



# Epidural Dexmedetomidine for Prevention of Intrapartum Fever During Labor Analgesia: A Randomized Controlled Trial

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## ABSTRACT

**Introduction:** Intrapartum fever occurs frequently during labor. The purpose of this study was to investigate the effects of epidural dexmedetomidine on maternal temperature, pain score and adverse effects during labor analgesia.

**Methods:** A total of 600 full-term primiparous parturients were randomly divided into two groups. The dexmedetomidine group (Group Dex,  $n = 300$ ) received 0.1% ropivacaine with 0.5  $\mu\text{g}/\text{mL}$  dexmedetomidine for epidural analgesia during labor, while the control group (Group C,  $n = 300$ ) received 0.1% ropivacaine alone. The maternal temperature, visual analogue scale (VAS) and Ramsay sedation score (RSS) were recorded, and the systolic blood

pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were monitored. Side effects, if any, were also recorded.

**Results:** The incidence of intrapartum fever was lower in Group Dex than in Group C (4.1% vs. 8.7%,  $\chi^2 = 5.07$ ,  $P = 0.024$ ). VAS values from the time of 3 cm cervical dilatation to 10 cm cervical dilatation were also lower in Group Dex than in Group C ( $1.0 \pm 0.9$  vs.  $1.3 \pm 0.7$ ,  $t = 3.62$ ,  $P < 0.001$ ;  $2.8 \pm 0.8$  vs.  $3.3 \pm 0.8$ ,  $t = 8.09$ ,  $P < 0.001$ ;  $3.1 \pm 0.9$  vs.  $3.3 \pm 0.8$ ,  $t = 3.88$ ,  $P < 0.001$ ;  $3.6 \pm 0.8$  vs.  $4.1 \pm 1.0$ ,  $t = 5.86$ ,  $P < 0.001$ , respectively). HR from the time of 3 cm cervical dilatation to 10 cm cervical dilatation was lower during labor in Group Dex than in Group C ( $80.0 \pm 4.3$  vs.  $83.1 \pm 5.4$  beats/min,  $t = 7.58$ ,  $P < 0.001$ ;  $81.1 \pm 4.0$  vs.  $83.7 \pm 5.5$  beats/min,  $t = 6.48$ ,  $P < 0.001$ ;  $78.9 \pm 5.4$  vs.  $81.5 \pm 6.3$  beats/min,  $t = 5.41$ ,  $P < 0.001$ ;  $83.1 \pm 5.3$  vs.  $84.8 \pm 5.6$  beats/min,  $t = 3.75$ ,  $P < 0.001$ , respectively), while SBP and DBP were similar between the two groups. The incidence of adverse events during labor was also similar between the two groups.

**Conclusion:** The present study showed that dexmedetomidine could reduce the incidence of intrapartum fever and relieve pain during labor without increasing adverse events.

**Trial Registration:** ChiCTR-OPC-16008548.

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**Keywords:** Analgesia; Epidural; Dexmedetomidine; Intrapartum fever; Labor

### Key Summary Points

The mechanisms of intrapartum fever are controversial.

Dexmedetomidine increases analgesic effects.

Dexmedetomidine may reduce the incidence of intrapartum fever.

## DIGITAL FEATURES

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## INTRODUCTION

The epidural technique is widely used for pain management during labor [1]. Intrapartum fever frequently occurs during labor, and women receiving epidural analgesia are at increased risk [2, 3]. Intrapartum fever is strongly associated with neonatal encephalopathy and cerebral palsy [4, 5]. However, the mechanisms of intrapartum fever are controversial. It is well known that anesthetics may inhibit the maternal temperature regulation center. Dexmedetomidine, an  $\alpha_2$ -adrenergic agonist, has been used successfully for epidural labor analgesia, with fewer side effects [6–8]. We hypothesized that dexmedetomidine could reduce the incidence of intrapartum fever during labor analgesia without increasing adverse events. The aim of this study was to investigate the effects of epidural dexmedetomidine on intrapartum fever, pain score and adverse effects during labor analgesia.

