BJA

Influence of anaesthetic and analgesic techniques on outcome after surgery

F. Bonnet* and E. Marret

*Service d'Anesthésie-Réanimation, Hôpital Tenon, Assistance Publique Hôpitaux de Paris,
4 rue de la Chine, F-75970 Paris cedex 20, France*
Corresponding author. E-mail: francis.bonnet@tnn.ap-hop-paris.fr

Postoperative symptoms and complications can be prevented by a suitable choice of anaesthetic and analgesic technique for specific procedures. The aim of analgesic protocols is not only to reduce pain intensity but also to decrease the incidence of side-effects from analgesic agents and to improve patient comfort. Moreover, adequate pain control is a prerequisite for the use of rehabilitation programmes to accelerate recovery from surgery. Thus, combining opioid and/or non-opioid analgesics with regional analgesic techniques not only improves analgesic efficacy but also reduces opioid demand and side-effects such as nausea and vomiting, sedation, and prolongation of postoperative ileus. Although all attempts to demonstrate that regional anaesthesia and analgesia decrease postoperative mortality are unsuccessful, there is evidence supporting a reduction in pulmonary complications after major abdominal surgery, and an improvement in patient rehabilitation after orthopaedic surgery. When such techniques are used, cost–benefit analysis should be considered to determine suitable analgesic protocols for specific surgical procedures.

Br J Anaesth 2005; **95**: 52–8

Surgery induces important disturbances in body homeostasis such as hypercatabolism, hypercoagulability, and inflammation, leading to a series of symptoms and signs such as hypoxaemia, pain, nausea, vomiting, ileus, sleep disturbances, and fatigue, and complications including pneumonia and myocardial infarction.[33 34] Each symptom or complication that contributes to postoperative morbidity is likely to prolong the duration of hospital stay. Anaesthetic and analgesic techniques not only aim to provide suitable conditions for surgery, but also to prevent postoperative complications and to decrease postoperative morbidity and mortality.

Assessment of the impact of anaesthetic and analgesic techniques on postoperative outcome commonly focuses on the incidence of mortality and major complications after major surgical procedures. Nevertheless, other postoperative adverse events such as pain, nausea, vomiting, and urinary retention may also impair patient comfort, recovery, and rehabilitation after minor and major surgical procedures. In addition, there is growing evidence that acute postoperative events may have long-term consequences. For example, uncontrolled postoperative pain is related to the development of chronic pain syndromes;[41] postoperative myocardial ischaemia and infarction are risk factors for death from cardiac causes in the following months;[22 37 54] and

postoperative increases in plasma creatinine concentration could be indicative of the development of chronic renal failure.

As postoperative pain is often the predominant symptom, it can be considered an important outcome of surgery. Patients may relate improved pain control to improved postoperative outcome. Several analgesic agents and techniques, including regional analgesia and i.v. patient-controlled analgesia (PCA) using opioids, have been demonstrated to effectively control postoperative pain.[5 9 29 63 72 78] Two issues need to be addressed. Is it possible to optimize pain control, improving the effectiveness of analgesic agents and reducing the incidence of their side-effects; and are we able to reduce postoperative morbidity and hasten recovery through the treatment of postoperative pain?

Improving the effectiveness of analgesic agents

Patient-controlled administration of i.v. opioids, and peripheral and central nerve blocks using local anaesthetic agents, are the corner stones of analgesic strategies, the latter being considered more effective than the former. Nevertheless, each technique has its own limitations and none can achieve complete postoperative pain control.

In 2003, a meta-analysis that reviewed 1404 abstracts published over 36 yr, and included 100 studies, provided conclusions supporting the common belief shared by many anaesthetists, that epidural analgesia provides better post-operative pain control than systemic analgesia.[9] Although epidural analgesia is considered the most effective technique in terms of pain control, its efficacy is improved by the addition of systemic analgesics such as opioids or cyclo-oxygenase-2 (COX-2) inhibitors.[16] Combining analgesic agents and techniques has been suggested to improve the efficacy of postoperative pain management.[33] Non-opioid analgesic agents are thus combined with opioid PCA. Non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, paracetamol, and nefopam have been demonstrated to reduce opioid demand, when combined with i.v. morphine PCA.[15 20 21 36 45 50 56 58 62 65 70] COX-2 inhibitors are equally potent relative to non-selective NSAIDs,[62] but paracetamol is possibly weaker.[29 63] Adding a non-opioid agent to i.v. morphine PCA more commonly results in a decrease in morphine requirement than in a reduction in pain intensity at rest. Pain on mobilization can be more consistently reduced by multimodal analgesia than opioid administration. This is indicative of the fact that pain at rest is often easily controlled by a single analgesic agent but pain on mobilization, as a result of its greater intensity, requires several analgesic treatments. Other studies have documented the morphine-sparing effect of ketamine,[72] and more recently gabapentin.[64 75 76] Those agents may act differently, preventing acute sensitization to pain following surgery and acute tolerance to opioid.[35 69 71] Finally, analgesic techniques such as infiltration of the incision with local anaesthetic solution, are associated with a morphine-sparing effect that is, however, limited to a few hours.[48 49]

