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Useful adjuvants for postoperative pain management

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Adjuvants are compounds which by themselves have undesirable side-effects or low potency but in combination with opioids allow a reduction of narcotic dosing for postoperative pain control. Adjuvants are needed for postoperative pain management due to side-effects of opioid analgesics, which hinder recovery, especially in the increasingly utilized ambulatory surgical procedures. NMDA antagonists have psychomimetic side-effects at high doses, but at moderate doses do not cause stereotypic behavior but allow reduction in opioid dose to obtain better pain control. Alpha-2 adrenergic agonists cause sedation, hypotension and bradycardia at moderate doses, but at low doses can be opioid sparing especially in spinal administration. Gabapentin-like compounds have low potency against acute pain, but in combination with opioids allow a reduction in opioid dose with improved analgesia. Corticosteroids may have only a limited role as adjuvants while acetylcholine esterase inhibitors may have too many side-effects. Newer adjuvants will be needed to reduce opioid dose and concomitant side-effects, even more as same day surgeries become more routine.

Key words: adjuvants; opioids; NMDA antagonists; alpha-2 adrenergic agonists; anticonvulsants; corticosteroids; acetylcholine esterase inhibitors; postoperative pain.

INTRODUCTION

Surgical incision leads to cell disruption and subsequent intracellular release of phospholipids and a state of widespread inflammation depending on the degree of surgical

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trauma. Enzymatic action on phospholipids results in the release of prostanoids at the site of injury that sensitizes the nociceptors to mechanical stimuli (primary hyperalgesia) and also to several chemical mediators, such as prostanoids, bradykinin and nerve growth factor. The chemical mediators may be the cause of secondary hyperalgesia since continued peripheral sensitization leads to central pain sensitization.¹ The vast number of mediators being released during this perioperative period necessitates a multitude of pharmacological agents to treat postoperative pain, as opposed to the traditional belief that opioids were the only drugs needed (Figure 1).

Fear of uncontrolled postsurgical pain is a major concern of patients undergoing surgery. With the current trends of surgery moving towards minimally invasive procedures, anesthesiologists are challenged to utilize a wider armamentarium of pharmacological agents. As such, adjuvants to opioids are needed for postoperative pain management to reduce side effects, usually by lowering opioid dose, although some adjuvants may directly reduce side effects.² In addition, high doses of opioids are a safety concern primarily due to respiratory depression. In some patients, opioids may have a long duration of action, which hinders faster recovery thereby delaying discharge. Opioids also produce a high incidence of postoperative nausea and vomiting (PONV) which exacerbates the patient's discomfort and prevents early discharge from the hospital. There are reasons to believe that faster postoperative recovery allowing earlier rehabilitation will produce better outcomes in procedures such as total knee arthroplasty (TKA).

Another concern is the more recent documentation of hyperalgesia with very high opioid doses, a phenomenon seen in animals.³ In some patients, even short-term opioid use may lead to opioid-induced hyperalgesia.⁴ Although opioids are considered the gold standard for postoperative pain management, paradoxically they may also facilitate postoperative pain in humans following abdominal and orthopedic surgeries. Further, the larger the intraoperative opioid dose, the greater will be the postoperative

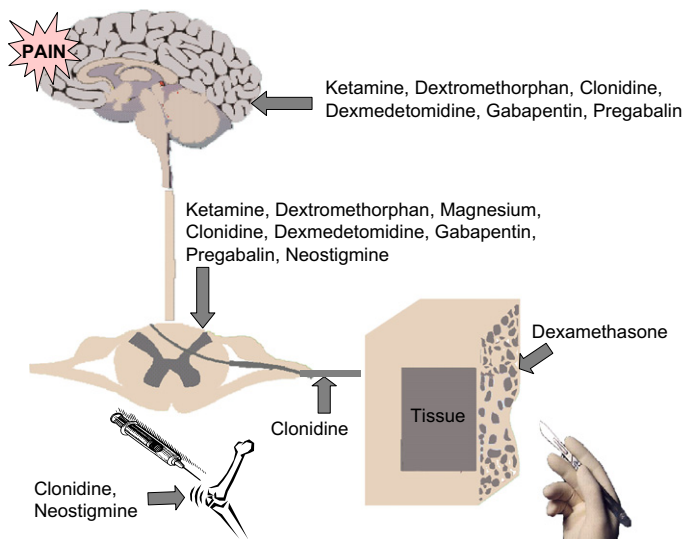


Figure 1. Anatomical sites where adjuvants can act to enhance opioid or local anesthetic activity to reduce postoperative pain.

opioid requirement.⁵ Therefore, short-term tolerance to an opioid may not be due to a decrease in its efficacy (pharmacological tolerance), but rather from an enhancement in pain sensitivity (opioid-induced hyperalgesia) leading to an apparent decrease in the effectiveness of morphine.⁴ Distinguishing between these two phenomena has significant implications for managing postoperative pain. If rapid escalation of opioids in the immediate postoperative period fails to provide beneficial effects, one must consider the possibility of opioid-induced hyperalgesia. If this is the case, a reduction in opioid therapy or switching to an alternative opioid (opioid rotation) may be more beneficial. Further, the use of adjuvant drugs may not only contribute to an opioid-sparing effect, but may potentially result in a reduction in opioid-induced hyperalgesia. Experimental studies suggest that opioids activate both NMDA⁶ and cyclooxygenase (COX)⁷ pronociceptive systems leading to hyperalgesia.

