

Single-dose extended-release epidural morphine for pain after hip arthroplasty

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ABSTRACT

This randomized, double-blind study compared the safety and efficacy of a new single-dose extended-release epidural morphine (EREM) formulation for postoperative pain following hip arthroplasty. Patients were administered a single dose of EREM (10, 20, or 30 mg, n = 93) or a single epidural dose of placebo (n = 27) before surgery and general anesthesia. Following surgery, patients had access to fentanyl with the use of intravenous patient-controlled analgesia. Postoperative fentanyl use, time to first postoperative fentanyl use, pain intensity at rest and with activity, patient ratings of pain control, and adverse events were recorded. Compared with placebo-treated patients, single-dose EREM patients used less total supplemental fentanyl ($p \leq 0.049$), had a longer time to first fentanyl use ($p < 0.001$), and were less likely to use any supplemental fentanyl ($p \leq 0.042$). EREM-treated patients reported lower pain intensity for up to 48 hours postdose compared with placebo-treated patients. Single-dose EREM was effective for postoperative pain relief for up to 48 hours following hip arthroplasty, with a safety and tolerability profile consistent with that of other epidurally administered opioids.

Key words: single-dose extended-release epidural morphine, postoperative pain management, orthopedic surgery

INTRODUCTION

Major orthopedic surgery of the lower extremities is accompanied by significant postoperative pain, as well as increased risks of serious medical morbidities.¹⁻⁴ Effective postoperative pain management following orthopedic surgery often requires opioid analgesics.⁵ The perioperative administration of opioid analgesics can reduce post-surgical pain,^{6,7} ameliorate postoperative complications,⁸ improve patient mobilization,⁹ shorten hospitalization stays,⁹⁻¹¹ and reduce hospital costs.¹¹

Because a single epidural injection of morphine typically relieves pain for 24 hours or less,^{12,13} control of postoperative pain beyond 24 hours often requires continuous infusion through an indwelling epidural catheter. Following major orthopedic surgery of the lower extremities,¹⁴ the placement and maintenance of indwelling epidural catheters in anticoagulated patients can lead to serious complications, such as the development of an epidural hematoma.^{15,16} This is of particular concern because prophylactic anticoagulation therapy is prevalent among patients undergoing major orthopedic procedures, such as joint replacement.^{15,16}

The need for effective, extended analgesia with epidural morphine, without the complications stemming from indwelling catheters, provided the basis for the development of extended-release epidural morphine (EREM; brand name DepoDur™, Endo Pharmaceuticals Inc., Chadds Ford, PA). EREM is a single-dose extended-release epidural formulation of morphine developed with the DepoFoam™ (SkyePharma, Inc., San Diego, CA) delivery system. Following epidural administration, single-dose EREM remains within the epidural space, gradually releasing morphine; this produces low, centrally localized systemic drug concentrations.^{17,18} In preclinical studies, the DepoFoam delivery system allowed for a slow release of morphine following a single dose of EREM to provide significant antinociceptive activity for up to 3.4 days; significant plasma and cerebrospinal fluid morphine concentrations were maintained longer for EREM compared with conventional morphine sulfate.¹⁹

The characteristics of EREM suggest that it might provide extended periods of analgesia in humans following single epidural injection, thus reducing the need for indwelling epidural catheters. Previous studies have examined EREM for postoperative pain management following abdominal surgery,²⁰ elective cesarean section,²¹ and hip arthroplasty²² at dosages ranging from 5 to 30 mg. This study was designed to evaluate the safety and efficacy of

a single dose of EREM at three dosages (10, 20, and 30 mg) for the management of postoperative pain in patients undergoing hip arthroplasty and to characterize its effect on patient-controlled analgesia (PCA) use.

METHODS

Patients

Patients scheduled for hip arthroplasty (including primary total arthroplasty, hemiarthroplasty, or revisions of previous hip arthroplasty) under general anesthesia were enrolled at 16 clinical sites in the United States. Men or women 18 to 75 years of age, with weight > 45 kg and American Society of Anesthesiologists Physical Status 1, 2, or 3, were included. Women of childbearing age were required to have a negative pregnancy test before enrollment. Eligible patients were able to use a PCA device and agreed to remain in the hospital for a minimum of 72 hours following surgery. Patients with a documented allergy to study medications, hepatic or renal dysfunction, morbid obesity, or laboratory evidence of coagulopathy were excluded.

All eligible patients were required to provide written informed consent. The protocol and informed consent form were reviewed and approved by the Institutional Review Board for each study center. This study was performed in accordance with the principles established by the Declaration of Helsinki.

