Ropivacaine at different concentrations on intrapartum fever, IL-6 and TNF-α in parturient with epidural labor analgesia

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Abstract. Effects of ropivacaine at different concentrations on intrapartum fever, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in parturient with epidural labor analgesia were compared to provide reference for the rational selection of anesthetics in clinic. Medical records of 198 cases of primiparas admitted to the Obstetrics and Gynecology Department, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, from January 2017 to January 2018 were analyzed retrospectively and divided into 2 groups. A total of 105 patients were treated with 0.075% ropivacaine injection 10 ml and 0.5 μg/ml sulfentanyl injection 100 ml in parturition as the experimental group, and 93 patients were treated with 0.1% ropivacaine injection 10 ml and 0.5 μg/ml sulfentanyl injection 100 ml in parturition as the control group. After patient-controlled epidural analgesia, the pain visual analogue score (VAS), labor duration, administration time and febrile rate of parturient after administration were compared between the two groups at different time-points. Venous blood 2 ml was taken at T1 (cervix open to 2 cm), T2 (cervix fully open) and T3 (24 h postpartum), and the concentration of IL-6 TNF-α was detected by enzyme-linked immunosorbent assay. The time of the second stage of labor and analgesia were shorter in the experimental group than that in the control group after administration (P<0.05). The febrile rate of parturient in the experimental group was lower than that in the control group (P<0.05). The concentration of IL-6 and TNF-α in the experimental group was lower than that in the control group at T2 (P<0.05; P<0.01). The effect of patient-controlled epidural administration with 0.075% ropivacaine injection combined with 0.5 mg/ml sulfentanyl injection on labor analgesia is shorter than that with 0.1% ropivacaine combined with sulfentanyl. It could also shorten the duration of the second stage of labor, reduce the intrapartum febrile rate, and alleviate inflammation.

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Introduction

Childbirth is a natural physiological process that every parturient has to go through. Because of the physiological pain of labor, labor analgesia has been applied in clinic for many years, and is increasingly used by parturients (1). The labor analgesia technique of epidural anesthesia has been widely used in clinic in recent years because of its obvious analgesic effect, good safety and convenient operation, and has created good conditions for parturient labor (2). Studies have shown that in clinical anaesthesia, the lower the concentration of local anesthetic, the less likely patients are to develop adverse reactions, but at the same dosage, the duration of drug action is relatively shorter. Therefore, finding a suitable anesthetic concentration is of great significance in clinical application (3). Ropivacaine, as a long-acting amide local anesthetic with a single enantiomer, blocked the excitation and transmission of nerves by inhibiting the sodium channel of nerve cells. Ropivacaine can bind to proteins to form macromolecules, so it cannot pass through the placental barrier for the central nervous system, and has fewer toxic side effects on the central nervous system. In addition, it has little adverse effects on the fetus and it is a common anesthetic in clinical delivery (4). There have been few studies on the effects of labor analgesia on the physical environment of parturient. However, there are also reports that one of the effects of epidural analgesia on parturient is to increase the febrile rate of parturient, which has certain adverse effects on the delivery of parturient and the safety of mothers and infants (5), and intrapartum fever caused by epidural labor analgesia has become a hot topic in obstetrics (6,7). At present, the mechanism of fever in parturient during epidural analgesia is not very clear, but some studies have reported that fever is related to the thermotaxic center of parturient, but the most likely mechanism is inflammation (8).

Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are very important cytokines and cellular activity factors

in parturition, which are closely related to the delivery process. It has been reported that IL-6 is not only closely related to pregnancy, but also plays a very important role in labor (9). IL-6 can increase the synthesis of prostaglandins and induce uterine contraction to initiate labor process. It is also a very important cell factor during the process of immune response and involved in inflammation (10). As an important inflammatory transmitter and immunomodulatory factor, TNF-α is produced by mononuclear macrophages, and its mechanism of labor facilitation during labor is similar to that of IL-6 (11). According to relevant reports, if epidural analgesia is used in labor, the level of IL-6 and TNF-α in maternal serum will increase significantly as analgesia time increases, and the IL-6 level in serum of febrile parturient is significantly higher than that of the non-febrile parturient (12). Therefore, some scholars believe that the increase in febrile rate during parturition may be due to the release of inflammatory factors caused by the use of extracellular analgesia (13).

