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CLINICAL RESEARCH

Lessons Learned with Extended-release Epidural Morphine after Total Hip Arthroplasty

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Abstract An extended-release epidural morphine (EREM) has been introduced to improve postoperative pain management. Studies have shown the effectiveness of this agent in providing better pain control and patient satisfaction for patients undergoing total joint arthroplasty. We evaluated postoperative pain relief by comparing average daily pain scores and opioid use with those of the control group. Safety was measured by comparing the occurrence of postoperative complications, nausea and vomiting, pruritus, and respiratory depression between the two groups. Between February 2006 and March 2008, we selected 203 patients to receive EREM for THA. These patients were matched in a 2:1 ratio with patients undergoing THA and receiving spinal anesthesia. We retrospectively reviewed all major and minor postoperative complications from a prospective database. Patients receiving EREM had lower pain scores than patients not receiving EREM on Postoperative Day 1 (POD 1) but not POD 2, or POD 3. Patients receiving EREM experienced a slightly higher incidence of pulmonary embolism and supraventricular tachycardia. Patients receiving EREM also experienced more nausea and vomiting and pruritus. We found EREM provided better pain relief on POD 1 at the expense of a slightly higher incidence of side effects compared with spinal anesthesia alone.
Level of Evidence: Level III, therapeutic study. See the Guidelines for Authors for a complete description of levels of evidence.

Introduction

The ability of pain management techniques to relieve pain and minimize the number of postoperative complications after THA is important to orthopaedic surgeons. Various studies show epidural anesthesia improves pain control [15, 19], allows earlier mobilization and quicker patient recovery [20], and decreases complication rates [21]. Numerous authors specifically have reported a decreased rate of deep vein thrombosis after total joint replacement using regional anesthesia [2, 4, 10, 14].

Despite these benefits, the use of regional anesthesia is not without risks, including oxygen desaturation, hypotension, urinary retention, constipation, nausea and vomiting, pruritus, anemia, headaches, dizziness, respiratory depression, hypotension, and motor weakness [15, 19]. The use of an indwelling epidural catheter can result in the development of an epidural hematoma when combined with thromboprophylaxis [15].

EREM was developed to alleviate some of these concerns. EREM uses a novel liposomal drug delivery system. After administering the drug into the epidural space, morphine is released from the liposomal vesicles over a period of time [1]. This delivery system potentially leads to

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extended pain control [6, 9, 16] and contributes to reduced systemic drug exposure and toxicity [6, 9, 16].

Numerous studies have reported improved pain control with the use of EREM compared with regional anesthesia [3, 5, 7, 8]. The reported complications occurring with EREM have been low, minor, and comparable to those of other opioids [3, 5, 7, 8]. The most common complications include respiratory depression, oxygen desaturation, hypotension, nausea and vomiting, and pruritus. However, no study to date has evaluated the in-house complication profile of this agent in addition to its common side effects.

We examined the ability of EREM to reduce (1) postoperative pain, (2) opiate consumption, and (3) postoperative complications including supraventricular tachydardia and pulmonary embolism, nausea and vomiting, pruritus, and respiratory depression, and compared the results of patients receiving EREM with those of control patients receiving spinal anesthesia.

Patients and Methods

Using a prospectively collected database, we identified 203 patients undergoing THA between February 2006 and March 2008 who received EREM. Fifty-five percent were male, and 45% were female. The mean age of the patients was 60 ± 10 years (range, 35–81 years). Their mean height was 172 ± 10 cm (range, 139.7–195.6 cm), mean weight was 82 ± 17 kg (range, 45–125 kg), and mean body mass index was 27 ± 4 kg/m^2 (range, 20–40 kg/m^2). Patients receiving EREM were matched in a 2:1 ratio with patients undergoing THA and receiving spinal anesthesia. Match criteria included year of surgery, surgeon, fixation method, prosthesis, race, gender, American Society of Anesthesiologists' Physical Status, body mass index (± 3 kg/m^2), and age (± 3 years). Twenty-five patients receiving EREM did not have a match in the ± three-increment range; therefore, the range subsequently was increased to ± five increments for this group. Nine of these patients had only one match in the increased range. This resulted in a total of 397 control patients.

