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Intrathecal morphine reduces breakthrough pain during labour epidural analgesia

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Background. When using the combined spinal-epidural (CSE) technique for labour analgesia, parturients often experience breakthrough pain after the spinal medication has receded. We tested the hypothesis that a small dose of intrathecal morphine would reduce breakthrough pain.

Methods. This was a randomized, double-blind, placebo-controlled trial. Subjects were randomized to receive either 100 μg of morphine (MS) or placebo (PLCB) with the spinal injection of bupivacaine and fentanyl. Assessments included need for supplementation during labour analgesia, use of pain medications for 24 h after delivery, and side-effects. The primary endpoint was the rate of breakthrough pain.

Results. Sixty subjects were enrolled, 55 subjects completed the trial. The MS group had a significantly lower rate of breakthrough pain than the PLCB group [0.6 (0.6) *vs* 1.1 (0.8) episodes per patient; $P<0.01$], and longer time to first episode of breakthrough pain (300 *vs* 180 min; $P=0.03$). The MS group used 75% less opioid medications during the subsequent 24 h, but had a 17% incidence of nausea.

Conclusions. The addition of small dose of morphine to the spinal component of the CSE technique improved the effectiveness of epidural labour analgesia and reduced the need for pain medications over 24 h, but resulted in a small increase in nausea.

The combined spinal-epidural (CSE) technique has gained popularity as a method of providing labour analgesia due to the rapid onset of effective pain relief, preservation of motor function, and minimal side-effects. The intrathecal medications provide rapid onset of pain relief with a limited duration, whereas the slower epidural medications maintain prolonged analgesia. Some clinicians believe that the pain relief provided by epidural medications is not as consistent and effective as that provided by the spinal injection. This leads to an increase in requests for supplemental medications. To improve the effectiveness of pain control with the CSE technique, several investigators have sought to prolong the duration of analgesia provided by spinal medications. One such method is to initiate the epidural infusion immediately after spinal injection.[1][2]

Alternatively, investigators have studied the use of intrathecal medications with a longer duration of action. Yeh and colleagues[3] found that morphine 150 μg added to a fentanyl-bupivacaine spinal injection prolonged the duration of labour analgesia; however, this increased duration was noted to be associated with significant side effects. Previously, we found that morphine 125 μg, when added to a spinal injection of bupivacaine 2 mg and fentanyl 12.5 μg, did not prolong the duration of the spinal component of analgesia, but appeared to improve the effectiveness of subsequent epidural analgesia.[4] Women who received intrathecal morphine had a 40% decrease in breakthrough pain. One criticism of that study was that we did not standardize the treatment of breakthrough pain after the initiation of epidural analgesia. In this present study, using a strict protocol for

breakthrough pain, we hypothesized that a small dose of intrathecal morphine would improve the quality of subsequent epidural analgesia.

Materials and methods

This placebo-controlled, double-blinded, randomized trial was approved by the hospital committee on clinical investigations. After written informed consent, 60 healthy parturients of mixed parity who requested neuraxial analgesia were randomized via a computer-generated list to receive a small dose of morphine or placebo during their CSE placement. The randomized assignments were maintained in opaque envelopes and opened by an independent investigator who prepared the medication; neither the patient nor assessor knew the randomization group. Inclusion criteria consisted of active labour with a term, singleton foetus in a vertex position. Women who had received analgesics within 4 h and those with chronic pain, pre-gestational diabetes, morbid obesity, or foetal abnormalities were excluded. A midline CSE was placed at the L3–4 or L4–5 interspace with the subject in the sitting position using the needle-through-needle technique. Spinal injection consisted of 12.5 µg (0.25 ml) of fentanyl with 2 mg (0.8 ml) of bupivacaine through a 24 g Sprotte needle. The morphine group (MS) received an additional 100 µg (0.2 ml) of morphine, whereas the placebo group (PLCB) received an equal volume of normal saline, for a final volume of 1.25 ml. After successful spinal injection, a three-holed epidural catheter was placed via a 17 g Tuohy needle. Immediately after successful placement, a test dose of lidocaine 1%, 3 ml with 1:200000 epinephrine was given through the epidural catheter. Promptly after confirming negative intrathecal and i.v. injection, the epidural catheter was infused with a standard epidural solution (bupivacaine 0.04%, fentanyl 1.7 $\mu g\ ml^{-1}$, and 1:600000 epinephrine) at a rate of 15 ml h^{-1}.