Adjuvants to local anesthetics are also needed, both for spinal analgesia and peripheral nerve block. Adjuvants can reduce side-effects, usually by lowering the local anesthetic dose. The primary concerns with local anesthetic dosing are cardiotoxicity and central nervous side-effects at high doses of local anesthetics.⁸ The concept of balanced or multimodal analgesia has evolved rapidly during recent years. A combination of several analgesic regimens also reduces the side effects of each agent when used alone. In this review, we focus on different classes of drugs that are commonly utilized as adjuvants for postoperative pain therapy via different routes of administration.

NMDA ANTAGONISTS

Since L-glutamate is the most important excitatory neurotransmitter in the central nervous system, blocking glutamate receptors offers an attractive method of reducing afferent stimulation of the spinal cord and therefore blocking pain transmission.⁹ In particular, many drugs or compounds that reduce central glutamate excitation are antagonists of the NMDA subtype of glutamate receptor. Magnesium ion was first identified as an inhibitor of NMDA receptors in the spinal cord.¹⁰ Subsequently, drugs already in wide use have been found to have their primary action by inhibiting this receptor. Although there are two other ion-gated glutamate receptor subtypes, the AMPA and kainite receptors, and G-protein coupled glutamate receptors, none of these pharmacological subtypes are represented by adjuvants in clinical use for pain. There are multiple binding sites for NMDA antagonists, and differences in pharmacological effect of each drug are attributed to differences in binding sites and receptor affinity.¹¹ The NMDA receptor requires binding at both glycine (NR1 subunit) and glutamate (NR2 subunit) binding sites for ion channel activation. A study using a foot incision model in mice has demonstrated that the NR2 ϵ 2 NMDA receptor subunit is involved in postoperative pain.¹² The primary reason for NMDA antagonists alone to be not useful as postoperative analgesics is that at efficacious doses they can produce side-effects in the brain, such as hallucinations.

Ketamine

Ketamine is a sedative/analgesic that is a non-competitive antagonist at the NMDA receptor. Since ketamine has been found to have a preventive role in animal neuropathic pain models¹³, it is possible that ketamine can preemptively reduce postoperative pain and supplemental opioid requirements. However, the results of preemptive studies in humans have been mixed. In one systemic review of 24 studies, ketamine was found to

have a significant immediate and preventive analgesic benefit in 58% of the studies (including both intravenous and neuroaxial administration).¹⁴ The doses ranged from 0.15 to 1 mg/kg, and the success of treatment in reducing postoperative pain did not depend on the type of surgery. The most likely mechanism is a reduction in NMDA receptor mediated central sensitization.¹⁵ Similar efficacy of reduced opioid consumption was concluded from a systemic review of 37 randomized trials of ketamine when utilized at small doses in the perioperative period.¹⁶ When ketamine was added to epidural opioids, there was improved analgesia in 5/8 clinical trials with no increase in psychotomimetic side effects.¹⁶ However, in another meta-analysis study of the efficacy of preemptive analgesia for acute postoperative pain, systemic NMDA antagonists, primarily intravenous ketamine, had poor efficacy.¹⁷ In that paper only 7 studies were included in the analysis as it was a comparison of preincisional versus postincisional clinical studies to determine the utility of administering pharmacological agents before surgery. In a recent database review, perioperative ketamine added to morphine reduced postoperative opioid consumption, postoperative nausea and vomiting (PONV), and pain intensity in 27 out of 37 trials.¹⁸ While the dose of ketamine varied over a 24 hour period, exceeding 30 mg/24 hours did not lead to additional analgesic benefit. Twenty-one of 37 trials stated that there were no psychotomimetic adverse effects such as hallucinations, bad dreams or dysphoria. A similar finding of decreased postoperative opioid consumption was noted in systemic review (included were children) of 53 randomized trials.¹⁹ It appears from multiple systemic review papers that intravenous ketamine decreases pain in the immediate (48 hours) postoperative period, although its long term benefit has not been clearly demonstrated. Clinical studies have demonstrated that intravenous ketamine can be useful as a supplement in postoperative epidural analgesia after thoracotomy, reducing postoperative pain over the days immediately after surgery and long-term.²⁰ Although there is no unanimity in the benefits of ketamine, in our clinical practice we use combinations of intravenous ketamine with propofol for several of the sedation anesthetic protocols. While the risk benefit ratio needs to be addressed when utilizing combination therapy, from the published literature and clinical practice, it is justifiable to use small doses of ketamine in the perioperative period, so that the opioid requirements can be reduced. Although there is only one clinical study demonstrating that administration of ketamine as an adjuvant can reduce chronic pain from surgery, more clinical studies are needed to address preventing analgesia after surgery.²¹