Study design

This phase II, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study evaluated single-dose EREM 10, 20, and 30 mg vs. placebo (DepoFoam without morphine sulfate, suspended in saline). The dosages of single-dose EREM were selected based on a previous Phase I dose-ranging study (SkyePharma Inc., Data on File, 2003). Patients were randomized in a 1:1:1:1 ratio to one of the four treatment arms; after a patient's eligibility was confirmed, the randomization envelope (provided by the study sponsor) containing the study medication was opened by an unblinded pharmacist. All study-site personnel involved in observing and reporting patient responses, including the anesthesiologist, remained blinded to the assigned treatment groups.

All study drugs were diluted to a volume of 5 mL with 0.9 percent normal saline. Using a standard loss-of-resistance technique, an epidural needle or catheter was inserted preoperatively into a lumbar vertebral interspace. If an epidural catheter was used, it was then advanced 3 to 4 cm into the epidural space. To rule out improper placement of the epidural needle or catheter, that is, inadvertent intravascular or intrathecal injection,

a test dose (lidocaine [2 percent] with epinephrine [1:200,000]) was administered. Patients were observed for hypertensive and/or tachycardic response suggestive of an intravascular injection. In addition, patients were examined for motor weakness suggestive of an intrathecal injection of lidocaine. Fifteen minutes were allotted for patient observation between administration of the test dose and beginning of procedure. Immediately before general anesthesia and within 30 minutes of surgery, a single bolus of study drug was administered through the epidural needle or catheter, at the discretion of the anesthesiologist and/or study investigator, and then the epidural needle or catheter was removed.

Intraoperative general anesthesia was limited to intravenous (IV) etomidate, thiopental, or propofol for induction, fentanyl, midazolam, oxygen, isoflurane, and a muscle relaxant. Intraoperative fentanyl was limited to a maximum of 500 µg per patient, and bolus administration of fentanyl was prohibited near the end of surgery.

Analgesia

Following surgery and on first request for pain medication, patients were given an initial dose of IV fentanyl (25 µg); if necessary, the dose was repeated until analgesic stability was achieved. Subsequently, each patient was given IV fentanyl through a PCA device programmed to deliver 10 to 20 µg/dose, with a lock-out time of six minutes. The dose could have been increased or supplemented with additional doses, or, if required, a basal rate could have been added to control pain. Opioids other than fentanyl and all other analgesic or anti-inflammatory agents were prohibited for the first 48 hours after study dose. Aspirin in a maximum dosage of 325 mg/24 hours or acetaminophen in a maximum dosage of 1000 mg/24 hours were permitted to inhibit platelet aggregation or for fever or headache, respectively. After 48 hours, alternate opioid therapies were permitted at the investigator's discretion. Naloxone was permitted for treatment of opioid-related adverse events (AEs).

Efficacy assessments

Total fentanyl use through 24 and 48 hours post-dose, fentanyl consumption for each successive six-hour period throughout the first 48 hours following study medication dosing, time from study drug administration to first fentanyl use, and the proportion of patients who required no postoperative fentanyl were recorded. Pain intensity was assessed on first request for supplemental pain medication and at regular intervals postdose (two, three, four, six, eight, 10, 12, 18, 24, 30, 36, 48, and 72 hours) using both the 0- to 100-mm

Table 1. Patient demographics

Demographic	Placebo (n = 27)	Single-dose EREM			p values
		10 mg (n = 35)	20 mg (n = 32)	30 mg (n = 26)	
Sex					0.871*
Men	12 (44.4)	20 (57.1)	17 (53.1)	13 (50.0)	
Women	15 (55.6)	15 (42.9)	15 (46.9)	13 (50.0)	
Race					0.514*
White	22 (81.5)	25 (71.4)	27 (84.4)	22 (84.6)	
Black	5 (18.5)	8 (22.9)	3 (9.4)	3 (11.5)	
Hispanic	0	1 (2.9)	2 (6.3)	1 (3.8)	
Other	0	1 (2.9)	0	0	
Age (y), mean (SEM)	57.5 (2.69)	54.1 (2.01)	56.4 (2.59)	54.6 (2.67)	0.079†
≥ 65 y, n (percent)	11 (40.7)	8 (22.9)	11 (34.4)	8 (30.8)	0.381*
Weight (kg), mean (SEM)	78.6 (3.27)	79.6 (2.12)	81.6 (3.07)	82.6 (3.98)	0.604†
Height (cm), mean (SEM)	170.0 (1.75)	171.0 (1.58)	169.3 (1.90)	170.6 (1.78)	0.938†
ASA Class					
1	4 (14.8)	6 (17.1)	5 (15.6)	3 (11.5)	
2	21 (77.8)	22 (62.9)	18 (56.3)	19 (73.1)	
3	2 (7.4)	7 (20.0)	9 (28.1)	4 (15.4)	

