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Effective doses 50% and 95% of subarachnoid injection of sufentanil with ropivacaine in lumbar anesthesia for cesarean section in severe preeclampsia

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Objective: This study aimed to determine the ED50 and ED95 of 10 mg of 0.5% ropivacaine combined with different doses of sufentanil in lumbar anesthesia for cesarean sections in patients with severe preeclampsia by the sequential method. *Methods*: A total of 47 patients with severe preeclampsia, who underwent cesarean section, were enrolled in the present study. The first patient was given a subarachnoid injection of 10 mg of isobaric 0.5% ropivacaine plus 2.5 μg of sufentanil. If the anesthetic effect was satisfactory, the dose of sufentanil used for the next patient was reduced by 0.5 μg. If the anesthetic effect was unsatisfactory, the dose of sufentanil used for the next patient was increased by 0.5 μg. *Results*: The ED50 of sufentanil was 1.830 μg, with a 95% CI ranging within 1.517-2.128 μg, while the ED95 of sufentanil was 2.852 μg with a 95% CI ranging within 2.429-4.338 μg. *Conclusion*: The ED50 and ED95 of 10 mg of isobaric 0.5% ropivacaine combined with different doses of sufentanil in lumbar anesthesia for cesarean sections in patients with severe preeclampsia were 1.830 μg and 2.852 μg, respectively.

Keywords

Ropivacaine; Sufentanil; Severe preeclampsia; Cesarean section; Dose-effect relationship

1. Introduction

Preeclampsia typically occurs in the third trimester and is characterized by hypertension, edema, and proteinuria. Preeclampsia can affect both the mother and the unborn baby and is estimated to affect between 5% and 8% of healthy pregnancies [1]. It is responsible for about 76,000 maternal deaths and 500,000 infant deaths per year worldwide [1]. Preeclampsia is subdivided into mild and severe forms, with 50% of preeclamptic women experiencing the latter.

Elective cesarean delivery (CD) is the most frequently adopted delivery mode to terminate pregnancy in women suffering from preeclampsia. The currently preferred anesthesia modality for women with preeclampsia undergoing CD is spinal anesthesia [2]. Intrathecal ropivacaine for spinal anesthesia is a widely accepted technique for cesarean sections. It has the following advantages: rapid onset of effect, satisfactory analgesic effect, reliable sacrococcygeal anesthesia, lower intensity motor block with a shorter duration, and high satisfaction of pregnant women and surgeons during the operation [3, 4]. However, in order to achieve a good anesthetic effect, it is often necessary to control the anesthetic level above the T6 vertebrae. This usually causes a large drop in blood pressure, resulting in maternal nausea, vomiting, and other discomforts.

Adding opioids to local anesthetics for spinal anesthesia can improve the quality of anesthesia, prolong the action time, reduce the dosage of local anesthetic, and shorten the onset time of local anesthesia [5, 6]. Sufentanil is a lipophilic opioid that has less headward diffusion and a stronger analgesic effect when compared with fentanyl [7]. It is a common drug used in cesarean sections in combination with the local anesthetic ropivacaine and has a good clinical effect and little hemodynamic frustration. The combined use of sufentanil with local anesthesia for spinal anesthesia in women having cesarean sections who suffer from severe preeclampsia has been occasionally reported. In these cases, the doses of sufentanil range between 2.5-7.5 μg [8–10]. However, the optimum effective dose remains unclear.

Our hospital carried out combined spinal-epidural anesthesia (CSE) for cesarean sections in patients with severe preeclampsia. The present study aimed to determine the effective dose 50% (ED50), effective dose 95% (ED95), and 95% confidence interval (CI) of lumbar anesthesia with 10 mg of 0.5% ropivacaine and sufentanil for cesarean sections in patients with severe preeclampsia using the sequential method, in order to provide a reference for clinical treatment.

2. Methods

We recruited pregnant women with severe preeclampsia at term who were due to undergo an elective cesarean section, from December 1, 2017, to February 28, 2018. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Fujian Maternity and Child Health Hospital (No. 2018-190).

