Dose–Response Relationship of Intrathecal Morphine for Postcesarean Analgesia

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Background: This series investigated the quality of analgesia and the incidence and severity of side effects of intrathecal morphine for post-cesarean analgesia administered over a dose range of 0.0–0.5 mg.

Methods: One hundred eight term parturients undergoing cesarean delivery at term and given spinal anesthesia were randomized to receive a single dose of intrathecal morphine (0.0, 0.025, 0.05, 0.075, 0.1, 0.2, 0.3, 0.4, or 0.5 mg). A patient-controlled analgesia (PCA) device provided free access to additional analgesics. PCA morphine use, incidence and severity of side effects, and need for treatment interventions were recorded for 24 h. Data were analyzed with analysis of variance and linear regression analysis for trends among groups.

Results: Patient-controlled analgesia use differed significantly between groups; PCA use was higher in the control group than in groups receiving 0.075, 0.1, 0.3, 0.4, or 0.5 mg. Twenty-four-hour PCA morphine use was 45.7 mg lower (95% CI, 4.8–86.6 mg lower) in the 0.075-mg group than the control group. There was no difference in PCA morphine use between the 0.075- and 0.5-mg groups (95% CI, 36.8 mg lower to 45.0 mg higher); despite a fivefold increase in intrathecal morphine dose, PCA morphine use remained constant. There was no difference between control and treatment groups or among treatment groups with respect to nausea and vomiting. Pruritus and the need for treatment interventions increased in direct proportion to the dose of intrathecal morphine (linear regression, P = 0.001 and P = 0.0002, respectively).

Conclusions: These data indicate there is little justification for use of more than 0.1 mg for post-cesarean analgesia. For optimal analgesia, increase of intrathecal morphine with systemic opioids may be necessary. (Key words: Hysterotomy; itching; opioids; pain; surgery.)

IN 1979, Wang et al.1 reported small doses of intrathecal morphine produced prolonged, effective analgesia in patients with chronic pain. In the decade that followed, intrathecal morphine also found application in the obstetric population, primarily for analgesia after cesarean delivery. A number of reports2–5 have appeared within the past decade describing administration of doses ranging from 0.1 to 0.6 mg for this purpose. The dose–response relationship of intrathecal morphine for post-cesarean analgesia has not been carefully evaluated, and the minimal effective dose, the relationship of side effects to morphine dose, and the analgesic failure rate at various doses have not been well defined. Our purpose of this study was to determine the dose–response relationship of intrathecal morphine for post-cesarean analgesia in terms of analgesic efficacy, incidence of side effects, and the need for treatment interventions.

Materials and Methods

One hundred eight American Society of Anesthesiologists physical status I and II term parturients presenting for elective or non-urgent cesarean delivery with spinal anesthesia gave written informed consent and were enrolled in this Institutional Review Board–approved study. Parturients with significant coexisting disease (pre-eclampsia, insulin-dependent diabetes, and so on) were excluded. After enrollment, the patients were randomized (based on a computer-generated table of random numbers) to one of nine treatment groups to receive between 0.0 and 0.5 mg (0.0, 0.025, 0.05, 0.075, 0.1, 0.2, 0.3, 0.4, or 0.5) intrathecal preservative-free morphine in conjunction with their spinal anesthetic. Initially the randomization plan called for randomizing patients into the 0.0, 0.1, 0.2, 0.3, 0.4, and 0.5 dose groups. A preliminary analysis of the data when sample sizes were 9,
Table 1. Scoring of Side Effects

<table>
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<th>Score</th>
<th>Pruritus</th>
<th>Nausea</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Mild with no treatment requested</td>
<td>Mild or transient and not requiring treatment</td>
<td>Transient with no treatment required</td>
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<tr>
<td>2</td>
<td>Moderate to severe and requesting treatment</td>
<td>Moderate to severe and requesting treatment; or associated with vomiting</td>
<td>Repeated episodes or treatment requested</td>
</tr>
</tbody>
</table>

8, 10, 9, 8, and 8, respectively, suggested little difference in effect among the highest dose groups. The study design was modified to include the lower dose groups, and randomization was continued until 12 patients were accrued to each group.