ASA, American Society of Anesthesiologists; EREM, extended-release epidural morphine; SEM, standard error of the mean.
 * p value based on Cochran-Mantel-Haenszel test for treatment mean row scores (stratified by study site). p value for race based on two categories (white, black); † p value based on treatment effect in a two-way analysis of variance with main effects treatment group and study site.

Visual Analog Scale (VAS; 0 = no pain and 100 = most severe pain possible) and a 4-point categorical scale (CAT; from 0 = none to 3 = severe). Pain intensity was assessed on both scales at rest and with activity; activity was defined as sitting up in bed at a 30° to 90° angle. Patients provided global ratings of their study medication (at 24, 48, and 72 hours) by responding to the question, “How would you rate the pain medication overall?” using a 5-point CAT (poor, fair, good, very good, or excellent). The time to any prescribed physical therapy, such as standing or walking, was recorded.

Safety

Objective safety measurements included vital signs and clinical laboratory results, and clinical assessments were performed by study personnel throughout 72 hours postdose. In general, classification and treatment of AEs were left to each investigator’s judgment. When AEs were identified, standard definitions were provided for assigning an intensity (mild, moderate, and severe) and causality AEs. Guidelines stipulated that persistent hypoventilation was to be treated with naloxone, pruritus with appropriate non-narcotic

Table 2. Mean (SEM) total fentanyl use (μg) after study drug dose

Time postdose	Placebo (n = 28*)	Single-dose EREM			
		10 mg (n = 34)	20 mg (n = 32)	30 mg (n = 26)	p values
					Overall treatment effect†‡
0 to 24 hours	1,548 (180)	599 (109)	396 (63)	361 (61)	< 0.001
24 to 48 hours	885 (129)	722 (150)	510 (115)	291 (113)	= 0.023
0 to 48 hours	2,433 (291)	1,321 (243)	905 (143)	652 (151)	< 0.001

EREM, extended-release epidural morphine; SEM, standard error of the mean; * One patient randomized to the placebo group received 10 mg EREM due to a pharmacy error and was analyzed as part of the placebo group for the primary endpoint; † Two-way analysis of variance in which main effects are treatment group and study site, all pairwise comparisons with placebo were significant ($p \leq 0.049$) with the exception of 10 and 20 mg EREM for the 24- to 48-hour interval; ‡ $p < 0.001$ for dose response based on Jonckheere-Terpstra test.

medication, and nausea and/or vomiting with non-narcotic antiemetics.

Physical examinations were performed, and blood pressure, heart rate, respiratory rate, hemoglobin oxygen saturation, and capnometry (end-tidal CO_2) were recorded at screening, predose, and/or postdose at regular intervals (at the first 30 minutes, hourly through the first 12 hours, and at 18, 24, 30, 36, 48, and 72 hours). Arterial blood gas measurements were taken if respiratory rate fell below eight breaths/minute, if oxygen saturation on 2 L/minute was continuously lower than 90 percent, or end-tidal CO_2 tension was > 50 mm Hg for two consecutive measurements. Female patients of childbearing potential received a pregnancy test at screening, and hematology, serum chemistry assessments, and urinalysis were performed at screening and 48 hours postdose. Electrocardiogram monitoring was performed predose, continuously throughout surgery, and at 0.5, one, 1.5, and two hours postdose.

Statistical methods

All patients who received any study drug were included in the safety and efficacy analyses. The study was designed to enroll 30 patients in each treatment group to detect a treatment difference of 410 μg in 24-hour fentanyl usage. For the primary endpoint, the sample size calculation was based on a 50 percent reduction in 24-hour fentanyl usage assuming a placebo mean of 820 μg fentanyl, using a standard deviation of 490 μg , $\alpha = 0.05$ (two-tailed) and 89 percent power.