Inclusion criteria were as follows: (1) pregnant woman scheduled for elective cesarean delivery under spinal anesthe-

sia with a diagnosis of severe preeclampsia; (2) the pregnant woman was over 18 years old; (3) healthy singleton pregnancy was beyond 36 weeks' gestation; (4) American Society of Anesthesiologists (ASA) physical status of the woman was grade II/III; (5) platelet count (PLT) was $> 100 \times 10^9$/L. Severe preeclampsia was diagnosed based on the criteria established by the American College of Obstetrics and Gynecology. Pregnant women were excluded from the study if they met any of the following criteria: (1) The pregnant woman had complications from heart and brain dysfunction, spinal deformity, a multiple pregnancy, diabetes mellitus or gestational diabetes mellitus and intraspinal block contraindication; (2) The pregnant woman had received preoperative injections of opioids.

All the pregnant women would receive antihypertensive drugs before the operation, in order to control blood pressure between 150-180/90-105 mmHg.

After entering the operating room, the pregnant women were routinely monitored using a multifunctional monitor for noninvasive systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), pulse oxygen saturation (SpO_2) and electrocardiogram (ECG). All pregnant women were placed in the left-lateral position. The puncture was performed at L_{3-4} using a lumbar puncture needle for spinal-epidural anesthesia. The epidural space was determined through the loss of resistance (LOR) of saline in the 18G Tuohy needle. A subarachnoid block (SAB) was performed with a 27G Whitacre needle using the needle-in-needle technique. Local anesthetics (0.5% ropivacaine mixed with different doses of sufentanil) were injected into the subarachnoid space when there was reflux of colorless and transparent cerebral fluid, and the injection duration was 15 seconds. After the injection, the spinal puncture needle was removed, and a 20G porous epidural catheter with metal wire was placed in the epidural space. Patients lay on their backs with left uterine displacement, and oxygen was supplied at the rate of 4 liters/minute through the mask. In line with our standard practice, blood pressure monitoring was started immediately after intrathecal injection and was assessed every two minutes within ten minutes of the injection. The formula for the anesthetics was as follows: 10 mg of 1% ropivacaine (AstraZeneca, Sweden) plus different doses of sufentanil (Yichang Humanwell, China). These were diluted with CSF to 2 mL.

The sequential method was designed in the up-to-down order. The first patient received lumbar spinal anesthesia with 10 mg of isobaric 0.5% ropivacaine + 2.5 μg of sufentanil. Then, the dose of sufentanil was adjusted according to the anesthetic effect, and the dose of sufentanil for the next patient was reduced by 0.5 μg. If the effect was not satisfactory, the dose of sufentanil for the next patient was increased by 0.5 μg. If the result was suspicious, the next patient received the same dose as the previous one.

Successful anesthesia was defined as when the bilateral sensory block level of acupuncture reached the T6 level within ten minutes of the intrathecal drug injection. Failure of anesthesia was defined as when the anesthetic level did not reach the T6 level, or the patient required additional analgesia, and the completion of surgery required adjuvant epidural analgesia, at ten minutes after intrathecal administration [11]. In cases of failure, the pregnant woman could request supplemental anesthesia to complete the surgery. The 100-mm VAS was used to evaluate the analgesic effect, in which 0 points represent no pain, and 100 points represent "the most severe pain". Successful anesthesia and failed anesthesia were regarded as the final endpoint for calculating the ED50 of spinal ropivacaine.

The time for the bilateral sensory block to reach the T6 level was detected by acupuncture and recorded. Hypotension was defined as an SBP lower than 80% of basal blood pressure. In this case, the anesthesiologist in charge would perform an intravenous injection of 50-100 μg of phenylephrine, and repeated administration would be performed when necessary. Bradycardia was defined as an HR lower than 50 bpm. In this case, 0.3 mg of atropine would be injected intravenously, and repeat administration would be performed when necessary. The total doses of phenylephrine and atropine were recorded.

The adverse events during and after the operation, such as hypotension, bradycardia, sedation, nausea, vomiting, shivering, and itching, were recorded.

