Multimodal analgesia for controlling acute postoperative pain

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Current Opinion in Anaesthesiology 2009, 22:588–593

Purpose of review

Multimodal analgesia is needed for acute postoperative pain management due to adverse effects of opioid analgesics, which can impede recovery; a problem that is of increasing concern with the rapid increase in the number of ambulatory surgeries. Yet, the literature on multimodal analgesia often shows variable degrees of success, even with studies utilizing the same adjuvant medication.

Recent findings

Nonsteroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors consistently reduce postoperative opioid consumption. The *N*-methyl-D-aspartate antagonists have produced variable results in studies, which may be due to the dose and timing of drug administration. Alpha-2 adrenergic agonists have been useful as adjuvant for regional analgesia but not when administered orally. The alpha-2-delta receptor modulators such as gabapentin have shown early promising results in multimodal analgesia. Local anesthetic injection at the surgical site, though not as a preemptive analgesic, has recently been demonstrated to be beneficial in multimodal analgesia. No new adjuvants have appeared in the last year, which robustly reduce opioid consumption and opioid-related adverse effects.

Summary

There is a continuing need to explore new drug combinations to achieve all of the purported goals of multimodal anesthesia.

Keywords

adjuvants, multimodal, opioids, postoperative pain

Curr Opin Anaesthesiol 22:588–593

0952-7907

Introduction

The concept of multimodal analgesia was introduced more than a decade ago as a technique to improve analgesia and reduce the incidence of opioid-related adverse events. The rationale for this strategy is the achievement of sufficient analgesia due to the additive or synergistic effects between different classes of analgesics. This allows for a reduction in the doses of individual drugs and thus a lower incidence of adverse effects from any particular medication used for perioperative pain management. A lower incidence of adverse effects and improved analgesia has been demonstrated with multimodal analgesia techniques, which may provide for shorter hospitalization times, improved recovery and function [1,2], and possibly decreased healthcare costs. Currently, the American Society of Anesthesiologists Task Force on Acute Pain Management advocates the use of multimodal analgesia [3].

What is multimodal analgesia? Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms and at different sites in the nervous system, resulting in additive or synergistic analgesia with lowered adverse effects of sole administration of individual analgesics [4]. The complex humoral and neuronal response that occurs with surgery requires a balanced approach for perioperative pain management [5]. As such, one approach for multimodal analgesia is the use of regional anesthesia and analgesia to inhibit the neural conduction from the surgical site to the spinal cord and decrease spinal cord sensitization. Spinal cord sensitization that has been well described and demonstrated in animal studies is challenging to demonstrate in humans [6]. Spinal cord sensitization from surgery is an evolving field with discoveries in neurotransmitters playing an integral role.

This review evaluates recent studies that explore new and improved methods of multimodal anesthesia for relieving moderate-to-severe postoperative pain. Although opioids remain the primary analgesic agent for management of acute postoperative pain after major surgery, opioid-related adverse effects inhibit rapid recovery and rehabilitation. We have emphasized randomized clinical trials in which there is a clear comparison between a multimodal drug combination: opioid and adjuvant(s) versus the opioid alone. Therefore, we

have not included studies in which there are two competing multimodal drug combinations without a unimodal control. All new references cited are prospective, randomized, double-blind, placebo-controlled trials.

NSAIDs and cyclooxygenase-2-selective inhibitors

Prostaglandins, including PGE_2, are responsible for reducing the pain threshold at the site of injury, resulting in central sensitization and a lower pain threshold in the surrounding uninjured tissue. The primary site of action of NSAIDs is believed to be in the periphery though recent research indicates that central inhibition of cyclooxygenase-2 (COX-2) may also play an important role in modulating nociception [7]. NSAIDs inhibit the synthesis of prostaglandins both in the spinal cord and at the periphery, thus diminishing the hyperalgesic state after surgical trauma. NSAIDs are useful as the sole analgesic after minor surgical procedures and may have a significant opioid-sparing effect after major surgery. Recent practice guidelines for acute pain management in the perioperative setting specifically state 'unless contraindicated, all patients should receive around-the-clock regimen of NSAIDs, COX-2 inhibitors, or acetaminophen' [3].