In order to make a further demonstration of the above conclusion, this study explored the effects of ropivacaine at different concentrations on intrapartum fever, IL-6 and TNF-α in the parturient with epidural labor analgesia.

Materials and methods

General materials. Medical records of 198 cases of primiparas admitted to Obstetrics and Gynecology Department in Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine (Shanghai, China) from January 2017 to January 2018 were analyzed retrospectively and divided into 2 groups. A total of 105 patients were treated with 0.075% ropivacaine injection 10 ml and 0.5 μg/ml sulfentanyl injection 100 ml in parturition as the experimental group. The average age of the patients in the experimental group was 25.9±1.7 years, the gestational age was 37-41 weeks, the average gestational age was 39.3±0.5 weeks, the body weight was 60.3±2.9 kg, and the dilatation degree of cervix before analgesia was 1.9±0.4 cm. A total of 93 patients were treated with 0.1% ropivacaine injection 10 ml and 0.5 μg/ml sulfentanyl injection 100 ml in parturition as the control group. The average age of the patients in the control group was 26.1±1.5 years, the gestational age was 38-42 weeks, the average gestational age was 38.9±0.7 weeks, the body weight was 60.1±3.1 kg, and the dilatation degree of cervix before analgesia was 2.0±0.6 cm.

Inclusion and exclusion criteria. Inclusion criteria: all parturients were primiparas, full-term singletons and transvaginal pregnancies. Regular uterine contraction was <10 h, and labor analgesia by epidural anaesthesia was requested by primiparas themselves. Exclusion criteria: parturients with cardiopulmonary dysfunction, endocrine disease history, contraindications for epidural puncture, and body temperature higher than 37.5˚C before analgesia were excluded. All parturients and their families signed an informed consent, and cooperated with the medical staff to complete the diagnosis and treatment. The study was approved by the Ethics Committee of Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine.

Experimental reagents and instruments. Sodium lactate was purchased from Shanghai Baxter Medical Supplies Co., Ltd. (SFDA Approval no. H19993749; Shanghai, China). Ropivacaine was purchased from Jiangsu Hengrui Medicine Co., Ltd. (SFDA Approval no. H20060137; Jiangsu, China). Sulfentanyl was purchased from Yichang Renfu Pharmaceutical Co., Ltd. (SFDA Approval no. H20054256; Yichang, China). IL-6 (ELISA) kit and TNF-α (ELISA) kit were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd. (Shanghai, China).

Methods. Sodium lactate 8 ml/(kg/h) was injected after the establishment of upper limb intravenous access, upper fetal heart monitoring and ECG monitoring were conducted when two groups of parturient entered the labor room, and the temperature was adjusted to 23-25˚C. Epidural puncture was performed from the L2-3 space and the catheter was inserted into side of head, and the depth was about 3-4 cm. 1.5% lidocaine 3 ml was injected into the body, if there was no adverse reaction after 5 min, the catheter was fixed and connected to the patient-controlled epidural analgesia pump. 0.075% ropivacaine injection 10 ml, 0.5 μg/ml sulfentanyl injection 10 ml in the experimental group, and 0.1% ropivacaine injection 10 ml, and 0.5 μg/ml sulfentanyl injection 100 ml in the control group were injected into the epidural analgesia pump for anaesthesia. In both groups, the loading dose was 3 ml, the background infusion dose was 4 ml/h, the single supplementary PCA dose was 2 ml/time, and the locking time was 15 min. Anaesthesia infusion was stopped at full opening of the uterus and epidural catheter was removed after the perineal stitch. Venous blood 2 ml was taken at T1 (cervix open to 2 cm), T2 (cervix fully open) and T3 (24 h postpartum) and the concentration of IL-6 TNF-α was detected by ELISA. All the operations were carried out strictly according to the instructions of the kit.