The bilateral sensory level detected by acupuncture was evaluated by the Hollmen scale [12]: 0 = ability to appreciate a pinprick as sharp; 1 = ability to appreciate a pinprick as less sharp; 2 = inability to appreciate a pinprick as sharp (analgesia); 3 = inability to appreciate a pin touching (anesthesia). The operation was allowed when the pregnant woman's sense reached the T6 level or above, or the Hollmen scale was grade 2, until the T6 sensory block.

Sedation was assessed on the 5-point scale: (1) fully awake and oriented patient; (2) drowsy; (3) eyes closed and arousable on command; (4) eyes closed and arousable to physical stimuli; (5) eyes closed, but the patient was not arousable to physical stimuli [16].

Data were statistically analyzed using the software SPSS 24.0. Normally distributed measurement data were expressed as mean $\pm$ standard deviation ($x \pm SD$). ED50 and ED95, as well as the 95% CI of sufentanil, were evaluated using the Probit regression model.

3. Results

Fifty women with a diagnosis of preeclampsia presenting for an elective cesarean section under spinal anesthesia were assessed for eligibility. Of these, three pregnant women failed to complete the study (one woman experienced a wrong dosage setting, and two women were injected with opiates before anesthesia). In these cases, the expected dose was used for the next patient. Therefore, 47 patients were included in the final data analysis.

Table 1. The maternal demographics and operative data of the puerperants (n = 47)

Characteristics	x ± s
Age (years)	28.3 ± 4.2
Weight (kg)	76.5 ± 3.3
Hight (cm)	160.6 ± 5.3
Gestational age (weeks)	36.1 ± 4.5
Operative time (min)	53.3 ± 4.2

Note: SD, standard deviation. Date are expressed as mean ± standard deviation (x ± SD). No significant differences were observed.

Table 2. The frequency of maternal adverse events (n = 47)

Adverse event	n (%)
Pruritus	12 (25.5)
Nausea	4 (8.5)
Vomit	2 (4.3)
Shiver	4 (8.5)
Sedation	18 (38.3)
Hypotension	0
Bradycardia	0

Date are expressed as percentage of group total.

The maternal demographics and operative data are presented in Table 1. The frequency of maternal adverse events is presented in Table 2. No neonatal side-effects have been observed. Fig. 1 reveals the up-to-down order. Among these patients, 24 patients were effective in analgesia, and 23 patients were ineffective in analgesia. According to the formula of Dixon and Massey [13], it was calculated that the ED50 of sufentanil was 1.830 μg with a 95% CI of 1.517-2.128 μg, while the ED95 was 2.852 μg with a 95% CI of 2.429-4.338 μg.

4. Discussion

The most important pathophysiological change in severe preeclampsia is systemic vasospasm, which can affect uterine placental perfusion, and it is one of the most serious pregnancy complications of the third trimester [1]. When these patients need a cesarean section, medical staff should strive for the quiet and complete analgesia of puerperants during anesthesia to reduce the stress response. Epidural anesthesia is the most commonly used anesthesia at present. However, approximately 23% of patients will suffer from an incomplete block [14], which seriously affects the hemodynamic stability of the puerperants. However, in general anesthesia, an abnormal increase in blood pressure will occur during the laryngoscope placement, endotracheal intubation, and extubation, causing hypertension crises and strokes. Patients with severe preeclampsia often have complications with airway edema, which can increase the risk of a difficult airway, resulting in a failure of intubation and ventilation, and difficult airway management is the main cause of morbidity and mortality in patients with preeclampsia [15]. Studies have reported that spinal anesthesia can be used in patients with severe preeclampsia for cesarean sections [16, 17], and this has often been used as the anesthesia method for emergency cesarean sections.

