Anesthesiology
2000; 93:418–21

Subarachnoid Meperidine (Pethidine) Causes Significant Nausea and Vomiting during Labor

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Background: **The combined spinal–epidural (CSE) technique using bupivicaine–fentanyl has become an established method of pain control during parturition. One limitation is the relatively short duration of effective analgesia produced by bupivicaine–fentanyl. In contrast, subarachnoid meperidine has been shown to provide a long duration of anesthesia in nonobstetric patients. Therefore, the authors tested the hypothesis that subarachnoid meperidine produces a significant increase in the duration of analgesia compared with bupivicaine–fentanyl.**

Methods: **Based on a power analysis of preliminary data, the authors intended to recruit 90 patients for the study, randomized to three groups: 2.5 mg bupivicaine–25 μg fentanyl, 15 mg meperidine, or 25 mg meperidine. However, after enrolling 34 patients, the study was discontinued because of a significant increase in nausea or vomiting in the study patients.**

Results: **Nausea or vomiting was substantially increased in both meperidine groups compared with the bupivicaine–fentanyl group: 16 with nausea or vomiting in the meperidine groups (n = 21), compared with 1 in the bupivicaine–fentanyl group (n = 11), P = 0.0011. The mean duration of analgesia provided by 25 mg meperidine was 126 ± 51 min, compared with 98 ± 29 min for bupivicaine–fentanyl and 90 ± 67 min for 15 mg meperidine. These data were not significant (*P* = 0.27).**

Conclusions: **Although intrathecal meperidine could potentially prolong subarachnoid analgesia during labor, its use was associated with a significant incidence of nausea or vomiting. These data do not support the use of subarachnoid meperidine in doses of 15 or 25 mg for labor analgesia. (Key words: Labor analgesia; spinal anesthesia.)**

THE combined spinal–epidural (CSE) technique is used in many institutions to provide labor analgesia. CSE anesthesia can offer advantages *versus* epidural analgesia alone, including rapid onset of analgesia and reduced motor block, resulting in greater ambulation.[1,2] A major limitation of the CSE technique is that the duration of analgesia provided by the spinal dose is only approximately 60–90 min.[3]

Meperidine is a synthetic opioid of intermediate lipid with opioid and local anesthetic properties.[3–5] It has been used extensively in spinal anesthesia for urologic and orthopedic procedures[6,7] and is used intramuscularly for labor analgesia in doses up to 100 mg.[8,9] Studies of its use in labor *via* the subarachnoid route have been limited to a dose of 10 mg or dosing by continuous infusion by microcatheter.[10–12] These studies indicate the drug to be effective during labor; however, the dose used conferred no advantage in duration or quality of analgesia compared with bupivicaine–fentanyl.

Therefore, we evaluated the effects of meperidine (15 or 25 mg) used during early labor on duration of analgesia provided by a single subarachnoid dose. In addition, we compared meperidine with our standard CSE technique of bupivicaine–fentanyl.

Materials and Methods

The Institutional Review Board at Duke University Medical Center approved all portions of the study de-

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Received from the Division of Women's Anesthesia, the Departments of Anesthesiology and Biostatistics, Duke University Medical Center, Durham, North Carolina. Submitted for publication December 15, 1999. Accepted for publication March 21, 2000. Supported by the Division of Women's Research Anesthesia Research Fund, Duke University Medical Center, Durham, North Carolina. Presented in part at the Society for Obstetric Anesthesiology and Perinatology 30th Annual Meeting, Vancouver, British Columbia, Canada, April 29–May 2, 1998.

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sign. Initially, a pilot study was performed in which six patients received meperidine (three at 15 mg, three at 25 mg) as part of a CSE technique. Subsequent power analysis indicated that 30 patients in each group ([1] bupivacaine 2.5 mg + fentanyl 25 μg, [2] meperidine 15 mg, or [3] meperidine 25 mg] would be necessary to provide 80% power to detect a 50% prolongation of analgesia. Healthy (American Society of Anesthesiologists physical status I or II) nulliparous women with singleton vertex pregnancies, cervical dilation less than or equal to 6 cm, and in spontaneous labor were eligible for enrollment in the study. Exclusion criteria included the following: preterm labor; cervical dilation greater than 6 cm; hypertension; bleeding diathesis; asthma or anticipated difficult intubation. After obtaining written informed consent, patients were randomized to one of the three arms of the study. To ensure a double-blind protocol, coded syringes were prepared by the research pharmacy.