There is at present no preservative-free version of ketamine available in the United States. However, ketamine is used throughout the world as an epidural adjuvant to opioids or opioid/local anesthetic mixtures in the epidural space. Following major upper-abdominal surgery, an epidural ketamine/morphine combination compared to morphine alone reduced intraoperative morphine consumption and prolonged time for rescue analgesic, but there was no overall reduction in postoperative opioid consumption.²² As a single agent spinal ketamine would probably not be efficacious, since available intrathecal NMDA receptor antagonists did not reduce postoperative pain in rats with plantar foot incision.²³ Intrathecal ketamine for patients undergoing prostate surgery, at 0.7–0.95 mg/kg, can produce sensory and motor block for about 30–60 minutes, however it was associated with significant side effects.²⁴ A subsequent study using intrathecal ketamine for perioperative analgesia again showed adverse central side effects.²⁵

Although animal experiments have suggested an additional peripheral mechanism for ketamine analgesia, studies in humans did not indicate a local tissue effect.²⁶ The belief that NMDA receptors exist on the peripheral sensory axons has led investigations into

the use of ketamine intra-articularly. Ketamine at 0.5 mg/kg intra-articular has been shown to be analgesic for outpatient arthroscopic surgery²⁷ and did not result in any systemic side effects. Although clinical studies have been carried out to demonstrate the benefit of topical ketamine for neuropathic pain, no literature exists as to the efficacy of topical ketamine for postoperative pain.

The risk of psychomimetic adverse effects such as hallucinations is the main reason for many clinicians to be apprehensive in using ketamine. This is not a major concern for patients undergoing general anesthesia. Though the practice of regional anesthesia is at an increase, most patients receive benzodiazepines for premedication prior to the block, and therefore the risk of adverse events is minimal. But in patients receiving ketamine with benzodiazepines without general anesthesia, the incidence of hallucinations was 2.9%.²⁸ These issues need to be discussed with patients and should be observed carefully during the procedure. Other side effects associated with ketamine include hypertension, diplopia, nystagmus, dizziness, confusion, cardiac arrhythmias, nausea and vomiting.

Dextromethorphan

Dextromethorphan was FDA approved for over the counter sale as a cough suppressant in 1958. Following oral administration, it is rapidly absorbed from the gut and crosses the blood brain barrier. Dextromethorphan and its metabolite dextrorphan antagonize NMDA receptors in brain slices.²⁹ Although dextromethorphan is an open-channel blocker similar to ketamine, it produces fewer psychomimetic effects, probably due to its lower affinity for the NMDA receptor.³⁰ The anti-hyperalgesic effect of 0.5 mg/kg intravenous dextromethorphan has been demonstrated in volunteers following injection of the noxious stimulant capsaicin.³¹ Dextromethorphan has been reported to produce a modest reduction in postoperative opioid (meperidine) consumption when given intramuscularly prior to laparoscopic cholecystectomy.³² Given orally preincision and continued for 2 days following surgery for bone malignancy, dextromethorphan reduced patient controlled epidural analgesia (PCEA) (ropivacaine/fentanyl) requirements postoperatively by 30–50%.³³ However, a large oral dextromethorphan (200 mg every 8 h) dose given postoperatively after knee surgery only produced a moderate reduction in morphine requirements (29%) and no reduction in postoperative pain levels.³⁴ A systematic review (28 double-blind studies) of peri-operative dextromethorphan in postoperative pain concluded that the drug has the potential to be a safe adjunctive agent to opioid analgesia, but the results were inconsistent.³⁵ The route of administration may be important for the beneficial effect. Due to the controversial data, it is currently not recommended for routine use for postoperative pain.³⁵ Since the safety of this drug is well-established (oral product dispensed over the counter), further clinical studies need to be carried out to determine if administration of dextromethorphan can decrease the incidence of chronic pain syndromes from developing from surgery. Studies of this nature will need to take into consideration the dosage and duration of administration of the drug dextromethorphan.

Magnesium

Similar to ketamine and dextromethorphan, the magnesium ion, acts to block the NMDA channel. Magnesium sulfate is available as a 500 mg/ml preservative-free solution for injection. Perioperative intravenous magnesium sulfate at very high doses has

been reported to reduce postoperative morphine consumption but not postoperative pain scores.^{36,37} Both studies conclude that intravenous magnesium (3–3.5 grams) can be a useful adjuvant in perioperative analgesia, but the exact dose needs to be determined. Recently, a dose finding study for intravenous magnesium determined that administration of magnesium at 40 mg/kg prior to induction, followed by a 10 mg/kg/hour infusion, resulted in a reduction in perioperative analgesic requirements without any major hemodynamic consequences.³⁸ Higher infusion doses did not offer any advantage, but decreased heart rate. However, since the magnesium ion poorly crosses the blood brain barrier in humans³⁹, it is not clear whether the therapeutic effect is related to NMDA antagonism in the central nervous system.