EREM was administered directly through an epidural needle into the epidural space if no cerebrospinal fluid or blood was present. EREM was administered after 15 mg of bupivacaine hydrochloride was injected into the intrathecal space. No local anesthetic was used with EREM. The EREM used in this cohort was DepoDur® (EKR Theraputics, Bedminster, NJ). Sixty patients (29.6%) received 7.5 mg, 133 patients (65.4%) received 10 mg, six patients (3.0%) received 12.5 mg, three patients (1.5%) received 15 mg, and one patient (0.5%) received 20 mg EREM. Dosing is based on patient gender, age, and size. Patients receiving spinal anesthesia, however, received 15 mg bupivacaine hydrochloride combined with 0.2 mg of morphine sulfate. Local anesthetics were not infiltrated into the wound in any patients. One hundred eighty-five (46.6%) patients receiving spinal anesthesia received patient-controlled analgesia consisting of hydromorphone hydrochloride, fentanyl, or morphine while in the postanesthesia care unit (PACU). The rest immediately were advanced to oral pain medications. Patients receiving EREM were not given patient-controlled analgesia and were advanced to oral pain medications immediately on arrival to the ward. No specific protocol exists for administering pain medication. All pain medication is administered by the nursing staff. Medications most frequently prescribed were oxycodone instant release 10 mg, propoxyphene 65 mg, and hydromorphone 2 mg, or tramadol.

Patients undergoing THA in our institution are admitted to a specialized orthopaedic ward where necessary monitoring of the patient is performed, including evaluation of the patients for motor function, sensation, lower extremity pulses, respiratory rate, heart rate, oxygen saturation, and determination of the pain level (using an 11-mm visual analog scale). These checks usually are performed once or twice per nursing shift (8 hours) unless indicated otherwise. Pain scores are measured with the patient resting. Monitoring of patients receiving EREM at our institution consists of observational monitoring by the nursing staff of respiratory rate and sedation, every hour for the first day. The protocol in place mandated all patients receiving EREM had respiratory rate, oxygen saturation, and sedation scales recorded every hour until 7 AM the next day (POD1). The majority of the patients receiving EREM also received 2 L oxygen during the night of surgery and until 7 AM the next day.

All patients received the same thromboprophylaxis, which consisted of warfarin with a goal international normalized ratio (INR) of 2.0. On the day of surgery, an initial dose between 5 and 10 mg is administered to the patients. The subsequent dose of warfarin then is adjusted based on the daily INR.

All comorbidities reported by the patient to the anesthesiologist were recorded in the prospective database. Complications occurring in the hospital and reported by the medical staff were similarly recorded. Diagnosis of an in-house complication was made by the internist, resident, or attending physician.

Respiratory depression was defined as a breathing rate of eight breaths or less per minute for 3 consecutive minutes. Hypoxia was defined as a pulse oximetry reading less than 90%. A pulse oximetry value less than 90% that persists for more than 5 minutes or is not responsive to oxygen therapy is investigated, including scanning of the chest using multidetector computerized tomography (MDCT) for possible pulmonary embolism.

Nausea and vomiting and pruritus were recorded for each postoperative day and analyzed for the first 2 postoperative days. Patients were determined to have experienced nausea and vomiting if the following medications were administered during the hospital stay: ondansetron, metoclopramide, or promethazine. On the day of surgery, patients receive a prophylactic dose of antiemetic and before administration of opiate agents. For this reason, nausea and vomiting on the day of surgery were defined as receiving more than one dose of antiemetic or the administration of a combination of multiple drugs. On the following postoperative days, nausea and vomiting were defined as receiving an antiemetic medication and severe nausea and vomiting were defined as receiving greater than one dose of one drug or the combination of drugs. Patients were determined to have experienced pruritus if the following medications were administered during the hospital stay: loratidine and diphenhydramine. Pruritus was defined as multiple administrations of the respective drugs or the combination of multiple drugs.

We used a visual analog scale to assess pain with 0 indicating no pain and 10 indicating the greatest pain imaginable. Average reported pain scores were recorded for each postoperative day and analyzed for the first 2 postoperative days. The details and the cumulative dose for opioid were recorded for each postoperative day. Each drug dosage was converted to the equivalent dose of intravenous morphine (mg) for statistical analysis.

We determined differences in pain scale, morphine equivalent dose, nausea and vomiting, and pruritus between control patients and patients receiving EREM using the nonparametric Wilcoxon test. Chi square and Fisher's exact tests were used to identify any difference in the number of postoperative complications in the EREM versus control groups. Logistic regression analysis was performed to determine if EREM was a significant predictor in any of the aforementioned categories. Logistic regression was not performed to compare incidence of respiratory depression between the two groups as we found no difference between the two groups. All statistical analyses were performed using SAS® Version 9.1 software (SAS Institute Inc, Cary, NC).

Results

Patients receiving EREM had decreased pain scores up to POD 2 (Table 1). There was no difference in average pain score on the day of surgery between patients receiving EREM and the control group. Patients receiving EREM had lower ($p = 0.004$) average pain scores than patients not receiving EREM on POD 1. On POD 2, the average pain scale was similar for the two groups. On POD 3, patients receiving EREM had higher ($p = 0.003$) mean pain scores than the control patients.

