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Forty-eight Hours of Postoperative Pain Relief after Total Hip Arthroplasty with a Novel, Extended-Release Epidural Morphine Formulation

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Background: **Epidural morphine has proven analgesic efficacy in the postoperative period and is widely used. This study evaluated the efficacy of extended-release epidural morphine (EREM; DepoDur; Endo Pharmaceuticals Inc., Chadds Ford, PA; SkyePharma, Inc., San Diego, CA) in providing pain relief for 48 h after surgery.**

Methods: **Patients (n = 200) scheduled to undergo total hip arthroplasty were randomized to receive a single dose of 15, 20, or 25 mg EREM or placebo. After surgery and after asking for pain medication, patients had access to intravenous patient-controlled analgesia fentanyl for breakthrough pain as needed. Postoperative intravenous patient-controlled analgesia fentanyl use, time to first postoperative fentanyl use, pain intensity at rest and with activity, patient and surgeon ratings of pain control, and adverse events were recorded.**

Results: **All EREM dosages reduced the mean (± SD) fentanyl use *versus* placebo (510 ± 708 *vs.* 2,091 ± 1,803 μg; $P < 0.0001$) and delayed the median time to first dose of fentanyl (21.3 *vs.* 3.6 h; $P < 0.0001$). All EREM groups had significantly improved pain control at rest through 48 h postdose (area under the curve [0–48 h]) compared with placebo ($P < 0.0005$). More EREM-treated patients rated their pain control as good or very good compared with placebo (at 24 h: 90 *vs.* 65%, $P < 0.0001$; at 48 h: 83 *vs.* 67%, $P < 0.05$). No supplemental analgesia was needed in 25% of EREM-treated patients and 2% of placebo-treated patients at 48 h ($P < 0.05$). The safety profile of EREM was consistent with that of other epidurally administered opioid analgesics.**

Conclusions: **EREM provided significant postoperative pain relief over a 48-h period after hip surgery, without the need for indwelling epidural catheters.**

THE management of postoperative pain remains a significant problem. Inadequate analgesia can hinder recovery and potentially play a role in the development of chronic pain.[1,2] Adequate pain control has been associated with several key clinical benefits, including fewer postoperative complications, earlier patient mobilization, and reduced costs due to shorter hospital stays and improved rehabilitation.[1] Although current technologies can effectively relieve postoperative pain, there are still limitations to most of the current analgesic options.

Epidural morphine has proven analgesic efficacy and advantages over systemically administered morphine for the treatment of postoperative pain with regard to local modulation of nociceptive input without other sensory, motor, or sympathetic blockade.[1,3] Epidural opioid analgesia has also been shown to have a positive impact on the recovery process, including out-of-bed mobilization and food intake.[4,5] Because pain is often most intense for the first 2–3 days after surgery and a single dose of the currently available morphine for epidural or intrathecal injection generally lasts 24 h or less,[3] use of an indwelling epidural catheter is usually a requirement for postoperative pain management.[6] However, the epidural indwelling catheters and patient-controlled analgesia (PCA) pumps used to deliver continuous epidural analgesia have been associated with several technical problems: Catheters can migrate and lead to infection,[7–10] and PCA pumps are subject to human programming errors.[11,12]

Indwelling epidural catheters are problematic with the prophylactic use of anticoagulants. Postoperative anticoagulation with heparinoids or warfarin has become a common practice and is often initiated shortly after surgery. However, use of low-molecular-weight heparin to reduce thrombotic risk in joint replacement surgery has increased the incidence of epidural hematomas,[13,14] which can result from removal of an indwelling epidural catheter.[14] A morphine delivery system that obviates the requirement of an indwelling epidural catheter could potentially eliminate complications stemming from the use of indwelling catheters and alleviate concerns related to anticoagulation.

The need for extended analgesia with epidural morphine provided the basis for the development of extended-release epidural morphine (EREM), an extended-release morphine formulation for epidural administration. EREM uses a delivery system known as DepoFoam (SkyePharma, Inc., San Diego, CA) to provide extended pain relief for 48 h after a single dose. The technology consists of microscopic lipid-based particles with numer-

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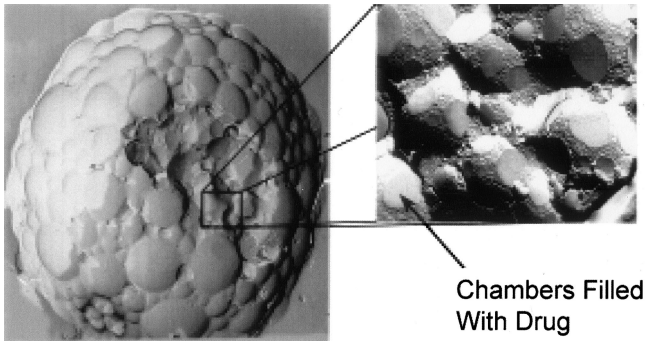

Fig. 1. Electron micrograph of DepoFoam particles. The nonconcentric vesicles are surrounded by a lipid membrane, and each contains an internal aqueous chamber with morphine sulfate solution.

ous internal vesicles containing morphine (fig. 1). Each vesicle is separated from the adjacent chambers by synthetic analogs of naturally occurring lipid membranes. When the drug is injected into a patient, the membranes reorganize and the drug is released.[15]

This phase III study was designed to evaluate the safety and efficacy of single-dose EREM at three dosages (15, 20, or 25 mg) compared with placebo in the management of postoperative pain after total unilateral hip arthroplasty.

