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*Review Article*

# Multimodal Analgesia for Postoperative Pain Control

**Fengling Jin, MD,* Frances Chung, FRCPC†**

Department of Anesthesia, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada

*Pain is one of the main postoperative adverse outcomes. Single analgesics, either opioid or nonsteroidal antiinflammatory drugs (NSAIDs), are not able to provide effective pain relief without side effects such as nausea, vomiting, sedation, or bleeding. A majority of double or single-blind studies investigating the use of NSAIDs and opioid analgesics with or without local anesthetic infiltration showed that patients experience lower pain scores, need fewer analgesics, and have a prolonged time to requiring analgesics after surgery. This review focuses on multimodal analgesia, which is currently recommended for effective postoperative pain control.* © 2001 by Elsevier Science Inc.

**Keywords:** Analgesia: multimodal; anesthesia: regional block, complications; nonsteroidal antiinflammatory drugs.

## Introduction

Postoperative pain is one of the main postoperative adverse outcomes causing distress to patients,[1] prolonging stays in ambulatory care units,[2] and increasing the incidence of unanticipated admissions after surgery.[3] Single analgesics alone, either opioid or nonsteroidal antiinflammatory drugs (NSAIDs), are not able to provide effective pain relief for most moderate or severe pain, and moreover, they are associated with side effects such as nausea, vomiting, sedation, or bleeding,.[2,4,5]

Multimodal analgesia is currently recommended for effective postoperative pain control.[6,7] Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms (*e.g.,* opioids, NSAIDs, and local anesthetics), resulting in additive or synergistic analgesia, lower total doses of analgesics, and fewer side effects.[8] The use of multimodal analgesia decreases pain scores and/or the requirement for postoperative analgesics in different surgical procedures.[7–18] This review focuses on the effect of multimodal analgesia on postoperative pain management and the recovery profile of adult surgical patients undergoing ambulatory or major surgical procedures.

## Multimodal Analgesia

It has been suggested that multimodal analgesia is a rational approach to pain management and is more effective (*Table 1*).[4,19] The aim of multimodal analgesia combinations is to reduce postoperative pain. Theoretically, multimodal analgesia is achieved by a combination of opioids, and regional blocks which attenuate the pain-related signals in the central nervous system (CNS), and NSAIDs, which act mainly in the periphery to inhibit the initiation of pain

Clinical/Research Fellow in Anesthesia

†Professor of Anesthesia, Department of Anesthesia, University of Toronto

Address correspondence and reprint requests to Dr. Chung at the Department of Anesthesia, Toronto Western Hospital, 399 Bathurst St., EC 2–046, Toronto, Ontario, Canada M5T 2S8. [Email: Frances.Chung@uhn.on.ca].

This paper is partially sponsored by Pharmacia Corporation, Skokie, IL.

Received for publication March 22, 2001; revised manuscript accepted for publication July 23, 2001.



655 Avenue of the Americas, New York, NY 10010

0952-8180/01/$–see front matter
PII S0952-8180(00)00320-8

**Table 1.** Recommended Approach to Analgesia in Patients Undergoing Surgical Procedures

| |
|---|
| **Minor surgery** |
| Wound infiltration with local anesthetic |
| Peripheral nerve blockade with local anesthetic |
| Oral or parenteral NSAIDs |
| Oral opioid with or without acetaminophen for Breakthrough pain |
| **Intermediate surgery** |
| Wound infiltration with local anesthetic |
| Peripheral nerve blockade with local anesthetic |
| Intravenous PCA opioid |
| Oral or parental NSAIDs |
| Single-injection intrathecal or epidural opioid |
| **Major surgery** |
| Wound infiltration with local anesthetic |
| Peripheral nerve blockade with local anesthetic |
| Epidural local anesthetic and opioid |
| Oral or injectable NSAIDs |
| Systemic opioid (intravenous, intermittent, or PCA) |

NSAIDs = nonsteroidal antiinflammatory drugs; PCA = patient-controlled analgesia. From Reference[4]. Reproduced with permission.

signals. Animal studies also demonstrate the synergistic effect between NSAIDs and opioids, and certain other analgesics in clinical pain states.[20] Many studies have shown additive and/or synergistic effects, with reductions in pain scores or postoperative analgesic requirements in humans and animals[7–12,14–18,21–27]. Therefore, multimodal analgesia should be given to control postoperative pain.

### *Opioids*

Opioids are the most effective analgesics, especially for moderate-to-severe postoperative pain.[28] Their effects are mediated by opioid receptors in the CNS that attenuate pain-related signals. Peripheral opioid receptors also can provide analgesic effects in humans.[29] The potency of individual opioids correlates with their affinity for their respective receptors.[30] However, the side effect profile of opioids, which includes nausea/vomiting, sedation, ileus, constipation, and respiratory depression, should be considered when using large doses of these drugs.[2,5,31]

### *NSAIDs*

Nonsteroidal antiinflammatory drugs (NSAIDs) have proved to be valuable in the management of postoperative pain because of their opioid-sparing actions[32] and antiinflammatory effects. NSAIDs achieve their hyperalgesia-suppressing effect by reducing the concentration of prostaglandins peripherally and centrally, and through several other peripheral and central mechanisms.[33–35] Cyclic prostaglandins are produced by the cyclooxygenase-catalyzed oxidation of arachidonic acid.

### *The Cyclooxygenase Pathway*

The cyclooxygenase (COX) pathway represents one of the major routes for oxidative metabolism of arachidonic acid. NSAIDs inhibit cyclooxygenases, a group that comprises two enzymes: COX-1 and COX-2. The two COX enzymes are very similar in structure, but they have a crucial difference in amino acid sequence at their active site.[36,37] Most COX-1 is constitutively expressed and involved in homeostasis, whereas COX-2 is inducible and involved in pathways of pain and inflammation.[35,38,39] Prostaglandins produced through metabolism of arachidonic acid by COX-1 are essential for maintaining the integrity of the gastric mucosa, and allowing normal platelet aggregation, and kidney function.[38]

### *COX-2-Specific Inhibitors*

Inhibition of COX-1 by NSAIDs results in the reduction of mucosal prostaglandin cytoprotective functions, in some cases leading to gastric erosions and ulcers.[35,40–43] In contrast, inhibition of COX-2 produces analgesia with fewer adverse effects, particularly gastric erosions, ulcerations, and bleeding (lack of effect on platelet aggregation times).[41,42,44–47] However, some studies have shown that COX-2 inhibition may delay gastric ulcer healing.[48–50]

For acute pain relief, studies with the first two COX-2 specific inhibitors to be developed (celecoxib and rofecoxib) have shown that these two drugs have similar analgesic effects compared with ibuprofen or aspirin in postdental surgery patients.[51–53] In more long-term studies, celecoxib has demonstrated sustained antiinflammatory and analgesic activity similar to both diclofenac[54] and naproxen[55] in rheumatoid arthritis patients, with a lower incidence of gastrointestinal (GI) ulceration and GI adverse events in both studies.

Celecoxib is available only in an oral formulation. A parenteral form of a new COX-2 specific inhibitor is currently under development. Parecoxib has already demonstrated excellent analgesic and antiinflammatory activities in patients with postoperative dental pain.*,†,56,57 It has also been shown to be effective as an analgesic postgeneral gynecologic surgery in a 24-hour study with ketorolac and morphine sulphate as comparators.‡ In a 7-day study of parecoxib and ketorolac in elderly patients, parecoxib was associated with similar GI effects to placebo, with significantly fewer gastric and duodenal erosions and ulcers than ketorolac.[58]

Finally, a 10-day study of the effects of celecoxib and

*Kuss M, Mehlisch D, Bauman A, Baum D, Hubbard R: Analgesic activity of single IV doses of parecoxib, a COX-2-specific inhibitor, and Toradol in postoperative dental pain [Abstract]. 9th World Congress on Pain, Vienna, Austria, August 2000. Abstract number 249.

†Mehlisch D, Kuss M, Bauman A, Baum D, Hubbard R: Onset and duration of analgesia of intramuscular doses of parecoxib, a new parenteral COX-2 inhibitor, in postoperative dental pain [Abstract]. 9th World Congress on Pain, Vienna, Austria, August 2000. Abstract number 250.

‡Langand F, Turpin M, Waller P, Kuss M, Hubbard R, LeComte D: A comparative analgesic efficacy study of parecoxib, a new COX-2 specific inhibitor, on post-gynecologic surgery patients [Abstract]. 19th Annual Scientific Meeting of American Pain Society, Atlanta, GA, November 2000. Abstract number 814.

naproxen on platelet function demonstrates clearly that celecoxib does not interfere with normal mechanisms of platelet aggregation and hemostasis, and had no effect on bleeding times.[59] This finding is of particular importance to patients undergoing surgery; an effective analgesic not associated with increased risk of hemorrhage is a useful tool for the surgeon.

For patients at high risk for gastropathy (such as the elderly[60]), COX-2 specific inhibitors provide useful alternatives to existing analgesic therapies. However, the safety profile of COX-2 specific inhibitors in postoperative patients requires further study.[61–63]

The timing of NSAID administration has been examined extensively in studies investigating the concept of preemptive analgesia. This concept suggests that the use of analgesics before surgery will attenuate the central neural effects of the "injury barrage" induced by c-fiber primary afferents as a result of surgical incision and subsequent noxious intraoperative events.[64,65] This minimization of central sensitization is hypothesized to yield reduced postoperative pain intensity and/or reduced postoperative analgesic consumption. Preemptive analgesia has been effective in animals or human volunteers; however, clinical evidence has been either controversial or has failed to support the notion following surgery.[33,66–70]

### *Regional Block or Wound Infiltration*

Regional block, or wound infiltration, can provide both intraoperative and postoperative pain analgesia. Infiltration of local anesthetics into the wound inhibits the transmission of nervous signals from damaged tissue and reduces neurogenic inflammation by blockade of the axon reflex and sympathetic efferent.[71] Preoperative nerve block or wound infiltration with local anesthetics can decrease the inflammatory reaction, reduce pain intensity, and decrease the usage of analgesics intraoperatively and postoperatively in human studies.[70,72,73] Neuraxial blockade reduces postoperative mortality and decreases the odds of deep vein thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression by 59%.[74] Neuraxial blockade is highly recommended as part of the pain armamentarium and should be used whenever possible.