The concept of multimodal analgesia also applies to the combination of epidural local anaesthetic and opioid. Addition of opioid to epidural local anaesthetics relieves pain more effectively than local anaesthetics alone. Nevertheless, lowering pain intensity could be outweighed by an increase in the incidence of opiate-related side-effects that could be partly responsible for a prolongation in the duration of hospital stay.[23] Prevention of opioid-related side-effects has consequently become a critical issue that may have economic consequences.

Can we reduce the incidence of side-effects from analgesic therapies?

Although pain intensity can be decreased by combining systemic analgesics, the major benefit of multimodal analgesia may be a decrease in the incidence of opioid side-effects rather than an increase in the effectiveness of pain control.

Respiratory depression is not the only side-effect related to opioid administration. In daily practice, patients more frequently complain of such problems as nausea, vomiting, urinary retention, pruritus, and prolongation of postoperative ileus. A series of randomized studies has concluded that opioid administration, and especially i.v. morphine PCA, is responsible for a significant delay in recovery of bowel function in patients who have undergone abdominal surgery.[30 31 38 40 44] This may prolong the time to first oral intake, and in some instances the duration of hospital stay.[38] This issue can be addressed in two ways: first, by reducing the amount of opioid administered through the concomitant administration of other analgesics; and second, by using opioid antagonists or other agents that prevent or treat opioid-related side-effects. The first approach has been documented to be successful when using NSAIDs or COX-2 inhibitors.[32 43 56 79] NSAIDs and COX-2 inhibitors, because of their significant opioid-sparing effect, may reduce the incidence of nausea and vomiting caused by morphine.[79] Conversely, Aubrun and colleagues noted that postoperative patients receiving paracetamol and morphine experienced nausea and vomiting, pruritus, and urinary retention as frequently as patients who received morphine alone, suggesting that paracetamol has a weaker opioid-sparing effect.[3] Such results have two implications. First, the preventive effect of a non-opioid analgesic agent on nausea and vomiting is only beneficial if it also has an opioid-sparing effect. Secondly, opioids and especially morphine that have been considered the gold standard for postoperative pain treatment, could now, in view of their efficacy/safety profile, be better used as rescue medication. This is especially relevant for ambulatory anaesthesia as opioid-induced side-effects could be responsible for re-hospitalization of these patients.

The second approach that aims to decrease opioid-related side-effects consists of combining morphine with drugs that prevent its side-effects or with μ receptor antagonists. Droperidol, dexamethasone, and ondansetron each reduce the risk of postoperative nausea and vomiting by 25%, and total i.v. anaesthesia with propofol or the use of nitrogen instead of nitrous oxide is also effective.[2] Interestingly, antiemetic agents act independently; they should be used with analgesics in patients having an increased risk of nausea and vomiting. More specifically, a quantitative review estimates that combining a small dose of droperidol with i.v. morphine PCA could avoid nausea and vomiting in three out of 10 patients.[74]

Opioid antagonists

The use of opioid antagonists has been developed to prevent the prolongation of postoperative ileus induced by opioid administration. *Methylnatrexone* and *alvimopan* are recently developed opioid antagonists with activity that is restricted to peripheral gut receptors. Both drugs have the ability to reverse opioid-induced ileus without reversing analgesia.[24 73] Alvimopan can be administered orally to act on μ receptors in the gastric wall. It is not absorbed through the gastric mucosa. The analgesic effect of i.v. morphine PCA is unaltered by the oral administration of alvimopan, but a 24 h

reduction in the time to recovery of bowel motility has been documented.[73] Methylnaltrexone, a quaternary derivate of naltrexone, does not cross the blood–brain barrier and acts as a selective peripheral opioid receptor antagonist. It should be able to prevent not only bowel dysfunction but also, at least partly, other side-effects such as urinary retention.