Materials and Methods

Subjects

Patients were enrolled at 23 clinical sites (see appendix), and the number of randomized patients per site ranged from 1 to 34. After institutional review board approval, patients at each site signed informed consent forms. Eligible patients included men or women aged 18 yr or older who were scheduled to undergo unilateral hip arthroplasty under general or regional (intrathecal) anesthesia, were willing and able to use an intravenous PCA device with fentanyl, and were willing to receive only intravenous fentanyl *via* PCA for 48 h postdose for rescue treatment of postoperative pain. Patients were also required to remain in the hospital for at least 48 h after study drug administration for assessments. Women of childbearing age were required to have a negative pregnancy test result during screening. Exclusion criteria included morbid obesity (body mass index $\geq$ 40 kg/m^2); intended bilateral total hip arthroplasty, metastatic bone cancer or Paget disease, or other concurrent surgical procedures, such as total knee arthroplasty or vascular surgery in addition to total hip arthroplasty (bone grafting was allowed); epidural anesthesia; chronic opioid use or history of hypersensitivity/idiosyncratic reaction to opioid medications; sleep apnea, narcolepsy, or excessive daytime sleepiness; and pregnancy or lactation.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study. Hip arthroplasty was chosen as the surgical model because the intensity and duration of pain typically requires treatment with potent opioids for 48 h. Study patients were randomized to one of the following four groups: 15, 20, or 25 mg EREM or an injectable saline placebo. On the day of surgery, eligible patients were randomized by calling a telephone-based computerized central randomization system to achieve a balanced number of patients with respect to general and regional anesthesia across all four treatment groups at each site. Study drug was administered by epidural injection before induction of general or regional anesthesia approximately 30 min before surgery. Patients received spinal anesthesia (consisting of bupivacaine) at a different lumbar interspace approximately 5–10 min before surgery. To rule out improper placement of the epidural needle or catheter, the anesthesiologist was permitted to aspirate to check for the absence of blood or cerebrospinal fluid and, if desired, to administer a 3-ml test dose of lidocaine (1.5%) with epinephrine (1:200,000). The catheter or needle was flushed with 1 ml saline after the test dose. Patients were observed for a hypertensive or tachycardic response to rule out an intravascular injection. Unintentional intrathecal injection was ruled out by a lack of sensory block. Because the literature suggests that the use of a test dose is not infallible,[16,17] anesthesiologists had the discretion to deliver EREM directly through the epidural needle without a test dose if neither cerebrospinal fluid nor blood was aspirated. The hospital pharmacy used the 0.9% saline placebo solution to dilute the various doses of study drug and placebo to a standardized volume of 5 ml.

Because EREM and placebo are visually distinct, the study drug was administered by an unblinded anesthesiologist. The unblinded anesthesiologist was permitted to provide intraoperative care, but the investigator and all study staff (including the surgeon) remained blinded to the assigned treatment groups. In addition, the intraoperative anesthesia protocols for both spinal and general anesthesia were controlled to ensure uniformity across treatment groups and study sites. Intraoperative intravenous fentanyl was limited to a dose of 250 μg per patient, and bolus administration of fentanyl near the end of surgery was prohibited. The administration of ketorolac was prohibited perioperatively. The administration of other opioids, nonsteroidal antiinflammatory drugs, and other forms of regional anesthesia was prohibited.

Analgesia

After surgery and after the first request for pain medication, all patients had access to a PCA pump to self-administer intravenous fentanyl for pain control. A blinded study coordinator or investigator performed pain intensity assessments at the first request for pain med-

ication. After the first 25-μg bolus of intravenous fentanyl, the PCA pump was connected to the intravenous line and programmed to deliver on-demand boluses of intravenous fentanyl of 10–20 μg with a lockout interval of 6 min. The bolus dose, lockout interval, or both could be titrated by the investigator to manage pain. No other opioid medication or other analgesic was permitted during the 48 h after study drug administration.

Evaluations

Fentanyl consumption postdose during 48 h was the primary efficacy endpoint. The time to first use of fentanyl postdose was also recorded. Pain intensity at rest was assessed using both the visual analog scale and a categorical scale at patients' first request for fentanyl and at regular intervals postdose (4, 8, 12, 18, 24, 30, 36, and 48 h). The visual analog scale is a 0- to 100-mm scale, with 0 representing no pain and 100 representing the most severe pain possible. The categorical scale measured pain intensity as none, mild, moderate, or severe. Pain intensity was also assessed with activity using the visual analog scale and categorical scale at 24 and 48 h postdose and at the time that patient activity level was measured. Patient activity level was assessed through a six-grade mobilization score (1 = sit up on bedside with assistance, 2 = sit up on bedside without assistance, 3 = stand with assistance, 4 = stand without assistance, 5 = walk with assistance, and 6 = walk freely without assistance). Patient and surgeon ratings of pain control were scored at approximately 24 and 48 h as 4 = very good, 3 = good, 2 = fair, or 1 = poor.

