Minimal Effective Dose of Ropivacaine Under Spinal Anesthesia for Cesarean Section After Failed Vaginal Delivery by Epidural Labor Analgesia

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Research Article

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Abstract

Background: The studies associated with EC50 of ropivacaine for spinal anesthesia are few worldwide during failed vaginal trial by epidural labor analgesia transfer to cesarean section. We preliminarily explore it to determine the minimum local analgesic dose (MLAD) of ropivacaine for spinal anesthesia during failed vaginal trial by epidural labor analgesia transfer to cesarean section(CS) and survey its adverse effect.

Trial design: a sequential experiment

Methods: The analgesia quality was defined as effective if VAS (Visual Analogue Scale) score was less than 3 from 15 min after spinal anesthesia to the end of CS. The Brownlee up-and-down sequential allocation was used to estimate the MLAD of subarachnoid ropivacaine and its 95% confidence intervals during failed vaginal trial by epidural labor analgesia transfer to CS.

Results: There were significant changes for the time to reach maximum sensory block, the time to reach maximum motor block and the duration from spinal anesthesia to starting operation and hypotension occurence (p□0.05, p□0.0001, respectively) between the effective group and ineffective group. Bradyarrhythmia, nausea, vomiting and chills were no significant changes between these two groups. The EC50 dose of f subarachnoid ropivacaine for failed vaginal trial conversion to CS by epidural labor analgesia was 8.2985 mg , and 95% CI(Confidence Interval) was 8.07947mg~8.52348mg.

Conclusion: The MLAD of ropivacaine was 8.2985 mg (95% CI: 8.0795mg~ 8.5235mg) for spinal anesthesia for failed vaginal trial by epidural labor analgesia conversion to CS. It was indicated that 8.2985 mg ropivacaine by subarachnoid block for failed vaginal trial transfer to CS can provide satisfactory and safe analgesia to parturients with low incidence rate of side effects.

Clinical Trial Registration: This clinical study has been registered at www.chictr.org.cn(ChiCTR1900027527).

Background

Epidural analgesia is an effective method for labor analgesia. However, when the mothers who receive labor analgesia have to transfer subsequently to CS for various reasons, by continuous epidural labor anesthesia often fails to meet the requirements of emergency CS surgery. Though we sometimes have to administrate general anesthesia to satisfy with it. The advantages of regional anesthesia must be fully realized. Therefore, the failed vaginal trial by epidural analgesia is transferred to CS, especially if the supplementation of continous epidural anesthesia is still unable to meet the requirements of surgical anesthesia, spinal anesthesia is an option in this situation. Due to prolonged labor epidural analgesia, a large amount of drug accumulation in the epidural space, if spinal anesthesia is chosen, low blood pressure and high anesthesia level certainly need be attentioned. Meanwhile, the choice of spinal anesthesia dose has become one of the difficulties in clinical anesthesia. There is currently no literature

or guidelines that clearly indicate the minimum effective dose of ropivacaine required for spinal anesthesia when a failed vaginal trial by epidural labor analgesia is transferred to CS. Few relevant researches about MLAD of ropivacaine for spinal anesthesia by failed vaginal trial under epidural labor analgesia transfer to CS were documented. So we explored that MLAD of ropivacaine through subarachnoid space during failed vaginal trial by epidural labor analgesia transfer to CS can provide satisfactory and safe analgesia to parturients with low incidence rate of side effects.

Methods

Patients

54 patients in our hospital were included from December 17 2019 to March 30 2020 in this study. These patients were transferred to the CS because of the failed vaginal trials by epidural labor analgesia. Each patient signed a research informed consent protocol. Once these women were determined to administrate cesarean delivery, we performed a combined spinal and epidural puncture and subarachnoid block to study the minimum effective dose of ropivacaine undergoing failed vaginal trial transfer to CS. This clinical study had been registered at www.chictr.org.cn(ChiCTR1900027527). The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies [1].

Selection criteria:

We chose women between 25 and 35 years old in ASAI ~ II level with more than 36 weeks of pregnancy, first birth, single pregnancy and head position; Exclusion criteria included prenatal application of painkillers, sedative hypnotics, history of neurological and psychiatric disorders, high risk pregnancy (placental abruption, placenta previa, preeclampsia, pregnancy with severe hypertension), epidural puncture difficulty or bleeding; interruption of analgesia caused by epidural catheter falling out, maternal weight greater than 100 kg and height less than 150cm.