## Multimodal Analgesia: Outcomes in Ambulatory Surgical Patients

Multimodal analgesia is highly recommended in ambulatory anesthesia. *Table 2* and *Table 3* summarize the randomized, controlled trials of multimodal analgesia in ambulatory anesthesia.

### *Systemic Opioids and/or NSAIDs With or Without Local Anesthetic Infiltration or Intraarticular (IA) Block*

Systemic opioids and/or NSAIDs combined with local anesthetic infiltration or IA block were also a means of effective pain relief after ambulatory surgical procedures. *Table 2* summarizes the available data from double-blind or single-blind studies investigating the systemic use of combinations of NSAIDs and opioid analgesics with or without local anesthetic infiltration or IA block. This approach was particularly useful for controlling moderate or even severe pain in patients who underwent ambulatory gynecologic procedures, breast lump excision, and laparoscopic cholecystectomy. Eleven of 14 studies demonstrated a decrease in pain score and/or postoperative analgesic requirements[6,7,10,12,16,18,72,75–78]. In most of the studies, local anesthetic infiltration together with systemic opioids or NSAIDs resulted in a significant improvement in analgesia compared with either drug alone. Combinations of systemic opioids and/or NSAIDs with local anesthetic infiltration or IA block improved recovery by lowering the incidence of postoperative nausea and vomiting (PONV), shortening the discharge time from the postanesthesia care unit (PACU ) and day surgery unit (DSU), and allowed patients to be cared for more easily.[6,7,72,75,77] Therefore, systemic opioids and NSAIDs plus local or regional anesthesia should be considered when patients experience severe postoperative pain.

Not all studies investigating multimodal analgesia demonstrated an improvement in analgesia or recovery profile. The patients in one study who did not show the benefit of combined IP bupivacaine and a preoperative single dose of diclofenac in postoperative pain control after laparoscopic cholecystectomy, had a very low pain score (2 or lower), and were given large doses of cyclimorph and co-proxamol postoperatively.[79] Systemic intravenous (IV) fentanyl and ketorolac significantly lowered the requirement for intraoperative fentanyl,[80] but did not have a better effect on postoperative pain management compared with either drug alone. Tylenol #3®, which contains hydrocodone and acetaminophen, was only more effective than placebo but not better than ketorolac. In addition, this effect was seen only in patients undergoing knee arthroscopy rather than laparoscopic tubal ligation.[78] The reason might be that placebo was used in the first instance, and then ketorolac was continued in this study.[78] Moreover, hydrocodone and acetaminophen were associated with a higher incidence of dizziness.[78] Other studies did not show any enhancement in recovery profile.[12,18,80]

Although three of 14 studies did not show the benefit of multimodal analgesia in outpatients, most studies proved that local or regional blocks plus systemic opioids and NSAIDs provided effective pain control with improved recovery profile. Therefore, multimodal treatment with local or regional block plus systemic opioids and NSAIDs is highly recommended.

### *Combined Use of Local Anesthetics and Analgesics in Knee Arthroscopy, Inguinal Hernia, or Hand Surgeries*

The efficacy of combinations of local anesthetics, opioids, and NSAIDs in wound infiltration; intraarticular, IV regional anesthesia; and axillary blocks for postoperative

**Table 2.** Combined Systemic Opioids and/or NSAIDs, and/or Local Anesthetic Infiltration in Ambulatory Surgery

| Study | Sample Size | Type of Surgery | Treatment | Control | Postoperative Pain Score | Postoperative Analgesics | Recovery Profile |
|---|---|---|---|---|---|---|---|
| Smith *et al.* (1992)[18] | 60 | Knee arthroscopy | IV and IM intraop ketorolac + IA bupivacaine | Ketorolac or bupivacaine | ↓ / ↓ | ↓ / ↓ | ↔ |
| Morrow *et al.* (1995)[76] | 60 | Knee arthroscopy | IA bupivacaine + IM intraop piroxicam | IA saline + IM piroxicam after induction | ↓ | ↓ | |
| White *et al.* (1997)[78] | 65 | Knee arthroscopy | PO hydrocodone-acetaminophen | PO ketorolac or placebo first dose then PO ketorolac | ↔/ ↓ | | Dizziness ↑ in treatment group |
| Chan *et al.* (1996)[10] | 100 | Breast lump excision | Preop and postop diclofenac + bupivacaine infiltration on closure | Diclofenac or bupivacaine or saline | ↓ / ↓ / ↓ ↓ | ↔ | |
| Nehra *et al.* (1995)[16] | 200 | Inguinal hernia | Ilioinguinal block + papaveretum-aspirin | Block or papaveretum-aspirin or saline | ↔/ ↓ / ↓ ↓ | ↔/ ↓ / ↓ ↓ | |
| Ben-David *et al.* (1995)[75] | 70 | Inguinal hernia | Preop local anesthetic infiltration + IM ketorolac | Preop local anesthetic + ketorolac wound infiltration or local anesthetic infiltration + IV ketorolac or PO ketorolac or saline | ↓ / ↓ / ↓ / ↓ ↓ | ↓ / ↓ / ↓ / ↓ ↓ | ↑ easy to care for in parental ketorolac groups |
| Ding *et al.* (1993)[80] | 109 | Gynecologic surgery | IV fentanyl + ketorolac | Fentanyl or IV ketorolac | ↔/↔ | ↔/↔ | ↔ |
| Fiddes *et al.* (1996)[12] | 59 | Laparoscopic tubal ligation | Lidocaine subserosal injection at the cornual end of the fallopian tubes + rectal diclofenac | Saline + rectal diclofenac | ↓ | ↓ | ↔ |
| Eriksson *et al.* (1996)[7] | 90 | Laparoscopic tubal ligation | Lidocaine gel on clips + preop and postop ketoprofen | Lidocaine gel or saline | ↓ / ↓ ↓ | ↓ / ↓ ↓ | PONV ↓ home readiness ↑ |
| Van Ee *et al.* (1996)[77] | 60 | Laparoscopic tubal ligation | PO preop ketoprofen + bupivacaine infiltration of mesosalpinx | PO ketoprofen or bupivacaine infiltration | ↓ / ↓ | ↓ / ↓ | Discharge time ↓ |
| White *et al.* (1997)[78] | 177 | Laparoscopic tubal ligation | PO hydrocodone-acetaminophen | PO ketorolac or saline first dose then PO ketorolac | ↔/↔ | | Dizziness ↑ in treatment group |
| Michaloliakou *et al.*[6] (1996) | 49 | Laparoscopic cholecystectomy | Preop meperidine + ketorolac + preincision bupivacaine + bupivacaine at gallbladder site | Saline | ↓ | ↓ | Nausea ↓ and discharge time from PACU and DSU ↓ in treatment group |
| Johnson *et al.* (1999)[79] | 60 | Laparoscopic cholecystectomy | Rectal preop diclofenac + bupivacaine at gallbladder site | Saline + bupivacaine at gallbladder site | ↔ | ↔ | |
| Bisgaard *et al.* (1999)[72] | 58 | Laparoscopic cholecystectomy | IV intraop ketorolac + postop rectal paracetamol + preincision bupivacaine + bupivacaine at gallbladder site | IV intraop ketorolac + postop rectal paracetamol + saline | ↓ | ↓ | Nausea ↓ |

Data indecipherable, IV = intravenous, IM = intramuscular, intraop = intraoperative, IA = intraarticular, preop = preoperative, postop = postoperative, PONV = postoperative nausea and vomiting, PACU = postanesthesia care unit, DSU = day surgery unit, ↔: Remains the same, ↓: Decrease, ↑: Increase.

pain in knee arthroscopy, inguinal hernia, or hand surgeries has been extensively investigated in randomized, controlled trials (*Table 3*). Twenty of 23 studies demonstrated that combinations of local anesthetics and opioids

**Table 3.** Combined Local Anesthetics, and Analgesics in Infiltration or Intraarticular (IA), Intravenous (IV), and Axillary Blocks in Ambulatory Surgery

| Study | Sample Size | Type of Surgery | Treatment | Control | Postoperative Pain Score | Postoperative Analgesics | Recovery Profile |
|---|---|---|---|---|---|---|---|
| Khoury *et al.* (1992)[86] | 33 | Knee arthroscopy | IA bupivacaine + morphine | IA bupivacaine or IA morphine | ↓ / ↓ | ↓ / ↓ | |
| McSwiney *et al.* (1993)[87] | 40 | Knee arthroscopy | IA bupivacaine + morphine | Saline or IA bupivacaine or IA morphine | ↓ ↓ / ↓ ↓ | ↓ /↔/ ↔ | |
| Allen *et al.* (1993)[85] | 120 | Knee arthroscopy | IA bupivacaine + morphine | IA morphine or IA bupivacaine | ↓ /↔ | ↓ /↔ | ↔ |
| Joshi *et al.* (1993)[88] | 40 | Knee arthroscopy | IA bupivacaine + morphine | IA morphine or IA bupivacaine + IA saline | ↔/ ↓ / ↓ | ↔/ ↓ / ↓ | |
| Heine *et al.* (1994)[90] | 31 | Knee arthroscopy | IA bupivacaine + morphine | IA bupivacaine | ↓ | ↓ | ↔ |
| Boden *et al.* (1994)[89] | 38 | Knee arthroscopy | IA bupivacaine + morphine | IA bupivacaine or IA morphine or Saline | ↔/↔/ ↓ | ↔/↔/ ↓ | ↔ |
| Haynes *et al.* (1994)[13] | 40 | Knee arthroscopy | IA bupivacaine + morphine | IA bupivacaine or IA morphine or saline | ↔/↔/ ↓ | ↔/ ↑ / ↔ | mobilization was slower in saline group |
| Laurent *et al.* (1994)[99] | 58 | Knee arthroscopy | IA bupivacaine + morphine | IA bupivacaine | ↔ | ↔ | |
| Reuben *et al.* (1995)[17] | 80 | Knee arthroscopy | IA ketorolac + IA bupivacaine | ketorolac or IA bupivacaine | ↓ / ↓ | ↓ / ↓ | |
| Gupta *et al.* (1999)[81] | 100 | Knee arthroscopy | Ketorolac + IA morphine | IA saline or IA morphine or IA ketorolac | ↓ / ↓ / ↓ | ↔/↔/ ↔ | |
| Reuben *et al.* (1999)[91] | 50 | Knee arthroscopy | IA bupivacaine + IA clonidine | IA bupivacaine or IA clonidine | ↔/↔ | ↓ /↔ | |
| Reuben *et al.* (1998)[84] | 100 | Reconstruction of ACL | IA bupivacaine + morphine | IA bupivacaine + IV morphine or IA bupivacaine or IA morphine | ↔/↔/ ↓ | ↔/↔/ ↓ | |
| Rasmussen *et al.* (1998)[73] | 60 | Meniscectomy | IA bupivacaine + morphine + methylprednisolone | IA bupivacaine + IA morphine or saline | ↓ / ↓ ↓ | ↓ / ↓ ↓ | convalescence ↑ |
| Ben-David *et al.* (1996)[83] | 32 | Inguinal hernia | Ketorolac + bupivacaine infiltration | Bupivacaine infiltration or ketorolac infiltration or saline infiltration + IM ketorolac | ↔/↔/ ↓ | ↔/↔/ ↓ | |
| Tverskoy *et al.* (1996)[98] | 18 | Inguinal hernia | Bupivacaine + ketamine infiltration | Bupivacaine infiltration | ↔ | ↔ | |
| Connelly *et al.* (1997)[95] | 30 | Inguinal hernia | Local lidocaine + ketorolac infiltration | Local lidocaine infiltration + IV ketorolac | ↓ in movement | ↓ | ↔ |
| Tverskoy *et al.* (1998)[82] | 20 | Inguinal hernia | Lidocaine + fentanyl infiltration | Lidocaine infiltration + IM fentanyl | ↓ | ↔ | |