Baseline vital signs were recorded before administration of the CSE anesthetic (blood pressure, heart rate, and fetal heart rate), whereas fluid loading occurred before commencement of the CSE anesthetic. In addition, pain visual analog scores (VAS), grade of motor block (Bromage scale),[13] nausea or vomiting, and itching were noted before CSE anesthetic administration. These measurements were continued at 3, 5, 6, 9, 12, 15, 18, 21, and 30 min after subarachnoid drug administration. Specifically, nausea and vomiting were noted by asking parturients about nausea at each of the time points. Nausea was not graded, but emetic episodes were counted. APGAR scores at 1 and 5 min were also recorded. Duration of analgesia, our primary end point, was defined as time from administration of subarachnoid drug until request for additional pain relief by the parturient. Effective spinal administration of the drug was confirmed by a rapid and sustained reduction in visual analog pain scores. Subsequent labor analgesia was provided by activation of the epidural catheter at the request of the parturient.

Statistical Analysis

Statistical analysis was performed using SAS Institute software (Cary, NC). Significant differences in duration of drug effect was tested by use of Kruskal–Wallis analysis when comparing three drugs and by use of the two-sample Wilcoxon rank sum test when comparing two drugs. Categorical data were analyzed with use of a two-sided Fisher exact test. All statistical tests were two-tailed and, because three comparisons were made, the critical α was set at $P = 0.017$. To preserve power to test main end points, the majority of measurements was not tested for statistical difference between treatment groups. Data are presented as the mean ± SD for continuous data or median (range) for ordinal or categorical data.

Results

The study was discontinued after enrollment of 34 patients after concern among investigators, patients, and nurses about the high incidence of nausea or vomiting evidenced in participating parturients. As a result, the study was unblinded and data analyzed. Two subjects were withdrawn from the study after intravenous butorphanol was administered in the time between informed consent and CSE placement. As a result, 32 patients were enrolled for analysis. Patient characteristics were similar between groups.

Nausea or vomiting were significantly increased in both of the meperidine groups, compared with the bupivicaine–fentanyl group: 16 of 21 with nausea or vomiting in the meperidine group, compared with 1 of 11 in the bupivicaine–fentanyl group, $P = 0.0011$, table 1. Itch was present in all groups of patients: 8 of 11 with itch in the bupivicaine–fentanyl group, compared with 6 of 21 in the meperidine groups. Duration of analgesia was 126 ± 51 min in the 25-mg meperidine group, compared with 90 ± 67 min in the 15-mg meperidine group and 98 ± 29 min in the bupivicaine–fentanyl

Table 1. Summary of Principle Data

Parameter	Bup/Fent (n = 11)	Mep 15 (n = 10)	Mep 25 (n = 11)
Duration of analgesia (min)	98 ± 29	90 ± 67	126 ± 51
N/V	1/11	9/10*	8/11*
Itch	9/11	3/10	3/11
Time to delivery (min)	268 ± 164	320 ± 208	339 ± 222
Motor block at 30 min (Bromage scale)†	0 (0–1)	0 (0–1)	0 (0–1)
VAS pain score at 15 min	0.2 ± 0.2	1.8 ± 0.53	0.4 ± 1
Apgar score at 1 min†	8 (7–9)	8 (7–9)	8 (7–9)
Apgar score at 5 min†	9 (8–9)	9 (8–9)	9 (8–9)

Time expressed in minutes. Data expressed as mean ± SD for continuous data.

* $P = 0.0011$.

† Data expressed as median (range) for ordinary data.

Bup/Fent = bupivicaine/fentanyl; Mep = meperidine; N/V = nausea/vomiting; VAS = Visual Analog Scale.

group. This difference was not statistically significant ($P = 0.15$).

Systolic blood pressure (baseline range, 129 ± 13–133 ± 14 mmHg) decreased in all groups, with a nadir of 110 ± 14 mmHg in the 15-mg meperidine group, 118 ± 13 mmHg in the 25-mg meperidine group, and 121 ± 12 mmHg in the bupivicaine–fentanyl group. The decrease was not not significant (fig. 1). In addition, three patients in each of the meperidine groups required intervention with use of ephedrine bolus because of a greater than 20% decrease in systolic blood pressure, whereas no patients in the bupivicaine–fentanyl group required such intervention. There was no difference between groups with respect to motor block or Apgar scores.

