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Differences in Systemic Opioid Use Do Not Explain Increased Fever Incidence in Parturients Receiving Epidural Analgesia

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Background: **It has been hypothesized that an increased incidence of fever in patients receiving epidural analgesia might result not from epidural *per se*, but rather from the antipyretic effect of opioids preferentially administered to women in the no-epidural group. If this were the case, then one would expect the incidence of fever in parturients who did not receive systemic opioids to be independent of whether they received epidural analgesia.**

Methods: **Using a cohort study design, the authors evaluated the records of 1,233 nulliparous patients whose labor analgesia was managed with (1) no medication (N = 170); (2) 10 mg intravenous systemic nalbuphine plus 10 mg intramuscular every 3 to 4 h as required (N = 327); (3) epidural analgesia with continuous infusion of 0.125% bupivacaine with 2 μg/ml fentanyl (N = 278); or (4) patients who received both systemic nalbuphine and epidural analgesia (N = 458). Fever was diagnosed if the maximum temperature during labor exceeded 100.4°F (38°C).**

Results: **The incidence of fever did not differ according to nalbuphine administration for women not receiving epidural analgesia (1% no nalbuphine, 0.3% with nalbuphine, $P = 0.27$) or for women receiving epidural analgesia (17% no nalbuphine, 17% with nalbuphine, $P = 1.0$). However, the incidence of fever differed significantly between patients who received no analgesia as compared to those who received epidural analgesia alone (1% *vs.* 17%, $P = 10^{-6}$). Controlling for confounding did not alter these associations.**

Conclusions: **Our findings suggest that an antipyretic effect of nalbuphine in patients who do not receive an epidural does not explain the greater incidence of fever observed in women who receive epidural analgesia for labor.**

EPIDURAL analgesia for labor is associated with a significant, time-related increase in both maternal and fetal temperatures.[1,2] Depending upon institution-specific criteria, this may lead to unnecessary administration of antibiotics to parturients[3] and sepsis evaluations for neonates.[4] Although the underlying mechanism is unclear, previous investigators have suggested that the temperature elevation may be related to an epidural-induced increase in the thermoregulatory threshold for heat loss, or to impaired diaphoresis below the level of the epidural block.[5]

Recently, Negishi *et al.*[6] suggested an alternative hypothesis: Temperature elevation commonly accompanies labor, but is selectively suppressed by opioids administered to patients who do not receive epidural analgesia. They demonstrated that intravenous fentanyl but not epidural ropivacaine (with or without epidural fentanyl) decreases the maximum temperature elevation following interleukin 2 administration by 0.6°C. Based on these findings in male volunteers, they concluded that maternal temperature elevations during labor observed in randomized trials are not caused by epidural analgesia but rather that maternal "fever is inhibited by opioid administration in the control subjects" who did not receive epidural analgesia. If this were true, one would expect that the rate of fever in patients who received neither epidural analgesia nor systemic opioids would be similar to that observed in patients receiving epidural analgesia alone since neither of these groups of patients had their fever suppressed by systemic opioids. Furthermore, the rate of fever in patients receiving systemic opioids alone should be less than the rate in parturients who received neither form of analgesia.

To determine whether suppression of fever by systemic opioids could be responsible for the higher rate of fever in parturients receiving epidural analgesia, we performed a secondary analysis of data from our previously published active management of labor trial. This data set includes at least 170 patients from each of four cohorts—(1) no analgesia, (2) systemic opioids only, (3) epidural analgesia only, or (4) both systemic opioids and epidural analgesia—allowing us to determine whether maternal temperature elevations are related to epidural analgesia *per se* or to the fact that some patients who received epidural analgesia did not benefit from the antipyretic effect of systemic opioids.

Methods

The base sample for this study was the 1,934 nulliparous women enrolled in the active management of labor (ACT) trial conducted at Brigham and Women's Hospital from May 1990 through October 1994. Approval for the study was obtained from the Human Research Commit-

