
ANESTHESIOLOGY 2012

TRANSFORMING PATIENT SAFETY THROUGH EDUCATION AND ADVOCACY

Current Concepts and Controversies in Acute Pain Management

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Acute pain management continues to be challenging. Studies have demonstrated continued unmet needs with the majority of patients experiencing significant pain at some point following surgery.¹ Analgesic gaps (periods of breakthrough pain) continue to be a problem for most patients. There is increasing awareness to opioid related side effects and the need to minimize opioids generally through the use of multimodal analgesic techniques. Opioid related respiratory depression and sleep apnea are now major considerations in the postoperative period. At the other end of the opioid spectrum, we have the challenge of managing postoperative pain in the presence of opioid tolerance and chronic opioid use. There is also an emerging theme of chronic pain following surgery.

Multimodal Analgesia

Historically, we have relied heavily on opioids as single agents for postoperative pain. While opioids are potent and effective analgesics, this comes at the price of opioid related side effects. Patients typically balance side effects with pain relieve –often requesting less pain relief rather than suffer opioid related nausea and vomiting.² Further, opioids have limited efficacy for some types of pain particularly visceral and neuropathic pain. Acute postoperative pain is usually a mixed pain syndrome with multiple components and hence may not be relieved well with opioids alone.

The concept of multimodal analgesia entered the acute pain literature in the early 1990's when Kehlet described the benefits of "balanced" analgesia.³ Today, multimodal analgesia, the application of two or more analgesics acting at different pain pathways and by different mechanisms, is considered standard practice to enhance analgesia and minimize reliance on opioids. The ASA Guidelines on Acute Pain Management support the use of nonopioids as around the clock agents with opioids as supplemental agent. The most commonly employed agents are local anesthetics, acetaminophen, NSAIDs, COX-2 selective inhibitors, gabapentin and pregabalin, and ketamine. While these agents may be viewed as less potent than opioids, emerging information suggests they may be able to play a more significant role than previously thought.⁴ Opioid minimalization is at the heart of many of the challenges and controversies in acute pain management. Future acute pain management is likely to rely much less on opioids.

Opioid Related Respiratory Depression and Sleep Apnea

The effects of opioids on respiration are well known. In recent years there has been increasing awareness to critical respiratory events.^{5,6} The emphasis place on "pain the 5th vital sign" by the Joint Commission several years back may have increased the use of opioids in the hospital setting in an attempt to improve pain assessments. The increasing incident of sleep apnea, often blamed on the increasing obesity in our society, is also considered a risk factor for opioid use.

Obstructive sleep apnea (OSA) is usually associated with obesity, snoring or other signs of airway obstruction. Yet, the majority of patients with OSA are undiagnosed and many are not obese.⁷ Further, OSA may coexist with central sleep apnea (CSA).⁸ Further, it has been demonstrated that patients with OSA may develop respiratory depression from opioids but that it is in fact on a central basis and not obstructive.⁹ Up to 5% of long term opioid dependent patients will exhibit CSA.¹⁰ (Chronic opioid use also suppresses REM sleep which may share a similar basis.) Opioids are potent analgesics and remain the most widely used analgesics for postoperative pain at this time. Hence, we will be dealing with these challenges for the foreseeable future.

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While respiratory depression (RD) is a serious problem, definitions of RD vary widely. Reported incidences range from 1% to approximately 40%.¹¹ However, these definitions include transient oxygen desaturation or transient respiratory rates below 10 breaths per minute. While these events should not be taken lightly, it is difficult to predict which or how many of these events will progress to *critical* situations requiring intervention. In one series of over 2000 patients with standard patient controlled analgesia settings, the incident of critical respiratory depression was 0.1-0.3%.¹² The controversy here is determining if and what type of monitoring is appropriate for patients receiving opioids and how to minimize opioid use.

