Editorial

When acute pain becomes chronic

In 1999, the International Association for the Study of Pain (IASP) published what remains the most widely accepted definition of chronic post-surgical pain (CPSP). This is defined as pain that develops following surgical intervention, after exclusion of other causes, lasting longer than two months, and unrelated to a condition preceding surgery. Within the past decade, CPSP has been intensively studied in order to quantify its epidemiology, risk factors, pathophysiology, prevention and treatment.

Although there have been considerable advances in our knowledge of CPSP, the incidence remains depressingly high. Conservative estimates indicate that 10% of patients may be affected, even after 'low-risk' surgery [1, 2]. This incidence has not changed appreciably over the years, suggesting both that our understanding of CPSP remains incomplete and that our approach to the problem needs to be reconsidered.

How and when acute pain becomes chronic

It is perhaps stating the obvious to say that all chronic pain, by definition, has to start as acute pain. While the initiating insult in many chronic pain states is not always clear, with CPSP we are in a unique position: we know in advance the time, place and nature of the injury. Thus anaesthetists are seemingly in an ideal position to influence the development of CPSP. However, despite our best efforts to date, we have not satisfactorily or reliably achieved this.

To understand CPSP and its prevention better, we need to take a broad overview of the problem and re-evaluate all facets of acute and chronic pain management. Historically and organisationally, acute pain has been regarded as a distinct entity from chronic pain. This was underpinned by the fact that acute pain is usually managed with a particular set of pharmacological agents (drug therapy extrapolated from the World Health Organization's analgesic ladder for the management of cancer pain) and by distinct acute pain services within secondary care. Conversely, chronic pain management utilised a different set of pharmacological and physical treatments, was treated by a different group of clinicians and was predominantly an outpatient service.

It is increasingly clear that this organisational model does not reflect the clinical problems seen in our patients. What the literature tells us, and what we see in practice, is that there is no clear boundary between acute and chronic pain and they should be viewed as a continuum. A further flaw implicit in this traditional model of service division is, broadly speaking, the perception that acute pain services primarily manage nociceptive pain while chronic pain services manage neuropathic pain. This perception is inaccurate. There is a substantial body of basic science and clinical evidence indicating that much acute postoperative pain has an important neuropathic component [3–11]. Even without overt nerve injury, acute pain shows both nociceptive and neuropathic features, so it is not surprising that many acute pain presentations cannot be managed satisfactorily with conventional anti-nociceptive strategies alone.

If we are to understand CPSP and its management better, it is useful to consider the fundamental underlying mechanisms. A surgical insult directly activates high-threshold nociceptors that relay action potentials signalling injury to the central nervous system. Nociceptive afferent tracts cross-link extensively in the spinal cord and project widely to the brainstem, limbic centres and somatosensory cortex. In response to intense afferent signals, extensive changes in the network of the somatosensory cortex are seen, together with profound changes in central neurochemistry and the balance between pro- and anti-nociceptive descending control. At the surgical site, the inflammatory

response to cellular injury causes localised pain. This inflammatory response is increasingly recognised as being crucially important to the maintenance of pain signalling. This response comprises the release of numerous pro-inflammatory mediators including hydrogen and potassium ions, bradykinin, prostaglandins and cytokines (IL-2, IL-6, IL-8 and TNF-α) [3]. These mediators lead to lowering of activation thresholds in peripheral nociceptors, secondary hyperalgesia and spontaneous pain in the absence of ongoing injury. Thus, even short exposure to an intense nociceptive stimulus can lead to profound and long-lasting changes within the nervous system; as Allan Basbaum, former Editor-in-Chief of the journal *Pain*, states: "*the nervous system after injury is very different to that before the injury*" (A. Basbaum, personal communication, 09/04/2015).