A decrease in the duration of postoperative ileus of more than 24 h is an advantage of epidural analgesia using local anaesthetic agents only over opioid administration.[31] In addition, the common belief that too rapid a recovery in bowel motility may promote the occurrence of anastomotic leakage has not been proven.[27]

Can we reduce postoperative morbidity and mortality?

For many years, anaesthetists committed to postoperative care management have attempted to improve postoperative morbidity through better pain control. To assess the impact of anaesthetic and analgesic techniques, mortality is a well-defined and important outcome but it is also a very rare event. Large multicentre trials or meta-analyses are necessary to determine the impact of an anaesthetic technique on postoperative mortality. To include in such trials a significant number of patients or studies that fulfil the necessary criteria requires the participation of many different centres. The broad range of practice that results from the inclusion of large series of patients may introduce bias and heterogeneity and make it difficult to control all the factors likely to influence outcome. This explains the contradictory results that have been reported on this topic. Consequently, although a considerable amount of evidence has been published on the effect of anaesthetic techniques and postoperative analgesia on postoperative morbidity, the conclusions remain controversial. Regional anaesthetic techniques used per- and postoperatively have been claimed to improve patient recovery not only through pain control but also by preventing the neuroendocrine response to surgery.[18 34] In 2000, a meta-analysis of studies published over 20 yr that had adequate methodology, provided impressive results concerning the effect of central blocks on postoperative morbidity and mortality.[61] Regional analgesia not only prevented respiratory complications but also decreased the incidence of cardiac complications such as myocardial infarction, deep vein thrombosis, and pulmonary embolism. It was not only effective when considering globally all the different surgical procedures but also when looking at specific procedures such as orthopaedic, abdominal, and vascular surgery. Among the criticisms that followed the publication of this key study, it was claimed that the management of postoperative patients had changed over the last 20 yr, making some alleged benefits of regional analgesia less impressive. For instance, thromboprophylaxis is now more commonly used after hip and knee surgery, and low molecular weight heparins have considerably decreased the incidence of deep vein

thrombosis,[1] masking the benefits of epidural analgesia that were described in the early 1980s.[47] Moreover, this practice is not without concern with respect to the risk of epidural haematoma in patients receiving spinal/epidural anaesthesia and thromboprophylaxis.[28] In addition, laboratory tests or radiological investigations used to diagnose certain complications have changed, making the results of some studies unreliable. For example, a CT scan is more accurate in identifying pulmonary atelectasis than a chest X-ray.[42] As another example, for a few years now the diagnosis of postoperative myocardial damage has relied on a very specific and sensitive increase in the plasma concentration of troponin Ic. Moreover, the increase in troponin Ic is predictive of mortality related to cardiac complications 6 months after surgery.[37] Studies performed some years ago, that did not use measurements of troponin Ic, may have missed a significant number of adverse cardiac events in postoperative patients.[37]

Other authors have collected evidence supporting the use of central blocks of local anaesthetic to decrease the incidence of postoperative pulmonary complications compared with the use of systemic opioids.[46] The incidence of postoperative myocardial infarction has been shown to be lowered by the use of thoracic epidural anaesthesia and analgesia.[4]

Mortality, morbidity, and surgical procedures

The causes of morbidity and mortality vary according to the surgical procedure. Postoperative myocardial infarction is the most frequent of the serious complications that occur after vascular surgery,[10 11 52] while pulmonary embolism is a leading cause of death after total hip or knee replacement.[68] Pneumonia is especially common after upper abdominal surgery.[14] Accordingly, it is appropriate to look at postoperative complications and the potential benefit of anaesthetic and analgesic techniques with respect to specific surgical procedures. Unfortunately, the results of recent large prospective double-blind, randomized, multicentre studies addressing the impact of analgesic techniques on postoperative morbidity and mortality in this way are disappointing.