Safety was assessed through routine laboratory testing and by monitoring respiratory rate, heart rate, and blood pressure. Physical and neurologic examinations were performed at baseline and at 48 h after study drug administration. Sedation scores and brief neurologic checks were also performed at regular intervals to determine the presence of any sensory or motor abnormalities of the lower extremities. All adverse events were collected through day 7; any serious or neurologic adverse events were collected through day 30; and the outcome, severity, and possible relation of the adverse event to study drug was documented. A serious adverse event was defined as any event that was fatal, life threatening, or disabling. Identification and management of adverse events were at the investigators' discretion. However, definitions of adverse events typically associated with opioids (hypotension, bradycardia, hypoventilation, hypercapnia, hypoxia, and urinary retention) were provided in the study protocol. Respiration was monitored every hour for the first 24 h and then every 2 h for 24–48 h postdose. Any patient exhibiting clinical signs of respiratory depression was monitored for oxygen saturation. Hypoxia was defined as a clinically significant reduction in oxygen saturation documented by pulse oximetry and requiring intervention. Urinary retention was defined as the absence of spontaneous voiding more than 7 h after surgery (or > 7 h after removal of the bladder catheter) with a urine volume at catheterization greater than 400 ml. A neurologic assessment questionnaire was administered to check for symptoms related to paresthesia at screening and at postoperative day 30. Its purpose was to assess potential neurologic sequelae of the study drug.

Statistical Analysis

All randomized patients who underwent the planned surgical procedure, regardless of whether they received their assigned study drug according to the randomization procedure (intent-to-treat population), and who were followed up for use of fentanyl or other opioids were included in efficacy analyses. Safety evaluations included all randomized patients who received any study drug regardless of whether they underwent the planned surgical procedure.

All statistical analyses were performed with a two-tailed test with a significance level of 5%. Continuous variables were summarized with means, SDs, and medians. Categorical variables were summarized by the frequency and count of patients in corresponding categories. Demographic characteristics were summarized and compared among treatment groups using analysis of variance (ANOVA) for continuous variables and the Cochran-Mantel-Haenszel test stratified by type of anesthesia for categorical variables. Differences among sites and treatment-by-site interactions were analyzed using various ANOVA models, including treatment, site, treatment-by-site, and type of anesthesia factors.

The average amount of total intravenous fentanyl used for 48 h postdose among the treatment groups was compared using ANOVA; the Dunnett test was used to compare each dose of EREM with placebo if the primary analysis was significant. Additional ANOVA models explored the effects of other covariates on total intravenous fentanyl usage. The time to first postoperative use of intravenous fentanyl was summarized with medians and analyzed with Kaplan-Meier curves. Pain intensity scores were also analyzed by ANOVA and the Cochran-Mantel-Haenszel test; pairwise analyses were performed if the overall test was significant.

Descriptive statistics were used to summarize safety data; in addition, laboratory values were summarized with shift tables (*i.e.*, low-normal-high at baseline *vs.* low-normal-high at 48 h postdose) to assess changes. The incidence of adverse events was compared between groups using the Fisher exact test.

Results

Patient Characteristics

A total of 200 patients were enrolled (fig. 2); 50 patients were randomized to placebo, and the remainder

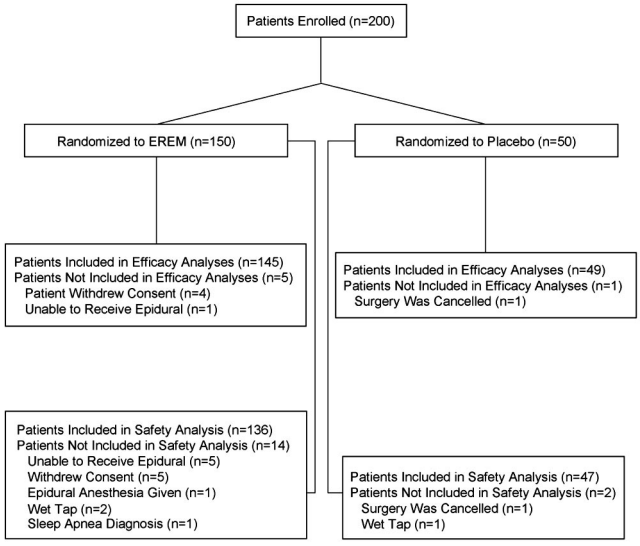

Fig. 2. CONSORT diagram. EREM = extended-release epidural morphine.