Discussion

The first large scale report of the use of meperidine in labor (intramuscular) was published in 1947.[8] However, there is a paucity of studies that relate the use of subarachnoid meperidine in labor.[10,11] Previous studies that investigated subarachnoid meperidine (10 mg bolus) have not shown any significant advantages in duration of

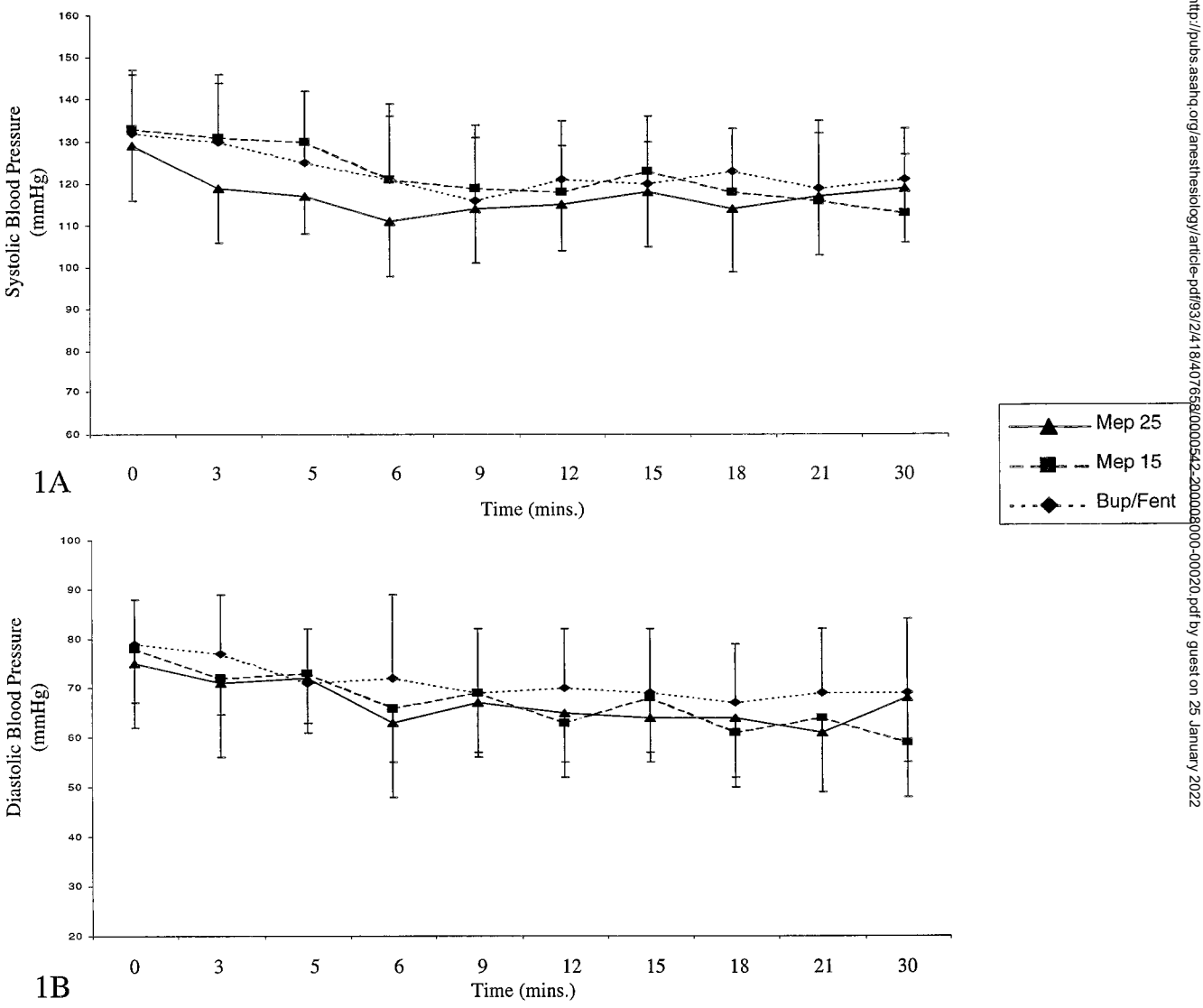

Fig. 1. (*A*) Graph of systolic blood pressure *versus* time in minutes after subarachnoid drug administration. Legend as below. Data are expressed as mean ± SD. (*B*) Graph of diastolic blood pressure *versus* time in minutes after subarachnoid drug administration. Data are expressed as mean ± SD.

quality of analgesia *versus* conventional subarachnoid drugs in labor.[10,11] However, much larger doses have been safely administered in nonobstetric practice.[6,7] In addition, the dose of meperidine used *via* subarachnoid route for elective cesarean section has been reported to be as high as 1 mg/kg.[14,15]

The study was primarily designed to evaluate the effects of different doses of meperidine, primarily on duration of labor analgesia. In addition, we evaluated potential side effects: nausea or vomiting and hypotension. As a result of these side effects, our study was discontinued prematurely. Reports to the investigators from patients and staff indicated that the frequency of nausea or vomiting was occurring at much higher rates in those patients enrolled in the study than in those parturients on the ward. The study was suspended, and subsequent analysis indicated that greater than 75% of the patients in each of the meperidine groups reported nausea or vomiting, compared with 9% in the bupivicaine–fentanyl group. Therefore we discontinued the study prematurely because of ethical considerations.