Table 1. Average daily pain scores as revealed by univariate analysis

Day	Average pain score (VAS, 0–10)		p Value
	EREM	Control	
DOS	1.68	1.93	Not significant
POD 1	2.54	2.96	0.004
POD 2	2.54	2.55	Not significant
POD 3	3.07	2.46	0.003

VAS = visual analog scale; EREM = extended-release epidural morphine; DOS = day of surgery; POD = postoperative day.

Table 2. Average daily opiate consumption as reported by univariate analysis

Day	Average opiate consumption (mg morphine equivalents)		p Value
	EREM	Control	
DOS	4.87	10.12	< 0.0001
POD 1	15.1	26.7	< 0.0001

EREM = extended-release epidural morphine; DOS = day of surgery; POD = postoperative day.

Table 3. Reported number of patients experiencing postoperative complications

Complication	Number of patients	
	EREM	Control
Pulmonary embolism	3 (1.5%)	0
Supraventricular tachycardia	3 (1.5%)	0

EREM = extended-release epidural morphine.

Opioid consumption was less for patients receiving EREM on the day of surgery ($p < 0.0001$) and POD 1 ($p < 0.0001$) (Table 2). EREM did not predict reduced pain and opiate consumption up to POD2. EREM predicted increased pain scores on POD 3.

We detected a few differences in incidences of postoperative complications between the two groups (Table 3). Twenty-four patients receiving EREM (11.8%) experienced postoperative complications (two of whom had two complications) whereas 27 control patients (6.8%) experienced complications. No control patient experienced greater than one complication. Univariate analysis revealed more ($p = 0.02$) patients in the EREM group experienced pulmonary embolism than in the control group. More ($p = 0.01$) patients in the EREM group had

Table 4. Differences in patients with nausea and vomiting as revealed by multivariate analysis

Day	Number of patients		p Value
	EREM	Control	
DOS	77 (37.9%)	66 (16.6%)	< 0.0001
POD 1	58 (28.3%)	72 (18.3%)	0.005

EREM = extended-release epidural morphine; DOS = day of surgery; POD = postoperative day.

Table 5. Differences in patients with pruritus as revealed by multivariate analysis

Day	Number of patients		p Value
	EREM	Control	
DOS	57 (27.8%)	55 (14.14%)	< 0.0001
POD 1	59 (28.8%)	29 (7.5%)	< 0.0001
POD 2	15 (7.32%)	11 (2.83%)	0.01

EREM = extended-release epidural morphine; DOS = day of surgery; POD = postoperative day.

supraventricular tachycardia than those in the control group. Multivariate logistical analysis could not be performed with such low incidences of complications in each group.

Patients receiving EREM had greater incidences of nausea and vomiting than the control patients on the day of surgery ($p < 0.0001$) and POD 1 ($p = 0.005$), as revealed by univariate analysis. Logistic analysis was performed to determine if the nausea and vomiting were attributable to EREM or opioid consumption. EREM was a predictor of nausea and vomiting on the day of surgery ($p < 0.0001$) and POD 1 ($p = 0.005$) (Table 4). Sixteen patients receiving EREM (27.59%) received greater than one treatment for nausea and vomiting on POD 1 versus 18 (25.00%) control patients. No difference was seen between these two groups on POD 1 for severe nausea and vomiting.

Patients receiving EREM experienced pruritus more frequently than control patients on the day of surgery ($p < 0.0001$), POD 1 ($p < 0.0001$), and POD 2 ($p = 0.01$), as revealed by univariate analysis. EREM predicted pruritus on day of surgery ($p < 0.0001$), POD1 ($p < 0.0001$), and POD 2, ($p = 0.01$) (Table 5). There was no difference in the proportion of patients who received greater than one treatment for pruritus on any day.

On the day of surgery, two patients receiving EREM (0.98%) experienced respiratory depression versus three control patients (0.76%). On POD 1, six patients receiving EREM (4.32%) experienced respiratory depression versus 10 control patients (3.68%). On POD 2, five patients receiving EREM experienced respiratory depression (3.62%) versus seven control patients (2.57%). No difference was seen with respect to these patients.

Discussion

EREM was introduced to improve postoperative pain management. Several studies suggest this agent provides better pain control and patient satisfaction for patients undergoing total joint arthroplasty. To confirm and extend these studies, we evaluated the safety (as defined by incidences of postoperative complications, nausea and vomiting, and pruritus) and efficacy (decreased pain and opiate use postoperatively) of EREM.