Researchers

The research team consisted of three persons. The first one was an anesthesiologist with more than 10 years of experience in clinical anesthesia. He was responsible for spinal and epidural puncture during the transition from failed vaginal trial transfer to CS. The second one was not aware of the anesthetic drugs and research results and participated in the judgment of all research results, the third one was responsible for configuring all anesthetic drugs according to the requirements of the study.

Anesthesia method

Labor Analgesia

After the patient entered the delivery room and she was ready to give birth, the veins of the upper limbs were opened immediately before labor analgesia, and 10 ml/kg/h lactated Ringer's solution was infused.

The person who configured the anesthetics prepared the anesthetics in advance and the formula was: 100mg of 0.75% ropivacaine (AstraZeneca company batch: LBSK) and fentanyl injection (Yichang Renfu Pharmaceutical Co., Ltd. batch number: 91D03051) 0.2mg, diluted with saline to 100ml containing 0.1% ropivacaine and 2 μg/ml fentanyl. Monitor maternal heart rate, blood pressure, fetal heart rate, and contraction intensity. The patient was put the left lateral position, and we selected the puncture point between L2-3 lumbar spine. 18G epidural needle was used for puncture. After that, an epidural tube was placed 4~5 cm towards the head. No blood and cerebrospinal fluid were drawn out, and a test dose of 1% lidocaine 5 ml was given. After 5 minutes, ,if there was no sign of spinal anesthesia, no sign of catheter inserting into the blood vessels and 10 ml local anesthetic(0.1% ropivacaine and 2 μg/ml fentanyl) was administrated into the epidural space. If the maternal VAS score is greater than 3 after 10 minutes, add another 5 ml anesthetic . If the VAS score is still greater than 3 scores, change the standard mixture to 0.15% ropivacaine + 2 μg / ml fentanyl and continue to observe the analgesic effect. If only one limb had analgesic effect, we tried to pull out the 1cm epidural catheter and give 8~10ml 0.2% ropivacaine + 2ug / ml fentanyl again. If the analgesic effect was still unsatisfactory, the epidural puncture and recanalization were required.

Cesarean delivery procedure

After cesarean delivery was determined due to the termination of vaginal trial because of various obstetric factors during epidural labor analgesia, we suspended the administration of the epidural anesthetic. If the patient had been injected with more than 5 ml of epidural mixture within 30 minutes before the subarachnoid block, or if accidental break of the dura mater occurred during labor analgesia, the patient was eliminated. After the patient entered the operating room, Lactated Ringer's solution was maintained at 5~8ml/kg/h. Electrocardiogram was routinely monitored, SpO_2, non-invasive blood pressure, and oxygen inhalation at 3 L/min. After the patient was scheduled in the left-lateral position, the preceding epidural tube was pulled out, and the combined spinal and epidural puncture was performed between $L_{3\sim4}$ lumbar spine. Then, 0.5% ropivacaine were slowly injected through the 25G spinal anesthesia needle. After withdrawing the spinal anesthesia needle, inject epidural space into the epidural space with 3ml of normal saline for water injection test. Place an epidural catheter 3 ~ 5cm towards the head side and fix the catheter. After more than about 1 minute, the patient was required to lie flat.

Ropivacaine dose

Tests were performed sequentially. The initial dose of 0.5% ropivacaine was 13mg, because the recommended dose of 0.5% ropivacaine in Chinese guidelines for obstetric anesthesia is 10mg to 15mg. And the dose of the latter case was increased and decreased according to the results of the previous patient. The dose of ropivacaine differed by 1 mg and the concentration remained unchanged. The CS operation of the patient after failed vaginal trial was determined by an operation researcher, and another researcher configured a dose of ropivacaine.

Judgment of anesthesia effect

The effect of anesthesia was evaluated during the operation by observing the highest block level, the onset time and duration of sensory block; In addition, Bromage classification of lower limb motion block and hip motor function score were also recorded.

The effect of sensory nerve block was evaluated by needle punching, and the degree of maternal pain was recorded by visual analog scale (VAS): 0 painless, mild pain <4 scores, moderate pain (4 to 6 scores), and severe pain (7 ~ 9 scores), 10 scores of severe pain. If the intraoperative pain score exceeded 3 scores, the next study dose was increased by 1 mg. If there was doubt about the effect of anesthesia, the next dose was repeated. We judged the effect of motor block by the motor score of any of the lower limbs within 5 minutes after the subarachnoid injection. The scoring criteria were based on the Bromage score and hip motor function score (Bromage score: 0, Free movement of knees and feet; 1, Only move the knee joint; 2, Can't move the knee joint, but can move the feet; 3, No movement of knees and feet; Hip motion score: 0, Raise leg□>30°□; 1, Raise leg□<30°□; 2, Can't lift leg). If the score of both lower limbs was 0 within 5 minutes after the injection, the motor nerve block was judged to be ineffective, and the next patient's ropivacaine would be added to the previous one by 1 mg. Conversely, if the movement score of the limb was greater than 0 within 5 minutes after the injection, the motor block was judged to be effective, and the ropivacaine of the next patient would be reduced by 1 mg compared with the previous one.

