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CLINICAL TRIAL REPORT

Efficacy of Intravenous Butorphanol for Preventing Epidural-Related Maternal Fever (ERMF) During Epidural Labor Analgesia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Purpose: The purpose of this research was to investigate whether intravenous low dose of butorphanol (1mg) at the onset of epidural analgesia (EA) can reduce the incidence of ERMF during labor.

Patients and Methods: Four hundred and twenty-four women, aged 18 to 40 years, BMI <=30 kg/m^2, more than 37 weeks' gestation, singleton pregnancy, American Society of Anesthesiology physical status I–II, normal maternal temperature and fetal heart rate, cervical dilation ≤ 3 cm, having EA were included in this double blinded randomized placebo-controlled trial. Women were randomized to receive intravenous butorphanol 1mL (Butor group) versus sterile saline 1mL (Con group), respectively. The primary outcome was the incidence of ERMF. Secondary outcomes included maternal temperature, pain score, the consumption of analgesic drugs, maternal and neonatal outcomes related to delivery.

Results: A total of 424 subjects (212 subjects in Butor group and 212 subjects in Con group) were included in the final analysis. There was a significant decrease for the incidence of maternal fever in Butor group compared to Con group (37.3% versus 48.6%, P=0.019, T≥37.5°C; 6.1% versus 17.0%, P=0.000, T≥38.0°C). For secondary outcomes, butorphanol showed a protective effect in decreasing the sustained rise of maternal temperature from 2th to 5th hour after EA (P<0.05). And no statistical differences were noted in maternal pain scores and consumption of analgesic drugs (P>0.05). In addition, mild dizziness related to butrophanol was only appeared in few subjects in the first 2 hours after EA (P<0.05). No severe maternal or neonatal adverse effects were observed in all subjects.

Conclusion: A low dose of butorphanol intravenously used at the onset of EA in women undergoing vaginal delivery could effectively reduce the incidence of ERMF. Butorphanol may serve as a potential intervention for preventing ERMF in future.

Keywords: butorphanol, ERMF, EA, maternal temperature, vaginal delivery

Introduction

Epidural analgesia (EA) is widely regarded as the gold standard for managing labor pain, with well-established safety profiles for both the mother and the infant. Despite its proven efficacy, it is associated with an increased risk of intrapartum fever, with reported incidence rates ranging from 15% to 25%.[1,2] Maternal fever during labor has been linked to a range of adverse outcomes, including prolonged hospital stays, increased use of antibiotics, higher cesarean section rates, and postpartum hemorrhage.[2–4] Neonatal risks such as low muscle tone, early-onset seizures, reduced Apgar scores, and a heightened risk of neonatal infections have also been observed.[5–7]

The pathophysiology of epidural-related maternal fever (ERMF) is complex, with sterile inflammation playing a central role.[1,2] Recent studies have concentrated on elucidating the mechanisms through which local anesthetics induce

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sterile inflammation, particularly in relation to ERMF. Research has demonstrated that local anesthetics, such as ropivacaine and bupivacaine, can trigger immune cell and mitochondrial dysfunction,[8–11] leading to the release of pro-inflammatory cytokines (such as IL-1β, IL-6, IL-8) and prostaglandin E2 (PGE2),[9,11] which contribute to the inflammatory and pyretic response observed during labor. To mitigate this response, some studies have investigated the use of prophylactic steroids to prevent intrapartum fever.[12,13] However, the findings have been inconsistent. For instance, high-dose methylprednisolone has been shown to reduce the incidence of fever, but it is also associated with an increased risk of neonatal bacteremia.[12] On the other hand, trials involving epidural steroids have failed to demonstrate consistent efficacy or safety.[13,14] Currently, there is no proven prophylactic strategy to prevent the occurrence of ERMF effectively and safely. This clinical dilemma highlights the urgent need to explore novel interventional targets.

Emerging evidence suggests that κ-opioid receptor (KOR) agonists may offer therapeutic potential by modulating inflammatory pathways.[15,16] These agonists have been shown to suppress pro-inflammatory mediators such as IL-1β, TNF-α, and IL-6 in both central and peripheral models, exhibiting effectiveness in neuroinflammation and sepsis-induced cytokine storms.[16,17] Additionally, activation of κ-receptors has been found to reduce body temperature in rats under psychological stress.[18] Butorphanol, a widely used κ-opioid agonist, has been proven both safe and effective for labor analgesia.[19] Intravenous butorphanol has been shown to enhance analgesia without adverse effects on maternal or neonatal outcomes.[20] Notably, KOR agonists exhibit unique advantages in regulating inflammatory pathways. Unlike traditional anti-inflammatory drugs, KOR agonists can selectively inhibit the release of key pro-inflammatory mediators including IL-1β and TNF-α through activation of both central and peripheral κ receptors, a characteristic that forms a targeted regulatory relationship with the febrile mechanism of ERMF. Based on these findings, we investigated butorphanol's role in mitigating ERMF for the first time, hypothesizing that prophylactic intravenous butorphanol administration following epidural analgesia would reduce its incidence without increasing adverse outcomes.