## METHODS

This study was approved by the Ethics Committee of Women and Children's Hospital of Jiaxing University (reference number: 2016-036). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All participants provided informed consent to participate in the study. The trial was registered at [www.chictr.org.cn](http://www.chictr.org.cn) (registration number: ChiCTR-OPC-16008548). A total of 600 full-term primiparous parturients were divided into two groups using a random number code. The dexmedetomidine group (Group Dex,  $n = 300$ ) received 0.1% ropivacaine with 0.5  $\mu\text{g}/\text{ml}$  dexmedetomidine for epidural analgesia, while the control group (Group C,  $n = 300$ ) received 0.1% ropivacaine alone for epidural analgesia. Inclusion criteria included American Society of Anesthesiologists (ASA) grade I/II status, age 20–35 years, weight 50–85 kg, gestational week  $\geq 37$  weeks, and the ability of the subject, following assessment, to undergo vaginal delivery. Exclusion criteria included temperature from the ear canal  $> 37^\circ\text{C}$ , platelet count  $< 90 \times 10^9/\text{L}$ , coagulation disorder, bradycardia, puncture point infection, serious cardiopulmonary disease, or liver or renal function disorder. The anesthesiologists, physicians and midwives were blinded to grouping.

The room temperature was set at  $24^\circ\text{C}$ . Blood pressure (BP), heart rate (HR) and pulse oxygen saturation ( $\text{SpO}_2$ ) were monitored at 10-min intervals, and venous access was established. With parturients positioned in the left lateral position, the epidural technique was performed at level  $\text{L}_{2-3}$  using the air loss-of-resistance technique when cervical dilation was about 2 cm. An epidural catheter was advanced 3–5 cm cephalad into the epidural space and fixed. A 3 ml test dose of 1.5% lidocaine was administered through the epidural catheter to determine whether it had entered a blood vessel or the subarachnoid space, after which an initial volume of 10 ml analgesic solution was administered. The analgesic solutions consisted of 0.1% ropivacaine with 0.5  $\mu\text{g}/\text{ml}$  dexmedetomidine (Jiangsu Hengrui Medicine Company, China) in Group Dex, and 0.1% ropivacaine in

Group C, which were infused with a patient-controlled analgesia pump (Jiangsu Aipeng Medical Devices Co., Ltd, China). The parameters of the pump were set as follows: maintenance dose of 6 ml/h, a bolus of 6 ml and locked time of 15 min. The parturients were instructed to use the pump to inject a bolus dose to relieve pain. Five units of oxytocin were administered intravenously to increase contractions when progress was insufficient. Fetal heart rate was monitored continuously using an ultrasonic Doppler system (Oxford Company, UK).

The highest level of sensory block was measured within 30 min after administration using an alcohol cotton ball placed in the middle of the torso. The temperature from the ear canal (T) was measured by a thermometer (Kaz USA, Inc., PRO 4000, MA, USA). Maternal temperature and pain scores were recorded at 60-min intervals during the time from the beginning of epidural analgesia to 10 cm cervical dilatation. The highest temperature was noted during the time from the beginning of epidural analgesia to 10 cm cervical dilatation. The time between initiation of epidural analgesia to the highest temperature was also noted during labor. Intrapartum fever was defined as maternal temperature  $\geq 38$  °C. Acetaminophen 0.5 g was administered orally if maternal temperature increased to  $\geq 39$  °C. Ephedrine 6 mg was given intravenously when systolic blood pressure was  $< 80\%$  of baseline. Supplemental oxygen was administered if SpO<sub>2</sub> was below 95%. Pain intensity was assessed using a visual analogue scale (VAS) (0, no pain; 10, worst pain). Motor block was assessed using the Bromage score (0 = no motor loss, 1 = inability to flex hip, 2 = inability to flex hip and knee, 3 = inability to flex hip, knee and ankle). The incidence of intrapartum fever, hypotension, respiratory depression, bradycardia, excessive sedation nausea and vomiting was recorded. Hypotension was defined as systolic blood pressure (SBP)  $< 80\%$  of baseline, respiratory depression was defined as SpO<sub>2</sub>  $< 94\%$  when inhaling air and respiratory rate  $< 10$  breaths/min, and bradycardia was defined as HR  $< 60$  beats/min. The level of sedation was evaluated every 60 min using the Ramsay sedation scale score (RSS: 1, patient anxious, agitated or restless; 2, patient

cooperative, oriented and tranquil alert; 3, patient responds to commands; 4, asleep, but with brisk response to light glabellar tap or loud auditory stimulus; 5, asleep, sluggish response to light glabellar tap or loud auditory stimulus; 6, asleep, no response) [9]. Excessive sedation was defined as RSS of greater than 4. APGAR scores were recorded at 1 and 5 min after delivery.

