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Improving Postoperative Pain Management

What Are the Unresolved Issues?

Paul F. White, Ph.D., M.D., F.A.N.Z.C.A.,* Henrik Kehlet, Ph.D., M.D.†

DESPITE recent advances in our understanding of the physiology of acute pain, the development of new opioid and nonopioid analgesics and novel methods of drug delivery, and more widespread use of pain-reducing minimally invasive surgical techniques, pain after surgical procedures remains a challenge for many practitioners.[1] Not surprisingly, recent surveys in the United States and Europe have emphasized the insufficient quality of postoperative pain management and the need for further improvements.[2,3] The increasing implementation of standardized pain evaluation and treatment protocols, and the use of multimodal analgesic techniques, are hopeful signs that improvements in pain management are likely to continue in the years ahead. What then are the major unresolved issues in the management of acute postoperative pain, and how should surgical patients be managed based on the available evidence from the peer-reviewed medical literature?

Multimodal Analgesia

The concept of multimodal "opioid-sparing" analgesic techniques (so-called balanced analgesia) was introduced more than 15 yr ago,[4] with the aim of improving analgesia by combining analgesics with additive or synergistic effects. Theoretically, the use of a combination of analgesics from different pharmacologic drug classes for managing perioperative pain should improve the safety and efficacy of pain therapy due to the differing mechanisms of action and the side-effect profiles of the individual drugs. Although only a limited number of well-conducted, prospective randomized clinical trials have demonstrated improved clinical outcomes with respect to analgesia and opioid-related side effects with multimodal (*vs.* single) therapy,[5,6] meta-analyses of single-modality, nonopioid analgesics have demonstrated clinically significant reductions (20–40%) in postoperative nausea and vomiting and sedation.[7] However, beneficial effects of multimodal therapy with respect to other common side effects (*e.g.*, bowel and bladder dysfunction and ventilatory depression) and improvement in dynamic analgesia have been less consistently reported. Clearly, a need exists for large-scale clinical investigations of drugs (and class) specific side effects when analgesics are administered as part of combination therapies in the postoperative period. Although opioid-related side effects (*e.g.*, postoperative nausea and vomiting, urinary retention, ileus, constipation, sedation, and ventilatory depression) have been extensively described in the literature, nonopioid analgesics such as acetaminophen, classic and cyclooxygenase selective nonsteroidal antiinflammatory drugs (NSAIDs), ketamine, and gabapentanoids also have their own unique side-effect profiles (*e.g.*, hepato- and renal toxicity, coagulation, confusion, sedation, and dizziness), which may be exacerbated when they are administered as a part of a multimodal regimen after surgery. The benefit–risk ratio for analgesic drug combinations is, therefore, largely dependent on the type of surgery (*i.e.*, risk of rebleeding after tonsillectomy, renal failure after vascular surgery, and ileus after colon surgery).

Despite available evidence showing the benefits of multimodal analgesic techniques,[4–6] major surveys have reported that these techniques are underused in clinical practice.[2,3] What is needed to improve the perioperative pain management is to first implement the existing evidence-based recommendations regarding the use of individual nonopioid

* Professor and Holder of the Margaret Milam McDermott Distinguished Chair in Anesthesiology, Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas, Visiting Scientist, Cedars Sinai Medical Center, Los Angeles, California, and Policlinico Abano–Leonardo Foundation in Abano Therme, Italy, and President, White Mountain Institute, † Professor of Perioperative Therapy, Section for Surgical Pathophysiology, Rigshospitalet, Copenhagen University, Copenhagen, Denmark.

