REVIEW ARTICLE

CNS Drugs 2007; 21 (3): 185-211
1172-7047/07/0003-0185/$44.95/0



# Perioperative Pain Management

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## Abstract

The under-treatment of postoperative pain has been recognised to delay patient recovery and discharge from hospital. Despite recognition of the importance of effective pain control, up to 70% of patients still complain of moderate to severe pain postoperatively.

The mechanistic approach to pain management, based on current understanding of the peripheral and central mechanisms involved in nociceptive transmis-

sion, provides newer options for clinicians to manage pain effectively. In this article we review the rationale for a multimodal approach with combinations of analgesics from different classes and different sites of analgesic administration. The pharmacological options of commonly used analgesics, such as opioids, NSAIDs, paracetamol, tramadol and other non-opioid analgesics, and their combinations is discussed. These analgesics have been shown to provide effective pain relief and their combinations demonstrate a reduction in opioid consumption.

The basis for using non-opioid analgesic adjuvants is to reduce opioid consumption and consequently alleviate opioid-related adverse effects. We review the evidence on the opioid-sparing effect of ketamine, clonidine, gabapentin and other novel analgesics in perioperative pain management. Most available data support the addition of these adjuvants to routine analgesic techniques to reduce the need for opioids and improve quality of analgesia by their synergistic effect. Local anaesthetic infiltration, epidural and other regional techniques are also used successfully to enhance perioperative analgesia after a variety of surgical procedures. The use of continuous perineural techniques that offer prolonged analgesia with local anaesthetic infusion has been extended to the care of patients beyond hospital discharge.

The use of nonpharmacological options such as acupuncture, relaxation, music therapy, hypnosis and transcutaneous nerve stimulation as adjuvants to conventional analgesia should be considered and incorporated to achieve an effective and successful perioperative pain management regimen.

The severity and frequency of postoperative pain depends on the site, nature and extent of surgery. Despite improvements in the understanding of pain mechanisms and the introduction of acute pain services, the under-treatment of postoperative pain has been recognised as an important issue.[1] The literature indicates that up to 75% of postsurgical patients have reported pain and 80% of these patients experienced severe pain at some time during their hospital stay.[2] A recent survey also demonstrated that approximately 70% of patients still have moderate or severe pain during the perioperative period.[3] Professional care providers have been noted as not believing that patients have pain,[4] and the lack of adequate knowledge and misinformation on pain management among nurses has been identified.[5]

Poorly controlled acute pain can result in increased catabolism, increased cardiorespiratory work, immunosuppression[6] and coagulation disturbances.[7,8] Pain and postoperative nausea and vomiting prolong recovery and discharge times and contribute to unexpected admission after ambulatory surgery.[9] Higher levels of postoperative pain can result in poor patient satisfaction, impair quality of recovery and increase healthcare costs.[10,11] Several clinical studies[12-14] support the notion that an approach based on the use of multimodal techniques to manage postsurgical pain is the most effective strategy for achieving optimal analgesia.

In this article, we provide a review of current strategies for the management of postoperative pain focusing on various analgesics and analgesic techniques. To prepare the article we performed a search of MEDLINE (1980–2006) and the Cochrane library (1980–2006) to identify published reports of randomised controlled trials and systematic reviews. The search terms used were ‘postoperative’, ‘pain’, ‘analgesics’, ‘analgesia’, ‘mechanisms’, ‘opioid’, ‘NSAIDs’, ‘COX-2 inhibitors’, ‘tramadol’, ‘paracetamol’, ‘adjuvants’, ‘regional’, ‘epidural’, ‘intra-articular’, ‘infiltration’, ‘complementary’, ‘acupuncture’, ‘TENS’, ‘music’, ‘hypnosis’ and ‘relaxation’.

## 1. A Mechanistic Approach to Pain Management

### 1.1 Mechanisms of Pain

A rational approach to the treatment of pain would be to identify the contributing mechanisms and specifically target treatment (figure 1). Despite recent progress in understanding nociceptive pathophysiology, wide variations in the management of postoperative pain are still observed. This may, in part, be due to the combination of innate individual and surgical factors that contribute to the development of pain. Nociceptive and inflammatory stimuli result in diverse effects, including nociceptive transduction, sensitisation of peripheral nerve endings and central neuronal sensitisation (figure 2).[15] Rarely, a single mechanism may contribute to the pain state; more often, a combination of mechanisms is involved.

This section primarily focuses on the common mediators involved in the transmission and augmentation of noxious stimuli. Most of the nociceptive signals arise from the activation of polymodal nociceptors. These nociceptors have little spontaneous activity under normal conditions but exhibit increased activity, with an increase in response magnitude to noxious stimuli or enhanced receptive field, when tissue injury occurs.[16] A complete review of acute pain mechanisms is beyond the scope of this article.

#### *1.1.1 Peripheral Mechanisms*

It is recognised that inflammatory response to tissue injury results in the activation of a cascade of events leading to peripheral and central sensitisation of the nociceptive pathway (figure 2). Noxious stimulation causes selective release of peptides and nonpeptides in peripheral tissues, which sensitise the peripheral nerve endings (table I). The source of these substances is varied: injured cells, nociceptors, enhanced capillary permeability and generation by local enzyme activity. These substances are also released in the spinal cord, resulting in sensitisation. For example, substance P is synthesised in the neuronal cell bodies in the dorsal root ganglion and transported to peripheral and central terminals where it is stored in vesicles.[17] It causes vasodilatation, oedema and the release of histamine. Substance

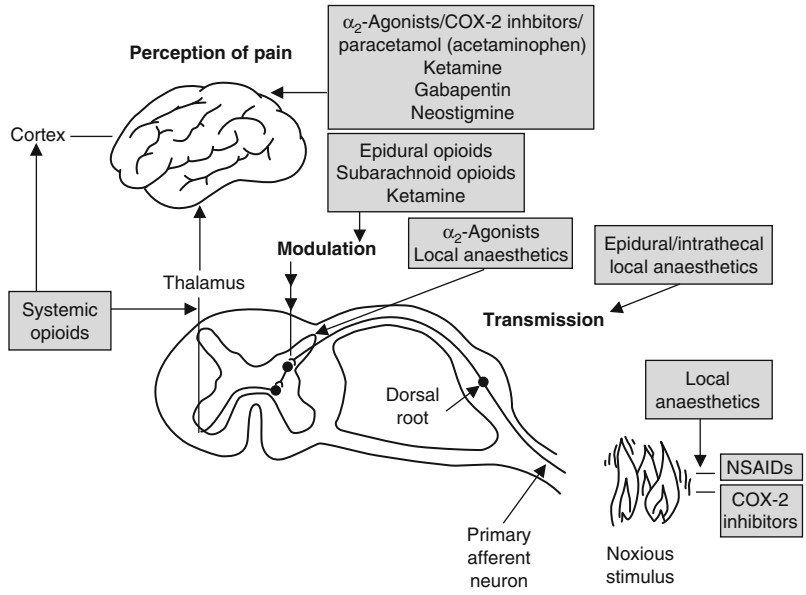


**Fig. 1.** Action of analgesics at various sites of the pain pathway. **COX** = cyclo-oxygenase.

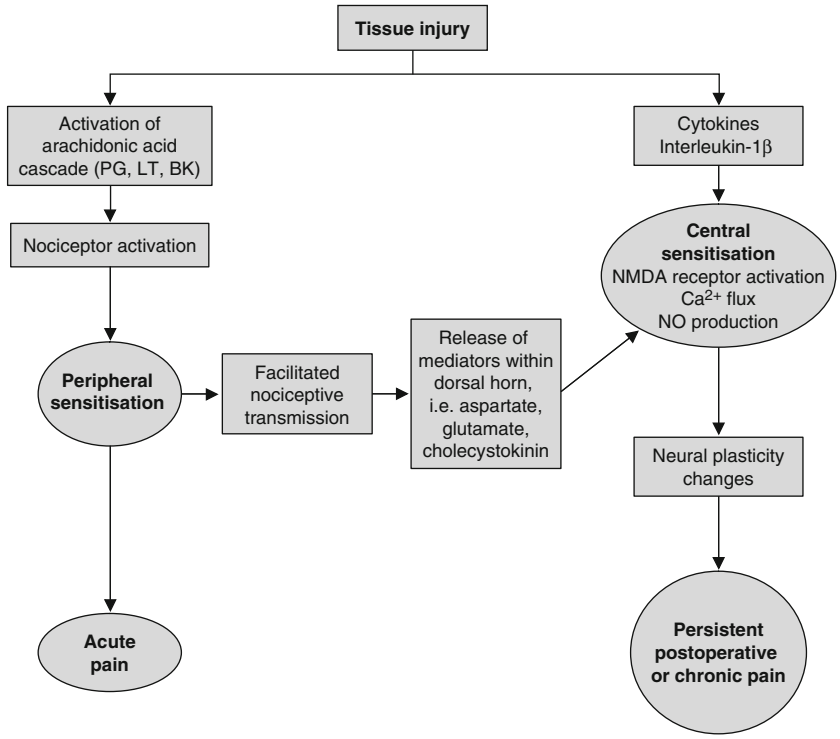


**Fig. 2.** Mechanism of peripheral and central sensitisation. **BK** = bradykinins; **LT** = leukotrienes; **NO** = nitric oxide; **PG** = prostaglandins.

P appears to have a role in potentiating both excitatory and inhibitory inputs in the spinal cord, thereby sensitising the neurons to nociceptive signals.[18] It has a slow and prolonged effect during sustained noxious stimulation, binding at neurokinin $NK_1$ receptors and resulting in calcium ion influx into neuronal cells. Substance P also induces the production of nitric oxide, a vasodilator for the endothelium, which, by complex mechanism, exacerbates pain.[19] This finding indicates a potential role for selective substance P antagonists with high affinity for $NK_1$ receptors to prevent the prolongation of nociceptive transmission.[20-22] However, studies to date have not found significant and consistent analgesic properties for $NK_1$ receptor antagonists in humans.[23,24] Serotonin – which is released from non-neuronal cells such as platelets and mast cells and within the digestive tract – is one of the components of the 'inflammatory soup' present in the extracellular space of injured tissues. The role of serotonin in nociception is complex. It can cause excitation of nociceptive afferents via the activation of its membrane-bound receptors ($5\text{-}HT_{1\text{-}3}$)[25] as well as sensitising nociceptors, especially to bradykinin.[26] Antagonists acting at peripheral serotonin receptors ($5\text{-}HT_{2A}$ and $5\text{-}HT_3$) may be of value in reducing pain arising from inflamed tissues.

### *1.1.2 Central Mechanisms*

In recent years, major developments have been made in our understanding of the role of the spinal cord in nociceptive transmission. Peripheral sensitisation can enhance the pain responses of nociceptive neurons in the CNS. One strategy to reduce pain arising from such a mechanism is to decrease the excitability of these central neurons. There are also a number of peptides involved in augmentation of nociception at the spinal level (figure 2). For example, cholecystokinin (CCK) found in intrinsic spinal neurons is believed to play a role in nociception and selectively reduces the analgesic actions of morphine.[27,28] This indicates that CCK antagonists may

enhance opioid analgesia while reducing opioid tolerance.

*In vitro* studies have shown that both A-beta and C fibre activation increases aspartate and glutamate outflow at the level of the spinal cord,[29,30] resulting in amplification and prolongation of nociceptive signals leading to a chronic pain state (figure 2). The action of these amino acids[31] is mediated via NMDA and non-NMDA receptors. Ketamine (at subanaesthetic doses of 0.15–0.5 mg/kg) and dextromethorphan[32] are clinically effective NMDA receptor antagonists.[33]

There is also a growing body of evidence from animal studies[34-37] which indicates that ascending nociceptive and descending noradrenergic pathways play a critical role in modulation of pain at various levels in the spinal cord. The spinal receptor target for this system is the $\alpha_2$-adrenoceptor. Agonists at this receptor, such as clonidine, produce antinociception and may potentiate the actions of morphine.[38]

As pain mechanisms rely on different receptor systems, it is prudent to adopt a multimodal approach to achieve pain relief in the perioperative period.

## 2. Rationale for Multimodal Analgesia

The ideal postoperative analgesic regimen would provide effective pain relief, reduce opioid-related adverse effects and the surgical stress response, and improve clinical outcome, e.g. morbidity, mortality and duration of hospital stay. The concept of multimodal analgesia was introduced to achieve these goals by combining various analgesic techniques and different classes of drugs to improve postoperative outcome.[39] However, available data are conflicting and do not necessarily show that multimodal analgesia has resulted in improved outcome and concomitant reduction in the adverse effects of opioids.[12,40,41] The failure to improve clinical outcome may be due to inappropriate combination and dosages of analgesics. In addition to adequate analgesia, postoperative morbidity and duration of hospital stay depend on other factors such as initiation of early nutrition, mobilisation and comprehensive rehabilitation programmes.[42] The lack of effect of multimodal analgesia may also be due to inappropriate timing of administration of analgesics. Although there is insufficient evidence to recommend preemptive analgesia routinely, it is prudent to attenuate postoperative pain as effectively as possible during the intraoperative period and initiate effective analgesic therapy in the early phase of the perioperative period.

