Chronic Post-surgical Pain: Prevention remains better than cure
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Citation

Abstract
Chronic pain following surgery remains a significant problem to which modern anaesthetic practice continues to pay insufficient attention. Anaesthesiologists' actions and the drugs they use need to take into account the fundamental importance of abolishing noxious reflexes at the spinal level and combine this with excellent postoperative analgesia, particularly for those patients or procedures at high risk, to minimise the transition of acute to chronic pain.

INTRODUCTION
The anaesthesiologist has a role in preventive medicine [1]. The challenge is to adapt our practice and adopt techniques that may avoid the transition from acute postoperative to chronic persistent pain which we have yet to achieve [2,4]. Second only to facilitation of the surgery itself (and much more important that short term postoperative nausea and vomiting (PONV)), the perioperative period is the ideal time to address the issues and translate theory with respect to pain memory, plasticity and sensitisation into practice [5]. Procedure specific postoperative pain management (PROSPECT) is fine for the immediate period following surgery but needs to also consider elements relevant to the prevention of chronic pain [6]. Acute noiceptive pain remains the risk for the transition to chronic postoperative neuropathic pain; a major health problem and it is important to find therapies to prevent or reduce it [7].

THE PROBLEM
We know that peripheral injury occurring in association with surgery is a repeated noxious stimulation due to acute tissue damage and the development of inflammation. Intense nociceptor activation, both directly and indirectly, through C-fibre evoked responses in the dorsal horn of the spinal cord results in the creation of a facilitated state and an exaggerated response to subsequent noxious stimuli, central sensitisation, through removal of the magnesium block on the N-methyl-D-aspartate (NMDA) glutamate receptor ion channel. The resultant characteristic excitation of spinal cord dorsal horn cells, wind-up, is the magnification and prolongation of response to subsequent sensory stimuli in the wide dynamic range (WDR) neurones. Following both new injury and peripheral inflammation associated with surgery this central sensitisation can also be induced by a modified A-fibre response. Wind-up is mediated through the NMDA receptor in post-synaptic location which is the key regulator involved in multisynaptic nociceptive transmission and associated with synaptic plasticity [8]. Preventative 'analgesic' techniques may be effective in reducing not only the acute pain following surgery but also the chronic pain that may follow. Though there is much that can, quite simply, be done our acceptance of the need to apply the knowledge in pre- intra- and postoperative periods including multimodal analgesic interventions to combat sensitisation and its consequences seems deficient [3]. We need to insulate the susceptible neural pathways from a continuous barrage of noiceptive input [3].
THE LATEST POSITION

5-hydroxytryptamine (5HT) pathways determine levels of pain by modulating nociceptive responses, the outcome of drug treatment and provide a mechanism for interplay of emotions \[^{10}\]. 5HT acting at multiple receptors exerts a complex long-recognised control of pain mechanisms through descending pathways. 5-HT3 receptors (5HT3R) expressed in primary afferent fibres that convey nociceptive messages from the periphery to the CNS mediate nociceptive effects. Activation of 5HT3R on WDR neurones leads to depolarization and renders NMDA receptors capable of activation by glutamate. 5HT3 receptor antagonists (5HT3RA) have been shown to reduce nociceptive responses in some dorsal horn neurones and primary nociceptive afferent fibres. Activity of dorsal horn neurones stimulated by noxious stimuli and NMDA is inhibited by 5HT3RA \[^{11,12}\]. Neuropathic pain states are associated with enhanced descending facilitatory control of mechanical responses of spinal neurones through activation of spinal 5HT3R which, being pro-nociceptive, contribute to central sensitization \[^{13}\].

The formalin test allows a measurement of the effect of central sensitization \[^{14}\]. 5-HT3R have been found to play a role in formalin-induced hyperalgesia in mice, the 5HT3RA granisetron markedly reducing phase II of the test \[^{15}\]. Peripheral 5HT3R may play a critical role in nociception and the transmission of orofacial pain. In the orofacial formalin test a good response to both local and systemic injection of 5HT3RA has been shown with benefit mainly in the late (II) phase \[^{16}\].

The 5HT3RA ondansetron has been demonstrated to have potential benefit in neuropathic pain \[^{17}\]. Beneficial effects in relation to acute surgical pain have, however, not been demonstrated and the role for these safe and everyday drugs is uncertain \[^{18,19,20}\].

Using a rat model to examine the effects of direct localized inflammation on dorsal root ganglion neurons particularly its role in the initiation of neuropathic pain, Li and colleagues have demonstrated the effectiveness of corticosteroid administration given at the time of injury but the role of proinflammatory cytokines remains unclear \[^{21}\]. Glucocorticoids not only suppress pro-inflammatory and induce expression of anti-inflammatory cytokines but also reduce prostaglandin synthesis with significant antihyperalgesic effects and just one dose can have a beneficial effect for days \[^{7}\].

A large (1299 patients) and well-conducted survey following hysterectomy with a 90.3% response rate found that 1 year following surgery 31.9% were experiencing (chronic) pain and, of these, 14.9% did not have any pain beforehand. Of patients receiving spinal anaesthesia 117/76 (14.5%) had pain at 1 year compared with 242/721 (33.6%) receiving general anaesthesia (GA) only and though this suggests, as before, spinal anaesthesia to have a significant advantage, a greater proportion receiving GA had pain before surgery and may therefore already have had an element of central sensitisation operating. Further study is required \[^{4}\].

Initiating a preventive multimodal analgesic regimen extended postoperatively for two weeks has been shown to reduce the incidence of CRPS I from 7 to 1% with the suggestion that continuing for longer might yield added benefit \[^{22}\].

CONCLUSION

Persistent neuropathic postoperative pain is a major health problem and it is important to find therapies to prevent or reduce it \[^{7}\].

Determination of risk factors at the time of formal preoperative assessment, including appropriate physical and psychological tests, will allow a prediction to be made with respect to postoperative pain and analgesic requirements and also enable the subsequent anaesthetic delivery to be properly tailored. The inclusion now of 5HT3RA and glucocorticoid such as dexamethasone may help that reduction.

Older agents that may be of value due to their antihyperalgesic properties are now, unfortunately, getting a bad press, often eschewed in favour of the latest development \[^{23}\].

Why should we wait any longer when surgery today is perhaps avoidably creating future patients for pain management services? We just need to modify what we normally do, it’s safe and everyday stuff, but entails direction, which may not be an easy path for anaesthesiologist and surgeon to follow \[^{5}\]. Further formal studies will help to elucidate what works but will take an age to deliver; how many more do we need before taking action \[^{24}\]?
What are the prospects for the future? Postoperative pain management now needs to consider not only the specific requirements of the procedure but also look beyond to include elements for the prevention of chronic post-surgical pain. Maybe we just need to look at things differently and with a change of emphasis, paying at least as much attention to this as PONV with some drugs in common.

References
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