anatomy for the interscalene block with ultrasound correlation**
Use of ultrasound can complement our understanding of patient anatomy and thus aid performance of nerve blocks. The upper left inset depicts the expected distribution of anaesthesia after an interscalene nerve block, which can be performed for shoulder surgery. The upper right and lower left insets depict the anatomy relevant for the interscalene nerve block—note the closeness of the brachial plexus to major arteries and the spinal canal. The classic ultrasound view (lower right) depicts the hypoechoic upper roots stacked on each other, within the interscalene groove. Reproduced from reference 74, by permission of the American Society of Regional Anesthesia and Pain Medicine and Jennifer Gentry.

to further define the role of this intravenous agent in multimodal analgesic regimens.

Ketamine is an older anaesthetic agent that can attenuate hyperalgesia related to opioid administration and has seen a resurgence of interest in its new role as an adjunct for multimodal analgesia. One of the reasons for the renewed interest in ketamine is its ability to block the NMDA receptor, which is central in the development of hyperalgesia and tolerance. A recent systematic review of randomised controlled trials of ketamine added to intravenous patient-controlled analgesia with opioids revealed that the addition of a low-dose infusion of ketamine was associated with a significant reduction in pain scores and overall morphine consumption.[80] Although low-dose ketamine infusion does not seem to be associated with an increased incidence of psychomimetic or adverse pharmacological effects,[65] further studies are needed to establish whether there is any long-term benefit in reduction of the incidence or severity of PPP.

Peripheral nerve catheters are another technique that has increased in popularity during the past decade. Anaesthetists can insert these catheters in several locations and, when a local anaesthetic-based analgesic regimen is used, peripheral nerve catheters provide superior analgesia compared with systemic opioids[57] and can result in early mobilisation and possibly reduced length of stay in some instances.[81,82] Some centres will allow use of peripheral catheters on an outpatient basis, further facilitating early discharge and patient recovery. Traditionally, the performance of nerve blocks or catheters for acute postoperative pain control has been with so-called blind techniques such as nerve stimulation of surface anatomy. Increasing use of ultrasound for placement of nerve blocks and catheters allows for real-time visualisation of patient anatomy (figure 2),[83] thus facilitating performance of nerve blocks (figure 3),[84] which can have many benefits including an increased block success rate, decreased time to onset of blocks, and possibly improved quality

of sensory block.[85–87] One of the theoretical benefits of injection of local anaesthetic under ultrasound guidance is a reduction in complication rates such as neurological injuries; however, this possibility has not been definitively proven.[88,89]

New analgesic agents or techniques

Advances

Although there have been many advances in the development of both analgesic agents and techniques since the previous review,[1] we have only described those that have been used or are very close to being available in the clinical setting. The analgesic agents and techniques described in this section are at different stages of development and might or might not be approved for use, depending on the location of the practitioner.

Sustained-release or extended-release formulations of conventional agents

Although agents such as opioids or local anaesthetics can provide effective pain control when administered as part of epidural or peripheral nerve-block analgesia, the duration of analgesia can be restricted when these agents are administered as a single dose. These agents can be delivered as a continuous infusion via catheters if an extended duration of pain control is desired; however, insertion of these catheters generally requires technical expertise and might be contraindicated in some instances. New formulations of these conventional analgesic agents have been developed to prolong the duration of analgesia to longer than 24 h, and might obviate the need for continuous catheters in some clinical settings.

Extended-release local anaesthetics

Many animal studies have described the administration of extended-release local anaesthetics. Typically, the local anaesthetics have been encapsulated in various biodegradable agents, which when degraded will allow the gradual release of anaesthetics. Local anaesthetics have been reported to be encapsulated in liposomes, lipospheres, polyglycolic acid microspheres, and hydrogels.[90] Many animal studies have shown an extended duration of analgesia with these agents.[90,91] Some clinical data also suggest that extended-release local anaesthetics might significantly prolong the duration of action of commonly used local anesthetics;[90,92] however, there are concerns about adverse effects such as neurotoxicity and myotoxicity.[93] Although the available data suggest that the duration of local anaesthetic can be prolonged by a period of several days, few clinical studies have been done and further safety studies will be needed before extended-release local anaesthetics can be routinely used in the clinical setting. Despite extensive research, none of the formulations are currently available for clinical use.