### Sample Size

The primary outcome was intrapartum maternal fever. Based on the incidence of intrapartum fever (7–10%) [4, 10], we calculated that a sample size of 250 women in each group would have 80% power to detect a difference of 4% in the incidence of intrapartum fever between the two groups with two-sided  $\alpha$  error of 0.05. Allowing for dropouts, 300 subjects in each group were needed to enroll in the study.

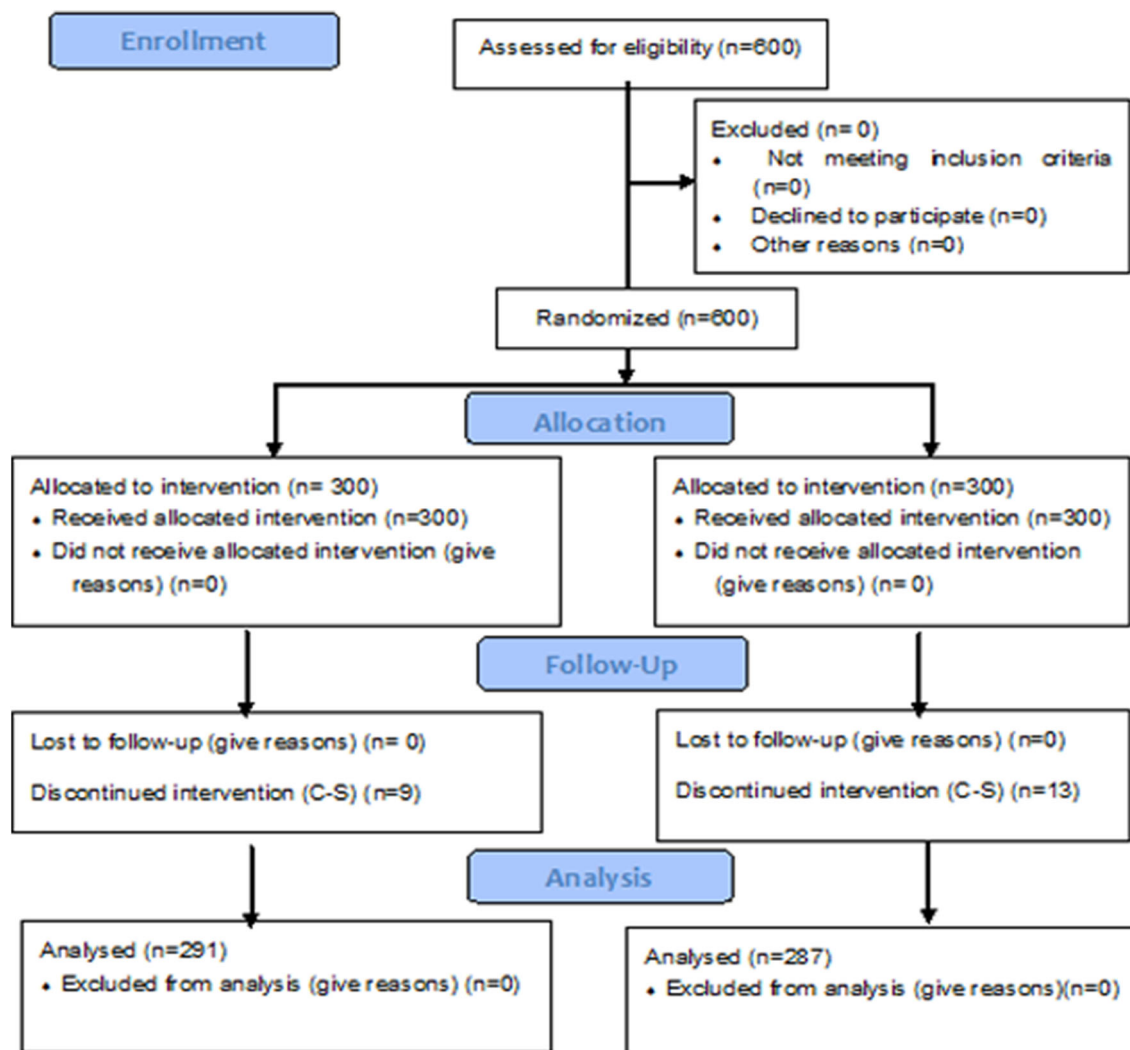
### Statistical Analysis

Statistical analysis was performed using the SPSS17.0 (IBM, NY, USA) software package. Numerical variables were presented as mean and standard deviation (SD) and analyzed by two-way analysis of variance for repeated measures. Intergroup comparison of parametric data was performed using a *t* test, and nonparametric data were analyzed by the Mann–Whitney *U* test. Categorical data were presented as numbers and analyzed using the chi-square test or Fisher's exact test. The significance level was set at  $P < 0.05$ .

## RESULTS

A total of 600 women were enrolled in the study. Five hundred and seventy-eight women completed the study, while 22 patients were excluded from the study due to a prolonged first labor stage ( $> 12$ – $16$  h) or to fetal distress in utero (1 case) or required cesarean section (Fig. 1).

The data for the women are shown in Table 1. There were no significant differences



**Fig. 1** Flow diagram of study

with respect to maternal age, height, weight, gestational weeks, labor type, highest level of sensory block or use of oxytocin between the two groups, but there were significant differences in terms of the first labor duration and time between initiation of epidural analgesia and the highest temperature in labor ( $358 \pm 72$  vs.  $375 \pm 84$  min,  $t = 3.36$ ,  $P = 0.01$ ;  $4.4 \pm 0.6$  vs.  $4.7 \pm 0.8$  h,  $t = 5.09$ ,  $P < 0.001$ , respectively), and the dose of analgesics was lower in Group Dex ( $51.4 \pm 6.8$  vs.  $53.8 \pm 7.6$  ml,  $t = 4.01$ ,  $P < 0.001$ ).

