Emerging Techniques in the Management of Acute Pain: Epidural Analgesia

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Epidural analgesia, often using opioids intraoperatively and postoperatively, is widely accepted as a valuable modality for perioperative pain management. In this review I present data from meta-analyses and recently published trials that evaluate the perioperative use of opioids administered epidurally or parenterally (as-needed or by patient-controlled analgesia) and their effect on outcome. Published effects of perioperative epidural techniques on cardiac and pulmonary function are reviewed. Clinical and practical issues associated with epidural anesthesia and analgesia include the existence of analgesic gaps (often related to technical difficulties with the pump or use of an indwelling catheter), the occurrence of hypotension, and compatibility with anticoagulation therapy. A new treatment option, a single epidural injection of morphine for continuous perioperative analgesia (DepoDur™; Endo Pharmaceuticals Inc, Chadds Ford, PA), may reduce some of these problems. Data from recent clinical studies are presented.

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The primary goal of perioperative pain management is to provide the patient with an adequate comfort level and an acceptable side effect profile. Regional anesthesia and analgesia techniques, including epidural analgesia and peripheral nerve blockade, are widely used in the United States to achieve this goal. In particular, epidural analgesia is quite common and the use of peripheral nerve blockade is expanding. In one report (1), nearly half of all anesthesiologists surveyed anticipated an increased use of peripheral nerve blocks in their practice. When used optimally, these techniques provide continuous, uninterrupted analgesia throughout the perioperative period, are associated with a high degree of patient satisfaction, and contribute significantly to meeting the central goals of pain management. In a prospective 7-year survey of 5969 surgical patients (2), neuraxial opioid analgesia was associated with a high degree of patient satisfaction, with patients reporting a mean satisfaction score of 8.5 on a scale of 1–10 (where 1 denotes complete dissatisfaction and 10 complete satisfaction). Unfortunately, satisfaction with other forms of analgesia was not assessed in this survey. Side effects with neuraxial opioids were minor and managed easily (2). These findings agree with the clinical experience of many practitioners. Despite these advantages, however, there is a growing awareness of the limitations associated with epidural analgesia. This review summarizes current and emerging knowledge in the use of continuous epidural analgesia with a focus on epidural opioids.

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Epidural Versus IV Opioid Analgesia

In current clinical practice, continuous uninterrupted analgesia for postoperative pain management is a primary aim of treatment, and opioids are usually used as a key element of the analgesic plan. While earlier studies showed that opioids administered in the epidural space provide better postoperative analgesia compared to IV administration (3,4), several studies have shown these two techniques to be equally effective (5–9).

To gain insight into this issue, the analgesic efficacy of epidural and parenteral opioids for postoperative analgesia was examined in a meta-analysis of 100 controlled trials that evaluated the use of postoperative epidural analgesia (10). The comparator was IV patient-controlled analgesia (PCA) in 48% of these trials and parenteral opioids, provided as needed, in 43%. Surgery was performed at thoracic, abdominal, pelvic (including cesarean section delivery), and lower extremity sites. Overall, analgesia provided by the

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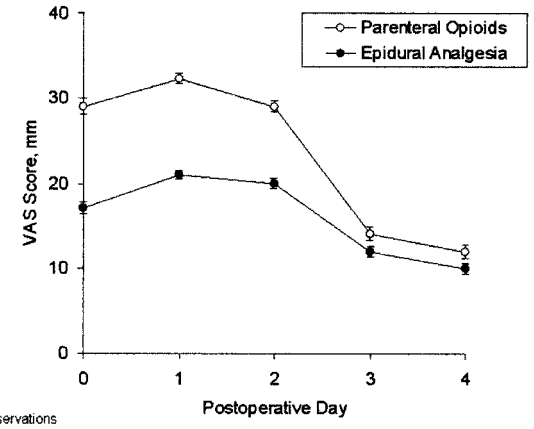

Figure 1. Mean visual analog scale (VAS) for each treatment group with 95% confidence intervals is shown from postoperative day 0 to 4. $P < 0.001$ for all days after surgery by Bonferroni correction for multiple comparisons. From Block et al. (10); used with permission.

