A New Look at DepoDur For the Management Of Postoperative Pain

Eugene R. Viscusi, MD
Associate Professor
Department of Anesthesiology
Director, Acute Pain Management Services
Thomas Jefferson University
Jefferson Medical College
Philadelphia, Pennsylvania

Richard H. Rothman, MD, PhD
Rothman Institute of Orthopaedics
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

Postoperative pain is a significant concern for patients undergoing the estimated 46 million inpatient surgical procedures performed each year in the United States. Although there is a standard of care following surgery, a high percentage of patients report moderate, severe, or extreme postoperative pain.

The link between undertreated perioperative pain and undesirable effects on patients and health care resources is well recognized. Thromboembolic and pulmonary complications, extended hospital stays, hospital readmission for additional pain management, reduced health-related quality of life, and the development of chronic pain are potential complications of suboptimally managed postoperative pain.

Greater patient satisfaction and early ambulation, which may speed discharge and prevent thromboembolic complications, can be realized with consistent, effective analgesia in the early postoperative period.

Practice guidelines for acute pain management in the perioperative setting recommend multidimensional assessment and multimodal therapy to achieve uninterrupted analgesia and to minimize adverse events. Opioids, the backbone of the analgesic strategy,
may be administered via IV, neuraxial, or local routes in the postoperative setting.

DepoDur (EKR Therapeutics), a single-injection, extended-release (ER) formulation of epidural morphine, is designed to provide up to 48 hours of pain relief for surgical inpatients.9,10 The purpose of this educational monograph is to bring together pertinent findings from the pivotal trials and, more importantly, the accrued clinical experience with DepoDur in real-world practice since its 2004 FDA approval. Pending label changes, including the administration of an analgesic dose of bupivacaine at least 30 minutes prior to DepoDur, also offer the opportunity to consider standard of care with DepoDur in the landscape of postoperative pain management.9

Overview of Options

For most patients, intravenous patient-controlled analgesia (IV-PCA) is standard practice after major surgery.7 Patient-controlled epidural analgesia (PCEA) and continuous peripheral nerve blocks (CPNB) are other commonly used strategies that improve postoperative pain control compared with on-demand analgesia. Each of these modalities presents advantages and disadvantages. Deciding which strategy is best not only depends on the patient and the type of surgery, but also on the availability of alternative analgesic modalities, sufficient staffing, and monitoring capabilities.

Whenever opioids are used, physicians should conduct an assessment that includes a patient history and physical examination to identify risk factors for respiratory depression (defined as <8 bpm), a rare, but potentially life-threatening side effect of opioid analgesics. Morbid obesity, advanced age, cardiopulmonary disease, obstructive sleep apnea, and opioid tolerance are risk factors that require careful dosing and increased patient monitoring in the perioperative period.11,12

Evaluating Patient-Controlled Analgesia

Intravenous Application

Evidence supporting the efficacy and safety of and patient satisfaction with IV-PCA is robust.13-15 Opioid doses administered with IV-PCA tend to be smaller than bolus doses administered by nurses. These smaller doses can minimize common side effects, such as constipation, nausea, and vomiting.16,17 PCA pumps also address hospital staff concerns about analgesic gaps and opioid dosing in postoperative care. Although this approach allows patients to self-manage their postoperative pain,17 it treats, rather than prevents pain, and also restricts patient mobility.18

Moreover, serious safety concerns have arisen in conjunction with PCA pumps, especially device malfunctions and operator programming errors.18 The risk for medication errors resulting in patient harm more than triples with PCA pumps.20 A 5-year review of medication errors in MEDMARX, a national voluntary medication error-reporting database, found that approximately 1% of all errors (9,571 of 919,241) were related to PCA, with a significantly higher incidence of respiratory depression for PCEA than for IV-PCA (1.1% vs. 0.7%; P < 0.002).21 By contrast, one prospective study reported a greater incidence of respiratory depression with IV-PCA than with PCEA,22 whereas a retrospective study and a prospective study detected no difference. Authors of the German study suggested that the use of background infusion with IV-PCA in other studies may have increased the incidence of respiratory depression.23-25 Rates of hypotension also were significantly higher in patients treated with PCEA than in those using IV-PCA (6.7% and 2.6%, respectively; P < 0.001), and in patients receiving lumbar versus thoracic PCEA (7.7% and 4.1%, respectively; P < 0.001) (Table 1).23

<table>
<thead>
<tr>
<th>IV-PCA</th>
<th>PCEA</th>
</tr>
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<tbody>
<tr>
<td>Respiratory depression</td>
<td>0.7%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6.7%</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>19.7%</td>
</tr>
</tbody>
</table>