Parenteral formulations of ketorolac tromethamine have been available for many years, and it is currently the only intravenous NSAID for treatment of emergent postoperative pain in the United States. As with any mixed COX-1/COX-2 inhibitor, the primary concern would be the increased postoperative bleeding that has been documented for NSAIDs because of their COX-1 component [8]. A new route of administration for ketorolac is as an intranasal spray. In a double-blind placebo-controlled study, patients undergoing major surgery (abdominal or orthopedic) received 30 mg ketorolac, 10 mg ketorolac, or placebo spray upon recovering from general anesthesia [9•]. All patients were then placed on a patient-controlled analgesia (PCA) morphine pump for the next 40 h. Mean morphine consumption over the initial 24 h was reduced in the 30 mg ketorolac group (37.8. mg) compared with the placebo group (56.5 mg) and the 10 mg ketorolac group (54.3 mg). Pain reduction over the first 6 h postoperatively was higher in the 30 mg ketorolac group than placebo. The incidence of opioid-related adverse events, such as nausea or pruritus, did not differ between groups. As other injectable NSAIDs such as ibuprofen (just approved in the United States) become available, postoperative patients, who have ilieus and in cases in which bleeding is not a concern, may benefit from the injectable NSAID formulations. In Europe, the intravenous use of acetaminophen is utilized as a foundation for multimodal perioperative analgesia.

COX-2-selective inhibitors have the advantage over NSAIDs in the perioperative setting of not increasing the risk of bleeding. One group of patients undergoing total knee arthroplasty under spinal anesthesia received the COX-2-selective inhibitor celecoxib 200 mg at 1 h before surgery and every 12 h for 5 days [10•]. The other group received placebo at the same time points. Over the first 24 h, PCA morphine usage was less in the celecoxib group (15.1 mg) than the placebo group (19.7 mg). Over the 48 h period, visual analogue scale (VAS) pain scores at rest were lower in the celecoxib group than in the placebo group, but there was no difference in pain scores with ambulation. Celecoxib also increased knee range of motion over the first 3 postoperative days. Incidences of postoperative nausea and vomiting (PONV) did not differ by group. As expected with a COX-2-selective inhibitor, there were no differences in intraoperative or postoperative blood loss between groups.

Etoricoxib is a new COX-2-selective inhibitor with a long half-life (not currently approved in the United States). With administration of etoricoxib versus placebo 1 h prior to thyroid surgery under general anesthesia, postoperative intravenous oxycodone use during the initial 6 h was not reduced in the etoricoxib group [11]. However, paracetamol–codeine tablet use over the 7–24 h postoperative period was less in the etoricoxib group (2.1 mg) than in the placebo (4.1 mg). Pain scores or incidence of adverse events did not differ among groups. In summary, though most studies with NSAIDs in multimodal analgesia show opioid sparing, few show a statistical reduction of opioid-related adverse effects.

Rofecoxib is a COX-2-selective inhibitor that is no longer used due to adverse cardiovascular events. However, clinical trials with acute use of rofecoxib during joint replacement surgery reveal mechanisms by which COX-2 inhibition can reduce postoperative pain. Perioperative use of rofecoxib reduced opioid consumption, pain, vomiting, and sleep disturbance, with improved knee range of motion compared with that of placebo, after total knee arthroplasty [1]. Rofecoxib 25 mg, given 1 h before total knee arthroplasty under epidural anesthesia, reduced postoperative epidural PCA morphine consumption over the initial 24 h, and pain scores were reduced at 24 and 48 h compared with placebo [12]. In the placebo group, peripheral site (knee drain) levels of the cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8) was elevated over time, and tumor necrosis factor-α (TNF-α) was unchanged 0–48 h after surgery. In the rofecoxib group, the IL-6 increase was less than that in the placebo group, and TNF-α did not vary with time but was still decreased compared with placebo. These results have similarity to a study of preoperative rofecoxib before total hip arthroplasty in which IL-6, IL-8, and PGE_2 increased at the peripheral site (hip drain) while TNF-α did not initially vary in the placebo group and then decreased by 24 h [7]. In the rofecoxib group, hip