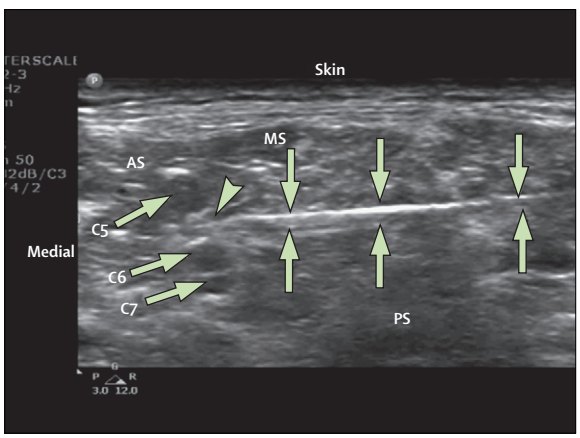

Figure 3: **Insertion of a needle into the sheath of the brachial plexus under ultrasound guidance**
The bevel of the needle (arrowhead) is seen as it enters the sheath of the brachial plexus (between the C5 and C6 nerve roots). The triangle shows the tip of the needle facing towards the skin and the large arrows outline the needle shaft. Reproduced from reference 75, by permission of Wolters Kluwer Health. AS=anterior scalene muscle. C=cervical. MS=middle scalene muscle. PS=posterior scalene muscle.

Extended-release epidural morphine

Morphine is commonly administered as one dose into the epidural or intrathecal space for postoperative analgesia, and the typical duration of analgesia is 12–24 h after administration. Continuous epidural analgesia with a local anaesthetic-based regimen might be preferred if analgesia is needed for longer than 24 h; however, this modality is contraindicated in some instances such as concurrent anticoagulation with specific agents or regimens.[94] An extended-release formulation of epidural morphine, which is enclosed in microscopic lipid-based particles, is available clinically and has been shown to provide postoperative pain relief for 48 h after a single dose.[95] Despite the extended duration of analgesia without the need for a continuous epidural catheter, a systematic review of available randomised controlled trials of extended-release morphine suggests that this formulation might be associated with an increased incidence of respiratory depression when compared with intravenous patient-controlled analgesia with morphine.[96]

Iontophoretic transdermal delivery of fentanyl

The traditional (passive) transdermal formulation of fentanyl is not recommended for routine treatment of acute or postoperative pain in opioid-naive patients, in part because it can take about 6–12 h to obtain analgesic plasma fentanyl concentrations after application of the transdermal fentanyl patch. A newer formulation of this fentanyl transdermal system has been developed and uses a low-intensity direct current (iontophoresis) to allow for a more rapid transfer of fentanyl from the patch into the skin and local circulation.[97] This type of fentanyl patch allows the patient to activate a demand dose of 40 μg of fentanyl with a lockout interval of 10 min—in

essence, transdermal patient-controlled analgesia.[98] The available randomised controlled trials suggest that this system provides similar analgesia to that seen with intravenous patient-controlled anaesthesia with morphine.[98,99] The iontophoretic transdermal delivery of fentanyl was previously approved by the US Food and Drug Administration and European regulatory agencies, but was withdrawn voluntarily because of technical challenges. This product is under continued development, but the specific role in acute postoperative pain for this new type of fentanyl patch is still uncertain.

