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Randomized trial demonstrates that extended-release epidural morphine may provide safe pain control for lumbar surgery patients

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Abstract

Background: Safe and effective postoperative pain control remains an issue in complex spine surgery. Spinal narcotics have been used for decades but have not become commonplace because of safety or re-dosing concerns. An extended release epidural morphine (EREM) preparation has been used successfully in obstetric, abdominal, thoracic, and extremity surgery done with epidural anesthesia. This has not been studied in open spinal surgery.

Methods: Ninety-eight patients having complex posterior lumbar surgery were enrolled in a partially randomized clinical trial (PRCT) of low to moderate doses of EREM. Surgery included levels from L3 to S1 with procedures involving combinations of decompression, instrumented arthrodesis, and interbody grafting. The patients were randomized to receive either 10 or 15 mg of EREM through an epidural catheter placed under direct vision at the conclusion of surgery. Multiple safety measures were employed to prevent or detect respiratory depression. Postoperative pain scores, narcotic utilization, and adverse events were recorded.

Results: There were no significant differences between the two groups as to supplemental narcotic requirements, pain scores, or adverse events. There were no cases of respiratory depression. The epidural narcotic effect persisted from 3 to 36 hours after the injection.

Conclusion: By utilizing appropriate safety measures, EREM can be used safely for postoperative pain control in lumbar surgery patients. As there was no apparent advantage to the use of 15 mg, the lower 10 mg dose should be used.

Key Words: Epidural morphine, extended-release, lumbar, pain control, postoperative, surgery

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INTRODUCTION

Epidural narcotics, originally used in obstetrics and over the past 30 years, may now also be safely used following spinal surgery.[21] Nevertheless, although epidural narcotic analgesia provides superior pain control when compared with intravenous opioids alone,[2] disadvantages include the need for an in-dwelling epidural catheter, re-dosing, and the risk of respiratory depression.[2,4,6,11,13,19,22,25,30]

There are over 400,000 spinal surgeries performed in the United States annually, representing a significant number of patients who would potentially benefit from better postoperative pain control. Extended release epidural morphine (EREM: liposomal formulation DepoDur*TM*), has already been demonstrated to be superior to short-acting epidural narcotics and to intravenous opioids alone when utilized for postoperative pain control in obstetric, abdominal, and lower extremity surgery.[3,7-9,16,28,29] Similarly, in spinal EREM should offer spinal analgesia without the need for indwelling catheters and repeat dosing.

The purpose of this study was to assess the safety of utilizing EREM in lumbar surgery at a dose of 10 and 15 mg to avoid respiratory depression. Previously, Hartrick, *et al.* reported and demonstrated the effectiveness of EREM for patients undergoing total knee replacement patients, but respiratory depression occurred at a dose of 20-30 mg. They advocated future trials of lower doses (10-15 mg) to avoid this complication.[9] Of interest, the EREM preparation cannot be mixed with other medications (e.g., saline or anything else) as this can cause an expedited release of the narcotic from the sustained release preparation.

MATERIALS AND METHODS

Patients

The study, registered with the National Institute of Health (NIH) (number NCT 00335517), was approved by the Research Subjects Review Board. This prospective, randomized (by computer) study involved 98 patients presenting to three spine surgeons for elective lumbar surgery who were to receive either 10 mg (Group I) or 15 mg (Group II) of EREM. Patients who gave informed consent had to be at least 18 years of age, underwent lumbar surgery from the L3-S1 levels, and anticipated being hospitalized for at least 48 hours. Patients were excluded if they were unable to give consent, were incarcerated, pregnant, or had allergies to narcotic analgesics.

Procedures

All patients underwent lumbar surgery with their attending surgeons. Details of the surgery included: The operating surgeon, the number of surgical levels, and the number of levels fused with and without instrumentation [Table 1].

Intervention: Catheter advancement to the L1 level and injection with 10 or 15 mg of extended release epidural morphine

At the conclusion of surgery, an epidural catheter was placed under direct visualization and was advanced at least 4 cm to the L1 level prior to the injection of 2 mL air to ensure patency. Surgical levels were confirmed with intraoperative radiography (fluoroscopy or portable X-ray). Aspiration was also performed to ensure no intradural injections. Subsequently, the undiluted (1 or 1.5 mL, corresponding to 10 or 15 mg) EREM was injected. The catheter was then removed.