Anesthesia and surgery procedure

In order to prove that ropivacaine accurately entered the subarachnoid space, we tested the sensory plane of the patient through a 25G puncture needle. If the sensory anesthesia level appeared quickly within 5 minutes, it could be determined that the anesthetic drug had successfully entered the subarachnoid space. Otherwise, we thought that the patient had failed, which was excluded from the statistics. If the anesthesia level could not meet the surgical requirements, we could add 2% lidocaine 5ml through the epidural catheter. If the surgical requirements could not be met within 5 minutes, we would give 2% lidocaine 5~15ml by 3~4 times. If the patient could not tolerate the pain of the operation, the anesthesia mode was changed into general anesthesia, and the relevant data about intravertebral or general anesthesia are recorded. All patients’ complications also were recorded after intravertebral anesthesia.

During the surgery, the systolic blood pressure decreased by more than 20% of the base value or the systolic blood pressure was <90mmHg. Ephedrine was injected 6~12mg, and repeated injection was given if necessary. Atropine was administrated at a heart rate of <50bpm, 0.3~0.5mg each time. We was extremely vigilant about high-level block, and regularly asked the patient if she had difficulty to speak, breath, swallow and other symptoms of high-level block during the CS.

Sample Size

Each average dose of ropivacaine was obtained through the intermediate point between effective and ineffective dose. According to Paul and Fisher's study [1], individual studies will have differences, and these differences would decrease when the number of patients increased. Therefore, our study was

completed when the average dose of our study exceeded 6 pairs. The number of effective and ineffective patients were recorded, and the minimum effective dose and 95% confidence interval of the patients were also calculated.

Statistical analysis

The distribution of anesthesia with effectiveness or no effect was analyzed using SPSS22.0 statistical software. The measurement data that conformed to the normal distribution were expressed as mean ± standard deviation, comparisons between groups were performed using t test, and count data were used χ^2 test. Hypotension, bradyarrhythmia and nausea, vomiting and chills were analysed by Pearson Chi-square test. P <0.05 was considered statistically significant. The ED50 value and its 95% confidence interval were calculated using the formula of the Dixon-Massey sequential allocation test method. LogED50 = $\frac{\sum n * logx}{\sum n}$, SmlogED50=d*$\sqrt{\sum p(1-p)/(n-1)}$, we calcualated the antilogarithm of LogED50-1.96*SmlogED50 and LogED50+1.96*SmlogED50 to get 95% CI value of ED50.

Results

A total of 54 women who had undergone epidural labor analgesia during vaginal trials were discontinued due to obstetric factors and were again undergoing subarachnoid for CS. Obstetric factors include: abnormal fetal heart or amniotic fluid, stagnation of labor, and prenatal fever. Among them, 2 women punctured the dura mater during epidural analgesia, and 4 women were excluded from the study due to the difficulty of combined spinal and epidural puncture. The remaining 48 patients successfully completed the operation (Shown in Fig. 1).

The remaining patients were divided into two groups (effective group and void group) according to the effectiveness and inefficiency. We showed comparison of maternal demographic data between the two groups (shown in Table 1). For the 48 patients, the average maternal height was 161.7cm, the average weight was 69.1 kg, the average epidural infusion time before CS was 245.8min, epidural dose before CS was 32.2ml, and the average anesthesia level before CS was T7, ranging from T5 to T10.

Table 1
Comparison of maternal demographic data between the two groups

Group	N	Age (y)	Height (cm)	Weight (kg)	Gestational week (weeks)	Preoperative epidural analgesic duration	Preoperative epidural dose
Effective group	26	31.2 ± 3.7	162.1 ± 4.1	70.5 ± 6.6	39.0 ± 1.0	244.2 ± 93.8	31.8 ± 6.8
Ineffective group	22	31.0 ± 3.8	161.1 ± 4.0	67.4 ± 5.6	38.6 ± 1.1	247.6 ± 85.0	28.3 ± 5.6
P		0.8546	0.3990	0.0892	0.1937	0.8967	0.0606
There were no significant difference for demographic data between the two groups(p□0.05).							