(*continued on next page*)

or NSAIDs in these settings decreased pain scores and/or postoperative analgesic requirements[13,17,73,81–97] compared with placebo therapy. In addition, some studies demonstrated a better analgesic effect with combination therapy than with a single analgesic[17,81,85–88-90,92,,93]. However, other studies failed to show the advantages of com-

**Table 3.** (Continued)

| Study | Sample Size | Type of Surgery | Treatment | Control | Postoperative Pain Score | Postoperative Analgesics | Recovery Profile |
|---|---|---|---|---|---|---|---|
| Reuben *et al.* (1996)[96] | 60 | Carpal tunnel or tenolysis surgery | Lidocaine + ketorolac (60 mg) IVRA + lidocaine wound infiltration | Lidocaine IVRA + lidocaine + ketorolac wound infiltration or Lidocaine IVRA + lidocaine wound infiltration | ↔/↓ | ↔/↓ | ↔ |
| Steinberg *et al.* (1998)[94] | 70 | Hand | Lidocaine + ketorolac (>20 mg) IVRA | Lidocaine + ketorolac (<10mg) IVRA or saline + lidocaine IVRA | ↓/↓/↓ | ↓/↓/↓ | ↔ |
| Reuben *et al.* (1999)[92] | 45 | Carpal tunnel or tenolysis surgery | Lidocaine + clonidine IVRA | Lidocaine IVRA or Lidocaine IVRA + clonidine IV | ↓/↓ | ↓/↓ | |
| Reuben *et al.* (1999)[93] | 60 | Carpal tunnel or tenolysis surgery | Lidocaine + meperidine (>30 mg) IVRA | Lidocaine + meperidine (<20 mg) or Lidocaine + saline | ↓/↓ | ↓/↓ | Sedation ↑ Dizziness ↑ postoperative nausea and vomiting ↑ |
| Bourke *et al.* (1993)[97] | 40 | Hand | Lidocaine + morphine axillary brachial plexus block | Lidocaine axillary brachial plexus block + IV morphine | ↔ | ↓ | ↔ |
| Singelyn *et al.* (1996)[100] | 80 | Hand | Mepivacaine + clonidine axillary brachial plexus block | Mepivacaine axillary brachial plexus block | ↔ | ↔ | ↔ |

ACL = anterior cruciate ligament, IM = intramuscular, IVRA = intravenous regional anesthesia. ↔ = remains the same, ↓ = decrease, ↑ = increase.

bination therapy over single analgesics,[98,99] and several studies showed that different ways of using combination therapy led to different results in postoperative pain management.[82,83,95] Not only was the combination of local anesthetics and opioids studied, but the combination of other medications such as clonidine or ketamine and local anesthetics was also investigated. The results showed that combining local anesthetic and clonidine significantly prolonged both the time until patients required analgesics and also the amount of analgesic medication required.[92,100] In one study, incisional injection of bupivacaine and ketamine did not show a decrease in visual analog (VAS) pain score or the need for rescue pain medication, but the duration of local anesthetic effect was significantly prolonged, by more than 100 minutes.[98]

Although the advantages in pain management were obvious, only one study reported that the time to mobilization was slower in the control group.[13] Convalescence in arthroscopic meniscectomy surgical patients was enhanced with the combined use of bupivacaine, morphine, and methylprednisolone, which played an important role in antiinflammatory treatment.[73] Most studies in knee arthroscopy, inguinal hernia, or hand surgeries did not show that combining local anesthetics and analgesics reduces the incidence of side effects or shortens the length of hospital stay. One study even showed that larger dose of meperidine (>30 mg) with lidocaine used in axillary brachial plexus worsened the side effects of sedation, dizziness, and PONV.[93]

In general, multimodal analgesia can improve postoperative pain management. Patients experience lower pain scores, and/or need fewer analgesics, and/or have a prolonged time to requiring analgesics after surgery if they are given multimodal analgesia. Theoretically, the recovery profile in terms of discharge time from hospital and mobilization should be improved. However, only a few studies demonstrated this advantage for multimodal analgesia[6,7,13,72,73,75,77]. Some studies did not show any benefit on recovery profile[12,18,41,80,85,89,90,94–96]. In addition, some studies did not even observe the recovery data[10,16,17,76,79,81–84,86–88,91,97–100]. Therefore, further studies of multimodal analgesia should not only investigate the

**Table 4.** Approach to Multimodal Pain Therapy in Ambulatory Anesthesia

| |
|---|
| **Is the patient already in pain?** |
| If so, preoperative analgesia, such as NSAIDs should be started in the preoperative period. |
| **Can I perform a peripheral or regional block?** |
| Nerve block, neuraxial blocks. |
| **What agents can I give at the beginning of, and during, the operation?** |
| Short-acting opioid, NSAIDs (rectal diclofenac, IV ketoralac, or tenoxicam), acetaminophen at the induction by rectal suppository, or IV propacetamol. |
| **What can be given at termination of surgery?** |
| Wound infiltration with bupivacaine or ropivicaine, IA local anesthetics and/or opioid, epidural analgesia with local anesthetic, opioids, or ketamine. |
| **What can be given for pain in the PACU?** |
| Short-acting opioid, NSAIDs, acetaminophen. |
| **What can I give postoperatively?** |
| Acetaminophen, NSAIDs, codeine, oxycodone. |

NSAIDs = nonsteroidal antiinflammatory drugs, IV = intravenous, IA = intraarticular, PACU = postanesthetic care unit. From reference[19]. Reproduced with permission.

effectiveness in pain management, but also observe the recovery profile, which is another important aspect of ambulatory anesthesia.

In summary, multimodal analgesia could be used for relieving postoperative pain in ambulatory surgical patients. For patients undergoing laparoscopic gynecologic procedures or laparoscopic chelecystectomy, shoulder, breast lump resection, reconstruction of anterior cruciate ligament surgical procedures, local or regional use of anesthetic plus systemic NSAIDs and systemic opioids would be the choice. For knee arthroscopy, inguinal herniorrhaphy, and hand surgeries, local or regional use of anesthetics and opioids plus NSAIDs would provide effective pain control. Opioids could be used for breakthrough pain. *Table 4* shows ways to approach multimodal pain therapy.

## Multimodal Analgesia: Outcomes in Inpatients

### *Systemic Use of Combinations of NSAIDs and Opioid Analgesics*

Combined use of systemic opioids and NSAIDs relieved postoperative pain more effectively than single-drug regimens[9,68,101–123] (*Table 5*). In addition, some studies demonstrated a benefit in recovery profile of shortened duration of ischemic attack, and decreased incidence of PONV, sedation, and respiratory depression[68,101,102,104,109,110,112,114,115]. Furthermore, the side effects of NSAIDs, such as gastritis, peptic ulceration, and depression of renal function, were not significantly higher compared with patients who did not use perioperative NSAIDs.[68,102–123] Only one study reported that the incidence of hemorrhage was increased with the use of indomethacin.[113] However, cautious use of NSAIDs is suggested in patients with a history of upper GI bleeding, renal and liver impairment, hypovolemia, and older age.[8,114]

One study showed that β-cyclodextrin piroxicam administered po plus continuous tramadol–propofol infusion significantly lowered the requirement for intraoperative propofol, although there was not a decrease in pain score and the requirement of analgesics.[124] Combined use of acetaminophen and oxycodone or hydrocodone and ibuprofen was reported to increase somnolence and postoperative nausea and vomiting.[123] Ileus was reported in two patients undergoing cesarean section or lower abdominal surgery who took acetaminophen/oxycodone. This drug combination provided better analgesia than did ibuprofen alone or placebo, but less analgesia than bromfenac sodium alone.[105] In general, combinations of systemic opioids and NSAIDs for major surgical procedure have been showed to be more rational and effective.

### *Epidural Combinations of Local Anesthetics and Opioids*

Epidural anesthesia not only provides intraoperative analgesia, but can also control postoperative pain in major surgical procedures.[125] Morphine enhances pain relief and the spread of sensory analgesia during continuous epidural bupivacaine infusion.[126,127] The analgesic efficacy of epidural combinations of local anesthetics and opioids has been investigated in randomized, controlled studies (*Table 6*). Almost all studies showed that combination therapy provided better analgesic efficacy than did bupivacaine alone.[126,128–140] Epidural combinations of fentanyl and morphine also improved pain management in postgastrectomy patients. In addition, combining local anesthetic with clonidine or ketamine showed an enhanced effect on pain relief, although more studies are required to prove their efficacy and safety.[129,136]

Adverse effects of combination therapy reported ranged from limb weakness, increased vomiting, slower recovery of bowel movement, and respiratory depression and hypotension[128,131,132,136,138,141,142]. However, some studies demonstrated that combination therapy hastened recovery in respiration, and decreased the incidence of hypotension and emetic episodes.[130] Therefore, more studies are required to investigate the issue of postoperative recovery and adverse effects of combination therapy.