Table 1: Conversion table of opiods to IV morphine equivalents[30]

Medication	Dose (mg)	Morphine equivalents (mg)	Route of administration
Morphine	1	1.00	IV
Hydromorphone	1.5	6.67	IV
Meperidine	100	10.00	IV
Oxycodone	10	5.00	Po
Hydrocodone	10	3.33	Po
Darvocet	200	10.00	Po

Postoperative care

Postoperatively, each patient was admitted to a nonacute level of care (floor bed). All patients were provided an intravenous patient-controlled analgesia (IV-PCA) system (morphine or hydromorphone) and oral analgesics (hydrocodone, oxycodone, or propoxyphene) as needed. The majority started with morphine PCA. This was at the surgeon's discretion. Narcotic consumption was recorded in morphine equivalents.

Safety measures

Postoperative orders included clear identification of "spinal narcotic" at patient's bedside and in patient's chart, and required multiple safety measures. First, elevation of the head of the bed to 30° avoided cephalad diffusion to the respiratory center. Second, the addition of 0.4 mg naloxone (low dose) to each liter of IV fluid minimized side effects like pruritis, nausea, and vomiting while avoiding reversal of the high concentration of narcotics at the spinal cord receptors. Third, continuous pulse oximetry monitoring allowed personnel to detect respiratory depression by an audible alarm. Vital signs, including respiratory rate and pupil size were recorded every hour for the first four hours and every four hours subsequently. As the receptors for pupil size and the respiratory center are located in close proximity, the observation of pin point pupils could signal the potential onset of respiratory depression.

Outcome measures

Perioperative data recorded for all patients included; the time of EREM injection, the amount of pain medication used at 6-hour intervals, and the patient reported pain scores during the 48-hour postoperative period. These data were used to compare the safety of the two EREM doses and differences based on the surgical details, as well as to evaluate the onset and duration of the EREM analgesia. Pain scores were also routinely recorded with vital signs using the Visual Analog Scale. Adverse outcomes were

recorded, including respiratory depression, reoperation, rehospitalization, pulmonary embolism (PE), and mortality. For ease of comparison, all narcotic analgesics were converted to equivalent doses of IV morphine (per our institution's algorithm). [Table 2-Equianalgesic Table for Adults: Half-Life, Duration, Costs, and Guidelines. University of Rochester Medical Center Palliative Care Programs; 2007].

Statistical methods

Significance was defined by $P < 0.05$. Data comparisons of total narcotic equivalent usage (NE) and pain scores between surgeon, surgical level, fusion level, instrumentation level, and use of interbody arthrodesis were made using analysis of variance (ANOVA). Additional comparisons of NE during consecutive 6-hour intervals were made using paired *t*-tests, and comparisons of EREM dose were made using independent Sample *t*-tests. Statistical analyses were performed with SPSS version 18 (SPSS Inc., Chicago, Illinois).

Funding source

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RESULTS

Safety

None of the participants in the study experienced serious adverse effects using an epidural narcotic including: Hypoxia/respiratory depression, hypotension, and bradycardia.

Total narcotic equivalent usage highly variable between subjects

Although there was a highly variable narcotic requirement between individual subjects, there was no significant difference for any specific parameter between patients receiving the 10 or 15 mg doses of EREM. Ranges, means, and standard deviations of total cumulative narcotic equivalent usage are provided in Figure 1. The cumulative narcotic equivalents ranged from 0 to 254 mg morphine, with a mean of 60 mg, and standard deviation of 50 mg. Of interest, 56.1% (55 out of 98 patients) of all study patients used less than 50 mg (95% confidence interval (CI): 46.3- 65.9%), and 81.6% (80 out of 98) used less than 100 mg (95% CI: 74.0-89.3%) [Table 3, Figure 2]. An independent sample *t*-test analysis further showed no difference between the two dosage groups in either narcotic equivalent or reported pain scores. Similarly, using ANOVA studies, there was no statistically significant difference among subjects (combining the two dosage groups) based on levels of surgery, fusion, instrumentation, use of interbody arthrodesis, or operating surgeon [Table 4].