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Address correspondence to Dr. White: White Mountain Institute, 144 Ashby Lane, Los Altos, California 94022. paul.white@utsouthwestern.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

analgesics (namely, NSAIDs, cyclooxygenase-2 inhibitors, acetaminophen, gabapentanoids, ketamine, and local and regional anesthetic techniques) when supplemented by opioid analgesics on an as needed basis.[8] Second, practicing clinicians need to use rational analgesic drug combinations to achieve reductions in opioid-related side effects, leading to improved early outcomes and more rapid resumption of normal activities of daily living (*e.g.*, mobilization, recovery of bowel function, and return to work).[6] In this context, clinicians should be aware that previous guidelines for perioperative pain management failed to consider procedure-specific issues. For example, different types of surgical procedures (*e.g.*, orthopedic, abdominal, thoracic, and laparoscopic) have their own unique postoperative pain characteristics and clinical consequences (*e.g.*, immobilization, paralytic ileus, urinary retention, and impairment of pulmonary function). Therefore, a procedure-specific approach is strongly recommended. As an example, continuous epidural analgesia is beneficial in reducing dynamic pain, ileus, and postoperative nausea and vomiting compared with other analgesic techniques after major abdominal procedures.‡ However, epidural analgesia is clearly not appropriate for many other types of abdominal surgery procedures (*e.g.*, open hysterectomy, laparoscopic colon resection, adrenalectomy, or nephrectomy). In addition, analgesic drugs or techniques may have different side-effect profiles depending on the type of surgical procedure (*e.g.*, bleeding after ears-nose-throat, hip and plastic surgery with nonselective NSAIDs [but not with cyclooxygenase-2 inhibitors], ventilatory depression after thoracotomy procedures with opioid-based techniques [but not with regional analgesics techniques], and postoperative ileus after colon resection with opioid analgesics). Therefore, the practicing clinician needs to be aware of the available procedure-specific evidence for optimizing multimodal pain management (table 1). Recently, updated evidence has been made available for several common orthopedic, abdominal, and thoracic procedures on the PROSPECT Web site‡ and published in recent review articles on this topic.[9,10]

Perioperative Analgesia and Postoperative Outcomes

Most clinicians inherently expect that better postoperative pain relief will lead to improved clinical outcomes such as reduced organ dysfunction, decreased morbidity, and shorter hospital stay. However, a recent review of the published literature reported a disappointing lack of major benefits with respect to clinically meaningful outcome measures.[11] The common explanation for this failure to demonstrate the expected improvement in clinical outcome is that many analgesic outcome studies have had major deficiencies in protocol design because they focused on surrogate endpoints (*e.g.*, changes in pain scores at rest, quantitative opioid sparing, and length of the recovery room and/or hospital stay) rather than more clinically meaningful endpoints (*e.g.*, resumption of dietary intake, recovery of bowel and bladder function, and resumption of normal physical activities).[12] Furthermore, by incorporating updated evidence-based care principles, recent evidence suggests that providing effective analgesia in the early postoperative period may lead to clinically important benefits with respect to long-term recovery (*e.g.*, less chronic pain).[13]

In future evaluations of perioperative analgesic regimens, the assessments should therefore be performed within the context of modern fast-track surgery rehabilitation paradigms where the benefits of an optimal procedure-specific analgesic regimen has been integrated into an enhanced recovery care program with early oral feeding, mobilization, and adjustments in other principles of surgical care (*e.g.*, drains, catheters, tubes, and monitoring) consistent with the existing evidence in the peer-reviewed literature.[14,15] In this context, the anesthesiologist(s) and acute pain management team responsible for the patient's analgesic therapy can play an important role in improving the patient's surgical outcomes.[15] The specific issue regarding the role of acute pain management in influencing persistent (chronic) postsurgical pain remains highly controversial despite the emerging relationship between early and persistent postoperative pain.[13,16] Unfortunately, most clinical trials have used only multimodal analgesia for a short period of time after surgery. Future studies should therefore include a highly effective multimodal treatment for as long as the surgical stimulus (inflammatory response) continues after the operation. The transition of acute postoperative pain into a chronic pain state is a complex process that involves psychologic, physiologic, and social–environmental factors.[17]

The potential role of more prolonged multimodal opioid-sparing analgesia in improving long-term functional outcomes after major surgery is of major importance to patients and healthcare providers.[18] Recent surveys would suggest that subacute pain lasting several weeks postoperatively represents another often neglected area of clinical investigation, with relatively sparse scientific data.[19] In addition, recent developments in fast-tracking methodology have emphasized the need for improved analgesia to enhance recovery and reduce the length of the hospital stay, medical and surgical morbidity, and the period of postdischarge convalescence.[14,15]