Materials and Methods

Study Setting and Population

This randomized controlled, double-blind study was approved by the Ethics Committee of the Women's Hospital of Nanjing Medical University (2021KY-093-1). Informed consents were obtained from all subjects participating in the trial. The study was registered at www.chictr.org.cn (registration number is ChiCTR2200057527). A total of 424 participants completed all the trial. Inclusion criteria included American Society of Anesthesiologists class (ASA) I–II, age 18–40 years, body mass index ≤30 kg/m^2, gestational age ≥37 weeks, single fetal head position primiparas, request for epidural analgesia and cervical dilation ≤3 cm, normal initial temperature, no contraindications to epidural anesthesia, and no abnormality of the fetal heart rate monitoring before labor analgesia (fetal heart rate in the range of 110–160 bpm). Exclusion criteria included premature rupture of membranes (PROM), allergy to the study drug or other drugs used in this study, use of opioids and other sedative-analgesic drugs within one week, use of magnesium sulfate, use of antipyretic-analgesic drugs, history of drug abuse, sleep apnea hypopnea syndrome, severe cardiac, pulmonary, hepatic, and renal dysfunction.

Randomization and Blinding

Prior to administering epidural analgesia, parturients were screened for eligibility based on the inclusion and exclusion criteria. After confirmation of effective epidural analgesia onset (NRS <4), those who provided informed consent were randomly assigned to 2 groups by a sequence of random numbers generated by SPSS software.The butorphanol group (Group Butor, n=212) received 1 mg butorphanol (Jiangsu Hengrui Pharmaceuticals Co., Ltd.) in 1 mL sterile saline intravenously as an adjunct for epidural labor analgesia, while the Control group (Group Con, n=212) received same volume of sterile saline intravenously alone for epidural labor analgesia. The randomized protocol was kept in sequentially numbered opaque envelopes, one opened for each enrolled patient. Both saline and butorphanol injections were configured by an unblinded nurse anesthetist's and injected into participants with the corresponding fluids according to grouping. Assessment and recording of results were performed by a researcher after the onset of analgesia. The researcher, midwives, and patient were unaware of the group assignment.

Initiation and Maintenance of Labor Analgesia

The temperature in the delivery room was set at 23°C. Non-invasive blood pressure, pulse oxygen saturation, electrocardiogram and fetal heart rate (HR) were routinely monitored on admission. Baseline systolic blood pressure (SBP) and HR, defined as the average of three readings between uterine contraction intervals, were recorded. Phenylephrine 100ug is administered intravenously when SBP is below 80% of baseline. If SpO_2 is below 95%, nasal cannula oxygen is administered. Prior to the initiation of analgesia, an infusion of 500 mL of lactated Ringer's solution was started.

The patient was placed in the left lateral position with an 18G Tuohy needle for epidural puncture in the L2-L3 vertebral interspace, and the successful puncture was confirmed using the disappearance of resistance technique, with the wire-reinforced epidural catheter placed 3–5 cm into the epidural space, and then a test dose (3 mL of 1.5% lidocaine containing 1:200,000 epinephrine) was injected through the catheter. After observing for 3–5 min to confirm that the catheter had not been placed into a blood vessel or subarachnoid space, 10 mL of 0.125% ropivacaine with 0.4 μg/ mL of sufentanil was epidural injected to start labor analgesia. Patients were allowed to continue in the trial if they achieved a Numeric Rating Scale (NRS) pain score of ≤3 (where 0 represents no pain and 10 represents the worst pain imaginable) at 30 minutes after the epidural bolus and were given either 1 mL of saline or 1 mL of 1 mg/mL of butorphanol intravenously.

Further analgesia was provided using programmed intermittent epidural bolus (PIEB) with ropivacaine 0.08% and sufentanil 0.4 μg/mL delivered by an infusion pump (Apon MC ZZB-IV, Jiangsu Apon Medical Technology). The pump was programmed to administer the first bolus of 10 mL 1 hour after initiation and every hour afterward. Patient-controlled epidural analgesia (PCEA) boluses of 8 mL were administered as needed, with a 20-minute lockout and a maximum dose of 35 mL/h. If the pain is not relieved by pressing PCEA, 5–10 mL of 0.125% ropivacaine with 0.4 μg/ mL of sufentanil was added manually by the anesthesiologist.

Data Collection

Demographics and Labor Characteristics

The following data were recorded after included for demographic infromation: maternal age, height, weight, week of gestation, degree of dilatation at the start of epidural analgesia, rupture of membranes, whether labor was induced by oxytocin or not, and the weight of the newborn.

Primary Outcome and Secondary Outcome Assessment

The patient's temperature, Numeric Rating Scale (NRS) pain score, drug consumption, and adverse effects such as dizziness, nausea, and vomiting were recorded every 1 h from the start of labor analgesia. A mercury thermometer was used to measure the maternal axillary temperature. Before measurement, ensure that the patient's axilla is dry, ask the patient to clamp the temperature head and keep it for five minutes to check the thermometer. The primary outcome was the incidence of ERMF, ERMF was defined as a maximum maternal temperature of ≥38°C,[21] and maternal temperature ≥37.5°C was also analyzed. Maternal outcomes including mode of delivery (vaginal, cesarean, or operative vaginal delivery), duration of labor, use of oxytocin and other uterotonics during labor, and hemorrhage were recorded. Fetal outcomes including fetal heart rate (HR) abnormalities (fetal HR <110 beats/min or fetal HR >160 beats/min), neonatal Apgar scores and transfers to the NICU were also recorded.