drain PGE_2 was reduced, but the other cytokines were not affected. Hip drain PGE_2 was positively correlated with poorer recovery [7]. In the total hip arthroplasty study, cerebrospinal fluid (CSF) IL-6 and PGE_2 also increased after surgery, and rofecoxib reduced CSF IL-6 and PGE_2 compared with placebo. CSF PGE2 was correlated with intensity of postoperative pain.

N-methyl-D-aspartate antagonists

With the discovery of the *N*-methyl-D-aspartate (NMDA) receptor and its links to nociceptive pain transmission and central sensitization, there has been renewed interest in utilizing noncompetitive NMDA receptor antagonists, such as ketamine, as potential antihyperalgesic agents.

Ketamine

Ketamine has been a well known general anesthetic and analgesic for the past 3 decades. Although high doses of ketamine have been implicated in causing psychomimetic effects (excessive sedation, cognitive dysfunction, hallucinations, nightmares), subanesthetic or low doses of ketamine have demonstrated significant analgesic efficacy without these side effects. Low-dose ketamine has not been associated with adverse pharmacological effects on respiration, cardiovascular function, nausea, vomiting, urinary retention, and constipation/prolonged adynamic postoperative ileus. There is evidence that low-dose ketamine may play an important role in postoperative pain management when used as an adjunct to opioids, local anesthetics, and other analgesic agents [13,14].

In patients having total knee replacement surgery under general anesthesia, ketamine or placebo was given during surgery (0.2 mg/kg followed by 2 μg/kg/min) and through the second postoperative day (10 μg/kg/min) [15•]. PCA morphine use was less over the 48 h postoperative period in the ketamine group (50.5 mg) compared with the placebo group (72.1 mg). Pain scores were lower at rest and with movement in the ketamine group versus placebo at all times. Time to achieve 90° knee flexion was shorter in the ketamine group, and the incidence of PONV was less.

Patients undergoing major abdominal surgery under general anesthesia were randomized to three groups: perioperative ketamine (intraoperative, 0.5 mg/kg then 2 μg/kg/min; and postoperative, 2 μg/kg/min for next 48 h), intraoperative ketamine only, or placebo [16•]. PCA morphine use was less in the perioperative ketamine group (27 mg) compared with the intraoperative ketamine (48 mg) or placebo (50 mg) group. Interestingly, pain scores at 24 and 48 h were lower in both the perioperative and the intraoperative ketamine groups compared with placebo. Incidence of PONV was greater in the placebo group than the perioperative ketamine group.

However, other studies failed to show any opioid-sparing effect of ketamine. After major gynecological surgery under general anesthesia, ketamine (0.15 mg/kg before incision, then combined PCA ketamine 0.5 mg/ml with 1 mg/ml morphine for 48 h) or placebo (PCA morphine alone) did not reduce PCA morphine requirements [17]. The total postoperative ketamine dose was 44 mg. Pain scores also were no different between groups. After pediatric (12–18 years) scoliosis surgery, intraoperative ketamine (0.5 mg/kg, then 4 μg/kg/min) did not reduce postoperative PCA morphine use over the next 24, 48, or 72 h compared with placebo [18]. Pain scores and incidence of PONV were not different between groups. The lack of a clinical effect in these two studies may be due to a low ketamine dose (about 0.2 μg/kg/min) [17] or not continuing the dose into the postoperative period [18].