The ability to identify patients with both high and low risk of developing clinically significant pain after surgery will enhance both the efficacy and safety of analgesic therapies. A recent study[20] reported that the most important predictors of postoperative pain after ambulatory surgery were (1) the presence of preoperative pain, (2) patient and physician expectations regarding the level of pain after the operation, (3) patient fear regarding the short-term outcome of their surgery, and (4) the age of the patient. Interestingly, hypervigilance (*i.e.*, a strong attention bias toward pain) proved to be a powerful predictor of acute postoperative pain.[21] In patients undergoing painful foot and ankle surgery,[22] preoperative pain and anticipated postoperative pain were indepen-

‡ www.postoppain.org. Accessed August 12, 2009.

Table 1. Evidence Supporting Procedure-specific Efficacy of Individual Analgesic Drugs and Recommendations Regarding the Use of Multimodal Analgesia Regimens in the Postoperative Period*

	Efficacy of Single Modality Analgesic Therapy	Multimodal Analgesic Recommendations		General Comments
		First Choice	Rescue Analgesic	
Laparoscopic cholecystectomy	1, 2, 3, 6	1 + 2 + 3 + 6	4/5	Epidural analgesia effective, but not recommended due to low benefit:risk ratio
Open groin hernia repair	1, 2, 6, 7, 10	1 + 2 + 6	4/5	Continuous LA wound infusion, spinal or epidural analgesia, and paravertebral block techniques are effective, but not recommended due to low cost-benefit:risk ratio
Open abdominal hysterectomy	1, 2, (6/7)	1 + 2 + 6	4/5	Consider LA wound infiltration and/or infusion; epidural analgesia not recommended due to low benefit:risk ratio
Open colonic resection	1, 2, 7, 9	9 + 1 + 2	4/5	Consider gabapentanoids (transferable evidence), and continuous wound LA infusion if continuous epidural infusion is not feasible
Thoracotomy	2, 9, 10	1 + 2 + 9 or 10	4/5	Consider continuous intercostal block if continuous epidural or paravertebral nerve blocks are not feasible
Knee replacement	1, 2, 6/7, 8, 11	1+ 2 + 7/8 or 9	4/5	Consider gabapentanoids (transferable evidence); epidural analgesia not recommended due to low benefit:risk ratio compared with continuous wound infusion, or peripheral nerve block, spinal LA + potent opioid analgesic

The above recommendations are primarily based on Level 1 evidence from the peer-reviewed literature as analyzed by the members of the PROSPECT study group (available at: www.postoppain.org; accessed May 11, 2009). Precautions are necessary due to drug-drug interactions and potential adverse effects in specific 'at risk' patient populations (*e.g.*, elderly, patients with comorbid illnesses). Drugs listed in the parentheses represent Level 2-3 evidence. Because ketamine and α2-agonist data have displayed a relatively low efficacy:side effect ratio, they were not included in our recommendations for routine clinical practice. The overall analgesic effects of gabapentanoids are positive across procedures, but procedure-specific data are inconclusive. Nevertheless, these compounds should be considered if adequate analgesia cannot be achieved with the recommended multimodal regimens.

*** Specific analgesic drugs and techniques:**

1. Acetaminophen
2. Nonsteroidal antiinflammatory drugs and cyclooxygenase type-2 inhibitors
3. Glucocorticoids
4. Strong opioid agonists (*e.g.*, morphone, hydromorphone, fentanyl, sufentanil)
5. Weak opioid agonists (*e.g.*, oxycodone, hydrocodone, tramadol)
6. Local anesthetic wound infiltration
7. Local anesthetic wound infusion
8. Continuous peripheral nerve block
9. Continuous epidural analgesia
10. Continuous paravertebral block
11. Subarachnoid block with local anesthetic + potent opioid agonist (*e.g.*, fentanyl, sufentanil)

LA = local anesthetic.

dently predictive of their level of pain during the first 72 h after surgery. In patients undergoing major abdominal surgery,[23] American Society of Anesthesiologists physical status, age, acute preoperative or chronic pain, and high trait anxiety levels and depressive mood states were factors associated with an increased risk of developing moderate-to-severe pain after surgery.

