Efficacy and safety of dexmedetomidine-ropivacaine versus sufentanil-ropivacaine for epidural labor analgesia: a randomized controlled trial

Mei Fan[1#], Juan Li[2#], Rong Cao[1], Lili Hu[3], Sunshan Lu[3*]

[1]Department of Anesthesiology, The Affiliated Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu Women's and Children's Central Hospital, No.1617, Riyue Avenue, Qingyang District, Chengdu 610091, Sichuan, P.R. China.

[2]Department of Anesthesiology, Chengdu Fifth People's Hospital. Chengdu 611130, Sichuan, P.R. China.

[3]Department of Anesthesiology, First Affiliated Hospital of Army Medical University. Chongqing 400038, P.R. China.

[#]Both authors contributed equally to this study.

*Corresponding author's information: Sunshan Lu, Department of Anesthesiology, First Affiliated Hospital of Army Medical University, No.30 Gaotanyan Road, Shapingba District, Chongqing 400038, P.R. China.

E-mail: lussdoctor @163.com

Abstract

Background: Sufentanil combined with ropivacaine is commonly used for epidural labor analgesia, but it may cause some adverse effects. Dexmedetomidine is suitable for long-term and short-term intraoperative sedation and analgesia, and it can reduce the use of the opioid sufentanil. This study compared the efficacy and safety of dexmedetomidine and sufentanil combined with ropivacaine for epidural labor analgesia.

Study design and participants: A randomized, triple-blinded and controlled trial was performed for epidural labor analgesia. From October 2020 to February 2021, 160 parturient women were randomized 1:1 to receive ropivacaine combined with dexmedetomidine or sufentanil.

Interventions: Ropivacaine combined with dexmedetomidine (group RD, n = 80; 10 mL 0.5 μg/mL dexmedetomidine + 0.1% ropivacaine) or sufentanil (group RS, n = 80; 10 mL 0.5 μg/mL sufentanil + 0.1% ropivacaine).

Main outcomes and measures: The primary outcomes were the pain relief of parturient women assessed by visual analog scale (VAS) score, and the physical status of newborns assessed by neonatal behavioral neurological assessment (NBNA) score and Apgar score. Second outcomes included duration of labor stages, and adverse reactions on parturient women and newborns.

Discussion: This current study can provide evidence for the efficacy and safety of dexmedetomidine versus sufentanil for labor epidural analgesia.

Ethics: The study is approved by Chengdu Women and Children's Central Hospital Ethics Committee.

Trial registration: Chinese Clinical Trial Registry (registration number: ChiCTR2000038702)

Keywords: Epidural labor analgesia; ropivacaine; dexmedetomidine; sufentanil

1. Introduction

The pain associated with delivery can cause a series of neurophysiological changes, such as increased maternal stress hormones, elevated blood pressure, hyperventilation, decreased fetal oxygen transport, and psychological distress [1, 2]. Epidural analgesia is a central nerve block technique achieved by injecting local anesthetics near the nerve that transmits pain, and it is widely used for epidural labor analgesia because of its obvious effects, good safety, and convenience of operation [3, 4]. However, epidural labor analgesia may have a poor prognosis due to the use of anesthetics, such as motor block, maternal hypotension, prolonged second stage of labor, and urinary retention [3]. Therefore, the selection of anesthetics is of great importance for epidural labor analgesia.

Ropivacaine is a long-acting amide local anesthetic, usually used in clinical delivery practice, which has less toxic side effects to the central nervous system and no adverse effects on the fetus [5, 6]. At present, the combined use of local anesthetics and adjuvant drugs is common for epidural labor analgesia, which can reduce the dose of local anesthetics, improve the analgesic effect, avoid motor block, and reduce the incidence of related side effects [7]. Sufentanil as an adjuvant combined with ropivacaine has been widely used for epidural labor analgesia, which can reduce the incidence of instrumental delivery, cesarean section, and postpartum hospitalization [8-10]. However, sufentanil as an opioid may cause adverse effects such as respiratory depression, vomiting, headache, and urinary retention [11, 12]. Dexmedetomidine is an α2-adrenoceptor agonist that has been successfully used for epidural labor analgesia with fewer adverse effects [13, 14]. Several studies have shown that dexmedetomidine combined with ropivacaine had better analgesic effect and a shorter first-stage labor than sufentanil mixed with ropivacaine [15, 16]. However, the efficacy and safety of dexmedetomidine combined with ropivacaine as a new type of epidural labor analgesia need to be further studied.