Orthopaedic surgery. A meta-analysis of 15 randomized studies of hip fracture repair, documented that regional anaesthesia could decrease the relative risk of postoperative mortality (0.66; 95% confidence interval [CI] 0.47–0.96), and the relative risk of deep vein thrombosis (0.41; 95% CI 0.23–0.72), but had no significant impact on other postoperative complications or on the 1-yr mortality rate.[77] This was confirmed by a meta-analysis of 17 trials including 2305 patients that noted a borderline statistical difference for 1-month mortality (6.8 *vs* 9.4%, relative risk 0.72, 95% CI 0.51–1), which disappeared at 3 months.[57] Moreover, the authors highlighted that all the studies had methodological flaws, making uncertain the conclusions drawn. O'Hara and colleagues have evaluated a retrospective cohort of 9598

patients who underwent surgical repair of hip fracture in 20 US hospitals under either general (6206 patients) or regional (3219 patients) anaesthesia.[53] Older patients and those who were more severely ill were more prone to receive regional (mainly spinal) anaesthesia. However, the adjusted relative risk for postoperative mortality, pneumonia, myocardial infarction, congestive heart failure, and changes in mental status were not demonstrative of a benefit from regional anaesthesia compared with general anaesthesia.

Abdominal aortic surgery. Controversy exists about the impact of epidural anaesthesia and analgesia on postoperative morbidity and mortality after abdominal aortic surgery.[6 10–12 25 52 55] To explain the discrepancy between the different studies, it has been claimed that certain studies consider only the effect of intraoperative epidural anaesthesia, and that others focus only on postoperative epidural analgesia, despite the importance of both parts of the perioperative period. Trying to provide a definite answer, Norris and colleagues have designed a prospective, double masked randomized trial comparing the effects of various combinations of intra-operative anaesthesia and postoperative analgesia on abdominal aortic surgery.[52] They looked at death during hospital stay, cardiac death, and mortality at 12 months, but failed to find any difference in patients having either: general anaesthesia and i.v. PCA postoperatively; a combination of epidural anaesthesia peroperatively with general anaesthesia; general anaesthesia and postoperative epidural analgesia; or a combination of general and epidural anaesthesia and postoperative epidural analgesia.[52] Conversely, Park and colleagues documented that patients who underwent abdominal aortic surgery were the only patients undergoing major abdominal surgery to benefit from an analgesic regimen combining epidural/general anaesthesia and postoperative epidural morphine.[55] The difference from patients operated upon under general anaesthesia who received PCA i.v. morphine postoperatively, was related to the incidence of new myocardial infarction, stroke and respiratory failure. Patients in the epidural group were extubated earlier and spent less time in the intensive care unit. In contrast, in a subgroup of patients undergoing abdominal aortic surgery and suffering from chronic obstructive pulmonary disease, selected from a broader series of patients undergoing abdominal surgery, epidural analgesia was no more effective in preventing pulmonary complications than it was in the whole population, even in patients without specific risk factors.[59]

Abdominal surgery. The effect of epidural anaesthesia and analgesia on outcome after major abdominal surgery was assessed in a large prospective multicentre trial that included 915 patients considered at risk of postoperative complications (patients suffering from chronic renal, hepatic, respiratory or cardiac failure, diabetes mellitus, obesity, previous myocardial infarction, or patients over 75 yr).[60] The analysis was based on an intention to treat, meaning that the 29 patients with technical failure in the epidural group, the seven with immediate postoperative

catheter withdrawal, and the 183 who had catheter withdrawal before postoperative day 3, were analysed in the epidural group.[60] Compared with i.v. morphine, epidural analgesia (using both bupivacaine and morphine) achieved better pain control during the 3 days of administration, as expected. The incidence of postoperative death was 5.2% in the epidural group and 4.3% in the i.v. morphine group. No difference was noted between the groups in the occurrence of cardiovascular events, renal failure, gastrointestinal bleeding, acute hepatic failure, or sepsis. Respiratory complications were the only ones to be less frequent in the epidural group (23.3 *vs* 30.2% in the i.v. morphine group, respectively). The intention-to-treat analysis of the results of this study was questioned because of the significant number of patients who failed to complete the anaesthetic protocol; but it could be considered that the study design took into account that, in daily practice, some epidurals fail.