### *Combined Use of Wound Infiltration, or Regional Block, or Neuroaxial Block with Systemic NSAIDs, and/or Opioid Analgesics*

Wound infiltration provides both intraoperative and postoperative analgesia (*Table 7*). First of all, combined use of incisional local anesthetic infiltration and NSAIDs, and/or opioid analgesics decreased the pain score or the requirement of analgesics,[143–152] compared with morphine or ketorolac alone. Secondly, incisional bupivacaine can enhance the analgesic effect of epidural bupivacaine and morphine in upper abdominal surgical patients.[145] Thirdly, epidural use of local anesthetics and opioids had better analgesic effect with decreased vomiting and sedation.[143,146] Finally, epidural or spinal local anesthetics and/or morphine combined with opioids or NSAIDs also

**Table 5.** Systemic Use of Combinations of Nonsteroidal Antiinflammatory Drugs (NSAIDs) and Opioid Analgesics for Postoperative Analgesia in Inpatients After Major Surgical Procedures

| Study | Sample Size | Type of Surgery | Treatment | Control | Postoperative Pain Score | Postoperative Analgesics | Recovery Profile |
|---|---|---|---|---|---|---|---|
| Segstro *et al.* (1991)[116] | 50 | Orthopedic | Postop rectal indomethacin + PCA/IV morphine | Placebo + PCA/IV, morphine | ↓ | ↓ | ↔ |
| Kinsella *et al.* (1992)[106] | 75 | Orthopedic | Postop IM ketorolac + IM morphine | Placebo + IM morphine | ↓ | ↓ | ↔ |
| Park *et al.* (1996)[109] | 44 | Orthopedic | Preop and postop clonidine PO + PCA/IV morphine | PO placebo + PCA/IV morphine | ↔ | ↓ | Sedation ↑ and PONV ↓ in treatment group |
| Beattie *et al.* (1997)[102] | 174 | Orthopedic | Postop IV ketorolac + PCA/IV morphine | IV saline + PCA/IV morphine | ↓ | ↓ | Duration of cardiac ischemia ↓ |
| Fletcher *et al.* (1997)[68] | 64 | Orthopedic | propacetamol + IV ketoprofen + PCA/IV morphine | Saline or propacetamol or ketoprofen + PCA/IV morphine | ↓ / ↓ / ↓ | ↓ / ↓ / ↓ | 1 respiratory depression episode in saline group |
| Reuben *et al.* (1997)[115] | 80 | Orthopedic | IV ketorolac + PCA/IV morphine | PCA/IV saline + morphine | ↓ | ↓ | Sedation ↑ in saline group |
| Reuben *et al.* (1998)[114] | 70 | Orthopedic | IV ketorolac (>7.5 mg) + PCA/IV morphine | Saline or IV ketorolac (<5 mg) + PCA/IV morphine | ↓ / ↓ | ↓ / ↓ | Sedation ↑ in saline group |
| Reasbeck *et al.* (1982)[113] | 90 | Major abdominal | Postop rectal indomethacin + IM morphine | Placebo + IM morphine | ↓ | ↓ | Hemorrhage ↑ in treatment group |
| Hodsman *et al.* (1987)[104] | 65 | Abdominal | Postop IM diclofenac + PCA/IV morphine | PCA/IV saline + morphine | ↓ | ↓ | $pCO_2$ ↑ in control group |
| Sevarino *et al.* (1992)[117] | 35 | Lower abdominal | Postop IM ketorolac + PCA/IV morphine | PCA/IV saline + morphine | ↔ | ↓ | |
| Gillies *et al.* (1987)[101] | 61 | Upper abdominal | Postop IM ketorolac + PCA/IV morphine | PCA/IV saline + morphine | ↓ | ↓ | $pCO_2$ ↑ in saline group |
| Burns *et al.* (1991)[103] | 67 | Upper abdominal | Postop IM ketorolac + PCA/IV morphine | PCA/IV saline + morphine | ↓ | ↓ | ↔ |
| Sevarino *et al.* (1994)[118] | 62 | Lower abdominal | Postop IM ketorolac + PCA/IV morphine | PCA/IV saline + morphine | ↓ | ↔ | |
| Watanabe *et al.* (1994)[122] | 80 | Cholecystectomy | Buprenorphine + rectal indomethacin | Rectal buprenorphine or rectal indomethacin or placebo | ↔/ ↓ / ↓ | ↔/ ↓ / ↓ | ↔ |
| Turner *et al.* (1994)[121] | 50 | Cholecystectomy | Intraop and postop rectal indomethacin + PCA/IV pethidine | Saline | ↓ | ↓ | ↔ |
| Parker *et al.* (1994)[110] | 210 | Lower abdominal | Postop IV ketorolac + IV morphine/ meperidine | IV saline + morphine/IV meperidine | ↓ | ↓ | Antiemetic drugs, sedation and discomfort ↑ in saline group |

(*continued on next page*)

**Table 5.** (Continued)

| Study | Sample Size | Type of Surgery | Treatment | Control | Postoperative Pain Score | Postoperative Analgesics | Recovery Profile |
|---|---|---|---|---|---|---|---|
| Blackburn *et al.* (1995)[9] | 60 | Lower abdominal | Postop IV ketorolac infusion + PCA/IV morphine | Saline | ↓ | ↓ | ↔ |
| Plummer *et al.* (1996)[111] | 108 | Lower abdominal | Preop and postop PO ibuprofen + PCA/IV morphine | Placebo | ↓ | ↔ | ↔ |
| Johnson *et al.* (1997)[105] | 238 | Cesarean section and lower abdominal | Acetaminophen + PO oxycodone | Bromfenac sodium or ibuprofen or placebo | ↑ / ↓ / ↓ | ↓ / ↑ / ↑ in time for remedication | 2 ileus in Acetaminophen + oxycodone group |
| Sunshine *et al.* (1997)[120] | 120 | Cesarean section and lower abdominal | Hydrocodone + PO ibuprofen | Ibuprofen or placebo | ↓ / ↓ ↓ | ↑ / ↑ ↑ in time for remedicaton | Somnolence ↑ in combination group |
| Lauretti *et al.* (1997)[124] | 48 | Minor abdominal | Preop PO beta-cyclodextrin piroxicam + continuous tramadol-propofol infusion | Saline + propofol infusion | ↔ | Time for rescue analgesic ↑ | ↔ |
| Sia *et al.* (1997)[119] | 60 | Cesarean section | Preop rectal diclofenac + IV morphine infusion | Saline + IV morphine infusion | ↓ | ↓ | ↔ |
| Wideman *et al.* (1999)[123] | 240 | Cesarean section and lower abdominal | Hydrocodone + PO ibuprofen | Hydrocodone or ibuprofen or placebo | ↓ / ↓ / ↓ ↓ | ↑ / ↑ / ↑ ↑ in time for remedication | PONV ↑ in hydrocodone + ibuprofen group |
| Olofsson *et al.* (2000)[108] | 50 | Cesarean section | Postop rectal diclofenac + PCA ketobemidone | PCA saline + ketobemidone | ↓ | ↓ | ↔ |
| Liu *et al.* (1993)[107] | 60 | Laparoscopic cholecystectomy | Preop + postop IM ketorolac + IV fentanyl | IV saline + fentanyl | ↓ | ↓ | ↔ |
| Ready *et al.* (1994)[112] | 207 | Major surgery | Postop IV ketorolac + PCA/IV morphine | Saline + PCA/IV morphine | ↓ | ↓ | Vomiting and fever ↑ in saline group |

Postop = postoperative, PCA = Patient-controlled analgesia, IV = intravenous, IM = intramuscular, preop = preoperative, PO = per PONV = postoperative nausea and vomiting, $pCO_2$ = partial pressure of carbon dioxide, Intraop = intraoperative. ↔ = remains the same, ↓ = decrease, ↑ = Increase.

provided better analgesia for major surgical procedures than these techniques alone.[143–145,148]

Regarding the improvement of recovery profile, however, only one study demonstrated that preincisional paravertebral block lowered the pain score and analgesic requirement with improved postoperative pulmonary functions for thoracic surgical patients.[150] Another study of thoracic surgical patients, in which intercostal block was combined with IV morphine and postoperative intramuscular ketorolac, did not show a significant advantage of multimodal analgesia.[153] The requirement for analgesia was decreased only in the first 6 hours postsurgery, but cumulative consumption of analgesics was no different from the placebo group at 72 hours.[147] In addition, ketamine IV supplement to epidural bupivacaine for renal surgical patients resulted in a higher incidence of sedation with no benefit for postoperative analgesia.[154] Although intraarticular bupivacaine and morphine had a superior analgesic effect in postoperative arthroscopic procedures than did single drug alone, this effect was not demonstrated in knee replacement procedures.[155] The reason might be that the dose of morphine used in this study (1 mg) was sufficient for arthroscopy, but not large enough for knee replacement, and the wound drain might have resulted in loss of drug.[155]