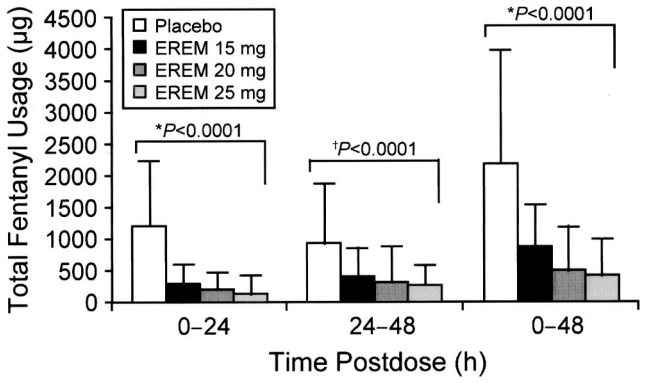

Fig. 3. Mean total postoperative fentanyl use by study group. * *P* value for overall treatment effect and for pairwise comparison between each extended-release epidural morphine (EREM) group *versus* placebo. † *P* value for overall treatment effect and $P \leq 0.0025$ for pairwise comparison between each EREM group *versus* placebo.

were randomized to EREM dosages of 15 mg (n = 51), 20 mg (n = 50), or 25 mg (n = 49). One hundred ninety-four underwent the planned surgical procedure, were assessed for postoperative pain medications, and were included in the efficacy analyses (opioid use was not quantified in 5 patients, and 1 did not undergo surgery). One hundred eighty-three of the 200 randomized patients received study drug or placebo and were included in the safety analyses. The type of anesthesia received by the patients (general or regional) was similar among treatment groups; 26 or 21 placebo patients and 69 or 65 EREM patients received general or regional anesthesia, respectively. There were no significant site or treatment-by-site interactions identified.

Demographic and baseline characteristics were similar across treatment groups (table 1), and there were no significant differences with regard to reason for hip surgery, site of surgery, type of surgical procedure/implant, duration of surgery, or the effect of test dose administration on efficacy. The most common reason for surgery was osteoarthritis (70% of patients). The predominant type of surgical procedure was primary total arthroplasty (81% of patients), followed by revision hip arthroplasty (17%), which were both equally distributed across treatment groups.

Efficacy

Total Fentanyl Use over 48 h Postdose. The mean postoperative fentanyl consumption was significantly lower in all study groups receiving EREM compared with placebo ($P < 0.0001$; fig. 3). Overall, during the 48-h postoperative assessment period, there was a 75% reduc-

Table 1. Patient Characteristics

Characteristic	Placebo	EREM				Total
		15 mg	20 mg	25 mg	All	
Patients, n	50	51	50	49	150	200
Age, yr						
Mean (SD)	59.2 (11.5)	63.0 (13.3)	57.8 (12.5)	62.2 (12.1)	61.0 (12.8)	60.6 (12.5)
Median	57.5	64.0	59.0	64.0	62.5	61.0
Min–max	39–85	19–86	26–77	38–88	19–88	19–88
Sex, n (%)						
Men	26 (52)	23 (45)	28 (56)	25 (51)	76 (51)	102 (51)
Women	24 (48)	28 (55)	22 (44)	24 (49)	74 (49)	98 (49)
Race, n (%)						
White	46 (92)	44 (86)	43 (86)	42 (86)	129 (86)	175 (88)
Black	3 (6)	6 (12)	6 (12)	5 (10)	17 (11)	20 (10)
Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hispanic	1 (2)	0 (0)	1 (2)	2 (4)	3 (2)	4 (2)
Other	0 (0)	1 (2)	0 (0)	0 (0)	1 (1)	1 (1)
ASA physical status, n (%)						
I	2 (4)	4 (8)	5 (10)	4 (8)	13 (9)	15 (8)
II	38 (76)	37 (73)	40 (80)	37 (76)	114 (76)	152 (76)
III	10 (20)	10 (20)	5 (10)	8 (16)	23 (15)	33 (17)

ASA = American Society of Anesthesiologists; EREM = extended-release epidural morphine; max = maximum; min = minimum.

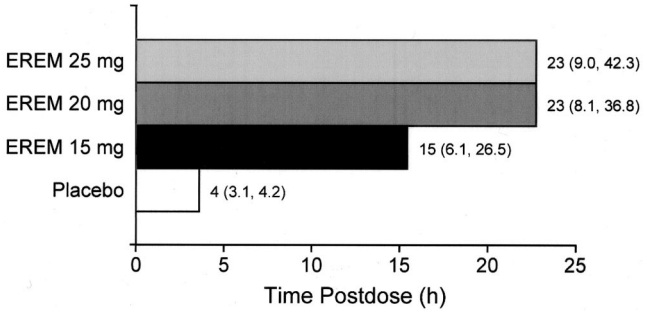

Fig. 4. Median time to first postoperative fentanyl use by study group. * Numbers in parentheses are 95% confidence intervals. $P < 0.0001$ for each extended-release epidural morphine (EREM) group *versus* placebo.

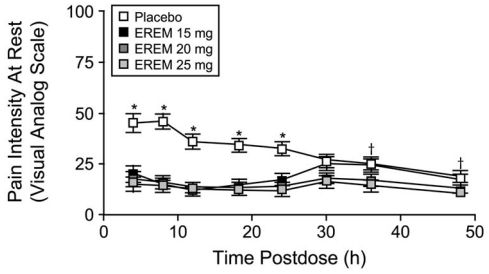

Fig. 5. Mean visual analog scale scores for pain intensity at rest over time. For overall treatment effect at 4, 8, 12, 18, and 24 h, $P < 0.0001$, and at 36 and 48 h, $P < 0.05$. * $P < 0.0005$ for pairwise comparison between 15, 20, or 25 mg extended-release epidural morphine (EREM) *versus* placebo. † $P < 0.05$ for pairwise comparison between EREM 25 mg *versus* placebo.

tion in mean intravenous fentanyl use among patients who received EREM treatment (pooled 15-, 20-, and 25-mg groups) *versus* placebo (510 ± 708 *vs.* 2,091 ± 1,803 μg; $P < 0.001$). The 20- and 25-mg doses of EREM were associated with the greatest reduction in total fentanyl use over 48 h postdose: 485 ± 715 and 371 ± 675 μg, respectively (fig. 3).