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tee of Brigham and Women's Hospital (Boston, Massachusetts), and informed consent was obtained from all participants. Study participants were low-risk, nulliparous women. Women with conditions associated with an increased risk of preterm or cesarean delivery (such as multiple pregnancy, diabetes, cervical incompetence, or pregnancy-induced hypertension) were ineligible. Overall, 64% of eligible women were enrolled. Women enrolling were randomly assigned to have their labor managed either under a protocol of active management of labor or to usual care. The active management of labor protocol specified the criteria for the diagnosis of labor, the timing and dose of oxytocin, and use of one-to-one nursing throughout the course of labor. Epidural analgesia was not part of the trial protocol; it was administered to women in both groups upon request. Active management of labor did not alter the rate of cesarean delivery. Patient outcomes were determined based upon chart review by trained medical record abstractors who were blinded to the current hypothesis. A complete description of the study methodology and results has been published elsewhere.[7]

The current analysis included women from both the active management and usual care groups but was limited to women with singleton, term pregnancies with infants in a cephalic presentation, and the spontaneous onset of labor resulting in liveborn infants (N = 1,303). Women were excluded if they were diabetic (N = 3), if they had a herpes infection (N = 4), if maternal temperature was never recorded (N = 30), or if maternal temperature was elevated (> 99.5°F) at admission (N = 31). Two women were also excluded because the birth weights of their infants were not recorded. After these exclusions, 1,233 women remained. Potential confounding variables examined included length of labor, duration of epidural, birth weight, fetal sex, need for cesarean section, and gestational age, as well as maternal age, race, hypertension, smoking history, and socioeconomic status.

Women in each arm of the study could choose natural childbirth without analgesia, parenteral nalbuphine analgesia, or epidural analgesia for pain relief. Patients who requested systemic analgesia received nalbuphine, 10 mg intravenous plus 10 mg intramuscular, repeated at 3- to 4-h intervals as required. Patients who initially chose no analgesia or systemic opioids had the option of subsequently requesting epidural analgesia.

The technique for epidural insertion was at the discretion of the attending anesthesiologist. Epidural block was initiated using 0.25% bupivacaine (12–16 ml) *via* a lumbar interspace, unless the cervix was at least 8 cm dilated, in which case the initial dose consisted of 0.5% bupivacaine (10–12 ml) because of its more rapid action. After confirming anesthesia of at least T10 level bilaterally, a continuous infusion of 0.125% bupivacaine with 2 μg/ml fentanyl was administered at a rate of 8–10 ml/h. If additional analgesia was required for perineal discomfort or forceps delivery, 6–8 ml chloroprocaine, 3%, was used just before delivery.

All maternal temperatures recorded during labor were abstracted from medical records. Most maternal temperatures were assessed orally. Nineteen percent of temperature measurements were axillary; this fraction did not differ among the treatment groups. Axillary temperatures were increased by 1°F to adjust for the difference in the site of measurement. This correction (1°F = 0.56°C) has been shown to be appropriate in previous studies comparing temperature measurement methods.[8,9] Maternal fever was diagnosed when the maximum intrapartum temperature exceeded 100.4°F (38°C). This temperature was chosen since maternal temperatures this high automatically trigger a neonatal sepsis workup both at our institution and at others.[10] Since patients whose initial temperature exceeded 99.5°F were excluded, this implies a minimum temperature increase of 1°F.

Statistical Analysis

Parturients were classified according to the analgesic agents they received (opioid only, epidural only, both, neither) and the proportion of febrile women determined for each group. The characteristics of the groups were compared using contingency tables (chi-square or Fisher exact test, as appropriate) for categorical variables, and analysis of variance (with *post hoc* Bonferroni-corrected *t* tests when overall significance was present) for continuous variables. Potential confounding factors were controlled using logistic regression analysis. In our initial regression, the analgesic group was modeled as three indicator variables (for patients receiving nalbuphine, epidural, and nalbuphine plus epidural), with the group receiving neither nalbuphine nor epidural serving as the referent group. This allowed us to evaluate each group independently relative to the referent group of patients who received no analgesia. We then performed separate logistic regression analyses to evaluate the effect of opioids on the incidence of fever in parturients who did and did not receive epidural analgesia. This allowed us to assess the effect of nalbuphine separately in patients who did and did not receive epidural analgesia while accounting for potential confounding variables. In each case, odds ratios were calculated from the logistic regression coefficients, and 95% confidence intervals (CIs) were based on the standard errors of those coefficients. $P < 0.05$ indicated significance throughout.