epidural route was better: parenteral analgesia was associated with visual analog scale (VAS) pain scores ranging from 16.2–42.5 mm, compared with 12.0–32.0 mm for epidural analgesia ($P < 0.001$) at all time points measured. Also, nearly all epidural regimens provided better analgesia compared with parenteral opioids for both pain at rest and incident pain. For patients who received parenteral analgesia, mean VAS scores ranged from 12.1–31.3 mm for pain at rest and from 36.2–60.2 mm for incident pain. In patients who received epidural analgesia, mean VAS scores ranged from 6.9–26.5 mm for pain at rest and from 24.7–43.1 mm for incident pain ($P < 0.001$ for all measures). VAS scores were reduced by 30%–33% for patients who had received epidural analgesia compared with parenteral analgesia, a magnitude of effect that can be considered clinically relevant (Fig. 1). Favorable results for epidural analgesia extended across patient populations. In patients undergoing abdominal surgery, all types of epidural regimens used (local anesthetic with or without opioid added, opioid alone) provided better analgesia than parenteral opioids. Mean VAS scores ranged from 16.0–31.4 mm for epidural analgesia compared with 33.9–38.1 mm for parenteral analgesia ($P < 0.001$). Similar results were observed in analyses for pelvic and lower extremity surgery. In patients who underwent thoracic surgery, thoracic epidural analgesia using a local anesthetic, with or without an opioid, was associated with the largest improvement in analgesia. Mean VAS scores were 16.5–21.8 mm for epidural analgesia, compared with 24.7–27.6 mm for parenteral analgesia ($P < 0.002$).

Similar results were observed for thoracotomy patients in a prospective, randomized, double-blind study (11). Thirty-six patients received postoperative analgesia either via an epidural infusion of fentanyl (10 μg/mL, 5 mL/h) or via IV PCA with morphine (1 mg/mL, 10-min lockout). Epidural catheters were placed at a thoracic interspace (T3-4 or T4-5) before induction of general anesthesia. For patients receiving epidural analgesia, VAS pain scores at rest were typically ~10 mm better ($P = 0.001$) and total pain relief scores (TOTPAR, the sum of 7 measurements, each of which ranked from 0 = no relief to 3 = complete pain relief) were higher (14.7 ± 1.5 versus 12.8 ± 1.6 on day 1; $P = 0.006$). During coughing, the increase in VAS score in the epidural group was also smaller in magnitude ($P < 0.001$). Sedation was measured on a five-point scale from 0–4 (0 = awake, 4 = asleep). On postoperative day 1, the PCA group reported sedation levels of 2 or 3 more frequently than did the epidural group ($P = 0.005$). Pruritus was experienced by more patients in the epidural group (72% versus 28%; $P < 0.02$). The incidence of mild nausea and vomiting was similar between groups. The authors of this report considered that, for postthoracotomy patients, epidural fentanyl infusion provided better postoperative analgesia than IV PCA morphine. The ability to cough more easily was considered a particularly important advantage after thoracic surgery.

Clinical Outcome Studies

In some clinical studies, several improvements in outcome variables have been associated with the use of postoperative epidural analgesia. A reduced incidence of postoperative complication rates, cardiovascular failure, and infection, as well as reduced duration of intensive care unit (ICU) and hospital stay were reported in one study (12). In lower extremity vascular surgery, a less frequent incidence of reoperation because of vascular graft failure has been reported (13,14).

In a randomized, controlled study (12) of 53 high-risk surgical patients undergoing a variety of surgical procedures, clinical outcomes were compared in patients who received epidural anesthesia and epidural morphine for postoperative analgesia (Group I) and general anesthesia versus those receiving conventional postoperative analgesia (Group II). In Group I, 32% (9/28) of patients developed one or more postoperative complications, compared with 76% in Group II (19/25; $P = 0.002$). The number of complications per patient was also smaller in Group I compared with Group II (12 complications in 9 patients versus 49 complications in 19 patients; $P = 0.004$). One patient in Group I died, compared with 4 in Group II. ICU and hospital stays tended to being shorter in Group I (2.5 ± 1.8 days [mean ± SD] in the ICU and 11.4 ± 4.6 days in the hospital compared to 5.7 ±

9.3 days and 15.8 ± 12.3 days, respectively, for Group II patients) but did not attain statistical significance. Tuman et al. (13) questioned some aspects of this study, noting that the number of patients was small and that subsequent studies did not confirm the findings in vascular patients. Many factors may influence perioperative morbidity in these patients, including age, significant coronary artery disease, hypertension and, congestive heart failure. The use of a heterogeneous population in this latter study may explain its nonsignificant findings.