Magnesium

The magnesium ion was the first agent discovered to be an NMDA channel blocker. At very high doses, perioperative intravenous magnesium sulfate has been reported to reduce postoperative morphine consumption but not postoperative pain scores [19,20]. In patients undergoing total abdominal hysterectomy under general anesthesia, magnesium sulfate (50 mg/kg, then 15 mg/kg/h) or placebo was given intraoperatively [21]. Postoperative PCA morphine use was less over the next 48 h in the magnesium group. Pain scores at rest and with movement were lower in the magnesium group at 24 and 48 h, and PONV incidence was also lower than with placebo. However, as the magnesium ion crosses the blood–brain barrier poorly in humans [22], it is not clear whether the therapeutic effect is related to the NMDA antagonist effect studied in the central nervous system.

Alpha-2 adrenergic agonists

Alpha-2 adrenergic activation represents an intrinsic pain control network of the central nervous system. The alpha-2 adrenergic receptor has high density in the substantia gelatinosa of the dorsal horn in humans and that is believed to be the primary site of action by which alpha-2 adrenergic agonists can reduce pain.

Clonidine

Due to the many side effects of systemic clonidine administration, such as hypotension, bradycardia, and sedation, the spinal route is preferred. For spinal surgery under general anesthesia, patients received epidural clonidine 25 μg/h or placebo infusion postoperatively for 36 h [23•]. PCA morphine use was less in the clonidine

group (35 mg) than placebo (61 mg). Pain scores with movement were less in the clonidine group over the 36 h period, and the PONV incidence was reduced. Blood pressure and heart rate were lower in the clonidine group, but the reductions were modest.

For elective cesarean delivery under spinal anesthesia, patients were randomized to three intrathecal groups: bupivacaine–sufentanil, bupivacaine–sufentanil–clonidine 75 μg, or bupivacaine–clonidine 150 μg [24]. Postoperative PCA morphine consumption and pain scores did not differ among groups. However, the area of mechanical hyperalgesia, when the wound was probed at 48 h after surgery, was greatly reduced in the bupivacaine–clonidine 150 μg group (1.0 cm^2) compared with the bupivacaine–sufentanil group (9.5 cm^2). In another study, patients undergoing radical prostatectomy under general anesthesia received a preoperative intrathecal injection of morphine 4 μg/kg, clonidine 1 μg/kg and morphine 4 μg/kg, or no injection at all [25]. Intraoperative sufentanil consumption was lowest in the clonidine and morphine group compared with the two other groups. Postoperative PCA morphine use over 48 h was highest in the no injection group (66 mg) versus the intrathecal morphine group (25 mg) or the intrathecal clonidine and morphine group (18 mg). Pain scores at rest were lower over the initial 18 h in the morphine alone group and over the initial 24 h in the clonidine and morphine group, compared with the no injection group. Side effects were the same among the three groups.

Dexmedetomidine

Patients undergoing abdominal total hysterectomy under general anesthesia were randomized to receive morphine 1 mg/ml alone or dexmedetomidine 5 μg/ml and morphine 1 mg/ml for postoperative analgesia over 24 h [26•]. Patients with dexmedetomidine and morphine required less morphine (23 mg) than the morphine alone group (33 mg) over the 0–24 h postoperative period. Postoperative pain scores at rest or with movement and the incidence of nausea during the 4–24 h period were lower in the dexmedetomidine and morphine group. There was lower blood pressure and heart rate in the dexmedetomidine and morphine group, but the decrease was small. Patients having laparoscopic bariatric surgery under general anesthesia were randomized to four intraoperative intravenous infusion groups: dexmedetomidine 0.2 or 0.4 or 0.8 μg/kg/h or placebo [27]. More patients in the placebo group required antiemetic therapy than in dexmedetomidine groups. However, PCA morphine use 0–48 h after surgery and pain scores through day 7 did not differ among groups. It may be that dexmedetomidine must be given during the postoperative period to reduce PCA morphine use.