Results

Demographic characteristics of the groups are shown in table 1. Among patients who did not receive nalbuphine, the incidence of fever in those who received

Table 1. Demographic Characteristics of Subjects with Unadjusted Comparisons among the Treatment Groups

	None (N = 170)	Nalbuphine Only (N = 327)	Epidural Only (N = 278)	Both (N = 458)
Fever 100.5°F	2 (1%)	1 (0.3%)	46 (17%)‡	77 (17%)‡
Maternal age < 30	90 (53%)	176 (53%)	145 (52%)	239 (52%)
Maternal race				
White	123 (72%)	246 (75%)	214 (77%)	338 (74%)
Black	17 (10%)	40 (12%)	33 (12%)	60 (13%)
Other	30 (18%)	41 (13%)	30 (11%)	59 (13%)
Premature rupture of membranes	31 (18%)	67 (20%)	50 (18%)	85 (19%)
Maternal hypertension	3 (2%)	9 (3%)	8 (3%)	12 (3%)
Smoker	5 (3%)	14 (4%)	12 (4%)	31 (7%)
Public assistance	10 (6%)	15 (5%)	10 (4%)	19 (4%)
Active management of labor	83 (49%)	195 (60%)*	92 (33%)†	230 (50%)
Temp at admission	98.0 ± 0.8	98.1 ± 0.7	98.1 ± 0.8	98.2 ± 0.7
Birth weight (g)	3,330 (± 438)	3,405 (± 411)	3,433 (± 400)*	3,478 (± 425)†
Gestational age (weeks)	39.9 (± 1.1)	39.9 (± 1.2)	40.2 (± 1.2)*	40.2 (± 1.2)*
Length of labor (h)*	5.1 ± 4.2	7.6 ± 4.2	10.7 ± 4.8‡	11.9 ± 5.2‡
Duration of epidural (h)	NA	NA	6.3 ± 3.6	5.7 ± 3.3

For categorical variables, values are shown as n (%). For continuous variables, values are shown as mean ± SD.

* $P < 0.05$ *versus* patients receiving neither epidural analgesia nor systemic nalbuphine. † $P < 0.005$ *versus* patients receiving neither epidural analgesia nor systemic nalbuphine. ‡ $P < 10^{-6}$ *versus* patients receiving neither epidural analgesia nor systemic nalbuphine.

NA = not applicable.

epidural was 46/278 (17%), while the incidence of fever in those who did not receive epidural was 2/170 (1%, $P = 10^{-6}$). Even after adjusting for potentially confounding factors, such as length of labor, birth weight, initial temperature, and active management of labor, the adjusted odds ratio for fever in patients receiving epidural but no opioids was 8.14 (95% CI = 1.82–36) compared to a referent group receiving neither epidural nor systemic opioid analgesia. In contrast, the incidence of fever among patients receiving nalbuphine (but no epidural) was 1/327 (0.3%, $P = 0.27$ *vs.* patients receiving neither nalbuphine nor epidural analgesia). In patients who received both epidural analgesia and systemic nalbuphine, the incidence of fever (77/458, 17%) did not differ from that in patients who received epidural analgesia alone (17%, $P = 1.0$). Interestingly, only one patient who did not receive epidural analgesia developed a temperature above 101.5°F; in contrast, 14 patients (5.0%) who received epidural analgesia but no nalbuphine and 22 patients (4.8%) who received both epidural and nalbuphine developed fever of this degree.

To explore the effect of duration of labor on the risk of fever in the four treatment groups, we stratified the results as shown in figure 1. This demonstrates that even if we limit consideration to patients laboring for less than 6 h, less than 12 h, or less than 18 h, the incidence of fever was always far higher in patients who received epidural (with or without opioids) than in those who did not. This figure also reveals a significant increase in likelihood of fever with increasing duration of labor (as confirmed by the logistic regression results in tables 2 and 3).

Our separate multivariate logistic regression analyses for the epidural and no-epidural groups revealed that systemic opioids were not significantly associated with the likelihood of developing fever in patients who received (table 2) or did not receive (table 3) epidural analgesia. Specifically, in patients who received epidural analgesia, the adjusted odds ratio for nalbuphine plus epidural *versus* epidural alone was 1.03 (95% CI = 0.65–1.64, $P = 0.9$). Similarly, among patients who did not receive epidural analgesia, the adjusted odds ratio for nalbuphine alone *versus* no analgesia was 0.20 (95%