In addition to in vitro studies showing the NMDA antagonist properties of magnesium ion in the central nervous system⁹, intrathecal magnesium sulfate has been shown to potentiate morphine antinociception in a postoperative pain model.⁴⁰ Intrathecal magnesium sulfate 50 mg prolongs spinal fentanyl analgesia in women in labor.⁴¹

Amantadine

Amantadine is an anti-viral drug, used also for Parkinson's disease, supplied in 100 mg tablets. In addition it has been determined to be a non-competitive NMDA receptor antagonist that has been investigated as an adjuvant to reduce postoperative pain. Intravenous amantadine given just prior to abdominal hysterectomy did not reduce pain scores over 48 h post-surgery nor were postoperative analgesic requirements reduced.⁴² Oral amantadine given before and after radical prostatectomy reduced intravenous PCA morphine consumption by 32% over the 48-h postoperative period, however it was suggested that the mechanism for this was a lowering of plasma morphine clearance.⁴³ The results for NMDA antagonists are summarized in Table I.

ALPHA-2 ADRENERGIC AGONISTS

In addition to the opiate system, alpha-2 adrenergic activation represents another inherent pain control network of the central nervous system. The alpha-2 adrenergic receptor exists in the substantia gelatinosa of the dorsal horn in both rats and humans, which is a primary site of action by which this class of drugs can inhibit somatic

Table I. NMDA antagonists used as adjuvants in postoperative pain management.

| Drug | Route of administration | Time of administration | Primary analgesic | Efficiency | Major side effects | References |
|------------------|-------------------------|------------------------|-------------------|------------|--------------------|------------|
| Ketamine | Intravenous | Preoperative | Opioid | + to ++ | None | 14,17 |
| Ketamine | Intravenous | Perioperative | Opioid | ++ | None | 16,18,19 |
| Ketamine | Intravenous | Perioperative | Epi Opioid/LA | + | None | 16,20 |
| Ketamine | Epidural | Perioperative | Epi Opioid | + | None | 22 |
| Ketamine | Intrathecal | Perioperative | LA | 0 | CNS | 24,25 |
| Dextromethorphan | Intramuscular | Preoperative | Opioid | + | None | 32 |
| Dextromethorphan | Oral | Perioperative | Opioid | + | None | 33–35 |
| Magnesium | Intravenous | Perioperative | Opioid | + | None | 36–38 |
| Magnesium | Intrathecal | Preoperative | Opioid | + | None | 41 |

0 = negligible effect, + = small effect, ++ = moderate effect, +++ = large effect.
LA = local anesthetic, Epi = epidural.

pain.^{44,45} This receptor system also exists in the brain where it can produce sedation. Cardiovascular depression from alpha-2 adrenergic agonists can occur at both brain and spinal cord sites.⁴⁶ These side-effects of sedation and sympathetic inhibition limit alpha-2 adrenergic agonists to only an adjuvant role as analgesics.

Clonidine

Although originally used to control blood pressure and heart rate, clonidine has antinociceptive properties in both rodents and humans. Clonidine binds to alpha-2 adrenergic receptors in the central nervous system, and also binds to imidazoline receptors in the brain.⁴⁷ It has been recently hypothesized that clonidine acts at alpha-2 adrenergic receptors in the spinal cord to stimulate acetylcholine release which acts at both muscarinic and nicotinic subtypes for postoperative pain relief.⁴⁸ Clonidine has been administered by various systemic routes as an adjuvant to reduce postoperative pain: oral, intravenous, transdermal patch. The results of such studies have been mixed. Premedication with oral clonidine did not prolong the analgesic effect of intrathecal morphine in patients undergoing radical prostatectomy.⁴⁹ Preanesthetic oral clonidine in parturients reduced PCA morphine for the first 2 postoperative days, but with no improvement in VAS scores.⁵⁰ Oral clonidine presurgery and 24 h after surgery reduced postoperative pain scores following abdominal hysterectomy; although PCA morphine use was not reduced, and patients were sleepier.⁵¹

Better results have been obtained when clonidine was added to epidural admixtures. Epidural clonidine as single agent can lead to analgesia but with increased risk for drowsiness and cardiovascular side effects.^{52,53} In patients recovering from abdominal surgery, an epidural clonidine/fentanyl mixture doubled the duration of postsurgical analgesia compared to epidural fentanyl alone, although with increased drowsiness and hypotension.⁵⁴ Hip arthroplasty patients receiving intrathecal clonidine/bupivacaine followed by epidural clonidine/ropivacaine infusion had improved postoperative analgesia and moderate hypotension compared to patients receiving local anesthetic alone.⁵⁵ In children, clonidine (0.08–0.12 µg/kg/h) added to a postoperative continuous epidural infusion of ropivacaine improved analgesia compared to ropivacaine alone, with no significant signs of sedation or other side effects.⁵⁶