The effectiveness of individual analgesics can be enhanced by combining those acting via different mechanisms, such that additive or synergistic effects are achieved. For example, the synergism between $\alpha$-adrenergic and opioid systems has been demonstrated, with the finding that clonidine can potentiate the effects of morphine.[43] Similarly, combinations of paracetamol (acetaminophen) and NSAIDs provide additive analgesic effect in mild to moderate acute pain.[44] The addition of cyclo-oxygenase-2 (COX-2) inhibitors or NSAIDs to opioids reduces opioid requirements by 20–30%, with a concomitant reduction in opioid-related adverse effects and bet-

**Table I.** Inflammatory pain mediators

| |
|---|
| Adenosine |
| Bradykinin |
| Calcitonin |
| Calcitonin gene-related peptide |
| Cholecystokinin |
| Cytokines |
| interleukin-1$\beta$ |
| TNF$\alpha$ |
| GABA |
| Galanin |
| Glutamate |
| Glycine |
| Histamine |
| Interleukins |
| Leukotrienes |
| Neurokinins |
| Nitric oxide |
| Potassium |
| Prostaglandins |
| Serotonin |
| Somatostatin |
| Substance P |

**TNF** = tumour necrosis factor.

ter analgesia. For example, in a recent study, patients undergoing total abdominal hysterectomy who were randomised to intravenous administration of parecoxib 40mg at induction of anaesthesia had a significant reduction (by 26%) in 24-hour morphine consumption and lower pain scores on sitting up in comparison with placebo.[45] Furthermore, ketamine, an NMDA receptor antagonist, has been shown to reduce the pain scores and lower analgesic requirement when added to a multimodal epidural analgesia.[46] Adding ketamine to patient-controlled epidural analgesia (PCEA) with morphine, bupivacaine and adrenaline (epinephrine) has been demonstrated to result in an enhanced analgesic effect – the mean visual analogue scale score for pain in the ketamine group during movement and cough were lower than the control group.[47] The cumulative total analgesic consumption in the ketamine group was also lower by 30% than the control group 24 hours following surgery. In another study, it was demonstrated that the combination of intraoperative ketamine and epidural analgesia may confer a long-term benefit in reducing the incidence of chronic pain.[48]

Similarly, transcutaneous electrical nerve stimulation (TENS) administered in an optimal frequency (85Hz) in the wound area can reduce analgesic consumption for postoperative pain. In a meta-analysis, Bjordal et al.[49] reported that TENS resulted in a mean reduction in analgesic consumption by 26% compared with placebo.

In addition to a reduction in total analgesic consumption and better pain scores, reports suggest that multimodal analgesia may confer long-term benefits in patient outcomes.[50-52] Evidence also suggests that inadequate postoperative pain relief may result in significant morbidity that leads to an increase in healthcare costs due to unanticipated hospital admission.[53,54] Epidural analgesia using local anaesthetics and opioids is widely practiced as an important component of a multimodal approach to control postoperative pain and hasten recovery.[55] The synergistic effect of a combination of local anaesthetics and an opioid such as morphine provides superior dynamic analgesia with minimal adverse effects compared with a local anaesthetic or opioid alone.[56] In addition to local anaesthetics and opioids, a number of adjuvants such as ketamine[47] and clonidine[57] have also been used epidurally; however, there are conflicting reports about the value of epidural analgesia in improving outcomes. In a study of patients undergoing abdominal aortic surgery receiving thoracic epidural analgesia, the incidence of thrombotic, infectious and cardiovascular complications as well as the duration of hospital stay was significantly reduced.[58] Furthermore, the combination of epidural analgesia and NSAIDs initiated in the preoperative period has been shown to shorten recovery time.[14] Conversely, in high-risk patients who received perioperative epidural analgesia for major abdominal surgery, Peyton et al.[59] showed no difference in the duration of intensive care or hospital stay, although the findings of this study raise questions about its design and conclusions.[60]

In some patients, the adverse effect profile of various analgesics may affect quality of recovery. Continuous perineural techniques offer the potential benefits of prolonged analgesia, reduced opioid requirements and fewer adverse effects. A prospective evaluation of over 1300 patients undergoing total hip arthroplasty who received continuous peripheral nerve block reported significantly higher satisfaction, fewer adverse effects and less opioid consumption compared with groups that received intravenous patient-controlled analgesia (PCA) with morphine or PCEA.[61]

## 3. Pharmacological Options and Analgesic Techniques

### 3.1 Opioids

Opioids are effective analgesics for moderate to severe pain, although their efficacy is limited by adverse effects. They act on opioid receptors in the periphery[62,63] and CNS.

Opioids and/or NSAIDs combined with local anaesthetic infiltration or intra-articular block may be a useful technique for controlling pain in patients after ambulatory surgery. In most studies, local an-

aesthetic infiltration with systemic opioids or NSAIDs showed improvement in analgesia, better recovery[9] and shortening of discharge time from day surgery unit compared with placebo.[64,65] A prospective 7-year survey of nearly 6000 patients revealed that a high degree of patient satisfaction and low incidence of adverse effects could be achieved with the administration of neuraxial opioid analgesia for major surgery.[66]

Recently, a novel extended-release morphine formulation (morphine in a lyposomal carrier; DepoDur™;[1] Endo Pharmaceuticals Inc., Chadds Ford, PA, USA) has become available for single-dose epidural use. Several studies in various surgical procedures such as knee replacement, abdominal surgery and caesarean sections have examined the efficacy of this formulation as an alternative to conventional intravenous opioid analgesia.[67-69] Extended-release morphine has been reported to provide analgesia up to 48 hours postoperatively for lower abdominal surgery.[68] Patients treated with 10, 20 and 25mg used significantly less fentanyl via the intravenous PCA system than patients receiving standard epidural morphine. Most frequently reported adverse effects were nausea, pruritus, pyrexia, vomiting and hypotension. In the extended-release morphine group who received 25mg, a decrease from baseline respiratory rate was observed and sedation was more pronounced up to 12 hours postoperatively than in groups that received lower doses. Delayed respiratory depression is the most serious adverse effect of morphine. The authors recommended the optimal dose with fewer adverse effects to be 15mg of extended-release morphine, and that dose reduction is warranted in older patients.

### 3.2 Paracetamol (Acetaminophen)

Paracetamol is an effective analgesic for mild to moderate pain, with a favourable adverse effect profile.[70] It is an effective adjuvant to opioid analgesia, and a reduction in opioid requirement by 20–30% can be achieved when combined with a regular regimen of oral or rectal paracetamol.[71] It has been shown that 1g of propacetamol results in a significant reduction in postoperative morphine consumption over a 6-hour period.[72] A meta-analysis of analgesic efficacy suggested that paracetamol and tramadol is an effective analgesic combination in dental and postsurgical pain; however, more patients experienced adverse effects such as dizziness, nausea and vomiting with this combination than with either agent alone.[73]

Propacetamol, a prodrug of paracetamol, may be a viable alternative to NSAIDs in the perioperative period in minor surgery.[74]

### 3.3 NSAIDs

NSAIDs have become the cornerstone in the treatment of acute pain in the early postoperative period because of their opioid-sparing effect.[75] Administration of ibuprofen and oxycodone in combination provides superior and effective analgesia in the postoperative period.[76] The combination of ibuprofen and paracetamol has also been reported to reduce the need for early analgesia by up to 34% in children undergoing tonsillectomy.[77]

#### *3.3.1 Cyclo-Oxygenase-2 Inhibitors*

There has been a renewed interest in the use of COX-2 inhibitors for postoperative pain. Because of their favourable adverse effect profile, COX-2 inhibitors provide a safer alternative to conventional NSAIDs. Nonselective NSAIDs are associated with adverse effects related to COX-1 inhibition, which include gastrointestinal ulceration, renal dysfunction and perioperative bleeding.[78] At normal doses, the COX-2 inhibitors selectively inhibit COX-2. In addition, they exhibit an opioid-sparing effect[79] and therefore constitute an important component of multimodal therapy for the treatment of postoperative pain.

Parecoxib (a prodrug of valdecoxib) has analgesic potency similar to that of ketorolac and has been studied extensively in postoperative dental pain and other models.[80-84] Single-dose parecoxib 40mg provided significantly better pain responses compared

**1** The use of trade names is for product identification purposes only and does not imply endorsement.

with placebo or morphine 4mg and was comparable to ketorolac 30mg after gynaecological surgery.[85] The main advantage of parecoxib is that it can be administered intraoperatively and immediately postoperatively before oral medication is tolerated. Gan et al.[79] have shown that preoperative parecoxib followed by postoperative oral valdecoxib reduces opioid requirements after laparoscopic cholecystectomy compared with placebo. The cumulative morphine equivalent dose (MED) of fentanyl in the treated group was lower compared with the placebo group up to 4 days postoperatively. In addition, significantly reduced incidences of opioid-related symptoms were observed in the parecoxib/valdecoxib group.

In another study, patients undergoing knee replacement surgery were randomly assigned to receive another COX-2 inhibitor rofecoxib or placebo perioperatively in conjunction with PCEA. It was shown that the rofecoxib group experienced significantly less breakthrough pain and fewer adverse effects compared with the placebo group. They also experienced quicker recovery based on range of motion and pain scores.[14]

Recently, much attention has focused on the ultimate risk-benefit ratio of COX-2 inhibitors.[86-88] Selective COX-2 inhibitors – by decreasing vasodilatory and anti-aggregatory prostacyclin (epoprostenol) production – may lead to increased prothrombotic activity. By doing this, they may affect the balance between prothrombotic and antithrombotic eicosanoids,[89] resulting in an increased risk of myocardial infarction. However, this theory was considered oversimplified and the underlying mechanism may be more complex.[90-92] As a result of the increased cardiovascular risks, rofecoxib and valdecoxib have been withdrawn from the market. Celecoxib is available for clinical use worldwide, while parecoxib is only available outside the US.

NSAIDs and COX-2 inhibitors are also known to reduce peripheral nociceptor discharge by reducing the local concentration of arachidonic acid metabolites. NSAIDs exhibit central and peripheral analgesic action that varies depending on the type of NSAID used and on the presence or absence of an inflammatory process.[93] Romsing et al.[94] investigated the evidence for a peripheral analgesic effect of local infiltration with NSAIDs. Five studies compared intra-wound infiltration of tenoxicam (7.5 or 10mg) or ketorolac (30 or 60mg) with similar systemic (intravenous or intramuscular) administration in patients undergoing inguinal hernia repair or mastectomy. Two of the five trials showed significantly lower pain scores at 2 hours and 24 hours after wound infiltration with NSAIDs. The 24-hour consumption of supplementary analgesics was significantly reduced by approximately 60% in the wound infiltration group. It should be emphasised that the observed benefit may be due to a systemic effect of the locally administered NSAID.

### 3.4 Tramadol

Tramadol is a synthetic, centrally acting analgesic with weak agonist activity at opioid receptors. It also inhibits serotonin and noradrenaline (norepinephrine) reuptake.[95] The tramadol metabolite, *O*-desmethyl tramadol, is a more potent analgesic than tramadol.[96] Unlike other opioids, tramadol lacks respiratory depressant effects and exhibits a lower risk of bowel dysfunction[97] at conventional doses.

Moore and McQuay,[98] in a meta-analysis, compared single oral doses of tramadol alone with a combination of standard analgesics (aspirin/codeine and paracetamol/propoxyphene) in post-surgical and dental pain. Tramadol 100mg and 150mg showed a number-needed-to-treat value of 4.8 and 2.4, respectively, compared with 3.6–4.0 with combination analgesics. Frequencies of adverse effects were higher with increasing doses of tramadol.

A meta-analysis[99] of a paracetamol and tramadol combination confirmed superior analgesia without additional toxicity. The most common adverse effects noted were diziness, headache, nausea and vomiting. Another study noted that the combination of tramadol with paracetamol increased the tolerability of tramadol.[100]

### 3.5 Ketamine

There has been renewed interest in the role of ketamine in enhancing postoperative analgesia. Several studies have focused on demonstrating the use of subanaesthetic doses of ketamine for various surgical procedures to enhance pain relief and reduce total analgesic consumption.[101-106] Central excitatory neurotransmitters acting on NMDA receptors have been identified to be involved in the development and perpetuation of pathological pain states causing hyperalgesia and allodynia.[107] Ketamine acts as an antagonist at the NMDA receptor.

There is much evidence (table II) to suggest that ketamine has an opioid-sparing effect and may confer advantages in patients in whom high postoperative opioid consumption is anticipated. At low doses, ketamine can provide improved analgesia in opioid-resistant pain.[108] Continuous infusion of ketamine has been used perioperatively. Adam et al.[109] evaluated intravenous ketamine with an initial bolus (0.5 mg/kg) followed by continuous infusion of 3 μg/kg/min intraoperatively in combination with continuous femoral nerve block in patients undergoing total knee arthroplasty. In this multimodal approach, the ketamine group required significantly less morphine than patients receiving only femoral nerve block and tolerated early mobilisation of the knee.[109]

A systematic review[113] of randomised double-blinded trials involving epidural ketamine added to various opioid-based regimens suggested improved analgesia with no increase in ketamine-associated adverse effects. Ketamine in a multimodal regimen of PCEA has been shown to reduce analgesic requirement after major surgery.[47,112] Wong et al.[114] demonstrated that the addition of ketamine to epidural morphine potentiates the analgesic effect of morphine in patients undergoing total knee replacement. Similarly, Chia et al.[47] showed that coadministration of a small dose of ketamine 0.4 mg/mL with a multimodal regimen (morphine, bupivacaine and adrenaline) via PCEA provides better pain relief at rest, during coughing or movement, and a reduction in analgesic consumption compared with PCEA alone. Recently, transdermal ketamine has been used as an adjuvant to epidural analgesia.[115] Patients who were treated with a ketamine patch after minor gynaecological surgery showed prolonged time to first rescue analgesia.

In essence, ketamine has found a role in the management of acute pain but its use as an analgesic has been limited by its unpleasant and unpredictable adverse effects; however, lower doses of ketamine have not been found to be associated with these effects.[116]

### 3.6 Clonidine

The $\alpha_2$-adrenoceptor agonists, clonidine and dexmedetomidine,[117] have anti-nociceptive activity via peripheral, supraspinal and primarily spinal cord mechanisms including activation of postsynaptic $\alpha_2$-adreoceptors of descending noradrenergic pathways.