Cardiac surgery. The benefits of epidural/spinal anaesthesia have been discussed in cardiac surgery. The benefits of thoracic epidural anaesthesia include a decrease in the risk of dysrhythmias and pulmonary complications, and a reduction in the time to tracheal intubation, but no statistically significant improvement in the incidence of myocardial infarction and mortality has been demonstrated.[39] However, in these circumstances, all benefits are outweighed by the risk of epidural haematoma related to full anticoagulation that is estimated to approximate 1/1500 patients.[26]

Surgical experience and the role of anaesthetists. Such controversial results highlight the role of anaesthetists in the reduction of morbidity and mortality after surgery. This issue is indirectly addressed in a recent epidemiological study that focuses on mortality according to the surgeon's experience of common procedures.[8] The conclusion is that the experience of surgeons (assessed by the number of procedures performed per year) plays a significant role in various operations including carotid endarterectomy, oesophagectomy, pulmonary resection, and pancreatectomy. For many procedures, the impact of a surgeon's volume of activity is critical and independent of the effect of hospital volume. When considering procedures such as carotid endarterectomy, mortality rate decreases exclusively with increasing surgeon experience. On the other hand, after pancreatectomy or thoracic surgery, mortality not only depends on surgeon volume but also on hospital volume, meaning that the experience and therapeutic choices made by other clinicians including anaesthetists, are a significant factor in patient outcome. For these procedures, the impact of anaesthetic and analgesic techniques on outcome is probably relevant and needs to be evaluated.

Chronic pain after surgery. Various surgical procedures such as thoracotomy for lung resection, inguinal hernia repair, and mastectomy are occasionally complicated by the development of chronic pain syndromes following surgery. High intensity and persisting postoperative pain could be risk factors for chronic pain after surgery.[41] Effective pain control using epidural analgesia is related to a

Table 1 Benefits and disadvantages of epidural analgesia *vs* opioid PCA

	Epidural analgesia (local anaesthetics)	Opioid PCA
Pain control		
At rest	+++	++
On mobilization	++	±
Side-effects		
Hypotension	−	+
Postoperative ileus	Shortening	Prolongation
Nausea–vomiting	−	++
Urinary retention	+	+
Sedation	−	+
Reduction in postoperative morbidity		
Cardiovascular	+	−
Respiratory	+	−
Nurses workload	+	+

lower incidence of chronic pain syndromes after thoracotomy,[67] but no clear information is provided to explain the mechanism of action. In contrast, epidural analgesia is unable to prevent the occurrence of phantom pain after amputation.[51] It is likely that several mechanisms such as central nervous system sensitization and peripheral nerve injury account for chronic pain syndromes after surgery, and consequently the questionable benefits of analgesic techniques to treat them.

Anaesthetic options, perioperative care, and patient rehabilitation

The treatment of postoperative pain not only aims to improve patient comfort but also to hasten recovery even after uncomplicated surgical procedures. Less invasive, stress-reducing surgical procedures, avoiding drains, nasogastric tubes, and bladder catheters, are the first steps in a programme, which included rapid mobilization, physiotherapy, oral feeding, and complete pain control, aiming to accelerate patient rehabilitation. Provision of effective pain relief is a prerequisite for accelerated convalescence. Fast track anaesthesia allows patients to recover organ function quickly. Following abdominal surgery, patients who have received epidural analgesia have a more rapid recovery of bowel motility, allowing prompt oral intake, and partly because of blunting of the neuroendocrine stress response to surgery, they experience less protein catabolism (Table 1).[19] They also mobilize more rapidly, avoiding the consequences of bed rest such as muscle wasting and fatigue.[7 19] Consequently, they are ready for hospital discharge earlier.[7 19 51] The reduction in the duration of intensive care and hospital stay could outweigh the extra cost of the use of epidural anaesthesia for several days.[13 66] In orthopaedic surgery, better analgesic control can improve the functional result of surgery and shorten the duration of rehabilitation, leading to a dramatic economic benefit.[17] Nevertheless, because of other considerations such as the administrative culture of the hospital, and the health care system and a patient's

expectation of it, readiness for discharge is not always associated with a decrease in the duration of hospital stay.[19] More appropriate organization of the postoperative management of surgical patients would include the benefit of epidural analgesia and the more extensive development of rehabilitation programmes.