In addition to concerns with pump technology, which were outlined earlier, another concern with PCEA is the increased risk for thromboembolic events after surgery.6 Prophylactic measures include the use of anticoagulants, but this creates a risk for life-threatening spinal hematomas in patients receiving epidural anesthesia with an indwelling catheter.6 Pöpping and colleagues reported 3 patients suffering lumbar epidural hematomas, for a rate of 7.5 per 10,000.26 No thoracic epidural hematomas were diagnosed. Two epidural abscesses were reported (1.4 per 10,000), with only one at the epidural insertion site.23

Peripheral Nerve Block

Paresthesia and motor block also are concerns in patients receiving PCEA and CPNB. In the Pöpping study, the overall incidence of paresthesia and motor block was 0.5% with PCEA, with a significantly higher incidence of motor impairment with lumbar PCEA than with thoracic PCEA.23 Similar to other findings,28 Two recent retrospective studies show the association between the use of CPNBs and patient falls in the postoperative period.32,33 Falls after total knee arthroplasty (TKA) were most common with CPNB.33 Other investigations suggest that lower-extremity nerve blocks reduce leg stiffness and lateral stability required for successful pivoting, which can lead to a loss of balance and falls.34 In the Pöpping study, the incidence of severe neurologic complications was 0.06% and the incidence of insertion-site infections was 1.8% in patients treated with CPNB.23
DepoDur

Although PCEA, CPNB, and IV-PCA are safe and effective, the associated risks, although rare, can be catastrophic. Therefore, continuous monitoring by the acute pain service is warranted.²³ DepoDur, a single-injection, ER epidural morphine option for the treatment of postoperative pain, simplifies the burden of technology associated with PCA. This is a distinct benefit for nurses and pharmacy staff. DepoDur also eliminates indwelling catheters and concomitant antiacogulation worries and prevents the need to tether the patient to a machine, which may be associated with greater patient satisfaction. Anesthesiologists find ease of use to be the main benefit from DepoDur as it is a single injection that provides pain relief for up to 48 hours.

Pharmacoeconomic Implications

Questions of pharmacoeconomics with PCA technologies have not been fully explored. Costs associated with PCA include initial capital expenses (eg, pumps, IV sets, etc), equipment maintenance and repair, and pharmacy and nursing staff time for set up and ongoing maintenance.³⁵ Health care costs associated with inpatient falls also are substantial and rise in relation to severity and frequency.³⁶ DepoDur’s impact on pharmacoeconomics is being explored. Several studies suggest DepoDur may reduce or eliminate the need for PCA pumps and equipment.³⁷,³⁸ In addition to ease-of-care benefits compared with opioids administered by IV or the epidural route with PCA or continuous infusion, the reduced need for rescue IV opioids in the postoperative period may lower costs and enable patients to switch directly to oral analgesics after 48 hours.³⁹ DepoDur also may decrease patient time in the postanesthesia care unit (PACU),³⁶ and even shorten the length of the patient’s hospital stay.³¹,⁴² Large-scale, prospective studies still are needed to confirm the economic benefits of DepoDur.

Single-Injection Option (DepoDur):
Pending Label Changes

Designed for epidural injection only, DepoDur is indicated for the treatment of pain following major surgery. DepoDur is morphine sulfate encapsulated in a liposomal delivery system that facilitates extended analgesia for up to 48 hours. The slow-release technology reduces peak plasma concentrations.⁹ A single dose of DepoDur may be administered by the epidural route, at the lumbar level, prior to surgery or after clamping the umbilical cord during cesarean delivery. The injection is not intended for intrathecal, IV, or intramuscular administration.⁹

Pending label changes have incorporated new pharmacokinetic data with an analgesic dose of bupivacaine 0.25% (20 mL) prior to DepoDur administration. Serum morphine Cmax levels were comparable after administration of 15 mg DepoDur alone or 15 mg DepoDur administered at least 30 minutes after the administration of the bupivacaine.⁹ To minimize the pharmacokinetic interaction of DepoDur with a previously administered analgesic dose of bupivacaine (0.25%, 20 mL), the epidural catheter should be flushed with 1 mL of preservative-free 0.9% normal saline and the clinician should wait at least 30 minutes after administration of bupivacaine to administer DepoDur.⁹ Once a 3-mL test dose of lidocaine 1.5% and epinephrine 1:200,000 is administered, the clinician should wait 15 minutes before administering DepoDur to protect the sustained-release mechanism.⁹ The most common AEs with DepoDur (>10%) are hypotension, vomiting, urinary retention, constipation, decreased oxygen saturation, nausea, pyrexia, headache, anemia, dizziness, and pruritus.⁹