The Way Forward

Given the large disparity between the amount of pathophysiologic data on the mechanisms responsible for acute pain and the subsequent translation of this scientific evidence into clinical practice,[2,3] the most immediate way forward is to begin by routinely implementing procedure-specific, evidenced-based pain management protocols in the perioperative period (table 1).[14,18] However, these procedure-specific analgesic care maps need to be combined with a fast-track recovery strategy[14,15] to obtain the desired improvements in patient outcomes. This approach represents a logical extension of the traditional acute pain service.[24] Although the existing evidence in the literature fails to support the concept that improvement in pain management automatically leads to enhanced recovery and reduced morbidity,[11] it is clear that improvements in patient satisfaction can be consistently achieved.[6,24]

In this context, integrated collaborations are necessary between the departments of anesthesiology and surgery, acute pain management teams, and the postsurgical nursing staff to achieve the full benefits of improved analgesic regimens.[14,15] Thus, as suggested in the recent national surveys examining acute pain management practices,[2,3] implementation of evidenced-based guidelines for pain management alone is not sufficient to achieve the desired improvements in patient outcomes. Therefore, a clear need exists for more effective communication among leaders from the different medical and nursing disciplines, which participate in the perioperative care process, and hospital administrators, insurance companies, and governmental and regulatory bodies. Another approach would be to increase public awareness of the existing possibilities for improved pain management and educating surgical patients and family members regarding steps that they can take to improve the quality of perioperative analgesia and facilitate the recovery process.

Therefore, the most immediate solutions to improving the quality of pain management may be at an organizational level. Further clinical research is clearly needed to better delineate the essential components of procedure-specific, multimodal, nonopioid analgesic regimens.[9,10] In the future, simple and more rational approaches directed toward the periphery (*i.e.*, the surgical wound and surrounding tissues) may offer the greatest promise for advancing acute pain management.[25] The potential for clinical improvement in pain-related outcomes by a peripheral approach is exciting because it is inherently simple, and targets pain at the site of origin before centrally mediated changes can occur in the spinal cord or the cerebral cortex. Clinical examples include use of catheter delivery systems of local anesthetics at the incision site for improving pain control and recovery after major cardiac surgery.[26] In the future, local application of long-acting local analgesic formulations (*e.g.*, depo-bupivacaine and extended-release [saber] bupivacaine), and topical capsaicin,[27] may eventually obviate the need for these cumbersome and expensive catheter delivery systems.

Novel receptor populations on sensory nerve endings (*e.g.*, transient receptor potential vanilloid 1 binding sites) may prove to be useful targets for developing new analgesic adjuvants to add to the current armamentarium of opioid and nonopioid analgesic compounds. Capsaicin, the active ingredient in chili peppers, produces prolonged inhibition of C-fibers by interacting with transient receptor potential vanilloid 1 binding sites and has recently been reported to produce sustained pain relief lasting 3–4 days after surgery.[27] Another potential new class of analgesic drugs are the selective cannabinoid receptor-1 agonists. Preliminary clinical data suggest that even "old drugs" (*e.g.*, glucocorticoid steroids [methylpredinsolone, dexamethasone]) may provide sustained analgesic effects without clinically significant side effects in the perioperative period.