SBP, diastolic blood pressure (DBP) and HR are shown in Fig. 2a–c. SBP and DBP were similar between the groups ( $P > 0.05$ ), while HR

during the time from 3 to 10 cm cervical dilatation after analgesia was lower in Group Dex than in Group C ( $80.0 \pm 4.3$  vs.  $83.1 \pm 5.4$  beats/min,  $t = 7.58$ ,  $P < 0.001$ ;  $81.1 \pm 4.0$  vs.  $83.7 \pm 5.5$  beats/min,  $t = 6.48$ ,  $P < 0.001$ ;  $78.9 \pm 5.4$  vs.  $81.5 \pm 6.3$  beats/min,  $t = 5.41$ ,  $P < 0.001$ ;  $83.1 \pm 5.3$  vs.  $84.8 \pm 5.6$  beats/min,  $t = 3.75$ ,  $P < 0.001$ , respectively).

VAS scores from the time of 3 cm cervical dilatation to 10 cm cervical dilatation were lower in Group Dex than in Group C (Fig. 3) ( $1.0 \pm 0.9$  vs.  $1.3 \pm 0.7$ ,  $t = 3.62$ ,  $P < 0.001$ ;  $2.8 \pm 0.8$  vs.  $3.3 \pm 0.8$ ,  $t = 8.09$ ,  $P < 0.001$ ;  $3.1 \pm 0.9$  vs.  $3.3 \pm 0.8$ ,  $t = 3.88$ ,  $P < 0.001$ ;

**Table 1** Data for women in both groups

Variables	Group Dex ( <i>n</i> = 291)	Group C ( <i>n</i> = 287)	<i>P</i> value
Age (years)	28.8 ± 2.8	29.1 ± 2.9	0.208
Height (cm)	160.2 ± 4.1	160.6 ± 4.4	0.258
Weight (kg)	69.4 ± 5.7	68.8 ± 6.3	0.231
Gestational week	39.2 ± 1.1	39.4 ± 1.2	0.753
Highest level of sensory block (T8/T10)	224/67	218/69	0.999
Induced/spontaneous labor ( <i>n</i> )	28/263	26/251	0.924
Time between initiation of epidural analgesia and the highest temperature (h)	4.4 ± 0.6	4.7 ± 0.8	0.000*
Duration of the first labor stage (min)	358 ± 72	375 ± 84	0.009*
Duration of second labor stage (min)	59.2 ± 8.7	57.8 ± 9.2	0.061
Dose of analgesics (ml)	51.4 ± 6.8	53.8 ± 7.6	0.000*
Use of oxytocin ( <i>n</i> )	12	18	0.244