Observation index. Visual analogue score (VAS) of parturient pain, labor duration, analgesic time, febrile rate of parturient after administration at cervix open to 2 cm, cervix open to 4 cm, cervix fully open, and the concentration changes of IL-6 and TNF-α in serum of parturient at T1, T2 and T3 were observed and compared. During epidural labor analgesia, the temperature of the parturient was measured and recorded once an hour until the end of labor. If body temperature was higher than 37.5˚C, it was considered febrile. VAS judging criteria (14): painless is 0 point, mild pain is 1-3 points, moderate pain is 4-7 points, and severe pain is 8-10 points.

Statistical analysis. The statistical analysis was conducted by SPSS 15.0 [AsiaAnalytics (formerly SPSS China)] statistical software, and the measurement data were represented by mean ± SD. Student's t-test was used for comparison between the two groups. Repeated analysis of variance was used at different time-points. Chi-square test was used for enumeration data. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of normal information between the two groups. There was no significant difference in age, body weight,

Table I. Basic information.

Factors	Experimental group n=105	Control group n=93	t	P-value
Age	25.9±1.7	26.1±1.5	0.873	0.384
Body weight (kg)	60.3±2.9	60.1±3.1	0.469	0.640
Height (cm)	160.2±4.2	159.7±6.3	0.664	0.508
Gestational age (week)	39.0±0.5	38.9±0.6	1.279	0.203
Cervix dilatation degree (cm)	1.9±0.4	2.0±0.6	1.394	0.165
Blood loss (ml)	249.35±78.14	261.47±80.71	1.073	0.285
Complete blood count				
Hemoglobin (g/l)	98±22	102±17	1.418	0.158
RBC ($x10^{12}$/l)	3.09±0.69	3.11±1.04	0.161	0.872
Leucocyte count (x10/l)	11.04±1.21	10.91±1.26	0.740	0.460
Blood sugar (mmol/l)	5.97±1.01	6.22±0.98	1.763	0.080

Table II. Comparison of VAS scores between the two groups at different time-points.

Time	Experimental group n=105	Control group n=93	t	P-value
Cervix open to 2 cm	7.2±1.3	6.9±1.2	1.680	0.095
Cervix open to 4 cm	4.1±1.5	4.2±1.1	0.529	0.597
Cervix fully open	1.9±0.4	1.8±0.4	1.756	0.081

VAS, visual analogue score.

gestational age, blood loss and blood sugar between the two groups (Table I).

Comparison of VAS scores between the two groups at different time-points. The VAS scores were 7.2±1.3, 4.1±1.5 and 1.9±0.4, respectively at cervix open to 2 cm, cervix open to 4 cm, cervix fully open in the experimental group, and the VAS scores were 6.9±1.2, 4.2±1.1 and 1.8±0.4 in the control group. There was no significant difference in VAS score between the two groups (P>0.05; Table II).

Comparison of body temperature and febrile rate between two groups at different time points. Before analgesia and 1, 2, 3 h after analgesia, the temperature of parturients in both groups did not increase significantly and there was no significant difference in body temperature between the two groups (P<0.05). While the body temperature was significantly higher at 4 and 5 h after analgesia, parturition and 1 h postpartum than that before analgesia, and the body temperature in the control group was significantly higher than that in the experimental group at 4 and 5 h after analgesia (P<0.05). There were 21 febrile parturients in the experimental group, and the febrile rate was 20.00%. There were 39 febrile parturients in the control group, and the febrile rate was 41.94%. The febrile rate in the experimental group was significantly lower than that in the control group (P<0.05; Table III).

Comparison of labor duration at different stages and analgesia time between the groups. There was no significant difference in the first and third stage of labor between the two groups (P>0.05). However, the second stage of labor and analgesic time in the experimental group were significantly shorter than those in the control group (P<0.05; Table IV).

Concentration changes of IL-6 and TNF-α in serum of parturient at T1, T2 and T3. There was no significant difference in IL-6 and TNF-α between the two groups at T1 and T3 (P>0.05). However, IL-6 and TNF-α concentrations in the experimental group were significantly lower than those in the control group at T2 (P<0.05; Figs. 1 and 2).