Onset and duration of depodur analgesia

Mean interval narcotic equivalent usage is enumerated and illustrated in Figure 3. These data, which represent the mean narcotic equivalent usage of study participants during successive 6-hour intervals, show that the mean narcotic equivalent during the 6-12 hours

Table 2: Patient characteristics

Characteristic	DepoDur 10 mg	DepoDur 15 mg	All
Patients	51	47	98
Age, yr			
Mean	58	59	59
Median	59	60	60
Min, Max	35, 83	36, 80	35, 83
Sex			
Men	19	21	40
Women	32	26	58
Surgeon			
1	21	24	45
2	8	11	19
3	22	12	34
Levels of Surgery			
1	0	3	3
2	15	15	31
3	23	20	43
4	8	7	15
5	4	1	1
Levels of Fusion			
0	17	14	31
1	18	24	42
2	13	6	19
3	3	3	6
Levels of Instumentation			
0	28	32	60
1	11	10	21
2	11	4	15
3	1	1	2
Interbody Arthrodeses			
0	37	34	71
1	13	10	23
2	1	3	4

Table 3: 48-Hour total narcotic equivalent usage by patient

48h Total narcotic equivalent usage (mg morphine)	No. of patients (98 total)
0	1
1≤10	10
11≤20	11
21≤30	11
31≤50	22
51≤100	25
101≤150	15
151≤200	0
≥200	3