Sample Size and Statistical Analysis

Based on retrospective data from our institution, the incidence of intrapartum fever was calculated as 15.2%. We evaluated use of butorphanol as an adjunct would reduce the incidence of intrapartum fever by about 60% derived from our pilot study of 30 participants, where the observed incidence of intrapartum fever after prior administration of butorphanol was 6.7% (two cases developed intrapartum fever). By setting a bilateral α=0.05, 1-β= 0.8, and considering a lost-to-follow-up rate = 15%, allocation ratio = 1:1, the final calculated sample size was 212 cases in each group using PASS 15.0.

The graphical display of the data was used to check whether continuous variables were normally distributed, Kruskal–Wallis test was used if the data did not meet normal distribution. Descriptive statistics were used for demographic data.

Normally distributed variables are described as mean ± standard deviation ($\overline{x} \pm S$) and analyzed between groups using independent samples t-tests. Variables that were not normally distributed were described using the median (25–75% percentile), and the Mann–Whitney test was used for between-group comparisons. Categorical variables were described using frequencies (%) and compared between groups using the either the x^2 test or Fisher's exact test. Logistic regression was used to analyze independent risk factors for ERMF. Risk ratio (RR), risk difference (RD) and difference were reported with 95% confidence intervals (CIs). P values less than 0.05 were considered statistically significant. All the analysis of data used SPSS 26.0 (SPSS Inc., Chicago, Illinois) software.

Results

Demographic and Clinical Characteristics of Participants

A total of 452 female participants were enrolled in the study between May 2023 and December 2023. Of these potential participants, 20 parturient women declined participation due to concerns about medication safety for their infants, while 8 were excluded from the study cohort due to inadequate epidural analgesia efficacy requiring supplemental analgesic administration. Finally, 424 participants completed this study and were finally included in the analysis (Figure 1). Demographic and labor characteristics are presented in Table 1.

Primary Outcomes

The rates of maternal fever in both groups are shown in Table 2. When we define intrapartum fever as a maximum maternal temperature ≥ 38°C, the incidence of maternal fever in the Group Butor was 6.1% and 17.0% in the Group Con, respectively (RR, 0.36; 95% CI, 0.20–0.66; *P*=0.000). If we defined intrapartum fever as a maximum maternal temperature ≥ 37.5°C, the incidence of intrapartum fever was still lower than in the Group Con (37.3% and 48.6%; RR, 0.77; 95% CI, 0.61–0.96; *P*=0.019).

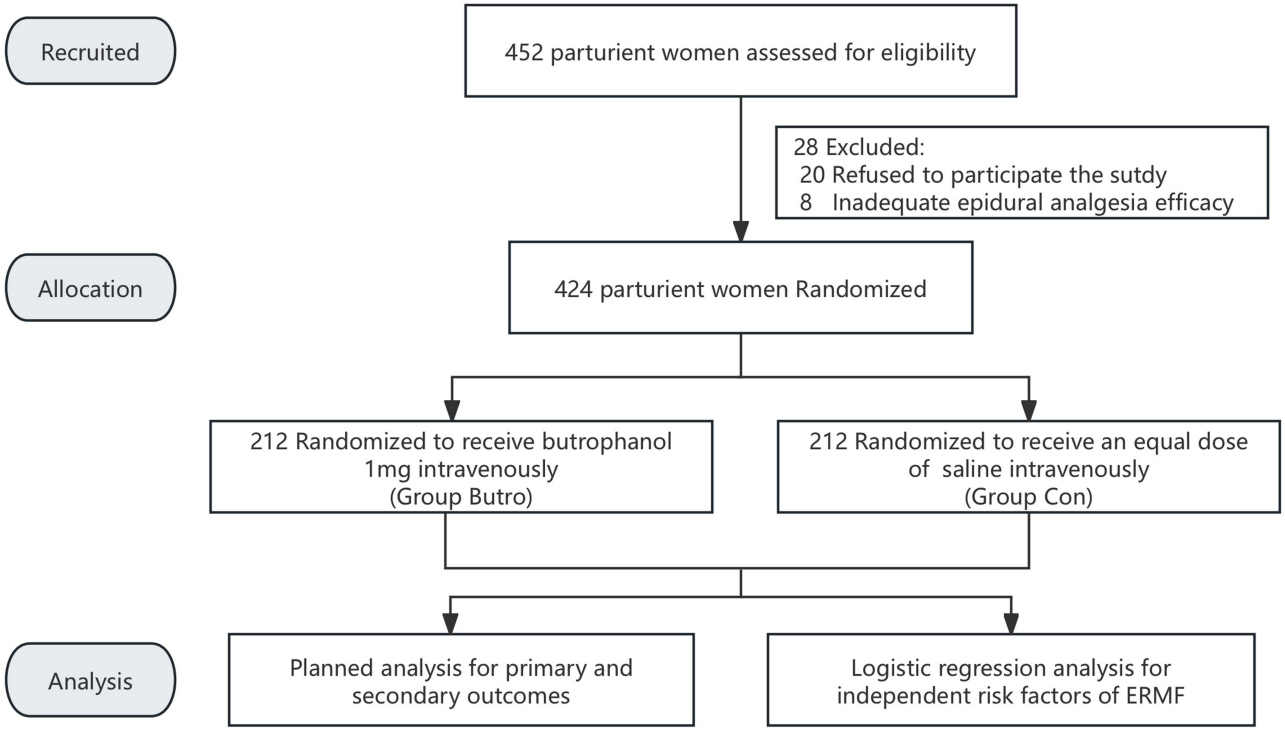


Figure 1 Flowchart describing patients' participation in this study.