In general, multimodal analgesia with combined local

**Table 6.** Epidural Combinations of Local Anesthetics and Opioids for Postoperative Analgesia After Major Surgical Procedures

| Study | Sample size | Type of surgery | Treatment | Control | Analgesic efficacy | Duration | Complication |
|---|---|---|---|---|---|---|---|
| Cullen *et al.* (1985)[130] | 81 | Major abdominal | Bupivacaine + morphine | Nonepidural or saline or bupivacaine | ↑ / ↑ / ↑ | 72 | Recovery of respiration was quicker in treatment group |
| Hjortso *et al.* (1986)[126] | 20 | Major abdominal | Bupivacaine + morphine | Bupivacaine | ↑ | 16 | 7 patients withdrew from control group due to the wide segment sensory block |
| Logas *et al.* (1987)[134] | 53 | Thoracic | Bupivacaine + morphine | Morphine or bupivacaine or saline or IM morphine | ↔/ ↑ / ↑ / ↑ ↑ | 72 | One respiratory depression episode in B group |
| Lee *et al.* (1988)[133] | 60 | Lower abdominal | Bupivacaine + diamorphine | Bupivacaine or diamorphine | ↑ / ↑ | 21 | One motor block in B group |
| Scott *et al.* (1989)[140] | 20 | Upper abdominal | Bupivacaine + morphine | Bupivacaine | ↑ | 16 | ↔ |
| George *et al.* (1991)[132] | 25 | Thoracic | Bupivacaine + fentanyl | Fentanyl | ↑ in first 24 hours | 48 | One limb weakness episode in B+F group |
| Asantila *et al.* (1991)[128] | 60 | Lower abdominal | Bupivacaine + morphine | Morphine or bupivacaine | ↔/ ↑ | 24 | Vomiting ↑ and recovery in bowel movement slower in treatment and morphine groups |
| Badner *et al.* (1991)[142] | 30 | Orthopedic | Bupivacaine + fentanyl | Fentanyl | ↔ | 48 | One respiratory depression episode and hypotension, one slight motor weakness episode in B+F group |
| George *et al.* (1992)[131] | 30 | Major abdominal | Bupivacaine + fentanyl | Fentanyl or bupivacaine | ↑ / ↑ | 24 | One limb weakness in B group and another one in study group |
| Badner *et al.* (1992)[141] | 30 | Major abdominal and thoracic | Bupivacaine + fentanyl | Fentanyl | ↔ | 48 | Two motor weakness episodes in B+F group |
| Mourisse *et al.* (1992)[135] | 50 | Thoracic | Bupivacaine + sulfentanil | Bupivacaine or sulfentanil | ↑ / ↑ | 72 | One orthostatic hypotension episode in B and One orthostatic hypotension episode in S group |
| Dahl *et al.* (1992)[139] | 24 | Major abdominal | Bupivacaine + morphine | Morphine | ↑ in mobilization and cough | 48 | ↔ |
| Badner *et al.* (1994)[138] | 39 | Abdominal and thoracic | Bupivacaine + fentanyl | Fentanyl | ↑ | 48 | 4 leg weakness episodes in B+F group |
| Tanaka *et al.* (1997)[137] | 120 | Major upper abdominal | Fentanyl + morphine | Morphine | ↑ | 24 | ↔ |
| Paech *et al.* (1997)[136] | 92 | Lower abdominal | Bupivacaine + fentanyl + clonidine | Bupivacaine + fentanyl | ↑ | 24 | BP ↓, emetic episodes ↓ in the treatment group |
| Chia *et al.* (1998)[129] | 91 | Major thoracic and abdominal | Bupivacaine + morphine + ketamine | Bupivacaine + morphine | ↑ | 72 | ↔ |

IM = intramuscular, BP = blood pressure. ↔ = remains the same, ↓ = decrease, ↑ = increase.

**Table 7.** Combined Use of Wound Infiltration and/or Epidural and/or Nonsteroidal Antiinflammatory Drugs (NSAIDs), and/or Opioid Analgesics for Postoperative Analgesia After Major Surgical Procedures

| Study | Sample Size | Type of Surgery | Treatment | Control | Postoperative Pain Score | Postoperative Analgesics | Recovery Profile |
|---|---|---|---|---|---|---|---|
| Moiniche *et al.* (1994)[148] | 42 | Knee and hip arthroplasty | Epidural bupivacaine/ morphine + oral piroxicam | IM/IV morphine + acetaminophen | ↓ | ↓ | ↔ |
| Badner *et al.* (1997)[155] | 75 | Knee replacement | Morphine + IA bupivacaine | IA bupivacaine or IA morphine | ↔/↔ | ↔/↔ | ↔ |
| Scott *et al.* (1994)[144] | 26 | Hysterectomy | IM diclofenac + epidural bupivacaine | IM saline + epidural bupivacaine | ↓ | | ↔ |
| Dahl *et al.* (1994)[143] | 32 | Cholecystectomy | Preop ibuprofen + incisional bupivacaine+ bupivacaine + epidural morphine | Preop ibuprofen + incisional bupivacaine+ IV morphine | ↓ | ↔ | Vomiting ↑ in control group |
| Bartholdy *et al.* (1994)[145] | 49 | Upper abdominal surgery | Incisional bupivacaine + bupivacaine + epidural morphine | Bupivacaine + epidural morphine | ↔ at rest and cough ↓ at mobilization | ↓ | |
| George *et al.* (1994)[146] | 21 | Upper abdominal | Bupivacaine + epidural fentanyl | Morphine PCA | ↓ | | ↓ vomiting, sedation ↓ |
| Pavy *et al.* (1995)[149] | 30 | Cesarean section | Postop rectal indomethacin + intrathecal morphine | Placebo + intrathecal morphine | ↓ | ↓ | ↔ |
| Rosaeg *et al.* (1997)[152] | 40 | Cesarean section | Intrathecal morphine + incisional bupivacaine + ibuprofen + PO acetaminophen | Morphine PCA | ↓ | | early bowel mobility |
| Wittels *et al.* (1998)[151] | 20 | Minilaparotomy Bupivacaine infiltration of the uterine tubes and mesosalpinx + intraop ketorolac | Saline infiltration + intraop ketorolac | ↓ | ↓ | | |
| Ilkjaer *et al.* (1998)[154] | 60 | Renal surgery | IV ketamine + epidural bupivacaine | Saline IV + epidural bupivacaine | ↔ | ↔ | Sedation ↑ in ketamine group |
| Kavanagh *et al.* (1994)[147] | 30 | Thoracic | Preop indomethacin + morphine IV + intraop bupivacaine intercostal block | Saline | ↔ | ↓ | ↔ |
| Richardson *et al.* (1994)[150] | 56 | Thoracic | Periop rectal diclofenac + morphine + preincisional paravertebral block | Saline | ↓ | ↓ | Postop pulmonary function ↓ in control group |
| Power *et al.* (1994)[153] | 75 | Thoracic | Postop IM ketorolac + bupivacaine intercostal block | Saline + bupivacaine intercostal block | ↔ | ↔ | |

IM = intamuscular, ↔: Remains the same, ↓: Decrease, ↑: Increase. IV = intavenous, IA = intraarticular, PCA = patient-controlled analgesia, PO = per os, oral administration, intraop = intraoperative, periop = perioperative, postop = postoperative.

anesthesia infiltration or block and systemic opioids or NSAIDs provided better analgesic effect for most major surgical procedures. Whether multimodal analgesia can improve the convalescence period is still unclear; only a few studies have focused on this area. One study proposes that the multimodal approach—in terms of preoperative information, attenuation of stress, dynamic pain relief, early mobilization, enteral nutrition, and administration of various growth factors in certain high-risk patients—will enable accelerated postoperative surgical recovery.[156] Nevertheless, effective postoperative pain relief has beneficial physiologic effects on different organ systems during the postoperative period and plays an important role in improving postoperative outcome.[157,158]

In summary, multimodal analgesia should be a routine practice to control postoperative pain in inpatients (*Table 1*). For major vascular, abdominal, thoracic, knee and hip replacement surgical procedures, neuraxial block with local anesthetics and/or opioids can provide effective intraoperative and postoperative pain control. Combined general and epidural anesthesia should be highly recommended for major surgery procedures. For neurologic surgical procedure such as cranial or spinal surgical procedures, in which nerve or regional block cannot be administrated, or for intermediate surgeries such as lower abdominal surgical procedures, or for patients who are not willing to have neuraxial blocks, systemic use of combinations of preoperative or intraoperative NSAIDs and PCA morphine could be used. Combined use of wound infiltration, or nerve block with systemic NSAIDs, or opioids could provide effective pain control for inpatients after minor surgical procedures such as laparoscopy or inguinal herniorrhaphy.

## Economic Impact

Some studies have demonstrated that multimodal analgesia combined with preoperative education, enforced mobilization, and nutrition decreases postoperative morbidity in terms of PONV and pain, and shortened the hospital stay.[6,73,158–164] One study reported reduced hospital costs for knee and hip replacement surgical patients.[165] Studies in the treatment of rheumatoid arthritis show that nonspecific NSAIDs were cost-effective for patients who were at low risk for developing side effects. However, for patients at high risk, such as elderly patients, the COX-2 specific inhibitors are likely to be more cost-effective.[166] Further studies are needed to clarify these issues.

## Conclusion

Multimodal analgesia is a promising approach to controlling postoperative pain, both for outpatients who have minor surgical procedures and for inpatients undergoing major surgical procedures. Different techniques are appropriate to different procedures. Perioperative NSAIDs and wound infiltration and block are more suitable for minor ambulatory surgical procedures. For patients who experience severe pain, combined systemic opioids, NSAIDs, and epidural analgesics or wound infiltration or block can provide more effective pain control. Multimodal analgesia has a great potential to enhance the postoperative recovery period.

## References


1. Sutters KA, Miaskowski C: Inadequate pain management and associated morbidity in children at home after tonsillectomy. *J Pediatr Nurs* 1997;12:178–85.
2. Chung F: Recovery pattern and home-readiness after ambulatory surgery. *Anesth Analg* 1995;80:896–902.
3. Fortier J, Chung F, Su J: Unanticipated admission after ambulatory surgery–a prospective study. *Can J Anaesth* 1998;45:612–9.
4. Carpenter RL: Optimizing postoperative pain management. *Am Fam Physician* 1997;56:835–44.
5. Watcha MF, White PF: Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology* 1992;77:162–84.
6. Michaloliakou C, Chung F, Sharma S: Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. *Anesth Analg* 1996;82:44–51.
7. Eriksson H, Tenhunen A, Korttila K: Balanced analgesia improves recovery and outcome after outpatient tubal ligation. *Acta Anaesthesiol Scand* 1996;40:151–5.
8. Dahl JB, Kehlet H: Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. *Br J Anaesth* 1991;66:703–12.
9. Blackburn A, Stevens JD, Wheatley RG, Madej TH, Hunter D: Balanced analgesia with intravenous ketorolac and patient-controlled morphine following lower abdominal surgery. *J Clin Anesth* 1995;7:103–8.
10. Chan A, Dore CJ, Ramachandra V: Analgesia for day surgery. Evaluation of the effect of diclofenac given before or after surgery with or without bupivacaine infiltration. *Anaesthesia* 1996;51:592–5.
11. Sutters KA, Levine JD, Dibble S, Savedra M, Miaskowski C: Analgesic efficacy and safety of single-dose intramuscular ketorolac for postoperative pain management in children following tonsillectomy. *Pain* 1995;61:145–53.
12. Fiddes TM, Williams HW, Herbison GP: Evaluation of postoperative analgesia following laparoscopic application of Filshie clips. *Br J Obstet Gynaecol* 1996;103:1143–7.
13. Haynes TK, Appadurai IR, Power I, Rosen M, Grant A: Intra-articular morphine and bupivacaine analgesia after arthroscopic knee surgery. *Anaesthesia* 1994;49:54–6.
14. Lacoste L, Thomas D, Kraimps JL, et al: Postthyroidectomy analgesia: morphine, buprenorphine, or bupivacaine? *J Clin Anesth* 1997;9:189–93.
15. Monagle J, Wongprasartsuk P, Shearer W: Ketorolac versus fentanyl for gynaecological day-case surgery. *Aust N Z J Obstet Gynaecol* 1993;33:430–2.
16. Nehra D, Gemmell L, Pye JK: Pain relief after inguinal hernia repair: a randomized double-blind study. *Br J Surg* 1995;82:1245–7.
17. Reuben SS, Connelly NR: Postoperative analgesia for outpatient arthroscopic knee sugery with intraarticular bupivacaine and ketorolac. *Anesth Analg* 1995;80:1154–7.
18. Smith I, Shively RA, White PF: Effects of ketorolac and bupivacaine on recovery after outpatient arthroscopy. *Anesth Analg* 1992;75:208–12.
19. Neligan PJ, Cunningham AJ: The multimodal approach to pain in ambulatory anesthesia. *Curr Anesthesiol Reports* 2000; 2: 320–6.
20. Malmberg AB, Yaksh TL: Pharmacology of the spinal action of ketorolac, morphine, ST-91, U50488H, and L-PIA on the for-