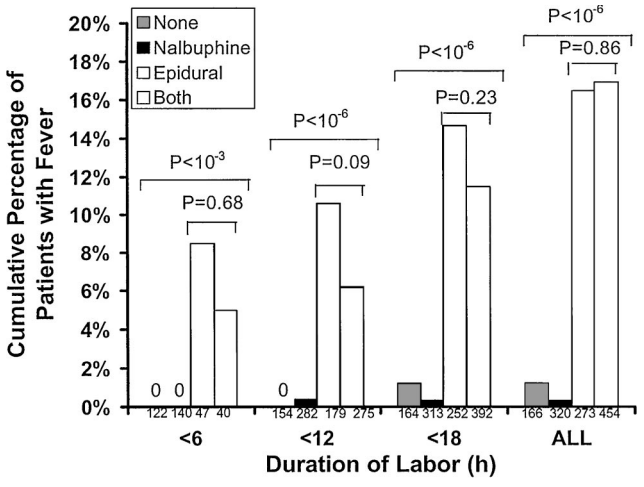

Fig. 1. Incidence of fever among patients laboring less than 6 h, less than 12 h, less than 18 h, and all patients. The number of patients in each group is shown immediately below the corresponding bar. *P* values are shown for comparisons between epidural alone *versus* epidural + systemic nalbuphine (both), and for patients receiving epidural (with or without opioid) *versus* patients not receiving epidural. Differences between no analgesia and nalbuphine alone were never significant ($P > 0.2$ for all comparisons). Twenty patients, whose length of labor could not be determined, are excluded from the figure and calculations.

Table 2. Adjusted Odds Ratios for Development of Fever among Patients Who Received Epidural Analgesia

Variable	Adjusted Odds Ratio	95% Confidence Limits
Opioid	1.03	0.65–1.64
Length of labor (h^{-1})	1.08	1.02–1.14
Duration of epidural analgesia (h^{-1})	1.19	1.10–1.29
Birth weight (100 g^{-1})	1.03	0.98–1.09
Initial temperature ($°F^{-1}$)	1.32	0.97–1.79
Active management of labor	0.92	0.57–1.48

CI = 0.02–2.45, $P = 0.2$). In patients who did not receive epidural analgesia, the likelihood of fever increased significantly with increasing length of labor, although the absolute rate of fever remained low regardless of whether systemic opioids were administered. For patients receiving epidural analgesia increases in both length of labor and duration of epidural were associated with increased likelihood of fever.

Discussion

Numerous studies from several centers, including two large randomized trials, have established that parturients receiving epidural analgesia are more likely to develop fever during labor than those who do not receive epidural analgesia.[11,12] Epidural-related maternal fever is associated with a higher rate of maternal intrapartum antibiotic use and neonatal evaluation and treatment for suspected sepsis. In addition, maternal fever *per se* may be associated with other adverse neonatal outcomes, such as hypotonia and an increased need for resuscitation immediately after birth.[13]

Negishi *et al.*[6] suggested that it is not epidural analgesia *per se* but rather the lack of systemic opioids in patients receiving epidural analgesia that predisposes patients receiving epidural analgesia to develop fever during labor. They hypothesize that mediators of inflammation (*e.g.*, interleukins, tumor necrosis factor) which are released during both premature and term labor predispose parturients to develop fever.[14] The well-known antishivering effect of opioids such as meperidine and nalbuphine[15] might then reduce the likelihood of fever in patients receiving these medications. However, their study was performed in male volunteers and thus could not determine (1) whether the cytokines released in the course of normal labor and delivery, in the absence of epidural analgesia, predispose parturients to develop fever and (2) whether opioids reduce the incidence of fever in laboring patients who have received epidural analgesia.

Table 3. Adjusted Odds Ratios for Development of Fever among Patients Who Did *Not* Receive Epidural Analgesia

Variable	Adjusted Odds Ratio	95% Confidence Limits
Opioid	0.20	0.02–2.45
Length of labor (h^{-1})	1.2	1.01–1.37
Duration of epidural analgesia (h^{-1})	NA	NA
Birth weight (100 g^{-1})	0.86	0.66–1.13
Initial temperature ($°F^{-1}$)	2.19	0.28–17
Active management of labor	0.87	0.05–14

NA = not applicable.