Statistical tests were two-tailed except for dose-response analysis and were performed at a 0.05 significance level, except for total fentanyl use through 48 hours postdose, which was set at 0.049 based on a Bonferroni inequality procedure. Measures of analgesia based on fentanyl

usage and pain intensity (VAS) used a two-way analysis of variance (ANOVA) with treatment group, study site, and treatment-group-by-study-site interaction included in the model; Dunnett's test was used to compare each dose of EREM with placebo if the overall ANOVA model was significant. The dose response for total fentanyl use through 48 hours postdose was tested using the Jonckheere-Terpstra test.²³ Analysis of covariance analyzed the effect of age or weight covariates on postoperative fentanyl use. Median time-to-event analyses for time to first postoperative opioid pain medication were calculated from the Kaplan-Meier product limit estimates, with p values being calculated using a log-rank test for equality. For CAT evaluations and overall medication ratings, the Cochran-Mantel-Haenszel test was used to compare treatment effects.

Safety data were summarized using descriptive statistics when appropriate. The incidence of AEs among treatment groups was compared using the Fisher exact or chi-square test.

RESULTS

Patient characteristics

A total of 126 patients were randomized to receive study drug. One hundred twenty patients were administered single-dose EREM 10, 20, or 30 mg or placebo (n = 35, n = 32, n = 26, and n = 27, respectively) (Table 1). Six patients were not included in the safety and efficacy analysis owing to ineligibility and noncompliance. None received any doses of study drugs.

Patient demographics and baseline characteristics were similar (Table 1). The major indication for surgery was degenerative hip disease (89 percent, 107/120 patients), and

Table 3. Time to first fentanyl use

Time	Placebo (n = 27)	Single-dose EREM			p values*
		10 mg (n = 35)	20 mg (n = 32)	30 mg (n = 26)	
Median time (h) between study drug and first postoperative fentanyl use	3.2	13.5	24.8	16.1	< 0.001
95 percent CI for median	(2.5, 3.8)	(4.1, 25.1)	(17.3, 30.6)	(9.8, 39.6)	
Median time (h) between recovery room arrival and first postoperative fentanyl use	0.3	10.0	21.1	12.8	< 0.001
95 percent CI for median	(0.2, 0.4)	(0.8, 20.7)	(14.8, 28.0)	(4.0, 36.1)	

EREM, extended-release epidural morphine; CI, confidence interval; * p values for time to first postoperative fentanyl use are based on log-rank test for equality of product-limit survival curves.

primary total arthroplasty was the most common procedure (72 percent, 86/120 patients). The mean duration of surgery was 2.2 hours (range one to six hours).

Efficacy

Fentanyl use. Mean total postoperative fentanyl usage from 0 to 24, 24 to 48, and 0 to 48 hours significantly decreased in a dose-related fashion with increasing dose of EREM (p < 0.001 dose response) (Table 2). Figure 1 illustrates the cumulative fentanyl usage throughout the 48-hour postoperative period. Fentanyl use by placebo-treated patients was consistently higher than by single-dose EREM patients, whereas the 20 and 30 mg single-dose EREM groups used the smallest amount of supplemental fentanyl (Table 2). Across all groups, patients ≥ 65 years old consistently used less total fentanyl than patients < 65 years old through the 24 hours following surgery (Figure 2).

Time to first postoperative fentanyl use among single-dose EREM-treated patients was significantly longer than among placebo-treated patients (p < 0.001 overall treatment difference) (Table 3). Through 24 and 48 hours following surgery, a larger percentage of patients in the single-dose EREM groups did not use fentanyl, compared with patients in the placebo group (33.3 percent vs. 3.7 percent, p = 0.001 at 24 hours; 15.0 percent vs. 3.6 percent, p = 0.042 at 48 hours).

Pain intensity evaluations. For up to 48 hours post-dose, patients receiving EREM reported low pain intensity scores as measured by VAS (Figures 3 and 4) and CAT (data not shown). Placebo-treated patients had significantly higher pain intensity scores at rest and during activity, as measured by the VAS (Figures 3 and 4) and

CAT, than EREM-treated patients from four through 18 hours (p = 0.003 at each time point). The single-dose EREM groups had significantly lower resting CAT scores at 24 hours compared with the placebo group (0.6 to 0.9 vs 1.1, p = 0.032). From four to 18 hours postdose, 3 percent to 15 percent of the EREM-treated patients reported moderate to severe pain at rest, whereas 41 percent to 63 percent of placebo-treated patients reported moderate to severe ratings of pain at rest (p < 0.001 for comparison of mean CAT scores at rest).

Patient ratings of study medications. At 24 and 48 hours postdose, patients receiving single-dose EREM rated their study medications significantly more favorably than those receiving placebo (p < 0.001 and p = 0.021, respectively). Approximately 55 to 75 percent of EREM-treated patients rated their study medication “very good” or “excellent,” compared with 37 percent of placebo-treated patients (Figure 5).