malin test and an isobolographic analysis of the NSAID interaction. *Anesthesiology* 1993;79:270–81.
21. Egan TM, Herman SJ, Doucette EJ, Normand SL, McLeod RS: A randomized, controlled trial to determine the effectiveness of fascial infiltration of bupivacaine in preventing respiratory complications after elective abdominal surgery. *Surgery* 1988; 104:734–40.
22. Fletcher D, Zetlaoui P, Monin S, Bombart M, Samii K: Influence of timing on the analgesic effect of intravenous ketorolac after orthopedic surgery. *Pain* 1995;61:291–7.
23. Guard BC, Wiltshire SJ: The effect of glycopyrrolate on postoperative pain and analgesic requirements following laparoscopic sterilisation. *Anaesthesia* 1996;51:1173–5.
24. Kehlet H, Dahl JB: The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993; 77:1048–56.
25. Levack ID, Holmes JD, Robertson GS: Abdominal wound perfusion for the relief of postoperative pain. *Br J Anaesth* 1986;58: 615–9.
26. Morisaki H, Masuda J, Fukushima K, Iwao Y, Suzuki K, Matsushima M: Wound infiltration with lidocaine prolongs postoperative analgesia after haemorrhoidectomy with spinal anaesthesia. *Can J Anaesth* 1996;43:914–8.
27. Shield MJ: Diclofenac/misoprostol: novel findings and their clinical potential. *J Rheumatol Suppl* 1998;51:31–41.
28. Claxton AR, McGuire G, Chung F, Cruise C: Evaluation of morphine versus fentanyl for postoperative analgesia after ambulatory surgical procedures. *Anesth Analg* 1997;84:509–14.
29. Stein C: Peripheral mechanisms of opioid analgesia. *Anesth Analg* 1993;76:182–91.
30. Stahl KD, van Bever W, Janssen P, Simon EJ: Receptor affinity and pharmacological potency of a series of narcotic analgesic, anti-diarrheal and neuroleptic drugs. *Eur J Pharmacol* 1977;46: 199–205.
31. Looi-Lyons LC, Chung FF, Chan VW, McQuestion M: Respiratory depression: an adverse outcome during patient controlled analgesia therapy. *J Clin Anesth* 1996;8:151–6.
32. Cashman JN: The mechanisms of action of NSAIDs in analgesia. *Drugs* 1996;52(Suppl 5):13–23.
33. Woolf CJ, Chong MS: Preemptive analgesia–treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993;77:362–79.
34. Cutler SJ, DeWitt BCJ, Akin DT, et al: Pharmacological evaluation of 1-(carboxymethyl)-3,5-diphenyl-2-methylbenzene, a novel arylacetic acid with potential anti-inflammatory properties. *Inflamm Res* 1998;47:316–24.
35. Schmassmann A, Peskar BM, Stettler C, et al: Effects of inhibition of prostaglandin endoperoxide synthase-2 in chronic gastro-intestinal ulcer models in rats. *Br J Pharmacol* 1998;123:795–804.
36. Picot D, Loll PJ, Garavito RM: The X-ray crystal structure of the membrane protein prostaglandin H2 synthase-1. *Nature* 1994; 367:243–9.
37. Kurumbail RG, Stevens AM, Gierse JK, et al: Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents. *Nature* 1996;384:644–8.
38. Vane JR, Bakhle YS, Botting RM: Cyclooxygenases 1 and 2. *Ann Rev Pharmacol Toxicol* 1998;38:97–120.
39. Power I, Chambers W A, Greer I A, Ramage D, Simon E: Platelet function after intramuscular diclofenac. *Anaesthesia* 1990;45: 916–9.
40. Valdrighi JB, Hanowell LH, Loeb RG, Behrman KH, Disbrow EA: Effect of intraoperative ketorolac on postanesthesia care unit comfort. *J Pain Symptom Manage* 1994;9:171–4.
41. Fosslien E: Adverse effects of nonsteroidal anti-inflammatory drugs on the gastrointestinal system. *Ann Clin Lab Sci* 1998;28: 67–81.
42. Shah AA, Fitzgerald DJ, Murray FE: Non-steroidal anti-inflammatory drugs (NSAIDs) and gastro-intestinal toxicity: current issues. *Ir J Med Sc* 1999;168:242–5.
43. Wallace JL, Bak A, McKnight W, Asfaha S, Sharkey KA, MacNaughton WK: Cyclooxygenase 1 contributes to inflammatory responses in rats and mice: implications for gastrointestinal toxicity. *Gastroenterology* 1998;115:101–9.
44. Kehlet H, Dahl JB: Are perioperative nonsteroidal anti-inflammatory drugs ulcerogenic in the short term?. *Drugs* 1992;44 (Suppl 5):38–41.
45. Laine L, Harper S, Simon T, et al: A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis.Rofecoxib Osteoarthritis Endoscopy Study Group. *Gastroenterology* 1999;117:776–83.
46. Mandell BF: COX 2-selective NSAIDs: biology, promises, and concerns. *Cleve Clin J Med* 1999;66:285–92.
47. Jones MK, Wang H, Peskar BM, et al: Inhibition of angiogenesis by nonsteroidal anti-inflammatory drugs: insight into mechanisms and implications for cancer growth and ulcer healing. *Nat Med* 1999;5:1418–23.
48. Wallace JL, Reuter BK, McKnight W, Bak A: Selective inhibitors of cyclooxygenase-2: are they really effective, selective, and GI-safe?. *J Clin Gastroenterol* 1998;27 (Suppl 1):S28–S34.
49. Mizuno H, Sakamoto C, Matsuda K, et al: Induction of cyclooxygenase 2 in gastric mucosal lesions and its inhibition by the specific antagonist delays healing in mice. *Gastroenterology* 1997; 112:387–97.
50. Hawkey CJ: COX-2 inhibitors. *Lancet* 1999;353(9149):307–14.
51. Morrison BW, Christensen S, Yuan W, Brown J, Amlani S, Seidenberg B: Analgesic efficacy of the cyclooxygenase-2-specific inhibitor rofecoxib in post-dental surgery pain: a randomized, controlled trial. *Clin Ther* 1999;21:943–53.
52. Ehrich EW, Dallob A, De Lepeleire I, et al: Characterization of rofecoxib as a cyclooxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999;65:336–47.
53. Malmstrom K, Deniels S, Kotey P, Seiderberg BC, Desjardins PJ: Comparison of rofecoxib and celecoxib, two cyclooxygenase-2 inhibitors, in postoperative dental pain: a randomized placebo- and active-comparator-controlled clinical trial. *Clin Ther* 1999; 21:1653–63.
54. Emery P, Zeidler H, Kvien TK, et al: Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999;354(9196):2106–11.
55. Simon LS, Weaver AL, Graham DY, et al: Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999;282:1921–8.
56. Daniels SE, Kuss M, Mehlisch D, Bauman A, Baum D, Karim A: Pharmacokinetic and efficacy evaluation of intravenous parecoxib in a postsurgical dental pain model. *Clin Pharmacol Ther* 2000; 67: PI-8.
57. Mehlisch D, Kuss M, Bauman A, Baum D, Karim A, Talwalker S: Correlation of pharmacokinetics (PK) with onset of action and duration of analgesia of intramuscular doses of parecoxib, in postoperative dental pain. *Clin Pharmacol Ther* 2000;67:PIII-7.
58. Hubbard R, Kuss M, LeComte D, Talwalker S, Geis G: An endoscopic study of the gastroduodenal effects of SC-69124A, a parenteral COX-2-specific inhibitor, in the elderly. *Gastroenterology* 2000;118(Suppl 2):A250.
59. Leese PT, Hubbard RC, Karim A, Isakson PC, Yu SS, Geis GS: Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: a randomized, controlled trial. *J Clin Pharmacol* 2000;40:124–32.