Patient assessments before spinal injection included vital signs, pain score, and cervical dilation. After spinal injection, vital signs, pain score, sensory block to cold and pinprick, motor blockade, and side-effects were evaluated at 5, 10, and 15 min. Successful spinal analgesia was defined as the relief of labour pain within the first 15 min. Failed spinal injection would constitute removal from further study. All pain scores were evaluated using a numeric pain score (NPS) of 0 to 10, with 0 being 'No pain' and 10 representing 'Worst possible pain'. Motor block was assessed using the modified Bromage scale described by Breen and colleagues.[5] Zero was defined as no movement, and five was defined as no weakness on hip flexion. Although parturient activity was not restricted after spinal injection, we did not test for success of deep knee bending. Evaluation of side-effects included direct questioning at each interval for pruritus, nausea, and sedation rated on a four-point scale: none, mild, moderate, or severe.

An episode of breakthrough pain during labour analgesia was defined as subjective discomfort due to pain or pressure increasing during a contraction, and which was successfully treated with supplemental medications. Patients were assessed during each episode of breakthrough pain for technical causes of the epidural failure, such as catheter dislodgement or migration. The treatment of each episode of breakthrough pain was by strict protocol as follows.

- The initial treatment of breakthrough pain consisted of epidural injection of bupivacaine 0.125%, 8 ml and fentanyl 100 µg (final solution was bupivacaine 10 mg and fentanyl 100 µg in 10 ml).
- Fifteen minutes after supplementation, the subject was assessed and, if needed, an additional 10 ml of bupivacaine 0.125% would be administered.
- A final reassessment was performed after an additional 15 min, and a final 10 ml of bupivacaine 0.125% would be given if the patient was still uncomfortable.
- Failure of adequate pain relief after completion of this sequence, or other evidence such as complete loss of anaesthetic level, would result in a replacement of the epidural catheter and elimination from further study.

Recurrent breakthrough pain was defined as three or more episodes of breakthrough pain and was treated by increasing the background infusion. The following protocol was used to determine the amount of background epidural infusion medication.

- On the third episode of breakthrough pain, the concentration of the background epidural infusion was increased to bupivacaine 0.08%, fentanyl 3.33 $\mu g\ ml^{-1}$, and 1:600000 epinephrine at 15 ml h^{-1}.
- On the sixth episode of breakthrough pain, the concentration of the background epidural infusion was increased to bupivacaine 0.125% and fentanyl 3.33 $\mu g\ ml^{-1}$ at 15 cc h^{-1}.

24 h follow-up

Subjects underwent evaluation of pain and side-effects every 4 h for 24 h after delivery. Subjects who delivered by Caesarean were eliminated from analysis due to the large requirements for pain medications after Caesarean delivery. Pain medications were prescribed by a standard protocol: 800 mg Ibuprofen initially, followed by oxycodone (5 mg)-acetaminophen (325 mg), one to two tablets every 4 h, as needed. Moderate or severe side-effects were treated by standing orders of medications as follows.

For pruritis: naloxone 40–80 µg, every 5 min, as needed up to 3 boluses, and naloxone 200 µg h^{-1}, continuous infusion for persistent pruritis.

For nausea: dolasetron 12.5 mg, every 8 h, as needed, and metoclopramide 10 mg, every 6 h, as needed.

Statistics

The primary outcome was the difference in the rate of breakthrough pain between groups. The rate of breakthrough pain was calculated as the number of episodes of breakthrough pain during labour analgesia divided by the duration of epidural analgesia. For subjects who delivered vaginally, the duration of labour analgesia was from the time of placement until the time of the birth. For subjects who went to Caesarean delivery, the duration of epidural analgesia ended at the time the patient was transferred to the operating room. Medications given for operative delivery were not included in the analysis. Furthermore, subjects who had an operative delivery (Caesarean or assisted vaginal) were not included in comparisons of postpartum pain control. Comparison of the rate of breakthrough pain was performed by t-test after square root transformation. The Kolmogorov–Smirnov test was used to test for a statistically normal distribution after transformation. Normally distributed continuous variables were compared using the t-test, the Mann–Whitney test was used for non–normal distributions, and Fisher's exact chi-squared was used for frequencies. Kaplan–Meier survival analysis was used to assess the duration of pain free labour analgesia after spinal injection, and the median analgesic duration was compared using log-rank analysis. Maternal pain scores, vital signs, and sensory level were analysed using a general linear model for repeated measures.