Analyzing the Data

FDA approval for DepoDur was based on safety and efficacy data from 4 double-blind, parallel-group randomized controlled trials (RCTs) evaluating 876 patients undergoing surgical procedures, such as hip arthroplasty, prostatectomy, colon resection, and cesarean delivery.⁵,³⁹,⁴³-⁴⁵ These trials compared the safety and efficacy of 2 or more doses of DepoDur (5-30 mg) with a control group receiving either conventional epidural morphine (5 mg) or epidural placebo. In these trials, DepoDur patients experienced significantly better pain relief than those managed with conventional epidural morphine, as well as those receiving IV-PCA alone, and required less rescue analgesia; some required no additional pain medication. In the orthopedic trials, the time to first request for additional analgesia was significantly longer in the DepoDur group than in the control or conventional epidural morphine groups.

In addition to these 4 RCTs, the evidence for the use of DepoDur has expanded to include an additional RCT of 70 women having elective cesarean delivery and an open-label pilot study of 39 patients undergoing hip arthroplasty. This RCT was the first to investigate the use of DepoDur as part of a multimodal pain regimen. Additionally, several studies of DepoDur have been presented at medical meetings⁴⁷,⁴⁰-⁴² and are reviewed here. A meta-analysis of safety events with DepoDur⁴¹ and a review of the foundational science and recent experience with DepoDur⁴² also have been published. Two reports from Duke University Medical Center provide additional insights into dosing strategies and important safety precautions with single-injection, ER epidural morphine.¹⁰,⁴⁷

Two studies by Carvalho and colleagues demonstrated the safety and efficacy of DepoDur in patients after cesarean delivery. In the original study, 73 patients received either standard epidural morphine (5 mg) or DepoDur (5-15 mg).⁴⁵ Over the 48-hour study period, patients who received 10 mg single-dose DepoDur required statistically significantly less supplemental opioid medication (P=0.0108).⁴⁵ Overall, the percentage of patients who did not receive supplemental opioids and the median time to request rescue analgesia were similar in all groups (2.2-3.1 hours).⁴⁵ Functional ability (defined as measures of resting, sitting, walking, and ability to use the toilet) also was significantly improved in patients in the DepoDur 10-mg group (P=0.05 at 24 and 48 hours).⁴⁵

The second study permitted the use of a multimodal pain-relief regimen that is now commonly employed in hospitals. In this study, 70 healthy parturients undergoing elective cesarean delivery also were randomized to DepoDur (10 mg) or conventional epidural morphine (4 mg) after surgery.⁴⁶ All participants also received 600 mg of ibuprofen orally every 6 hours during the 48-hour study period.⁴⁶ DepoDur significantly improved pain scores at rest and during activity (P=0.033 and P=0.003, respectively) compared with conventional epidural morphine.⁴⁶ Supplemental analgesics included an oral opioid (oxycodone 5 mg with acetaminophen 325 mg), as well as IV morphine for severe or unresponsive pain.⁴⁶ The majority of patients in both groups required supplemental analgesia: 83% of the DepoDur group and 94% of the morphine group.⁴⁶ Patients in both groups first requested additional analgesics approximately 3.5 hours after administration of the study drug.⁴⁶ Oral opioid consumption was 35% less for patients in the DepoDur group (P=0.07).⁴⁶ IV morphine was required by 3% of the DepoDur group and
The second Carvalho trial that employed a multimodal analgesic strategy with 10-mg doses of DepoDur in 70 healthy patients may be more clinically useful in terms of real-world dosing and effective multimodal therapy. Extensive use of DepoDur in routine clinical practice has shown that effective analgesia with an acceptable side-effect profile can be obtained with low doses of DepoDur (≤10-15 mg) in orthopedic patients as well.

In a retrospective study of 206 randomly selected patients who underwent total joint arthroplasty, patients in the total hip arthroplasty (THA) cohort received either DepoDur 7.5 mg (n=40), DepoDur 10 mg (n=17), combined intrathecal morphine (preservative-free) with IV fentanyl PCA (n=24), or IV fentanyl PCA (n=13). Patients in the TKA cohort received DepoDur 10 mg (n=44), DepoDur 12.5 mg (n=18), indwelling epidural catheter with 0.2% ropivacaine (Naropin, APP) and IV fentanyl PCA (n=25), or single-injection femoral nerve block (FNB) and IV fentanyl PCA (n=25). Primary outcome data indicated that for THA, DepoDur (7.5 and 10 mg) provided greater pain control compared with traditional modes of postoperative analgesia. The average morphine requirements for patients who underwent THA were significantly less in the DepoDur groups (P<0.001) compared with the traditional treatment groups. For patients who underwent TKA, DepoDur (10 and 12.5 mg) improved pain control and decreased supplemental opioid usage when compared with other modalities. A significant difference in morphine requirements was noted in the DepoDur groups (P<0.001) on postoperative days 0 and 1 compared with the control groups for both TKA and THA.