Table 1 Basic Characteristics

Variables	Group Con, (n=212)	Group Butor, (n=212)	*P* value
Ages, yr	29.2±2.7	29.5+2.8	0.394
Height, cm	162.4±4.4	163.3±4.7[a]	0.046
Weight, kg	68.4±9.3	70.1±10.4	0.083
Gestational age, weeks	39.8±1.0	39.8±1.0	0.937
Labor induction with oxytocin, n(%)	151(75.5)	180(89.1)[a]	0.000
Rupture of membranes before analgesia, n(%)	57(28.8)	83(42.1)[a]	0.006
CD at the time of epidural analgesia, cm	2.22±0.41	2.33±0.47[a]	0.012
Weight of newborn, kg	3.3±0.33	3.2±0.33	0.224

Notes: The data are expressed as means ± SD, number of participants (percentage). [a]Indicates P <0.05 compared with Con group.
Abbreviation: CD, cervical dilation.

Table 2 Incidences of Intrapartum Fever in Two Groups

Variables	Group Con, (n=212)	Group Butor, (n=212)	RR, Difference (95% CI)	*P* value
Intrapartum fever (T≥38.0°C), n(%)	36(17.0)	13(6.1)[a]	0.36 (0.20 to 0.66)	0.000
Intrapartum fever (T≥37.5°C), n(%)	103(48.6)	79(37.3)[a]	0.77 (0.61 to 0.96)	0.019

Notes: The data are expressed as means ± SD, number of participants (percentage); [a]Indicates P <0.05 compared with Con group.
Abbreviations: T, temperature; RR, risk ratio; CI, confidence intervals.

Secondary Outcomes

The Temperature During the First 6 hours After EA

Since the duration of labor was less than 8 hours for most of the women in this study, maternal temperature was monitored only in the first 6 hours after labor analgesia. The maternal temperature in both groups showed an increasing trend over time after the initiation of analgesia (Figure 2). However, at 2h to 5h after analgesia, the mean maternal temperature in Group Butor was lower than those in Group Con (P=0.034, P=0.001, P=0.021 and P=0.017, respectively).

The NRS Scores and Consumption of Anesthetic Drugs During the First 6 hours After EA

As shown in Figure 3, effective analgesia was achieved in both groups and there was no significant difference in pain NRS scores at all time points (P>0.05, Figure 3A). In addition, there was no difference in the cumulative consumption of analgesic drugs between the two groups (P>0.05, Figure 3B).

Maternal and Fetal Outcomes in Two Groups

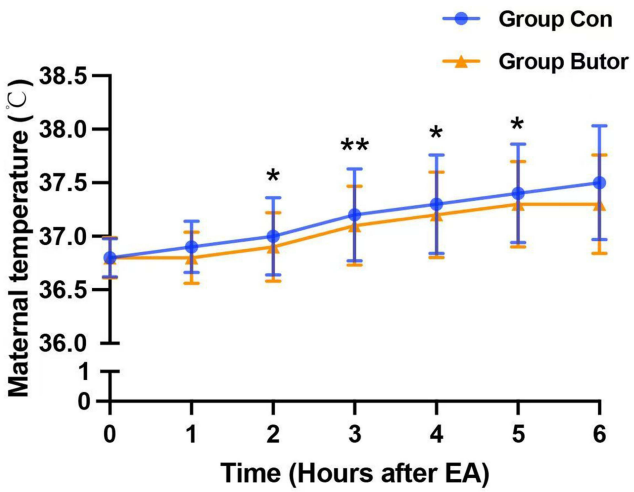
Maternal and fetal outcomes are presented in Table 3, where the duration of the first stage of labor was longer in Group Butor than those in Group Con (468.7±164.0 vs 434.5±147.7, P=0.031). There were no differences in mode of delivery, use of oxytocin and other uterotonics during labor, hemorrhage, incidence of abnormal fetal HR, 1- and 5-minute Apgar scores and rate of neonatal transfers to NICU between the two groups.

Furthermore, occurrence of butorphanol related adverse effects are shown in Table 4, the incidence of dizziness at 1h and 2h after analgesia was higher in Group Butor than those in Group Con, and there were no significant differences in the incidence of maternal nausea and vomiting between the two groups.

