

Intravenous Butorphanol, Meperidine, and Their Combination Relieve Pain and Distress in Women in Labor

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Background: Systemic opioids are commonly administered during labor, but their efficacy has been recently questioned. In addition, laboratory and clinical studies provide a strong rationale for combining μ - and κ -opioid receptor agonists for analgesia. The authors therefore studied, using validated intensity and affective scales and definitions of effective pain relief, the efficacy of intravenous meperidine, butorphanol, and their combination for labor analgesia.

Methods: Healthy women with singleton term pregnancy requesting analgesia during active labor were studied. Women were randomly assigned to receive 50 mg meperidine, 1 mg butorphanol, or 25 mg meperidine plus 0.5 mg butorphanol ($n = 15/\text{group}$). Pain intensity was assessed using a 0-10 numerical rating scale, and affective magnitude was assessed using a ratiometric descriptive scale before drug administration and between the sixth and seventh uterine contractions after drug administration.

Results: All three treatments reduced pain intensity equally. Butorphanol alone did not reduce pain affective magnitude, whereas the other treatments did. There was a significant correlation between reduction in pain intensity and affective magnitude in all groups, with greater reductions in affective magnitude than intensity. Overall, 29% of women exhibited clinically meaningful pain relief, with no difference among groups. Groups did not differ in incidence of opioid-induced adverse effects.

Conclusions: These doses of meperidine and butorphanol do reduce pain intensity and affective magnitude, although a minority of patients achieve meaningful pain relief as defined in multiple patient populations, including laboring women. Combination of these drugs did not improve their therapeutic benefit.

OPIOIDS have been administered to laboring women for analgesia for centuries.¹ Despite consistent demonstration of opioid-induced adverse events in mother, fetus, and neonate, analgesic efficacy with systemic opioids in labor has been less obvious. A recent trial of 0.15 mg/kg morphine and 1.5 mg/kg meperidine showed sedation but no reduction on pain intensity in laboring women, and the authors concluded that “. . . it seems unethical and medically incorrect to meet the parturient’s request

for analgesia by giving her heavy sedation” and “. . . it can be concluded that systemic opioids could be excluded for this indication.”² Similarly, a recent systematic review of systemic opioids for labor analgesia concluded that meperidine and other opioids produced clear adverse events but dubious analgesia and that studies relying on patient reports of pain at the time of drug administration, rather than on observer assessments or recall many hours or days later, were needed.³

Pain is a sensory-emotional experience, and most previous studies of systemic opioids in labor, including the recent study showing lack of efficacy, assessed only the intensity of pain. This is despite the existence of well-validated ratiometric measures of affective magnitude of pain.^{4,5} It is often said that opioids reduce the affective response to pain without altering the perceived intensity, although the converse has been observed in volunteers with experimental pain who received systemic opioids.⁶ One purpose of the current study was to determine the effect of systemic opioids on pain intensity and affective magnitude and whether they altered one of these aspects of pain more than the other.

In addition, there has been considerable interest in determining how much pain must be reduced to be meaningful to patients. One can use the calculated percent reduction in pain report using 0-10 verbal or visual analog scores for this purpose, because this calculated value correlates strongly with the patient’s estimate of percent reduction in pain with analgesics.⁷ Several recent studies have defined a percent reduction in pain report of 30-45% as being clinically meaningful to patients.⁸⁻¹⁰ In the acute pain setting, a 35% reduction in pain of moderate intensity (4-6 in a 0-10 scale) or 45% reduction in pain of severe intensity (7-10 in a 0-10 scale) was considered by patients to represent much improvement in their pain.¹⁰ In addition, a review of 311 patients receiving epidural analgesia has further defined the meaning of pain in this setting by determining the proportion of patients who request additional analgesia at any point on the 0-10 pain scale.¹¹ A second purpose of the current study was to determine what proportion of patients receiving systemic opioids for labor analgesia met these defined criteria for meaningful pain in terms of percent reduction in pain intensity and in terms of absolute pain intensity. The study was powered to observe a 30% reduction in pain intensity, which is the smallest reduction proposed to represent meaningful pain relief.⁸

Finally, κ -opioid receptor agonists may be more effective in women than in men,¹² reduce responses to uterine cervical distension in animals,¹³ and can act syner-

This article is featured in “This Month in Anesthesiology.”
Please see this issue of ANESTHESIOLOGY, page 5A.

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Received from the Section of Obstetric Anesthesia, Wake Forest University School of Medicine, Winston-Salem, North Carolina. Submitted for publication September 30, 2004. Accepted for publication January 5, 2005. Supported in part by grant No. NS41386 from the National Institutes of Health, Bethesda, Maryland.