Epidural clonidine has several potential advantages over epidurally administered local anaesthetics and opioids because it is devoid of some of the adverse effects associated with these drugs such as motor block, urinary retention, respiratory depression and pruritus. In addition, clonidine exhibits a synergistic action when used as an adjuvant to local anaesthetics or opioids, resulting in a reduction in postoperative analgesic requirement.[57,118] Paech et al.[119] have demonstrated that postoperative epidural analgesia (with bupivacaine and fentanyl) is enhanced significantly by the addition of clonidine. They reported a reduction in opioid requirement and lower pain scores on coughing.

The adverse effects of clonidine are dose related. When tested in healthy volunteers in a dose of 700μg epidurally, Eisenach et al.[120] found that clonidine significantly reduced pain induced by ice water immersion, decreased plasma noradrenaline levels and caused haemodynamic changes, but resulted in intense sedation that lasted up to 6 hours.

Dexmedetomidine has also been used for sedation in intensive care[121] and as an analgesic adjunct during the intraoperative period. It has been demonstrated to provide an opioid-sparing effect with minimal adverse effects.[122,123]

**Table II.** Studies on perioperative use of ketamine (KET)

| Study | Type of surgery/ anaesthesia | Regimen (no. of patients) [duration of study] | Pain scores vs control | Analgesic consumption vs control | Adverse effects |
|---|---|---|---|---|---|
| Adam et al.[109] | Total knee arthroplasty/ continuous FNB | Bolus KET 0.5 mg/kg followed by infusion 3 μg/kg/min intraop and 1.5 μg/kg/min postop (n = 20); placebo using similar regimen with saline (n = 20) [48h] | ↓ VAS (no significant difference between groups); early knee mobilisation better ($p < 0.03$) | ↓ morphine consumption ($p < 0.02$) | No difference between groups |
| Reeves et al.[102] | Major abdominal surgery/GA | PCA morphine 1 mg/mL (n = 35); PCA morphine 1 mg/mL plus KET 1 mg/mL (n = 36) [48h] | No difference between groups | No difference between groups | Cognitive impairment ($p < 0.037$) in KET group with vivid dreaming |
| Weinbroum[108] | Surgical patients/GA | Postop patients; IV morphine 30 μg/kg plus saline (n = 114); IV morphine 15 μg/kg plus IV KET 250 μg/kg (n = 131) [2h] | ↓ VAS at 10 and 120 min ($p < 0.001$) | ↓ morphine consumption ($p < 0.001$) | Drowsiness ($p < 0.001$), oxygen desaturation ($p < 0.001$) and PONV ($p < 0.001$) common in morphine group |
| De Kock et al.[33] | Rectal cancer surgery with combined epidural/ GA | Placebo; IV KET bolus 0.25 mg/kg followed by 0.125 mg/kg/h (group 1); IV KET bolus 0.5 mg/kg followed by 0.25 mg/kg/h (group 2); epidural KET 0.25 mg/kg followed by 0.125 mg/kg/h (group 3); epidural KET 0.5 mg/kg followed by 0.25 mg/kg/h (group 4) (n = 20 per group) [72h] | ↓ VAS in KET group 2 ($p < 0.001$) | ↓ morphine consumption in IV KET group 2 ($p < 0.05$) | No difference between groups |
| Snijdelaar et al.[101] | Radical prostatectomy/GA | KET 100 μg/kg bolus preop plus 2 μg/kg/min intraop followed by PCA morphine 1mg plus KET 0.5mg per bolus (n = 14); placebo (n = 14) [48h] | ↓ VAS ($p = 0.01$) | ↓ morphine consumption ($p = 0.049$) | No difference between groups |
| Kwok et al.[104] | Gynaecological laparoscopic surgery/GA | Preincision (n = 45) or post skin closure (n = 45) KET 0.15 mg/kg; IV saline (n = 45) [4wk] | ↓ VAS in preincision KET group ($p = 0.001$) | ↓ morphine consumption in preincision KET group ($p = 0.04$) | No difference between groups |
| Argiriadou et al.[110] | Major pelvic surgery/ GA/intraop and postop EA with LA | IV KET 0.5 mg/kg preincisional plus placebo (n = 15); IV KET 0.5 mg/kg preincisional plus 0.2 mg/kg repeated intraop (n = 15); placebo (n = 15) [6h] | ↓ VAS over 6h postop in pre- and intraop group ($p = 0.05$) | ↓ analgesic need up to 24h in pre- and intraop group ($p = 0.05$) | No difference between groups |

*Continued next page*

**Table II.** Contd

| Study | Type of surgery/ anaesthesia | Regimen (no. of patients) [duration of study] | Pain scores vs control | Analgesic consumption vs control | Adverse effects |
|---|---|---|---|---|---|
| Menigaux et al.[103] | Outpatient knee arthroscopy/GA | IV KET 0.15 mg/kg (n = 25) or placebo (n = 25) at induction [3 days] | ↓ VAS up to 72h ($p < 0.001$) | ↓ analgesic consumption ($p < 0.01$) | No difference between groups |
| Chia et al.[47] | Intrathoracic and upper abdominal surgery/GA | PCEA morphine 0.02 mg/mL, bupivacaine 0.8 mg/mL and KET 0.4 mg/mL (n = 45); placebo (n = 46) [3 days] | ↓ VAS ($p < 0.05$) | ↓ analgesic consumption up to 48h ($p < 0.05$) | No difference between groups |
| Subramaniam et al.[111] | Major abdominal surgery/GA | Preincision epidural morphine alone (group 1; n = 24); epidural KET plus morphine (group 2; n = 26) [48h] | Not reported | ↓ morphine consumption in group 2 ($p = 0.018$), time for first analgesia request was prolonged in group 2 ($p = 0.021$); supplemental epidural morphine doses were similar in both groups ($p = 0.1977$) | No difference between groups |
| Kararmaz et al.[105] | Renal surgery/GA/ EA | IV KET 0.5 mg/kg bolus followed by 0.5 mg/kg/h KET intraop (n = 20); placebo (n = 20) [48h] | ↓ VAS in KET group for 48h ($p < 0.01$) | ↓ PCEA doses in KET group for 48h ($p = 0.001$) | Nausea/vomiting common in control group ($p < 0.05$) Dreams/diplopia no difference between groups |
| Aida et al.[106] | Gastrectomy (pre-emptive analgesia) | Epidural morphine (group 1; n = 30); IV KET plus epidural saline (group 2; n = 29); IV KET plus epidural morphine (group 3; n = 31); IV saline plus epidural saline (group 4; n = 31) [48h] | ↓ VAS in group 1 ($p < 0.005$) ↓ VAS in group 2 ($p = 0.05$) ↓ VAS in group 3 ($p < 0.005$) | ↓ morphine consumption in group 2 ($p < 0.05$) and lowest in group 3 ($p < 0.005$) | Not reported |
| Tan et al.[112] | Lower abdominal surgery | PCEA morphine (group 1; n = 30); PCEA morphine plus ketamine (group 2; n = 30) [24h] | ↓ VAS in group 2 for 3h postop ($p < 0.05$) and no difference between groups during 3–24h ($p < 0.05$) | ↓ morphine consumption up to 24h in group 2 ($p < 0.05$) | Vomiting common in group 1 ($p < 0.05$); sedation, pruritus and pyschomimetic effects were not different between groups |

**EA** = epidural anaesthesia; **FNB** = femoral nerve block; **GA** = general anaesthesia; **intraop** = intraoperative; **IV** = intravenous; **LA** = local anaesthetic; **PCA** = patient-controlled analgesia; **PCEA** = patient-controlled epidural analgesia; **PONV** = postoperative nausea and vomiting; **postop** = postoperative; **preop** = preoperative; **VAS** = visual analogue scale score; ↓ indicates reduction.

### 3.7 Epidural Analgesia

Epidural analgesia provides superior pain relief and attenuates the stress response to surgery and pain, particularly when used in the form of continuous infusion both during and after surgery. However, clinical opinion remains divided regarding the benefits of epidural analgesia despite several studies demonstrating benefits such as greater patient satisfaction, less postoperative morbidity and improved clinical outcome.[55,59,124-133] The results of some of the more recent studies, meta-analyses and reviews are summarised in table III. A recent meta-analysis confirmed the value of epidural analgesia in reducing cardiac, pulmonary, thromboembolic and renal complications, in addition to providing superior postoperative analgesia.[126]

Combined use of epidural local anaesthetics and adjuvants not only provides intraoperative analgesia but can also control postoperative pain effectively after major thoracic, abdominal and lower limb surgeries.[135] Using adjuvants in the epidural space reduces the total dose of local anaesthetic. In children, several adjuvants have been used in caudal blocks, including ketamine and clonidine, for prolongation of analgesia after common paediatric operations.[136]

A study conducted in patients undergoing major intra-abdominal surgery demonstrated better pain relief and reduced postoperative analgesic consumption with epidural analgesia.[133] For hip and knee replacements, epidural anaesthesia with sedation during surgery followed by postoperative epidural infusion of a combination of local anaesthetics and opioids has been used.[137] Lee et al.[138] demonstrated a clear advantage of the combination of epidural bupivacaine and diamorphine for analgesia after major gynaecological surgery. The combination provided superior pain relief with fewer adverse effects.

Nonetheless, there are problems associated with the continuous epidural technique such as hypotension, motor blockade and incompatibility with anticoagulation. In addition, the failure rate with epidural analgesia is approximately 30%.[139]

### 3.8 Wound Infiltration with Local Anaesthetics

Infiltration of the surgical wound with local anaesthetics is commonly performed to achieve wound analgesia. This method has been shown to be effective in providing analgesia in trials where patients have undergone inguinal hernia repair, although there is lack of evidence for any clinically useful effect for most other abdominal procedures (see review by Moiniche et al.[140]). Inadequate doses of local anaesthetics may explain the poor results in some trials. Wound infiltration does not provide a beneficial effect on pulmonary function after surgery.[129]

The role of adjuvants to local anaesthetics is unclear. For example, wound infiltration with bupivacaine and ketamine has not been shown to decrease pain score or the need for rescue analgesia, but the duration of analgesia has been reported to be prolonged by the addition of ketamine.[141] The routine use of adjuvants in wound infiltration is currently not recommended.

### 3.9 Intra-Articular Analgesics

There are conflicting reports about the efficacy of intra-articular analgesics.[142-144] Intra-articular NSAIDs when used alone are unlikely to exert any clinically useful analgesic effect, but NSAIDs in combination with local anaesthetics may provide prolonged analgesia.[145] Many orthopaedic surgeons use intra-articular local anaesthetics following arthroscopic surgery. In a systematic review, Moiniche et al.[146] observed that the use of intra-articular local anaesthetics seemed to provide moderate pain relief of short duration. Although the pain relief in the early postoperative period was statistically significant, evidence was not overwhelming in favour of intra-articular local anaesthetics because the majority of the studies did not demonstrate improved pain relief beyond the immediate postoperative period.

Peripheral anti-nociceptive actions of opioids have been reported,[147] and thus opioids appear to be effective in pain control when administered intra-articularly. Stein[148] showed that morphine exerts its

**Table III.** Studies on epidural analgesia in the perioperative period

| Study | Design | Procedure | Sample size | Key findings in EA group | Comment |
|---|---|---|---|---|---|
| Rigg et al.[130] | RCT (MASTER Trial) | Major abdominal surgery in high-risk patients | 915 patients; 255 in epidural group, 268 in control group | ↓ incidence of respiratory failure (23% vs 30%) [p = 0.02], ↓ pain scores in epidural group on day 1 after coughing (p < 0.0001) | No difference in mortality between groups; EA does not decrease perioperative major adverse complications; supports widespread use of EA for analgesia |
| Rodgers et al.[126] | Systematic review of RCTs of EA or SA | All types of surgery | 141 RCTs, 9559 patients | ↓ mortality by a one-third; ↓ DVT, PE; ↓ transfusion; ↓ pneumonia; ↓ respiratory depression [all p < 0.001] | Reduction in postop morbidity; supports use of EA |
| Beattie et al.[128] | Meta-analysis of RCTs | Aortic/peripheral vascular/abdominal surgeries | 11 RCTs, 1173 patients | ↓ pain scores for 24h (p-value not reported); ↓ postop MI especially with thoracic epidural (p = 0.04) | No difference in mortality between groups |
| Park et al.[133] | RCT GA plus parenteral opioids/EA plus light GA | Major intra-abdominal surgery | 1021 patients | ↓ mortality (p = 0.74) and major complications in abdominal aortic surgery (22% vs 37%); MI (p = 0.21), stroke (p = 0.98), respiratory failure (p = 0.06) ↓ concurrent analgesic consumption (p < 0.01) | Overall no significant difference in morbidity/mortality up to 30 days between groups; EA provides better pain relief; supports use in AAA surgery |
| Peyton et al.[59] | Subgroup analysis of MASTER Trial | Major abdominal surgery | Subgroup of 915 patients | No difference between groups in patients at risk of respiratory, cardiac complications or aortic surgery; no difference in duration of hospital stay | No evidence to support reduction in mortality or morbidity with EA |
| Block et al.[55] | Systematic review of RCTs; EA vs parenteral opioids | All types of surgery | 100 RCTs (no. of patients not reported) | ↓ pain scores with EA vs opioids (p < 0.001); ↓ nausea, vomiting (p = 0.61) and pruritus (p < 0.001) | Supports use of EA |
| Ballantyne et al.[129] | Meta-analysis of RCTs | All types surgery | 200–250 patients | ↓ pulmonary infection (95% CI 0.21, 0.65); ↑ $PaO_2$ (95% CI 0.058, 9.075); no difference in $FEV_1$/FVC/ PEFR | EA decreases pulmonary complications |
| Choi et al.[131] | Cochrane systematic review of RCTs (lumbar epidural vs systemic analgesia) | Hip and knee replacements | 13 studies, 639 patients | Short-term ↓ in pain scores (4–6h) postop (95% CI −1.24, −0.31); ↓ in pain scores on movement (p-value not reported); no difference in PONV and respiratory depression; more frequent itching, retention of urine (95% CI 1.63, 7.51) and hypotension (95% CI −1.15, −6.72) | Supports use of EA for short-term pain relief; insufficient data to show ↓ in hospital stay, morbidity and mortality due to EA |
| Nishimori et al.[132] | Cochrane systematic review (EA vs systemic opioid analgesia) | Abdominal aortic surgery | 1224 patients; EA in 597 patients, systemic opioids in 627 patients | ↓ pain score; ↓ duration of postop ventilation (p = 0.048); ↓ postop morbidity in EA group | Supports use of EA for pain relief up to third postop day; no difference in postop mortality |
| Werawatganon and Charuluxanum[134] | Cochrane systematic review (continuous EA vs opioid PCA) | Abdominal surgery | 711 patients | ↓ pain scores in EA group during 72h (WMD 0.63; 95% CI 0.24, 1.01); pruritus in PCA group (OR 0.27; 95% CI 0.11, 0.64) | EA superior to PCA. No difference in hospital stay |