Peripherally acting μ-opioid receptor antagonists

Postoperative ileus is a complication of surgery that can be associated with increases in patient morbidity, hospital costs, and length of stay in hospital. Although the cause of postoperative ileus is typically multifactorial, opioids used to treat acute pain can exacerbate postoperative ileus. Peripherally acting μ-opioid receptor antagonists (ie, methylnaltrexone and alvimopan) have been developed to attenuate the adverse effects of opioids on postoperative ileus while providing analgesia.[100] The available trials suggest that peripherally acting μ-opioid receptor antagonists seem to accelerate return of gastrointestinal function in patients undergoing bowel resection without compromising centrally mediated opioid analgesia.[101,102] Both methylnaltrexone and alvimopan are available clinically and seem to be well tolerated; however, there is some concern about the use of alvimopan, which was associated with a raised incidence of myocardial infarction in one study.[102] As with other new agents, the precise role of these agents in the treatment of acute pain has yet to be established, but they might be of benefit to patients who have postoperative paralytic ileus.

Continuous infusions of local anaesthetics

Subcutaneous infiltration of local anaesthetics has long been used for postoperative pain management; however, the analgesic efficacy is limited to the duration of analgesia of the local anaesthetic (typically 4–8 h at most). During the past decade, there has been increasing interest in the use of disposable elastomeric devices that allow infusion of local anaesthetics over a period of days and on an outpatient basis. This fairly straightforward technique typically involves the surgeon directly placing catheters into wounds at the end of the surgical procedure, can be widely used, is technically efficient, and provides reasonable analgesia with a reduction in need for opioids and their related side-effects.[103] One concern with the infusion of local anaesthetics intra-articularly is the association of this technique with catastrophic chrondrolysis.[104]

Complementary and alternative modalities

Several complementary and alternative modalities for postoperative analgesia have been investigated to some extent, although the number of high-quality studies is low. Perioperative acupuncture might be a valuable adjunct for acute postoperative pain management, because a systematic review incorporating 15 randomised controlled trials noted a significant decrease in opioid consumption, risk of opioid-related side-effects (eg, nausea), and postoperative pain intensity at 8 and 72 h in the acupuncture group.[105] Another systematic review of randomised clinical trials on the treatment of postoperative pain with auricular acupuncture noted that in eight of nine trials, auricular acupuncture was superior to control for reduction of postoperative pain.[106] Systematic reviews examining transcutaneous electrical stimulation (TENS) for postoperative analgesia suggest that TENS might be associated with decreased use of postoperative analgesic agents and might be useful as an adjunct to other treatments for moderate post-thoracotomy pain.[107,108] The advantages of other modalities are less clear. Listening to music during acute postoperative pain might be associated with a reduction in pain and opioid requirements; however, the overall extent of these benefits is small and their clinical importance is uncertain.[109] The efficacy of relaxation therapy, massage, or hypnosis or intraoperative suggestion on treatment of acute postoperative pain is uncertain at this time, because of the paucity of high-quality data.[110,111]

Conclusion

Although postoperative pain remains incompletely controlled in some settings and the reasons why are not entirely clear, a comprehensive understanding of its mechanisms and the development of several therapeutic approaches have substantially improved pain control in past years. The use of more effective analgesic techniques (eg, regional analgesia) might be helpful not only for provision of superior analgesia, but also for improvement of conventional outcomes, particularly in high-risk patients or those undergoing high-risk surgical procedures. Finally, additional studies on predictors of postoperative pain and persistent postsurgical pain, efficacy of specific multimodal analgesic regimens, and growth of promising new technologies might lead to substantial gains in the treatment of acute postoperative pain and potential reduction in the development of persistent pain states.

Contributors

CLW and SNR contributed equally to this report, including literature search, figures, data collection, data analysis, data interpretation, and writing. The corresponding author (CLW) had full access to all the data in the report and had final responsibility for the decision to submit for publication.

Conflicts of interest

CLW declares that he has no conflicts of interest. SNR has been a consultant for Alpharma, Allergan, Schering-Plough, Medtronic, King Pharmaceuticals, Pfizer, and Respironics.

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