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gistically in some settings with μ -opioid receptor agonists.¹⁴ A final purpose was to test whether a combination of meperidine and the κ -opioid receptor-preferring agonist butorphanol was more effective than either drug alone to reduce labor pain. The study was powered to observe a difference among treatment groups as small as 1.4 on a 0-10 verbal pain intensity score.

Materials and Methods

Patients

The study was approved by the Forsyth Memorial Hospital Institutional Review Board for Human Studies (Winston-Salem, North Carolina), and all patients provided written informed consent. Forty-five healthy women who had an American Society of Anesthesiologists physical status of I or II, had an uncomplicated singleton pregnancy, and requested systemic analgesia were included. Patients with allergies to meperidine or butorphanol, those having received intravenous opioids at any time during their hospital stay, and those taking oral opioids chronically were excluded. Patients with a diagnosis of fetal stress by heart rate monitoring were also excluded.

Both multiparous and nulliparous women as well as spontaneous and oxytocin-augmented labors were included, and the study was powered based on the increased variability in pain reported by these populations. If any of the following conditions occurred after study drug administration and before the seventh contraction after study drug administration, the data from the patient was dropped from analysis, and their randomization was reentered for another patient: artificial rupture of membranes, change or commencement of oxytocin infusion, or request for epidural analgesia. In addition, data from patients who reached complete cervical dilatation within 1 h of study drug administration were dropped from analysis, and randomization was reentered for another patient.

Prestudy Measures

Patient height, weight, gravidity, parity, gestation, cervical dilatation, concurrent medical conditions, medications, admitting blood pressure, heart rate, and fetal heart rate were recorded. Level of sedation and nausea were assessed just before drug administration using a 0-10 verbal scale, with 0 representing none and 10 representing the maximum possible. Pain intensity was measured just before drug administration by asking the woman to rate the average pain of her last several contractions using a 0-10 verbal scale. In addition, women were asked to choose a word representing pain affective magnitude from a list. This list has been extensively validated in large patient populations with acute and

chronic pain, and the words can be assigned numeric values that behave in a ratiometric manner with changing levels of pain and analgesia.^{4-6,15,16}

Drug Administration

Patients were randomly assigned, using a computer-generated, balanced design, to receive 1 mg butorphanol, 50 mg meperidine, or the two in combination (0.5 mg butorphanol plus 25 mg meperidine) as an intravenous bolus. The drug was prepared by an anesthesiologist not involved with the treatment of the patient or obtaining study measures. The study was double blind. Patients could request epidural analgesia at any time, and additional intravenous opioid analgesic could be ordered at the obstetrician's discretion 30 min after study drug administration.

Study Measures

Continuous fetal heart rate and uterine contraction monitoring was in place. Between the sixth and the seventh contractions after receiving study drug, the patient was asked to rate the average intensity of the past two contractions, using a 0-10 verbal scale. She was also asked to choose from the pain affective magnitude word list to describe the pain of these past two contractions. In addition, sedation and nausea scores were obtained using a 0-10 verbal scale.

Statistics

Data are presented as mean \pm SEM or median as appropriate. Word descriptors were converted to magnitude (arbitrary units) as previously validated in acute and chronic pain settings.^{4,5} Demographic and labor characteristics were compared across groups by one-way analysis of variance or Kruskal-Wallis test. The proportion of subjects with abnormal fetal heart rate tracings after drug treatment was compared across groups by chi-square test. Pain (intensity and affective magnitude), nausea, and sedation were analyzed by three approaches. First, differences among groups in these variables before and after treatment and the change from before to after were assessed by one-way analysis of variance. Second, correlation between pain intensity and pain affective magnitude or between these variables and sedation was assessed by linear regression. Finally, the proportions of patients with baseline pain scores less than 7 who achieved a 35% reduction in pain intensity score and those with baseline pain scores greater than 7 who achieved a 45% reduction in pain intensity score were calculated, because this has been proposed to represent clinically meaningful pain relief in those with acute pain.¹⁰ $P < 0.05$ was considered significant.

Results

All subjects completed the protocol, and there were no emergent deliveries during the study period. Groups

Table 1. Demographic and Labor Characteristics

Group	Age, yr	Height, cm	Weight, kg	G/P	Proportion Primiparous, %	Gestation, weeks	Cervical Dilatation, cm	FHR Changes	Apgar 1	Apgar 5
Butorphanol	27	64	81	1/0	53	40	3	5	8	9
SEM	1.8	0.8	4.1			0.3				
Meperidine	27	64	93	2/1	33	40	3	3	8	9
SEM	2.1	0.7	5.3			0.3				
Both	26	63	81	2/0	33	40	3	5	8	9
SEM	1.7	0.6	5.0			0.3				

Values are presented as mean \pm SEM or median values for 15 subjects.