Data are presented as mean ± SD or number. Compared with Group C, \**P* < 0.05

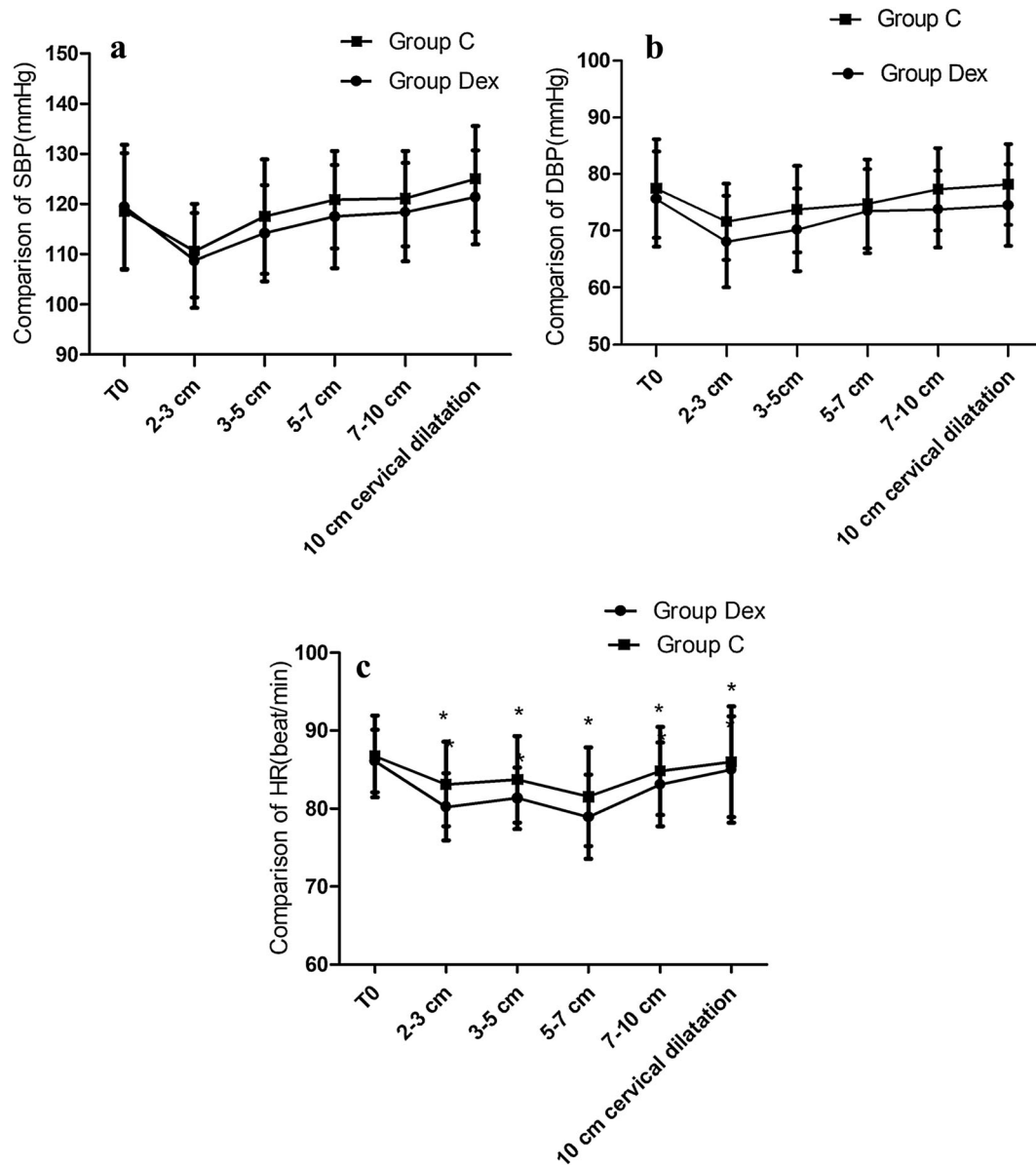
3.6 ± 0.8 vs. 4.1 ± 1.0, *t* = 5.86, *P* < 0.001, respectively).

