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There have been considerable advances in the management of postoperative pain in the last decade. Patient-controlled analgesia, epidural techniques, improvements in healthcare staff education and attitudes, increased patient awareness and expectations, establishment of acute pain teams and new analgesic preparations have all contributed to improved postoperative pain management. However, delivering consistently good postoperative pain control remains a therapeutic and organisational challenge. Respiratory depression and nausea limit opioid use, local anaesthetic techniques are often short lasting or require interventional procedures and close monitoring, and the use of non-steroidal anti-inflammatory drugs (NSAID) and cyclo-oxygenase type-2 (COX-2) specific inhibitors is limited by concerns with respect to renal and platelet function, gastrointestinal ulceration and haemorrhage, and potential adverse cardiovascular outcomes.

**CHRONIC PAIN AFTER SURGERY**

It is now recognised that chronic pain after surgery is a major problem for many patients. Early studies probably exaggerated the phenomenon; much of the data was retrospective and little or no consideration was given to the severity or effect on quality of life. However, more recent studies of improved design have confirmed a significant incidence and severity.

In 1999, Callesen and colleagues reported that 19% of patients undergoing inguinal hernia repair complained of chronic pain after the procedure [1]. These data may seem surprising but a more recent, randomised, controlled study investigating 319 patients demonstrated an even higher incidence. Nienhuij and colleagues [2] reported that 43% of patients undergoing mesh inguinal hernia repair complained of chronic pain 7-33 months after surgery; pain was moderate in 50% of these patients and severe in 15%. Features suggestive of neuropathic pain were present in 81% of patients.

**TABLE 1. INCIDENCE OF CHRONIC PAIN AFTER SURGERY: \*NEUROPATHIC PAIN**

Surgery	Incidence (%)	Reference
Breast	22-56	Wallace et al, 1996 [3]
Inguinal hernia	19	Callesen et al, 1999 [1]
Inguinal hernia (mesh)	43 (35*)	Nienhuij et al, 2005 [2]
CABG	56	Eisenberg et al, 2001 [4]
	44	Bar-El et al, 2005 [5]
Pelvic trauma	48	Meyhoff et al, 2006 [7]
Femoral popliteal bypass	23*	Greiner et al, 2004 [6]
Hip arthroplasty	28	Nikolajsen et al, 2006 [8]

Chronic pain is associated with several other surgical procedures (table 1). Wallace and colleagues demonstrated that a high proportion of women suffered from pain over 1 year after breast surgery [3]. The incidence of pain after mastectomy, mastectomy and reconstruction, cosmetic augmentation and breast reduction was 31%, 49%, 38% and 22%, respectively. There have been consistent reports of chronic pain after coronary artery bypass surgery via sternotomy; for example, 2 recent studies reported an incidence of 56% [4] and 44% [5]. In the former study, 65% of patients with chronic pain described it as moderate or worse and the pain significantly affected quality of life in 72%. In the latter study, life style was affected adversely in 86% of patients in pain. Recent work has examined specifically the occurrence of chronic neuropathic pain after surgery. For example, Greiner and colleagues [6] investigated 53 patients after femoral-popliteal bypass. After a mean postoperative period of 14 months, 23% complained of pain suggestive of a neuropathic origin; however, pain in this study was mostly mild or moderate. A high incidence of chronic pain after surgery for pelvic trauma (48%) was reported by Meyhoff and colleagues [7]. Patterns of pain were mixed and included nociceptive, neuropathic and visceral characteristics; quality of life was affected significantly. Finally, a Danish nationwide questionnaire survey of 1231 patients after total hip arthroplasty revealed that 28% of patients were complaining of chronic ipsilateral hip pain which affected quality of life in 12% [8].

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## FACTORS LEADING TO CHRONIC PAIN

Perkins and Kehlet were one of the first group to consider factors associated with the occurrence of chronic pain after surgery in a systematic review [9]. Preoperative factors associated with chronic pain included moderate and severe pain for > 1 month after surgery, “psychological vulnerability”, repeat surgery and medicolegal issues. Operative and postoperative factors included risk of nerve damage, moderate to severe pain, radiation, chemotherapy, depression and “psychological vulnerability”. One of the most predictive factors was poorly controlled postoperative pain.

## PATHOPHYSIOLOGY OF ACUTE AND CHRONIC PAIN

Traditionally, the pathophysiology (and management) of acute and chronic pain have been considered by many as separate entities; scientists and clinicians often specialised in acute or chronic pain. However, it is now recognised that there is considerable overlap between acute and chronic pain and this relationship is now under intense investigation; indeed, most chronic pain starts with an episode of acute pain. In addition, it may be that we have concentrated too much on the differences between nociceptive and neuropathic pain rather than their similarities. For example, allodynia and hyperalgesia are classical signs and symptoms of neuropathic pain but they are also often present after trauma and surgery.