Meanwhile, there were no significant changes for level of sensory block immediately after the operation between the two groups (p = 0.184)(Shown in Table 2). Seven patients received subarachnoid anesthesia again, and ephedrine or phenylephrine was used for hypotension. Three women who had bradyarrhythmia after receiving a second subarachnoid anesthesia needed atropine to increase heart rate. There were significant changes for the time to reach maximum sensory block, time to reach maximum motor block, the duration from spinal anesthesia to starting operation and hypotension occurence ($p<0.05$, $p<0.0001$, respectively). Hypotension, bradyarrhythmia and nausea, vomiting and chills were no significant changes by Pearson Chi-square analysis between the two groups (Shown in Table 3).

Table 2
Comparison of level of sensory block immediately after the operation between the two groups

Level of maximum sensory block	Effective group(n = 26)	Ineffective group(n = 22)	P
>T4(n)	2	0	0.184
T4-T6(n)	24	22	
Below T6(n)	0	0	
There were no significant changes for level of sensory block immediately after the operation between the two groups(p = 0.184).			

Table 3
Comparison of the effects of subarachnoid block in the effective and ineffective groups

Observation indicators	Effective group(26)	Ineffective group (22)	p-value
Time to reach maximum sensory block(mins)	11.1 ± 2.1	14.4 ± 2.0	< 0.0001
Time to reach maximum motor block(mins)	3.4 ± 1.3	7.8 ± 3.6	< 0.0001
The duration from spinal anesthesia to lying flat(sec)	91.3 ± 22.7	95.8 ± 21.2	0.4842
The duration from spinal anesthesia to starting operation(mins)	13.9 ± 3.2	18.5 ± 4.3	0.0001
The duration from spinal anesthesia to end of the surgery(mins)	44.7 ± 7.3	47.6 ± 7.9	0.1931
Hypotension(n)	5	2	0.038
Bradyarrhythmia(<60bpm)(n)	3	0	0.100
Nausea, vomiting and chills.	6	4	0.677
There were significant changes for the time to reach maximum sensory block, time to reach maximum motor block, the duration from spinal anesthesia to starting operation and hypotension occurence (*p□0.05, ****p□0.0001). Hypotension, bradyarrhythmia and nausea, vomiting and chills were no significant changes by Pearson Chi-square analysis between the two groups.			

ropivacaine dose for subarachnoid block

The average dose of all 0.5% ropivacaine for subarachnoid block is (8.42mg), the range (6mg ~ 13mg), and the calculation method was shown in Fig. 2. According to the formula of Dixon and Massery, the ED50 of ropivacaine could be calculated as 8.2985 mg, and the 95% confidence interval was 8.0795mg ~ 8.5235mg.

Discussion

At present, epidural labor analgesia is recognized as the most effective method of labor analgesia. Obstetricians and anesthesiologists now generally believe that the mother does not have any contraindications to intravertebral anesthesia as long as the mother requires, the size of the uterine orifice should not be a reason to postpone epidural analgesia for all parturients who undergo failed vaginal delivery have to transfer to CS.

Huang [2] et al. showed that the failure rate of choosing an extradural catheter to continue dose of epidural anesthesia and anesthesia for subarachnoid block (SA) was similar in the case of cesarean delivery under labor analgesia. Choosing epidural anesthesia method, though the anaesthesia requirements for CS are reached, the maternal hemodynamic stability is stable, ephedrine or phenylephrine and other vasoconstrictors are used in small dose, but it takes a long time and it is possible to add more sedative drugs; The advantages of choosing anesthesia with subarachnoid space puncture mainly include quick onset of anesthesia and low postoperative analgesia scores. In our hospital, some women who underwent failed vaginal delivery under epidural labor analgesia had to transfer to CS, even if they had reserved epidural catheters, and the analgesia effect was accurate, the ratio of subarachnoid anesthesia was higher than epidural anesthesia for CS, because most obstetricians thought that the subarachnoid block made the newborn delivery faster.