Subgroup analysis revealed that the analgesic effect of EREM was consistent across the patient population when analyzed by sex, age, race, type of anesthesia, and American Society of Anesthesiologists physical status class. However, mean (± SD) postoperative fentanyl use was lower in patients aged 65 yr or older who were treated with 15 mg EREM compared with mean postoperative fentanyl use in patients younger than 65 yr who were treated with 20 mg EREM (403 ± 393 *vs.* 588 ± 855 μg, respectively).

Time to First Postoperative Fentanyl Use. The median time to first postoperative use of PCA fentanyl was 3.6 h in the placebo group compared with 21.3 h for all patients receiving EREM ($P < 0.0001$; fig. 4). The median time to first postoperative use of fentanyl was similar in the two higher-dosage EREM groups (22.7 and 22.8 h in the 20- and 25-mg groups, respectively), with both of longer duration than that in the 15-mg EREM group (15.4 h).

Almost half (46%) of the EREM-treated patients received no postoperative fentanyl through 24 h postdose (placebo, 2%; $P < 0.0001$) and many required no supplemental fentanyl through 48 h (16% of patients in the 15-mg group, $P = 0.0155$; 29% of patients in the 20-mg group, $P = 0.0003$; 30% of patients in the 25-mg group, $P = 0.0002$; placebo, 2%).

Pain Intensity Evaluations. Despite the fact that patients in the EREM group used significantly less fentanyl postoperatively, they exhibited significant reductions in pain intensity at rest and with activity *versus* placebo as measured by the visual analog scale (figs. 5 and 6, respectively) and categorical ratings of pain intensity (table 2). Large clinical differences were evident within the first 24 h; thereafter, pain in the intravenous PCA group declined toward the level experienced by the EREM groups. During the first 24 h, mean patient pain scores were clinically similar across the EREM treatment groups (*e.g.*, differences of ≤ 10 mm on the visual analog scale between 15- and 25-mg EREM groups).

Activity Level. The activity levels in the EREM treatment groups did not differ from that of the placebo group despite significantly less postoperative fentanyl use. At 24 h, the mean (± SD) activity scores for 15-, 20-, and 25-mg EREM-treated patients were 3.0 ± 1.7, 3.0 ± 1.8, and 3.1 ± 1.6, respectively, and that for placebo-treated patients was 2.7 ± 1.7. At 48 h postdose, the overall mean activity scores were 3.8 ± 1.6 for EREM-treated patients and 4.2 ± 1.5 for placebo-treated patients.

Patient and Surgeon Ratings of Pain Control. At 24 and 48 h, more EREM-treated patients rated their pain control as good or very good *versus* placebo (90 *vs.* 65% and 83 *vs.* 67%, respectively), and mean ratings were superior at all doses ($P < 0.001$ and $P < 0.05$ at 24 and 48 h, respectively; table 3). Mean surgeon ratings of patients' pain control were also significantly better for all doses of EREM compared with intravenous PCA ($P < 0.001$ and $P < 0.01$ at 24 and 48 h, respectively). Smaller differences in the patient and surgeon ratings were observed within the EREM groups (table 3).

Safety

Table 4 presents the adverse events by study group. With the exception of anemia due to surgical causes, the

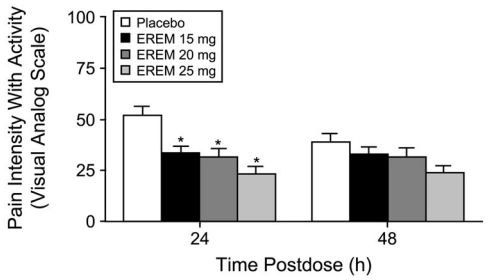

Fig. 6. Mean Visual Analog Scale scores for pain intensity with activity at 24 and 48 h. $P < 0.0001$ for overall treatment effect. * $P < 0.005$ for pairwise comparison between 15, 20, or 25 mg extended-release epidural morphine (EREM) *versus* placebo.

Table 2. Summary of Pain Intensity Evaluations Using the Categorical Scale

		EREM			
	Placebo (n = 49)	15 mg (n = 50)	20 mg (n = 49)	25 mg (n = 46)	All (n = 145)
Scores at rest at 24 h postdose, mean ± SD	1.4 ± 0.71	0.8 ± 0.80	0.6 ± 0.65	0.6 ± 0.78	0.7 ± 0.75
P value (EREM *vs.* placebo)*	—	0.0004	< 0.0001	< 0.0001	—
Scores at rest at 48 h postdose, mean ± SD	0.9 ± 0.59	0.8 ± 0.82	0.6 ± 0.62	0.6 ± 0.62	0.7 ± 0.70
Scores with activity at 24 h postdose, mean ± SD	1.9 ± 0.86	1.3 ± 0.94	1.2 ± 0.97	1.0 ± 0.94	1.2 ± 0.95
P value (EREM *vs.* placebo)†	—	0.0052	0.0014	< 0.0001	—
Scores with activity at 48 h postdose, mean ± SD	1.6 ± 0.78	1.2 ± 0.92	1.3 ± 1.05	1.0 ± 0.90	1.2 ± 0.96

P values were determined using the Cochran-Mantel-Haenszel (row-mean-score) test stratified by type of anesthesia. Pairwise comparisons were evaluated only if the overall treatment group effect was significant. Categorical scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain.