Animal studies have shown that intrathecal clonidine in rats reduces postoperative hyperalgesia, although only with moderate efficacy.^{57–59} Intrathecal clonidine in humans undergoing hip replacement did not reduce postoperative analgesic requirements.^{60,61} However, 25 µg clonidine added to intrathecal morphine reduced 24-h intravenous PCA morphine consumption following knee arthroplasty compared to intrathecal morphine alone.⁶² In patients undergoing colonic surgery, 300 µg intrathecal clonidine prior to intravenous propofol general anesthesia reduced PCA morphine requirements over a 72-h postoperative period and also reduced the area of hyperalgesia around the surgical incision, although hypotension was a frequent side effect.⁶³ Therefore intrathecal clonidine can reduce postoperative opioid use after some surgeries, although the drug appears to be more effective with epidural administration.

Clonidine at low doses (150 µg) has been shown to increase the duration of lidocaine brachial plexus blockade.⁶⁴ Animal studies suggest that the mechanism for clonidine's potentiation of lidocaine nerve block is inhibition of the hyperpolarization-activated cation current, not by binding to alpha-adrenoreceptors.⁶⁵ Clonidine has been added to lidocaine for axillary nerve blocks, over a dose range of 30–300 µg, but produced increased sedation and hypotension at the highest dose.⁶⁶ Clonidine is added to peripheral

nerve blocks at doses from 70–150 μg and has been shown with multiple studies to improve and prolong the duration of postoperative analgesia.⁸ The advantage of utilizing a non-local anesthetic for producing analgesia in peripheral nerve blocks is that the patient can still move their arm or leg. The motor function of the operated extremity can be confirmed by the surgeons, without compromising the analgesia.

Intra-articular clonidine has been shown at low doses (1–2 $\mu\text{g}/\text{kg}$) to reduce postoperative pain and supplemental analgesic consumption for arthroscopic knee surgery^{67,68}, and has been utilized extensively in several ambulatory centers.⁶⁹ Clonidine has also been added to local anesthetic drugs intra-articularly to reduce postoperative pain following arthroscopic knee surgery.⁷⁰

Dexmedetomidine

Injectable dexmedetomidine was approved by the FDA in 1999 for use in the intensive care unit. Since its approval and clinical use, it has been utilized for sedation during surgery and postoperative periods. Dexmedetomidine is an alpha-2 adrenergic agonist with even better selectivity for that receptor than clonidine.⁷¹ The primary use of dexmedetomidine is as an analgesic due to its sedative properties.⁴⁷ The elimination half life is 2 hours and therefore discontinuing the infusion rapidly leads to a state of consciousness. Intravenous dexmedetomidine administered postoperatively after major surgery reduced postoperative morphine use, and also reduced heart rate.⁷² Continuous intravenous dexmedetomidine during abdominal surgery reduced 48-h postoperative morphine requirements.⁷³ Intravenous dexmedetomidine when used as an adjunct to epidural bupivacaine anesthesia reduced supplemental epidural fentanyl requirements, although epidural bupivacaine use and pain scores were not improved.⁷⁴ The results for alpha-2 adrenergic agonists are shown in Table 2.

ANTICONSULSANTS

Although anticonvulsants have been used for many years as adjuvant therapy for chronic pain, only recently have they been examined for adjuvant use for postoperative pain. In particular, one class of anticonvulsants, which acts to inhibit the $\alpha_2\delta$ subunit of a voltage sensitive calcium channel, has proven effective in postoperative pain studies.⁷⁵

Table 2. Alpha-2 adrenergic agonists used as adjuvants in postoperative pain management.

| Drug | Route of administration | Time of administration | Primary analgesic | Efficiency | Major side effects | References |
|-----------------|-------------------------|------------------------|-------------------|------------|--------------------|------------|
| Clonidine | Oral | Preoperative | Opioid | 0 | None | 49,50 |
| Clonidine | Oral | Perioperative | Opioid | + | Sedation | 51 |
| Clonidine | Epidural | Perioperative | Opioid or LA | ++ | Sedation, Hypo | 54–56 |
| Clonidine | Intrathecal | Perioperative | LA | + | Hypo | 60–63 |
| Clonidine | Nerve block | Perioperative | LA | ++ | None | 8,64,66 |
| Clonidine | Intraarticular | Perioperative | LA | ++ | None | 67–70 |
| Dexmedetomidine | Intravenous | Perioperative | Opioid | + | None | 72,73 |
| Dexmedetomidine | Intravenous | Perioperative | Epi LA | + | Hypo | 74 |

0 = negligible effect, + = small effect, ++ = moderate effect, +++ = large effect.

LA = local anesthetic, Epi = epidural, Hypo = hypotension.

Gabapentin

Gabapentin was originally synthesized to be an analog of the inhibitory transmitter GABA; however its actual mechanism of action has been revealed to be as an antagonist to the $\alpha_2\delta$ subunit of a calcium channel.⁷⁶ It was originally approved by the FDA in 1994 for the treatment of partial seizures and then in 2002 for treatment of post-herpetic neuralgia. Gabapentin has a half life of about 5–7 hours. It is used extensively in chronic pain management as an adjuvant, but dose is often limited by the adverse effect of sedation.