Another study (13) confirmed the benefit of epidural anesthesia and analgesia in 80 high-risk surgical patients with atherosclerosis undergoing major vascular surgery. Postoperatively, opioids were delivered either epidurally ($n = 40$) or by the parenteral and/or oral routes ($n = 40$) as needed. Patients who received epidural anesthesia and analgesia had fewer serious complications and fewer cardiovascular complications than did those who received general anesthesia (13 versus 52 complications; $P = 0.011$). The vascular graft failed in eight patients in the general anesthesia group and in one in the epidural anesthesia group. In the general anesthesia group, vascular graft failure was also associated with a larger incidence of reoperation on the affected limb (7 of 40 versus 1 of 40; $P = 0.025$). Postoperative thrombosis of a coronary artery, deep vein, or vascular graft occurred in 11 patients with general anesthesia alone but in only one patient who had received general plus epidural anesthesia and analgesia ($P = 0.002$). In addition, patients in the epidural anesthesia and analgesia group had shorter ICU stays (1.5 ± 1.4 days versus 3.3 ± 6.9 days in ICU, $P = 0.031$). The authors proposed that these benefits on postoperative hypercoagulability relate to attenuation of the surgical stress response and to increased blood flow to the legs, an effect enhanced by the inclusion of a dilute solution of local anesthetic to maintain sympathetic block after arterial reconstruction (13). A similar result was observed in a study of perioperative morbidity in 100 patients at high risk for cardiac and other morbidity undergoing elective vascular reconstruction of the lower extremity (14). In this study, 2 of 49 patients who received epidural anesthesia and analgesia required reoperation for inadequate tissue perfusion compared with 11 of 51 patients who received general anesthesia followed by IV PCA postoperatively.

Despite the demonstrated benefits of epidural anesthesia/analgesia on cardiac outcomes in these earlier studies, clinical opinion remains divided regarding the use of postoperative epidural analgesia in high-risk cardiac patients. Meta-analyses have attempted to address this issue. One such analysis (15) evaluated the potential for epidural analgesia to reduce the rate of postoperative myocardial infarction (PMI). Because the incidence of PMI peaks within 24 h after surgery, the primary goal of these investigators was to evaluate studies in which epidural analgesia was administered for at least 24 hours postoperatively. Of 17 studies, 11 were randomized, controlled trials comprising 1173 patients. Overall, the rate of PMI was 6.3%; in patients who received an epidural, the rate decreased by 3.8% (95% confidence interval [CI]: 0.2%–7.4%; $P = 0.049$). The incidence of in-hospital death, 3.3%, did not differ between groups. Subgroup analysis demonstrated that thoracic placement of the epidural catheter results in a 40% reduction in PMI, a finding supported by other reports (16–18). Some differences failed to reach significance if the Yeager et al. study (12) was excluded. The authors noted the limitations of this early study (poor analgesia in the control group, a decision to terminate early, a large difference between treatment groups). A trend toward a reduction in PMI was preserved when excluding this study, but the remaining studies did not have the power to demonstrate a statistical difference at this level of morbidity.

In another study, the effects of various analgesic modalities on postoperative pulmonary function were examined, based on results from 24 randomized, controlled trials (17). In this analysis, epidural administration of either opioids or local anesthetics was associated with improvement in pulmonary outcome compared with administration of systemic opioids. Epidural opioid use reduced the risk of atelectasis (risk ratio (RR), 0.53; 95% CI: 0.33–0.85). The incidence of pulmonary complications (RR 0.51; 95% CI: 0.20–1.33) and the incidence of pulmonary infection (RR 0.53; 95% CI: 0.18 to 1.53) was reduced but the differences did not attain statistical significance.

