Postcesarean Epidural Morphine: A Dose-Response Study

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Abstract

The purpose of this study was to describe the dose–response relationship of epidural morphine for postcesarean analgesia for quality of analgesia and relation to the side effects of pruritus, nausea, and vomiting. Sixty term parturients undergoing nonurgent cesarean delivery were enrolled and randomized to receive a single dose of epidural morphine after delivery (0, 1.25, 2.5, 3.75, or 5 mg). A patient–controlled analgesia (PCA) device provided free access to additional analgesics. PCA morphine use and the incidence and severity of side effects were recorded for 24 h. Data were analyzed with analysis of variance, Student’s t-tests, and χ² analysis. Nonlinear regression was used to describe a dose–response curve. PCA use differed significantly among groups (P < 0.001); PCA use was significantly greater in Group 0 mg than Groups 2.5, 3.75, and 5 mg (P < 0.05). PCA use was also significantly greater in Group 1.25 mg than Groups 3.75 and 5 mg (P < 0.05). Pruritus scores were significantly higher in all groups given epidural morphine than the control group (0 mg) (P < 0.05), but did not differ among the treatment groups (1.25–5 mg), although pruritus scores were significantly higher in treatment groups than in the control (P < 0.05). No relation was found between epidural morphine dose and incidence or severity of nausea and vomiting. We concluded that, for optimal analgesia, augmentation of epidural morphine with systemic analgesics or other epidural medications may be necessary.

Abstract

Implications: Quality of analgesia increases as the dose of epidural morphine increases to at least 3.75 mg; increasing the dose further to 5 mg did not improve analgesia. Side effects were not dose related. For optimal analgesia, augmentation of epidural morphine with systemic analgesics or other epidural medications may be necessary.

Epidural morphine was first reported as an effective analgesic in humans by Behar et al. (1). In 1979; shortly after, reports of its use in obstetric patients were published (2, 3). At present, epidural morphine is often used for postoperative analgesia after cesarean delivery, but despite the widespread use, few studies have investigated the dose–response properties of epidural morphine. Youngstrom et al. (3) (4 mg), Writer et al. (4), and Kotelko et al. (5) (both 5 mg) each investigated only a single dose of epidural morphine for postcesarean analgesia. Rosen et al. (6) reported a dose–response study with three doses of epidural morphine (2, 5, and 7.5 mg), but focused only on the duration of analgesia. Fuller et al.’s (7) retrospective review of doses ranging from 2 to 5 mg concluded that 3 mg is an “adequate” dose based on duration of analgesia. No previous reports clearly document whether the degree of pain relief increases as the dose of epidural morphine increases, whether there is a “threshold” dose or “ceiling” effect associated with the analgesia, or whether the severity of side effects is related to the dose of morphine. This information is necessary for meaningful comparisons between studies and to accurately assess the effect of epidural or systemic medications used in conjunction with epidural morphine. The purpose of this study was to define the dose–response relationship of epidural morphine for postcesarean analgesia for quality and duration of analgesia and related side effects.

Methods
Sixty ASA physical status I and II term parturients undergoing nonurgent cesarean delivery under epidural anesthesia gave written informed consent and were enrolled in this institutional review board approved study. Parturients having elective cesarean delivery were eligible for inclusion, as were parturients in labor (with or without epidural labor analgesia). After enrollment, parturients were randomized (by using a table of random numbers) to one of five groups to receive a single dose of epidural morphine between 0 and 5 mg during the procedure.

All patients were hydrated with 2000 mL lactated Ringer’s solution IV and received sodium citrate 30 mL by mouth before the induction. Epidural anesthesia was induced via a 20-gauge, open-tip epidural catheter placed at the L2–3, L3–4, or L4–5 interspace, with parturients supine with left uterine displacement. All patients received lidocaine 2% with epinephrine 1:200,000; an initial total volume of 20 mL was injected in divided doses of not more than 5 mL. If an adequate anesthetic level had not been achieved within 15 to 20 min, up to 10 additional mL of lidocaine 2% with epinephrine 1:200,000 was injected in divided doses. If an adequate level of anesthesia had not been achieved within 30 min of the initial injection, the patient was dropped from the study and her group assignment rerandomized.

During and after the induction, oxygen was administered via a face mask until delivery. Electrocardiogram and Sa\textsubscript{O}\textsubscript{2} were monitored continuously; maternal blood pressure was monitored at 1-min intervals until stable. IV fluids and ephedrine, 5 to 10 mg IV, were administered as necessary to maintain maternal systolic pressure above 100 mm Hg. After delivery, oxytocin (20 U/L) was added to the IV infusion. If supplemental analgesia was required intraoperatively, IV fentanyl was administered in 10 to 20 µg increments; for subsequent analysis, fentanyl 10 µg was considered equivalent to 1 mg IV morphine.