Logistic Analysis of Intrapartum Fever

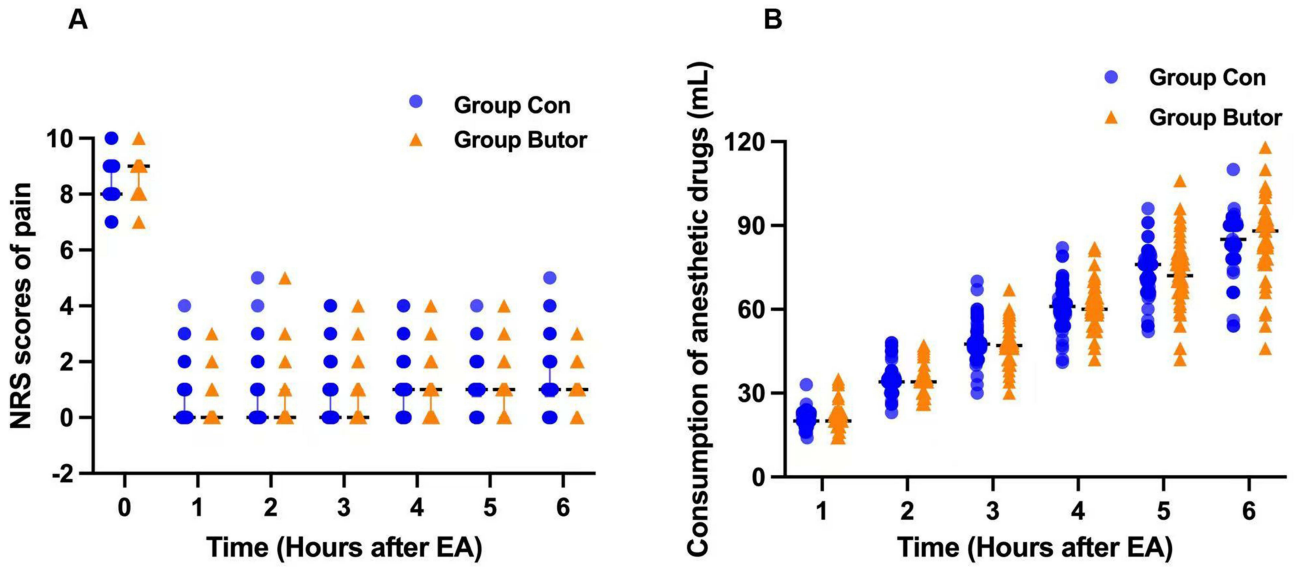
Maternal and Neonatal Outcomes of Intrapartum Fever

To confirm the impacts of intrapartum maternal fever, our comparison between febrile and afebrile patients revealed that intrapartum fever brings numerous adverse effects to both maternal and neonatal outcomes as shown in Table 5. Even



Groups	1h	2h	3h	4h	5h	6h
Con (n)	212	207	192	164	119	87
Butor (n)	212	207	189	158	121	83
Total (n)	424	414	381	322	240	170

Figure 2 Maternal temperature at different time points in two groups. **Indicates P<0.001 compared with Group Con at the same time point; *Indicates P<0.05 compared with Group Con at the same time point.
Abbreviation: EA, epidural analgesia.



Groups	1h	2h	3h	4h	5h	6h
Con (n)	212	207	192	164	119	87
Butor (n)	212	207	189	158	121	83
Total (n)	424	414	381	322	240	170

Figure 3 Maternal NRS of pain and consumption of anesthetic drugs at different time points in two groups. (**A**) NRS of maternal pain before and during 1–6 h after epidural analgesia. (**B**) The consumption of maternal anesthetic drugs after epidural analgesia.
Abbreviations: EA, epidural analgesia; NRS, numeric rating scale.

Table 3 Maternal and Neonatal Outcomes Comparison Between Two Groups

Variables	Group Con, (n=212)	Group Butor, (n=212)	RR, Difference (95% CI)	*P* value
C-section rate, n(%)	15(7.1)	15(7.1)	-	1.00
Duration of labor, min				
First duration	434.5±147.7	468.7±164.0[a]	-	0.031
Second duration	41.9±23.9	40.9±32.5	-	0.730
Third duration	8.4±8.0	8.3±4.0	-	0.861
Oxytocin needed during labor, U	29.7±2.5	29.8±2.0	-	0.654
Other uterotonics needed during labor, n(%)	105(53.8)	108(55.4)	1.02 (0.90 to 1.16)	0.760
Blood volume, mL	296.1±88.8	298.3±56.0	-	0.768
Abnormal FHR, n(%)	104(53.3)	91(46.7)	0.84 (0.73 to 0.96)	0.105
Neonatal Apgar scores				
1min	10(10–10)	10(10–10)	-	0.997
5min	10(10–10)	10(10–10)	-	0.318
Neonatal transfer to the NICU, n(%)	89(54.5)	92(46.9)	1.02 (0.88 to 1.78)	0.761

Notes: The data are expressed as means±SD, median (25th to 75th percentiles), or number of patients (percentage); [a]Indicates P <0.05 compared with Group Con.
Abbreviations: C-section, cesarean section; FHR, fetal heart rate; NICU, neonatal intensive care unit; RR, risk ratio; CI, confidence intervals.

Table 4 Side-Effects Related to Butorphanol as an Adjunct to EA Compared with Con Group

Variables	Group Con	Group Butor	*P* value
1h after EA	n=212	n=212	0.001
Dizziness, n(%)	2(0.9)	19(9.0)[a]	
Nausea, n(%)	1(0.5)	0(0.0)	
Vomiting, n(%)	0(0.0)	1(0.5)	
Other, n(%)	0(0.0)	0(0)	
2h after EA	n=207	n=207	0.001
Dizziness, n(%)	2(0.9)	15(7.2)[a]	
Nausea, n(%)	1(0.5)	5(2.4)	
Vomiting, n(%)	0(0.0)	3(1.4)	
Other, n(%)	0(0.0)	0(0.0)	
3h after EA	n=192	n=189	0.229
Dizziness, n(%)	2(1.0)	1(0.5)	
Nausea, n(%)	6(3.1)	2(1.1)	
Vomiting, n(%)	2(1.0)	5(2.6)	
Other, n(%)	0(0.0)	2(1.1)	

(*Continued*)

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Table 4 (Continued).

