Research program

Name: A Multicenter Study of the Efficacy and Safety of Esketamine for Analgesia During Cesarean Section

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Project Guidance:

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Statistical setting: Women’s Hospital, School of Medicine, Zhejiang University

1. Research Background:

In recent years, with the development of anesthesiology and the continuous improvement of anesthesia technology and drugs, the focus of anesthesiologists' work has changed from the successful completion of surgery in the past to the comfort and safety of the present, and anesthesia also pays more attention to reducing the impact of surgical operation and anesthesia factors on the physiological, psychological and spiritual aspects of patients. Epidural anesthesia is widely used in cesarean section because of its good controllability and high safety. Although epidural

anesthesia can provide relatively perfect analgesia and muscle relaxation, it can not completely block the visceral nerve, so the pregnant women often cry out due to the pain and discomfort of peritoneal traction during the operation to explore the uterus, pull the peritoneum and deliver. Even if the block effect is good, the parturients are often accompanied by different degrees of mental tension and anxiety due to the fear of surgery. These phenomena not only bring painful memories and mental trauma to the maternal, but also affect the operation and operation process of the surgical operator, resulting in the need to change the anesthesia method or the maternal satisfaction with anesthesia is reduced. Therefore, it is necessary for epidural anesthesia and cesarean section operation to assist appropriate intravenous analgesics in order to reduce the tension, anxiety and peritoneal traction reaction of the pregnant women.

Ketamine is the only intravenous anesthetic with analgesic effect. As a non-specific antagonist of methyl-D-aspartate receptor (NMDA), ketamine has the characteristics of rapid analgesic effect, short duration of anesthetic effect and slight effect on protective reflex of throat, etc. Ketamine is widely used in intraoperative and postoperative analgesia, which can increase maternal tolerance and comfort of surgery. It has been widely used in cesarean section [1]. However, studies have confirmed that ketamine can cause hallucinations, delirium, nightmares and other mental symptoms, affecting patients' cognitive function and leading to

postoperative cognitive dysfunction [2,3]. Esketamine is a right-optical isomer of ketamine, and its affinity to NMDA, opioid receptor and M-choline receptor is 3 to 4 times, 2 to 4 times and 2 times higher than that of levoketamine, respectively, while its inhibition of 5-hydroxytryptamine receptor is only half of that of levoketamine, and its inhibition of norepinephrine reuptake is stronger [4]. Esketamine anesthetic analgesic hypnosis intensity is twice that of ketamine, to achieve the same anesthetic effect using only half the dose of the latter. The induction dose of intravenous anesthesia is 0.5 to 1 mg/kg, and the maintenance dose is 0.5 to 3 mg/kg*h. A single administration of 0.125 ~ 0.25 mg/kg can achieve analgesic and sedative effects [5]. Since the side effects of ketamine are dose-dependent, the use of lower doses of esketamine can reduce the occurrence of side effects of anesthesia [6].

At present, many narcotic drugs can pass through the placenta to a certain extent and have a certain impact on the mother and child. Due to the characteristics of the placental barrier, whether a drug passes through the placenta and its transport volume are jointly determined by the physical and chemical properties of the mother, placenta, fetus and drug. Any change in the internal environment of the mother and the fetus can have an impact on the way the drug is present. Maternal factors: maternal blood concentration, route of administration, internal environment, pregnancy complications, etc. Fetal factors: liver development degree,

internal environment, drug metabolism and excretion ability, etc. Placental factors: metabolic environment, hemodynamics, maturity, etc. Drug factors: concentration, plasma protein binding power, fat solubility, molecular weight, etc. High concentration, low molecular weight, low plasma protein binding rate, high fat solubility and maternal fetal acidosis can promote placental transfer of drugs [7]. Ketamine is highly fat soluble and easily passes the placental barrier. Clinical Guidelines for Obstetric anaesthesia (2008) state that ketamine can cross the placenta rapidly, but intravenous administration of 1-1.5mg/kg of ketamine has no significant effect on the fetus. Chinese Expert Consensus on obstetric anesthesia (2017) pointed out that ketamine has advantages for pregnant women with asthma and mild hypovolemia, while pregnant women with hypertension and severe hypovolemia are contrainidated. Intravenous injection of 1-1.5 mg/kg ketamine has no significant effect on the fetus, and if the dose is too high, it may cause mental symptoms and increase of uterine tone and respiratory depression of the newborn. The Miller Anesthesiology report states that 25-50μg of ketamine can be used to assist cesarean section when intra spinal anesthesia block is incomplete, and that large doses of ketamine (> 2mg/kg) can cause psychiatric symptoms and increased uterine tone, as well as lower Apgar scores and abnormal muscle tone in newborns.

However, the analgesic effect of intravenous esketamine for cesarean section under intravertebral anesthesia has not been studied, especially the analgesic effect and safety of esketamine in cesarean section, such as placental transport of the drug and its effects on the newborn and the mother have not been clarified.

2. Method

2.1. Randomization and Blinding

Random allocations were generated using SPSS software, version 22.0 (IBM Corp) in a 1:1 ratio. Assignments were concealed in sequentially numbered opaque envelopes. Before anesthesia, study coordinators who otherwise were not involved in the trial opened the envelopes according to the recruitment sequence, prepared esketamine or an identical-appearing saline placebo, and gave the study drugs to the attending anesthesiologists. All patients, anesthesiologists, other health care team members, and investigators who were responsible for data collection and follow-ups were blinded to group allocation.