Safety

The most common treatment-related AEs across EREM groups were pruritus (67 percent), nausea (66 percent), vomiting (46 percent), hypoxia (32 percent), and urinary retention (25 percent) (Table 4). The onset of opioid-related AEs primarily occurred before 24 hours postdose; the majority were mild, with less than 4 percent rated severe. Laboratory and chemistry measurements showed no consistent, clinically significant drug-related abnormalities.

Adverse events related to respiratory function in all patients occurred within 48 hours postdose; the majority occurred within the first 24 hours after dosing, and only three patients had decreases in respiratory function 24 to

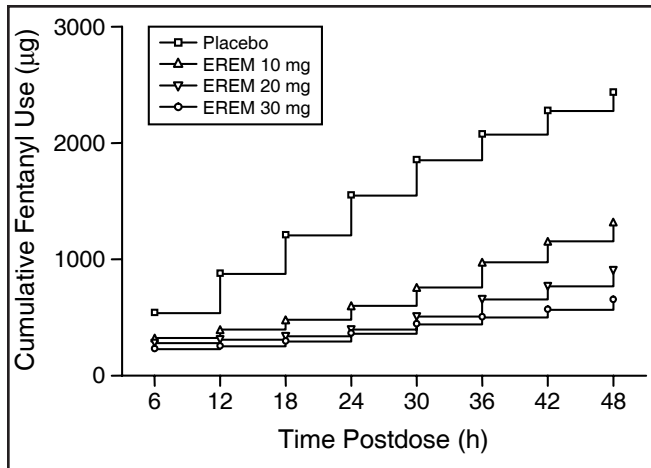


Figure 1. Cumulative fentanyl use over time postdose. Cumulative fentanyl use in six-hour intervals is plotted against the upper boundary for each interval. EREM = extended-release epidural morphine.

48 hours postdose (patient in each of the placebo and 10 and 30 mg single-dose EREM groups). Decreased hemoglobin oxygen saturation was recorded more frequently in the single-dose EREM groups (34 percent, 31 percent, and 58 percent for 10, 20, and 30 mg, respectively) than in the placebo group (7 percent) (Table 5). Most alterations of respiratory function were rated mild and resolved spontaneously or with oxygen therapy. Five cases of severe respiratory depression occurred 2.5 to five hours postdose and resolved with oxygen therapy and/or naloxone treatment (Table 6). Naloxone treatment as

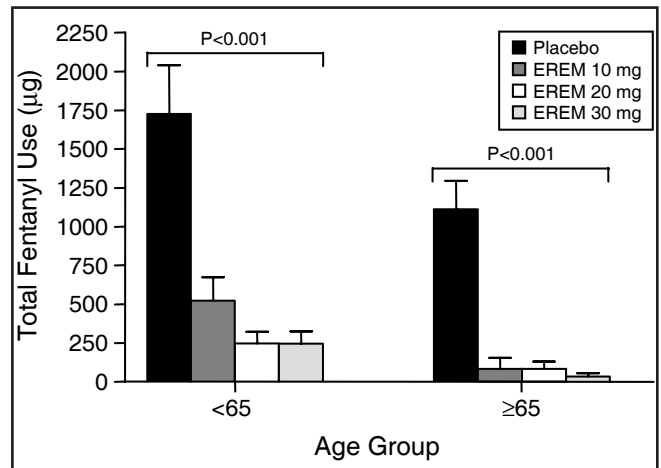


Figure 2. Total fentanyl use through 24 hours following surgery for < 65- and > 65-year age groups. Two-way analysis of variance in which main effects are treatment group and study site.

intermittent boluses or continuous infusion was administered to four patients for a duration of 20 to 62 hours, until resolution of the last respiratory event.