However, spinal anesthesia can cause a series of physiological changes, resulting in complications relevant to spinal anesthesia, such as decreased blood pressure, bradyarrhythmia, respiratory depression, nausea and vomiting, full urine retention and so on, are positively related to the amount of local anesthetic. The degree of complications is also related closely to the level of anesthesia. The higher the level of anesthesia is the more obvious physiological disturbance. The spinal anesthesia level is positively correlated with the amount of local anesthetic, and the dose of local anesthetic is related to the duration of the nerve block. The local anesthetic dose is more important than the drug volume in determining the height of the block level [3]. Fewer local anaesthetics in spinal anesthesia can help patients recover faster and have fewer side effects. Therefore, it is very meaningful to use as few local anesthetics as possible in spinal anesthesia when the need for surgery is fully satisfied. In order to evaluate the relative intensity of local anesthetics, many scholars have established a clinical research model for sequential studies to determine the half effective dose of motor nerve block [4]. These models were initially designed to evaluate the minimum local anesthetic concentration of motor nerve blocks during maternal epidural anesthesia, and they were later applied to study the minimum dose of motor nerve blocks in subarachnoid block. So we also use the Dixon sequential method.

A variety of factors can affect the degree of local anesthetic diffusion in the subarachnoid cavity of the parturient, including the puncture interval, the speed and direction of injection, the concentration of anesthetic, and the specific gravity. Khaw and other studies[5, 6] reported that the ED50 of ropivacaine subarachnoid block for CS was 16.7 mg, previous study showed that the ED50and ED95 of intrathecal hyperbaric ropivacaine along with 5 μg sufentanil were 8.28 mg and 12.24 mg, respectively when a CSEA technique is to use in patients with scarred uterus for an elective cesarean delivery[7].The ED50of intrathecal hyperbaric ropivacaine for CS is 8.29 mg, and it is reduced by epidural normal saline bolus[8].

The effect of epidural volume extension with saline in the enhancement of spinal block includes the volume effect, resulting in squeezing of cerebrospinal fluid and more cephalic spread of subarachnoid local anesthetic. Injected saline extends the anesthesia level by a mechanical volume effect (time-dependent effect) and increases the regression time, thereby providing a longer duration of anesthesia

with a smaller dose of hyperbaric bupivacaine given in subarachnoid space that may result in better hemodynamic stability and an early motor recovery[9].

However, some studies have suggested that low-dose spinal anesthesia has little to do with epidural injection, and a 5ml saline injection after spinal anesthesia does not affect the anesthesia effect. Therefore, the study believes that the relationship between the changes in the volume of the epidural space and the effect of low-dose spinal anesthesia is ambiguous. Therefore, when the volume of fluid in the epidural space is unknown, the dose of spinal anesthesia is still worthy of further discussion. Pan [10] and other studies suggested that the failure rate of combined spinal and epidural anesthesia for subarachnoid anesthesia was 0.5%, and the failure rate of subarachnoid anesthesia for failed vaginal delivery transfer to CS after epidural analgesia was as high as 14.2%. The exact reason for the increase in failure rate is not clear, but we can at least speculate the following: (1) After long-term epidural analgesia, the epidural fluid squeezed the subarachnoid space, leading to reduced puncture opportunities or uneven diffusion of intrathecal injection of drugs; (2) A large amount of epidural fluid after epidural analgesia may interfere with the recognition of outflowing cerebrospinal fluid when the subarachnoid block is performed, leading the anesthetist to think the "cerebrospinal fluid" has some false positives. Therefore, even if the subarachnoid block is effective when the failed vaginal test is transferred to CS after epidural analgesia, however, it puts forward higher puncture requirements for the clinical doctors.

This study has several limitations. First, based on the sample size, no side effect such as difficulty in voicing after subarachnoid block, upper limbs, movement difficulty and breathing difficulty occurred. Second, this study did not include pregnant women with hypertension or preeclampsia. Therefore, the minimum local analgesic dose (MLAD) of ropivacaine during failed vaginal trial transfer to CS under special circumstances needs further discussion.

Conclusions

The MLAD of ropivacaine was 8.2985 mg (95% CI: 8.0795mg ~ 8.5235mg) for spinal anesthesia for failed vaginal trial by epidural labor analgesia conversion to CS. It was indicated that 8.2985 mg ropivacaine by subarachnoid block for failed vaginal trial transfer to CS can provide satisfactory and safe analgesia to parturients with low incidence rate of side effects.

Abbreviations

MLAD: minimum local analgesic dose; CS: cesarean section; VAS: Visual Analogue Scale

Declarations

Acknowledgements

Not applicable.