**AAA** = abdominal aortic aneurysm; **DVT** = deep vein thrombosis; **EA** = epidural analgesia; **$FEV_1$** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **GA** = general anaesthesia; **MI** = myocardial infarction; **OR** = odds ratio; **$PaO_2$** = partial pressure of oxygen; **PCA** = patient-controlled analgesia; **PE** = pulmonary embolism; **PEFR** = peak expiratory flow rate; **PONV** = postoperative nausea and vomiting; **postop** = postoperative; **RCT** = randomised controlled trial; **SA** = spinal anaesthesia; **WMD** = weighted mean difference; ↓ indicates reduction; ↑ indicates increase.

effect on peripheral opioid receptors when injected intra-articularly; however, a systemic effect cannot be excluded. Gupta et al.,[149] in a meta-analysis, evaluated 27 studies where intra-articular morphine was directly compared with placebo. In 13 of the studies, intra-articular morphine had a mild beneficial effect (mean reduction in pain intensity, 12–17mm on a visual analogue score). Several studies reported a reduction in analgesic requirement in the morphine group. The efficacy of morphine depends on the dose used. A higher dose (5mg) injected intra-articularly is likely to provide analgesia during the first 24 hours after surgery, whereas lower doses are ineffective.

Romsing et al.[94] in a systemic review highlighted four studies that compared intra-articular ketorolac 60mg or tenoxicam 20mg with systemic (intravenous) administration. In two of these ketorolac reports intra-articular bupivacaine was added in both groups.[145,150] All four studies showed significantly lower pain scores after intra-articular administration compared with systemic administration of NSAIDs. In the intra-articular groups, time to first analgesic request was significantly increased postoperatively.

Data also suggest that using a combination of analgesics intra-articularly has beneficial effects. Patients who received intra-articular ketorolac in addition to morphine demonstrated significantly lower pain scores compared with patients receiving either drug alone postoperatively.[151] Similarly, a combination of clonidine and neostigmine[152,153] have also been shown to exhibit peripheral analgesic effects when used intra-articularly after knee arthroscopy. At a dose of 150µg intra-articularly, clonidine exerted analgesia comparable to morphine but the combination of both did not provide prolonged analgesia.[154]

### 3.10 Peripheral Nerve Blocks

Appropriate nerve blocks, depending on the site of surgery, are useful in providing short-term pain relief post-operatively. Direct visualisation of neural tissue with ultrasound technology and the utility of stimulating catheters has made placement of indwelling catheters safer and accurate.

Continuous infusion of local anaesthetics through a peripheral nerve catheter is becoming increasingly popular in both hospital and ambulatory settings to achieve prolonged analgesia.[155,156] For example, continuous femoral nerve block has been shown to reduce the duration of hospital stay and the frequency of serious complications after total knee arthroscopy.[157] Similarly, several other studies have demonstrated the benefits of peripheral nerve blocks (PNBs), including reduced duration of stay and costs,[155] decreased incidence of postoperative nausea and vomiting,[158] and lower rates of unexpected hospital admissions after ambulatory surgery.[155,157,159]

In a recent meta-analysis involving over 600 patients, PNBs provided superior postoperative analgesia when compared with administration of oral and systemic opioids alone.[160] Patients who received perineural blocks with local anaesthetic also demonstrated a significant reduction in opioid consumption, fewer opioid-related adverse effects and better patient satisfaction. Of the six studies that evaluated clonidine,[161] five found improvement in analgesia.

Evidence that the addition of peripherally administered opioids during PNB[162,163] improves the quality of either intraoperative regional anaesthesia or postoperative analgesia has not been established, with mixed results from different trials. Five trials measuring postoperative efficacy reported a significant difference in favour of the opioid;[162] however, the authors did not consider the findings important enough to advocate routine use of opioids in the acute setting.

### 3.11 Pre-Emptive Analgesia

With a greater understanding of acute pain mechanisms, it is known that tissue injury initiates peripheral and central neuronal sensitisation, resulting in perpetuation of the 'pain state'.[164-166] Pre-emptive analgesia is analgesia given before the initiation of nociceptive stimulus. Several clinical studies hypothesised that preoperative administration of

analgesics or regional blockade would prevent or result in less postoperative pain[106,167-170] by protecting the nervous system from sensitisation. However, the effectiveness of pre-emptive analgesia in routine clinical practice is debatable.[171,172] For pre-emptive analgesia to be clinically important the duration of analgesia obtained should be longer and with a minimal increase in adverse effects, and the pre-emptive intervention should have an effect on acute postoperative pain or in preventing the development of chronic pain.

A recent review of the literature found that around 40% of studies demonstrated a beneficial effect (reduction in pain and analgesic consumption) of pre-incision (pre-emptive) analgesia as opposed to analgesic administration after surgical incision (preventive).[173] Therefore, along with other factors (drug, dose and duration) it appears that the timing of analgesic initiation in relation to surgical incision affects postoperative analgesic requirement when analgesic activity of the agent has worn off.[174,175] The timing of administration of an agent may be pre-incision,[176] during surgery[177] or in the postoperative period.[178]

NMDA antagonists,[172] NSAIDs,[179] epidural analgesia[180] and local anaesthetic infiltration[170,181,182] have all been used in pre-emptive analgesia, with variable results.

## 4. Novel Analgesic Therapy

### 4.1 Gabapentin

Gabapentin, which primarily has anticonvulsant properties, is used extensively in the treatment of neuropathic pain. Despite its structural similarity to GABA, gabapentin does not bind to GABA receptors.[183] It has high affinity for $\alpha_2$-$\delta$ subunits of voltage-dependent calcium channels, resulting in postsynaptic inhibition of calcium influx and thereby reducing presynaptic excitatory neurotransmitter release.[184] It has been suggested that gabapentin is useful in reducing the central neuronal sensitisation that occurs in postoperative pain, and postsurgical pain has been regarded by some as transient neuropathic pain.[185]

Numerous studies have demonstrated the efficacy of gabapentin, and another GABA analogue pregabalin, as non-opioid analgesic adjuvants in postoperative pain management.[50,186-196] Table IV summarises some of these studies.

In a randomised study using single-dose gabapentin (1200mg) versus placebo, Dirks et al.[192] found that there was a substantial reduction in morphine consumption after mastectomy in the gabapentin group (total morphine consumption, 29mg in the placebo group versus 15mg in the gabapentin group). In addition, pain scores were lower in the treatment group in the early postoperative period. Dierking et al.[193] also demonstrated a reduction in morphine consumption (by 32%) when gabapentin (3000mg) was administered before and during the first 24 hours after abdominal hysterectomy. A recent meta-analysis confirmed that gabapentin in doses <1200mg has an analgesic and opioid-sparing effect in acute postoperative pain management when used in conjunction with opioids; however, it was associated with an increased risk of sedation but reduced opioid-related adverse effects such as vomiting.[194] In a multi-modal approach, Gilron et al.[195] reported that the combination of gabapentin and rofecoxib is superior to either agent alone after abdominal hysterectomy. With all patients receiving intravenous PCA, the gabapentin-rofecoxib combination (1800/50mg) demonstrated a significant reduction in morphine consumption, from 130mg in the placebo group to 57mg in the combination group.

Based on the current evidence it appears that gabapentin reduces supplementary postoperative analgesic requirement. The optimal dose ratio devoid of adverse effects needs to be identified when gabapentin is used alone or in combination.

### 4.2 Corticosteroids

Corticosteroids have been used as anti-inflammatory and anti-immunological agents for manifestations of many autoimmune disorders. Corticosteroids act by suppressing arachidonic acid production through lipocortin-induced phospholipase inhibition, which ultimately inhibits production of both

**Table IV.** Studies on perioperative use of gabapentin (GAB) and pregabalin (PGB)

| Study | Type of surgery | Regimens (no. of patients) [duration of study] | Pain scores vs control | Analgesic consumption vs control | Adverse effects |
|---|---|---|---|---|---|
| Dirks et al.[192] | Mastectomy | GAB 1200mg 1h preop (31); PL (34) [4h] | ↓ VAS on movement at 2h ($p < 0.0001$) and 4h ($p = 0.018$) | ↓ morphine consumption ($p < 0.0001$) | No difference between groups |
| Fassoulaki et al.[197] | Cancer breast surgery | GAB 1200 mg/day for 10 days (n = 22); mexiletine 600 mg/day for 10 days (21); PL for 10 days (34) [3mo] | VAS rest and movement ↓ by both drugs on day 3 ($p = 0.001$); VAS on movement ↓ by GAB days 2–5 ($p = 0.001$) | 50% ↓ codeine and paracetamol use days 2–10 ($p = 0.003$) | No difference between groups |
| Turan et al.[190] | Spinal surgery | GAB 1200mg 1h preop (25); PL 1h preop (25) [24h] | ↓ VAS at 1, 2 and 4h ($p < 0.01$) | ↓ morphine consumption ($p < 0.000$) | Vomiting and urinary retention lower in GAB group ($p < 0.05$) |
| Dierking et al.[193] | Abdominal hysterectomy | GAB 1200mg 1h preop followed by 600mg at 6, 8 and 24h after first dose (39); PL 1h preop followed by PL at 6, 8 and 24h after first dose (32) [24h] | No difference | 32% ↓ morphine consumption ($p < 0.001$) | No difference between groups |
| Turan et al.[188] | Abdominal hysterectomy | GAB 1200mg 1h preop (25); PL 1h preop (25) [24h] | ↓ VAS up to 20h ($p < 0.02$) | ↓ tramadol consumption ($p < 0.0001$) | No difference between groups |
| Pandey et al.[187] | Laparoscopic cholecystectomy | GAB 300mg 2h preop (153); tramadol 100mg 2h preop (153); PL 2h preop (153) [24h] | ↓ VAS compared with tramadol (except 0–6h) and PL ($p < 0.05$) | ↓ fentanyl consumption vs tramadol and placebo ($p < 0.05$) | Sedation and PONV higher in GAB group ($p < 0.05$) |
| Rorarius et al.[189] | Vaginal hysterectomy | GAB 1200mg 2.5h preop (38); oxazepam 15mg 2.5h preop (37) [20h] | Trend towards ↓ VAS in the first 2h | 40% ↓ fentanyl consumption ($p < 0.005$) | Trend towards less PONV in the GAB group |
| Turan et al.[191] | ENT surgery under MAC | GAB 1200mg 1h preop (25); PL 1h preop (25) [24h] | ↓ VAS postop ($p < 0.001$) and at 45 and 60 min intraop ($p < 0.05$) | ↓ intraop fentanyl use ($p < 0.05$) and postop diclofenac use ($p < 0.0010$; prolonged time to first rescue analgesia ($p < 0.001$) | More dizziness in the GAB (24%) versus the PL group (4%, $p < 0.05$) |
| Gilron et al.[195] | Abdominal hysterectomy | GAB 1800mg 1h preop (25); rofecoxib 50mg 1h preop (30); GAB/rofecoxib 1800/50mg combination 1h preop (28); PL 1h preop (27) [72h] | ↓ VAS at rest ($p < 0.05$ vs all treatments) and on cough ($p < 0.05$ vs all treatments) in GAB/rofecoxib group | ↓ morphine consumption in GAB/rofecoxib group ($p < 0.05$) [$p < 0.05$ vs placebo] | Sedation more frequent with GAB group |

*Continued next page*

**Table IV.** Contd

| Study | Type of surgery | Regimens (no. of patients) [duration of study] | Pain scores vs control | Analgesic consumption vs control | Adverse effects |
|---|---|---|---|---|---|
| Turan et al.[186] | Lower extremity surgery | GAB 1200mg 1h preop (20); PL 1h preop (20) [72h] | ↓ VAS in GAB group ($p < 0.001$) | ↓ PCEA bolus requirements ($p < 0.05$); ↓ paracetamol consumption ($p < 0.05$) | Higher incidence of dizziness in GAB group ($p < 0.05$) |
| Ho et al.[194] | All types of surgery | Systematic review: 16 RCTs (n = 1151; GAB = 614); varying doses of GAB (300–1200mg) | ↓ VAS (WMD = 16.55 at 6h and 10.87 at 24h for single dose). Multiple dosing does not reduce pain scores | ↓ opioid consumption (WMD = −7.25mg) | Sedation risk increased with higher doses |
| Reuben et al.[196] | Spinal surgery | Placebo preop/postop (n = 20); CLB preop 400mg/postop 200mg (n = 20); PGB preop 150mg/postop 150mg (n = 20); CLB/PGB preop 400/150mg, postop 200/150mg (n = 20) [24h] | ↓ VAS in combination group ($p < 0.05$) over 24h period | ↓ 24h morphine consumption in combined group ($p < 0.01$) | Combination superior to other groups |

**CLB** = celecoxib; **ENT** = ear, nose and throat; **intraop** = intraoperative; **MAC** = monitored anaesthesia care; **PCEA** = patient-controlled epidural analgesia; **PONV** = postoperative nausea and vomiting; **preop** = preoperative; **postop** = postoperative; **RCT** = randomised controlled trial; **VAS** = visual analogue scale score; **WMD** = weighted mean difference; ↓ indicates reduction.

prostaglandins and leukotrienes.[198] Corticosteroids also prevent the production of cytokines, which play a role in the mechanism of inflammatory pain. At the spinal level, corticosteroids exert anti-nociceptive effects.[199]

Despite evidence for analgesic actions of corticosteroids, there has not been widespread clinical use of these agents for the management of postoperative pain. This may be due to the adverse effects of corticosteroids when given in repeated doses for longer periods postoperatively; however, most studies have reported their analgesic effect after single doses. Several clinical investigations have evaluated the effect of systemic corticosteroids on pain after surgical procedures, demonstrating effective pain relief and early recovery.[200-202] In a double-blind, placebo-controlled, single-dose, randomised study, Romundstad et al.[203] compared intravenous ketorolac with intravenous methylprednisolone 125mg in patients with moderate to severe pain one day after orthopaedic surgery. They demonstrated that the pain intensity in the corticosteroid group was significantly lower up to 6 hours postoperatively compared with placebo, and similar to ketorolac. Opioid consumption in the first 72 hours was significantly lower in the methylprednisolone group than in the ketorolac and placebo groups. No serious adverse effects were reported.