Serious AEs occurred in five single-dose EREM-treated patients, three patients in the 10 mg group and two patients in the 30 mg EREM group. One serious AE was considered possibly related to study medication. The case involved a 63-year-old woman who received 10 mg of single-dose EREM and developed somnolence and required a nasopharyngeal airway. She also developed oliguria and tachycardia during the postoperative period

Table 4. Number (percent) of patients with treatment-related adverse events*

Adverse event, n (percent)	Placebo (n = 27)	Single-dose EREM			
		10 mg (n = 35)	20 mg (n = 32)	30 mg (n = 26)	All (n = 93)
Constipation	1 (4)	6 (17)	7 (22)	6 (23)	19 (20)
Hypoventilation	1 (4)	4 (11)	7 (22)	4 (15)	15 (16)
Hypoxia	2 (7)	8 (23)	11 (34)	11 (43)	30 (32)
Nausea	9 (33)	20 (57)	20 (62)	21 (81)	61 (66)
Pruritus	6 (22)	22 (63)	21 (66)	19 (73)	62 (67)
Somnolence	2 (7.4)	5 (14)	8 (25)	5 (19)	18 (20)
Urinary retention	3 (11)	7 (20)	7 (22)	9 (35)	23 (25)
Vomiting	4 (15)	18 (51)	12 (38)	13 (50)	43 (46)

EREM, extended-release epidural morphine; * Adverse events reported more frequently by EREM than placebo and expected with opiate use.

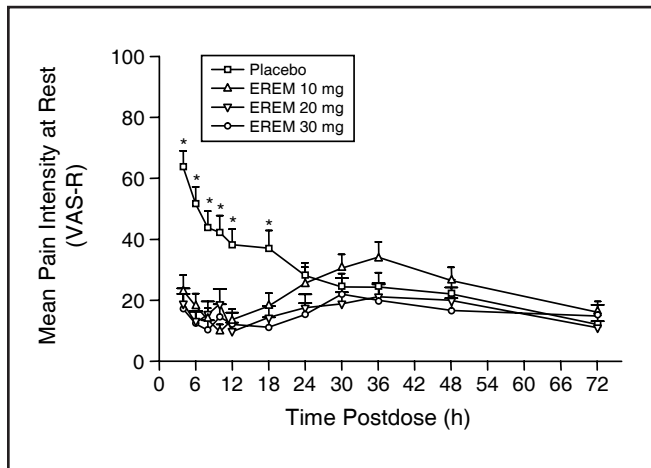


Figure 3. Pain intensity evaluation at rest over time (VAS-R). VAS-R = Visual Analog Scale-Rest; EREM = extended-release epidural morphine. * $p = 0.003$ at each time point from three through 18 hours.

and was treated with IV fluids and a blood transfusion. All events resolved completely, and the patient was discharged four days after receiving study drug. The remaining four serious AEs were fat embolism syndrome, a dislocated right hip, non-Q-wave myocardial infarction, and an infection of the hip. No patients terminated the study due to an AE, and there were no deaths.

DISCUSSION

In the present study of patients undergoing hip arthroplasty, single-dose EREM provided dose-related efficacy in the management of postoperative pain for up to 48 hours postdose. The improved analgesia among EREM-treated patients was reflected in the reduced use of supplemental opioids and the longer time to first postoperative fentanyl use compared with placebo. The efficacy of single-dose EREM was also supported by the significantly

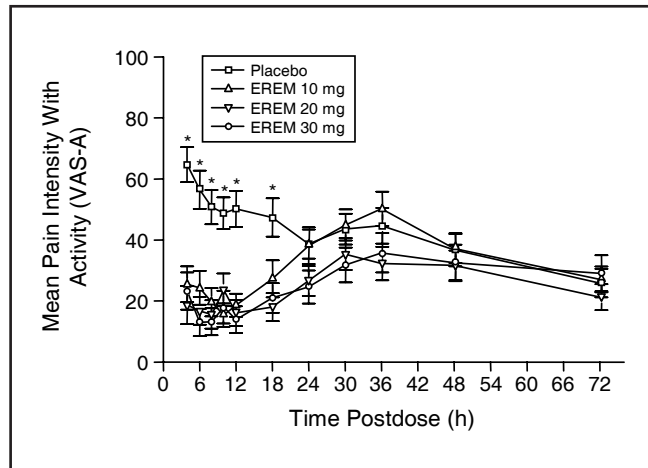


Figure 4. Pain intensity evaluation with activity over time (VAS-A). VAS-A = Visual Analog Scale-Activity; EREM = extended-release epidural morphine. * $p \leq 0.002$ at each time point from four through 18 hours.

greater proportion of EREM-treated patients requesting no supplemental postoperative fentanyl for pain control compared with placebo-treated patients. Although patients were instructed to self-titrate supplemental IV fentanyl to optimize pain relief, placebo-treated patients frequently reported moderate to severe pain reflecting undertreatment of pain, whereas most EREM-treated patients reported low pain intensity for up to 48 hours postdose. In this study, patients' ratings of pain reflected a combination of responses to study drug and supplemental pain medications. Single-dose EREM patients experienced predominantly mild pain, and when asked to rate their pain medication, they reported higher satisfaction with their study drug than did placebo-treated patients. This is consistent with previous studies that have evaluated single-dose EREM for the management of postoperative pain following hip surgery and abdominal surgery and reported higher patient ratings of pain control compared