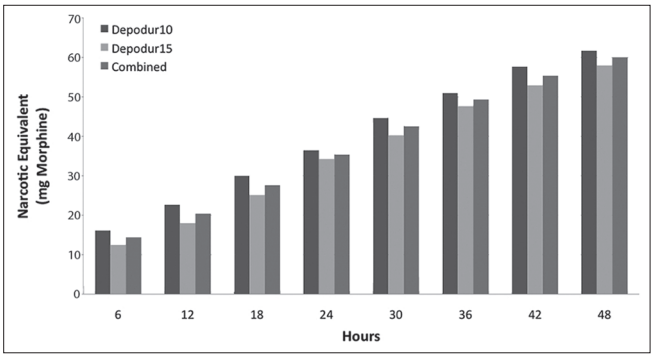

Figure 1: Mean cumulative narcotic equivalent by Depodur Dose

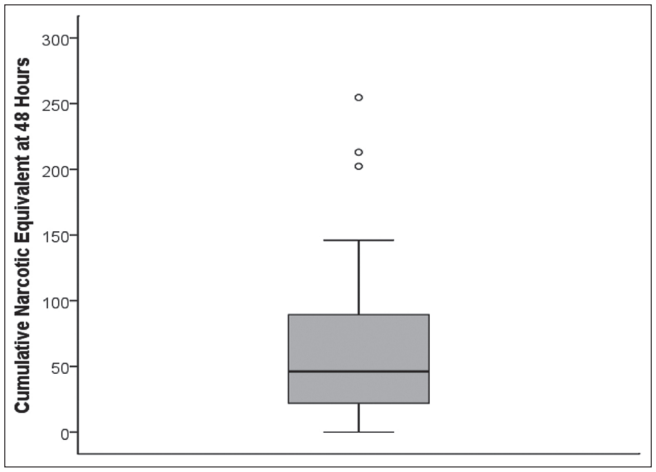

Figure 2: 48-Hour total narcotic equivalent usage by patient

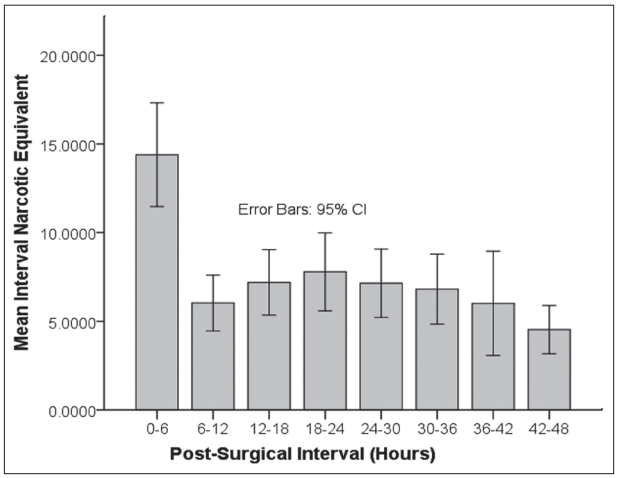

Figure 3: Mean interval narcotic equivalent, pooled

interval (6.03 ± 7.86 mg) was 58% less than that during the 0-6 hours interval (14.39 ± 14.59) ($P < 0.001$) [Table 5].

This suggests that the onset of DepoDur® analgesia does not fully take place immediately after injection. Similarly diminished mean narcotic equivalent usage during all subsequent 6-hour intervals also suggests that DepoDur® continues to provide significant analgesia for the entire 48 hours. A study of the pain scores show

Table 4: Summary of statistical comparisons

Comparative factors	Narcotic equivalent		Pain scores	
	F (or t)	*P*	F (or t)	*P*
DepoDur Dosage (10 mg vs. 15 mg)	0.36	0.72	-0.05	0.10
Levels of Surgery (1-5)	0.75	0.56	1.29	0.03
Levels of Fusion (0-3)	0.75	0.53	1.56	0.20
Levels of Instrumentation (0-3)	0.18	0.91	2.25	0.09
Levels with Interbody Arthrodesis (0-2)	0.34	0.71	2.92	0.06
Surgeon (one of three)	1.39	0.25	1.76	0.18

that the mean reported pain during the 6-12 hours interval (2.71 ± 2.43) was 31% less than that during the 0-6 hours interval (3.93 ± 2.60) ($P < 0.001$) [Table 6].

Pain scores

The pain scores were higher in the 0-3 hour time frame than the 3-6 hour window. This suggests the onset of the narcotic effect was about 3 hours after injection. This is consistent with Martin's observations.[15] Our study is one of the first to be able to analyze this effect as the medication was administered at the conclusion of surgery. In the other surgeries (abdominal, thoracic, hip, and knee), the epidural analgesia is placed before the start of surgery.

The collective pain scores indicate that the patients were relatively comfortable with our combination, multimodal anesthetic regimen. The average of all patients' pain scores varied between an average pain of 2.75 to 4.6 and a maximum pain of 3.7 to 6 during the 48 hours of monitoring [Table 7, Figure 4].

Side effects

Common side effects of narcotic analgesia – whether via regional, intravenous, or oral routes – include nausea, vomiting, and pruritis. These side effects were successfully prevented by treating all patients with naloxone preemptively in IV fluid. This approach is supported by previous studies.[14,20,30] Additionally, diphenhydramine, ondansetron, and phenergan were administered on an as-needed basis. To avoid urinary retention, Foley catheters were placed intraoperatively and maintained for at least 36 hours.

Adverse events

Adverse events were reported in four patients, while there was one death. Two patients were readmitted on postoperative days 11 and 19, respectively, and returned to the operating room for irrigation, debridement, and reclosure of draining incisions; cultures were negative for infection. Two patients with histories of atrial fibrillation, developed pulmonary emboli on the first postoperative day; both received inferior venal cava (IVC) filters and heparin followed by warfarin, and were discharged home. One patient with a history of coronary artery disease succumbed to an acute myocardial infarction 5 days postoperatively in a rehabilitation facility.

Table 5: Paired comparison of mean interval narcotic equivalent, pooled

Time intervals	Paired Differences					*t*	df	Sig (2-tailed)
	Mean	Std. deviation	Std. error mean	95% confidence interval of the difference				
				Lower	Upper			
0-6 hours vs. 6-12 hours	8.36	12.33	1.25	5.89	10.83	6.71	97	<0.001

Table 6: Paired comparison of mean pain score

Time intervals	Paired Differences					*t*	df	Sig. (2-tailed)
	Mean	Std. deviation	Std. error meanc	95% confidence interval of the difference				
				Lower	Upper			
Avg 0-6 vs. Avg 6-12	1.22	2.63	0.28	0.66	1.79	4.32	85	0.00