Systemic administration of gabapentin has been shown to reduce hyperalgesia in animal models of postoperative pain.^{59,77} Gabapentin 600 mg given before surgery or after surgical incision for open donor nephrectomy reduced PCA fentanyl use postoperatively with lower pain scores, but there was no difference between the pre-incision and post-incision gabapentin groups, and so no preemptive effect was evident.⁷⁸ Preoperative gabapentin 800 mg in patients undergoing lumbar laminectomy or discectomy did not reduce postoperative PCA morphine use.⁷⁹ However, a review of 6 clinical trials from 2002 to 2004 reported that preoperative 1200 mg gabapentin reduced postoperative opioid usage.⁸⁰ A single preoperative dose of gabapentin 1200 mg was shown to reduce preoperative anxiety, postoperative pain scores and opioid use, and improve range of motion for up to 48 hours following anterior cruciate ligament surgery.⁸¹ Movement evoked pain after surgery is of clinical relevance, as mobilization after major surgery leads to earlier recovery and discharge from the hospital, with possible improved long term outcome. Administration of gabapentin in combination with a COX-2 inhibitor has been demonstrated to improve movement-evoked postoperative pain and 48-h PCA morphine consumption after hysterectomy.⁸² In a recent review of 16 randomized trials, 1200 mg gabapentin administered as an adjunct to opioids led to decreased pain scores and 24-h opioid consumption postoperatively. Similar results of decreased pain scores, but with less dramatic reduction in opioid use, were observed when the dose was less than 1,200 mg gabapentin. However, gabapentin was associated with an increased risk of sedation, but fewer opioid-related side effects such as vomiting and pruritus.⁸³ In another recent meta-analysis of 12 randomized trials using gabapentin as an adjunct for postoperative pain, a similar conclusion of decreased postoperative pain scores were observed, with slightly increased sedation.⁸⁴ Therefore there appears to be a definite benefit in utilizing gabapentin as part of a multimodal analgesia for postoperative pain.

Administration of gabapentin in the perioperative period following abdominal hysterectomy has been shown to decrease pain scores at 1 month and may therefore decrease chronic pain syndromes from developing from surgery.⁸⁵ Further studies need to address this phenomena of preventing long term pain with perioperative $\alpha_2\delta$ subunit voltage sensitive calcium channel inhibitors, before it becomes accepted as the standard of care. However, while awaiting these long term clinical studies, patients at high risk for the development of chronic pain from surgery may benefit from the perioperative use of gabapentin, such as patients undergoing amputation.⁸⁶

Pregabalin

Pregabalin also binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels in the spinal cord.⁸⁷ Like gabapentin it is used for seizures and neuropathic pain, and was approved by the FDA in 2005 as a scheduled class V drug. Pregabalin is more potent than gabapentin and achieves its efficacy at lower doses, and therefore may be associated with

fewer side effects. Systemic pregabalin reduces hyperalgesia in an animal model of postoperative pain.⁷⁷ One advantage of pregabalin in clinical use is that it has high bioavailability and linear pharmacokinetics, in comparison to the plasma saturation effect that occurs with higher doses of gabapentin.⁸⁸ The combination of pregabalin and celecoxib was recently shown to be superior to either agent alone for postoperative pain following spinal fusion surgery.⁸⁹ This was evidenced by a significant ($p < 0.001$) reduction in pain scores, morphine use, and fewer side effects during the first 24 postoperative hours with the perioperative administration of celecoxib and pregabalin. The results for anticonvulsants are summarized in Table 3.

GLUCOCORTICOIDS

Glucocorticoids (corticosteroids) are steroids that bind with high affinity to the glucocorticoid receptor in the cytosol of cells. There are multiple sites of action at which glucocorticoid-activated receptors produce anti-inflammatory and immunosuppressive effects.⁹⁰ The ligand-bound glucocorticoid receptor moves into the nucleus where it can bind to DNA sequences known as glucocorticoid-responsive elements. This complex can either directly inhibit or activate the expression of target genes (such as cytokines like IL-2), or can interact with certain transcription factors such as NF- κ B which in turn limit expression of these genes. Inhibition of inflammation can occur at various sites, especially within the prostaglandin synthesis pathway. Glucocorticoids can induce the activation of lipocortin-1 (annexin-1), which then acts to block production of the prostaglandin substrate arachidonic acid, by inhibition of cytosolic phospholipase A₂ (PLA₂). Downstream, glucocorticoids inhibit expression of cyclooxygenase-2 (COX-2) probably by blocking NF- κ B. Side effects of glucocorticoids are due to their lack of selectivity, so that healthy metabolic processes are impaired.

There is a long history of using glucocorticoids to reduce inflammation and postoperative pain in many surgical procedures.^{91–94} However, the powerful anti-inflammatory nature of corticosteroids, which produces inhibition of prostaglandin synthesis, may also have detrimental side-effects with high or repeated dosing.