* $P < 0.0001$ for overall test among the treatment groups. † $P = 0.0003$ for overall test among the treatment groups.

EREM = extended-release epidural morphine.

most common adverse events were related to and typical of opioid administration. There was a significantly greater incidence of vomiting ($P < 0.01$) and pruritus ($P < 0.001$) in the EREM groups, and the rates were similar across the EREM dose range. The rates of hypotension and respiratory depression were also higher in the EREM groups, although the differences were not statistically significant. Respiratory depression occurred in 4% of 15- and 25-mg EREM–treated patients and 0% of 20-mg EREM–treated and placebo patients. Respiratory events associated with EREM were most often mild to moderate in severity and resolved spontaneously with supplemental oxygen therapy. A pairwise analysis between the EREM groups indicated that the incidence of decreased oxygen saturation was significantly greater in both the 20-mg ($P = 0.0272$) and the 25-mg ($P = 0.0492$) groups compared with the 15-mg group. Otherwise, there were no clear dose-related differences in the number of patients reporting at least one adverse event from days 1–7.

Neurologic checks conducted at regular intervals postdose identified sensory abnormalities in 9, 7, 5, and 5 patients in the placebo and 15-, 20-, and 25-mg EREM groups, respectively. Motor abnormalities were noted in 1 patient each of the placebo and 15-mg EREM group, and in 2 patients in the 25-mg EREM group. Two placebo-treated patients and 2 and 3 patients in the 20- and 25-mg EREM groups, respectively, reported both sensory and motor abnormalities. The majority of motor and sensory abnormalities occurred within 4 to 24 h postdose and resolved within the first 24 h. Fewer neurologic adverse events were reported from days 8–30 in the combined EREM treatment group than in the placebo treatment group (5 patients [4%] *vs.* 4 patients [9%]; *P* = not significant). Specifically, 4 EREM-treated patients (3%) and 2 placebo-treated patients (4%) had hypesthesia or paresthesia; 2 EREM-treated patients (2%) and 2 placebo-treated patients (4%) had musculoskeletal and connective tissue disorders (arthralgia, muscle spasms, limb pain, peripheral swelling); and no EREM-treated patients and 1 placebo-treated patient (2%) had urinary incontinence. At day 30, there were no significant differences among the treatment groups in neurologic status.

Serious adverse events occurred in 12 patients (9%) who received EREM (3, 5, and 4 patients in the 15-, 20-, and 25-mg EREM groups, respectively) and 4 patients (9%) who received placebo. Three of these events in the EREM groups were considered related to the study drug.

Table 3. Patient and Surgeon Ratings of Pain Control Using a Categorical Scale

		EREM			
	Placebo (n = 49)	15 mg (n = 50)	20 mg (n = 49)	25 mg (n = 46)	All (n = 145)
Patient ratings					
24 h, mean (SD)	2.7 (0.98)	3.6 (0.72)	3.6 (0.61)	3.8 (0.60)	3.6 (0.65)
P value (EREM *vs.* placebo)*	—	< 0.0001	< 0.0001	< 0.0001	—
48 h, mean (SD)	3.0 (0.91)	3.4 (0.77)	3.4 (0.84)	3.6 (0.57)	3.5 (0.74)
P value (EREM *vs.* placebo)†	—	0.0277	0.0180	0.0002	—
Surgeon ratings					
24 h, mean (SD)	2.9 (0.88)	3.7 (0.52)	3.8 (0.43)	3.8 (0.48)	3.7 (0.47)
P value (EREM *vs.* placebo)*	—	< 0.0001	< 0.0001	< 0.0001	—
48 h, mean (SD)	3.0 (0.95)	3.5 (0.75)	3.6 (0.76)	3.6 (0.54)	3.6 (0.69)
P value (EREM *vs.* placebo)‡	—	0.0075	0.0025	0.0003	—

P values were determined using the Cochran-Mantel-Haenszel (row-mean-score) test stratified by type of anesthesia. Pairwise comparisons were evaluated only if the overall treatment group effect was significant.

* $P < 0.0001$ for overall test among the treatment groups. † $P = 0.0016$ for overall test among the treatment groups. ‡ $P = 0.0004$ for overall test among the treatment groups.

EREM = extended-release epidural morphine.