Gabapentin-type drugs

Pregabalin and gabapentin bind to the α2δ subunit of voltage-gated calcium channels in the spinal cord and brain [28]. Both drugs are used for seizures and neuropathic pain. One advantage of pregabalin in clinical use is that it has higher bioavailability than gabapentin and linear pharmacokinetics [29]. Earlier clinical trials with gabapentin for early postsurgical pain have recently been reviewed [30].

Pregabalin

Patients undergoing laparoscopic cholecystectomy were randomized to receive pregabalin 150 mg or placebo orally 1 h before surgery [31•]. PCA fentanyl use over the 0–24 h postoperative period was less in the pregabalin group (555 μg) than in the placebo group (758 μg). Pain scores at rest or with coughing were less in the pregabalin group. PONV incidence, or sedation, did not differ between the two groups.

In a study of hip arthroplasty with spinal anesthesia, patients were randomized to three groups given medication 1 h before surgery: pregabalin 300 mg, dexamethasone 8 mg and pregabalin 300 mg, or placebo. PCA morphine use over 0–24 h was less in the pregabalin alone group (24 mg) and dexamethasone and pregabalin group (25 mg) than in the placebo group (47 mg) [32•]. Pain scores at rest or with movement did not differ among groups. The dexamethasone and pregabalin group had a lower incidence of vomiting than the pregabalin alone group, but nausea did not differ among groups. Sedation was highest in the pregabalin alone group. A similar protocol was used in patients having abdominal hysterectomy under general anesthesia [33], except paracetamol was added to all three groups. In this study, however, there was no difference in PCA morphine consumption over the 24 h postoperative period among the three groups nor did pain scores differ. In patients undergoing laparoscopic hysterectomy under general anesthesia, patients were randomized to three groups: pregabalin 300 mg 1 h before surgery and 12 h later, pregabalin 150 mg 1 h before surgery and 12 h later, and diazepam 10 mg (active placebo) 1 h before surgery [34]. PCA oxycodone use 0–24 h after surgery was less in the pregabalin 300/300 group (0.34 mg/kg) than in the placebo group (0.45 mg/kg). Pain scores at rest or with movement did not differ between groups nor did PONV incidence. Pruritus was less in the pregabalin 300/300 group. However, the pregabalin 300/300 group had a higher incidence of dizziness, blurred vision, and headache compared with placebo. In a trial of gynecological laparoscopic surgery under general anesthesia, patients were randomized to three groups that received medication 1 h before surgery: pregabalin 150 mg, pregabalin 75 mg, or diazepam 5 mg (active placebo) [35]. Requested

postoperative intravenous fentanyl and supplementary oral acetaminophen/codeine did not differ among groups. Pain scores at rest or with movement were lower in the pregabalin 150 mg group than placebo but only over the 1–8 h period. Incidence of side effects did not differ among groups. Therefore, it appears that pregabalin is not effective in patients undergoing gynecological surgery.

The recent retraction of several manuscripts published by Dr Scott Reuben has led to editorials questioning the validity of multimodal analgesia for perioperative pain management [36–40]. Some of the retracted articles focused specifically on the use of pregabalin for perioperative pain management. That makes these recent articles even more timely in that they show an opioid-sparing effect of pregabalin in both laparoscopic cholecystectomy and hip arthroplasty patients.

Glucocorticoids

There is a long history of using glucocorticoids, including dexamethasone, to reduce inflammation and postoperative pain in surgical procedures [41].

Dexamethasone

Patients undergoing total hip arthroplasty under spinal anesthesia with propofol sedation were randomized to receive a single preoperative intravenous dose of dexamethasone 40 mg or placebo [42]. PCA morphine consumption from 0 to 48 h and pain at rest did not differ between groups, but pain upon standing at 24 h was lower in the dexamethasone group (2.6/10) than in the placebo group (6.9/10). C-reactive protein, an inflammatory marker, measured at 48 h after surgery in venous blood was lower in the dexamethasone group (47 mg/ml) than in the placebo group (200 mg/ml). One negative finding was an increase in propofol consumption during surgery in the dexamethasone group (235 mg) versus placebo (139 mg).