After delivery, parturients received a single injection of epidural morphine (either 1.25, 2.5, 3.75, or 5 mg) or epidural saline (control, 0.0 mg); all injections were diluted with normal saline solution to a total volume of 10 mL. Parturients were blinded to their group assignment.

Patients were followed for 24 h after the injection of the epidural study solution. An investigator blinded to the dose of morphine and group assignment recorded all observations. Intraoperatively, the occurrence of pruritus, nausea and vomiting, and the need for supplemental analgesics was noted.

On the first complaint of pain and request for analgesia in the postanesthesia care unit (PACU), morphine, 2 to 4 mg IV, was titrated until the patient was comfortable. The protocol allowed PACU nurses (who were blinded to group assignment) to administer up to 30 mg IV morphine, until the patient indicated her analgesia was satisfactory. Patients were then placed on a patient controlled analgesia (PCA) device supplying IV morphine, 1.5 mg each 8 min on demand only, for 24 h after the induction. Settings on the PCA device were adjusted if the patient continued to complain of inadequate pain relief or had an excessive number of unsuccessful “demands.” If the patient did not complain of pain before discharge from the PACU, the PCA was started and the patient was instructed in its use should they need it. Supplemental analgesic use (intraoperative, in PACU, and PCA) was recorded for 24 h after the induction.

Treatment of pain and side effects was at patient request only. Nausea and vomiting were treated with droperidol 0.625 mg IV. Pruritus was treated with nalbuphine, 5–10 mg IV up to a total of 20 mg in 4 h and then diphenhydramine 25 mg IV if necessary. During the intraoperative period (at skin closure), and in each 4-h period after the administration of the epidural morphine dose, side effects (nausea, vomiting, and pruritus) were scored on a scale of 0–2; a “0” was recorded if the side effect was absent, a “1” if the side effect was minimal and did not require treatment, or a “2” if the side effect was moderate or severe and required treatment. The patient’s 24-h score for each side effect was the sum of these seven scores. Respiration was monitored with a standing protocol that required hourly determination and recording of respiratory rate; no further assessment of respiratory effects was attempted.

Data were analyzed by using analysis of variance (ANOVA) and \textit{a posteriori} tests between groups, Student’s \textit{t}-tests, and \textit{χ}\textsuperscript{2} analysis, as appropriate. A \textit{P} value of 0.05 was considered significant. Twenty-four-hour PCA dose–response data were analyzed with nonlinear analysis for best fit of total 24-h PCA morphine use corresponding to log epidural morphine dose.
Results

Sixty ASA physical status I and II term parturients were enrolled, and all completed the protocol for this study \((n = 12, \text{ each group})\). Groups were demographically similar (Table 1).

Table 1.

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Total 24-h PCA morphine use differed significantly among groups (ANOVA, \(P < 0.001\), Figure 1). A posteriori tests revealed that patients in the control group used significantly more PCA morphine than patients who received 2.5 mg, 3.75 mg, and 5.0 mg (\(P < 0.05\)); patients who received 1.25 mg used significantly more than patients who received larger doses (3.75 mg and 5.0 mg) (\(P < 0.05\)). PCA morphine use over time also differed significantly among groups (ANOVA, \(P < 0.001\), Figure 2). Only 3 of the 60 patients in the study used no PCA morphine in the first 24 h postoperatively (one in Group 3.75 mg, and two in Group 5 mg, \(\chi^2\) contingency analysis, \(P = \text{not significant}\)).

When analyzed in aggregate with all treatment groups combined, pruritus scores were significantly higher in the treatment groups that received epidural morphine than the control group (4.1 ± 3.3 vs 1.8 ± 2.8, \(P < 0.05\)); no significant differences were found among the groups receiving epidural morphine (Table 2). There were no differences among the groups in nausea or vomiting scores. No difference was found between the control and treatment groups in nausea or vomiting scores (Table 2). There was no difference among the groups in the proportion of patients receiving treatment for either nausea (droperidol) or pruritus (nalbuphine or diphenhydramine).