The minimum local effective anesthetic dose (MLAD) of sufentanil is equivalent to ED50; that is, the effective dose of analgesics for 50% patients, which has important significance for selecting a suitable dose in clinics. In the present study, the Dixon-Massey method was adopted. Its characteristics are that the sequential trials of subjects were performed one by one, and the dose used for the next subject was determined according to the response of the previous subject. This trial method can concentrate the dosing process close to the most effective reaction rate ED50 to avoid an inefficient reaction rate. The advantage is that it can make full use of the information provided by the data, and it can decrease the number of observation cases by 30%-40% accordingly when compared with other methods [18]. The ED50 value assessed by the up-to-down sequential allocation method represents only a single point along the dose-response curve but does not show the steepness of the curve [19]. In clinical practice, ED95 may be more important.

The dose of ropivacaine was chosen as a reference to the literature [20]. In the present study, the applied dose of ropivacaine was 10 mg. Gautier *et al.* reported that local anesthetic combined with 2.5 μg of sufentanil could achieve a satisfactory anesthetic effect in lumbar anesthesia for cesarean sections [21]. In the present study, the initial dose of sufentanil was set at 2.5 μg, to investigate the best effective dose of ropivacaine combined with sufentanil for a cesarean section in severe preeclampsia. Finally, 47 puerperants were included in the present study. The ED50 of sufentanil was 1.830 μg with a 95% CI of 1.517-2.128 μg, while the ED95 was 2.852 μg with a 95% CI of 2.429-4.338 μg. The combined use of sufentanil with local anesthesia for spinal anesthesia in women with severe preeclampsia who were undergoing cesarean sections has been reported occasionally. In these reports, the doses of sufentanil range from 2.5-7.5 μg [8–10]. The ED50 of sufentanil obtained in the present study was much lower than the doses used in previous studies.

Shivering is a common event during spinal anesthesia for cesarean sections (the incidence occurs in 38%-70.7% of cases) [22, 23], and may make the patient feel uncomfortable, increase oxygen consumption, and produce lactic acidosis. The study by De Figueiredo *et al.* [24] suggested that the addition of sufentanil to bupivacaine and morphine during spinal anesthesia provided a beneficial effect for the prevention of shivering. Thus, sufentanil could have promising uses as an agent for shivering prevention in parturients. In the present study, the investigators noted that the incidence of shivering was low, and this is consistent with previous studies [5, 24].

With the increase in the dose of sufentanil in the subarachnoid space, patients may have a sedative depth significantly correlated to sufentanil dose [25, 26]. However, in the present study, the highest level of sedation was level 2,