Peripheral nociceptor sensitisation is a major contributor to acute pain but sensitisation of neurons in the dorsal horns, a classic mechanism in chronic neuropathic pain, has also been demonstrated in acute pain models [10]. As the tissue damage resolves, so does peripheral and central sensitisation, thus resulting in the return to preoperative pain thresholds and perceptions. It may be that failure of this process of resolution is a major contributor to chronic pain after surgery in some patients.

## PREVENTING CHRONIC PAIN AFTER SURGERY

When considering the prevention of a condition or disease, interventions may be primary or secondary. Primary prevention stops the condition occurring; this may be possible for postoperative pain with effective regional anaesthetic techniques. However, in clinical practice, the technique is often discontinued before the stimulus has resolved and pain becomes a significant symptom in most patients. Secondary prevention is the early treatment of symptoms; this is the goal of most postoperative pain regimens in reality. Good pain relief may influence the incidence of chronic pain, at least in theory, by reducing the effect of spinal cord hyperexcitability and aiding the return to normal physiology. Pharmacotherapy may have a large part to play in this but there are several other strategies that should be used in combination with drugs. These include: appropriate patient selection and choice of surgery; avoidance of excessive tissue and nerve damage; rapid rehabilitation; early detection of postoperative problems; and appropriate psychological support (Table 2).

**TABLE 2. POSSIBLE STRATEGIES FOR PREVENTING CHRONIC PAIN AFTER SURGERY**

Appropriate patient selection for surgery
Appropriate choice of surgical technique
Preoperative screening for chronic pain risk factors
Provision of psychological support for vulnerable patients
Minimise surgical trauma
Avoid nerve damage
Excellent per- and postoperative analgesia
Active rehabilitation
Early identification and treatment of unresolving pain
Early use of chronic pain therapies and management

## FTHERAPY FOR ACUTE PAIN

There are many theoretical reasons to believe that excellent pharmacological pain management should result in a reduction of the incidence and severity of chronic pain after surgery. However, to date, there is no direct evidence of this in clinical studies.

## OPIOIDS

Animal work suggests that opioids can prevent or reduce spinal hyperexcitability; in fact, this was demonstrated as early as 1986 [11]. This may translate to an early return to the preoperative neurophysiological state and reduced likelihood of chronic pain. The pre-emptive nature of this effect is well documented in animal studies but it has not been demonstrated consistently in clinical studies. Much of the controversy has been around the definition of pre-emptive analgesia, further complicated by the fact that postoperative pain in clinical practice is a continuous noxious stimulus rather than a discrete stimulus that is often utilised in animal models.

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The study by Woolf's team has been much cited; they showed that morphine 10 mg, given before surgery, had a significant effect on subsequent postoperative pain [12]. However, several others have failed to confirm this. The side-effects of morphine preclude the use of large doses in an attempt to further suppress cord hyperexcitability; epidural use may be more effective, particularly when used with low-dose local anaesthesia.

#### **REGIONAL ANALGESIA**

An effective method of preventing spinal cord hyperexcitability is to reduce or prevent nociceptive input; regional analgesia is the best way of achieving this. The benefits of regional analgesia with respect to pain control, particularly in the early postoperative period, are well accepted. However, our ability to provide prolonged analgesia is limited by the pharmacology of available drugs (e.g. need for repeated administration or infusion, toxicity) and technical issues (e.g. motor block, catheter-related problems). Local anaesthetics have been synthesised with a much extended duration of action but they have not made it to clinical practice because of problems with toxicity. There is still interest in slow-release preparations of standard local anaesthetics (e.g. bupivacaine) but these also have been associated with problems and they are not generally available. There are many proven advantages of regional analgesia but, as yet, there is no evidence that the technique leads to a reduction in the incidence of chronic postoperative pain.

#### **NSAIDs AND COX-2 SPECIFIC INHIBITORS**

NSAIDs and COX-2 specific inhibitors assert their analgesic action by inhibiting cyclo-oxygenases involved in prostaglandin formation (predominantly COX-2). It has been known for many years that prostaglandins play a major role in the sensitisation of peripheral nociceptors after acute injury. In addition, recent work has confirmed that prostaglandins also modulate transmission of nociceptive information (particularly within the spinal cord) and have a significant influence on central sensitisation [13]. Therefore, at least in theory, these drugs not only provide analgesia but should also affect the pathophysiological processes that may lead to the development of chronic pain.