FHR = fetal heart rate; G/P = median gravidity/parity.

did not differ in demographic or labor characteristics (table 1).

Pain intensity was 7.5 ± 0.3 before drug treatment. The time from drug injection to pain assessment was similar among groups, being 14 ± 1 , 14 ± 0.7 , and 15 ± 1 min for the butorphanol, meperidine, and combination groups, respectively. Butorphanol, meperidine, and their combination reduced pain intensity similarly by an average of 25–35% (fig. 1, left). There was no difference among groups in the amount of change in pain intensity after drug treatment, and the largest difference in reduction in pain from treatment was 1.0 between the butorphanol and combination groups. Pain affective magnitude was 15 ± 1.0 before drug treatment, corresponding to between descriptors of *dreadful* and *horrible*. Meperidine and the combination but not butorphanol significantly reduced pain affective magnitude to 7.4 ± 1.2 , corresponding to between descriptors of *distressing* and *oppressive* (fig. 1, right). Groups did not differ in post-drug pain affective magnitude score, and the largest difference in reduction among groups was 4.8 between the meperidine and butorphanol groups.

Overall in the study population, there was a significant linear relation between change in pain intensity and change in pain affective magnitude with drug treatment (fig. 2; $r = 0.60$). In separate analysis of study groups, this relation was significant for all groups (fig. 2).

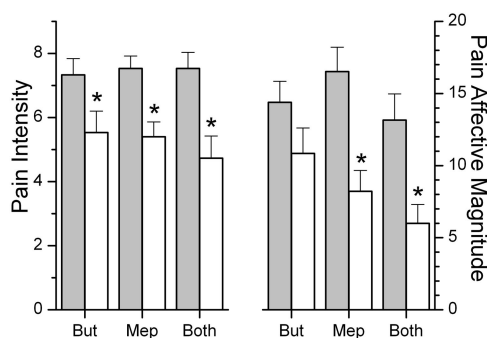


Fig. 1. Pain intensity (0–10 verbal score; left) or pain affective magnitude (0–30.2 arbitrary units; right) before and after intravenous administration of butorphanol (But), meperidine (Mep), or their combination (Both). Each bar represents the mean \pm SEM of 15 subjects. * $P < 0.05$ compared with predrug value within groups. Groups do not differ before or after drug administration.

slopes of the regression lines for percent change in pain affective magnitude and pain intensity were all significantly less than 1, ranging from 0.34 ± 0.14 in the butorphanol group to 0.56 ± 0.20 in the combination group, indicating a greater ratiometric reduction in affective magnitude than intensity. We hypothesized that there may be a relation between sedation and affective verbal pain descriptors. However, there was no significant correlation between level of sedation after drug and change in either pain affective magnitude or pain intensity (data not shown).

Sedation increased after all drug treatments to a similar degree (fig. 3, left). Nausea was unaffected by drug treatment (fig. 3, right). There was no difference among groups in the amount of change in sedation after drug treatment. New fetal heart rate abnormalities were observed in five, three, and five subjects in the butorpha-

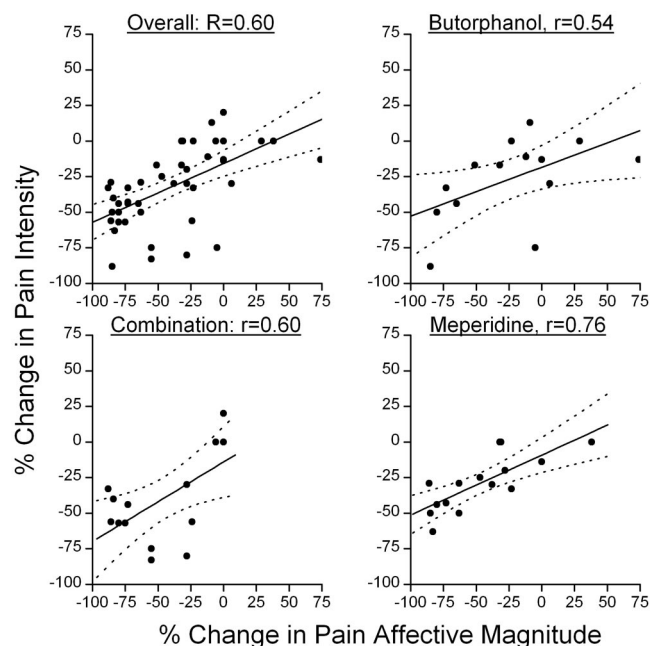


Fig. 2. Linear regression analysis of the relation between change in pain intensity and change in pain affective magnitude after intravenous drug treatment for all groups (upper left), butorphanol (upper right), meperidine (lower right), or the combination (lower left). Significant correlations were present in all groups ($P < 0.01$). Regression lines are solid and 95% confidence limits are dotted, with r value indicated.