After prehydration with 2 l of intravenous lactated Ringer’s solution and 30 ml of oral sodium citrate, anesthesia was induced with the patient in the sitting position. A 21-gauge Sprotte needle was introduced to the subarachnoid space at the L2-L3, L3-L4, or L4-L5 interspace. After return of clear, free-flowing cerebrospinal fluid, bupivacaine, 12.75 mg, (1 ml 0.75% bupivacaine in dextrose 8.25%) was injected with the morphine dose according to the patient’s randomization. Parturients were blinded to their group assignment. The dose of morphine in all groups, including the control group (0.0 mg), was mixed with normal saline solution for a total volume of 0.5 ml; this 0.5-ml volume was added directly to the bupivacaine in the same syringe.

After injection of the bupivacaine-morphine solution, the Sprotte needle was withdrawn, and the parturients were placed in the supine position with left uterine displacement on the operating table. Oxygen was administered via face mask after induction until delivery. Electrocardiography and SaO2 were monitored continuously; maternal blood pressure was monitored at 1-min intervals until stable. Intravenous fluids and ephedrine, 5-10 mg, were administered as necessary to maintain maternal systolic pressure above 100 mmHg. After delivery, oxytocin, 20 U/l, was added to the intravenous infusion. If supplemental analgesia was required intraoperatively, intravenous fentanyl was administered in 10- to 20-µg increments; for subsequent analysis, fentanyl, 10 µg, was considered equivalent to 1 mg intravenous morphine.

Patients were followed for 24 h after injection of the spinal anesthetic. An investigator blinded to the dose of morphine and group assignment recorded all observations. The level of sensory anesthesia to pinprick was recorded 10, 20, and 30 min after injection. Intraoperatively, the occurrence of pruritus, nausea, vomiting, and the need for treatment interventions and supplemental analgesics was noted. At first complaint of pain in the post-anesthesia care unit (PACU), intravenous morphine, 2–4 mg, was titrated until the patient was comfortable. The protocol allowed PACU nurses (who were blinded to group assignment) to administer up to 30 mg intravenous morphine. The patients were then placed on a patient-controlled analgesia (PCA) device supplying intravenous morphine, 1.5 mg every 12 min on demand only, for 24 h after induction. If the patient continued to complain of inadequate pain relief or had an excessive number of unsuccessful “demands,” settings on the PCA

Table 2. Demographics

<table>
<thead>
<tr>
<th>Group</th>
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<th>0.05</th>
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Data are mean (standard deviation), except gravidity and parity, which are mean (range).

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device were adjusted accordingly. There were no programmed limits on maximum PCA morphine use. If the patients did not complain of pain before discharge from the PACU, the PCA was started, and the patient was instructed in its use should she need it. Supplemental analgesic use (intraoperative, in PACU, and PCA) was recorded for 24 h after induction.

Treatment of pain and side effects was at patient request only. Nausea and vomiting were treated with intravenous droperidol, 0.625 mg, or intravenous prochlorperazine, 10 mg. Pruritus was treated with intravenous nalbuphine, 10 mg, up to 20 mg in 4 h and then intravenous diphenhydramine, 25 mg, if necessary. The number of interventions necessary for treatment of side effects was recorded for 24 h postoperatively. During the intraoperative period and in each 4h period after administration of the intrathecal morphine dose, side effects were scored on a scale of 0–2 (table 1), with the patient’s 24-h score for each side effect being 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 intrathecal morphine-induced respiratory effects was attempted.

Data were analyzed with analysis of variance (ANOVA) on an intent to treat basis. Comparisons among groups were effected using Tukey’s studentized range test. Tests for trends were based on linear regression with dose modeled continuously. A particular nonlinear dose response was explored by modeling a threshold effect resulting from a dose of intrathecal morphine greater than zero and then by a linear dose effect for doses above 0 mg; this model considered the possibility of a nonlinear effect between 0 mg and 0.025 mg. Inference regarding these two contrasts was adjusted for multiple comparisons using a Bonferroni correction. Potential confounding by baseline variables was analyzed via linear regression (analysis of covariance). Nonlinear regression was used to explore a logistic dose–response relationship.