The purpose of this study was to compare the efficacy of dexmedetomidine and sufentanil combined with ropivacaine for epidural labor analgesia, and to evaluate the

influences on parturient women and newborns to explore a more effective and safe labor analgesia protocol in the clinic.

2. Methods/Design

2.1 Study design

This study is a randomized, triple-blinded and controlled trial and will be conducted in Chengdu Women and Children's Central Hospital from October 2020 to February 2021. This study was approved by the Chengdu Women and Children's Central Hospital Ethics Committee (approval number: No.2020(89)). Written informed consent will be obtained from all parturient women.

2.2 Participants

2.2.1 Inclusion criteria

(1) Age ≥ 18 years;

(2) Full-term primigravidae with singleton (≥ 37 gestation weeks) and required labor analgesia in the hospital;

(3) Eligible for American Society of Anesthesiology Physical Status I/II;

(4) Be informed and willing to participate in the trail.

2.2.2 Exclusion criteria

(1) Severe heart, lung, liver and kidney diseases, hemorrhagic diseases, or other systemic diseases;

(2) Contraindications to the epidural anesthesia or allergic to the anesthetics used;

(3) Body temperature >37.5℃ before analgesia;

(4) Cervical dilatation >3 cm, non-cephalic pregnancy, cesarean section history or labor induction history;

(5) Known genetic or congenital fetal malformations, fetal growth restriction, or oligohydramnios;

(6) Malignant tumors or severe preeclampsia;

(7) Lower abdominal surgery or urological surgery history;

(8) Spinal deformity or previous spinal surgery.

2.3 Interventions

Parturient women were randomly divided into 2 groups: dexmedetomidine- ropivacaine group (group RD) and sufentanil-ropivacaine group (group RS).

2.3.1 Control group

Participants in the RS group served as the control group and received 10 mL 0.5 μg/mL sufentanil combined with 0.1% ropivacaine.

2.3.2 Trial group

Participants in the RD group served as the trial group and received 10 mL 0.5 μg/mL dexmedetomidine combined with 0.1% ropivacaine.

The mixed solutions of two groups were infused continuously by the patient-controlled analgesia pump at a rate of 6 mL/h. Participants in both groups received the same treatments and obstetric care.

2.4 Outcomes

The primary outcomes were the pain relief of parturient women and the physical status of newborns. The duration of labor stages and adverse reactions of parturient women and newborns were secondary outcomes. Pain relief was quantified by visual analog scale (VAS) scores measured at 0, 15, and 120 min. The physical status of newborns was assessed through Apgar and neonatal behavioral neurological assessment (NBNA) scores. Apgar scores were measured at 1 and 5 min after delivery, and NBNA scores were measured 3 days later.

2.5 Sample size

According to the previous study [17], by setting the VAS score after epidural administration as the primary variable. The sample size was calculated by PASS software (two independent means), and 80 participants were assigned to each group with an α-error of 0.05 and a power of 0.9 (two-sided).

2.6 Randomization and blinding

Eligible participants were randomly assigned in a 1: 1 ratio to two groups before the start of labor. Randomization was computer-generated, and the allocation was hidden through opaque serially numbered sealed envelopes. The computer randomly generated numbers from 0 to 160, and each participant randomly corresponded to a number, and the epidural labor analgesia plan corresponding to each number was executed by a designated person. Study physicians and outcome evaluators were blinded to the analgesic plan. Participants were blinded to the sufentanil or dexmedetomidine groups throughout the trial. Data collectors and statisticians were also unaware of group assignments.

2.7 Data collection and measurement

2.7.1 Data collection

The demographic and baseline measurements including age, gestational age, body mass index (BMI), cervical dilation before analgesia, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, temperature, mean arterial pressure (MAP), and heart rate were recorded. Outcome indicators included VAS scores, Ramsay Sedation Scale (RSS) scores, blood loss, duration of labor stages (first and second stages), onset time of analgesia, the dose of analgesics, Apgar scores, NBNA scores, and adverse reactions (hypotension, tremble, nausea and vomiting, motor nerve block, bradycardia, and respiratory depression).

2.7.2 Measurement

VAS

The total score of VAS is 10, with higher scores indicating greater pain intensity (0=no pain; 1-3=mild pain; 4-6=moderate pain, which was tolerable but disrupted sleep; 7-10=severe pain which was unbearable).