Table 4. Adverse Events by Study Group

		EREM			
	Placebo (n = 47), n (%)	15 mg (n = 48), n (%)	20 mg (n = 45), n (%)	25 mg (n = 43), n (%)	*P* Value
Nausea	26 (55)	35 (73)	34 (76)	31 (72)	0.1521
Vomiting	9 (19)	24 (50)	24 (53)	18 (42)	0.0024
Constipation	8 (17)	7 (15)	2 (4)	6 (14)	0.2432
Pyrexia	23 (49)	24 (50)	27 (60)	22 (51)	0.7115
Hypotension	19 (40)	29 (60)	25 (56)	22 (51)	0.2477
Pruritus	7 (15)	21 (44)	23 (51)	19 (44)	0.0009
Anemia	14 (30)	14 (29)	19 (42)	14 (33)	0.5374
Headache	8 (17)	7 (15)	2 (4)	7 (16)	0.2074
Dizziness	2 (4)	5 (10)	7 (16)	8 (19)	0.1416
Urinary retention	1 (2)	8 (17)	6 (13)	7 (16)	0.0612
Decreased oxygen saturation	2 (4)	1 (2)	7 (16)	6 (14)	0.0441
Bradycardia	2 (4)	3 (6)	5 (11)	1 (2)	0.3633

EREM = extended-release epidural morphine.

A 20-mg EREM–treated patient experienced hypotension (blood pressure = 71/38 mmHg), and a 25-mg EREM–treated patient experienced hypoventilation (respiratory rate = 4–5 breaths/min) and hypotension (blood pressure = 78/45 mmHg).

Seventeen patients (12.5%) who received EREM and no placebo-treated patients required opioid antagonist (table 5). The primary reasons for administration of the opioid antagonist were respiratory depression (5 patients), nausea (3 patients), and somnolence (2 patients) (table 5). The proportion of patients requiring an opioid antagonist was greatest in the 25-mg EREM group (9 patients [21%]) compared with the 20- and 15-mg groups (4 [9%] and 4 patients [8%], respectively). When patient subgroups were analyzed, the likelihood of therapy with an opioid antagonist was greater with male sex, white race, general anesthesia, and American Society of Anesthesiologists physical status of II.

In 15 of 17 patients who required an opioid antagonist, the initial administration was required within 24 h after

Table 5. Opioid Antagonist Administration

		EREM			
	Placebo (n = 47)	15 mg (n = 47)	20 mg (n = 45)	25 mg (n = 43)	All (n = 136)
Patient receiving any opioid antagonists days 0–7, n (%)	0 (0.0)	4 (8.3)	4 (8.9)	9 (20.9)	17 (12.5)
Any opioid administration, n (%)*§					
0–12 h	0	3 (75.0)	3 (75.0)	4 (44.4)	10 (58.8)
> 12–24 h	0	2 (50.0)	4 (100.0)	6 (66.7)	12 (70.6)
> 24–48 h	0	1 (24.0)	0 (0.0)	4 (44.4)	5 (29.4)
Time to first administration, h, mean (SD), n†	0	8.0 (5.5) (n = 4)	9.7 (4.5) (n = 4)	13.1 (9.4) (n = 9)	11.1 (7.7) (n = 17)
Duration of administration, h, mean (SD), n‡	0	4.5 (5.4) (n = 4)	5.7 (4.4) (n = 4)	9.1 (9.0) (n = 9)	7.2 (7.4) (n = 17)
Indication, n (%)§					
Excessive somnolence	0	0 (0)	1 (25.0)	0 (0)	1 (5.9)
Hypotension	0	0 (0)	0 (0)	1 (11.1)	1 (5.9)
Hypoventilation	0	0 (0)	1 (25.0)	0 (0)	1 (5.9)
Nausea	0	1 (25.0)	0 (0)	2 (22.2)	3 (17.6)
Opioid overdose	0	0 (0)	0 (0)	1 (11.1)	1 (5.9)
Periods of apnea while asleep	0	0 (0)	1 (25.0)	0 (0)	1 (5.9)
Respiratory depression	0	3 (75.0)	0 (0)	2 (22.2)	5 (29.4)
Reversal-hypotension	0	0 (0)	0 (0)	1 (11.1)	1 (5.9)
Somnolence	0	0 (0)	1 (25.0)	1 (11.1)	2 (11.8)
Somnolence/hypercapnia	0	0 (0)	0 (0)	1 (11.1)	1 (5.9)
Urinary retention	0	0 (0)	0 (0)	1 (11.1)	1 (5.9)
Agent given					
Naloxone	0	1 (25.0)	2 (50.0)	1 (11.1)	4 (23.5)
Narcan	0	2 (50.0)	2 (50.0)	6 (66.7)	10 (58.8)
Nubain	0	1 (25.0)	0 (0.0)	2 (22.2)	3 (17.6)

* Medications in which start time and stop time overlap more than one time category are included in all categories in which the medication overlaps.

† Time from study drug administration to first opioid antagonist administration. ‡ Time from start of first administration to time of end of last administration.
§ Patients may be included in more than one category.

EREM = extended-release epidural morphine.

study drug administration. Two patients in the 25-mg EREM group required an opioid antagonist between 24 and 48 h postdose, one for nausea and the other for urinary retention. None of the patients required opioid antagonist after 48 h postdose. The mean time to administration of opioid antagonist was 11.1 h (median, 8.1 h) and the mean duration (from start to end of opioid antagonist therapy) was 7.2 h (median 6 h). There were no deaths or treatment discontinuations due to adverse events.