Results

Demographics

Demographic variables are listed in table 2. There were no significant differences among groups with respect to age, height, weight, body mass index (BMI), gravidity, or parity.

Twenty-four-hour PCA Morphine Use

Twenty-four-hour PCA morphine use differed significantly between groups (ANOVA, $P = 0.0002$; table 3). Intergroup comparisons indicated only that the 0.0-mg group used significantly more PCA morphine than the 0.075-, 0.1-, 0.3-, 0.4-, and 0.5-mg groups ($P < 0.05$). Twenty-four-hour PCA morphine use in the 0.075-mg group was $45.7$ mg lower than the 0.0-mg group (95% CI, adjusted for multiple comparisons, 4.8–86.6 mg lower). Twenty-four-hour PCA morphine use in the 0.5-mg group was $4.1$ mg lower than the 0.075-mg group (95% CI, 36.8 mg lower to 45.0 mg higher (figs. 1 and 2).

![Graph showing mean 24-h patient-controlled morphine use for each group (mean ± 95% CI). *$P < 0.05$ versus 0.075, 0.1, 0.3, 0.4, and 0.5-mg groups.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931257/)
Linear regression indicated a statistically significant trend in 24-h PCA morphine use resulting from the dose of intrathecal morphine (P = 0.0007). When modeled with a threshold effect however, there is statistical evidence against a linear dose response for the entire dose range studied (P = 0.006). After adjustment for multiple comparisons, there is no trend toward lower PCA morphine use with higher intrathecal morphine doses than 0.025 (P = 0.66).

Age, BMI, gravidity, and parity were not found to significantly confound dose effects or to be significant predictors of PCA morphine use.

**Side Effects**

There was no difference among groups with respect to the incidence of nausea (ANOVA, P = 0.77) or vomiting (ANOVA, P = 0.68). There was no evidence of a trend among groups in either side effect (linear regression: nausea, P = 0.76; vomiting, P = 0.20; table 4).

The severity of pruritus varied significantly among groups (ANOVA, P = 0.003); intergroup comparisons showed only that the 0.0-mg group had a significantly lower score than the 0.5-mg group. A significant trend toward increasing pruritus (fig. 3) was found as dose increased (linear regression, P = 0.003) with no evidence against a linearly increasing trend (i.e., no evidence of a threshold effect) for the entire dose range (P = 0.56). This model predicts an increase of 0.6 in mean pruritus score for each increase in intrathecal morphine dose of 0.1 mg (95% CI, 0.2–0.98 increase in mean score).

Nalbuphine use differed significantly among groups (ANOVA, P = 0.00002); there was no difference among groups 0.0–0.1 in mean nalbuphine use or among groups 0.2–0.5, but groups 0.0–0.1 were all significantly different (lower) from groups 0.2, 0.3, and 0.5 (P < 0.05). Group 0.4 was significantly different (higher) than groups 0.0 and 0.075 (P < 0.05).

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Table 4. Side Effects and Treatment Interventions

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Values are median (range). Each patient’s score (for nausea, vomiting, and pruritus) is the sum of the scores received in each of the six 4-h intervals after injection, plus the intraoperative score; therefore, the minimum possible score is 0 and the maximum possible score is 21 (7 × 3 × 3).

The need for treatment interventions also varied significantly by dose (ANOVA, P = 0.0004); comparisons among individual groups found only the 0.075- and 0.3-mg groups to differ significantly from each other. Linear regression analysis revealed a trend toward a greater need for interventions (fig. 4) as dose increased (P = 0.0002), with no evidence against a linear trend (no threshold effect) for the entire dose range (P = 0.76). For each increase in intrathecal morphine dose of 0.1 mg, the model estimates the average number of treatment interventions to increase by 0.5 (95% CI, 0.22-0.75).

Discussion

Intrathecal morphine has been known to be an effective postoperative analgesic in humans for almost two decades and has been used in the obstetric population as an analgesic for almost as long. The first report of intrathecal morphine used in the obstetric population was by Baraka et al., who administered doses of 1 or 2 mg to laboring parturients for labor analgesia. Although effective for the first stage of labor, they found a high incidence of pruritus, somnolence, and nausea (85-100%) after a 1-mg dose.