In a prospective, observational, case–control study, Sugar and colleagues stratified patients undergoing TKA, patients to receive either DepoDur (7.5-10 mg) combined with an FNB (0.25-0.5% bupivacaine, 10-40 mL) PCEA with various regimens. In this study, 24- and 48-hour postoperative pain scores and incidence of AEs were not significantly different between groups; however, the time spent in the PACU was significantly shorter for patients receiving DepoDur/FNB compared with PCEA (2.4±0.3 vs 3.8±0.3 hours; P=0.02). Sugar and colleagues estimated the total PACU cost savings at $991, and a yearly institutional cost savings greater than $14,000.

A retrospective analysis of patients who had undergone a THA or TKA over a 6-year period examined the incidence of pulmonary embolus (PE) during the 48-hour period following surgery. Of the 662 patients included in the analysis, 328 received DepoDur and 334 received a control treatment. The mean DepoDur dose was 9.7 mg (range 5-15 mg) and 44% of the control group used indwelling epidural catheters to provide analgesia. Of the patients in the control group, 6 experienced PEs versus none of the patients in the DepoDur group (P<0.05). Pain control was significantly better in the DepoDur group compared with the control group (visual analog scale scores [VAS], 1.54±0.75 vs 2.5±1.07; P<0.05). Length of hospital stay was significantly reduced in DepoDur patients compared with the control group (3.9±1.50 vs 4.5±1.94 days; P<0.0001).

AE profiles of the DepoDur and control groups were consistent with prior published studies.

A recent meta-analysis of safety events with DepoDur recommended a multimodal approach to postoperative analgesia with DepoDur at lower dosages (≤10 mg) to minimize the risks of AEs. The success of this approach is underscored in the retrospective analysis of clinical practice patterns with DepoDur. Respiratory depression requiring treatment with a narcotic antagonist after 24 hours with a single dose of DepoDur (10 mg) has not been reported. The incidence of respiratory depression after 48 hours potentially related to DepoDur is 0.6%. Some patients did not experience significant pain levels, while others had hypoxic events, which resolved spontaneously or with supplemental oxygen.

**Selecting the Right Patient and The Right Dose**

Patients enrolled in the DepoDur clinical trials were at least 18 years old, with an American Society of Anesthesiologists (ASA) physical status classification of I (normal and healthy) to III (severe systemic disease that limits activity, but is not incapacitating) and a body mass index of less than 40 kg/m². Trials did not include patients with obstructive sleep apnea, chronic obstructive pulmonary disease, other significant lung disease, or patients who were chronic opioid users.
Surgeon's Commentary

Therapeutic Options for Pain Control Following Total Joint Arthroplasty

Richard H. Rothman MD, PhD

Although control of pain following surgical procedures has improved significantly in recent years, inadequate pain control continues to be an important concern for patients undergoing surgery. The medical community has initiated extensive efforts to address this issue. The use of regional anesthesia for patients undergoing total joint arthroplasty (TJA) is one such effort. The use of regional anesthesia has been shown to be both efficacious and beneficial. Studies have reported improved pain control, earlier mobilization and quicker recovery, and decreased complication rates with the use of epidural anesthesia. A number of studies have specifically reported a decreased rate of deep vein thrombosis after TJA using regional anesthesia. Still, the use of regional anesthesia is not without risks and carries the potential for significant adverse events.

Extended-release epidural morphine (DepoDur, EKR Therapeutics) was developed to alleviate some of these complications, and uses a novel liposomal drug delivery system. Following administration of the drug into the epidural space, morphine is released from the liposomal vesicles over a period of time. This delivery system potentially leads to extended pain control, and contributes to reduced systemic drug exposure and toxicity. A number of studies have reported improved pain control with the use of DepoDur compared with conventional epidural morphine. The reported complications occurring with extended-release epidural morphine have been minor and comparable with other opioids.