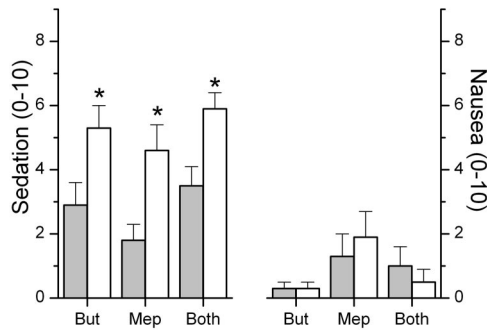


Fig. 3. Sedation (0–10 verbal score; *left*) or nausea (0–10 verbal score; *right*) before and after intravenous administration of butorphanol (But), meperidine (Mep), or their combination (Both). Each bar represents the mean \pm SEM of 15 subjects. * $P < 0.05$ compared with predrug value.

nol, meperidine, and combination groups, respectively ($P =$ not significant). These were decreased variability, with the exception of transient sinusoidal heart rate pattern in two individuals (one in the meperidine group and one in the combination group) and isolated decelerations (one in the butorphanol group and one in the meperidine group). Neonates appeared healthy, with only two Apgar scores less than 8 at 1 min (one score of 6 in the butorphanol group and one score of 7 in the meperidine group), and all neonates had Apgar scores greater than 7 at 5 min.

Discussion

Whether laboring women should be provided analgesia has engendered controversy for centuries in Western society, and the recent study demonstrating sedation but no reduction in pain score from intravenous morphine or meperidine has led to the proposal that it is unethical to provide ineffective treatment for pain in this setting, given the well-documented adverse events associated with opioids.² It is within this context that the current study was performed. In contrast to that report, we observed clear reductions in both sensory and emotional dimensions of pain from meperidine and butorphanol.

A few methodologic differences might explain the discrepancy between these studies. First, the study of Olofsson *et al.*² included only nulliparous women in spontaneous labor with contractions of at least 60 s in duration and a rate of at least 3 beats/10 min. Pain scores in that study averaged approximately 8.3 before drug administration, which was numerically greater than in the current study, and it is conceivable that opioids were inactive in this more homogeneous group with greater pain scores. Separate analyses of only women with pain scores greater than 6 and only nulliparous women also showed significant reductions in pain intensity and affective magnitude in the current study (data not shown), making this explanation unlikely. Study drug was also administered differently in the two studies. In our study, the dose was fixed (50 mg meperi-

dine) and administered as a single bolus, whereas in the Swedish study, the dose was based on weight (approximately 36 mg) and was administered repeatedly, every three contractions (approximately every 10 min), for a cumulative dose of 108 mg.

Publication of the study of Olofsson *et al.* led for a call for a placebo-controlled trial to determine whether meperidine truly did provide analgesia during labor.¹⁷ We believed that meperidine truly did provide analgesia during labor and were therefore not in a position of equipoise that would ethically justify a placebo-controlled trial. While this manuscript was being prepared, however, just such a placebo-controlled trial appeared in the literature.¹⁸ The authors observed no analgesia from placebo (pain intensity score 7.3 before and 7.8 after) but a significant reduction in pain intensity score, from 7.3 to 5.4, 30 min after intramuscular 100 mg meperidine. This reduction in pain intensity is virtually identical to that observed in the current study (from 7.5 to 5.4), although we used a smaller dose of meperidine than in that study and assessed pain at 15 min rather than 30 min after administration, in accord with the different route of administration (intravenous) in the current study. We therefore conclude that the reduction in pain observed in the current study is unlikely to be due to a placebo response and that these drugs truly do reduce pain in laboring women.