60. Fries JF: NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal. *J Rheumatol Suppl* 1991;28:6–10.
61. Souter AJ, Fredman B, White PF: Controversies in the perioperative use of nonsterodial antiinflammatory drugs. *Anesth Analg* 1994;79:1178–90.
62. Fort J: Celecoxib, a COX-2–specific inhibitor: the clinical data. *Ame J Orthop* 1999;28 (Suppl 3):13–8.
63. Kam PC, See AU: Cyclo-oxygenase isoenzymes: physiological and pharmacological role. *Anaesthesia* 2000;55:442–9.
64. Dahl JB, Kehlet H: The value of pre-emptive analgesia in the treatment of postoperative pain. *Br J Anaesth* 1993;70:434–9.
65. Woolf CJ: Generation of acute pain: central mechanisms. *Br Med Bull* 1991;47:523–33.
66. Espinet A, Henderson DJ, Faccenda KA, Morrison LM: Does pre-incisional thoracic extradural block combined with diclofenac reduce postoperative pain after abdominal hysterectomy? *Br J Anaesth* 1996;76:209–13.
67. Fletcher D, Benoist JM, Gautron M, Guilbaud G: Isobolographic analysis of interactions between intravenous morphine, propacetamol, and diclofenac in carrageenin-injected rats. *Anesthesiology* 1997;87:317–26.
68. Fletcher D, Negre I, Barbin C, et al: Postoperative analgesia with i.v. propacetamol and ketoprofen combination after disc surgery. *Can J Anaesth* 1997;44(5 Pt 1):479–85.
69. Kissin I: Preemptive analgesia. Why its effect is not always obvious. *Anesthesiology* 1996;84:1015–9.
70. Pedersen JL, Crawford ME, Dahl JB, Brennum J, Kehlet H: Effect of preemptive nerve block on inflammation and hyperalgesia after human thermal injury. *Anesthesiology* 1996;84:1020–6.
71. Dahl JB, Moiniche S, Kehlet H: Wound infiltration with local anaesthetics for postoperative pain relief. *Acta Anaesthesiol Scand* 1994;38:7–14.
72. 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;89:1017–24.
73. Rasmussen S, Larsen AS, Thomsen ST, Kehlet H: Intra-articular glucocorticoid, bupivacaine and morphine reduces pain, inflammatory response and convalescence after arthroscopic meniscectomy. *Pain* 1998;78:131–4.
74. 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: 1493.
75. Ben-David B, Katz E, Gaitini L, Goldik Z: Comparison of i.m. and local infiltration of ketorolac with and without local anaesthetic. *Br J Anaesth* 1995;75:409–12.
76. Morrow BC, Milligan KR, Murthy BV: Analgesia following day-case knee arthroscopy–the effect of piroxicam with or without bupivacaine infiltration. *Anaesthesia* 1995;50:461–3.
77. van Ee R, Hemrika DJ, de Blok S, Van Der Linden C, Lip H: Effects of ketoprofen and mesosalpinx infiltration on postoperative pain after laparoscopic sterilization. *Obstet Gynecol* 1996; 88(4 Pt 1):568–72.
78. White PF, Joshi GP, Carpenter RL, Fragen RJ: A comparison of oral ketorolac and hydrocodone-acetaminophen for analgesia after ambulatory surgery: arthroscopy versus laparoscopic tubal ligation. *Anesth Analg* 1997;85:37–43.
79. Johnson RC, Hedges AR, Morris R, Stamatakis JD: Ideal pain relief following laparoscopic cholecystectomy. *Int J Clin Pract* 1999;53:16–8.
80. Ding Y, Fredman B, White PF: Use of ketorolac and fentanyl during outpatient gynecologic surgery. *Anesth Analg* 1993;77: 205–10.
81. 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;24:225–30.
82. Tverskoy M, Braslavsky A, Mazor A, Ferman R, Kissin I: The peripheral effect of fentanyl on postoperative pain. *Anesth Analg* 1998;87:1121–4.
83. Ben-David B., Baune-Goldstein U., Goldik Z., Gaitini L: Is preoperative ketorolac a useful adjunct to regional anesthesia for inguinal herniorrhaphy? *Acta Anaesthesiol Scand* 1996;40: 358–63.
84. Reuben SS, Steinberg RB, Cohen MA, Kilaru PA, Gibson CS: Intraarticular morphine in the multimodal analgesic management of postoperative pain after ambulatory anterior cruciate ligament repair. *Anesth Analg* 1998;86:374–8.
85. Allen G C, St. Amand MA, Lui AC, Johnson DH, Lindsay MP: Postarthroscopy analgesia with intraarticular bupivacaine/morphine. A randomized clinical trial. *Anesthesiology* 1993;79:475–80.
86. Khoury GF, Chen AC, Garland DE, Stein C: Intraarticular morphine, bupivacaine, and morphine/bupivacaine for pain control after knee videoarthroscopy. *Anesthesiology* 1992;77:263–6.
87. McSwiney MM, Joshi GP, Kenny P, McCarroll SM: Analgesia following arthroscopic knee surgery. A controlled study of intra-articular morphine, bupivacaine or both combined. *Anaesth Intensive Care* 1993;21:201–3.
88. Joshi GP, McCarroll SM, O'Brien TM, Lenane P: Intraarticular analgesia following knee arthroscopy. *Anesth Analg* 1993;76: 333–6.
89. Boden BP, Fassler S, Cooper S, Marchetto PA, Moyer RA: Analgesic effect of intraarticular morphine, bupivacaine, and morphine/bupivacaine after arthroscopic knee surgery. *Arthroscopy* 1994;10:104–7.
90. Heine MF, Tillet ED, Tsueda K, et al: Intra-articular morphine after arthroscopic knee operation. *Br J Anaesth* 1994;73:413–5.
91. Reuben SS, Connelly NR: Postoperative analgesia for outpatient arthroscopic knee surgery with intraarticular clonidine. *Anesth Analg* 1999;88:729–33.
92. Reuben SS, Steinberg RB, Klatt JL, Klatt ML: Intravenous regional anesthesia using lidocaine and clonidine. *Anesthesiology* 1999;91:654–8.
93. Reuben SS, Steinberg RB, Lurie S, Gibson CS: A dose-response study of intravenous regional anesthesia with meperidine. *Anesth Analg* 1999;88:831–5.
94. Steinberg RB, Reuben SS, Gardner G: The dose-response relationship of ketorolac as a component of intravenous regional anesthesia with lidocaine. *Anesth Analg* 1998;86:791–3.
95. Connelly NR, Reuben SS, Albert M, Page D: Use of preincisional ketorolac in hernia patients: intravenous versus surgical site. *Reg Anesth* 1997;22:229–32.
96. Reuben SS, Duprat KM: Comparison of wound infiltration with ketorolac versus intravenous regional anesthesia with ketorolac for postoperative analgesia following ambulatory hand surgery. *Reg Anesth* 1996;21:565–8.
97. Bourke DL, Furman WR: Improved postoperative analgesia with morphine added to axillary block solution. *J Clin Anesth* 1993; 5:114–7.
98. Tverskoy M, Oren M, Vaskovich M, Dashkovsky I, Kissin I: Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: a study in postoperative patients. *Neurosci Lett* 1996;215:5–8.
99. Laurent SC, Nolan JP, Pozo JL, Jones CJ: Addition of morphine to intra-articular bupivacaine does not improve analgesia after day-case arthroscopy. *Br J Anaesth* 1994;72:170–3.
100. Singelyn FJ, Gouverneur JM, Robert A: A minimum dose of clonidine added to mepivacaine prolongs the duration of

