

Update on Advances in Peri-operative Acute Pain Management in the Surgical Patient

a report by

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Overview of Peri-operative Pain Management

More than 40 million surgical procedures are performed annually in the US, with only one in four post-surgical patients receiving adequate treatment for acute pain.^{1,2} Acute pain refers to short-term pain that has an easily identifiable cause from the tissue damage that results from a surgical event. Acute pain is marked by a rapid onset, is perceived to be sharp in nature and may be followed by a dull, aching pain. The most severe post-surgical pain occurs within the first 24 to 36 hours after the procedure. Poorly managed peri-operative pain may lead to untoward systemic events such as cardiovascular, pulmonary, thromboembolic or gastrointestinal complications. Local complications may be exacerbated such as pronounced weakness, muscle breakdown, insufficient wound healing and reflex sympathetic dystrophy.³ These detrimental physiologic effects may result in prolonged hospitalisation and rehabilitation requirements. Thus, by optimally controlling post-surgical pain, improvement may be achieved in overall patient outcome. In addition, post-operative emotional effects such as anxiety and depression may be more pronounced in patients who receive less than adequate pain management. Advances in peri-operative acute pain management for the surgical patient will be reviewed.

Pre-operative (Pre-emptive) Management Strategies

The most commonly used methods of anaesthesia for surgical procedures are general and regional.

General anaesthesia requires the placement of either an endotracheal tube or laryngeal mask to assist and maintain a steady flow of oxygen for the patient throughout the operative procedure. The muscles are relaxed, and because the patient is unconscious he/she is unaware of the procedural events. The disadvantage is that the medications utilised for general anaesthesia leave the patient somewhat sedated for the first 24 to 48 hours after surgery. Once the general anaesthetic is reversed, the onset of post-operative pain is often sudden and severe. Controlling this level of pain, especially in the elderly population, may present a therapeutic challenge.

Pre-emptive analgesia refers to the reduction or prevention of pain prior to the noxious stimulus, thereby reducing the pain experienced as well as overall analgesic requirements. Pre-emptive analgesia can be achieved with non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and longer-acting opioids such as codeine and propoxyphene.

Non-opioid agents are used to manage moderate to severe pain and can be combined with opioid drugs to enhance pain relief. Examples of non-opioid drugs include acetaminophen and NSAIDs. The primary mechanism of action of the NSAID is inhibition of prostaglandin formation. NSAIDs work by inhibiting COX-1, the enzyme that converts arachidonic acid to prostaglandins. COX-1 is a protein that acts as an enzyme to speed up the production of prostaglandins, which work to perpetuate the inflammatory process. The major disadvantage of this class of drugs is the effects on the gastrointestinal, renal and haematologic systems.



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1. DeFrances C J and Hall M J, Advance data from vital and health statistics: 2002 national hospital discharge survey, (2004) 342, US Department of Health and Human Services, Center for Disease Control and Prevention, National Center for Health Statistics, available at: <http://www.cdc.gov/nchs/data/ad/ad342.pdf> (accessed 24 August 2004).
2. Williams G W, Gitlin M C, Eaton K and Dieckgraefe B K, "Safe and effective management of the patient with acute or chronic pain: a case-based, multidisciplinary approach: CME. Release Date: 26 August 2003. Finch University of Health Sciences, Chicago Medical School.
3. Schaffer J L, "Acute and postoperative pain management", Committee on Operating Room Environment: Adult Reconstruction Section, Department of Orthopedic Surgery; and Information Technology Division; The Cleveland Clinic, available at <http://www.facs.org/education/congress2002/gso6schaffer.pdf> (accessed 17 September 2004).