Glucocorticoids may have sustained analgesic effects after surgery; however, the disadvantage of repeated corticosteroid administration and adverse effects in postoperative patients needs further investigation in adequately powered trials.

### 4.3 Opioid Receptor Antagonists

Naloxone and nalbuphine (a partial opioid receptor agonist) are used to treat neuropathic pain.[204] *In vitro* studies have demonstrated that a long-acting nalbuphine preparation had antinociceptive action for up to 55 hours.[205] Evidence from animal studies also illustrates that opioid antagonists enhance the potency of morphine and attenuate opioid tolerance.[206,207]

In one study, low-dose naloxone infusion in the postoperative period after gynaecological surgery

was shown to reduce opioid-related adverse effects and opioid requirements.[208] However, there is inconclusive evidence from several other clinical trials on the effectiveness of opioid antagonists to attenuate postoperative pain and reduce opioid requirements.[209,210] In a recent randomised, double-blinded clinical study, Cepeda et al.[211] compared a naloxone-morphine combination with morphine alone in PCA. There was no difference in opioid requirements and pain between the groups. The combination group experienced less nausea and pruritus than the morphine only group; however, naloxone was unable to reduce the vomiting, sedation and urinary retention seen in the morphine only group.

### 4.4 Magnesium Sulfate

Recently, the role of magnesium sulfate as an NMDA receptor antagonist and as an adjuvant to analgesic therapy has been investigated. Intravenous magnesium sulfate 50 mg/kg preoperatively followed by an infusion postoperatively in patients undergoing open cholecystectomy has been reported to result in less discomfort than saline treatment,[212] although there was no effect on opioid requirement. In another study,[213] patients randomised to 20% intravenous magnesium sulfate before surgery showed reductions in postoperative PCA morphine requirements in the first 48 hours compared with patients receiving saline.

Contrary to the above findings, in a systematic review examining the efficacy of NMDA antagonists, McCartney et al.[214] reported that none of the four studies examining magnesium to reduce postoperative pain and analgesic requirements demonstrated any evidence in favour of preventive analgesia; in contrast, ketamine and dextromethorphan were effective in this regard.

### 4.5 Lidocaine (Lignocaine) Patches

Lidocaine (lignocaine) provides analgesia by blocking the sodium neuronal channels locally and thereby dampens peripheral nociceptor sensitisation. Transdermal lidocaine (5%) has been used to treat pain associated with post-herpetic neuralgia.[215] When lidocaine is applied as a topical agent, its serum concentrations are insignificant.[216] There may be a potential role of topical lidocaine in acute postoperative pain but this needs further investigation.

### 4.6 Patient-Controlled Transdermal Fentanyl

Patient-controlled transdermal fentanyl offers a non-invasive opioid delivery system for acute pain management. Using iontophoresis technology, fentanyl 40μg is delivered on demand.[217] A multicentre trial reported that patient-controlled transdermal fentanyl was superior to placebo in controlling moderate to severe pain up to 24 hours after major surgery.[218]

## 5. Nonpharmacological Options

Nonpharmacological therapy should be considered as complimentary to pharmacological options for postoperative pain management. It provides additional benefit in reducing the total dose of analgesics required and therefore minimising the adverse effects of the analgesics.

### 5.1 Transcutaneous Electrical Nerve Stimulation

TENS has been used widely in chronic pain conditions. The evidence for its efficacy in acute postoperative pain is inconclusive, mainly due to a lack of well-conducted, randomised controlled trials. Many published studies have methodological flaws. Blinding is difficult in trials associated with TENS because patients easily notice the presence or absence of paraesthesia; therefore, inadequate randomisation may exaggerate the efficacy by up to 40%.[219]

A systematic review by Carroll et al.[220] demonstrated TENS to be no better than placebo in the treatment of acute postoperative pain. A wide variety of procedures from hernia to thoracotomy were studied and ten different TENS units were used with different control settings and duration of treatment. Fourteen trials compared TENS with sham TENS. None found any difference between the two treatments. However, when TENS was compared with

opioids, one trial[221] reported significantly fewer pethidine injections and better pain scores on the first postoperative day in patients receiving TENS.

Previous systematic reviews[49,222] on TENS and postoperative pain showed several inconsistencies in the effectiveness of TENS. All available trials of postoperative pain used TENS as an adjuvant to medication, and it is possible that the effect of TENS was masked by the analgesic effect of the medication.

### 5.2 Relaxation Techniques

Relaxation has become increasingly popular as an adjuvant to conventional analgesic therapy. It has been suggested that it works by breaking the pain-tension-pain cycle.[223]

Seers and Carroll[224] conducted a systematic review to investigate the effectiveness of relaxation techniques when used alone in the management of acute pain. Three of the seven studies they assessed demonstrated significantly less pain or pain distress with relaxation. Most studies were poorly designed with a lack of adequate controls, and a variety of relaxation techniques was used. This meta-analysis proposed the need for better quality trials to establish the efficacy of relaxation techniques for acute postoperative pain before it is widely accepted as a routine analgesic intervention.

### 5.3 Music Therapy

Music therapy during and after surgery has been used as complimentary to other methods of pain management. Several studies claim benefit of music therapy in reducing pain scores and anxiety.[225-227] Nilsson et al.[226] in a controlled trial examined 151 patients undergoing day case surgery for inguinal hernia repair or varicose veins surgery under general anaesthesia. Patients who were exposed to music intraoperatively or postoperatively reported lower pain intensity in the early postoperative period than a control group who were exposed to 'white noise'. It is interesting to note that the postoperative music group required less morphine at 1 hour compared with the control group in the recovery room. The pain scores at home on the day of surgery and up to 48 hours afterwards were low and there were no significant differences between the three groups. This study suggests that music therapy has a short-term benefit in reducing pain and anxiety, decreasing the pain perception through cognitive coping.[227] The type and duration of music therapy needed are still unclear. However, a recent systematic review demonstrated a small reduction in pain scores and opioid consumption after music therapy.[228]

### 5.4 Acupuncture

Acupuncture, a form of traditional Chinese medicine, has been a topic of interest in managing postoperative pain. Several studies of acupuncture have demonstrated an analgesic effect and a reduction in the incidence of nausea and vomiting.[229,230] The success of acupuncture as an adjuvant in balanced analgesia depends on several factors, including the skills of the acupuncturist,[231] method of stimulation and duration of acupuncture therapy. The mechanism by which acupuncture produces analgesia is still unclear. The 'gate control theory' and secretion of endogenous opioids such as endorphins, encephalins and dynorphins may contribute to acupuncture-induced analgesia.[232,233]

Kotani et al.[234] tested the effect of acupuncture on postoperative pain in a controlled and double-blind study involving patients undergoing abdominal surgery. The investigators preoperatively inserted intradermal needles at acupoints 2.5cm bilaterally from the spinal vertebrae (bladder meridian). All these patients had an epidural catheter inserted for abdominal surgery. The pain relief was significantly better in the treatment group than in the control group until the second postoperative day. The treatment group required less morphine, by up to 50%. In contrast, Sim et al.[235] have shown that preoperative electro-acupuncture-induced analgesia did not reduce 24-hour morphine requirements after gynaecological lower abdominal surgery. This may be due to the short duration of action of electro-acupuncture when used during the preoperative period.

### 5.5 Hypnosis

Numerous studies have demonstrated the efficacy of hypnosis for reducing pain in the laboratory setting and case reports have indicated reductions in clinical pain.[236-239] There is evidence to suggest that hypnosis may modify pain perception, at least to some degree, through inhibition at the spinal level.

In acute pain, there is a substantial amount of anecdotal evidence and some controlled studies to support the efficacy and use of hypnosis. Montgomery et al.[240] conducted a meta-analysis to estimate the effectiveness of adjunctive hypnosis in controlling signs and symptoms after surgery. This meta-analysis suggested that an average 89% of surgical patients in hypnosis groups benefited relative to control patients. They also observed that the patients in the treatment group reflected greater satisfaction than the controls.

Evidence suggests that hypnosis is a useful tool to modulate pain and to alter a patient's perception to change their expectations about pain;[241] however, not all patients necessarily exhibit similar responses to hypnotic suggestions.[242]

## 6. Conclusion

The management of acute postoperative pain continues to pose a major challenge for healthcare providers. Advances in understanding of the mechanisms of pain, including the receptors involved in the transmission of pain, have led to improvements in postoperative pain management. Nevertheless, available data indicate that acute pain is undertreated.

It has been demonstrated that patients who are exposed to multimodal pain therapy experience less postoperative complications and a reduced duration of hospital stay, indicating that a combination of modalities will result in an improvement in postoperative pain and better clinical outcomes. The analgesic techniques used should be individualised to the patient and the type of surgical procedure. For minor surgeries, a combination of NSAIDs, paracetamol and local anaesthetic infiltration may be sufficient to provide analgesia. For patients in whom severe pain is anticipated, a combination of paracetamol, NSAIDs, systemic opioids or continuous epidural analgesia with local anaesthetic and opioid combination should be considered. PNBs are likely to be more effective for limb surgeries. Evidence suggests that acute pain can trigger long-term plastic neuronal changes leading to a chronic pain state. Drugs such as ketamine and gabapentin given in the perioperative period may reduce the incidence of chronic pain. Combination analgesics supplemented by nonpharmacological therapy will continue to play a vital role in the everyday comprehensive management of acute postoperative pain.

## Acknowledgements

Dr Gan has received research support and honoraria from Merck, Ortho-McNeil and Pfizer. Dr Pyati has no conflicts of interest that are directly relevant to the contents of this review. No sources of funding were used to assist in the preparation of this review.

## References

1. Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. Evidence from published data. Br J Anaesth 2002 Sep; 89 (3): 409-23
2. Warfield CAMD, Kahn CHMD. Acute pain management: programs in U.S. hospitals and experiences and attitudes among U.S. adults. Anesthesiology 1995 Nov; 83 (5): 1090-4
3. Apfelbaum JL, Chen C, Mehta SS, et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003; 97 (2): 534-40
4. Ferrell B, Virani R, Grant M, et al. Analysis of pain content in nursing textbooks. J Pain Symptom Manage 2000 Mar; 19 (3): 216-28
5. Salantera S, Lauri S, Salmi TT. Nurses knowledge about pharmacological and non-pharmacological pain management in children. J Pain Symptom Manage 1999 Oct; 18 (4): 289-99
6. Page GG. The immune-suppressive effects of pain. Adv Exp Med Biol 2003; 521: 117-25
7. Rosenfeld BA, Faraday N, Campbell D, et al. Hemostatic effects of stress hormone infusion. Anesthesiology 1994; 81 (5): 1116-26
8. Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiol Clin North America 2005; 23 (1): 21-36
9. Michaloliakou C, Chung F, Sharma S. Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. Anesth Analg 1996; 82 (1): 44-51
10. Wu C, Richman J. Postoperative pain and recovery profile. Curr Opin Anesthesiol 2004; 17: 455-60
11. Strassels SA, Chen C, Carr DB. Postoperative analgesia: economics, resource use, and patient satisfaction in an urban teaching hospital. Anesth Analg 2002; 94 (1): 130-7
12. Kehlet H, Werner M, Perkins F. Balanced analgesia: what is it and what are its advantages in postoperative pain? Drugs 1999; 58 (8): 793-7

 