Table 2.

| Side Effect Scores |

By using nonlinear analysis for best fit of total 24-h PCA morphine use corresponding to log epidural morphine dose, a dose–response curve (for a complete discussion of the derivation and assumptions underlying construction of the curve, see Ref. 8) was derived (Figure 3). The curve was derived by using
the equation:

\[ Y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom})}{1 + 10^{(\log ED_{50} - \log X)(\text{Hillslope})}} \]

where \( Y = 24\text{-h PCA morphine use, } X = \text{dose of epidural morphine, Bottom = lowest mean 24-h PCA morphine use, Top = highest mean 24-h PCA morphine use, } ED_{50} = \text{dose of epidural morphine predicted to decrease PCA use by half, Hillslope = a constant describing variability of slope, and log refers to the base 10 algorithm.}

Using observed mean values from this series for the Top and Bottom values (70 mg and 14 mg, respectively) describes the curve in Figure 3 and an estimate of the \( ED_{50} \) of 1.8 mg (95% confidence interval, 1.2–2.4 mg), and a Hillslope of \(-0.56 \) (95% confidence interval \(-0.96 \) to \(-0.17 \)).

**Discussion**

Our data indicate that the degree and duration of analgesia increase as the dose of epidural morphine increases over the range of 0 to 3.75 mg. Even the smallest dose in this series, 1.25 mg, had a modest PCA morphine-sparing effect that persisted through the 24-hour study period. Analgesia (as measured by PCA morphine use) did not further increase beyond a dose of 3.75 mg. It is possible that improved analgesia may have been found if the dose of epidural morphine was increased beyond 5.0 mg; in designing this study however, we felt that larger doses were beyond the clinically acceptable range and might unacceptably increase the risk of significant side effects.

Persistent PCA use by parturients in the large-dose groups indicates that systemic morphine appears to augment the analgesia produced by epidural morphine. We hypothesize that this systemic augmentation activates supraspinal opioid receptors, and enhances analgesia. This finding of enhanced analgesia is consistent with animal studies demonstrating that the analgesic potency of intraspinal administered morphine is potentiated by concurrent administration of intracerebroventricular morphine \((9,10)\). A similar ceiling effect, and analgesic potentiation by systemic morphine, has been described in association with intrathecal morphine \((11)\) for postcesarean analgesia. Alternatively, systemic morphine may augment epidural morphine analgesia via a peripheral mechanism \((12,13)\).

Given the doses of epidural morphine administered in this study, no threshold effect is evident. If smaller doses between 0 and 1.25 mg were studied, it is possible a threshold dose might be identified. At the larger doses in this study (3.75 mg and above), a ceiling effect is apparent; increasing epidural morphine dose to 5.0 mg does not improve analgesia, and parturients will continue to self-medicate with PCA morphine to augment analgesia at a relatively constant rate.

Little relation was found between dose and side effects over the range studied. The threshold dose for inducing pruritus is apparently quite small (below 1.25 mg), as all the treatment groups had higher pruritus scores than the control group. Beyond this threshold, neither the incidence nor the severity of pruritus was associated with dose of epidural morphine. This is in contrast to the dose-related pruritus described after intrathecal morphine administration \((11)\), but can probably be explained by the relatively smaller dose range studied in this series.
If a wider dose range had been studied, which included larger epidural morphine doses, it is possible that dose–dependent pruritus scores would be seen at larger dose levels.

No relation was found between the incidence and severity of nausea and vomiting and the dose of epidural morphine. Had a wider scale for scoring side effects been used (rather than the 0–2 scale), it is possible that subtle differences among groups may have been found, but use of the 0–2 scale decreases the possibility of subjective interpretation and results in a more readily reproducible score. Further, such subtle differences would not likely be clinically significant. Nausea and vomiting in patients who have received epidural morphine is sometimes considered to be a side effect of the morphine; the mechanism is alleged to be activation of opioid receptors in the chemoreceptor trigger zone of the fourth ventricle caused by cephalad migration of the morphine. Because the severity of nausea and vomiting observed was not different between control and treatment groups, however, a different mechanism is likely in most patients. For this reason, initial treatment of nausea and vomiting with an antiemetic, rather than an opioid antagonist, may be more effective in parturients who have received epidural morphine.

In summary, analgesia from epidural morphine after cesarean delivery increased in a dose–related fashion as the dose increased. The dose further to 5.0 mg did not enhance analgesia. Although all groups receiving epidural morphine had higher pruritus scores than the control group, neither pruritus nor nausea and vomiting was clearly dose related over the dose range studied. While there is little justification for the use of an epidural morphine dose beyond 3.75 mg, for optimal analgesia, augmentation with systemic opioids may be necessary.

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References


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