Basis science research has shown us that the mechanisms of acute pain are more complicated and far reaching than previously thought. The difficulty resides in the realisation that although the fundamental pathophysiological changes that occur in the nervous system following surgery are common to all patients, they do not inevitably lead to CPSP in all cases. The reasons for this are still unclear but there are identifiable risk factors associated with the development of CPSP. These include: surgery involving (or at high risk of involving) direct neural trauma e.g. amputation or thoracotomy; pre-existing pain (either at the site of surgery or an anatomically distant site); severe acute postoperative pain; polypharmacy; high-doses of strong opioids; and psychological factors such as depression, anxiety and post-traumatic stress disorder [12–16]. At a basic level, all these factors can be summarised as being indicative of either peripheral or central neural sensitisation, neural trauma or adverse psychology. These risk factors are important both individually and cumulatively in peri-operative pain management. We are clearly unable to influence all of them peri-operatively; however, some factors are readily amenable to acute intervention in our capacity as anaesthetists. In particular, we are well placed to try to attenuate unfavourable changes within the nervous system, one of the most obvious areas being the prevention and control of severe acute postoperative pain.

Stopping acute pain from becoming chronic

The presence of severe postoperative pain is generally regarded as the single biggest risk factor and predictor for developing CPSP. Severe pain is still surprisingly common, even following relatively minor surgical procedures [17]. Our first goals in seeking to prevent CPSP must therefore be to ensure that patients do not wake from anaesthesia in severe pain, even if that means a slightly longer time to wakefulness, and to be pro-active and aggressive in our management of severe pain in the recovery room. This includes the utilisation of all analgesic modalities available to us, including gabapentinoids, NMDA antagonists, intravenous lidocaine and α_2-adrenergic agonists. These medicines are not only useful adjuvant analgesics in their own right but can potentially contribute to the prevention of CPSP [18].

Regional anaesthetic techniques, either central neuraxial or perineural, are invaluable in the prevention of severe postoperative pain and, potentially, in the prevention of CPSP [19]. In many circumstances, regional anaesthesia remains the gold standard for acute-phase analgesia. There are, however, a number of problems with regional anaesthetic techniques: a need for specific procedural skills outwith the expertise of many anaesthetists; a failure rate of up to 10% even in the most skilled hands; the need for more intensive monitoring; and the risk of discontinuation, or wearing off, too early postoperatively, exposing the patient to unopposed severe pain. This last point is particularly important. It leads to patients' perceiving that the technique has failed and exposes the nervous system to high levels of nociceptive stimulus, immediately negating the beneficial effects of the nerve block. Despite these issues, regional anesthesia is an important part of our armoury and should be utilised where practicable.

In the prevention of severe postoperative pain, we do not advocate proscriptive or didactic approaches to peri-operative management. Many protocols exist that are highly procedure-specific, such as those widely used for enhanced recovery. While the general principles of protocol-driven surgery are commendable, and work for many patients, they make no allowance for those with more complex needs

or those in whom one or more elements of the protocol are either contra-indicated or unachievable. Guidance for when the first choice of analgesia fails is notably lacking in many protocols Maintaining a broad knowledge base of available therapeutic modalities is therefore vital. A better way forward requires a change in emphasis to promote the development of more individualised, tailor-made analgesia, taking into account the nature of the surgery and specific risk factors. In effect, we should be aiming to 'risk-stratify' patients pre-operatively for the likelihood of developing CPSP, in order to inform an appropriate and proportionate analgesic management plan.

The opportunity already exists to risk-stratify patients in such a fashion within pre-assessment clinics: simple, questionnaire-based assessments can be undertaken to recognise pre-existing abnormal pain states, psychological risk factors and chronic high-dose opioid requirements [20, 21]. By risk-stratifying in this way, a pain 'pre-optimisation' approach allows opportunities to intervene, e.g. with formal psychological assessment and preparation for surgery, rationalising of medicines, management of expectations for patients with chronic pain, and even re-evaluation of the necessity of surgery.

To be successful in preventing CPSP, we must not restrict ourselves to examining pain in the immediate peri-operative period. The acute inflammatory response to surgery does not resolve by the time a patient returns to the ward from the recovery area. We must aim to optimise analgesia throughout an inpatient stay. A suitable goal to strive for should be 'no more than mild pain' experienced throughout the postoperative period [22]. It is impractical for an individual anaesthetist to be in attendance throughout an entire inpatient stay to facilitate analgesia. The aim of minimising pain for all patients to the time of discharge is the responsibility of the whole surgical team, both medical and nursing. Embedding acute pain management as a marker of quality of care would help to reinforce this. Ensuring all team members are actively involved and engaged requires considerable time, effort and resources.