2.2. Anesthesia Management and Intervention

No premedication was administered. In the operating room, heart

rate and oxygen saturation were monitored continuously, and blood pressure was noninvasively measured every 5 minutes. Epidural catheterization was performed with parturients in the left lateral decubitus position. A 16-G Tuohy needle was used for epidural puncture in the L2-L3 intervertebral space. After confirmation of the epidural space by the loss of resistance to air method, a catheter was inserted 3 to 4 cm in a cephalad direction. Parturients were returned to the supine position with a 15° tilt to the left. Oxygen was provided at 5 L/min via a face mask.

A test dose of 5 mL of 1.5% lidocaine was given. After a 5-minute observation, 10 mL of 0.75% ropivacaine was given, followed by an infusion of 0.75% ropivacaine at 3 to 5 mL/h. The upper sensory block was targeted between the T4 and T6 levels. If not achieved, a supplemental dose of 5 mL of 0.75% ropivacaine was given. Study drugs were administered when the targeted upper sensory block level was achieved (approximately 2 minutes before incision). Specifically, 0.25 mg/kg of esketamine was administered intravenously for 1 minute for patients in the esketamine group; the same volume of normal saline was injected for patients in the control group. During epidural anesthesia, fluid infusion was administered per routine. Blood pressure was maintained within 20% from baseline. At the end of surgery, a patient-controlled epidural analgesia device was attached for postoperative analgesia, which was established with 0.2% ropivacaine

and programmed to deliver a continuous infusion at 2 mL/h.

2. 3. Data Collection and Outcome Assessment

Baseline data included demographic characteristics, pregestational comorbidity, number of gravidity and parturitions, duration of gestation, and ASA classification. Intraoperative data included durations of anesthesia and surgery, fluid balance, use of vasopressors, intervals from study drug administration and uterine incision to delivery, and neonatal data. Intervals from study drug administration to neonatal delivery and from uterine incision to neonatal delivery were also recorded.

Primary outcomes included maternal pain intensity and sedation score immediately after fetal delivery. Pain intensity was assessed with the numeric rating scale (NRS; an 11-point scale, with 0 indicating no pain and 10 indicating the worst pain). Maternal sedation level was assessed with the Ramsay Sedation Scale (with 1 indicating restless; 2, completely awake, quiet, and cooperative; 3, drowsy but responding to verbal commands; 4, lightly asleep but responding to touch or pain; 5, asleep but slowly responding to touch or pain; and 6, deeply asleep and does not respond) at the same time points as above.

Secondary outcomes included maternal pain intensity and sedation score at other time points(before anesthesia, immediately after anesthesia, surgical incision, 5 minutes after study, end of surgery, 6 hours after

surgery, and 12 hours after surgery. drug administration), neonatal Apgar score assessed at 1 and 5 minutes after birth, and postnatal umbilical vein blood gas pH value. Among other outcomes, mean blood pressure, heart rate, and pulse oxygen saturation were measured before anesthesia, immediately after anesthesia, at incision (2 minutes after study drug administration), 5 minutes after study drug administration, immediately after fetal delivery (10 minutes after study drug administration), at end of surgery, and 1 hour after surgery. The requirement of neonatal ward admission and length of hospital stay after surgery were recorded. After childbirth, samples of maternal arterial blood, neonatal umbilical arterial blood, and umbilical venous blood were collected in the esketamine group (n = 13) and stored in a −20 °C refrigerator. Esketamine concentrations were measured with reverse-phase high-performance liquid chromatography

Other Pre-specified Outcomes included Adverse events including hypotension, hypertension, bradycardia, tachycardia and desaturation. Adverse events were recorded as Frequency of occurrence between the time the patient entered the operating room and the end of surgery. Offspring's neurodevelopment was measured by the Ages and Stages Questionnaire, third edition (ASQ-3) at 2 years after birth.The ASQ-3 assesses 5 developmental domains: gross motor skills, fine motor skills, problem-solving ability, communication, and personal and social skills.

Each domain is assessed by 6 questions ascertaining achievement of relevant skills and answered as yes (10 points), sometimes (5 points), or not yet (0 points). Scores for individual items are summed to give an overall continuous score for each of the 5 domains (possible range, 0-60). Mothers' memories of childbirth was assessed by The Birth Memories and Recall Questionnaire (BirthMARQ) at 2 years after childbirth,which focused on parents' positive, negative or mixed emotions at the birth/in recalling the event. Each item (e.g. 'my emotions at the time were extremely negative') was rated on a scale ranging from 1 (strongly disagree) to 7 (strongly agree).

3. Ethical considerations (subject protection, informed consent, privacy and confidentiality, etc.)

(1) All subjects will sign informed consent before the start of the study, and the experimenters will keep patient information and experimental results absolutely confidential;

(2) The purpose of this study was to study the efficacy and safety of esketamine for analgesia during cesarean section, and it was carried out on the basis of ensuring the normal implementation of daily anesthesia; The blood collection operation required by the project is a very mature and common test item in clinical practice, so it will not bring any adverse

effects on the psychological and physiological of the subjects.

(3) The cost of esketamine is within the scope of medical insurance, and the cost of blood sample delivery does not need to charge patients additional costs, and will not increase the financial burden on patients;

(4) Through the study on the effectiveness and safety of esketamine in the analgesia during caesarean section, in order to guide the intravenous analgesia during epidural anesthesia caesarean section operation, so as to reduce the tension and anxiety of parturient women and improve the comfort and satisfaction of patients in the perioperative period.

4. Data management

The Case Report Form shall be filled out by the investigator and must be completed by each enrolled case. The completed Case Report Form shall be uniformly submitted to the group leader, and the group leader shall designate two physicians or secretaries who are not directly involved in this experiment to conduct data entry and management. In order to ensure the accuracy of the data, two data managers should independently make two copies of the input and proofread. After the completion of statistical analysis, the statistical analyst will write the general and sub-reports of statistical analysis, and submit the analysis report to the main researcher of this experiment.