Two previous studies evaluated the effect of subarachnoid meperidine (10 mg) during labor[10,11] but, although they have reported higher incidence of nausea or vomiting in the meperidine groups compared with the bupivicaine–fentanyl group, they did not discuss this as clinically significant. In the nonobstetric population, nausea or vomiting after subarachnoid meperidine has been reported between 0 and 55%.[6,7,14] In our study, the incidence of nausea or vomiting was extremely high and, in most cases, occurred as emetic episodes.

Duration of time to request of subsequent analgesia was not significantly different among groups, though this came as no surprise because of our pilot data, which indicated that a sample size of 90 was necessary for 80% power to detect a difference in duration of effective analgesia. However, the data suggest a trend toward prolongation of effective analgesia in the 25-mg meperidine group (table 1). Nevertheless, any benefit from prolongation of analgesia would have to be balanced against meperidine side-effect profile.

In conclusion, we demonstrated that subarachnoid meperidine, in doses of 15 or 25 mg, induces significant nausea or vomiting during labor. Therefore, we suggest that subarachnoid meperidine should not be administered for labor analgesia.

The authors thank Emily Heath and Mary Carnell for their tireless secretarial assistance.

References

1. Collis RE, Davies DWL, Aveling W: Randomised comparison of combined spinal-epidural and standard epidural analgesia in labour. Lancet 1995; 345:1413–6

2. Collis RE, Baxandall ML, Srikantharajah ID, Edge G, Kadim MY, Morgan BM: Combined spinal epidural (CSE) analgesia: Technique, management and outcome of 300 mothers. Int J Obst Anesth 1994; 3:75–81

3. Norris MC, Grieco WM, Borkowski M, Leighton BL, Arkoosh VA, Huffnagle HJ, Huffnagle S: Complications of labor analgesia: Epidural versus combined spinal epidural techniques. Anesth Analg 1994; 79: 529–37

4. Ngan Kee WD: Intrathecal Pethidine: Pharmacology and clinical applications. Anaesth Intensive Care 1998; 26:137–46

5. Cousins MJ, Mather LE: Intrathecal and epidural administration of opioids. ANESTHESIOLOGY 1984; 61:276–310

6. Kavuri S, Robalino Y, Janardhan K, Shevde K: Low-dose intrathecal meperidine for lower limb orthopaedic surgery. Can J Anaesth 1990; 37:947–8

7. Patel D, Janardhan Y, Merai B, Robalino J, Shevde K: Comparison of intrathecal meperidine and lidocaine in endoscopic urological procedures. Can J Anaesth 1990; 37:567–70

8. Barnes J: Pethidine in labour: Results in 500 cases. BMJ 1947; 5:437–42

9. Robinson JO, Rosen M, Evans JM, Revill SI, David H, Rees GA: Self-administered intravenous and intramuscular pethidine: A controlled trial in labour. Anaesthesia 1980; 35:763–70

10. Honet JE, Arkoosh VA, Norris MC, Huffnagle HJ, Silverman NS, Leighton BL: Comparison among intrathecal fentanyl, meperidine, and sufentanil for labor analgesia. Anesth Analg 1992; 75:734–9

11. Swayze CR, Skerman JH, Walker EB, Sholte FG: Efficacy of subarachnoid meperidine for labor analgesia. Reg Anesth 1991; 16: 309–13

12. Johnson MD, Hurley RJ, Gilbertson LI, Datta S: Continuos microcatheter spinal anesthesia with subarachnoid meperidine for labor and delivery. Anesth Analg 1990; 70:658–61

13. Bromage PR: A comparison of the hydrochloride and carbon dioxide salts of lignocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand 1965; 16:55–69

14. Kafle SK: Intrathecal meperidine for elective cesarean section: A comparison with lidocaine. Can J Anaesth 1993; 40:718–21

15. Nguyen Thi TV, Orliaguet G, Ngu TH, Bonnet F: Spinal anaesthesia with meperidine as the sole agent for cesarean delivery. Reg Anesth 1994; 19:386–9