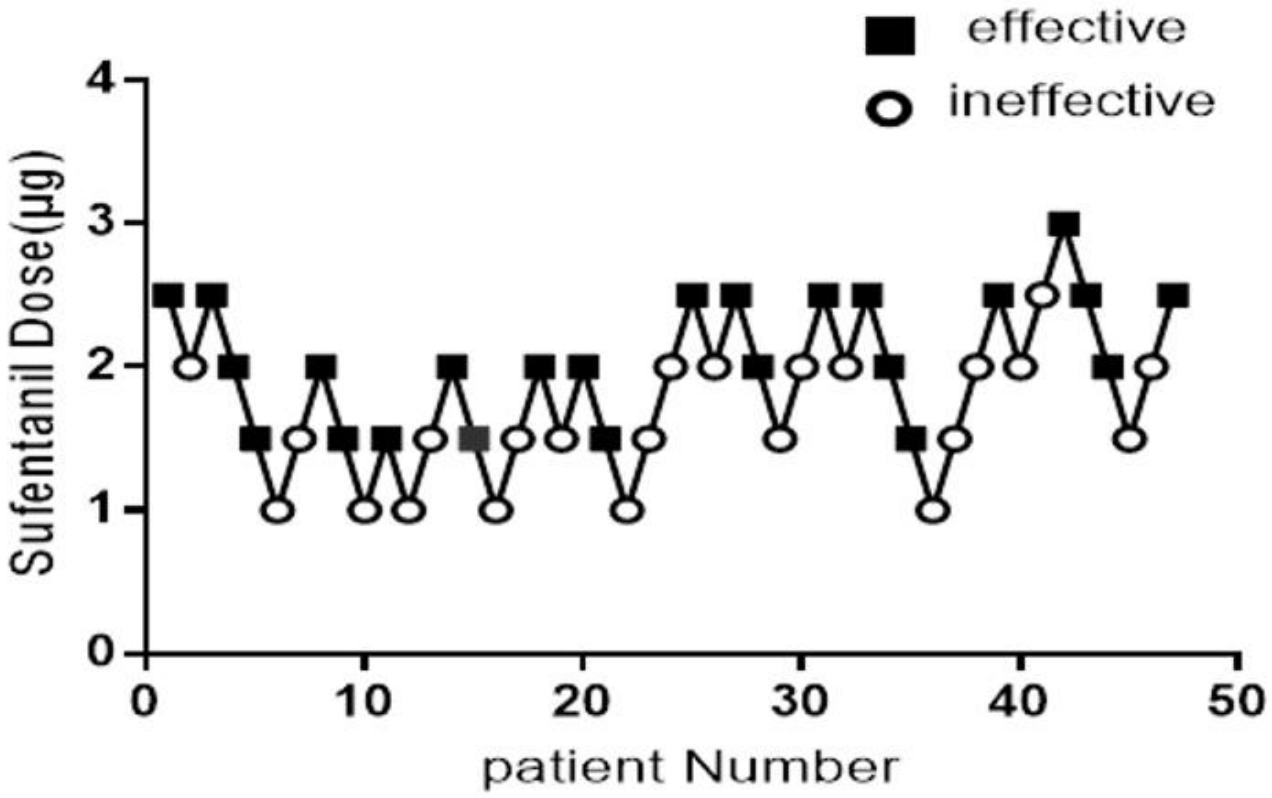

Fig. 1. The dose of sufentanil was used in the up-to-down order. The effective dose was expressed as a square, while the ineffective dose was expressed as a round.

and none of these patients required a strong level of sedation. Although the results of sedation during cesarean sections are controversial, according to the investigators' experience in clinical practice, the investigators considered that mild to moderate sedation levels can reduce intraoperative anxiety, and that mild sedation below level 2 is beneficial for patients undergoing a cesarean section.

With the increase in the dose of sufentanil, dose-related adverse events, such as pruritus, often occur [27]. Pruritus is a common unwanted side-effect of intrathecal opioid administration that can decrease patient satisfaction with anesthesia. In the present study, the investigators observed that the incidence of pruritus was high (25.5%), which was similar to the results reported by Demiraran *et al.* [28]. However, its intensity was mild and of short duration. Hence, the treatment was not required.

There were several limitations to the present study. First, the present study was carried out in a single center. Hence, the intraoperative fluid and anesthetic management may differ from those in other institutions. Second, the investigators only analyzed the data from puerperants of the same ethnic group. There may be regional or racial differences in other groups. Hence, similar studies in other countries are needed to confirm this. Third, obstetricians have different surgical experience and skill levels, and these may have an impact on the results. Finally, recent developments in pharmacogenetic research have identified numerous genetic variations that may impact on the analgesic response to opioids [29]. For example, a previous study revealed that women carrying the variant allele of p.118A/G of OPRM1 (G118) had a lower ED50 for sufentanil given for early labor analgesia than women homozygous for the wild-type allele [29]. But in this study, we did not investigate the role of genetic polymorphisms on the ED50 of sufentanil. Future studies in this field are needed.

In summary, in 10 mg of 0.5% isobaric ropivacaine, combined with different doses of sufentanil in lumbar anesthesia for cesarean sections in patients with severe preeclampsia, the ED50 of sufentanil was 1.830 μg, with a 95% CI of 1.517-2.128 μg, while the ED95 was 2.852 μg, with a 95% CI of 2.429-4.338 μg.

Author contributions

Jing Wang and Min Zhou designed the research study. Jing Wang and Li Zhang performed the research. Min Zhou provided help and advice on the experiments. Long-Xin Zhang analyzed the data. Jing Wang, Li Zhang and Min Zhou wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

Authors declare that there is no conflict of interest.

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