Recovery From Joint Arthroplasty

A recent study performed at Thomas Jefferson University Hospital evaluated the in-hospital profile of DepoDur in patients undergoing TJA and compared its profile with those of conventional spinal anesthesia and intrathecal opioids. Findings showed that DepoDur provided significantly better pain control and patient satisfaction than spinal anesthesia. The incidence of gastrointestinal tract complications (nausea and vomiting) and pruritus were marginally higher in the group receiving DepoDur. No cases of respiratory depression or arrest were reported in patients receiving DepoDur. In particular, the superiority of DepoDur in terms of pain relief and reduced systemic opioid consumption was dramatic within the first 2 days following surgery.

In addition to analgesic superiority, the use of DepoDur offers numerous other advantages, most important of which is catheter- and pump-free modality. The absence of an epidural catheter reduces the risk for epidural hematoma formation with anticoagulation. The absence of external paraphernalia also facilitates patient mobility and reduces the burden of care related to catheter maintenance. An untethered patient also may have greater overall satisfaction.

Based on results from this study, it appears that DepoDur reduces pain and overall opioid consumption during the early postoperative period following TJA. As a result, the use of DepoDur is advocated in regional anesthesia for the majority of patients undergoing TJA at Thomas Jefferson University Hospital. In order to avoid opiate-related complications, lower doses of DepoDur (5, 7.5, and 10 mg) are preferred and use of the drug is avoided in patients with morbid obesity and/or history of obstructive sleep apnea.

References

Table 2. Monitoring After Opioid Administration

<table>
<thead>
<tr>
<th>Type of Administration</th>
<th>Duration of Monitoring, h</th>
<th>1-12 Hours</th>
<th>12-24 Hours</th>
<th>After 24 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>DepoDur</td>
<td>48-h minimum</td>
<td>≥1 per h</td>
<td>≥1 every 2 h</td>
<td>≥1 every 4 h</td>
</tr>
<tr>
<td>Single-injection hydrophilic opioid</td>
<td>48-h minimum</td>
<td>≥1 per h</td>
<td>≥1 every 2 h</td>
<td>Based on patient’s condition</td>
</tr>
<tr>
<td>Patient-controlled epidural analgesia</td>
<td>Through the infusion and post-infusion based on patient</td>
<td>≥1 per h</td>
<td>≥1 every 2 h</td>
<td>≥1 every 4 h</td>
</tr>
</tbody>
</table>

Adapted from reference 11.

Key findings include:

- **Multimodal Therapy**
  - Postoperative pain is both continuous and dynamic in nature. Rarely will a single modality and a single analgesic provide patients with sufficient comfort. The recommendation for a multimodal approach to acute pain management (i.e., combining different classes of analgesics and different sites of administration) is based on insights into peripheral and central pain mechanisms involved in nociceptive pain.
  - Lower doses of DepoDur also may require prophylactic anti-emetic therapy covering the 48-hour postoperative period,
  - particularly for patients with a higher risk for postoperative nausea and vomiting (i.e., nonsmokers, females, previous postoperative nausea and vomiting, and/or history of motion sickness).
  - Unmanaged, these side effects can postpone ambulation and discharge.

- **Keys to Success**
  - Insights into the successful incorporation of DepoDur into clinical practice have been provided by Duke University Health Systems, which phased in use of DepoDur with orthopedic patients undergoing total hip or knee replacements. The hospital trained its anesthesiologists and nurses on the proper use of DepoDur and added an order set with appropriate safety parameters for DepoDur’s ER mechanism to the hospital’s computerized order entry system.
  - Similar to the standard order set for morphine, the prescribing anesthesiologist selects nonopioid co-analgesics and drugs to manage nausea and vomiting, pruritus, and breakthrough pain. A sticker on the patient’s chart ensures that all members of the health care team are aware that the patient has received ER epidural morphine.
  - In January 2009, the ASA published practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. The ASA recommendations are similar for patients receiving single-injection morphine, as well as continuous infusion or PCEA with morphine. Monitoring should occur throughout the duration of the infusion (Table 2). Fentanyl administered via single injection, continuous infusion, or PCEA requires continual monitoring for the first 20 minutes after administration because of its short duration of action.
Conclusion

DepoDur, the first ER epidural morphine, offers the opportunity to have a comfortable patient without the need for an indwelling catheter. The single-injection, ER formulation simplifies the pain management strategy for clinicians. To account for potential AEs, clinicians should assess each patient for the most appropriate dosing. The ease-of-use and care benefits for the health care team are matched by patient benefits: DepoDur improves pain relief, patient satisfaction, and functional ability compared with conventional epidural morphine sulfate and IV-PCA.

References

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49. Data on file, EKR Therapeutics, Inc.