Laboratory Values

There were no clinically significant changes in clinical hematology and laboratory values noted in either the EREM or placebo groups.

Discussion

In this multicenter, randomized, placebo-controlled, dose-ranging study, a novel formulation of morphine, single-dose EREM, was effective in the management of postoperative pain after total hip arthroplasty. All doses of EREM were associated with significant reductions in pain and in the use of intravenous fentanyl through 48 h postdose compared with placebo.

Although all patients had access to intravenous fentanyl through a PCA bolus to treat postoperative pain, more patients in the EREM treatment groups rated their pain control as good or very good at 48 h postdose. Patients given EREM exhibited superior (lower) pain scores compared with the standard therapy of intravenous PCA opioid alone, both at rest and with activity. It has been suggested that PCA with intravenous opioids may provide adequate pain relief at rest but inadequate pain relief with movement.[18] Our data for all three groups administered EREM demonstrate superior pain scores with activity as measured by the visual analog scale at 24 h. Because inadequate pain control with activity hinders patient rehabilitation,[19] these data suggest that EREM may offer benefits over intravenous PCA with respect to earlier mobilization and hospital discharge.[4]

In this study, an active control group, *i.e.*, conventional morphine sulfate, was not used for comparison. Historical data have shown that a safe and effective dose of conventional morphine injected epidurally is approximately 5 mg,[20] with duration of action that ranges from 12 to 24 h.[3] Effective pain control was shown for up to 48 h with EREM, and in the current trial, use of EREM obviated the need for a PCA pump in 16–30% of patients, thereby decreasing the number of patients exposed to the complications associated with continuous intravenous PCA.

Extended-release epidural morphine may be particularly well suited as an analgesic for total hip arthroplasty patients because these patients typically require anticoagulation. This study shows that EREM provides up to 48 h of pain relief from a single injection and could obviate the need for an indwelling epidural catheter, thus reducing the potential for epidural hematoma. The simplified technical aspects of this therapy, when compared with continuous infusion, may result in fewer adverse events and complications associated with indwelling epidural catheters. Ng *et al.*[10] showed that there was a high incidence of adverse events associated with indwelling epidural catheters; at least one or two interventions by the acute pain service were required in 60% of cases to achieve adequate postoperative pain control with epidural catheter infusions. Despite these interventions, Ng *et al.*[10] noted that one third of the patients had their epidural terminated because of inadequate pain control. Because of the prolonged analgesic activity of EREM with a single dose, patients may be able to transition directly to oral medications.

Extended-release epidural morphine was generally well tolerated, with a safety profile largely consistent with the safety profiles reported for other epidurally administered opioid analgesics.[4] The most frequently reported adverse events in the EREM and placebo groups were nausea (69%), pyrexia (53%), hypotension (52%), vomiting (41%), pruritus (38%), and anemia (33%). A significant increase in vomiting and pruritus was reported in all EREM treatment groups compared with placebo. These results are not unexpected. A previous study of 3 mg epidural morphine sulfate resulted in an incidence of pruritus in 74% of patients.[21] The most consistent disadvantage of using lumbar epidural analgesia compared with parenteral opioid is its increased rate of pruritus.[4] In a study of patients undergoing elective total knee or hip replacement, the incidence of nausea (53%) was slightly lower than in the current study.[22]

Although the rates for most adverse events were not statistically different compared with the intravenous PCA group, the rate of respiratory depression was numerically higher in the EREM-treated groups, with five EREM-treated patients (3.7%) receiving an opioid antagonist for respiratory depression. Of these five patients, two patients received the 25-mg dose. Of the three patients receiving a lower dose (15 mg), one was an older patient (75 yr) and one had clinical obesity (body mass index = 41), which was outside the study guidelines. These results suggest that patient characteristics are important in choosing an appropriate dose of EREM.

It is also important to note that there was a significant dose relation observed for decreased oxygen saturation, with the 20- and 25-mg doses associated with higher rates. In contrast, the rate of decreased oxygen saturation with the 15-mg dose was slightly lower than the rate in the placebo group (2 and 4%, respectively). The number of patients receiving an opioid antagonist also varied with dose, with nine patients in the 25-mg group receiving an antagonist compared with four patients in the 15-mg group. Recently, EREM was approved at dose

levels of 10–20 mg and with the caveat that older patients may require less medication than younger patients. The safety and efficacy results presented here are consistent with these dosing recommendations. Although there were dose-related improvements in the opioid-sparing endpoints, measures of patient pain, activity, and satisfaction were clinically comparable between groups given EREM. Moreover, mean postoperative fentanyl use in elderly patients who received 15 mg EREM was comparable with mean postoperative fentanyl use in younger patients who received 20 mg EREM. Use of a lower dose of EREM in elderly patients is consistent with a trend toward lower dosing of standard epidural opioids in older patients.[23]

Extended-release epidural morphine may provide a new option for the management of postoperative pain after lower extremity orthopedic surgery. The results of this controlled study demonstrate the ability of EREM to provide pain control for 48 h postoperatively without an indwelling epidural catheter. Additional studies are required to assess whether the ease of administration of EREM and the absence of an indwelling catheter can have an impact on anesthesia preparation time, physical therapy, and activities of daily living.

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