13. Hyllested M, Jones S, Pedersen JL, et al. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. Br J Anaesth 2002; 88 (2): 119-214
14. Buvanendran A, Kroin JS, Tuman KJ, et al. Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement: a randomized controlled trial. JAMA 2003; 290 (18): 2411-8
15. Woolf CJ, Bennett GJ, Doherty M, et al. Towards a mechanism-based classification of pain? Pain 1998; 77 (3): 227-9
16. Sorkin LS, Wallace MS. Acute pain mechanisms. Surg Clin North Am 1999; 79 (2): 213-29
17. Brimijoin S, Lundberg JM, Brodin E, et al. Axonal transport of substance P in the vagus and sciatic nerves of the guinea pig. Brain Res 1980; 191 (2): 443-57
18. DeVane CL. Substance P: a new era, a new role. Pharmacotherapy 2001 Sep; 21 (9): 1061-9
19. Meller ST, Gebhart GF. Nitric oxide (NO) and nociceptive processing in the spinal cord. Pain 1993; 52 (2): 127-36
20. Yamamoto T, Sakashita Y. The role of the spinal opioid receptor like1 receptor, the NK-1 receptor, and cyclooxygenase-2 in maintaining postoperative pain in the rat. Anesth Analg 1999; 89 (5): 1203-8
21. Dionne RA, Max MB, Gordan SM, et al. The substance P receptor antagonist CP-99, 994 reduces acute postoperative pain. Clin Pharmacol Ther 1998 Nov; 64 (5): 562-8
22. Gonzalez MI, Field MJ, Holloman EF. Evaluation of PD 154075, a tachykinin NK1 receptor antagonist, in a rat model of postoperative pain. Eur J Pharmacol 1998 Mar 5; 344 (2-3): 115-20
23. Goldstein DJ, Wong O, Todd LE, et al. Study of the analgesic effect of lanepitant in patients with osteoarthritis pain. Clin Pharmacol Ther 2000 Apr; 67 (4): 419-26
24. Hill R. NK1 (substance P) receptor antagonists: why are they not analgesic in humans? Trends Pharmacol Sci 2000 July; 21 (7): 244-6
25. Dray A. Peripheral mediators of pain: the pharmacology of pain. Handbook Exp Pharmacol. 1997; 130: 21-42
26. Lang E, Novak P, Reeh P. Chemosensitivity of fine afferents from rat skin in vitro. J Neurophys 1990; 63: 887-901
27. Stanfa LC, Dickenson AH, Xu X-J, et al. Cholecystokinin and morphine analgesia: variations on a theme. Trends Pharmacol Sci 1994; 15: 65-6
28. Baber NS, Dourish CT, Hill DR. The role of CCK caerulein, and CCK antagonists in nociception. Pain 1989; 39 (3): 307-28
29. Headley PM, Grillner S. Excitatory amino acids and synaptic transmission: the evidence for a physiological function. Trends Pharmacol Sci 1990; 11 (5): 205-11
30. Kangrga I, Randic M. Outflow of endogenous aspartate and glutamate from the rat spinal dorsal horn in vitro by activation of low- and high-threshold primary afferent fibers: modulation by mu-opioids. Brain Res 1991; 553 (2): 347-52
31. Dickenson AH. Spinal cord pharmacology of pain. Br J Anaesth 1995; 75 (2): 193-200
32. Rogawski MA. Therapeutic potential of excitatory amino acid antagonists: channel blockers and 2,3-benzodiazepines. Trends Pharmacol Sci 1993; 14 (9): 325-31
33. De Kock M, Lavand'homme P, Waterloos H. 'Balanced analgesia' in the perioperative period: is there a place for ketamine? Pain 2001; 92 (3): 373-80
34. Monconduit L, Bourgeais L, Bernard JF, et al. Ventromedial thalamic neurons convey nociceptive signals from the whole body surface to the dorsolateral neocortex. J Neurosci 1999; 19 (20): 9063-72
35. Yoshimura M, Furue H. Mechanisms for the anti-nociceptive actions of the descending noradrenergic and serotonergic systems in the spinal cord. J Pharmacol Sci 2006; 101 (2): 107-17
36. Jones SL. Descending noradrenergic influences on pain. Prog Brain Res 1991; 88: 381-94
37. Li P, Zhuo M. Cholinergic, noradrenergic, and serotonergic inhibition of fast synaptic transmission in spinal lumbar dorsal horn of rat. Brain Res Bull 2001; 54: 639-47
38. Segal IS, Jarvis DJ, Duncan SR, et al. Clinical efficacy of oral-transdermal clonidine combinations during the perioperative period. Anesthesiology 1991; 74 (2): 220-5
39. Kehlet H, Dahl JB. The value of 'multimodal' or 'balanced analgesia' in postoperative pain treatment. Anesth Analg 1993; 77: 1048-56
40. Kehlet HH, Holte K. Effect of postoperative analgesia on surgical outcome. Br J Anaesth 2001; 87 (1): 62-72
41. Kehlet H. Effect of postoperative pain treatment on outcome-current status and future strategies. Langenbecks Arch Surg 2004; 389: 244-9
42. Werner MU, Soholm L, Rotboll-Nielsen P, et al. Does an acute pain service improve postoperative outcome? Anesth Analg Nov 2002; 95 (5): 1361-72
43. Spaulding TC, Fielding S, Venafro JJ, et al. Antinociceptive activity of clonidine and its potentiation of morphine analgesia. Eur J Pharmacol 1979; 58 (1): 19-25
44. Altman RD. A rationale for combining acetaminophen and NSAIDs for mild-to-moderate pain. Clin Exper Rheumatol 2004; 22 (1): 110-7
45. Ng A, Smith G, Davidson AC. Analgesic effects of parecoxib following total abdominal hysterectomy. Br J Anaesth 2003; 90 (6): 746-9
46. Manzo S, Takao K, Takehiko K, et al. Determining the plasma concentration of ketamine that enhances epidural bupivacaine and morphine induced analgesia. Anesth Analg 2005; 101 (3): 777-84
47. Chia YY, Liu K, Liu YC, et al. Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic consumption. Anesth Analg 1998; 86 (6): 1245-9
48. Lavand'homme P, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. Anesthesiology Oct 2005; 103 (4): 813-20
49. Bjordal JM, Johnson MI, Ljunggreen AE. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption: a meta-analysis with assessment of optimal treatment parameters for postoperative pain. Eur J Pain 2003; 7 (2): 181-8
50. Fassoulaki A, Triga A, Melemeni A. Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. Anesth Analg 2005; 101 (5): 1427-32
51. Bisgaaard T, Klarskov B, Kehlet H, et al. Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomised double-blind placebo-controlled trial. Ann Surg 2003 Nov; 238 (5): 651-60
52. Schumann R, Shikora S, Weiss JM, et al. A comparison of multimodal perioperative analgesia to epidural pain management after gastric bypass surgery. Anesth Analg 2003 Feb; 96 (2): 469-74

53. Wu CL, Naqibuddin M, Rowlingson AJ, et al. The effect of pain on health-related quality of life in the immediate postoperative period. Anesth Analg 2003; 97 (4): 1078-85
54. Fortier J, Chung F, Su J. Unanticipated admission after ambulatory surgery: a prospective study. Can J Anaesth 1998 Jul; 45 (7): 612-9
55. Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA 2003; 290 (18): 2455-63
56. Kaneko M, Saito Y, Kirihara Y, at al. Synergistic antinociceptive interaction after epidural coadministration of morphine and lidocaine in rats. Anesthesiology 1994; 80: 137-50
57. Förster JG, Rosenberg PH. Small dose of clonidine mixed with low-dose ropivacaine and fentanyl for epidural analgesia after total knee arthroplasty. Br J Anaesth 2004; 93: 670-7
58. Renghi A, Gramaglia L, Ciarlo M, et al. Fast track in abdominal aortic surgery. Minerva Anestesiol 2001; 67 (6): 441-6
59. Peyton PJ, Myles PS, Silbert BS, et al. Perioperative epidural analgesia and outcome after major abdominal surgery in high-risk patients. Anesth Analg 2003; 96 (2): 548
60. De Leon-Casasola OA. When it comes to outcome, we need to define what a perioperative epidural technique is. Anesth Analg 2003 Feb; 96 (2): 315-18
61. Singelyn F, Gouverneur J. Postoperative analgesia after total hip arthroplasty: a prospective evaluation by our acute pain service in more than 1300 patients. J Clin Anesth 1999; 11: 550-4
62. Likar R, Sittl R, Gragger K, et al. Peripheral morphine analgesia in dental surgery. Pain 1998; 76 (1-2): 145-50
63. Likar R, Koppert W, Blatnig H, et al. Efficacy of peripheral morphine analgesia in inflamed, non-inflamed and perineural tissue of dental surgery patients. J Pain Symptom Manage 2001; 21 (4): 330-7
64. Eriksson H, Tenhunen A, Korttila K. Balanced analgesia improves recovery and outcome after outpatient tubal ligation. Acta Anaesthes Scand 1996; 40 (2): 151-5
65. Bisgaard T, Klarskov B, Kristiansen VB, et al. Multi-regional local anesthetic infiltration during laparoscopic cholecystectomy in patients receiving prophylactic multi-modal analgesia: a randomized, double-blinded, placebo-controlled study. Anesth Analg 1999; 89 (4): 1017-24
66. Gwirtz KH, Young JV, Byers RS, et al. The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain: seven years' experience with 5969 surgical patients at Indiana University Hospital. Anesth Analg 1999; 88 (3): 599-604
67. Hartrick CTM, Martin GM, Kantor GM, et al. Evaluation of a single dose extended release epidural morphine formulation for pain relief after knee arthroplasty. J Bone Joint Surg 2006; 88 (2): 273-81
68. Gambling D, Hughes T, Martin G, et al. A comparison of Depodur, a novel, single dose extended-release epidural morphine, with standard epidural morphine for pain relief after lower abdominal surgery. Anesth Analg 2005; 100: 1065-74
69. Carvalho B, Riley E, Cohen SE. Single-dose, sustained-release epidural morphine in the management of postoperative pain after elective cesarean delivery: results of a multicenter randomized controlled study. Anesth Analg 2005; 100: 1150-8
70. Kehlet H, Werner MU. Role of paracetamol in acute pain management [in French]. Drugs 2003; 63 Spec No. 2: 15-21
71. Cobby TF, Crighton IM, Kyriakides K. Rectal paracetamol has a significant morphine-sparing effect after hysterectomy. Br J Anaesth 1999 Aug; 83 (2): 253-6
72. Sinatra RS, Jahr JS, Reynolds LW, et al. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. Anesthesiology 2005; 102 (4): 822-31
73. Edwards JE, McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. J Pain Symptom Manage 2002; 23 (2): 121-30
74. Zhou TJ, Tang J, White PF. Propacetamol versus ketorolac for treatment of acute postoperative pain after total hip or knee replacement. Anesth Analg 2001; 92 (6): 1569-75
75. Alexander R, El-Moalem HE, Gan TJ. Comparison of the morphine-sparing effects of diclofenac sodium and ketorolac tromethamine after major orthopedic surgery. J Clin Anesth 2002; 14 (3): 187-92
76. Van Dyke T, Litkowski LJ, Kiersch TA, et al. Combination oxycodone 5 mg/ibuprofen 400mg for the treatment of postoperative pain: a double-blind, placebo- and active-controlled parallel-group study. Clin Therap 2004; 26 (12): 2003-14
77. Pickering AE, Bridge HS, Nolan J, et al. Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children. Br J Anaesth 2002; 88 (1): 72-7
78. Reinhart D. Minimising the adverse effects of ketorolac. Drug Saf 2000; 22: 487-97
79. Gan TJ, Joshi GP, Zhao SZ, et al. Presurgical intravenous parecoxib sodium and follow-up oral valdecoxib for pain management after laparoscopic cholecystectomy surgery reduces opioid requirements and opioid-related adverse effects. Acta Anaesthes Scand 2004; 48 (9): 1194-207
80. Mehlisch DR, Desjardins PJ, Daniels S, et al. The analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain. J Am Dental Assoc 2004; 135 (11): 1578-90
81. Daniels S, Kuss M, Mehlisch D, et al. Pharmacokinetic and efficacy evaluation of intravenous parecoxib in postsurgical dental pain. Clin Pharmacol Ther 2000; 67: 1-8
82. Tang J, Li S, White PF, et al. Effect of parecoxib, a novel intravenous cyclooxygenase type-2 inhibitor, on the postoperative opioid requirement and quality of pain control. Anesthesiology 2002 Jun; 96 (6): 1305-9
83. Rasmussen GL, Steckner K, Hogue C, et al. Intravenous parecoxib sodium for acute pain after orthopedic knee surgery. Am J Orthop 2002 Jun; 31 (6): 336-43
84. Barton SF, Langeland FF, Snabes MC, et al. Efficacy and safety of intravenous parecoxib sodium in relieving postoperative pain following gynecologic laparotomy surgery. Anesthesiology 2002; 97: 306-14
85. Bikhazi GB, Snabes MC, Bajwa ZH, et al. A clinical trial demonstrates the analgesic activity of intravenous parecoxib sodium compared with ketorolac or morphine after gynecologic surgery with laparotomy. Am J Obstet Gynecol 2004; 191 (4): 1183-91
86. Ott E, Nussmeier NA, Duke PC, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. J Thoracic Cardiovasc Surg 2003; 125 (6): 1481-92
87. Bresalier R, Reicin A, Woodcock J. The APPROVe study: what we should learn from VIOXX withdrawal. Curr Hypertens Rep 2005; 7: 41-3
88. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis: VIGOR Study Group. N Engl J Med 2000; 343 (21): 1520-8