Discussion

Labor pain is a complex, subjective, multidimensional response to sensory nerve stimulation during labor (15). For many parturients, labor analgesia not only alleviates the pain during delivery, but also reduces the stress and cesarean section rate of parturient. Therefore, an increasing number of parturients choose labor analgesia during delivery (16,17). Epidural labor analgesia creates a good labor condition for parturients, but there are also some problems, among which fever in parturient due to epidural anaesthesia is a subject of great concern at present (18). Fever or even ardent fever during delivery may lead to intrauterine fetal death, neonatal septicemia and other problems (19). Therefore, clarifying the mechanism of epidural anesthesia in increasing maternal temperature and controlling the temperature rise of parturient by adjusting the way of administration and

Table III. Comparison of body temperature and febrile rate between the two groups at different time-points.

Time	Experimental group n=105	Control group n=93	t/χ^2	P-value
Before analgesia	36.3±0.3	36.4±0.3	2.341	0.020
1 h after analgesia	36.6±0.3	36.7±0.4	2.004	0.047
2 h after analgesia	36.8±0.4	36.7±0.5	1.728	0.086
3 h after analgesia	36.8±0.6	36.7±0.5	1.265	0.208
4 h after analgesia	36.9±0.3[a]	37.1±0.5[a]	3.457	<0.001
5 h after analgesia	37.0±0.5[a]	37.3±0.6[a]	3.836	<0.001
At parturition	37.0±0.6[a]	37.1±0.6[a]	1.170	0.243
1 h postpartum	36.9±0.7[a]	37.0±0.6[a]	1.072	0.285
Febrile rate [n, (%)]	21 (20.00)	39 (41.94)	11.24	<0.001

[a]P<0.05, body temperature was significantly higher than that before analgesia.

Table IV. Comparison of labor duration at different stages and analgesia time between two groups (min).

Factors	Experimental group n=105	Control group n=93	t	P-value
First stage	639.18±45.27	634.31±43.41	0.770	0.442
Second stage	52.75±1.66	74.74±3.42	58.57	<0.001
Third stage	8.76±0.69	8.51±0.85	2.282	0.024
Analgesic time	169.72±14.98	257.32±25.09	30.21	<0.001

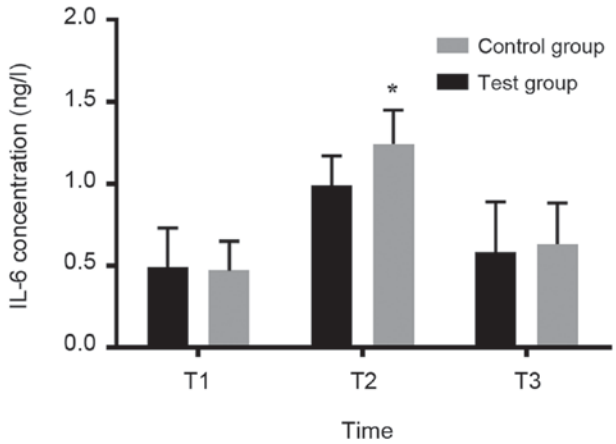

Figure 1. Concentration changes of IL-6 in serum at different time-points in the two groups (ng/l). There was no significant difference in IL-6 concentration between the experimental and control groups at T1 and T3 (P>0.05). However, IL-6 concentration in the experimental group was significantly lower than that in the control group at T2 (P<0.05). Concentration in the experimental group was significantly lower than that in the control group (*P<0.05); IL-6, interleukin-6.

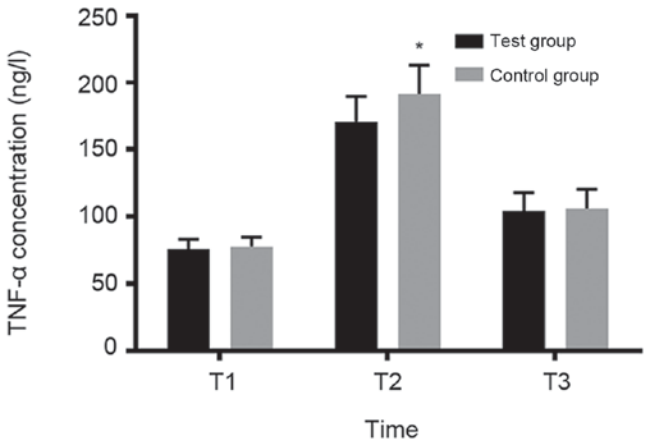

Figure 2. Concentration changes of TNF-α in serum at different time-points in the two groups (ng/l). There was no significant difference in TNF-α concentration between the experimental and control groups at T1 and T3 (P>0.05). However, TNF-α concentration in the experimental group was significantly lower than that in the control group at T2 (P<0.05). Concentration in the experimental group was significantly lower than that in the control group (*P<0.05), TNF-α, tumor necrosis factor-α.