Another very important area for future clinical research includes the need to develop a more in-depth understanding of the basis of the large interindividual variability in the pain response to similar noxious surgical stimuli.[28,29] In the future, an improved and individualized approach to acute pain management may be possible if we can determine a patient's pain threshold before the operation.[28] In the low pain responders (*i.e.*, high pain threshold), less aggressive and simpler approaches could be implemented postoperatively, whereas more sophisticated invasive pain management techniques would be reserved for the high-pain responders. Overly aggressive use of opioid analgesics (*e.g.*, basal infusions) in low pain responders has contributed to significant morbidity and even mortalities after surgery.[30] Previous studies using preoperative nociceptive testing with thermal (heat) or electrical stimuli and psychosocial testing procedures have suggested practical approaches to evaluating high *versus* low pain responders.[28,29] In the future, genetic research may also increase the ability of clinicians to identify high and low pain responders before surgery or specific genotypes that may influence the pharmacokinetics of analgesics.[31]

Pharmacogenetics is an intriguing area for future investigations aimed at improving pain management. For example, Janicki *et al.*[32] reported an association between functional polymorphism of the μ-opioid receptor gene in patients with acute and chronic pain. Although the presence of the minor allele did not affect opioid use in the management of acute pain, the gene was less common in chronic pain patients with high opioid analgesic requirements. Chou *et al.*[33] have reported an association between μ-opioid receptor gene polymorphism and the variation in the morphine requirement after lower abdominal surgery. Therefore, genetic variation in the μ-opioid receptor may contribute to interindividual

differences in postoperative pain and the need for opioid analgesic medication. Recently, Tan *et al.*[34] reported that ethnicity and μ-opioid receptor genotype were independent and significant contributors to individual variations in pain perception and postoperative opioid usage. Genetically mediated interindividual variation may also influence the analgesic response of patients to NSAIDs and cyclooxygenase-2 inhibitor drugs.[35] The ability to identify these genetic polymorphisms may eventually prove to be useful to clinicians in optimizing the use of both opioid and nonopioid analgesic medications.

Other potentially important areas for future research in acute pain management relate to the influence of metabolic factors, aging and sex (gender) on patient responses to analgesic medications. Although the proportion of population in the elderly age category continues to increase at a rapid rate, surprisingly few clinical studies have carefully examined the effect of aging on the response to opioid and nonopioid analgesic medications in the postoperative period. Similarly, few well-controlled studies have examined the role of gender in the management of acute postoperative pain, because it is difficult to conduct comparative studies because of the potential confounding effect of different types of surgical procedures performed in men and women.[36]

Finally, the concept of "preemptive analgesia" (as distinct from "preventive analgesia") needs to be carefully reexamined because data from randomized trials on the timing issue (*i.e.*, initiating analgesia before *vs.* after the surgical stimulus) have produced confusing findings.[37,38] Studies that compared the same dose of an analgesic given before *versus* after the surgical stimuli have failed to document advantages of the so-called preemptive approach.[39] Although preoperative administration is clearly better than giving a placebo, few well-controlled studies have actually compared perioperative *versus* postoperative administration of analgesic drugs. Sun *et al.*[40] recently demonstrated that perioperative administration of the NSAID cyclooxygenase-2 inhibitor celecoxib was no better than simply administering the drug after surgery. It is clearly important to achieve effective analgesia in the early postoperative period and then ensure that an effective "preventative" analgesic regimen is continued into the postdischarge period for as long as the nociceptive input from the wound persists after surgery.[4,12,17] However, additional information is clearly needed regarding the optimal duration of the postdischarge treatment on a procedure-specific basis, and these recommendations should be modified based on individual patient pain response factors.

Summary

Despite the tremendous progress that has been made in our understanding of the pathophysiologic basis of acute pain, there remains a need for clinicians to implement evidence-based procedure-specific multimodal analgesic protocols, which are modified to meet the needs of individual patients to enhance the quality of postoperative pain management. Importantly, there is a critical need for collaborations between the various heathcare providers involved in perioperative patient care (*e.g.*, anesthesiologists, surgeons, nurses, and physiotherapists) to integrate improved perioperative pain management with the recently described fast-track recovery paradigms.[14,15] This type of combined approach is well documented to improve the quality of the recovery process and reduce the hospital stay and postoperative morbidity, leading to a shorter period of convalescence after surgery. Rather than simply performing more meta-analysis and systematic reviews of the pain management literature,[12] clinical investigators need to return to the hard work of performing prospective, randomized clinical trials on a procedure-specific basis, evaluating the use of different analgesic combinations as part of multimodal analgesic treatment regimens in the postoperative period.