Poor assessment of pain has been recognised as the single biggest barrier to effective pain management [23] – if pain goes unrecognised or unrecorded, what chance is there of good treatment? Sadly, even at this basic level there are considerable challenges. Pain assessment is often not performed reliably or consistently and junior staff may lack the confidence to treat severe pain, even when it is identified. These shortfalls are not insurmountable with training and introduction of some simple interventions. For example, a 'pain pause' could be introduced into surgical ward rounds, when specific thought is given to pain and review of analgesia, and a standardised pain assessment tool implemented as a means of providing a structured, systematic method of assessing and managing acute pain.

The challenge of promoting good pain assessment has become more difficult in recent years, owing to staffing problems and a change in emphasis on outcome measures from surgery, and concern that pain scores are viewed as of secondary importance to time to mobilisation and discharge from hospital. This is troubling, as these latter two, though easy to measure and appealing from a managerial perspective, do not reliably equate to adequate analgesia. Failed discharge and re-admission to hospital for inadequate pain control are rarely reported but extremely important.

Moving forward

The steps required to improve this situation are two-fold. First, training should be enhanced to give acute pain greater recognition as a subspecialty, with dedicated time and teaching during medical school and anaesthetic training, rather than merely including acute pain as an element of other specialist blocks. Particular emphasis must be placed on pain assessment and anti-neuropathic therapeutics. Second, chronic pain consultants should have greater active involvement in inpatient pain services. This would bring a more holistic approach to acute pain problems, offer specific expertise in challenging cases of acute neuropathic pain and polypharmacy, and provide continuity of care with follow-up of difficult acute pain problems on a formal outpatient basis.

We must renew efforts to research pain in the days and weeks following surgery. Although rarely examined in the literature, this period is important in pain management as the time when 'sub- or post-acute' pain may lead to the

'tipping point' when acute pain will either resolve or begin to show signs of becoming pathological and chronic. At this time, the nervous system is still in a state of flux, with the neuroplastic changes from injury not yet deeply entrenched. It is in this phase that the beginnings of a chronic pain disorder may manifest and is likely to be at its most amenable to modification. The difficulty is that this period does not attract attention since the general expectation is that residual pain from surgery will diminish leading up to and following discharge. While this is true for many, we know that in some circumstances up to 80% of patients will have pain that does not resolve [1].

Identification of patients who may be developing a pathological pain problem at an early stage is difficult and requires specific consideration. There are many reasons for delay in the diagnosis of persistent pain but part of the problem is a lack of continuity of care. Anaesthetists typically do not see patients before discharge following surgery, and may only encounter them again sometime later when they are referred to the pain clinic. Surgeons increasingly do not routinely review all patients following uncomplicated elective surgery so may not be aware of persistent pain. In practice, the majority of CPSP will be diagnosed in primary care where initial management may be instigated.

Therein lies a problem. The specialties that have most direct influence over the occurrence or prevention of CPSP are generally not those that diagnose or provide initial management. Chronic postsurgical pain requires not only enhancements in secondary care; greater emphasis is needed in educating general practitioners to identify patients who are at risk of developing CPSP and those who fail to recover normally from surgery. This could be initiated by identifying patients at the time of pre-assessment. Once back in the community, early identification of a developing pain problem could be aided by more stringent monitoring of ongoing use of analgesics, particularly strong opioids, the requests for which would in effect act as a surrogate marker for unresolving pain as well as encouraging rational prescribing. A simple approach would be to set a limit on repeat analgesic prescriptions issued without a face-to-face clinical review. With appropriate training, this surveillance role could be delegated to community pharmacies to avoid over-burdening primary care.

Conclusion

While pain medicine has made considerable advances in recent years there is still much to do, as rates of CPSP remain high. We may never eliminate CPSP and it is clear that having too narrow a focus on a single anaesthetic technique or drug does not hold the answer. However, evidence from individual studies and meta-analyses points to improved long-term outcome with better acute pain management, and we are well placed to deploy a substantial armoury.