Dexamethasone

Dexamethasone is a synthetic glucocorticoid with high potency and long duration of action (half life: 2 days), but with no mineralocorticoid activity. In addition to reducing inflammation, dexamethasone can also reduce PONV. Prostaglandins are one of the main inducers of inflammation after tissue injury, and one mechanism by which glucocorticoids reduce prostaglandin synthesis is by inhibiting the expression of cyclooxygenase-2

Table 3. Anticonvulsants used as adjuvants in postoperative pain management.

| Drug | Route of administration | Time of administration | Primary analgesic | Efficiency | Major side effects | References |
|------------|-------------------------|------------------------|-------------------|------------|--------------------|------------|
| Gabapentin | Oral | Preoperative | Opioid | + | None | 78–81 |
| Gabapentin | Oral | Perioperative | Opioid | ++ | None | 82–84 |
| Pregabalin | Oral | Perioperative | Opioid | ++ | None | 89 |

0 = negligible effect, + = small effect, ++ = moderate effect, +++ = large effect.

without effecting cyclooxygenase-1.⁹⁵ Subcutaneous dexamethasone also prevents the induction of cyclooxygenase-2 and prostaglandins in the lumbar spinal cord in an animal model of inflammation.⁹⁶ Studies using dexamethasone for postoperative pain relief have produced mostly positive results, especially with surgical procedures involving a large amount of tissue trauma, such as orthopedic and neurological surgery.⁹⁴ The ability of dexamethasone to reduce prostaglandin levels does not ensure that it will reduce postoperative pain because in a dental surgery model, oral dexamethasone given prior to surgery reduced peripheral prostanoid levels without achieving an analgesic effect.⁹⁷ Although preoperative intravenous dexamethasone did not reduce postoperative pain scores and analgesic requirements after laparoscopic cholecystectomy, it did reduce PONV, which may be the main advantage of dexamethasone postoperatively.⁹⁸ Dexamethasone when added to solutions for intravenous regional nerve blocks has been demonstrated to reduce pain and acetaminophen supplementation for the first 24 h after hand surgery.⁹⁹ There might be a concern about possible impairment of the immune system with dexamethasone, but at the doses used and the frequency with which it is administered, it is a safe drug to be used in the perioperative period.

ACETYLCHOLINE ESTERASE INHIBITORS

Acetylcholine esterase inhibitors and muscarinic receptor agonists increase pain thresholds.¹⁰⁰ Muscarinic receptors occur at high density in the superficial dorsal horn, and it is hypothesized that nearby cholinergic neurons stimulate these receptors to reduce postoperative pain.¹⁰¹ Acetylcholine may cause analgesia through direct action on spinal cholinergic muscarinic receptors M1 and M3 and nicotinic receptors subtypes and indirectly through stimulation of release of the second-messenger nitric oxide in the spinal cord. Several mechanisms such as the hyperpolarization of neurons, reduction in the release of pronociceptive neurotransmitters, or activation of the nitric oxide-cyclic guanosine monophosphate pathway might mediate the peripheral cholinergic antinociception by elevating endogenous acetylcholine.¹⁰²

Neostigmine

Neostigmine is an anticholinesterase agent with the following ingredients: neostigmine methylsulfate, phenol and sodium acetate. It is intended for intravenous, intramuscular or subcutaneous use, and due to its phenol mixture, caution needs to be exercised in administering it intrathecally. Neostigmine is used to improve the muscle tone in patients with myasthenia gravis and routinely at the end of general anesthesia for reversal of the non-depolarizing muscle relaxants. In animals, spinal administration of neostigmine reduces thermally evoked pain and the drug acts synergistically with intrathecal morphine.¹⁰³ Intrathecal neostigmine is also a potent inhibitor of postoperative mechanical hyperalgesia in rats.⁵⁹ Adding neostigmine to other spinal medications has produced mixed results clinically. Doses used in clinical studies for intrathecal administration have been from 50–750 µg; the higher doses being associated with side effects. A meta-analysis study on the use of intrathecal neostigmine as an adjunct to other spinal medications only improved perioperative and peripartum analgesia marginally, with increased side effects such as PONV, bradycardia, and agitation.¹⁰⁴ Motor block can occur with spinal neostigmine, though there have been no reports of neurotoxicity. Although there have been phase I clinical studies, attempting to evaluate intrathecal neostigmine, the challenge is to obtain the preservative-free drug

commercially. Economic considerations often preclude commercial development of a parental drug for intrathecal indication. Epidural neostigmine when added to morphine increased the time to first rescue analgesic by eleven hours compared to morphine alone following knee surgery.¹⁰⁵ After caesarian delivery an epidural bolus of neostigmine added to spinal bupivacaine/fentanyl produced modest analgesia for 24 h, but also induced sedation for several hours.¹⁰⁶ Epidural neostigmine (1, 2, or 4 µg/kg) in lidocaine has been shown to produce a dose-independent analgesic effect over 8 hours following knee surgery, compared with the lidocaine-alone group of patients, without increase in the side effects.¹⁰⁷