Variables	Group Con	Group Butor	*P* value
4h after EA	n=164	n=158	0.426
Dizziness, n(%)	1(0.6)	0(0.0)	
Nausea, n(%)	7(4.3)	4(2.5)	
Vomiting, n(%)	1(0.6)	3(1.9)	
Other, n(%)	0(0.0)	0(0.0)	
5h after EA	n=119	n=121	0.469
Dizziness, n(%)	2(1.7)	2(1.7)	
Nausea, n(%)	2(1.7)	0(0.0)	
Vomiting, n(%)	5(4.2)	3(2.5)	
Other, n(%)	0(0.0)	0(0.0)	
6h after EA	n=87	n=83	0.368
Dizziness, n(%)	0(0.0)	1(1.2)	
Nausea, n(%)	1(1.1)	0(0.0)	
Vomiting, n(%)	3(3.4)	0(0.0)	
Other, n(%)	0(0.0)	0(0.0)	

Notes: The data are expressed as number of patients (percentage); [a]Indicates P <0.05 compared with Group Con.
Abbreviation: EA, epidural analgesia.

Table 5 Maternal and Neonatal Outcomes of Maternal Fever

Variables	T≥37.5°C		*P* value	T≥38.0°C		*P* value
	No Fever n=221	Maternal Fever n=171		No Fever n=348	Maternal Fever n=44	
Delivery mode, n(%)	n=240	n=182	0.745	n=373	N=49	0.004
Vaginal birth	203(84.6)	158(86.8)		326(87.4)	35(71.4)[b]	
C-section	19(7.9)	11(6.0)		25(6.7)	5(10.2)[b]	
Instrumental delivery	18(7.5)	13(7.1)		22(5.9)	9(18.4)[b]	
Duration of labor, min						
First duration	417.5±151.32	495.8±152.91[a]	0.000	441.3±152.44	533.5±167.71[b]	0.000
Second duration	33(26.0–46.5)	38.0(28.0–54.0)[a]	0.010	41.5±29.43	40.2±19.85	0.775
Third duration	7.9±4.11	8.9±8.33	0.135	8.4±6.63	7.9±2.85	0.640
Oxytocin needed during labor, U	30(30–30)	30(30–30)[a]	0.048	30(30–30)	30(30–30)	0.424
Other uterotonics needed during labor, n(%)	108(49.3)	105(61.4)[a]	0.017	183(52.9)	30(68.2)	0.055
Blood volume, mL	290(265–310)	305(280–320)[a]	0.000	294.9±71.91	315.3±89.04	0.085
Abnormal FHR, n(%)	91(41.4)	101(59.4)[a]	0.000	162(46.7)	30(69.8)[b]	0.004

(*Continued*)

Table 5 (Continued).

Variables	T≥37.5°C		*P* value	T≥38.0°C		*P* value
	No Fever n=221	Maternal Fever n=171		No Fever n=348	Maternal Fever n=44	
Neonatal Apgar scores						
1min	10(10–10)	10(10–10)	0.740	10(10–10)	10(10–10)	0.381
5min	10(10–10)	10(10–10)	0.256	10(10–10)	10(10–10)	0.722
Neonatal transfer to the NICU, n(%)	96(43.4)	85(49.7)	0.217	153(44.0)	28(63.6)[b]	0.014

Notes: The data are expressed as means±SD, median (25th to 75th percentiles), or number of patients (percentage); [a,b]Indicates P <0.05 compared with those without maternal fever.
Abbreviations: C-section, cesarean section; FHR, fetal heart rate; NICU, neonatal intensive care unit.

low-grade fever (T ≥ 37.5°C) prolonged the first and second duration of labor (*P*=0.000, *P*=0.010), increased the requirement for oxytocin and other agents that promote uterine contraction (*P*=0.048, *P*=0.017). Simultaneously, low-grade fever also statistically increased maternal bleeding during labor, although without clinical significance [290 (265–310) mL and 305 (280–320) mL, respectively, *P*=0.000). For the fetus, low-grade fever increases the likelihood of fetal heart rate (FHR) abnormalities (P=0.000). Moreover, when the maternal temperature exceeded 38°C, the number of women requiring cesarean delivery or instrumental delivery increased (*P*=0.004). The occurrence of abnormal FHR became more pronounced and the risk of newborn admission to NICU after birth were higher than those without intrapartum fever (*P*=0.004, *P*=0.014).

Factors Associated with Intrapartum Fever Analyzed by Multivarious Logistic Analysis

Logistic regression analysis was performed with age, height, weight, gestational week, whether labor was induced by oxytocin, whether membranes were ruptured prior to analgesia, and the degree of dilatation at the start of epidural analgesia as the independent variables, and the occurrence of maternal fever as the dependent variable, and the results are shown in Table 6. Regardless of whether a temperature threshold of ≥37.5°C or 38°C was defined as intrapartum maternal fever, the gestational week (*P*=0.010, *P*=0.047) was risk factors for ERMF, and the absence of rupture of fetal membranes prior to analgesia (*P*=0.008, *P*=0.029) was a protective factor.