References

1. White PF: Pain management after ambulatory surgery—Where is the disconnect? Can J Anaesth 2008; 55:201–7
2. Apfelbaum JL, Chen C, Mehta SS, Gan TJ: Postoperative pain experience: Result from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003; 97:534–40
3. Benhamou D, Berti M, Brodner G, De Andres J, Draisci G, Moreno-Azcoita M, Neugebauer EA, Schwenk W, Torres LM, Viel E: Postoperative Analgesic Therapy Observational Survey (PATHOS): A practice pattern study in 7 central/southern European countries. Pain 2008; 136:134–41
4. Kehlet H, Dahl JB: The value of "multimodal" or "balanced analgesia" in post-operative pain treatment. Anesth Analg 1993; 77:1048–56
5. Gilron I, Orr E, Tu D, Mercer CD, Bond D: A randomized, double-blind controlled trial of perioperative administration of gabapentin, meloxicam and their combination for spontaneous and movement-evoked pain after ambulatory laparoscopic chole-cystectomy. Anesth Analg 2009; 108: 623–30
6. White PF, Sacan O, Tufanogullari, Eng M, Nuangchamnong N, Ogunnaike B: Effect of short-term postoperative celecoxib administration on patient outcome after outpatient laparoscopic surgery. Can J Anesth 2007; 54:342–8
7. Marret E, Kurdi O, Zufferey P, Bonnet F: Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: Meta-analysis of randomized controlled trials. ANESTHESIOLOGY 2005; 102:1249–60
8. White PF: The changing role of non-opioid analgesic techniques in the management of postoperative pain. Anesth Analg 2005; 101:5–22
9. Joshi GP, Bonnet F, Shah R, Wilkinson RC, Camu F, Fischer B, Neugebauer EA, Rawal N, Schug SA, Simanski C, Kehlet H: A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. Anesth Analg 2008; 107:1026–40
10. Fischer HB, Simanski CJ, Sharp C, Bonnet F, Camu F, Neugebauer EA, Rawal N, Joshi GP, Schug SA, Kehlet H: A procedure-specific systematic review and consensus recommendations for postoperative analgesia following total knee arthroplasty. Anaesthesia 2008; 63:1105–23
11. Liu SS, Wu CL: Effect of postoperative analgesia on major postoperative complications: A systematic update of the evidence. Anesth Analg 2007; 104:689–702
12. White PF, Kehlet H: Postoperative pain management and patient outcome: Time to return to work! Anesth Analg 2007; 104:487–9
13. Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ: Perioperative oral pregabalin reduces chronic