An ASA task force provided guidance on managing patients with OSA.¹³ There are no specific analgesic recommendations but rather favor minimal opioids use and multimodal analgesia. Local anesthetic techniques are encouraged. One specific recommendation is to avoid discharge to an unmonitored setting until there is no further risk of respiratory depression.

There are various monitoring techniques recommended for the OSA patient but no definitive approach. Pulse oximetry is generally recommended although capnometry may be a more sensitive indicator. Observational monitoring in the PACU with an OSA prescreening tool may have a role in risk stratifying patients who would benefit from the most aggressive monitoring.¹⁴ The STOP-Bang scoring system has also shown merit in identifying at-risk patients.¹⁵

Using the STOP-Bang questionnaire, one team of investigators found 41.5% of a standard preoperative elective population had OSA. These investigators also identified a ten-fold increase in pulmonary and cardiac complications in patients with OSA.¹⁶ Clearly, patients with OSA may benefit from advance planning. Early identification is key. This allows planning an anesthetic to minimize reliance on opioids both intra- and post- operatively as well as designing an appropriate multimodal approach with appropriate monitoring.

Emerging Views on Opioids

Mu-opioid receptors are ubiquitous within the CNS and at peripheral sites. The analgesic action of opioids within the CNS is well known. Opioid adverse events are related to both central and peripheral receptors. Peripheral opioid receptors have a role in ileus, constipation, hormonal regulation, tumor growth, angiogenesis and immunological function. While long term opioid use has clear risks, there is emerging evidence that the short term use of opioids may have significant consequences. Use of opioids for as little as one month may produce lasting changes in the brain.¹⁷ Elderly patients given opioids for postoperative pain are at risk for long term opioid use.¹⁸

Opioids may reduce survival after cancer surgery.¹⁹ Perioperative plans that reduce opioids have been shown to increase cancer survival in surgery for breast cancer, prostate cancer and possibly bowel cancer. These typically involve regional anesthetic techniques (paravertebral blocks, epidurals). Opioids are known to enhance angiogenesis leading to tumor growth and to inhibit the immunological response which may alter survival. Recent work in rodents with peripheral opioid antagonism demonstrated an inhibition of tumor growth.²⁰

Opioid Tolerance and Hyperalgesia

Long term use of opioids is known to produce tolerance or decreased efficacy requiring dose escalation. Some patients on chronic opioids also exhibit hyperalgesia or altered pain sensitivity.²¹ As a group, patients on chronic opioid therapy for pain or methadone maintenance are well known to present significant postoperative pain challenges.

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For these patients in the postoperative period, increased opioid requirements are expected but often pain is unrelieved with opioids alone.²² Opioid tolerant patients benefit from aggressive multimodal analgesia with regional anesthetic techniques. Recently, ketamine has shown efficacy in this setting. In opioid tolerant spine surgery patients, Loftus and colleagues demonstrated that pre- and intra-operative ketamine reduced pain and opioid requirements in the immediate postoperative period and up to six weeks following surgery.^{23,24,25} Low dose ketamine is now commonly employed in opioid tolerant patients. There is some controversy as to when and where ketamine should be administered. Loftus and colleagues demonstrated benefit from pre and intraop administration. Postoperative ketamine infusion is a useful adjunct in multimodal analgesia for these patients but further studies are warranted to evaluate dosing and duration of treatment.

Chronic Pain Following Surgery

Chronic pain may be a consequence of surgery. Until recently, normal resolution of acute pain was expected to be a routine occurrence. There is a significant burden of long-term pain following surgery. The incidence following thoracotomy and radical mastectomy may exceed 50%. The incidence following inguinal hernia repair is 19-40%. There is now an understanding that healing with neuronal plasticity may occur resulting in chronic postsurgical pain (CPSP). CPSP has been linked to severity of acute pain.²⁶ Following thoracotomy, patients who experience pain of greater intensity and for a longer duration had a higher risk of persistent pain. Kehlet has identified not only intense acute pain but also, nerve injury and intense inflammatory response as associated factors.²⁷

Surgery often results in an intense peripheral inflammatory response (peripheral sensitization) as a consequence of the release of local inflammatory mediators. This “inflammatory soup” causes peripheral sensitization that results in central sensitization (the release of central inflammatory mediators) which in turn results in further pain sensitization.²⁸ Even in the presence of total neuronal blockade, there is still a central humoral response to peripheral inflammation. Hence, local anesthetic techniques alone cannot inhibit this process of central sensitization.