The use of intrathecal morphine for postcesarean an-

![Fig. 3. Mean 24-h pruritus score for each group (mean ± SD). Groups were significantly different (analysis of variance, P = 0.003). Dotted line represents trend toward higher pruritus score with increasing dose (linear regression analysis, P = 0.001); the model predicts an increase of 0.6 (95% CI, 0.23-0.98) for each increase in intrathecal morphine dose of 0.1 mg.](image)

![Fig. 4. Mean 24-h intervention total for each group (mean ± SD). Need for interventions varied significantly between groups (analysis of variance, P = 0.0004). Dotted line represents trend toward increasing need for interventions with increasing dose (linear regression analysis, P = 0.0002); the model predicts the number of interventions necessary will increase by 0.5 (95% CI, 0.22-0.75) for each increase in intrathecal morphine dose of 0.1 mg.](image)

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algesia is a more recent development. In 1988, Abboud et al. reported that 0.25- and 0.1-mg doses of intrathecal morphine reduced VAS pain scores by 50% or more for a mean of 27.7 and 18.6 h, respectively. Abouleish et al. found a mean of 27 h to first request for additional analgesia after a 0.2-mg dose of intrathecal morphine. Chadwick and Ready retrospectively reported experience with intrathecal morphine after cesarean delivery with doses from 0.3 to 0.5 mg; although a non-significant “trend” toward longer analgesia was noted, no dose effect was found regarding side effects. Subsequent reports further established the safety and effectiveness of intrathecal morphine in this population, but they focused largely on a single dose of the opioid. Surprisingly, despite the widespread use of intrathecal morphine in obstetrics during the past decade, few dose–response investigations have been reported or been widely available. Lin et al. reported a dose–response study with intrathecal morphine doses ranging from 0 to 1.0 mg, but no English translation is available. Jiang et al. studied doses of intrathecal morphine between 0 and 0.125 mg; they found a linear relation between morphine dose and duration of analgesia for this range. Side effects were not significantly dose-related, although pruritus was more common in treatment groups than in the control group.

In characterizing the response to intrathecal morphine, each of these studies has focused on the duration of analgesia obtained from a given dose. The duration of analgesia clearly increases as the dose of morphine increases, but parturients requiring cesarean delivery generally recover quickly, with the majority resuming oral intake of liquids and medications within 12–24 h. As such, increasing intrathecal opioid dose to increase the duration of analgesia makes little sense, particularly if bothersome side effects also increase as the dose increase. Further, in focusing on the duration of analgesia, these series have overlooked a second important characteristic of analgesia—quality. PCA devices allow each parturient to titrate analgesia without necessity of intervention and assessment by nurses or physicians and without enduring painful intramuscular injections; they provide a powerful tool to objectively assess the quality of analgesia from intrathecal opioids.

The original design of this study called for only six groups: a control group to receive no intrathecal morphine, and five groups to receive varying doses of intrathecal morphine (0.1, 0.2, 0.3, 0.4, and 0.5 mg). Our original hypothesis was that we would see an inverse but linear correlation between the amount of PCA morphine
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vomiting after cesarean delivery with intrathecal morphine should perhaps be an antiemetic rather than an opioid antagonist. Finally, the need for interventions to treat specific patient complaints or problems was directly proportional to intrathecal morphine dose; these interventions were largely reflective of the need to manage pruritus.

One significant side effect of intrathecal morphine that this series was not designed to assess is respiratory depression. All parturients in this series were monitored for respiratory depression by hourly assessment of respiratory rate, which is the means routinely used to monitor parturients after intrathecal morphine in our institution. Respiratory depression after intrathecal morphine has been previously reported to be an infrequent complication; in a series of more than 1,600 parturients who had received 0.2 mg of intrathecal morphine after cesarean delivery, eight exhibited episodes of desaturation (SaO₂ below 85%, assessed by pulse oximetry) during sleep. All eight parturients were markedly obese with partial upper airway obstruction while asleep; use of a naloxone infusion failed to eliminate the episodes of desaturation. Intrathecal morphine, 0.25 mg, produced no depression of respiratory response to to carbon dioxide challenge in another report. Within the dose range reported in our series, clinically significant respiratory depression should be rare.