The side effects are shown in Table 2. The incidence of intrapartum fever was lower in Group Dex (4.1% vs. 8.7%,  $\chi^2 = 5.07$ , *P* = 0.024). Maternal temperature was higher at 4 h after analgesia and 10 cm cervical dilatation in Group Dex compared to Group C (37.3 ± 0.4 vs. 37.5 ± 0.5 °C, *t* = 5.51, *P* < 0.001; 36.7 ± 0.4 vs. 36.9 ± 0.4 °C, *t* = 4.45, *P* < 0.001, respectively), while maternal temperature was similar at other time points during labor (Fig. 4). No excessive sedation (RSS > 4) was observed. The incidence of hypotension, respiratory depression, bradycardia, excessive sedation, nausea and vomiting was similar between groups.

## DISCUSSION

The present study found that dexmedetomidine could reduce the incidence of intrapartum fever and increase the analgesic effects of local anesthetics, without increasing adverse events.

Intrapartum fever likely has multiple causes. The infectious etiology of maternal fever includes chorioamnionitis and viral infections, among others. Noninfectious factors include high room temperature, administration of medications raising maternal temperature and the administration of neuraxial analgesia. Epidural analgesia leads to an increased incidence of intrapartum fever; however, the exact mechanism of maternal fever is unknown [3, 11]. The most current evidence supports the mechanistic involvement of noninfectious inflammation [12]. Intrapartum maternal fever is strongly associated with systemic and/or regional noninfectious inflammation, likely mediated by interleukin-6 [13, 14]. The mechanism of epidural-related maternal fever is complex and controversial. It may be related to an imbalance in heat and cold after epidural analgesia. Fusi et al. [15] posited that epidural block might inhibit heat dissipation, thus resulting in an increase in temperature during labor, while another study reported that epidural analgesia led to redistribution of heat from the core to the periphery, and thus loss of



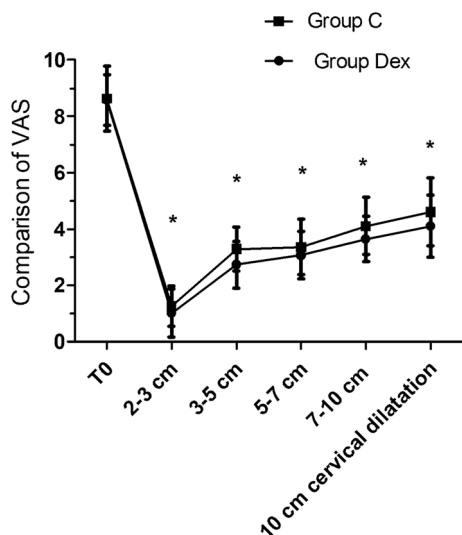
**Fig. 2** a–c Comparison of SBP, DBP and HR in the two groups. SBP and DBP were similar between groups ( $P > 0.05$ ), while HR at the time from 4 to 10 cm cervical dilatation after analgesia were lower in the

dexmedetomidine group than in the control group ( $*P < 0.01$ ). *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate

heat to the environment [16]. The exact mechanism of action for dexmedetomidine related to fever is unknown. Documents show that the  $\alpha_2$ -adrenergic receptor is associated with thermoregulation, and dexmedetomidine produces a reduction in body temperature through the  $\alpha_2$  receptors [17, 18]. In this study,

dexmedetomidine decreased the incidence of intrapartum maternal fever during labor. The possible reasons are as follows: Dexmedetomidine, an  $\alpha_2$ -adrenoceptor agonist, inhibited the maternal thermoregulation center by the central  $\alpha_2$ -adrenoceptor activity and reduced heat production. On the other hand, heat loss





**Fig. 3** Comparison of VAS between the two groups. VAS values from the time of 3 cm cervical dilatation to 10 cm cervical dilatation were obviously lower in the dexmedetomidine group than in the control group (\* $P < 0.01$ )

was increased with vasodilatation under epidural analgesia. In addition, dexmedetomidine inhibited tumor necrosis factor- $\alpha$  and interleukin-6 expression to alleviate inflammation by suppression of c-Jun N-terminal kinases [19]. A recent document reported that lower concentrations of ropivacaine reduced the rate of intrapartum fever during labor analgesia [20].