Total knee arthroplasty has a reported incidence of CPSP approaching 9%. A recent study utilizing a complex multimodal regimen with pregabalin for total knee arthroplasty showed a marked reduction in chronic neuropathic pain.²⁹ While this is one study, it provides a basis for the potential use of multimodal analgesia as an approach to reducing the prevalence of CPSP. Still, another study with chronic pain following total joint arthroplasty supports that patients may have underlying vulnerabilities such as major depression or chronic pain elsewhere.³⁰ There is some evidence correlating CPSP to individual pain response with experimental pain models.³¹

In a number of surgical models, perioperative pregabalin either alone or within a complex multimodal regimen has been shown to reduce pain in the immediate postoperative period and in some studies in the months following surgery.³²⁻³⁷ Recently, intraoperative lidocaine infusion was shown to reduce chronic pain following breast surgery.³⁸

Ultimately chronic post-surgical pain is likely to be multifactorial in origin. Current best evidence suggests that a multimodal analgesic approach may offer the best current approach for reducing long-term pain after surgery. If at-risk individuals can be identified in the future, targeted approaches might be possible.

Conclusions

Acute pain management continues to be challenging. While significant strides have been made in many areas, specific patient populations and surgical pain models remain underserved. Multimodal analgesia is now recognized as a standard of care and is familiar to our surgical colleagues. The most current literature supports opioid reduction

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techniques and multimodal analgesia from the preoperative period and through the recovery period. Integration of multimodal analgesia into our anesthetic plan will promote early utilization both pre- and intra-operative to maximize the benefits. The emerging information on opioids suggests that these agents will likely play a lesser role in our future approaches to acute pain management.

References

1. Apfelbaum JL, Chen C, Mehta SS, et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg* 2003;97:534-40
2. Gan TJ, Lubarsky DA, Flood EM, et al. Patient preferences for acute pain treatment. *Brit J Anaesth* 2004;92:681-8
3. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993;77:1048-56
4. Moore RA, Derry S, McQuay HJ, et al. Single dose oral analgesics for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 9
5. Weinger MB. Dangers of postoperative opioids: APSF workshop and white paper addresses prevention of postoperative respiratory complications. *APSF Newsletter* 2006-07;21:61, 63-7
6. Overdyk FJ. Letter to the editor: Postoperative opioids need system-wide overhaul. *APSF Newsletter* 2009-10;244, 61
7. Young T, Evans L, Finn L, et al. Estimation of clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 1997;20:705-6
8. Badr MS, Toiber F, Skatrud JB, et al. Pharyngeal narrowing/occlusion during central sleep apnea. *J Appl Physiol* 1995;78:1806-15
9. Bernards CM, Knowlton SL, Schmidt DF, et al. Respiratory and sleep effects of remifentanyl in volunteers with moderate obstructive sleep apnea. *Anesthesiology* 2009;110:41-49
10. Ecker DJ, Jordan AS, Merchia P, et al. Central sleep apnea: pathophysiology and treatment. *Chest* 2007;131:595-607
11. Overdyk FJ, Carter R, Maddox RR, et al. Continuous oximetry/capnometry monitoring reveals frequent desaturation and bradypnea during patient-controlled analgesia. *Anesth Analg* 2007;105:412-8
12. Viscusi ER, Sicardi M, Damaraju CV, et al. The safety and efficacy of fentanyl iontophoretic transdermal system compared with morphine intravenous patient-controlled analgesia for postoperative pain management: an analysis of pooled data from three randomized, active-controlled clinical studies. *Anesth Analg* 2007;105:1428-36
13. ASA Task Force on Perioperative Management of Patients with OSA *Anesthesiology* 2006;104:1081-1952
14. Gali B, Whalen FX, Schroeder DR, et al. Identification of patients at risk for postoperative respiratory complications using a preoperative obstructive sleep apnea screening tool and postanesthesia care assessment. *Anesthesiology* 2009;110:869-77
15. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology* 2008;108:812-21
16. Vasu T, Doghramji K, Cavallazzi R, et al. Obstructive sleep apnea syndrome and postoperative complications. *Arch Otolaryngo Head Neck Surg* 2010;136:1020-4
17. Younger JW, Chu LF, D'Arcy NT, et al. Prescription opioid analgesics rapidly change the human brain. *Pain* 2011;152(8):1803-10
18. Alam A, Gomes T, Zheng H, et al. Long-term analgesia use after low-risk surgery: a retrospective cohort study. *Arch Intern Med* 2012;172(5):425-30
19. Lennon FE, Moss J, Singleton PA. The u-opioid receptor in cancer progression: is there a direct effect? *Anesthesiology* 2012;116(4):1-6