The present study directly addresses these issues. If the theory of Negishi *et al.*[6] were correct, patients receiving no analgesia would be expected to have an incidence of fever similar to that observed in patients receiving epidural analgesia alone. We found that this is not the case: Only two of 170 patients who received neither epidural nor systemic opioid analgesia developed fever compared with 17% of the parturients receiving epidural analgesia. This makes it unlikely that the increased incidence of epidural-related fevers observed in previous, randomized trials is related to the fact that control patients received systemic opioids while epidural patients did not. Even after correction for length of labor and other potentially confounding factors, epidural analgesia strongly influenced the incidence of fever, independently of whether opioids were administered. Furthermore, if the theory of Negishi *et al.*[6] were correct, the incidence of fever among patients receiving systemic opioids alone should be lower than that in patients who received neither epidural nor systemic opioid analgesia. However, we found that the incidence of fever was similarly low between these two groups, casting further doubt on the hypothesis of Negishi *et al.*[6]

Our unadjusted data suggest ($P = 0.09$) the possibility that among patients laboring for 12 h or less, those who received both systemic nalbuphine and epidural analgesia had a somewhat lower incidence of fever than those receiving epidural analgesia alone. However, in our logistic regression analysis, which controlled for potentially confounding factors, nalbuphine administration was not associated with a lower rate of fever among patients receiving epidural analgesia (odds ratio = 1.03, 95% CI = 0.65–1.64). This lack of association may be explained by the interrelationship between total duration of labor and duration of epidural analgesia: In patients who received both nalbuphine and epidural analgesia, nalbuphine was administered first, with epidural being initiated some time later, when pain relief from nalbuphine was inadequate. Therefore, among patients whose labors were relatively short, those who received nalbuphine prior to epidural analgesia necessarily had a shorter duration of epidural analgesia (4.1 ± 1.9 h) than those who received epidural analgesia from the outset (4.7 ± 2.0 h, $P = 0.002$). Both the present data (table 2) and previous studies demonstrate that the likelihood of epidural-associated temperature elevation increases with the duration of epidural analgesia. Thus, patients with relatively short labors who received nalbuphine before their epidural were less likely to have a sufficient dura-

tion of epidural analgesia to develop a fever. As shown in figure 1, this effect disappeared when patients with longer labors were included in the analysis, most likely because even those patients who received nalbuphine before their epidural had a sufficient duration of epidural analgesia for fever to develop.

As in all observational studies, we cannot rule out the possibility of residual confounding by an unmeasured and uncontrolled factor, which might have independently influenced both the decision to ask for an epidural and the risk of fever. In addition, patients who were not comfortable with no analgesia or nalbuphine could subsequently receive epidural analgesia. This is one possible explanation for why patients with longer labor were more likely to have an epidural; another possibility is that epidural analgesia prolonged the course of labor. The present study was not designed to distinguish between these possibilities. However, even after controlling for length of labor, we could not detect any association between opioid administration and fever development. However, in this case, the magnitude of the effect of epidural analgesia was much greater than that of systemic opioids on the rate of maternal fever. Therefore, it is highly improbable that a confounder could be identified whose inclusion would make systemic opioids a more important predictor of maternal fever than epidural analgesia.

One might argue that our results differ from those of Negishi *et al.*[6] because our patients received a different opioid (nalbuphine) by a different route (intermittent intramuscular and intravenous injection) than their research subjects (fentanyl by continuous infusion). This would imply that our inability to demonstrate an effect of nalbuphine on the risk of fever was related to decreased antipyretic efficacy of nalbuphine as compared to fentanyl. However, this leads to a logical inconsistency: If nalbuphine were ineffective in reducing the risk of labor-associated fever, how can the difference in fever rates between our patients who did and did not receive epidural analgesia be attributed to an antipyretic effect of nalbuphine?

In conclusion, if the hypothesis were true that the increased incidence of fever accompanying epidural analgesia in previous studies resulted from the antipyretic effect of opioids preferentially administered to control patients (who did not receive epidural analgesia), one would expect that patients receiving neither epidural analgesia nor systemic opioids would have a similar rate of fever to patients receiving epidural analgesia. In contrast, we found a highly significant difference in rates of fever between these two groups. Furthermore, in patients who did not receive an epidural, systemic nalbuphine did not significantly decrease the incidence of fever. This suggests that systemic opioids are not acting as a unique antipyretic, and therefore, the concept that fever associated with epidural analgesia is due to an antipyretic effect of drugs given to control patients rather than a propyretic effect of epidural analgesia may not be correct. Therefore, given the limitations of the data set from which our observations were drawn, the mechanism by which fever develops preferentially in parturients receiving epidural analgesia needs to be examined in a formal, prospective fashion.

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