anesthesia and analgesia after axillary brachial plexus block. *Anesth Analg* 1996;83:1046–50.
101. Gillies GW, Kenny GN, Bullingham RE, McArdle CS: The morphine sparing effect of ketorolac tromethamine. A study of a new, parenteral non-steroidal anti-inflammatory agent after abdominal surgery. *Anaesthesia* 1987;42:727–31.
102. Beattie WS, Warriner CB, Etches R, et al: The addition of continuous intravenous infusion of ketorolac to a patient-controlled analgetic morphine regime reduced postoperative myocardial ischemia in patients undergoing elective total hip or knee arthroplasty. *Anesth Analg* 1997;84:715–22.
103. Burns JW, Aitken HA, Bullingham RE, McArdle CS, Kenny GN: Double-blind comparison of the morphine sparing effect of continuous and intermittent i.m. administration of ketorolac. *Br J Anaesth* 1991;67:235–8.
104. Hodsman NB, Burns J, Blyth A, Kenny GN, McArdle CS, Rotman H: The morphine sparing effects of diclofenac sodium following abdominal surgery. *Anaesthesia* 1987;42:1005–8.
105. Johnson GH, Van Wagoner JD, Brown J, Cooper SA: Bromfenac sodium, acetaminophen/oxycodone, ibuprofen, and placebo for relief of postoperative pain. *Clin Ther* 1997;19:507–19.
106. Kinsella J, Moffat AC, Patrick JA, Prentice JW, McArdle CS, Kenny GN: Ketorolac trometamol for postoperative analgesia after orthopaedic surgery. *Br J Anaesth* 1992;69:19–22.
107. Liu J, Ding Y, White PF, Feinstein R, Shear JM: Effects of ketorolac on postoperative analgesia and ventilatory function after laparoscopic cholecystectomy. *Anesth Analg* 1993;76:1061–6.
108. Olofsson CI, Legeby MH, Nygards EB, Ostman KM: Diclofenac in the treatment of pain after caesarean delivery. An opioid-saving strategy. *Eur J Obstet Gynecol Reprod Biol* 2000; 88: 143–6.
109. Park J, Forrest J, Kolesar R, Bhola D, Beattie S, Chu C: Oral clonidine reduces postoperative PCA morphine requirements. *Can J Anaesth* 1996;43:900–6.
110. Parker RK, Holtmann B, Smith I, White PF: Use of ketorolac after lower abdominal surgery. Effect on analgesic requirement and surgical outcome. *Anesthesiology* 1994;80:6–12.
111. Plummer JL, Owen H, Ilsley AH, Tordoff K: Sustained-release ibuprofen as an adjunct to morphine patient-controlled analgesia. *Anesth Analg* 1996;83:92–6.
112. Ready LB, Brown CR, Stahlgren LH, et al: Evaluation of intravenous ketorolac administered by bolus or infusion for treatment of postoperative pain. A double-blind, placebo-controlled, multicenter study. *Anesthesiology* 1994;80:1277–86.
113. Reasbeck PG, Rice ML, Reasbeck JC: Double-blind controlled trial of indomethacin as an adjunct to narcotic analgesia after major abdominal surgery. *Lancet* 1982;2(8290):115–8.
114. Reuben SS, Connelly NR, Lurie S, Klatt M, Gibson CS: Dose-response of ketorolac as an adjunct to patient-controlled analgesia morphine in patients after spinal fusion surgery. *Anesth Analg* 1998;87:98–102.
115. Reuben SS, Connelly NR, Steinberg R: Ketorolac as an adjunct to patient-controlled morphine in postoperative spine surgery patients. *Reg Anesth* 1997;22:343–6.
116. Segstro R, Morley-Forster PK, Lu G: Indomethacin as a postoperative analgesic for total hip arthroplasty. *Can J Anaesth* 1991; 38:578–81.
117. Sevarino FB, Sinatra RS, Paige D, Ning T, Brull SJ, Silverman DG: The efficacy of intramuscular ketorolac in combination with intravenous PCA morphine for postoperative pain relief. *J Clin Anesth* 1992;4:285–8.
118. Sevarino FB, Sinatra RS, Paige D, Silverman DG: Intravenous ketorolac as an adjunct to patient-controlled analgesia (PCA) for management of postgynecologic surgical pain. *J Clin Anesth* 1994;6:23–7.
119. Sia AT, Thomas E, Chong JL, Loo CC: Combination of suppository diclofenac and intravenous morphine infusion in post-caesarean section pain relief–a step towards balanced analgesia? *Singapore Med J* 1997;38:68–70.
120. Sunshine A, Olson NZ, O'Neill E, Ramos I, Doyle R: Analgesic efficacy of a hydrocodone with ibuprofen combination compared with ibuprofen alone for the treatment of acute postoperative pain. *J Clin Pharmacol* 1997;37:908–15.
121. Turner GA, Gorringe J: Indomethacin as adjunct analgesia following open cholecystectomy. *Anaesth Intensive Care* 1994;22: 25–9.
122. Watanabe S, Kondo T, Asakura N, Inomata S: Intraoperative combined administration of indomethacin and buprenorphine suppositories as prophylactic therapy for post-open-cholecystectomy pain. *Anesth Analg* 1994;79:85–8.
123. Wideman GL, Keffer M, Morris E, Doyle RT Jr, Jiang JG, Beaver WT: Analgesic efficacy of a combination of hydrocodone with ibuprofen in postoperative pain. *Clin Pharmacol Ther* 1999;65: 66–76.
124. Lauretti GR, Mattos AL, Lima IC: Tramadol and beta-cyclodextrin piroxicam: effective multimodal balanced analgesia for the intra- and postoperative period. *Reg Anesth* 1997;22:243–8.
125. Grass JA: The role of epidural anesthesia and analgesia in postoperative outcome. *Anesthesiol Clin No Am* 2000; 18: 407–28.
126. Hjortso NC, Lund C, Mogensen T, Bigler D, Kehlet H: Epidural morphine improves pain relief and maintains sensory analgesia during continuous epidural bupivacaine after abdominal surgery. *Anesth Analg* 1986;65:1033–6.
127. Lund C, Mogensen T, Hjortso NC, Kehlet H: Systemic morphine enhances spread of sensory analgesia during postoperative epidural bupivacaine infusion. *Lancet* 1985;2(8465):1156–7.
128. Asantila R, Eklund P, Rosenberg P H: Continuous epidural infusion of bupivacaine and morphine for postoperative analgesia after hysterectomy. *Acta Anaesthesiol Scand* 1991;35:513–7.
129. Chia YY, Liu K, Liu YC, Chang HC, Wong CS: Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic consumption. *Anesth Analg* 1998;86:1245–9.
130. Cullen ML, Staren ED, el-Ganzouri A, Logas WG, Ivankovich AD, Economou SG: Continuous epidural infusion for analgesia after major abdominal operations: a randomized, prospective, double-blind study. *Surgery* 1985;98:718–28.
131. George KA, Chisakuta AM, Gamble JA, Browne GA: Thoracic epidural infusion for postoperative pain relief following abdominal aortic surgery: bupivacaine, fentanyl or a mixture of both? *Anaesthesia* 1992;47:388–94.
132. George KA, Wright PM, Chisakuta A: Continuous thoracic epidural fentanyl for post-thoracotomy pain relief: with or without bupivacaine? *Anaesthesia* 1991;46:732–6.
133. Lee A, Simpson D, Whitfield A, Scott DB: Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. *Br J Anaesth* 1988;60:845–50.
134. Logas WG, el-Baz N, el-Ganzouri A, et al: Continuous thoracic epidural analgesia for postoperative pain relief following thoracotomy: a randomized prospective study. *Anesthesiology* 1987;67: 787–91.
135. Mourisse J, Hasenbos MA, Gielen MJ, Moll JE, Cromheecke GJ: Epidural bupivacaine, sufentanil or the combination for post-thoracotomy pain. *Acta Anaesthesiol Scand* 1992;36:70–4.
136. Paech MJ, Pavy TJ, Orlikowski CE, Lim W, Evans SF: Postoperative epidural infusion: a randomized, double-blind, dose-finding trial of clonidine in combination with bupivacaine and fentanyl. *Anesth Analg* 1997;84:1323–8.
137. Tanaka M, Watanabe S, Matsumiya N, Okada M, Kondo T, Takahashi S: Enhanced pain management for postgastrectomy patients with combined epidural morphine and fentanyl. *Can J Anaesth* 1997;44:1047–52.

138. Badner NH, Bhandari R, Komar WE: Bupivacaine 0.125% improves continuous postoperative epidural fentanyl analgesia after abdominal or thoracic surgery. *Can J Anaesth* 1994;41(5 Pt 1):387–92.
139. Dahl JB, Rosenberg J, Hansen BL, Hjortso NC, Kehlet H: Differential analgesic effects of low-dose epidural morphine and morphine-bupivacaine at rest and during mobilization after major abdominal surgery. *Anesth Analg* 1992;74:362–5.
140. Scott NB, Mogensen T, Bigler D, Lund C, Kehlet H: Continuous thoracic extradural 0.5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response. *Br J Anaesth* 1989;62:253–7.
141. Badner NH, Komar WE: Bupivacaine 0.1% does not improve post-operative epidural fentanyl analgesia after abdominal or thoracic surgery. *Can J Anaesth* 1992;39:330–6.
142. Badner NH, Reimer EJ, Komar WE, Moote CA: Low-dose bupivacaine does not improve postoperative epidural fentanyl analgesia in orthopedic patients. *Anesth Analg* 1991;72:337–41.
143. Dahl JB, Hjortso NC, Stage JG, et al: Effects of combined perioperative epidural bupivacaine and morphine, ibuprofen, and incisional bupivacaine on postoperative pain, pulmonary, and endocrine-metabolic function after minilaparotomy cholecystectomy. *Reg Anesth* 1994;19:199–205.
144. Scott NB, Forbes DW, Binning AR: The effect of parenteral diclofenac and morphine on duration and height of blockade of continuous epidural infusion of bupivacaine 0.5%. *Anaesthesia* 1994;49:594–6.
145. Bartholdy J, Sperling K, Ibsen M, Eliasen K, Mogensen T: Preoperative infiltration of the surgical area enhances postoperative analgesia of a combined low-dose epidural bupivacaine and morphine regimen after upper abdominal surgery. *Acta Anaesthesiol Scand* 1994;38:262–5.
146. George KA, Wright PM, Chisakuta AM, Rao NV: Thoracic epidural analgesia compared with patient controlled intravenous morphine after upper abdominal surgery. *Acta Anaesthesiol Scand* 1994;38:808–12.
147. Kavanagh BP, Katz J, Sandler AN, et al: Multimodal analgesia before thoracic surgery does not reduce postoperative pain. *Br J Anaesth* 1994;73:184–9.
148. Moiniche S, Hjortso NC, Hansen BL, et al: The effect of balanced analgesia on early convalescence after major orthopaedic surgery. *Acta Anaesthesiol Scand* 1994;38:328–35.
149. Pavy TJ, Gambling DR, Merrick PM, Douglas MJ: Rectal indomethacin potentiates spinal morphine analgesia after caesarean delivery. *Anaesth Intensive Care* 1995;23:555–9.
150. Richardson J, Sabanathan S, Mearns A J, Evans C S, Bembridge J, Fairbrass M: Efficacy of pre-emptive analgesia and continuous extrapleural intercostal nerve block on post-thoracotomy pain and pulmonary mechanics. *J Cardiovasc Surg Torino* 1994;35:219–28.
151. Wittels B, Faure EA, Chavez R, et al: Effective analgesia after bilateral tubal ligation. *Anesth Analg* 1998;87:619–23.
152. Rosaeg OP, Lui AC, Cicutti NJ, Bragg PR, Crossan ML, Krepski B: Peri-operative multimodal pain therapy for caesarean section: analgesia and fitness for discharge. *Can J Anaesth* 1997;44:803–9.
153. Power I, Bowler GM, Pugh GC, Chambers WA: Ketorolac as a component of balanced analgesia after thoracotomy. *Br J Anaesth* 1994;72:224–6.
154. Ilkjaer S, Nikolajsen L, Hansen TM, Wernberg M, Brennum J, Dahl JB: Effect of i.v. ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery. *Br J Anaesth* 1998;81:707–12.
155. Badner NH, Bourne RB, Rorabeck CH, Doyle JA: Addition of morphine to intra-articular bupivacaine does not improve analgesia following knee joint replacement. *Reg Anesth* 1997;22:347–50.
156. Weingarten S, Riedinger MS, Sandhu M, et al: Can practice guidelines safely reduce hospital length of stay? *Results from a multicenter interventional study. Am J Med* 1998;105:33–40.
157. Camp JF: Patient-controlled analgesia. *Am Fam Physician* 1991;44:2145–50.
158. Bardram L, Funch-Jensen P, Jensen P, Crawford ME, Kehlet H: Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. *Lancet* 1995;345(8952):763–4.
159. Brodner G, Pogatzki E, Van Aken H, et al: A multimodal approach to control postoperative pathophysiology and rehabilitation in patients undergoing abdominothoracic esophagectomy. *Anesth Analg* 1998;86:228–34.
160. Collier PE: Are one-day admissions for carotid endarterectomy feasible? *Ame J Surg* 1995;170:140–3.
161. Coveney E, Weltz CR, Greengrass R, et al: Use of paravertebral block anesthesia in the surgical management of breast cancer: experience in 156 cases. *Ann Surg* 1998;227:496–501.
162. Kehlet H, Mogensen T: Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. *Br J Surg* 1999;86:227–30.
163. Rawal N: Analgesia technique and post-operative morbidity. *Eur J Anaesthsiol Suppl* 1995;10:47–52.
164. Worwag E, Chodak GW: Overnight hospitalization after radical prostatectomy: the impact of two clinical pathways on patient satisfaction, length of hospitalization, and morbidity. *Anesth Analg* 1998;87:62–7.
165. Macario A, Horne M, Goodman S, et al: The effect of a perioperative clinical pathway for knee replacement surgery on hospital costs. *Anesth Analg* 1998;86:978–84.
166. Peterson WL, Cryer B: COX-1-sparing NSAIDs–is the enthusiasm justified? *JAMA* 1999;282:1961–3.