Doubts have been expressed that NSAIDs and COX-2 specific inhibitors penetrate the human central nervous system in sufficient therapeutic concentrations after administration of normal doses. However, a healthy volunteer study measuring drug concentrations in blood and cerebrospinal fluid showed that celecoxib, rofecoxib and valdecoxib rapidly penetrate the central nervous system in sufficient concentrations to inhibit prostaglandin synthesis [14]. In addition, the rapid therapeutic effect of many NSAIDs on hyperpyrexia probably indicates that they also penetrate the central nervous system relatively easily.

#### **MEDICATION FOR CHRONIC PAIN: DO THEY HAVE A ROLE IN ACUTE PAIN?**

Traditionally, some drugs used for the treatment of chronic and/or neuropathic pain (e.g. anticonvulsants, tricyclic antidepressants) have found no place in the acute pain setting. However, we have seen that there is much overlap in the pathophysiology of acute and chronic pain and many clinicians are beginning to use these medications, albeit in an unlicensed manner, in the postoperative period. Apart from providing potential pain relief, they could play a role in preventing the development of chronic pain.

#### **GABAPENTIN AND PREGABALIN FOR ACUTE PAIN**

Gabapentin is licensed in many countries for the treatment of neuropathic pain. It binds to the  $\alpha_2\delta$  subunit of the presynaptic voltage-gated calcium channels, thus inhibiting calcium influx and the subsequent release of excitatory neurotransmitters in the pain pathways. Gabapentin is an effective analgesic in some laboratory models of acute pain in humans. For example, gabapentin 1200 mg reduced the mechanical pain threshold in first-degree burns in volunteers [15].

There is now considerable interest in the role of gabapentin in the postoperative period and data from several studies has been reviewed recently [16, 17]. Significant reductions in postoperative analgesic requirements have been reported after several types of surgical procedures e.g. abdominal hysterectomy, spinal surgery, vaginal hysterectomy, radical mastectomy, laparoscopic cholecystectomy, plastic surgery, and rhinoplasty. Investigators have utilised doses of 1200–1800 mg preoperatively and reported remarkably few side-effects. However, significant side-effects have been reported in a few studies. For example, in a study of patients undergoing scar revision and/or skin grafting, there was a considerable increase in the incidence of dizziness (35% vs. 5%) and a non-significant increase in the incidence of somnolence (25% vs. 10%) compared with placebo [18].

The dose of dose of gabapentin is a particular issue. The recommended starting dose for chronic pain is 300 mg on day 1, 300 mg twice daily on day 2 and 300 mg three times daily thereafter. The dose is further titrated and 1800 mg per day or more may be required. Giving a first dose of 1200 mg immediately before anaesthesia and surgery is in direct contravention to the licensed dose. In chronic pain, the dose is titrated in an attempt to reduce the incidence of side-effects.

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Dizziness and drowsiness are relatively common and, although most of the early perioperative studies have not found this to be a problem, it has been associated with delayed readiness for discharge in day-case procedures. Only one study has investigated the effect of a 300 mg dose; it was found to be ineffective in patients after day-case laparoscopic surgery [19].

Psychological vulnerability has been identified as a factor for the development of chronic pain. Anxiety may play a role in this mechanism; gabapentin (and the related drug pregabalin) have anxiolytic properties. In a study comparing gabapentin and placebo given 2 hours before cruciate ligament repair, mean preoperative VAS anxiety scores were 28 mm with gabapentin and 68 mm with placebo ( $P < 0.0001$ ) [20]. Pregabalin has recently obtained a license for neuropathic pain and anxiety states in many countries and its mechanism of action is probably the same as gabapentin; however, it has a superior pharmacokinetic profile. There is some preliminary evidence that this drug may also be efficacious in the perioperative period.

Although theoretically attractive, considerably more work is required before gabapentin or pregabalin become accepted for use in the perioperative period. For example, the side effect profile and any pharmacodynamic or pharmacokinetic interactions in the perioperative period need to be elucidated and the significance of any short and/or long term analgesic effects confirmed.

## CONCLUSION

There is no doubt that chronic pain after surgery is a significant condition worthy of attention. There are likely to be many etiological factors and we need to identify the nature and relative importance of them all. Presently, there is every reason to believe that ensuring the best possible pain control after surgery is likely to be helpful in reducing the incidence of chronic pain. This can be achieved by the expert utilisation of standard drugs and techniques and possibly by the use of other drugs that have not traditionally been associated with the management of pain in the perioperative period.

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