Cholinergic drugs

Acetylcholine may cause analgesia through direct action on spinal cholinergic muscarinic receptors M1 and M3 and nicotinic receptors subtypes.

Nicotine

Nonsmoker patients having radical retropubic prostatectomy under general anesthesia were randomized to preoperative application of a 7 mg nicotine patch or placebo patch 30–60 min before surgery and left in place for 24 h [43]. Cumulative PCA morphine use decreased in the nicotine group (33 mg) versus the placebo group (45 mg) by 24 h. Pain scores at rest or with coughing did not differ between groups. PONV incidence or pruritus did not differ between groups, but the intensity of nausea was greater in the nicotine group.

Local anesthetic injections at wound site

Local anesthetics can be administered for perioperative pain management via different routes. Infiltrating local anesthetics into the skin and subcutaneous tissue prior to making an incision may be the simplest approach to analgesia. It is a safe procedure with few side effects and low risk for toxicity. Although the benefit of local wound infiltration has been documented, controversy exists as to the appropriate timing of administering local anesthesia for surgery. In the rat, subcutaneous infiltration of the plantar foot region and blocking the sural and tibial nerves with 0.5% bupivacaine 15 min before incision or immediately after incision only reduced postoperative pain for 4 h compared with placebo isotonic saline injections, with no long-term effect over the next 5 days [44].

Patients undergoing total abdominal hysterectomy under general anesthesia were randomized to receive a bilateral block of the abdominal wall with 1.5 mg/kg ropivacaine or placebo on each side just before incision [45•]. PCA morphine use over the 48 h period after surgery was less in the ropivacaine group (27 mg) than in the placebo group (55 mg). Pain scores at rest and with movement were reduced in the ropivacaine group. The incidence of PONV did not differ between groups, but the incidence of sedation was reduced in the ropivacaine group. Patients undergoing total abdominal hysterectomy under general anesthesia were randomized into four groups and in whom a local anesthetic mixture (1% lidocaine, 0.25% bupivacaine, 2 μg/ml adrenaline) was infiltrated under the skin: preoperative and postoperative; preoperative alone; postoperative alone; or placebo [46]. In this study, PCA morphine consumption over 0–24 h and pain scores did not differ among the four groups. Perhaps the block of the abdominal wall (musculature and skin) is a more effective approach than skin infiltration.

Conclusion

Further prospective, randomized, double-blind, placebo-controlled trials with multimodal regimes of analgesia need to be carried out to establish which combinations achieve the goals of superior analgesia with fewer side effects. Each regime needs to be tailored towards the particular type of surgery and not a blanket treatment that will work for all kinds of surgical trauma.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 689).

1 Buvanendran A, Kroin JS, Tuman KJ, *et al.* Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor of pain management and recovery of function after knee replacement. JAMA 2003; 290:2411–2418.

2 White PF, Sacan O, Tufanogullari, *et al.* Effect of short term postoperative celecoxib administration on patient outcome after outpatient laparoscopic surgery. Can J Anaesth 2007; 54:342–348.

3 Ashburn MA, Caplan RA, Carr DB, *et al.* Practice guidelines for acute pain management in the perioperative setting. An updated report by the American Society of Anesthesiologists task force on acute pain management. Anesthesiology 2004; 100:1573–1581.

4 Kehlet H, Dahl JB. The value of multimodal or balanced analgesia in the postoperative pain treatment. Anesth Analg 1993; 77:1048–1056.