The treatment of side effects may have influenced PCA morphine use with this protocol. Nalbuphine has been shown to be an effective treatment for pruritus resulting from administration of neuraxial morphine. Nalbuphine is a mixed opioid agonist-antagonist, and its effect on analgesia caused by neuraxial opioids is unpredictable. Alternative treatments such as diphenhydramine lack any opioid antagonist effect, but they may be associated with somnolence, which may interfere with self-medication via PCA techniques. Faced with this choice, we chose to primarily use nalbuphine for management of pruritus in this series, hypothesizing that actual use would be minimal and therefore the effect on analgesia would be minimal. As nalbuphine use was significantly greater in the higher-dose groups than in the lower-dose groups, it is possible that its opioid antagonist properties caused parturients in the higher-dose groups to increase PCA morphine consumption. This artificial increase in morphine consumption may have prevented differences among groups from attaining statistical significance.

Unfortunately, in the presence of a nonlinear dose-response curve such as suggested by figure 1, it is difficult to quantify exactly which dose might be optimal. If we were to use statistical significance as the sole yardstick by which to interpret these data, there would be no evidence to suggest that 0.5 mg of intrathecal morphine provides substantially better analgesia than 0.025 mg. The pairwise comparisons that were used to assess statistical significance do not have sufficient statistical power to detect all differences between groups, even though such differences might exist. For that reason we believe that statistical significance should be used merely as a guide.

Because of the heterogeneity of the data, it is not possible to fit the data in figure 1 to a sigmoidal dose-response curve as in figure 5. This is largely because of the large standard error in the 0.2-mg group (in turn caused by two parturients who each used more than 130 mg of PCA morphine in 24 h), which indicates that the experience of this group is estimated less precisely. Descriptively, the data indicate a reasonably linear decrease in PCA morphine use as the dose of intrathecal morphine increases from 0.0 to 0.075 mg. Discounting somewhat the data from the 0.2-mg group, PCA morphine use is fairly stable between 0.1 and 0.5 mg. This finding leads us to hypothesize that the analgesic response to intrathecal morphine could be described by a sigmoidal dose-response curve such as figure 5, with point A lying at or below 0.025 mg and point B lying at or near 0.075 mg.

Beyond 0.1 mg, the curve is horizontal (or nearly so), at least within the clinically relevant range investigated here. Increasing the dose of intrathecal morphine does not enhance analgesia; despite a fivefold increase in the dose of intrathecal morphine, analgesia remained largely unchanged. Further, this analgesia is not perfect or maximal; given free access to additional analgesics, most parturients will choose to supplement the analgesia from intrathecal morphine and, for this dose range, will do so at a relatively constant rate. This finding is consistent with animal studies that have shown that the analgetic potency of intraspinally administered morphine is potentiated by concurrent administration of intracerebroventricular morphine. Our data indicate that for maximal analgesia, opioid agonism at both spinal and supraspinal sites is necessary. Although rostral spread of neuraxial morphine administered at lumbar levels has been shown to occur within this dose range (0.0–0.5 mg), the spread is either not high enough or is of insufficient concentration to fully activate this spinal-supraspinal interaction. Systemically administered (PCA) morphine provides the supraspinal opioid agonism necessary for maximal opioid-induced analgesia.

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In summary, the dose-response relationship of intrathecal morphine for post-caesarean analgesia was investigated. Doses of 0.1 mg or less were found to produce analgesia comparable with doses as high as 0.5 mg. Observed levels of pruritus and the need for interventions to manage it were consistent with an incidence of side effects that was directly proportional to the dose for the range of 0.0 - 0.5 mg. The side effects of nausea and vomiting did not appear to be dose-related, being similar in the control and treatment groups. Given free access to additional analgesics, most parturients will continue to self-administer additional morphine at a low but constant rate, indicating that analgesia resulting from intrathecal morphine can be further enhanced by systemic morphine administration.

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