A priori power analysis performed with a significance of 0.05 and power of 0.8 to detect a 25% difference in the rate of breakthrough pain determined that 18 patients were needed in each group. On the basis of previous experience, we increased the number of enrolled patients to correct for the potential of subject dropouts. Baseline characteristics and outcomes were compared after elimination of dropouts. Data were analysed using SPSS for windows 12.0, SPSS Inc. The level of significance was set at $P<0.05$.

Results

Of the sixty patients who were enrolled in the study, five patients were eliminated due to protocol violations: two spinal injections failed, one patient was diagnosed during the procedure with a cardiac rhythm abnormality (further workup revealed depressed cardiac function with a diagnosis of peripartum cardiomyopathy), one patient required lateral position for placement rather than the sitting position, and there was one epidural catheter that failed and required replacement. The patient characteristics and obstetric outcomes were similar between groups (Table 1).

Outcome analysis was conducted on the remaining 27 subjects in the MS group and 28 in the PLCB group. Vital signs, analgesic level to cold and pinprick, motor block, and pain scores were similar in both groups (Table 2). The MS group had significantly fewer episodes of breakthrough pain compared with the PLCB group [0.6 (0.6)

Table 1 Maternal and obstetric characteristics. Data reported as mean (range), mean (SD) or number of patients (percentage of group), as appropriate; cervical dilation at placement and duration of labour reported as median (range). There were no significant differences between groups

Characteristic	Group	
	PLCB (n=28)	MS (n=27)
Age (yr)	32 (20–43)	32 (23–41)
Height (cm)	165 (6)	166 (8)
Weight (kg)	85 (15)	85 (16)
Nulliparity	10 (36%)	13 (48%)
Dilation at placement (cm)	4 (1–6)	3 (1–6)
Normal vaginal delivery	22 (79%)	22 (82%)
Operative vaginal delivery	1 (4%)	2 (7%)
Caesarean delivery	5 (18%)	3 (11%)
Duration of labour (min)	250 (40–600)	315 (80–765)

episodes vs 1.1 (0.8) episodes, $P=0.008$] (Figure 1). Adjusting for the duration of labour analgesia, the hourly rate of breakthrough pain was significantly lower in the MS groups [0.1 (0.2) episodes h^{-1} vs 0.3 (0.2) episodes h^{-1}, $P=0.005$]. Using Kaplan–Meier analysis, the median time from spinal injection to the first episode of breakthrough pain was 300 min (MS) vs 180 min (PLCB), which was significant by log-rank analysis ($P=0.03$) (Figure 2). The incidence of all side-effects during labour was similar (nausea, pruritus, sedation, $P=$NS for all).

24 h follow-up

The MS group had slightly more nausea in the 24 h after delivery than did the PLCB group, but the incidences of other side-effects were similar (Table 2). We found that the requirement for postpartum pain medications was significantly reduced. Among those subjects who had a successful vaginal delivery, there was a 40% reduction in the doses of

Table 2 Comparison of groups after spinal injection. NPS, numeric pain scores. NPS, sensory and motor block reported as median (range). Sensory block represents maximum height of block within the first 15 min. Motor block represents the lowest score achieved at any time. Evaluation of 24 h effects was conducted every 4 h for 24 h after delivery on subjects who delivered vaginally. Subjects who delivered by Caesarean were eliminated due to the increased requirements for pain medications after Caesarean. Side-effects are reported as the number of patients (percentage of each group) requiring treatment at any time during the 24 h period