5 Kehlet H, Dahl JB. Anaesthesia, surgery and challenges in postoperative recovery. Lancet 2003; 362:1921–1928.

6 Woolf CJ. Central sensitization. Anesthesiology 2007; 106:864–867.

7 Buvanendran A, Kroin JS, Berger RA, *et al.* Upregulation of prostaglandins E2 and interleukin in the central nervous system and peripheral tissue during and after surgery in humans. Anesthesiology 2006; 104:403–410.

8 Marret E, Flahault A, Samama CM, Bonnet F. Effects of postoperative, nonsteroidal, antiinflammatory drugs on bleeding risk after tonsillectomy: meta-analysis of randomized, controlled trials. Anesthesiology 2003; 98:1497–1502.

9 • Moodie JE, Brown CR, Bisley EJ, *et al.* The safety and analgesic efficacy of intranasal ketorolac in patients with postoperative pain. Anesth Analg 2008; 107:2025–2031.
A new route of NSAID administration is shown in this article.

10 • Huang YM, Wang CM, Wang CT, *et al.* Perioperative celecoxib administration for pain management after total knee arthroplasty: a randomized, controlled study. BMC Musculoskelet Disord 2008; 9:77.
Multimodal analgesia with a widely used COX-2-selective inhibitor is shown in this article.

11 Smirnov G, Terävä M, Tuomilehto H, *et al.* Etoricoxib for pain management during thyroid surgery: a prospective, placebo-controlled study. Otolaryngol Head Neck Surg 2008; 138:92–97.

12 Feng Y, Ju H, Yang B, An H. Effects of a selective cyclooxygenase-2 inhibitor on postoperative inflammatory reaction and pain after total knee replacement. J Pain 2008; 9:45–52.

13 Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain 1999; 82:111–125.

14 Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg 2004; 99:482–495.

15 • Aveline C, Gautier JF, Vautier P, *et al.* Postoperative analgesia and early rehabilitation after total knee replacement: a comparison of continuous low-dose intravenous ketamine versus nefopam. Eur J Pain 2009; 13:613–619.
This article shows effective analgesia with ketamine infusion through 2 postoperative days.

16 • Zakine J, Samarcq D, Lorne E, *et al.* Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. Anesth Analg 2008; 106:1856–1861.
This article shows effective analgesia with ketamine infusion through 2 postoperative days.

17 Aubrun F, Gaillat C, Rosenthal D, *et al.* Effect of a low-dose ketamine regimen on pain, mood, cognitive function and memory after major gynaecological surgery: a randomized, double-blind, placebo-controlled trial. Eur J Anaesthesiol 2008; 25:97–105.

18 Engelhardt T, Zaarour C, Naser B, *et al.* Intraoperative low-dose ketamine does not prevent a remifentanil-induced increase in morphine requirement after pediatric scoliosis surgery. Anesth Analg 2008; 107:1170–1175.

19 Tramer MR, Schneider J, Marti R-A, Rifat K. Role of magnesium sulfate in postoperative analgesia. Anesthesiology 1996; 84:340–347.

20 Koinig H, Wallner T, Marhofer P, *et al.* Magnesium sulfate reduces intra- and postoperative analgesic requirements. Anesth Analg 1998; 87:206–210.

21 Ryu JH, Kang MH, Park KS, Do SH. Effects of magnesium sulphate on intraoperative anaesthetic requirements and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. Br J Anaesth 2008; 100:397–403.

22 Thurnau GR, Kemp DB, Jarvis A. Cerebrospinal fluid levels of magnesium in patients with preeclampsia after treatment with intravenous magnesium sulfate: a preliminary report. Am J Obstet Gynecol 1987; 157:1435–1438.

23 • Farmery AD, Wilson-MacDonald J. The analgesic effect of epidural clonidine after spinal surgery: a randomized placebo-controlled trial. Anesth Analg 2009; 108:631–634.
This article shows maintained analgesia with 36-h epidural infusion.