Table 5. Alterations in respiratory function within 0 to 48 hours

Variable n (percent)	Placebo (n = 27)	Single-dose EREM			
		10 mg (n = 35)	20 mg (n = 32)	30 mg (n = 26)	All (n = 93)
Respiratory rate < eight breaths/ minute	10 (37.0)	15 (42.9)	17 (53.1)	15 (57.7)	47 (50.5)
End-tidal CO ₂ > 50 mm Hg	2 (7.4)	12 (34.3)	10 (31.3)	15 (57.5)	37 (39.8)
SaO ₂ < 90 percent	1 (3.7)	4 (11.4)	2 (6.3)	0	6 (6.5)

EREM, extended-release epidural morphine.

Table 6. Patients with respiratory depression rated severe in intensity

Single-dose EREM	Age (y)	Time of onset postdose (h)	Lowest respiratory rate (breaths/min)	Highest end-tidal CO ₂ (mm Hg)	Lowest SaO ₂ (percent)	Therapy†	Duration of therapy (h)‡
10 mg	63	3.5	10	46	92	Oxygen	24
20 mg	73	5	6	49	93	Naloxone	22
20 mg	58	4	0*	50	94	Naloxone	62
20 mg	72	2.5	8	50	77	Naloxone	46
30 mg	54	3.5	8	56	96	Oxygen and naloxone	20.5

EREM = extended-release epidural morphine; * The zero value noted by telemetry was due to improperly functioning instrumentation; † Naloxone was administered as intermittent boluses or continuous infusion over time; ‡ From time of onset of first episode to resolution of last episode.

with standard epidural morphine sulfate or placebo control.^{20,22} The improved patient satisfaction experienced by patients treated with single-dose EREM may indicate that patients are spending less time self-monitoring and self-treating postoperative pain, which may lead to a perception of improved care.

Inadequate pain control during patient mobilization can hinder patient rehabilitation and, consequently, patient recovery.^{9,24} In general, PCA with opioids provides adequate pain relief at rest, but its effectiveness with movement has been questioned.¹⁴ In this study, patients treated with single-dose EREM reported improved pain scores at rest and with activity for up to 18 hours postdose compared with placebo. The VAS with activity for all EREM-treated patients remained mild

(below 40 mm), with the exception of 30- to 36-hour postdose periods at the 10 mg dose only. In contrast, the placebo-treated patients' VAS with activity remained above 40 mm until 48 hours postdose. Improved pain control at rest and with activity and the ability to deliver EREM without the need for epidural catheters and infusion pumps may lead to improved rehabilitation postoperatively.

In the present study, the AE profile of single-dose EREM was typical of that reported in the published literature in patients undergoing hip replacement surgery with epidural anesthesia and IV opioid administration for postoperative pain management.^{25,26} The incidences of vomiting (34 to 55 percent) and pruritus (62 to 73 percent) in EREM-treated patients are similar to those previously reported in patients receiving epidural morphine (50 percent and 77