We need to have a fundamental review of our approach to acute pain management, and we call for improved training and recognition of acute pain as a subspecialty within anaesthesia. Acute pain services need improved staffing to deliver better clinical care and teaching. Inpatient services would benefit from greater involvement of dedicated consultant pain specialists to deal with increasingly complex acute pain problems and provide continuity of care following discharge. Organisationally, pain management should begin preoperatively to include identification of risk factors for pain, prompt and aggressive treatment of severe pain, and surveillance for early identification of abnormal postoperative pain states. Only by taking on all these issues will we begin to make a real difference.

Competing interests

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References

1. Macrae WA. Chronic pain after surgery. *British Journal of Anaesthesia* 2001; **87**: 88–98.
2. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; **367**: 1618–25.
3. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011; **152** (Suppl P): S2–S15.

4. Macintyre P, Schug S, Scott D, Visser E, Walker S. *Acute Pain Management: Scientific Evidence*. Melbourne: ANZCA & FPM, 2010.
5. Jung BF, Ahrendt GM, Oaklander AL, Dworkin RH. Neuropathic pain following breast cancer surgery: proposed classification and research update. *Pain* 2003; **104**: 1–13.
6. Mikkelsen T, Werner MU, Lassen B, Kehlet H. Pain and sensory dysfunction 6 to 12 months after inguinal herniotomy. *Anesthesia and Analgesia* 2004; **99**: 146–51.
7. Wildgaard K, Ringsted TK, Aasvang EK, Ravn J, Werner MU, Kehlet H. Neurophysiological characterization of persistent postthoracotomy pain. *Clinical Journal of Pain* 2012; **28**: 136–42.
8. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annual Review of Neuroscience* 2009; **32**: 1–32.
9. Lai J, Porreca F, Hunter JC, Gold MS. Voltage-gated sodium channels and hyperalgesia. *Annual Review of Pharmacology and Toxicology* 2004; **44**: 371–97.
10. Scholz J, Broom DC, Youn DH, et al. Blocking caspase activity prevents transsynaptic neuronal apoptosis and the loss of inhibition in lamina II of the dorsal horn after peripheral nerve injury. *Journal of Neuroscience* 2005; **25**: 7317–23.
11. Scholz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. *Nature Neuroscience* 2007; **10**: 1361–8.
12. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Human Molecular Genetics* 2005; **14**: 135–43.
13. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert Review of Neurotherapeutics* 2009; **9**: 723–44.
14. Hinrichs-Rocker A, Schulz K, Järvinen I, Lefering R, Simanski C, Neugebauer EA. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) – a systematic review. *European Journal of Pain* 2009; **13**: 719–30.
15. Rapp SE, Ready LB, Nessly ML. Acute pain management in patients with prior opioid consumption: A case-controlled retrospective review. *Pain* 1995; **61**: 195–201.
16. Yarnitsky D, Crispel Y, Eisenberg E, et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain* 2008; **138**: 22–8.
17. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013; **118**: 934–44.
18. Humble SR, Dalton AJ, Li L. A systematic review of therapeutic interventions to reduce acute and chronic post-surgical pain after amputation, thoracotomy or mastectomy. *European Journal of Pain* 2014; **19**: 451–65.
19. Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. *British Journal of Anaesthesia* 2013; **111**: 711–20.
20. Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. *British Journal of Anaesthesia* 2008; **101**: 17–24.
21. Mendoza TR, Chen C, Brugger A, et al. The utility and validity of the modified brief pain inventory in a multiple-dose postoperative analgesic trial. *Clinical Journal of Pain* 2004; **20**: 357–62.
22. Moore RA, Straube S, Aldington D. Pain measures and cut-offs – no worse than mild pain as a simple, universal outcome. *Anaesthesia* 2013; **68**: 400–12.
23. Herr K, Titler MG, Schilling ML, et al. Evidence based assessment of acute pain in older adults: current nursing practices and perceived barriers. *Clinical Journal of Pain* 2004; **20**: 331–40.

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