pain after total knee arthroplasty: A prospective, randomized, controlled trial. Anesth Analg November 12, 2009 [Epub ahead of print]
14. Kehlet H, Wilmore DW: Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg 2008; 248: 189–98
15. White PF, Kehlet H, Neal JM, Schricker T, Carr DB, Carli F: The role of the anesthesiologist in fast-track surgery: From multimodal analgesia to perioperative medical care. Anesth Analg 2007; 104:1380–96
16. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: Risk factors and prevention. Lancet 2006; 367:1618–25
17. Brennan TJ, Kehlet H: Preventive analgesia to reduce wound hyperalgesia and persistent postsurgical pain: Not an easy path. ANESTHESIOLOGY 2005; 103:681–3
18. White PF, Kehlet H, Liu SS: Perioperative analgesia: What do we still know? Anesth Analg 2009; 108:1364–7
19. Andersen LØ, Gaarn-Larsen L, Kristensen BB, Husted H, Otte KS, Kehlet H: Subacute pain and function after fast-track hip and knee arthroplasty. Anaesthesia 2009; 64: 508–13
20. Gramke HF, de Rijke JM, van Kleef M, Kessels AG, Peters ML, Sommer M, Marcus MA: Predictive factors of postoperative pain after day-case surgery. Clin J Pain 2009; 25: 455–60
21. Lautenbacher S, Huber C, Kunz M, Parthum A, Weber PG, Griessinger N, Sittl R: Hypervigilance as predictor of postoperative acute pain: Its predictive potency compared with experimental pain sensitivity, cortisol reactivity, and affective state. Clin J Pain 2009; 25:92–100
22. Chou LB, Wagner D, Witten DM, Martinez-Diaz GJ, Brook NS, Toussaint M, Carroll IR: Postoperative pain following foot and ankle surgery: A prospective study. Foot Ankle Int 2008; 29:1063–8
23. Caumo W, Schmidt AP, Schneider CN, Bergmann J, Iwamoto CW, Adamatti LC, Bandeira D, Ferreira MB: Preoperative predictors of moderate to intense acute postoperative pain in patients undergoing abdominal surgery. Acta Anaesthesiol Scand 2002; 46:1265–71
24. Werner MU, Søholm L, Rotbøll-Nielsen P, Kehlet H: Does an acute pain service improve postoperative outcome? Anesth Analg 2002; 95:1361–72
25. Kehlet H, Liu SS: Continuous local anesthetic wound infusion to improve postoperative outcome: Back to the periphery? ANESTHESIOLOGY 2007; 107:369–71
26. White PF, Rawal S, Latham P, Markowitz S, Issioui T, Chi L, Dellaria S, Shi C, Morse L, Ing C: Use of a continuous local anesthetic infusion for pain management after median sternotomy. ANESTHESIOLOGY 2003; 99:918–23
27. Aasvang EK, Hansen JB, Malmstrøm J, Asmussen T, Gennevois D, Struys MM, Kehlet H: The effect of wound instillation of a novel purified capsaicin formulation on postherniotomy pain: A double-blind, randomized, placebo-controlled study. Anesth Analg 2008; 107:282–91
28. Werner MU, Duun P, Kehlet H: Prediction of postoperative pain by preoperative nociceptive responses to heat stimulation. ANESTHESIOLOGY 2004; 100:115–9
29. Lundblad H, Kreicbergs A, Jansson KA: Prediction of persistent pain after total knee replacement for osteoarthritis. J Bone Joint Surg 2008; 90:166–71
30. White PF, Kehlet H: Improving pain management: Are we jumping from the frying pan into the fire? Anesth Analg 2007; 105:10–2
31. Max MB, Stewart WF: The molecular epidemiology of pain: A new discipline for drug discovery. Nat Rev Drug Discov 2008; 7:647–58
32. Janicki PK, Schuler G, Francis D, Bohr A, Gordin V, Jarzembowski T, Ruiz-Velasco V, Mets B: A genetic association study of the functional A118G polymorphism of the human mu-opioid receptor gene in patients with acute and chronic pain. Anesth Analg 2006; 103:1011–7
33. Chou WY, Wang CH, Liu PH, Liu CC, Tseng CC, Jawan B: Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. ANESTHESIOLOGY 2006; 105:334–7
34. Tan EC, Lim EC, Teo YY, Lim Y, Law HY, Sia AT: Ethnicity and OPRM variant independently predict pain perception and patient-controlled analgesia usage for post-operative pain. Mol Pain 2009; 5:32
35. Lee YS, Kim H, Wu TX, Wang XM, Dionne RA: Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. Clin Pharmacol Ther 2006; 79:407–18
36. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL III: Sex, gender, and pain: A review of recent clinical and experimental findings. J Pain 2009; 10:447–85
37. Moiniche S, Kehlet H, Dahl JB: A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: The role of timing of analgesia. ANESTHESIOLOGY 2002; 96:725–41
38. Ong CK, Lirk P, Seymour RA, Jenkins BJ: The efficacy of preemptive analgesia for acute postoperative pain management: A meta-analysis. Anesth Analg 2005; 100:757–73
39. Dahl V, Ernoe PE, Steen T, Raeder JC, White PF: Does ketamine have preemptive effects in women undergoing abdominal hysterectomy procedures? Anesth Analg 2000; 90:1419–22
40. Sun T, Sacan O, White PF, Coleman J, Rohrich RJ, Kenkel JM: Perioperative *versus* postoperative celecoxib on patient outcomes after major plastic surgery procedures. Anesth Analg 2008; 106:950–8