Is this statistically significant reduction in pain also clinically meaningful? In the chronic pain setting, a review of data from 2,700 patients in analgesic trials concluded that a reduction in 2 points on a 0–10 numerical pain intensity score or 30% reduction from baseline on this scale represented a clinically meaningful endpoint as determined by the likelihood that patients would consider their state much improved.⁸ In one postoperative study of 123 patients, a reduction of 0–10 numerical

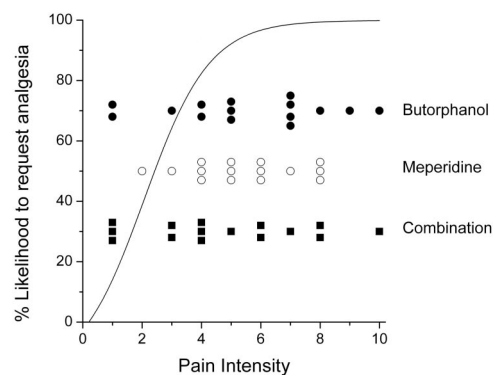


Fig. 4. Pain scores after drug treatment in the context of meaningful analgesia. Individual pain scores for each group are plotted for women receiving butorphanol (closed circles), meperidine (open circles), or their combination (closed squares). The line represents the Boltzmann fit of data from Beilin *et al.*¹¹ indicating the likelihood that women will request additional analgesia as a function of level of pain. A minority of pain scores after drug administration fall in a low enough range where women would not normally request additional analgesia.

pain intensity score of 15% was rated by patients as little relief, whereas a reduction of 30–33% was rated as some relief, and these authors concluded that a 33% reduction was considered clinically meaningful.⁹ A second study of 700 postoperative patients also defined clinically meaningful relief as when the patients stated that their pain was much improved, and these authors found that a greater reduction in 0–10 numerical pain intensity score (45%) was required for patients in severe pain than for patients in moderate pain (35% reduction) to meet this criterion.¹⁰

Based on these studies, we conclude that relatively few women in the current study had large enough reductions in pain report to likely represent clinically meaningful pain relief. With a fixed definition of 35% reduction in pain intensity score, 27, 33, and 53% of women receiving butorphanol, meperidine, and their combination, respectively, met this criterion for meaningful relief. With a definition of 35% reduction for those with moderate baseline pain and 45% reduction for those with severe pain, the latter representing the majority of our subjects, these drugs were yet less effective, with only 20, 20, and 47% of women receiving butorphanol, meperidine, and their combination, respectively, meeting this criterion for meaningful relief. A weakness of the current study is that we did not directly ask patients to rate their assessment of the adequacy of pain relief. Other data, however, support our conclusion that a minority of patients had meaningful relief. In a review of 311 women receiving additional medication for labor analgesia, Beilin *et al.*¹¹ determined the likelihood of requesting additional analgesia as a function of 0–10 numerical pain intensity score. This sigmoidal relation is plotted in figure 4; it indicates that 80% of women with a pain intensity score of 4 would request additional analgesia, and essentially 100% of women with scores greater than 4 would request additional analgesia. The pain scores obtained after drug administration in our treatment groups are shown overlying this relation (fig. 4). Using a cutoff of pain intensity score less than 4 as meaningful pain relief, only 20, 13, and 33% of women receiving butorphanol, meperidine, and their combination, respectively, met this criterion for meaningful relief.

It has been suggested that κ -opioid receptor agonists are more effective than μ -opioid receptor agonists in women than in men,¹² and κ -opioid receptor agonists, unlike μ -opioid receptor agonists, are effective in reducing responses to acute uterine cervical distension in animals by a peripheral mechanism not reduced by estrogen administration.^{13,19} However, we did not observe better analgesia in women receiving butorphanol, which exhibits κ -opioid receptor activity, than in women receiving meperidine. Dose responses were not performed, and it is conceivable that some separation be-

tween these agents could exist at certain doses, but the similar effects on pain and adverse effects by these two agents in the commonly used clinical range suggest that this is unlikely. Finally, we did not observe an increase in analgesic efficacy with the combination of meperidine and butorphanol. The study was not adequately powered to observe a subtle improvement with the combination, but because the incidence of adverse effects was clearly the same with the combination as with either agent alone, it is unlikely that this combination would offer significant advantages over either drug alone.

In summary, intravenous butorphanol, 1 mg, and meperidine, 50 mg, reduce pain intensity and pain affective magnitude by a statistically significant amount 15 min after injection in women with moderate to severe labor pain. We conclude that it is ethically appropriate to administer systemic opioids to women requesting analgesia for labor pain. There was no difference regarding drug efficacy or maternal adverse effects between these agents alone or when combining half the dose of each, arguing against selection of one drug over the other or combining them based on improved efficacy. Whether larger doses would produce greater analgesia was not addressed in this study, but the doses studied produced maternal sedation, and concerns over maternal and fetal adverse effects clearly limit dosing of opioids in this setting. Finally, a minority of women receiving these drugs achieved pain intensity reductions large enough to meet criteria for meaningful pain relief, suggesting that these drugs at these doses are not ideal for treatment of pain in this setting, and other approaches, including new drugs, are necessary for reliable pain relief.

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