Table 6 Logistic Regression Analysis of Associated Effective Factors for Maternal Fever

Conviates	Maternal Fever (T≥37.5°C) n=182	*P* value	Maternal Fever (T≥38°C) n=49	*P* value
	OR (95 CI%)		OR (95 CI%)	
Age	1.029(0.954, 1.109)	0.458	0.989(0.882, 1.110)	0.856
Height	0.968(0.968, 1.018)	0.204	0.941(0.870, 1.018)	0.128
Weight	0.988(0.966, 1.010)	0.281	0.993(0.959, 1.028)	0.681
Gestational age	1.359(1.077, 1.716)[a]	0.010	1.469(1.006, 2.145)[b]	0.047
Labor induction with oxytocin	1.594(0.881, 2.886)	0.123	1.376(0.510, 3.714)	0.528
Rupture of membranes before analgesia	1.938(1.185, 3.175)[a]	0.008	2.299(1.089, 4.854)[b]	0.029
CD at the time of epidural analgesia	0.602(0.362, 1.003)	0.051	0.620(0.266, 1.446)	0.269

Notes: The data are expressed as OR (95 CI%); [a,b]Indicates P <0.05 as an effective factor for maternal fever.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; CD, cervical dilation.

Discussion

This randomized controlled trial is the first to examine the use of butorphanol in preventing epidural-related maternal fever (ERMF) during labor. The administration of butorphanol significantly decreased the incidence of intrapartum fever, defined as a temperature ≥38°C, in women receiving epidural analgesia. This effect was also observed for fevers ≥37.5°C. Furthermore, although both study groups experienced a general increase in temperature during the 6 hours following epidural analgesia, butorphanol consistently resulted in lower maternal temperatures at critical time points (2–5 hours post-analgesia). These findings suggest that butorphanol may help mitigate the onset of ERMF without interfering with analgesic efficacy, as no significant differences were observed in pain scores or analgesic consumption between the two groups.

Intrapartum fever significantly escalates risks of neonatal morbidity (especially neurologic injury and sepsis) and maternal complications (endometritis, postpartum hemorrhage, cesarean delivery). Intrapartum fever severity correlates with significantly higher rates of composite neonatal morbidity.[21] Compared to afebrile mothers (5.4%), neonates born to mothers with mild fever (18.0%) or severe fever (29.7%) show progressively elevated morbidity risks. Severe fever specifically increases the adjusted odds of morbidity nearly twofold compared to mild fever (adjusted OR 1.93). Even mild fever (37.5–37.9°C) in mothers could significantly increases postpartum endometritis (OR 9.0) and neonatal ICU admission rates (OR 4.8).[22] In this research, we adopted high-grade fever (≥38°C) and low-grade fever (≥37.5°C) as diagnostic criteria for intrapartum fever. Similarly, it was found that high-grade temperature (≥38°C) elevation increases the rates of conversion to cesarean section and instrumental delivery, and also raises the likelihood of neonatal admission to the NICU. Low-grade temperature (≥37.5°C) elevation not only prolongs maternal labor progress, increases the use of oxytocic drugs during delivery, but also elevates the risk of maternal hemorrhage and fetal heart rate abnormalities. In light of the potential adverse outcomes associated with elevated maternal temperature during childbirth, the reduction in intrapartum fever rates with butorphanol observed in our study carries important clinical implications, even a reduction of 11.3% at a lower temperature threshold (≥37.5°C). This highlights butorphanol's potential for improving perinatal maternal and neonatal safety by reducing the rise in maternal temperature after epidural analgesia.

Several studies have highlighted a significant association between elevated maternal serum pro-inflammatory cytokine levels and the onset of ERMF during epidural analgesia.[23–25] Pregnant women with higher serum pro-inflammatory cytokine levels at the time of hospital admission are more prone to developing ERMF,[23] suggesting that epidural analgesia may exacerbate underlying inflammation. Local anesthetics administered epidurally may elevate the levels of these pro-inflammatory cytokines, contributing to the condition.[26]

As a κ-opioid receptor agonist, butorphanol has demonstrated significant anti-inflammatory effects in various experimental models, providing a pharmacological basis for its potential use in preventing ERMF. Tang et al[27] showed that butorphanol alleviates lipopolysaccharide (LPS)-induced myocardial inflammation by activating KOR, effectively reducing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. This KOR-mediated mechanism is further supported by butorphanol's ability to suppress carrageenan-induced paw edema in rats.[28] In acute lung injury models, butorphanol promotes macrophage polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype through dual inhibition of NF-κB/MAPK signaling and TRIF-mediated interferon pathways, significantly reducing pulmonary inflammatory infiltration.[29] In clinical settings, butorphanol administration (40 μg/kg) during anesthesia induction in elderly surgical patients resulted in more favorable anti-inflammatory outcomes compared to sufentanil, characterized by reduced TNF-α and IL-1β levels, along with increased IL-10 concentrations.[30] These cytokine-modulating effects are particularly relevant to the pathogenesis of intrapartum fever, where inflammatory responses associated with epidural analgesia contribute to maternal temperature elevation. Although current evidence is primarily derived from non-obstetric models, butorphanol's ability to modulate both peripheral and central inflammatory pathways support its therapeutic potential in addressing the multifactorial inflammation associated with ERMF. Further clinical research is needed to optimize butorphanol dosing regimens and evaluate its impact on intrapartum cytokine profiles and thermoregulatory responses.