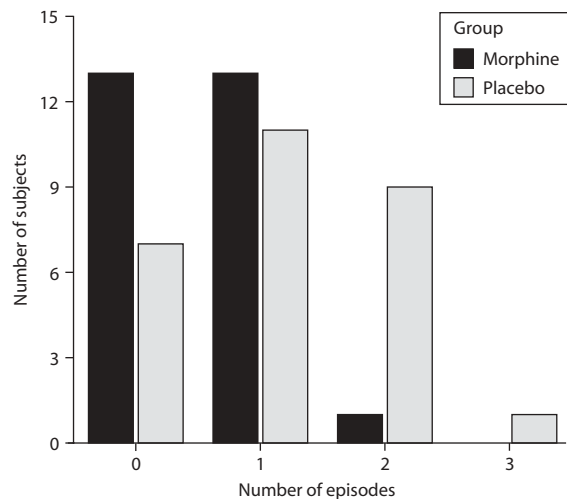|	PLCB	MS	P-value
Labour effects	n=28	n=27	
NPS at baseline	7 (4–10)	7 (6–10)	NS
NPS at 5 min	0 (0–8)	0 (0–5)	NS
NPS at 10 min	0 (0–5)	0 (0–5)	NS
NPS at 15 min	0 (0–2)	0 (0–2)	NS
Hypotension	16%	11%	NS
Sensory block to cold	T7 (T4–T12)	T6 (T3–T10)	NS
Sensory block to sharp	T10 (T4–L3)	T9 (T3–L1)	NS
Motor block	5 (4–5)	5 (4–5)	NS
24 h effects	n=23	n=24	
Nausea	0	4 (17%)	0.02
Pruritus	0	1 (4%)	NS
Sedation	0	0	NS

Fig 1 Number of episodes of breakthrough pain during epidural analgesia. The MS group received 100 μg morphine and the PLCB group received an equal volume of saline. Episode of breakthrough pain was defined as pain or pressure that was successfully treated by supplemental medications. Breakthrough pain was treated by protocol. The morphine group had significantly fewer episodes than the placebo group [0.6 (0.6) *vs* 1.1 (0.8), *P*=0.008].

pain medication taken [PLCB=2 doses (range 0–6), MS=1 dose (range 0–3), *P*<0.05], a 75% reduction in the use of oral opioid pain medications [PLCB=1 dose (range 0–4), MS=0 doses (range 0–2), *P*<0.05]. In fact, only three of the women in the MS group required oral opioid pain medications compared with 13 in the PCLB group.

Discussion

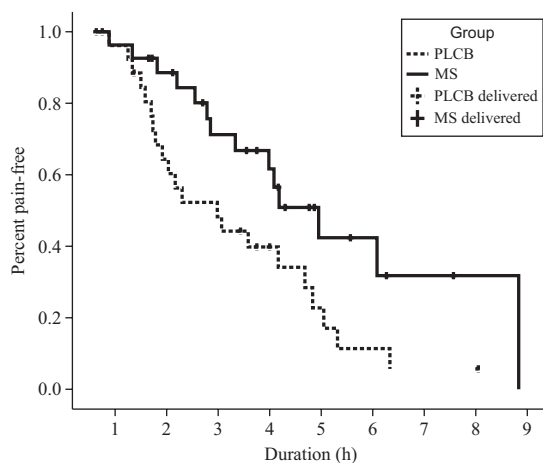This study showed that the addition of 100 μg of morphine to a small dose of spinal bupivacaine and

Fig 2 Pain-free survival. This figure shows the Kaplan–Meier survival curve for the cumulative duration of pain-free analgesia in the MS group *vs* the PLCB group. The MS group had a significantly longer pain-free period (300 min) than did the PLCB group (180 min); *P*=0.03 by log-rank analysis. Crosses represent subjects who delivered without requesting supplementation.

fentanyl significantly reduced the rate of breakthrough pain during subsequent labour analgesia. We found approximately a 50% reduction in both the number and rate of breakthrough pain episodes during ultra-low dose epidural analgesia. We also found that this small dose of morphine significantly prolonged the time to first request for supplementation. Although the overall incidence of side-effects was low in both groups, the MS group had slightly more nausea and vomiting than the PLCB group; the incidence of vomiting was similar to that found in our previous study using 125 μg of morphine.[4] This is consistent with the findings of Palmer and colleagues[6] who noted little change in the incidence of nausea with higher doses of intrathecal morphine. The incidence of hypotension was similar in both groups (11% in the MS group and 16% in the PLCB group), but slightly higher than in our previous study. We believe that the higher incidence of hypotension may be due to the early initiation of epidural analgesia. Administration of volume into the epidural space after spinal injection has been shown to increase the effect of spinal medications.[7] Although we used a test dose before initiation of the epidural infusion, this has been debated with the CSE technique. Some practitioners avoid a test dose due to the increased motor block, whereas others promote the added margin of safety.[8][9] We do not think that giving a test dose equally to both groups had any influence on the results between groups.