RSS

The RSS value is divided into 6 levels, with RSS value ≥2 representing better sedation (1=anxiety, restless; 2=patients cooperative and tranquil; 3=responsive to the

commands; 4= asleep, brisk response to stimulus; 5= asleep, sluggish response to stimulus; 6=asleep, no response).

Apgar score

The total score of Apgar score is 10, which is based on five signs of neonatal activity, pulse, grimace, appearance, and respiration (10=normal newborn; <7=mild asphyxia; <4=severe asphyxia).

NBNA score

The NBNA score is a 20-item assessment of neonatal behavioral nerves with a total score of 40. A neonatal NBNA score >37 within one week is considered normal, and the neonatal NBNA score within two weeks cannot exceed 37, and long-term follow-up is required.

Hypotension

Hypotension is defined as a 20% decrease in systolic blood pressure from baseline.

Bradycardia

Fetal bradycardia is defined as fetal heart rate <120 beats/min.

Respiratory depression

Respiratory depression is defined as SpO2 < 90% on inspiration.

2.8 Anesthesia procedures

After entering the delivery room, the parturient women's venous channels were opened, and they were provided with cannulas for oxygen inhalation 1 - 2 L/minutes (min). The vital signs of parturient women, such as heart rate, respiratory rate, pulse oxygen saturation, and non-invasive blood pressure were monitored, and meanwhile, fetal heart rate was monitored by Doppler fetal heart monitor. When cervical dilation was about 2 cm, epidural analgesia should be performed. Parturient women were placed in the left decubitus position, with an 18-gauge epidural needle used for epidural puncture in the $L_{2\text{-}3}$ interspace, and the head of epidural catheter was inserted 3-4 cm into the epidural space. When the blood and cerebrospinal fluid aspiration test was negative, a test dose of 3 mL 1% lidocaine was given and observed 5 min. If no adverse reactions were observed, parturient women received 10 mL 0.5 μg/mL dexmedetomidine or 0.5 μg/mL

sufentanil combined with 0.1% ropivacaine as loading dose, which was infused continuously by the patient-controlled analgesia pump at a rate of 6 mL/h. When the visual analog scale (VAS) scores (0 = no pain, 10 = worst pain) were ≥ 5, a rapid bolus injection of 6 mL (lockout for 20 min) was given by pump. The patient-controlled analgesia pump stopped during full cervical dilation. Local-anesthetic solutions for epidural labor analgesia were prepared by another anesthetist, and the investigators knew nothing about these solutions. The progress of cervical dilation was assessed by skilled midwives every 2 hours during the incubation period and every hour during the active period.

2.9 Statistical analysis

Statistical analysis was performed with SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean ± standard deviation (SD) and the groups were to be compared by using t-test, or presented as median and interquartile range [M (Q25, Q75)] and the groups were to be compared by using Mann-Whitney U-test. Categorical variables were displayed as number and percentage [n (%)] and the comparison between groups was performed by Chi-square test ($\chi 2$ test). Because of the low incidence of adverse reactions in the parturient women and newborns, more than 20% of the expected values were less than 5 when the $\chi 2$ test was performed; therefore, Fisher's exact test was used instead. Statistical analyses were two-sided test and $P<0.05$ was considered statistically significant.

2.10 Data registration and monitoring

Each selected case must be filled out by the investigator and completed the Case Report Form (CRF). After verification, the relevant personnel (data management personnel) will be transferred to the data entry, management and statistical work. For questions on the CRF, the data manager will generate a Question Answer Form (DRQ) and send the inquiry to the researcher. The researcher should answer and return as soon as possible. Data curators will revise the data based on the researcher's responses, confirm and enter the data. If necessary, the DRQ can be issued again.

2.11 Ethics and informed consent

Clinical research must follow the Declaration of Helsinki and relevant Chinese clinical research norms and regulations. Before the start of clinical research, the clinical research plan must be approved by the Medical Ethics Committee of Chengdu Women and Children's Central Hospital before clinical research can be carried out. Before selecting subjects for this study, the investigator will introduce the background, purpose, procedures, risks and other issues of the clinical study to the subjects in detail, and answer the research-related questions raised by the subjects. Informed consent for the trial will be obtained voluntarily from all patients prior to investigator inclusion in the study.

Trial status

Recruitment started in October 2020 and the trial has been completed.

Conflict of interest

The authors report no conflicts of interest with regard to this study.

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Author contributions

Conception and design: M Fan, S Lu;

Collection and assembly of data: R Cao, L Hu;

Data analysis and interpretation: All authors;

Manuscript writing: M Fan;

Final approval of manuscript: All authors.

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