Table 7: Average pain score by post-surgical interval

Post-surgical interval (Hours)	Avg	Max
0 to 3	4.4	5.8
3 to 6	3.2	3.8
0 to 6	4.0	6.1
6 to 12	2.7	3.4
12 to 18	2.8	3.3
18 to 24	3.6	4.5
24 to 30	4.1	4.9
30 to 36	4.5	5.3
36 to 42	4.1	4.8
42 to 48	4.6	5.3

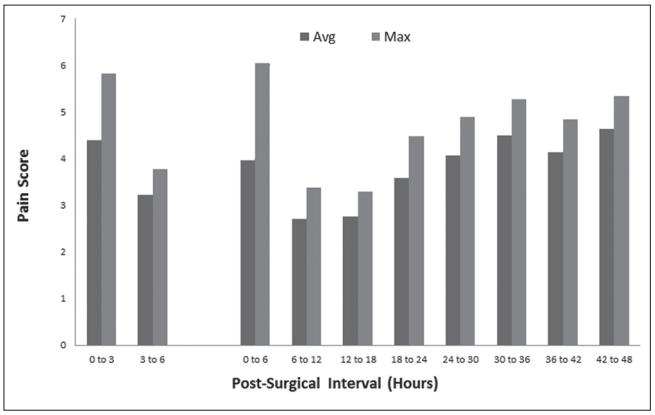

Figure 4: Average and maximum pain scores over time

DISCUSSION

Single-dose EREM: Effective epidural analgesia (L1 level) in spine surgery

In this randomized, prospective trial, low-moderate single-dose EREM (10 and 15 mg) injected through an epidural catheter at the L1 level at the end of surgery provided adequate pain control for 98 patients undergoing elective lumbar spine surgery. Patients also underwent multiple types of surgical procedures performed by three surgeons.[Table 1] This was a safe and effective means of controlling postoperative spinal pain even in a heterogeneous population of patients that included those who were narcotic naïve, or on high doses of narcotics preoperatively.

Two low dose EREM regimens produced comparable results

EREM (5-30 mg) provides equivalent or superior analgesia compared with standard morphine (5 mg) following lower extremity, abdominal, and obstetric surgery.[3,7-9,16,28,29] As short-acting morphine administered epidurally can provide analgesia for 12-24 hours following spine surgery,[4,13,27] the decision to compare the effects of the different low dosages of EREM for similar procedures. We concluded that there were no significant differences between the two dosage groups in the total narcotic equivalents used or reported pain scores at any single time point, any interval, or overall. There were also no differences based on levels of surgery, fusion, instrumentation, nor based on surgeon or use of interbody arthrodesis.

Duration of epidural analgesia following single low-dose EREM for spinal surgery

In addition, this study confirms the findings of others that the EREM analgesic effect does not occur until approximately 3 hours postinjection. The superiority of epidural analgesia over parenteral opioids for postoperative pain has been previously established. Cata *et al.* specifically reported how short-acting narcotics administered via patient-controlled epidural analgesia systems (PCEA) after lumbar spine surgery was superior to IV-PCA.[4] Spine surgery patients treated with PCEA reported better pain control, used less narcotics, had lower incidence of deep venous thrombosis, and had shorter hospital stays.

Orthopedic patients treated with EREM required less rescue narcotics

Orthopedic patients treated with EREM have also required less overall rescue narcotic, and none at all in some cases. Hartrick and colleagues showed that 48 hours

after knee arthroplasty, patients averaged a cumulative narcotic consumption of 132 mg morphine when treated with PCA alone, 44 mg when treated with 20 mg EREM and PCA, and 39 mg when treated with 30 mg EREM and PCA. In that study, the incidence of respiratory depression was a dose-related phenomenon beginning with 20 mg and even stronger at 30 mg.[9] This is why our study was designed with doses lower than this.

36-Hour perceived duration of efficacy of EREM

In our own study, both nursing staff and surgeons anecdotally noted that patients subjectively appeared comfortable postoperatively, and around 36 hours postoperatively began to experience more discomfort with increased mobility. However, like Hartrick *et al.*,[9] we found that patients required less narcotic overall: 55 patients required ≤50 mg IV morphine, 34 patients required ≤20 mg IV morphine, and one required no additional pain medication.