89. Schmedtje JF, Ji YS, Liu WL, et al. Hypoxia induces cyclooxygenase-2 via the NF-kappaB p65 transcription factor in human vascular endothelial cells. J Biol Chem 1997; 272 (1): 601-8
90. Clark DWJ, Layton D, Shakir SAW. Do some inhibitors of COX-2 increase the risk of thromboembolic events? Linking pharmacology with pharmacoepidemiology. Drug Saf 2004; 27: 427-56
91. Kasliwal R, Layton D, Harris S. A comparison of reported gastrointestinal and thromboembolic events between rofecoxib and celecoxib using observational data. Drug Saf 2005; 28 (9): 803-16
92. Layton D, Wilton LV, Shakir SA. Safety profile of celecoxib as used in general practice in England: results of a prescription-event monitoring study. Eur J Clinical Pharmacol 2004 Sept; 60 (7): 489-501
93. Ferreira SH, Lorenzetti BB, Correa FM. Central and peripheral antialgesic action of aspirin-like drugs. Eur J Pharmacol 1978; 53 (1): 39-48
94. Romsing J, Moiniche S, Ostergaard D, et al. Local infiltration with NSAIDs for postoperative analgesia: evidence for a peripheral analgesic action. Acta Anaesthesiol Scand 2000; 44 (6): 672-83
95. Raffa RB, Friderichs E, Reimann W. Opioid and non-opioids components independently contribute to the mechanisms of action of tramadol: an atypical opioid analgesic. J Pharmacol Exp Ther 1992; 260: 275-85
96. Horishita T, Minami K, Uezono Y, et al. The tramadol metabolite, O-desmethyl tramadol. Pharmacology 2006; 77 (2): 93-9
97. Wilder-Smith CH, Bettiga A. The analgesic tramadol has minimal effect on gastrointestinal motor function. Br J Clin Pharmacol 1997; 43: 71-5
98. Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. Pain 1997; 69 (3): 287-94
99. McQuay H, Edwards J. Meta-analysis of single dose oral tramadol plus acetaminophen in acute postoperative pain. Eur J Anaesthesiol 2003; 28 Suppl.: 19-22
100. Smith AB, Ravikumar TS, Kamin M, et al. Combination tramadol plus acetaminophen for postsurgical pain. Am J Surg 2004; 187 (4): 521-7
101. Snijdelaar DG, Cornelisse HB, Schmid RL, et al. A randomised, controlled study of peri-operative low dose s(+)-ketamine in combination with postoperative patient-controlled s(+)-ketamine and morphine after radical prostatectomy. Anaesthesia 2004; 59 (3): 222-8
102. Reeves M, Lindholm DE, Myles PS. Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery. Anesth Analg 2001; 93: 116-20
103. Menigaux C, Guignard B, Fletcher D, et al. Intraoperative small-dose ketamine enhances analgesia after outpatient knee arthroscopy. Anesth Analg 2001; 93 (3): 606-12
104. Kwok RF, Lim J, Chan MT, et al. Preoperative ketamine improves postoperative analgesia after gynecologic laparoscopic surgery. Anesth Analg 2004; 98 (4): 1044-9
105. Kararmaz A, Kaya S, Karaman H, et al. Intraoperative intravenous ketamine in combination with epidural analgesia: postoperative analgesia after renal surgery. Anesth Analg 2003; 97 (4): 1092-6
106. Aida S, Yamakura T, Baba H, et al. Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: a randomized double-blind study. Anesthesiology 2000; 92 (6): 1624-30
107. Urban L, Thompson SW, Dray A. Modulation of spinal excitability: co-operation between neurokinin and excitatory amino acid neurotransmitters. Trends Neurosci 1994 Oct; 17 (10): 432-8
108. Weinbroum AA. A single small dose postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistance pain. Anesth Analg 2003; 96: 789-95
109. Adam F, Chauvin M, Manoir BD, et al. Small dose ketamine infusion improves postoperative analgesia and rehabilitation after knee arthroplasty. Anesth Analg 2005; 100: 475-80
110. Argiriadou H, Himmelseher S, Papagiannopoulou P. Improvement of pain treatment after major abdominal surgery by intravenous S+ ketamine. Anesth Analg 2004 May; 98 (5): 1413-8
111. Subramaniam B, Subramaniam K, Pawar DK. Preoperative epidural ketamine in combination with morphine does not have a clinically relevant intra- and postoperative opioid-sparing effect. Anesth Analg 2001 Nov; 93 (5): 1321-6
112. Tan PH, Kuo MC, Kao PF, et al. Patient controlled epidural analgesia with morphine or morphine plus ketamine for postoperative pain relief. Eur J Anaesthesiol 1999; 16 (12): 820-5
113. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg 2004; 99 (2): 482-95
114. Wong CS, Liaw WJ, Tung CS, et al. Ketamine potentiates analgesic effect of morphine in postoperative epidural pain control. Region Anesth 1996; 21 (6): 534-41
115. Azevedo VM, Lauretti GR, Pereira NL, et al. Transdermal ketamine as an adjuvant for postoperative analgesia after abdominal gynecological surgery using lidocaine epidural blockade. Anesth Analg 2000; 91 (6): 1479-82
116. Taura P, Fuster J, Blasi A, et al. Postoperative pain relief after hepatic resection in cirrhotic patients: the efficacy of a single small dose of ketamine plus morphine epidurally. Anesth Analg 2003 Feb; 96 (2): 475-80
117. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. Drugs 2000; 59 (2): 263-8
118. Sites BD, Beach M, Biggs R. Intrathecal clonidine added to a bupivacaine-morphine spinal anesthetic improves postoperative analgesia for total knee arthroplasty. Anesth Analg 2003; 96: 1083-8
119. Paech MJ, Pavy TJ, Orlikowski CE, et al. Postoperative epidural infusion: a randomized, double-blind, dose-finding trial of clonidine in combination with bupivacaine and fentanyl. Anesth Analg 1997; 84 (6): 1323-8
120. Eisenach JC, Detweller D, Hood D. Hemodynamic and analgesic actions of epidurally administered clonidine. Anesthesiology 1993; 78 (2): 277-87
121. Szumita PM, Baroletti SA, Anger KE. Sedation and analgesia in the intensive care unit: evaluating the role of dexmedetomidine. Am J Health Syst Pharm 2007 Jan 1; 64 (1): 37-44
122. Gurbet A, Basaqan-Moqol E, Turker G. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anaesth 2006 July; 53 (7): 646-52
123. Wahlander S, Frumento RJ, Wagener G. A prospective, double-blind, randomized, placebo-controlled study of dexmedetomidine as an adjunct to epidural analgesia after thoracic surgery. J Cardiothorac Vasc Anesth 2005 Oct; 19 (5): 630-5
124. Yeager MP, Glass DD, Neff RK, et al. Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 1987; 66 (6): 729-36

 

125. Tuman KJ, McCarthy RJ, March RJ, et al. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Analg 1991; 73 (6): 696-704
126. Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000; 321 (7275): 1493
127. Fillinger MP, Yeager MP, Dodds TM, et al. Epidural anesthesia and analgesia: effects on recovery from cardiac surgery. J Cardiothor Vasc Anesth 2002; 16 (1): 15-20
128. Beattie W, Badner N, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. Anesth Analg 2001; 93: 853-8
129. Ballantyne JC, Carr DB, deFerranti S, et al. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. Anesth Analg 1998; 86 (3): 598-612
130. Rigg JA, Jamrozik K, Myles PS. Epidural anesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet 2002; 359: 1276-82
131. Choi PT, Bhandari M, Scott J. Epidural analgesia for pain relief following hip or knee replacement. Cochrane Database Syst Rev 2003; (3): CD003071
132. Nishimori M, Ballantyne JC, Low JHS. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database Syst Rev 2006; (3): CD005059
133. Park WY, Thompson JS, Lee KK. Effect of Epidural anesthesia and analgesia on perioperative outcome: a randomised, controlled Veterans Affairs cooperative study. Ann Surg 2001; 234: 560-71
134. Werawatganon T, Charuluxanun S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. Cochrane Database Syst Rev 2004; (3): CD004088
135. Jorgensen H, Wetterslev J, Moiniche S, et al. Epidural local anesthetics versus opioid based regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev 2001; (1): CD001883
136. Lonnqvist PA. Adjuncts to caudal block in children: quo vadis. Br J Anaesth 2005; 95 (4): 431-3
137. Rosenberg AG. Anesthesia and analgesia protocols for total knee arthroplasty. Am J Orthop 2006 Jul; 35 (7 Suppl.): 23-6
138. Lee A, Simpson D, Whitfield A, et al. Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. Br J Anaesth 1988; 60 (7): 845-50
139. Ready L. Acute pain: lessons learned from 25000 patients. Reg Anesth Pain Med 1999; 24: 499-505
140. Moiniche S, Mikkelsen S, Wetterslev J, et al. A qualitative systematic review of incisional local anaesthesia for postoperative pain relief after abdominal operations. Br J Anaesth 1998; 81 (3): 377-83
141. Tverskoy M, Oren M, Dashkovsky I, et al. Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: a study in postoperative patients. Neurosci Lett 1996; 215: 5-8
142. Dauri M, Polzoni M, Fabbi E, et al. Comparison of epidural, continuous femoral block and intraarticular analgesia after anterior cruciate ligament reconstruction. Acta Anaesthesiol Scand 2003; 47 (1): 20-5
143. Dal D, Tetik O, Altunkaya H, et al. The efficacy of intra-articular ketamine for postoperative analgesia in outpatient arthroscopic surgery. Arthroscopy 2004; 20 (3): 300-5
144. Calmet J, Esteve C, Boada S, et al. Analgesic effect of intra-articular ketorolac in knee arthroscopy: comparison of morphine and bupivacaine. Knee Surg Sports Traumatol Arthrosc 2004 Nov; 12 (6): 552-5
145. Reuben SS, Connelly NR. Postoperative analgesia for outpatient arthroscopic knee surgery with intraarticular bupivacaine and ketorolac. Anesth Analg 1995; 80 (6): 1154-7
146. Moiniche S, Mikkelsen S, Wetterslev J, et al. A systematic review of intra-articular local anesthesia for postoperative pain relief after arthroscopic knee surgery. Reg Anesth Pain Med 1999; 24 (5): 430-7
147. Stein C, Yassouridis A. Peripheral morphine analgesia. Pain 1997; 71: 119-21
148. Stein C. Opioid receptors on peripheral sensory neurons. Adv Exp Med Biol 2003; 521: 69-76
149. Gupta A, Bodin L, Holmstrom B, et al. A systematic review of the peripheral analgesic effects of intraarticular morphine. Anesth Analg 2001; 93 (3): 761-70
150. Reuben SS, Connelly NR. Postarthroscopic meniscus repair analgesia with intraarticular ketorolac or morphine. Anesth Analg 1996; 82 (5): 1036-9
151. Gupta A, Axelsson K, Allvin R, et al. Postoperative pain following knee arthroscopy: the effects of intra-articular ketorolac and/or morphine. Reg Anesth Pain Med 1999; 24 (3): 225-30
152. Yang LC, Chen LM, Wang CJ. Postoperative analgesia by intra-articular neostigmine in patients undergoing knee arthroscopy. Anesthesiology 1998; 88: 334-9
153. Lauretti GR, de Oliveira R, Perez MV. Postoperative analgesia by intra-articular and epidural neostigmine following knee surgery. J Clin Anesth 2000; 12: 444-8
154. Gentili M, Juhel A, Bonnet F. Peripheral analgesic effect of intra-articular clonidine. Pain 1996; 64 (3): 593-6
155. White PF, Issioui T, Skrivanek GD, et al. The use of a continuous popliteal sciatic nerve block after surgery involving the foot and ankle: does it improve the quality of recovery? Anesth Analg 2003; 97 (5): 1303-9
156. Buckenmaier CC, Klein SM, Nielsen KC, et al. Continuous paravertebral catheter and outpatient infusion for breast surgery [published erratum appears in Anesth Analg 2004 Jan; 98 (1): 101]. Anesth Analg 2003; 97 (3): 715-7
157. Chelly JE, Greger J, Gebhard R, et al. Continuous femoral blocks improve recovery and outcome of patients undergoing total knee arthroplasty. J Arthro 2001; 16 (4): 436-45
158. Singelyn FJ, Aye F, Gouverneur JM. Continuous popliteal sciatic nerve block: an original technique to provide postoperative analgesia after foot surgery. Anesth Analg 1997; 84 (2): 383-6
159. Chelly JE, Greger J, Al Samsam T, et al. Reduction of operating and recovery room times and overnight hospital stays with interscalene blocks as sole anesthetic technique for rotator cuff surgery. Minerva Anestesiol 2001; 67 (9): 613-9
160. Richman JM, Liu SS, Courpas G. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. Anesth Analg 2006; 102: 248-57
161. Murphy DB, McCartney CJ, Chan VW. Novel analgesic adjuncts for brachial plexus block: a systematic review. Anesth Analg 2000; 90 (5): 1122-8
162. Picard PR, Tramer MR, McQuay HJ, et al. Analgesic efficacy of peripheral opioids (all except intra-articular): a qualitative systematic review of randomised controlled trials. Pain 1997; 72 (3): 309-18
163. Candido KD, Franco CD, Khan MA. Buprenorphine added to the local anesthetic for brachial plexus block to provide post-