metering of anesthesia has become a hot research topic in recent years. IL-6 and TNF-α are important factors during parturition. The concentration of IL-6 and TNF-α changes with the concentration change of epidural anesthetic, which affects maternal body temperature in a different degree (20). Observing the effect of ropivacaine at different concentrations on cell factor level in parturient with epidural labor analgesia is helpful to provide reference for clinical use of epidural labor analgesia.

In this study, it was found that there was no significant difference in VAS score between the experimental and control groups (P>0.05) at cervix open to 2 cm, cervix open to 4 cm and cervix fully open, which indicated that there was no significant difference in the analgesic effect of parturients when ropivacaine concentration was 0.1 and 0.075%, respectively. When comparing the body temperature and febrile rate of the groups at different time-points, it was found that before analgesia and at 1, 2, 3 h after analgesia, the temperature

of parturients in both groups did not increase significantly and there was no significant difference in body temperature between the two groups (P>0.05). The body temperature significantly increased at 4 and 5 h after analgesia, parturition and 1 h postpartum, and the body temperature in the control group was significantly higher than that in the experimental group at 4 and 5 h after analgesia (P<0.05). There were 21 febrile parturients in the experimental group, and the febrile rate was 20.00%. There were 39 febrile parturients in the control group, and the febrile rate was 41.94%. The febrile rate in the experimental group was significantly lower than that in the control group (P<0.05). The results indicated that the increase in body temperature and febrile rate of epidural labor analgesia with 0.075% ropivacaine combined with sulfentanyl were smaller than that with 0.1% ropivacaine, which was consistent with the results of Gogarten *et al* (21). The comparison of labor duration at different stages and analgesia time showed that the duration of the first and third stages of labor was the same, and there was no significant difference between the two groups (P>0.05). However, the second stage of labor and analgesic time in the experimental group were significantly shorter than those in the control group (P<0.05). Studies have also shown that epidural anesthesia with 0.075% ropivacaine combined with sulfentanyl could not only achieve a good analgesic effect, but also result in a shorter second stage of labor (22,23). The reason is that the concentration of ropivacaine is positively correlated with the time of analgesia, and the effect of low dose of anaesthesia on uterine contraction is small. IL-6, as the main pro-inflammatory cytokine, has been used as a marker of perioperative inflammatory response in many studies. TNF-α, as an inflammatory cytokine closely related to the pain acceleration, can cause late immunologic injury (4,24). The concentration changes of IL-6 and TNF-α levels in serum of parturients at T1, T2 and T3 were evaluated in this study. The result showed that there was no significant difference in IL-6 and TNF-α concentration between the two groups at T1 and T3 (P>0.05). However, the IL-6 and TNF-α concentrations in the experimental group were significantly lower than those in the control group at T2 (P<0.05). This suggested that the use of 0.075% ropivacaine contributed to inflammation <0.1% ropivacaine.

In conclusion, the effect of patient-controlled epidural administration with 0.075% ropivacaine injection combined with 0.5 mg/ml sulfentanyl injection on labor analgesia is shorter than that with 0.1% ropivacaine combined with sulfentanyl. It can also result in a shorter second stage of labor and analgesia time, lower intrapartum febrile rate, and contributed to inflammation <0.1% ropivacaine combined with sulfentanyl. However, labor itself is a complex process, and is affected by many factors. We mainly studied the influence of the preliminary test of anesthesia record on labor, so we did not record the auxiliary anesthesia dosage used by the labor in the experiment, which is also a negligence of this study. Therefore, the way and dosage of labor analgesia in clinical application need to be further explored and studied.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XZ and JL recorded and analyzed the general information of patients. SD was responsible for upper fetal heart monitoring and ECG monitoring. ZX and ZL contributed to observation index analysis. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine (Shanghai, China) and written informed consents were signed by the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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