24 Lavand'homme PM, Roelants F, Waterloos H, *et al.* An evaluation of the postoperative antihyperalgesic and analgesic effects of intrathecal clonidine administered during elective cesarean delivery. Anesth Analg 2008; 107: 948–955.

25 Andrieu G, Roth B, Ousmane L, *et al.* The efficacy of intrathecal morphine with or without clonidine for postoperative analgesia after radical prostatectomy. Anesth Analg 2009; 108:1954–1957.

26 • Lin TF, Yeh YC, Lin FS, *et al.* Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. Br J Anaesth 2009; 102:117–122.
This article shows maintained analgesia with 24-h epidural infusion.

27 Tufanogullari B, White PF, Peixoto MP, *et al.* Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. Anesth Analg 2008; 106:1741–1748.

28 Bian F, Li Z, Offord J, *et al.* Calcium channel alpha2-delta type 1 subunit is the major binding protein for pregabalin in neocortex, hippocampus, amygdala, and spinal cord: an ex vivo autoradiographic study in alpha2-delta type 1 genetically modified mice. Brain Res 2006; 1075:68–80.

29 Randinitis EJ, Posvar EL, Alvey CW, *et al.* Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol 2003; 43:277–283.

30 Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Curr Opin Anaesthesiol 2007; 20:456–472.

31 • Agarwal A, Gautam S, Gupta D, *et al.* Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. Br J Anaesth 2008; 101:700–704.
That multimodal pregabalin was opioid-sparing and reduced pain without side effects was shown in this article.

32 • Mathiesen O, Jacobsen LS, Holm HE, *et al.* Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. Br J Anaesth 2008; 101:535–541.
This article showed that multimodal pregabalin was opioid-sparing in major orthopedic surgery.

33 Mathiesen O, Rasmussen ML, Dierking G, *et al.* Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. Acta Anaesthesiol Scand 2009; 53:227–235.

34 Jokela R, Ahonen J, Tallgren M, *et al.* A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. Pain 2008; 134:106–112.

35 Jokela R, Ahonen J, Tallgren M, *et al.* Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. Br J Anaesth 2008; 100:834–840.

36 Shafer SL. Notice of retraction. Anesth Analg 2009; 108:1953.

37 Shafer SL. Tattered threads. Anesth Analg 2009; 108:1361–1363.

38 Shafer SL. Notice of retraction. Anesth Analg 2009; 108:1350–1351.

39 Eisenach JC. Data fabrication and article retraction. How not to get lost in the woods. Anesthesiology 2009; 110:955–956.

40 White PF, Kehlet H, Liu S. Perioperative analgesia: what do we still know? Anesth Analg 2009; 108:1364–1367.

41 Salerno A, Hermann R. Efficacy and safety of steroid use for postoperative pain relief. Update and review of the medical literature. J Bone Joint Surg Am 2006; 88:1361–1372.

42 Kardash KJ, Sarrazin F, Tessler MJ, Velly AM. Single-dose dexamethasone reduces dynamic pain after total hip arthroplasty. Anesth Analg 2008; 106:1253–1257.

43 Habib AS, White WD, El Gasim MA, *et al.* Transdermal nicotine for analgesia after radical retropubic prostatectomy. Anesth Analg 2008; 107:999–1004.

44 Pogatzki EM, Vandermeulen EP, Brennan TJ. Effect of plantar local anesthetic injection on dorsal horn neuron activity and pain behaviors caused by incision. Pain 2002; 97:151–161.

45 • Carney J, McDonnell JG, Ochana A, *et al.* The transversus abdominis plane block provides effective postoperative analgesia in patients undergoing total abdominal hysterectomy. Anesth Analg 2008; 107:2056–2060.
This article showed that a well-placed local anesthetic injection was opioid-sparing and reduced pain after abdominal hysterectomy.

46 Hariharan S, Moseley H, Kumar A, Raju S. The effect of preemptive analgesia in postoperative pain relief: a prospective double-blind randomized study. Pain Med 2009; 10:49–53.