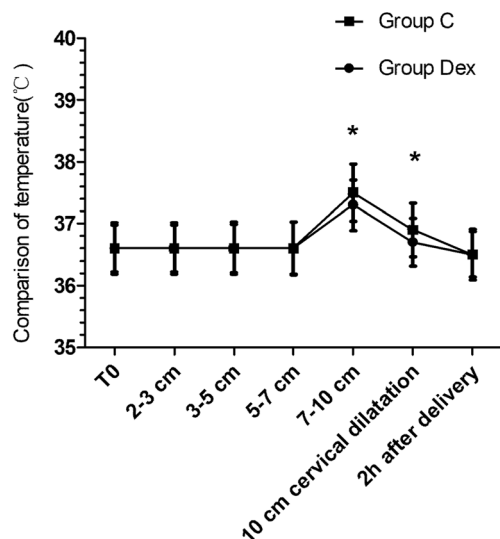
However, intrapartum fever in that study was defined as a body temperature of  $> 37.5$  °C, whereas in our study it was defined as temperature of  $> 38.0$  °C. Lange et al. [4] reported that intrapartum magnesium administration reduced the incidence of intrapartum fever during labor, as it inhibited the expression of interleukin-6. In our study, the highest temperature in labor occurred 4–8 h after analgesia, and a prolonged labor stage was associated with a higher risk of maternal fever, in concordance with previous research [4]. Douma et al. [21] reported that patient-controlled intravenous administration of remifentanyl decreased the incidence of intrapartum maternal fever during labor compared with epidural analgesia. Camann et al. [22] suggested that maternal temperature was increased during labor using bupivacaine with or without fentanyl for epidural analgesia. Temperatures at 5 h and longer after analgesia were significantly greater than the pre-epidural temperatures, while maternal temperatures did not increase using only parenteral opioids for analgesia.

Local anesthetics combined with other analgesics can improve analgesic effects and reduce adverse events [23–25]. In our study, the incidence of hypotension, bradycardia, respiratory depression, excessive sedation, motor block nausea and vomiting was similar between

**Table 2** Adverse events in women and infants

Complications	Group Dex ( $n = 291$ )	Group C ( $n = 287$ )	$P$ value
Intrapartum fever	12 (4.1)	25 (8.7)	0.024*
Hypotension	5 (1.7)	2 (0.6)	0.725
Bradycardia	0 (0)	0 (0)	0.999
Respiratory depression	0 (0)	0 (0)	0.999
Excessive sedation	0 (0)	0 (0)	0.999
Vomiting and nausea	4 (1.4)	7 (2.4)	0.349
Bromage score $> 0$	0 (0)	0 (0)	0.999
Maternal temperature $\geq 39$ °C	0 (0)	0 (0)	0.999
Apgar score $< 7$	0 (0)	0 (0)	0.999

Data are shown as number (%), compared with the Group C, \* $P < 0.05$



**Fig. 4** Comparison of maternal temperature between the two groups. Maternal temperature was higher at 4 h after analgesia and 10 cm cervical dilatation in the dexmedetomidine group compared with the control group ( $*P < 0.05$ )

groups, indicating that dexmedetomidine did not increase the incidence of side effects during labor. There were no significant differences in labor duration or delivery outcome between the two groups, and no adverse events were observed in the neonates. Epidural use of dexmedetomidine was safe for the mother and baby during labor.

The present study had several limitations. First, the exact mechanism of intrapartum fever is unknown. Second, other factors that lead to increases in body temperature may have influenced the results. Lastly, further research is needed to better understand the mechanism of intrapartum fever.

## CONCLUSIONS

In conclusion, dexmedetomidine may reduce the incidence of intrapartum fever and increase analgesic effects during labor, without increasing adverse events.

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**Authorship Contributions.** Study design: Z.W. Data collection: Z.Y and Z.W. Data analysis: Z.Y. Writing of manuscript: Z.W and L.L.

**Disclosures.** Li Li, Yang Zeyong and Zhang Wangping have nothing to disclose.

**Compliance With Ethics Guidelines.** This study was approved by the Ethics Committee of Women and Children's Hospital of Jiaxing University (Reference number: 2016-036). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All participants consented to participate in this study.

**Data Availability.** The data will be accessible 6 months after publication. The documents will be available at <http://www.qq.com>, by contacting the corresponding author.

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