 

operative analgesia in outpatients. Reg Anesth Pain Med 2001; 26 (4): 352-6

164. Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature Biotech 2001; 413: 203-10
165. Perkins FM, H K. Chronic pain as an outcome of surgery: a review of predictive factors. Anesthesiology 2000; 93: 1123-33
166. Macrae WA. Chronic pain after surgery. Br J Anaesth 2001; 87: 88-98
167. Wu CT, Yeh CC, Yu JC, et al. Pre-incisional epidural ketamine, morphine and bupivacaine combined with epidural and general anaesthesia provides pre-emptive analgesia for upper abdominal surgery. Acta Anaesthesiol Scand 2000 Jan; 44 (1): 63-8
168. Weinbroum AA, Lalayev G, Yashar T, et al. Combined pre-incisional oral dextromethorphan and epidural lidocaine for postoperative pain reduction and morphine sparing: a randomised double-blind study on day-surgery patients. Anaesthesia 2001 Jul; 56 (7): 616-22
169. Ke RWM, Portera SGM, Bagous WM, et al. A randomized, double-blinded trial of preemptive analgesia in laparoscopy. Obstet Gynecol 1998 Dec; 92 (6): 972-5
170. Papaziogas B, Argiriadou H, Papagiannopoulou P, et al. Preincisional intravenous low dose ketamine and local infiltration with ropivacaine reduces postoperative pain after laparoscopic cholecystectomy. Surg Endosc 2001 Sep; 15 (9): 1030-3
171. Ong KS, Seymour RA. Evidence based medicine approach to pre-emptive analgesia. Am J Pain Manage 2003; 13 (4): 158-72
172. Katz J, Schmid R, Snijdelaar DG. Pre-emptive analgesia using intravenous fentanyl plus low dose ketamine for radical prostatectomy under general anesthesia does not produce short term or longterm reductions in pain or analgesic use. Pain 2004; 110 (3): 707-18
173. Katz J, McCartney CJ. Current status of pre-emptive analgesia. Curr Opinion Anesthesiol 2004; 15 (4): 435-41
174. Salonen A, Kokki H, Tuovinen K. I.V. ketoprofen for analgesia after tonsillectomy: comparison of pre- and post-operative administration. Br J Anaesth 2001 Mar; 86 (3): 377-81
175. Kilickan L, Toker K. The effect of pre-emptive intravenous morphine on postoperative analgesia and surgical stress response. Panminerva Med 2001; 43: 171-5
176. Ong KSD, Seymour RAD, Yeo JFD, et al. The efficacy of preoperative versus postoperative rofecoxib for preventing acute postoperative dental pain: a prospective randomized crossover study using bilateral symmetrical oral surgery. Clin J Pain 2005; 21 (6): 536-42
177. Reuben SS, Vieira P, Faruqi S, et al. Local administration of morphine for analgesia after iliac bone graft harvest. Anesthesiology 2001; 95 (2): 390-4
178. Nguyen A, Girard F, Boudreault D. Scalp nerve blocks decrease the severity of pain after craniotomy. Anesth Analg 2001; 93: 1272-6
179. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of pre-emptive analgesia for postoperative pain: the role of timing of analgesia. Anesthesiology 2002; 96: 725-41
180. Richards JT, Read JR, Chambers WA. Epidural anaesthesia as a method of pre-emptive analgesia for abdominal hysterectomy. Anaesthesia 1998; 53: 296-8
181. Dahl V, Raeder JC, Erno PE, et al. Pre-emptive effect of pre-incisional versus post-incisional infiltration of local anaesthesia on children undergoing hernioplasty. Acta Anaesthesiol Scand 1996 Aug; 40 (7): 847-51
182. Updike GM, Manolitsas TP, Cohn DE, et al. Pre-emptive analgesia in gynecologic surgical procedures: preoperative wound infiltration with ropivacaine in patients who undergo laparotomy through a midline vertical incision. Am J Obstet Gynecol 2003 Apr; 188 (4): 901-5
183. Yaksh T, Reddy S. Studies in the primate on the analgesic effect associated with intrathecal actions of opiates, alpha-adrenergic agonists and baclofen. Anesthesiology 1981; 54: 451-67
184. Gee NS, Brown JP, Dissanyake VU. The novel anticonvulsant drug, gabapentin binds to the alpha 2 delta subunit of a calcium channel. J Biol Chem 1996; 271: 5768-76
185. Dahl JB, Mathiesen O, Moiniche S. Protective premedication: an option with gabapentin and related drugs? Acta Anaesthes Scand 2004; 48 (9): 1130-5
186. Turan A, Kaya G, Karamanlioglu B, et al. Effect of oral gabapentin on postoperative epidural analgesia. Br J Anaesth 2006 Feb; 96 (2): 242-6
187. Pandey CK, Priye S, Singh S. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. Can J Anaesth 2004; 51: 358-63
188. Turan A, Karamanlioglu B, Memis D. The analgesic effects of gabapentin after total abdominal hysterectomy. Anesth Analg 2004; 98 (5): 1370-3
189. Rorarius MG, Mennander S, Souminen P. Gabapentin for the prevention of postoperative pain after vaginal hysterectomy. Pain 2004; 110: 175-81
190. Turan A, Karamanlioglu B, Memis D. Analgesic effects of gabapentin after spinal surgery. Anesthesiology 2004; 100: 935-8
191. Turan A, Memis D, Karamanlioglu B. The analgesic effects of gabapentin in monitored anesthesia care for ear-nose-throat surgery. Anesth Analg 2004; 99: 375-8
192. Dirks J, Fredensborg BB, Christensen D, et al. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology 2002; 97 (3): 560-4
193. Dierking G, Duedahl TH, Rasmussen ML, et al. Effects of gabapentin on postoperative morphine consumption and pain after abdominal hysterectomy: a randomized, double-blind trial. Acta Anaesthes Scand 2004; 48 (3): 322-7
194. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain: a systematic review of randomised controlled trials. Pain 2006 Dec; 126 (1-3): 91-101
195. Gilron I, Orr E, Tu D, et al. A placebo controlled randomised clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked after abdominal hysterectomy. Pain 2005; 113 (1-2): 191-200
196. Reuben SS, Buvanendran A, Kroin JS, et al. The analgesic efficacy of celecoxib, pregabalin and their combination for spinal fusion surgery. Anesth Analg 2006 Nov; 103 (5): 1271-7
197. Fassoulaki A, Patris K, Sarantopoulos C, et al. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 2002; 95 (4): 985-91
198. Schimmer BP, Parker KL. Adrenocorticotrophic hormone: inhibitors of the synthesis and actions of adrenocortical hormones. In: Goodman and Gilman's the pharmacological basis of therapeutics. New York: McGraw Publishing, 1996: 1459-81

 

199. Svensson CI, Yaksh TL. The spinal phospholipase-cyclooxygenase-prostanoid cascade in nociceptive processing. Annu Rev Pharmacol Toxicol 2002; 42: 553-83
200. Steward DL, Welge JA, Myer CM. Steroids for improving recovery following tonsillectomy in children. Cochrane Database Sys Rev 2003; (1): CD003997
201. Skjelbred P, Lokken P. Reduction of pain and swelling by a corticosteroid injected 3 hours after surgery. Euro J Clin Pharmacol 1982; 23 (2): 141-6
202. Bisgaard T, Klarskov B, Kehlet H, et al. Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial. Ann Surg 2003; 238 (5): 651-60
203. Romundstad L, Breivik H, Niemi G, et al. Methylprednisolone intravenously 1 day after surgery has sustained analgesic and opioid-sparing effects. Acta Anaesthes Scand 2004; 48 (10): 1223-31
204. Schmidt BL, Gear RW, Levine JD. Response of neuropathic trigeminal pain to the combination of low-dose nalbuphine plus naloxone in humans. Neurosci Lett 2003; 343 (2): 144-6
205. Liu KS, Hu OY, Ho ST, et al. Antinociceptive effect of a novel long-acting nalbuphine preparation. Br J Anaesth 2004; 92 (5): 712-5
206. Shen KF, Crain SM. Ultra-low doses of naltrexone or etorphine increase morphine's antinociceptive potency and attenuate tolerance/dependence in mice. Brain Res 1997; 757 (2): 176-90
207. Crain SM, Shen KF. Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability. Pain 2000; 84 (2-3): 121-31
208. Gan TJ, Ginsberg B, Glass PS, et al. Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. Anesthesiology 1997; 87 (5): 1075-81
209. Mehlisch DR. The combination of low dose of naloxone and morphine in patient-controlled (PCA) does not decrease opioid requirements in the postoperative period. Pain 2003; 101 (1-2): 209-11
210. Joshi GP, Duffy L, Chehade J, et al. Effects of prophylactic nalmefene on the incidence of morphine-related side effects in patients receiving intravenous patient-controlled analgesia. Anesthesiology 1999; 90 (4): 1007-11
211. Cepeda MS, Alvarez H, Morales O, et al. Addition of ultralow dose naloxone to postoperative morphine PCA: unchanged analgesia and opioid requirement but decreased incidence of opioid side effects. Pain 2004; 107 (1-2): 41-6
212. Bhatia A, Kashyap L, Pawar DK, et al. Effect of intraoperative magnesium infusion on perioperative analgesia in open cholecystectomy. J Clin Anesth 2004; 16 (4): 262-5
213. Tramer MR, Schneider J, Marti RA, et al. Role of magnesium sulfate in postoperative analgesia. Anesthesiology 1996; 84 (2): 340-7
214. McCartney CJ, Sinha A, Katz J. A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesth Analg 2004; 98 (5): 1385-400
215. Comer AM, Lamb HM. Lidocaine patch 5%. Drugs 2000; 59 (2): 245-9
216. Gammaitoni AR, Alvarez NA, Galer BS. Safety and tolerability of the lidocaine patch 5%, a targeted peripheral analgesic: a review of the literature. J Clin Pharmacol 2003; 43 (2): 111-7
217. Chelly J. An iontophoretic, fentanyl HCL patient controlled transdermal system for acute postoperative pain management. Expert Opin Pharmocother 2005; 6 (7): 1205-14
218. Chelly JE, Grass J, Houseman TW, et al. The safety and efficacy of a fentanyl patient-controlled transdermal system for acute postoperative analgesia: a multicenter, placebo-controlled trial. Anesth Analg 2004; 98 (2): 427-33
219. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273 (5): 408-12
220. Carroll D, Tramer M, McQuay H, et al. Randomisation is important in studies with pain outcome: systematic review of TENS in acute postoperative pain. Br J Anaesth 1996; 77: 798-803
221. Hamza M, White P, Hesham H, et al. Effect of the frequency of transcutaneous electrical stimulation on the postoperative analgesic requirement and recovery profile. Anesthesiology 1999; 91: 1232-8
222. McQuay HJ, Moore RA. Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review. Health Technol Assess 1998; 2 (12): 1-236
223. Linton SJ. Applied relaxation as a method of coping with chronic pain: a therapists guide. Scand J Behav Ther 1982; 11: 161-74
224. Seers K, Carroll D. Relaxation techniques for acute pain management: a systematic review. J Adv Nurs 1998; 27 (3): 466-75
225. Wang SM, Kulkarni L, Dolev J, et al. Music and preoperative anxiety: a randomized, controlled study. Anesth Analg 2002; 94 (6): 1489-94
226. Nilsson U, Rawal N, Unosson M. A comparison of intra-operative or postoperative exposure to music: a controlled trial of the effects on postoperative pain. Anaesthesia 2003; 58 (7): 699-703
227. Fernandez E, Turk DC. The utility of cognitive coping strategies for altering pain perception: a meta-analysis. Pain 1989; 38 (2): 123-35
228. Cepeda MS, Carr DB, Lau J. Music for pain relief. Cochrane Database Syst Rev 2006 Apr 19; (2): CD004843
229. Wang B, Tang J, White PF, et al. Effect of the intensity of transcutaneous acupoint electrical stimulation on the postoperative analgesic requirement. Anesth Analg 1997; 85 (2): 406-13
230. Ho CM, Hseu SS, Tsai SK, et al. Effect of P-6 acupressure on prevention of nausea and vomiting after epidural morphine for post-cesarean section pain relief. Acta Anaesthes Scand 1996; 40 (3): 372-5
231. Chernyak GV, Sessler DI. Perioperative acupuncture and related techniques. Anesthesiology 2005; 102 (5): 1031-49, quiz 1078
232. Cao X. Scientific bases of acupuncture analgesia. Acupuncture Electrother Res 2002; 27 (1): 1-14
233. Han JS. Acupuncture and endorphins. Neurosci Lett 2004; 361 (1-3): 258-61
234. Kotani N, Hashimoto H, Sato Y, et al. Preoperative intradermal acupuncture reduces postoperative pain, nausea and vomiting, analgesic requirement, and sympathoadrenal responses. Anesthesiology 2001; 95 (2): 349-56
235. Sim CK, Xu PC, Pua HL, et al. Effects of electroacupuncture on intraoperative and postoperative analgesic requirement. Acupuncture Med 2002; 20 (2-3): 56-65
236. Meurisse M, Defechereux T, Hamoir E, et al. Hypnosis with conscious sedation instead of general anaesthesia? Applications in cervical endocrine surgery. Acta Chir Belg 1999 Aug; 99 (4): 151-8

237. Faymonville ME, Fissette J, Mambourg PH. Hypnosis as adjunct therapy in conscious sedation for plastic surgery. Reg Anesth 1995 Mar; 20 (2): 145-51
238. Lang EV, Benotsch EG, Fick LJ, et al. Adjunctive non-pharmacological analgesia for invasive medical procedures: a randomised trial. Lancet 2000; 335 (9214): 1486-90
239. Schupp CJ, Berbaum K, Berbaum M, et al. Pain and anxiety during interventional radiologic procedures: effect of patients' state anxiety at baseline and modulation by nonpharmacologic analgesia adjuncts. J Vasc Interv Radiol 2005; 16 (12): 1585-92
240. Montgomery GH, David D, Winkel G, et al. The effectiveness of adjunctive hypnosis with surgical patients: a meta-analysis. Anesth Analg 2002; 94 (6): 1639-45
241. Montgomery GH, Weltz CR, Seltz M, et al. Brief presurgery hypnosis reduces distress and pain in excisional breast biopsy patients. Int J Clin Exp Hypnosis 2002; 50 (1): 17-32
242. Melzack R, Germain M, Belanger E, et al. Positive intrasurgical suggestion fails to affect postsurgical pain. J Pain Symptom Manage 1996; 11 (2): 103-7

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