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20. Mathew B, Lennon F, Siegler J, et al. The novel role of the mu opioid receptor in lung cancer progression: a laboratory investigation. *Anesth Analg* 2011;112(3):558-67
21. Angst M, Clark D. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 2010;113:514-5
22. Viscusi ER, Pappagallo M. A review of opioids for in-hospital pain management. *Hospital Practice* 2012;40(1):149-59
23. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology* 2010;113:639-46
24. Angst MS, Clark JD. Ketamine for managing perioperative pain in opioid-dependent patients with chronic pain: a unique indication? *Anesthesiology* 2010;113:514-5
25. Domino EF. Taming the ketamine tiger. *Anesthesiology* 2010;113:678-86
26. Pluijms WA, Steegers MA, Verhagen AF, et al. Chronic post-thoracotomy pain: a retrospective study. *Acta Anaesthesiol Scand* 2006;50:804-8
27. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006;367:1618-25
28. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science* 2000;288:1765-8
29. Buvanendran A, Kroin JS, Della Valle CJ, et al. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg* 2010;110:199-207
30. Wylde V, Hewlett S, Learmouth ID, et al. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. *Pain* 2011;152:566-73
31. Werner MU, Mjobo HN, Nielsen PR, et al. Prediction of postoperative pain: a systemic review of predictive experimental pain studies. *Anesthesiology* 2010;112:1494-502
32. Kim JC, Choi YS, Kim KN, et al. Effective dose of peri-operative oral pregabalin as an adjunct to multimodal analgesic regimen in lumbar spinal fusion surgery. *Spine* 2011;36:428-33
33. Burke SM, Shorten GD. Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. *Anesth Analg* 2010;110:1180-5
34. Giancesello L, Pavoni V, Barboni E, et al. Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. *J Neurosurg Anesthesiol* 2012;24(2):121-6
35. Trabulsi EJ, Patel J, Viscusi ER, et al. Preemptive multimodal pain regimen reduces opioid analgesia for patients undergoing robotic-assisted laparoscopic radical prostatectomy. *J Urology* 2010;76(5):122-4
36. Balaban F, Yagar S, Ozgok A, et al. A randomized, placebo-controlled study of pregabalin for postoperative pain intensity after laparoscopic cholecystectomy. *J Clin Anesth* 2012;24:175-8
37. Bornemann-Ciment H, Lederer AJ, Wejbor M, et al. Preoperative pregabalin administration significantly reduces postoperative opioid consumption and mechanical hyperalgesia after transperitoneal nephrectomy. *Br J Anaesth* 2012;108:845-9
38. Grigoras A, Lee P, Sattar F. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. *Clin J Pain* (ahead of print).

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