In a recent observational study on epidural analgesia-related labor fever, Jeffrey et al[31] found no association between nalbuphine use and a reduced fever rate in patients receiving epidural analgesia, contrasting with the results of our study.

In their research, nalbuphine was administered first, followed by epidural analgesia only after insufficient pain relief from nalbuphine. In contrast, our study administered butorphanol after epidural analgesia initiation. Additionally, in Jeffrey et al's study, the average duration of epidural analgesia for women who received nalbuphine was about 4.1 hours, whereas in our study, the duration was approximately 5.8 hours. The authors noted that women with relatively short labors, who received nalbuphine before epidural analgesia, were less likely to experience prolonged epidural analgesia, which is necessary for fever development.[32] Several studies suggest that the duration of epidural analgesia influences the development of ERMF, with the risk increasing as epidural analgesia duration lengthens.[33–35] Our study observed peak maternal temperature between 6 and 8 hours after analgesia, consistent with previous research. These differences in study outcomes may be attributed to variations in epidural analgesia duration. Furthermore, administering butorphanol after labor analgesia in our study may coincide with the peak of the inflammatory response following epidural analgesia, enhancing its effectiveness in blocking fever-related inflammatory pathways.

Meanwhile, butorphanol was demonstrated good efficacy with minimal severe adverse effects compared to traditional opioids when used in clinical analgesia.[36] In labor analgesia, butorphanol showed no significant adverse effects on women or neonatal outcomes, making it a safer option in obstetric settings.[37] Consistent with it, we found the side effects of butorphanol appeared in the first two hours after EA only in few people, mainly manifested as mild dizziness. Its unique pharmacology contributes to a lower risk profile than full opioid agonists, but clinicians should monitor for dependency and adjust dosing or combination strategies to minimize adverse events. Overall, butorphanol appears safer than conventional opioids, with fewer drug-related complications.

Logistic regression analysis identified gestational age as a risk factor for ERMF, particularly when the intrapartum fever threshold was set at ≥37.5°C. A retrospective study also reported that women with intrapartum fever had significantly shorter mean gestational ages compared to the control group.[34] However, gestational age was not confirmed as an independent risk factor in multivariate analysis. No significant association was found between gestational age and intrapartum fever risk in term (≥36 weeks) or late-term pregnancies (≥40 weeks).[33,38] Although gestational age may correlate with an increased likelihood of developing ERMF, the findings from existing studies are inconsistent, underscoring the need for further research.

Regression analysis also identified pre-analgesia fetal membrane rupture as a risk factor for ERMF. A cohort study of epidural labor analgesia found that PROM was an independent risk factor for intrapartum fever (OR = 2.008),[39] potentially linked to ascending infections leading to chorioamnionitis.[40] After membrane rupture, macrophages are recruited to the injury site, where they release IL-1β and TNF to promote epithelial-mesenchymal transition (EMT) for wound healing.[41] While our study excluded women with PROM, membrane rupture before analgesia (non-PROM) was still considered in analysis for its increased risk of sterile inflammatory responses and infection exposure. Notably, the butorphanol group had a higher proportion of women with membrane rupture before analgesia, yet the incidence of intrapartum fever was lower in this group, suggesting that butorphanol may exert an anti-inflammatory effect. However, since microbiological examinations of amniotic fluid and placenta were not performed, we cannot definitively conclude whether butorphanol protects against infection exposure. Moreover, no evidence supports the antimicrobial properties of butorphanol. Further studies are needed to examine the risk associated with fetal membrane rupture before analgesia, as it remains a significant risk factor for intrapartum fever, warranting further research and clinical attention.

While this study offers valuable insights, several limitations should be acknowledged, as they may affect the generalizability of the findings. First, excluding women with a BMI greater than 30 kg/m² and those with comorbidities may limit the relevance of the results to obese or high-risk populations. Second, the 6-hour temperature monitoring period may not fully capture fever risk throughout the entire labor process, especially in cases of prolonged labors lasting more than 8 hours. Third, the higher incidence of dizziness in the butorphanol group may have compromised the integrity of the double-blind design. Fourth, The use of axillary temperature in this study is not the optimal measurement for core body temperature and may therefore underestimate the true degree of maternal hyperthermia. These limitations highlight the necessity for further research to confirm and expand upon these findings.

Conclusion

In conclusion, this study demonstrates that intravenous butorphanol administration significantly reduces the incidence of intrapartum fever without negatively affecting maternal or neonatal outcomes. The observation of mild dizziness as a side effect should be acknowledged, indicating the need for its inclusion in the patient management strategy through careful monitoring. Butorphanol may serve as an effective intervention for preventing ERMF, warranting further multicenter research to confirm its broader applicability in diverse populations.

Ethics Approval

This study was performed in line with the Declaration of Helsinki and was registered in the China Clinical Trial Registry (registration number is ChiCTR2200057527). The study protocol was approved by the Ethics Committee of the Women's Hospital of Nanjing Medical University (2021KY-093-1).

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Disclosure

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