Nevertheless, findings of these meta-analyses have failed to predict the results of several published, large, randomized clinical trials (19–21). The conclusion drawn from these randomized trials is that perioperative epidural techniques do not decrease the incidence of perioperative cardiopulmonary complications. Some clinicians may disagree with these findings. As has been noted, a central issue in the interpretation of these trials is the definition of perioperative epidural technique in protocol design (22). Key issues in epidural technique include the timing of epidural administration (preoperative or postoperative), duration of epidural analgesia, the location of the epidural catheter and infusion drug composition.

In one large randomized clinical trial, the protocol for epidural treatment was not strictly defined but rather allowed for variations in practice based on "real world" clinical use (19). Numerous variables, including intraoperative anesthetics and IV opioids, location of epidural catheter placement, and the use of rescue analgesia in the epidural group, were not controlled and could have affected the results of this trial. Similarly, a second trial (20) did not specify the proportion

of patients who received lumbar epidural versus thoracic epidural catheters, and postoperative analgesia was provided via intermittent bolus. A third trial (21) reported a retrospective subset analysis of high-risk patients from a published study (19) and concluded that epidural analgesia provided no advantage in terms of outcome. Serious statistical issues have been noted regarding this analysis; specifically that no statistical correction was made for multiple testing, allowing an inflated Type I error rate (22). Had the authors controlled for this error, there would not have been any significant differences in analgesia between the two subgroups. In addition, subgroup stratification may have occurred with knowledge of the outcome, biasing the results. Similarly, the endpoints might have been defined with knowledge of the differences between subgroups. Also, the study does not identify whether there were multiple complications in individual patients, which could significantly affect its conclusions (22).

Unmet Needs

Many clinicians agree that, compared with intermittent parenteral opioid injection, continuous epidural analgesia provides superior pain relief with fewer fluctuations and fewer adverse effects (23). In addition, there is reasonable evidence indicating improvements in intermediate outcome variables. Nonetheless, there are limitations associated with continuous drug delivery through an indwelling catheter. In practice, analgesic gaps occur often and dose adjustments may be frequent. Outcome may be impacted by these gaps in effective analgesia. Sometimes, gaps are associated with technical difficulties related to pump or catheter problems. Clinical issues include a relatively frequent incidence of hypotension, compatibility with anticoagulation therapy and, in orthopedic patients, interference with mobility and physical therapy treatments.

The failure rate of epidural analgesia can be frequent. In a survey of 26,000 patients at the University of Washington, failure rates were 32% for thoracic catheters and 27% for lumbar catheters (24). Reasons for failure included dislodgement of the catheter (17%), not placing the catheter in the epidural space (11%), and leaks (7%). In 7% of patients, block was unilateral. Other potential causes of catheter failure include kinks in the catheter, migration of the tip of the catheter, or catheter occlusion. Similarly, a prospective survey of 1062 surgical patients receiving epidural analgesia, reported that 23% of catheters were removed prematurely because of catheter-related problems (25). Patient-controlled infusion pumps also malfunction frequently. At many institutions, the need to program, troubleshoot, and replace infusion pumps consumes health care providers' time. This author estimates that technical problems relating to indwelling catheters or pumps are observed in at least 20%–25% of patients receiving epidural analgesia.

The incidence of hypotension associated with the use of epidural analgesia can be frequent. In a survey of more than 25,000 patient records, hypotension that required contacting the pain service occurred in 8% of patients with lumbar epidural analgesia and in 11% of patients with thoracic epidural analgesia. In addition, motor impairment affecting ambulation may occur with dilute local anesthetic solutions delivered through a lumbar catheter. Rates of motor impairment sufficient to prevent independent ambulation range from 24%–51% (24).

The potential for thromboembolic events is a primary concern after surgery. As many as 600,000 North American patients are hospitalized each year for deep venous thrombosis (DVT) (26). In the absence of thromboprophylaxis in patients undergoing total hip replacement, the risk of postoperative DVT is at least 40% and the risk of pulmonary embolism (PE) ranges from 1.8%–30% (27). For patients undergoing general surgery without thromboprophylaxis, the risk of DVT is 16% and the risk of PE is 1.6% (28). To reduce these risks, many patients receive an anticoagulant and/or antiplatelet medication perioperatively.