References

1 Anderson FA, Hish J, White K, Fitzgerald RH, for the hip and knee registry investigators. Temporal trend in prevention of venous thromboembolism following primary total hip replacement or knee arthroplasty 1996–2001. *Chest* 2003; **124**: 349S–56S
2 Apfel CC, Korttila K, Abdalla M, *et al.* A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004; **350**: 2441–51
3 Aubrun F, Kalfon F, Mottet P, *et al.* Adjunctive analgesia with intravenous propacetamol does not reduce morphine-related adverse events. *Br J Anaesth* 2003; **90**: 31–49
4 Ballantyne JC, Carr DB, deFerranti S, *et al.* The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomised, controlled trials. *Anesth Analg* 1998; **86**: 598–612
5 Barden J, Edwards J, Moore A, McQuay H. Single dose oral paracetamol (acetaminophen) for postoperative pain. *Cochrane Database Syst Rev* 2004; 1: CD004602
6 Baron JF, Bertrand M, Barre E, *et al.* Combined epidural and general anesthesia versus general anesthesia for abdominal aortic surgery. *Anesthesiology* 1991; **75**: 611–8
7 Basse L, Jakobsen DH, Billesbolle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg* 2000; **232**: 51–7
8 Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003; **349**: 2117–27
9 Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA* 2003; **290**: 2455–63
10 Bode RH, Lewis KP, Zarich SW, *et al.* Cardiac outcome after peripheral vascular surgery. Comparison of general and regional anesthesia. *Anesthesiology* 1996; **84**: 3–13
11 Bois S, Couture P, Boudreault D, *et al.* Epidural analgesia and intravenous patient-controlled analgesia result in similar rates of postoperative myocardial ischemia after aortic surgery. *Anesth Analg* 1997; **85**: 1233–9
12 Boylan JF, Katz J, Kavangh BP, *et al.* Epidural bupivacaine-morphine analgesia versus patient-controlled analgesia following abdominal aortic surgery. *Anesthesiology* 1998; **89**: 585–93
13 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
14 Brooks-Brunn JA. Predictors of postoperative pulmonary complications following abdominal aortic surgery. *Chest* 1997; **111**: 564–71
15 Burns JW, Aitken HA, Bullingham RES, 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
16 Buvanendran A, Kroin JS, Tuman KJ, *et al.* Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain

management and recovery of function after knee replacement: a randomized controlled trial. *JAMA* 2003; **290**: 2411–18

17 Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999; **91**: 8–15

18 Carli F, Halliday D. Continuous epidural blockade arrests the postoperative decrease in muscle protein fractional synthesis rate in surgical patients. *Anesthesiology* 1997; **86**: 1033–40

19 Carli F, Mayo N, Kluben K, Schniker T, Trudel J, Belliveau P. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. *Anesthesiology* 2002; **97**: 540–9

20 Danou F, Paraskeva A, Vassilakopoulos T, Fassoulaki A. The analgesic efficacy of intravenous tenoxicam as an adjunct to patient-controlled analgesia in total abdominal hysterectomy. *Anesth Analg* 2000; **90**: 672–6

21 Delbos A, Boccard E. The morphine-sparing effect of paracetamol in orthopedic postoperative pain. *J Pain Symptom Manage* 1995; **10**: 279–86

22 Filipovic M, Jeger R, Probst C, et al. Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. *J Am Coll Cardiol* 2003; **42**: 1767–76

23 Finucane BT, Ganapathy S, Carli F, et al. Canadian Ropivacaine Research Group. Prolonged epidural infusions of ropivacaine (2 mg/mL) after colonic surgery: the impact of adding fentanyl. *Anesth Analg* 2001; **92**: 1276–85

24 Foss FJ. A review of the potential role of methylnaltrexone in opioid bowel dysfunction. *Am J Surg* 2001; **182**: 19S–26S

25 Garnett RL, MacIntyre A, Lindsay P, et al. Perioperative ischaemia in aortic surgery: combined epidural/general anaesthesia and epidural analgesia vs general anaesthesia and iv analgesia. *Can J Anaesth* 1996; **43**: 769–77

26 Ho AM, Chung DC, Joynt GM. Neuraxial blockade and hematoma in cardiac surgery: estimating the risk of a rare adverse event that has (not) yet occurred. *Chest* 2000; **117**: 551–5

27 Holte K, Kehlet H. Epidural analgesia and risk of anastomotic leakage. *Reg Anesth Pain Med* 2001; **26**: 111–7

28 Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risk (the second ASRA consensus conference on neuraxial anesthesia and anticoagulation). *Reg Anesth Pain Med* 2003; **28**: 172–97

29 Hyllestted M, Jones S, Pedersen JL, Kehlet H. Comparative effects of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. *Br J Anaesth* 2002; **88**: 199–214

30 Jorgensen H, Fomsgaard JS, Dirks J, Wetterslev J, Andreasson B, Dahl JB. Effect of peri- and postoperative epidural anaesthesia on pain and gastrointestinal function after abdominal hysterectomy. *Br J Anaesth* 2001; **87**: 577–83