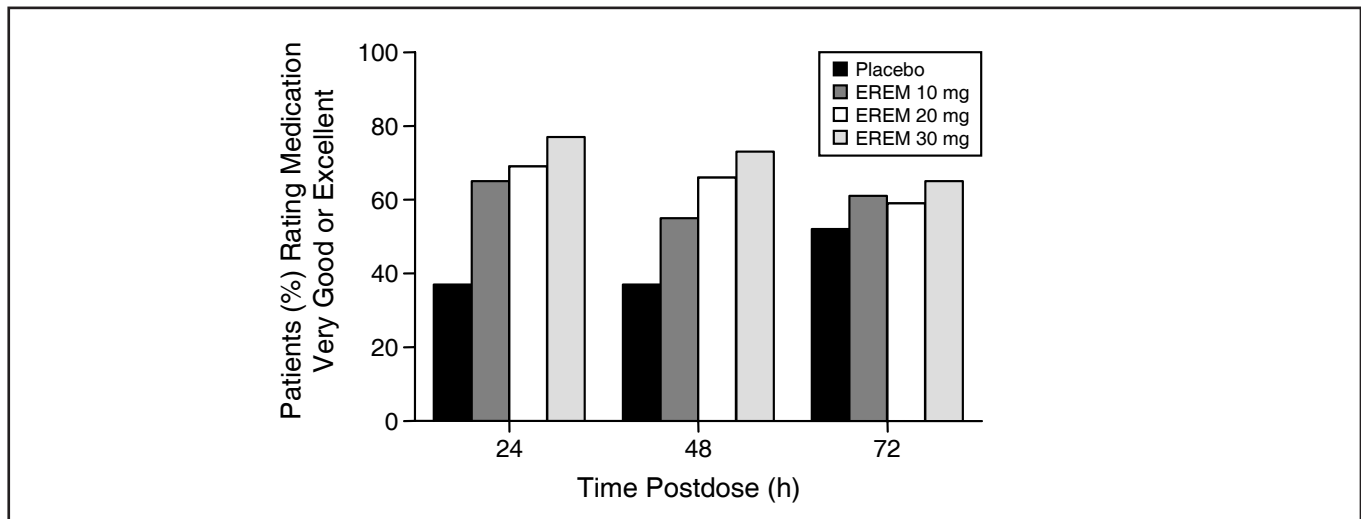


Figure 5. Patients rating pain medication "very good" and "excellent" at 24, 48, and 72 hours postdose. EREM = extended-release epidural morphine.

percent, respectively).^{25,26} Although EREM-treated patients experienced a higher incidence of opioid-related AEs compared with placebo-treated patients, the majority (96 percent) of AEs were rated mild or moderate. These results, coupled with the general improvement in pain control, may explain why the majority of EREM-treated patients rated their medication “very good” or “excellent.”

The rates of respiratory depression for epidural analgesics vary widely across studies because of differences in the monitoring methodology, the criteria for defining respiratory depression, and the types of analgesic techniques being assessed. When oxygen saturation is used to identify respiratory depression in the current study, the incidence of respiratory depression is 6 percent among EREM-treated patients, whereas the historical rate for epidural analgesics ranges from 5.6 percent to 34.8 percent (mean of 15.1 percent).²⁷ The rate of severe respiratory depression as indicated by opioid antagonist use observed here (5.4 percent) is higher than that previously published for epidural analgesics (range of 0.1 to 0.2 percent, mean of 0.1 percent).²⁷ However, given the small number of patients in this study and the variability in monitoring techniques, more controlled trials with well-defined endpoints are required to provide a more accurate assessment of the respiratory depression with EREM administration.

In this study, 57 percent of the respiratory AEs (hypoxia, hypoventilation, and respiratory acidosis) occurred within six hours after EREM administration, 93 percent within 24 hours of administration, and the remaining 7 percent within 24 to 48 hours of administration. Although the majority of AEs occurred within a few hours after study drug administration, all patients who receive EREM should be closely monitored for the first 48 hours, and any patient who develops a respiratory AE should be monitored until the respiratory AE resolves.

Recently, 10 to 20 mg dose levels of single-dose EREM were approved for treatment of postoperative pain in the United States.²⁸ Results of this study are consistent with these recommendations because the largest fentanyl-sparing effects appeared to occur between the 10 and 20 mg doses. Increasing the dose to 30 mg did not appear to offer significant additional benefits. Therefore, doses of EREM greater than 20 mg are not recommended. The present study also suggests that older patients may achieve analgesic benefits that are comparable to younger patients but at a lower dose of EREM than received by their younger counterparts.

It is also important to note that the goal of this Phase II registration study was to assess the efficacy of EREM as a single agent. As indicated by a recent meta-analysis, multimodal analgesia with nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce morphine consumption through IV PCA with significant decreases in AEs (e.g., nausea, vomiting, and sedation).²⁹ In principle,

multimodal analgesia with a preoperative low dose of EREM (e.g., 10 mg) could provide an analgesic foundation upon which nonopioid medications such as NSAIDs could be layered in the postoperative period. Such a strategy may help to maximize analgesia and tolerability and is an important subject for future study.

After joint replacement surgery, severe, persistent postoperative pain beyond the first 24 hours may necessitate an indwelling epidural catheter, which is contraindicated in patients receiving anticoagulation therapy.^{16,30} This study shows that single-dose EREM provides up to 48 hours of pain relief and a reduced need for supplemental postoperative analgesics while avoiding the need for an indwelling epidural catheter, thus permitting prophylactic anticoagulation therapy in patients undergoing total joint replacement. Additional studies will be required to explore whether patients' decreased need for supplemental postoperative analgesics directly improves patient satisfaction and contributes to improved patient care and recovery.

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