Depending on the type of anticoagulation used, patients who receive anticoagulation therapy may not be candidates for spinal or epidural anesthesia/analgesia because of a potential increased risk of spinal hematoma. In December 1997, the United States Food and Drug Administration (FDA) issued a health advisory regarding the risk of spinal hematoma with concurrent use of low molecular weight heparin and spinal/epidural anesthesia or spinal puncture. In support of this, one review reports that 55% of spinal hematoma cases resulted from a neuraxial block procedure in a patient concurrently receiving anticoagulant therapy (29). In addition, use of low molecular weight heparins with a longer duration of effect and newer, irreversible antiplatelet drugs contribute to concerns regarding the risk of intraoperative or postoperative hemorrhage. Aggressive thromboprophylaxis regimens have caused some clinicians to reduce their use of continuous epidural catheters.

Novel Approaches

DepoDur™ (Endo Pharmaceuticals Inc, Chadds Ford, PA) is a novel analgesic formulation of morphine for postoperative pain management, intended for epidural administration, which has recently been approved by the FDA. It consists of morphine encapsulated within liposomes to provide extended release of

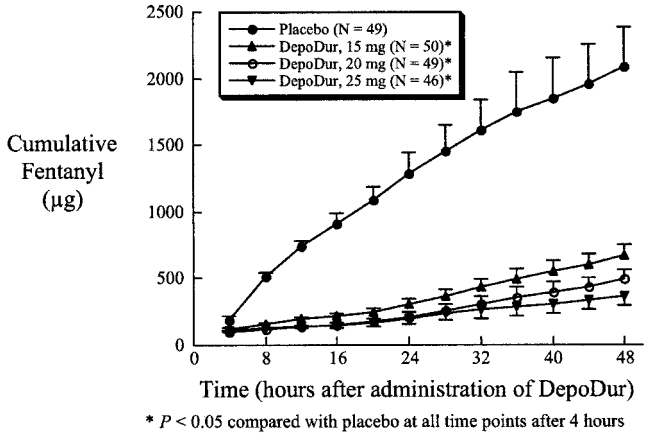

Figure 2. Cumulative fentanyl consumption during 48 h postsurgery is shown for three groups of patients given DepoDur™ and a placebo group. Values are mean ± SE. Fentanyl consumption decreased markedly with all three doses of DepoDur™ (from DepoDur™ prescribing information).

morphine after epidural injection. The liposome delivery vehicle (DepoFoam™, SkyePharma PLC, London UK) is microscopic spherical particles with internal aqueous chambers containing suspended morphine. After injection, in physiological conditions, the chambers degrade to release drug slowly (30). In clinical studies, DepoDur™ was given as a single epidural injection before surgery and provided pain relief for 48 h, after which time most patients were transitioned to oral analgesics.

In a randomized, blinded study of 194 hip arthroplasty patients (31), DepoDur™ (15, 20, or 25 mg) or saline placebo was administered as a single epidural injection before induction of anesthesia; patients were allowed *ad lib* access to fentanyl IV PCA postoperatively. In patients given DepoDur™, fentanyl requirement during the 48 h after surgery was markedly reduced (Fig. 2) and time to first fentanyl request was markedly longer (Table 1; $P < 0.0001$). The incidence of adverse effects did not differ between groups and all side effects were managed easily.

In a randomized, blinded study in 75 patients undergoing cesarean delivery, DepoDur™ showed similar efficacy for postoperative analgesia (32). Patients received intrathecal bupivacaine (12–15 mg) and fentanyl (10 μg). After umbilical cord clamping, a single epidural dose of DepoDur™ (5, 10, or 15 mg) or morphine sulfate (5 mg) was given. Patients received additional oral or IV opioids as needed for postoperative analgesia. Patients who received DepoDur™ used significantly less rescue analgesic drug (expressed as IV morphine equivalents) throughout the 48-h postsurgical period (median values of 30.8, 19.0, and 18.0 mg for 5, 10, and 15 mg study groups, respectively, versus 38.2 mg for morphine sulfate; $P < 0.05$). The authors suggested that DepoDur™ holds promise for the management of postcesarean delivery pain.