31 Jorgensen H, Wetterslev J, Moiniche S, Dahl J. Epidural local anaesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Systemat Rev* 2003; 1

32 Joshi GP, Viscusi ER, Gan TJ, et al. Effective treatment of laparoscopic cholecystectomy pain with intravenous followed by oral COX-2 specific inhibitor. *Anesth Analg* 2004; **98**: 336–42

33 Kehlet H, Willmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002; **183**: 630–44

34 Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; **362**: 1921–8

35 Kissin I, Bright CA, Bradley EL. The effect of ketamine on opioid-induced acute tolerance: can it explain reduction of opioid consumption with ketamine-opioid analgesic combination? *Anesth Analg* 2000; **91**: 1483–8

36 Laitinen J, Nuutinen L. Intravenous diclofenac with PCA fentanyl for pain relief after total hip replacement. *Anesthesiology* 1992; **76**: 194–200

37 Landesberg G, Shatz V, Wolf YG, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 2003; **42**: 1547–54

38 Liu SS, Carpenter RL, Mackey DC, et al. Effects of perioperative analgesic technique on rate of recovery after colon surgery. *Anesthesiology* 1995; **83**: 757–65

39 Liu SS, Block BM, Wu CL. Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. *Anesthesiology* 2004; **101**: 153–61

40 Liu SS. Anesthesia and analgesia for colon surgery: evidence-based case report. *Reg Anesth Pain Med* 2004; **29**: 52–7

41 Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001; **87**: 88–98

42 Magnusson L, Spahn DR. New concepts of atelectasis during general anaesthesia. *Br J Anaesth* 2003; **91**: 61–72

43 Malan TP, Marsh G, Hakki SI, Grossman E, Traylor L, Hubbard RC. Parecoxib sodium a parenteral cyclooxygenase 2 selective inhibitor, improves morphine analgesia and is opioid-sparing following total hip arthroplasty. *Anesthesiology* 2003; **98**: 950–6

44 Mann C, Pouzeratte Y, Boccara G, et al. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology* 2000; **92**: 433–41

45 McLintock TTC, Kenny GNC, Howie JC, McArdle CS, Lawrie S, Aitken H. Assessment of the analgesic efficacy of nefopam hydrochloride after upper abdominal surgery: a study using patient controlled analgesia. *Br J Surg* 1988; **75**: 779–81

46 Meissner A, Rolf N, Van Aken H. Thoracic epidural anesthesia and the patient with heart disease: benefits, risks, and controversies. *Anesth Analg* 1997; **85**: 517–28

47 Modig J, Borg T, Kalstrom G, Maripuu E, Sahlstedt B. Thromboembolism after total hip replacement: role of epidural and general anesthesia. *Anesth Analg* 1983; **62**: 174–80

48 Moiniche S, Mikkelsen S, Wetterslev J, Dahl JB. A qualitative systematic review of incisional local anaesthesia for postoperative pain after abdominal operations. *Br J Anaesth* 1998; **81**: 377–83

49 Moiniche S, Jorgensen H, Wetterslev J, Dahl JB. Local anesthetic infiltration for postoperative pain relief after laparoscopy: a qualitative and quantitative systematic review of intraperitoneal port site infiltration and mesosalpinx block. *Anesth Analg* 2000; **90**: 899–912

50 Moore A, Collins S, Caroll D, McQuay H. Paracetamol with and without codeine in acute pain: a quantitative systematic review. *Pain* 1997; **70**: 193–201

51 Nikolajsen L, Ilkjaer S, Christensen JH, Kroner K, Jensen TS. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. *Lancet* 1997; **350**: 1353–7

52 Norris EJ, Beattie C, Perler BA, et al. Double-masked randomised trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery. *Anesthesiology* 2001; **95**: 1051–3

53 O'Hara DA, Duff A, Berlin JA, et al. The effects of anesthetic technique on postoperative outcomes in hip fracture repair. *Anesthesiology* 2000; **92**: 947–57

54 Oscarsson A, Eintrei C, Anskar S, *et al.* Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. *Acta Anaesthesiol Scand* 2004; **48**: 1071–9

55 Park WY, Thompson JS, Lee K. Effect of epidural anesthesia and analgesia on perioperative outcome. A randomized, controlled Veteran Affairs Cooperative study. *Ann Surg* 2001; **234**: 560–71

56 Parker RK, Holtmann B, Smith I, White P. Use of ketorolac after lower abdominal surgery. Effect on analgesic requirements and surgical outcome. *Anesthesiology* 1994; **80**: 6–12