COX-2 Inhibitors

COX-2 is an inducible enzyme with increased concentration in the presence of inflammation and appears to be restricted to the brain, kidney, bones, testicles, ovaries, uterus, tracheal epithelial cells and small intestine in very low levels.² COX-2 inhibitors are now a mainstay of anti-inflammatory therapy because they have no effect on platelet function and the risk of gastrointestinal bleeding is significantly lower.⁴ Currently approved COX-2 inhibitors for the management of acute pain are Vioxx® (rofecoxib; Merck and Co., Inc., Whitehouse Station, NJ) and Celebrex® (celecoxib; Pfizer, Inc., New York, NY). Rueben and colleagues⁵ reported on the pre-emptive analgesic effect of rofecoxib after ambulatory arthroscopic knee surgery in which patients were given 50mg rofecoxib one hour either before surgery or after procedure completion. All patients received intra-articular bupivacaine 0.25% pre- and post-operatively and intravenous (IV) sedation using medazolam and propofol. Pre-operative administration of rofecoxib provided a longer duration of post-operative analgesia, less 24-hour total opioid use and lower incidental pain scores. The recommended dose of rofecoxib for acute pain management is 50mg once daily. The maximum recommended daily dose is 50mg. Use of rofecoxib for more than five days in the management of pain has not been studied; however, chronic use of rofecoxib 50mg daily is not recommended.⁶ Of note, effective 30 September 2004, Merck & Co. announced a voluntary worldwide withdrawal of rofecoxib.⁷

Intra-operative Management Strategies

Spinal

Spinal analgesia involves placing a small needle through the dura followed by injection of a small dose and volume of local anaesthetic. Spinal analgesia may be used in combination with epidural anaesthesia or analgesia. Its advantages include technical ease, effective and rapid onset and minimal drug dose requirement. Hypotension caused by

sympathetic blockade reduces the risk of blood loss and thromboembolic disease. The regional nature of the technique does not disrupt the patient's ability for spontaneous ventilation. Risks include profound hypotension, post-spinal headache and meningeal infection (rare).

Epidural

Epidural anaesthesia involves placing a larger needle into the epidural space, usually at a low thoracic or lumbar level, and injecting a higher volume of local anaesthetic. A catheter may be threaded into the space and secured for post-operative use. Improvements in equipment, drugs and technique have made epidural anaesthesia popular and versatile, with applications in surgery, obstetrics and pain control. Both single injection and catheter techniques can be used. It can be used as an analgesic adjuvant to general anaesthesia and for post-operative analgesia in procedures involving the lower limbs, perineum, pelvis, abdomen and thorax.

Surgical anaesthesia requires dense sensory block and usually moderate to dense motor block. Low-concentration local anaesthetics, opioids or combinations of both are effective in the control of post-operative pain in patients undergoing abdominal and thoracic procedures.

Epidural analgesia allows earlier mobilisation, reduces the risk of deep venous thrombosis and allows better co-operation with chest physiotherapy thus helping to prevent chest infections. Post-operatively, the epidural anaesthesia may continue to have an effect for four to six hours, providing a relatively comfortable early post-operative period. When pain relief becomes necessary, the catheter can be used to administer a continuous dose or a patient-controlled dose of local analgesic. When used in total hip and knee replacement, epidural anaesthesia tends to lower the blood pressure, which results in less blood loss, reduced need for post-operative blood transfusions and a decreased rate of lower extremity thrombotic events.⁸

Mayo and co-workers⁹ reported that patients undergoing elective colonic resection were

4. Ekman E F, "Recent trials investigating the efficacy of COX-2 specific inhibitors in pain and arthritis", Paper presented at: "A New Era in Pain Management With COX-2 Specific Inhibitors" symposium; 14 February 2002, Dallas, TX.
5. Reuben S S, Bhopalkar S, Maciolek H, Joshi W and Sklar J, "The preemptive analgesic effect of rofecoxib after ambulatory arthroscopic knee surgery", *Anesth. Analg.* (2002) 94: pp. 55–59.
6. Vioxx® [package insert], Whitehouse Station, NJ: Merck & Co. Inc. (2002).
7. Available at <http://www.Pharmalive.com/news> (accessed on 30 September 2004).
8. http://www.georgetownuniversityhospital.org/documents/Orthopedic%20Surgery/Protocols/jointreplacement/Anesthesia_for_Total_hip_and_Knee_Replacement.htm (accessed 17 September 2004).
9. Mayo C F, Klubien K, Schrickler T, Trudel J and 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: pp. 540–549.

randomised to either patient-controlled analgesia (PCA) with morphine or thoracic epidural analgesia with bupivacaine and fentanyl. Results showed that the superior quality of pain relief provided by epidural analgesia had a positive impact on out-of-bed mobilisation, bowel function and intake of food with long-lasting effects on exercise capacity and health-related quality of life. Disadvantages of a continuous epidural include hypotension, cardiac arrhythmias, decubitus ulcers and epidural haematoma with potential for permanent paralysis.