Neostigmine added to lidocaine did not improve postoperative analgesia with axillary plexus blocks for patients undergoing carpal tunnel release.¹⁰⁸ In addition, there was no enhancement of sensory or motor blockade by neostigmine added to mepivacaine for the same procedure.¹⁰⁹ Neostigmine 1 mg added to lidocaine had no analgesic effect when utilized for intravenous regional anesthesia for patients undergoing hand surgery.¹¹⁰ However, intra-articular neostigmine 500 µg produced a significant analgesic effect in patients undergoing knee arthroscopy.^{68,111,112} This is still a new application and further studies are required. Furthermore, animal experiments have shown histopathological changes in knee joints following intra-articular neostigmine.¹¹³

FUTURE DIRECTIONS

New adjuvants are needed to achieve greater reductions in opioid requirements and to more profoundly decrease postoperative pain scores. Postoperative pain is not only a fifth vital sign now in all hospitals in the USA, but superior control of pain has been shown to improve long term outcome in patients after surgery. New classes of drugs being considered include: adenosine agonists, prostaglandin receptor antagonists, bradykinin antagonists, peripheral nerve channel blockers, and nerve growth factor inhibitors. Pre-clinical studies with some of these classes of drugs are underway. The advantage of developing receptor specific pharmacological therapy is that pain can be controlled more efficiently with fewer adverse effects.

Although the concept of preemptive treatment to reduce postoperative pain seems attractive, both animal experiments¹¹⁴ and clinical trials have been mostly negative.¹¹⁵ Nevertheless, the concept of preventive analgesia in postoperative pain control has gained acceptance among anesthesiologist and surgeons. Nationally, there is an increase in the use of regional anesthesia and analgesia for surgery and postoperative pain. Recent pre-clinical data demonstrate that anesthesia with propofol suppresses central PGE₂ compared with spinal anesthetic¹¹⁶; however, this needs to be confirmed in humans. The neuronal blockade providing surgical anesthesia does not prevent local inflammatory mediators released from an incision to up-regulate the noxious mediators (humoral response) in the CNS, probably via systemic circulation.¹¹⁷ Therefore, regional anesthesia and analgesia combined with a multimodal pharmacological approach, which leads to the suppression of inflammatory mediators to surgery, is of essence for improved perioperative pain control to our patients, which can lead to improved outcome. The use of certain adjuvant medications as compared to opioids as the sole agent for the treatment of postoperative pain can suppress the inflammatory response to surgery. This improved long term outcome has been demonstrated in studies where multimodal approach has been utilized.¹¹⁸ In addition, appropriate therapeutic management of acute postoperative pain can reduce the incidence of chronic pain syndromes from developing after surgery.¹¹⁵ These chronic pain

syndromes can be debilitating for the patients and treatment is often challenging and expensive. This is of significance given that this decade has been dedicated by the US Congress as the “Decade of Pain Control and Research,” and too little attention has been directed at preventing chronic pain from surgical trauma.

SUMMARY

None of the adjuvant compounds described in this chapter are as opioid-sparing as NSAIDs or COX-2 inhibitors in reducing postoperative pain.^{2,119,120} The ideal NMDA antagonist, one without psychomimetic actions, is not available yet. However, ketamine can be a very useful adjuvant for perioperative pain control and may prevent chronic pain. Alpha-2 adrenergic agonists are dose-limited by their sedative and sympathetic nervous system inhibitory effects, and clonidine achieves good potency only as an additive to local anesthetics. More experience is being gained with gabapentin and pregabalin as adjuvants, which have been shown to have opioid sparing effect, the dose being the limiting factor due to excessive sedation. Corticosteroids reduce prostaglandin and cytokine levels and so reduce the inflammatory component of pain, but usage must be limited to the immediate postoperative period to reduce potential side-effects due to the non-specific action of these compounds. Neostigmine is best delivered by the epidural route, but CNS side-effects are still a problem.

Practice points

- surgery and postoperative pain are complex processes with activation of a multitude of receptors, and adjuvant agents that can achieve a receptor specific blockade of the activation in the perioperative period will lead to improved outcome in patients
- judicious use of perioperative adjuvants can reduce opioid and local anesthetic doses and thereby lessen side effects of each of these agents
- intravenous ketamine can supplement opioids to decrease opioid dosing
- epidural clonidine can supplement opioids but doses must be kept low to reduce drowsiness and hypotension
- small amounts of clonidine can be added to local anesthetic solutions to extend the duration of peripheral nerve block
- oral gabapentin/pregabalin reduce postoperative opioid use
- multi-modal analgesia utilizing adjuvants for postoperative pain is opioid sparing which is associated with improved outcome

Research agenda

- improve on selectivity within current classes of adjuvants to reduce their side effects
- bring new classes of adjuvant drugs into clinical practice
- greater understanding of the pathophysiology of acute postoperative pain

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