Some limitations regarding this retrospective study must be considered. First, the number of subjects in this study may have been inadequate therefore raising the possibility of a Type II error. We attempted to perform a power analysis before initiation of this study to minimize the chance of such a statistical problem. However, as all reports to date have not observed any difference in the incidence of complications between the two groups and consistently have reported better analgesic efficacy for EREM, the determination of our subject size was based on analgesic effect size and not anticipated difference in complication rate. Second relates to the nature of the study with variations in data collection and missing data.

Our data suggest that EREM reduces pain and overall opioid consumption during the first postoperative day after THA. The agent used in this cohort, DepoDur®, consists of a liposomal carrier (DepoFoam™) that is designed to deliver morphine during a 48-hour period. Therefore, the superiority of EREM in terms of pain relief and reduced systemic opioid consumption was dramatic during the first 2 days after surgery. In addition to the analgesic superiority, EREM offers the advantage of catheter- and pump-free pain relief and is particularly appealing for patients receiving anticoagulants [7]. The absence of an epidural catheter reduces the risk of epidural hematoma formation with anticoagulation. The absence of external paraphernalia facilitates patient mobility and reduces the burden of care related to catheter maintenance. A patient who is untethered also may have greater overall satisfaction.

The use of this agent, however, may come with an increased incidence of nausea, vomiting, pruritus, and possibly pulmonary embolism and arrhythmia. We identified an increased risk of nausea and vomiting and pruritus during the postoperative stay. These results are concerning, and efforts must be made to minimize these complications during the postoperative period. Respiratory depression did not seem to be increased with the use of this agent compared with a standard opioid. This

finding is in contrast to previous studies showing the complication profile of EREM was similar to that of other opioids [3, 5, 7, 18]. Although one may be inclined to assume the higher percentage of complications observed in our study are real, and the latter in fact may be the case, a very important point needs to borne in mind. The patients in the EREM cohort were subjected to more vigorous postoperative monitoring than their control counterparts. The latter was particularly true during the period of this study. The diligent monitoring may have contributed to the higher incidence of detected complications in the EREM group. The use of pulse oximetry and frequent respiratory status checks may have resulted in more episodes of hypoxia to be detected, leading to additional investigations and PE diagnosis that potentially could have gone undetected otherwise. Some of these findings may be the result of more vigilant monitoring recommended on the package insert rather than a true increased incidence [1].

All patients with hypoxia at our institution, including those in this cohort, are subjected to cross-sectional imaging by MDCT for detection of emboli [11]. Parvizi et al. found that owing to increased sensitivity, MDCT was more likely to detect small emboli in peripheral vessels of the lung than traditional imaging modalities such as perfusion-diffusion scans [11]. Thus, detection of hypoxia as a result of diligent monitoring and investigation of these patients by a sensitive cross-sectional study may explain the higher than expected incidence of PE in these patients.

We continue to use regional anesthesia, including EREM, because of its advantage in reducing the rate of thromboembolic disease [4, 10, 12, 14]. Although a higher incidence of arrhythmia has been reported with the use of epidural anesthesia [13], we believe close monitoring of patients receiving EREM may have accounted for the higher percentage of supraventricular tachycardia in our cohort. However, we do not dispute the fact that use of any opioid agent, including EREM, is associated with the aforementioned complications and the adverse effects are dose dependent [1, 8, 17]. To minimize these adverse effects, we limit the dose of DepoDur® to 7.5 to 10 mg in our patients undergoing THA. Patients usually receive multimodal analgesia to reduce reliance on opioids. Some of the patients in this cohort did receive what is considered a high dose of DepoDur® (15 mg). Because of the small number of patients in the latter category, we could not perform a meaningful statistical analysis to evaluate the effect of dose on the incidence of postoperative complications.

Our data confirm that on POD 1, EREM is an effective analgesic comparable to and better than spinal anesthesia with opioids for patients undergoing THA. Its main advantage is that it reduces the need for indwelling epidural catheters and intravenous patient-controlled analgesia. The use of this agent may be associated with a higher incidence of some opioid-related complications. Although reported occurrences of these complications may be attributed to more diligent monitoring of patients or advanced imaging modalities, our observations are sufficiently concerning to engender the need for a detailed large-scale study. Additional studies also should evaluate the potential benefits of greater patient mobility without indwelling pumps and catheters for pain management, and reduced cost of care by eliminating these devices. Strict surveillance and rigorous data collection are being done at our institution for all patients receiving EREM. All analgesic techniques have risks and benefits. Clinicians should select analgesic techniques based on patient characteristics and an assessment of this risk/benefit balance.

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