Post-operative Management Strategies

Patient-Controlled Analgesia

IV PCA allows the patient to manage his/her pain with a self-activated pump that delivers a controlled dose of medication through an IV line. The pump's built-in governor helps prevent patient over-medication. Patients who use PCA report better analgesia and lower pain scores than those patients who have to request analgesia from the nursing staff.¹⁰ Disadvantages of this system include opioid-induced sedation, respiratory suppression and mechanical difficulties in drug delivery.

Opioids

Opioid analgesics are used to manage moderate to severe pain. They act on central and peripheral opioid receptors, inhibiting the transmission of nociceptive signals from peripheral and central inputs. The most effective opioids have full agonist properties such that they do not exhibit a ceiling effect on dose increase. Opioid partial agonists, or mixed agonist-antagonists, have low intrinsic opioid receptor activity and thus have a ceiling effect. Adverse events associated with opioid use include constipation, nausea, vomiting, sedation, impaired judgment, impaired psychomotor function and respiratory depression. The combination of low-concentration local anaesthetic and low-concentration mixtures of opioids, administered by slow epidural infusion rather than intermittent boluses, has, in particular, been shown to be very effective in the management of post-operative pain. Balanced analgesia incorporates a combination of opioids and non-opioids to improve analgesic safety

and efficacy. Enhanced pain relief may be achieved with decreased individual medication doses.

Future Advances

There is a clear need for improvements in post-operative analgesic techniques and a greater number of therapeutic options.

DepoDur™ (morphine sulphate [MS] extended-release liposome injection; Endo Pharmaceuticals, Chadds Ford, PA) was approved by the US Food and Drug Administration (FDA) on 19 May 2004. It is intended for single-dose administration by the epidural route at the lumbar level for the treatment of pain following major surgery. DepoDur is administered prior to surgery or after clamping the umbilical cord during caesarean section. A single dose of DepoDur provides many of the benefits of epidural administration, including pain relief superior to that provided by IV PCA, without the increased risk of neurologic sequelae or infection associated with infusions or repeat injections. DepoDur reduces use of supplemental analgesia compared with a standard dose of conventional MS given by epidural injection and it eliminates the need for supplemental IV PCA in some patients.¹¹

To date, more than 900 patients (including more than 250 patients greater than 65 years of age) have received DepoDur for orthopaedic hip arthroplasty or knee replacement, visceral lower abdominal surgery or elective caesarean section. The side effect profile is typical for epidural opiates and would be expected in the surgical population studied, with the potential for dose-dependent respiratory depression, especially in the first 24 hours post-injection (90% of patients started within 24 hours, 0.6% started within 48 hours and 4% were given opioid antagonists). No evidence of increased neurologic complications has been observed compared with any of the control groups. At present, therapeutic doses of local anaesthetic should not be given with DepoDur. Whether DepoDur can reduce or eliminate the need for other parenteral opiates in the first 24 to 48 post-operative hours is currently under investigation¹². DepoDur is a promising new therapy that could have an important role in managing post-operative pain following major surgery. ■

10. Farlex Inc. resource page, "Patient controlled analgesia", available at: <http://encyclopedia.thefreedictionary.com/Patient%20controlled%20analgesia> (accessed 24 August 2004).

11. DepoDur™ Product Monograph. Endo Pharmaceuticals. (September 2004).

12. Hartrick C T and Manvelian G, "Sustained-Release Epidural Morphine (DepoDur™)L: A Review", *Today's Therapeutic Trends* 2004; 22: 167-180.