Table 1. Time from Completion of Surgery to First Fentanyl Request for Patients Given DepoDur™ or Placebo Before Hip Arthroplasty

	Time (h)
Placebo	3.6 (3.1–4.2)
DepoDur™, 15 mg	15.4 (6.1–26.5)
DepoDur™, 20 mg	22.7 (8.1–36.8)
DepoDur™, 25 mg	22.8 (9.0–42.3)

Values are median (95% confidence interval).
From Viscusi et al. (31).

Investigators in these studies observed that a single epidural injection of DepoDur™ provided consistent pain relief through 48 h after surgery, the period during which pain is often worst. Need for rescue medication was minimal, analgesic gaps were few, and there were no problems related to catheter or pump maintenance issues. In addition, unlike catheter-based epidural analgesia, there was no need for intermittent adjustment of medication levels. In addition, the incidence of hypotension was less than that seen with epidural local anesthetics. In orthopedic patients, DepoDur™ analgesia was compatible with anticoagulation therapy because it did not require an indwelling epidural catheter. The absence of an additional pump and IV pole with extra tubing, which can sometimes limit a patient's ambulation, was also considered an advantage.

During clinical trials with DepoDur™, the majority of adverse events were typical of opioid medications and consistent with the surgical populations being studied. Adverse events occurring in more than 10% of patients included decreased oxygen saturation, hypotension, urinary retention, vomiting, constipation, nausea, pruritus, pyrexia, anemia, headache, and dizziness (DepoDur™ full prescribing information). Of note, 90% of all episodes of respiratory depression in the clinical trials occurred within 24 h. Only 0.6% of episodes of respiratory depression occurred after 48 h. In these clinical trials, 4% of patients received an opioid antagonist for respiratory depression. As with all opioids, the chief hazard is respiratory depression, especially in elderly and debilitated patients and in those with compromised respiratory function.

Multimodal Therapy

In current clinical practice, pain management protocols often use multimodal therapy with a variety of drugs (e.g., local anesthetics, opioids, nonsteroidal antiinflammatory drugs [NSAIDs], cyclooxygenase [COX]-2 inhibitors, acetaminophen, and α-2 agonists) (33–35). Perioperative analgesia typically begins preoperatively and continues throughout the intraoperative and postoperative periods. The use of NSAIDs

and opioids together often improves analgesia by interrupting nociceptive impulses at both central and peripheral sites of the pain transmission pathway and reduces the need for opioids in the postoperative period (36–38). Often, the combination of COX-2 inhibitors with epidural analgesia is preferred. Unlike other NSAIDs, COX-2 inhibitors have no effect on platelet function. With epidural analgesia, addition of a coanalgesic (e.g., an NSAID or COX-2 inhibitor) may improve the incidence of undesirable side effects by allowing a reduced dose of epidural infusion. On occasion, NSAIDs or COX-2 inhibitors may be used for rescue analgesia if, as occurs for some patients, standard treatment fails to provide adequate analgesia.

Recently, controversies have arisen about the potential cardiac effects of COX-2 inhibitors. Current evidence associating these drugs with cardiac events comes from studies with long-term administration. This may lead to decreased use of these drugs in the postoperative period.

Conclusions

Continuous epidural drug delivery for postoperative analgesia offers advantages in terms of improvements in analgesia, patient satisfaction, and clinical outcome. Technologies associated with use of an indwelling catheter, such as IV-PCA or continuous epidural analgesia, have been used widely and are accepted at many institutions, yet these methods may be associated with various problems including incompatibility with anticoagulation therapy and technical failure of the catheter or pump, which may lead to analgesic gaps. Epidural catheter and pump-related issues are viewed as labor intensive by many clinicians. A continuous drug delivery system offers greater convenience while maintaining delivery of consistent analgesia. This is often facilitated significantly by the use of multimodal therapy. Optimal pain management is still best achieved through frequent, periodic assessment and reassessment of the patient's comfort level and the side effects of concurrent therapy. Newer technologies may influence a relative shift in practice from technology-focused care to patient-centered care.

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