57 Parker MJ, Handoll HH, Griffiths R. Anesthesia for hip fracture surgery in adults. *Cochrane Database Syst Rev* 2001; **4**: CD000521

58 Peduto VA and the Italian Collaborative Group on Propacetamol, Ballabio M, Stefanini S. Efficacy of propacetamol in the treatment of postoperative pain. Morphine-sparing effect in orthopedic surgery. *Acta Anaesth Scand* 1998; **42**: 293–8

59 Peyton PJ, Myles PS, Silbert BS, Rigg JA, Jamrozik K, Parsons R. Perioperative epidural analgesia and outcome after major abdominal surgery in high-risk patients. *Anesth Analg* 2003; **96**: 548–54

60 Rigg JRA, Jamrozick K, Myles PS, *et al.* Epidural anaesthesia and analgesia and outcome of major surgery: a randomized trial. *Lancet* 2002; **359**: 1276–82

61 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. *Br Med J* 2000; **321**: 1493–7

62 Romsig J, Moiniche S. A systematic review of COX-2 inhibitors compared with traditional NSAIDs, or different COX-2 inhibitors for postoperative pain. *Acta Anaesthesiol Scand* 2004; **48**: 525–46

63 Romsig J, Moiniche S, Dahl JB. Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs for postoperative analgesia. *Br J Anaesth* 2002; **88**: 215–26

64 Rorarius MG, Mennander S, Suominen P, *et al.* Gabapentin for the prevention of postoperative pain after vaginal hysterectomy. *Pain* 2004; **110**: 175–81

65 Schug SA, Sidebotham DA, McGuinnety M, Thomas J, Fox L. Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain. *Anesth Analg* 1998; **87**: 368–72

66 Schuster M, Gottschalk A, Freitag M, Standl T. Cost drivers in patient-controlled epidural analgesia for postoperative pain management after major surgery. *Anesth Analg* 2004; **98**: 708–13

67 Senturk M, Ozcan PE, Talu GK, *et al.* The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg* 2001; **94**: 11–5

68 Sharrock NE, Cazan MG, Hargett MJ, Williams-Russo P, Wilson PD jr. Changes in mortality after total hip and knee arthroplasty over a ten-year period. *Anesth Analg* 1995; **80**: 242–8

69 Shimoyama N, Shimmoyama M, Inturrisi C, Elliott K. Ketamine attenuates and reverses morphine tolerance in rodents. *Anesthesiology* 1996; **85**: 1357–66

70 Souter AJ, Fredman B, White P. Controversies in the perioperative use of nonsteroidal antiinflammatory drugs. *Anesth Analg* 1994; **79**: 1178–90

71 Stubhaug A, Breivik H, Eide PK, *et al.* Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Surg* 1997; **41**: 1124–32

72 Subramanian K, Subramaninan B, Steinbrook RA. Ketamine as adjuvant to opioids: a quantitative and qualitative systematic review. *Anesth Analg* 2004; **99**: 482–95

73 Taguchi A, Sharma N, Saleem RM, *et al.* Selective postoperative inhibition of gastrointestinal opioid receptors. *N Engl J Med* 2001; **27**: 935–40

74 Tramer MR, Walder B. Efficacy and adverse effects of prophylactic antiemetics during patient-controlled analgesia therapy: a quantitative systematic review. *Anesth Analg* 1999; **88**: 1354–61

75 Turan A, Karamanlioglu B, Mennis D, Usar P, Pamuku Z, Ture M. The analgesic effect of gabapentin after total abdominal hysterectomy. *Anesth Analg* 2004; **98**: 1370–3

76 Turan A, Karamanlioglu B, Mennis D, *et al.* Analgesic effect of gabapentin after spinal surgery. *Anesthesiology* 2004; **100**: 935–8

77 Urwin SC, Parker MJ, Griffiths R. General versus regional anaesthesia for hip fracture surgery: a meta-analysis of randomized trials. *Br J Anaesth* 2000; **84**: 450–5

78 Walder B, Schafer M, Henzi I, Tramer MR. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. *Acta Anaesthesiol Scand* 2001; **45**: 795–804

79 Zhao SZ, Chung F, Hanna DB, Raymundo AL, Cheung RY, Chen C. Dose-response relationship between opioid use and adverse effects after ambulatory surgery. *J Pain Symptom Manage* 2004; **28**: 35–46