Advantage of single-dose EREM: Avoidance of in-dwelling catheter/risk infection

In addition to effective pain control, EREM affords other benefits. Because EREM does not require an in-dwelling catheter, the risk of catheter infection and concern for catheter failure or premature removal are eliminated while still ensuring steady analgesia. Extended release delivery allows for a lower peak systemic concentration and less sedation. Good pain control and reduced sedation is a desirable combination for patient comfort, mobility, and overall recovery.

EREM enables better mobility potentially reducing risk of PE and length of stay (LOS)

Utilizing EREM for pain control enables better mobility, thereby reducing risk of PE and hospital stay duration. Previous studies report a 0.5-6% incidence of symptomatic PE after spinal surgery.[5,17,23,25,26] A recent study in 2011 showed an incidence of 1.2% and this is not in-consistent with our data.[12] Moreover, Blackshear and Crosson reported a significant decrease in the incidence of PE among arthroplasty patients who received EREM compared with patients who had an in-dwelling catheter for epidural analgesia or relied on parenteral and oral opioids for pain relief.[1] Their finding correlated with significantly improved pain scores and shorter hospital stays. Similarly, Hartrick and colleagues found that knee arthroplasty patients treated with EREM tolerated physical therapy better and sooner than patients treated with parenteral narcotics alone. The 2% incidence of PE among the patients in our study falls within the reported incidence range. It is also worth noting that the two patients who did develop PE had perioperatively held their anticoagulation thus placing them in a hypercoagulable state. This emphasizes the importance of the balance between minimizing hemorrhage risk and utilizing prophylactic anticoagulation with any spinal surgery, regardless of the analgesic method.

Low to moderate dose EREM administered without respiratory depression

With any form of opioid analgesia, the risk of respiratory depression must be considered, especially with older patients and patients with preexisting respiratory compromise.[10,18,24] Previous studies have shown that there is no significant difference in the incidence of respiratory depression with the use of EREM compared with intravenous morphine or short-acting epidural morphine. Respiratory depression, as well as other adverse effects like hypotension, nausea, vomiting, and puritis, appears to be dose-related.[18] With this in mind, our study looked at the safety and efficacy of low to moderate doses of EREM. We found that low to moderate doses could be used in a multimodal pain control plan without respiratory depression. There was no evidence to suggest that there was an effect of the mode of administration on the release of medication from the liposomal preparation.

Close attention paid to safety measures

Close attention must be paid to the safety measures employed in this study. (1) Mark the chart as an epidural narcotic patient, (2) Keep the head of bed elevated at least 30°, (3) add 0.4 mg of naloxone to each liter of IV fluid starting at the time of injection, (4) continuous pulse oximetry, and (5) monitor pupil size with vital signs. This series was done without intensive care unit monitoring but if the individual surgeon has concerns, a step down unit or other monitoring device could be used.

Weaknesses of this study

One major weakness of this study was the heterogeneous population of patients (including prior surgeries, use of narcotics, etc.), the multiple types of surgical procedures performed, and the fact that three different surgeons participated in the study. Furthermore, no control group was included as the efficacy of epidural narcotics and EREM have been established by multiple studies.

Questions regarding specific method of administration

The two questions to be answered were related to the specifics of the method of administration; through open surgery versus an epidural injection. Here the question was whether the open wound (delivery of single dose at L1 level at the end of surgery) impacts the release of the drug with the potential of creating a higher risk of respiratory depression? In this study, there was no suggestion that either was true.

CONCLUSIONS

Low to moderate dose EREM (10 or 15 mg) with concomitant use of a PCA, while following safety precautions appropriate for epidural narcotic use, provides safe and effective postoperative pain control for patients undergoing lumbar spine surgery. Both dosages resulted

in significant reduction in the demand for narcotic analgesics starting 6-12 hours postoperatively, and this effect persisted for the rest of the 48-hour postoperative period. Because both doses were equally effective, and because unwanted side effects are typically dose-related, we recommend using 10 mg EREM for postoperative pain control after lumbar surgery.

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