Many clinicians believe that epidural analgesia is less effective with the CSE technique. Because pain relief from spinal medications is more effective, the transition to epidural analgesia may be interpreted as an increase in pain. Alternatively, less effective pain relief from epidural medications may be unmasked when relief from the spinal injection subsides. Two approaches could be used to solve this issue: prolonging the duration of spinal analgesia or increasing the effectiveness of epidural analgesia. Beilin and colleagues[1] showed that administering epidural bupivacaine could extend the median duration of pain free labour after combined spinal procedure. Women who received one of the two ultra-low doses remained pain free significantly longer than women who received saline. Those women in the fourth group in this study who received the highest dose (bupivacaine 0.125%) remained pain free the longest, 300 min; however, these women also experienced the side-effects of higher bupivacaine concentrations, namely motor blockade. We hypothesize that by providing a small dose of morphine with the spinal injection, we improved the effectiveness of epidural analgesia without increasing the degree of motor blockade. The women in our study had a median of 300 min of analgesia, which was significantly longer than the PLCB group. Due to the use of an ultra-low concentration of bupivacaine, the subjects in our study did not have significant loss of motor strength; however, we did find a small increase in the incidence of nausea. This side-effect must be weighed

against the increase in motor block found when using higher concentrations of bupivacaine.

The most common methods used to compare the efficacy of epidural analgesia assess the potency (median dose, ED_{50}) or the effectiveness (maximum dose, ED_{95}) of solutions. Both of these methods assess the initiation of epidural analgesia and not the success of pain relief throughout labour. That is, these methods assess whether pain relief is achieved within the first 30–60 min but not whether it is maintained over the subsequent several hours. Our comparison of the effectiveness of epidural analgesia is based on the rate of breakthrough pain throughout labour. We believe that the rate of breakthrough pain during epidural analgesia represents a robust measure for comparison of epidural solutions during labour. In this current investigation, we compared the effectiveness of the identical epidural solution after the administration of intrathecal morphine or placebo; however, the same comparison could be made using two different solutions. One advantage of this method of comparison is that it may result in a clinically meaningful value.

We combined two opioids, fentanyl, and morphine, for the intrathecal injection. This combination is very commonly used for single-shot spinal analgesia, where it has been shown to be effective for the first stage of labour in many people.[10] Although a bit unusual with the CSE technique, our concept was to take advantage of the characteristics of both opioids; that is, the rapid onset of fentanyl and the prolonged duration of morphine. We believe that no single medication has been shown to be a uniformly effective analgesic; the combination of medications with different characteristics allows significant versatility. The 'ideal' combination of medications remains to be determined, and we suspect that it may vary with the individual needs of each patient.

There are some limitations to our study that we can identify. First, although we did evaluate patients for the common side-effects of intrathecal morphine, namely pruritus and nausea, we limited our evaluation to those subjects who had moderate to severe reactions or those who required treatment. Clearly, if we had included the subjects who had mild symptoms, we may have reported a higher incidence of side-effects; however, our feeling is that we identified those subjects who have clinically important side-effects. A second point that could be raised is our use of a very low concentration of bupivacaine. This solution produces effective pain relief with negligible motor blockade in the majority of patients and has been the standard at our institution for 15 yr.[5] The concentration of bupivacaine does influence the frequency of breakthrough pain, but the use of a solution with a higher concentration of bupivacaine results in a small reduction, not an elimination, of breakthrough pain.[11] Whether intrathecal morphine would have a similar magnitude of effect when combined with epidural solutions containing a higher concentration of bupivacaine cannot be gleaned from our

study. Similarly, the ideal dose of intrathecal morphine to use in labour cannot be identified from our results; a formal dose–response study is needed. It would also be interesting to compare the use of intrathecal morphine and ultra-low dose bupivacaine with a solution containing a higher concentration of bupivacaine, with special attention paid to the magnitude of side-effects. Finally, although we did measure pain scores and analgesic usage in the postpartum period, this was not a primary outcome for our study. We did not evaluate the degree of perineal trauma in the subjects and, therefore, cannot ensure that both groups were equivalent. Further work is needed to document this effect.

In conclusion, a small dose of intrathecal morphine added to a spinal injection of fentanyl and bupivacaine appeared to increase the effectiveness of subsequent epidural labour analgesia. Although we found a small increase in the incidence of nausea, this may be an effective way of treating women at risk for breakthrough pain.

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