Author's Contributors

Study design: W.Y and M.R, Data collection: W.JW, M.R Data analysis: W.Y. Writing of manuscript: W.Y and M.R, Review of manuscript: W.Y and W.JW

All authors read and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and analyzed in the current study are available from the corresponding author in response to reasonable requests.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was approved by the National science and technology ethics committee (approval number: 2017–101) and registered in the Chinese Clinical Trial Register (registration number: ChiCTR1900027527). Written informed consent was obtained from each participant.

Conflicts of interest

None declared

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Figures

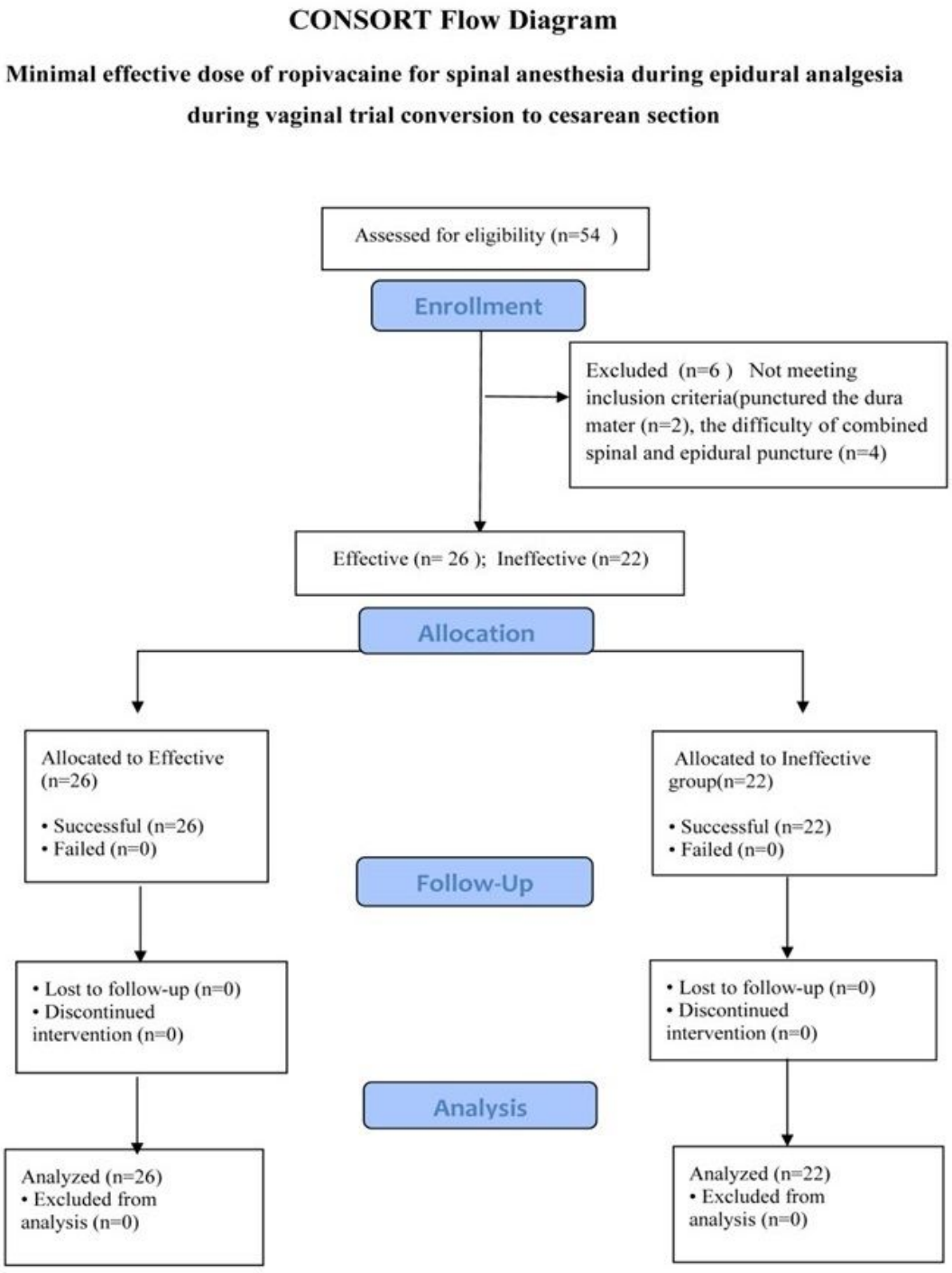

Figure 1

Consort Flow Diagram for minimal effective dose of ropivacaine under spinal anesthesia for cesarean section after failed vaginal delivery by epidural analgesia.

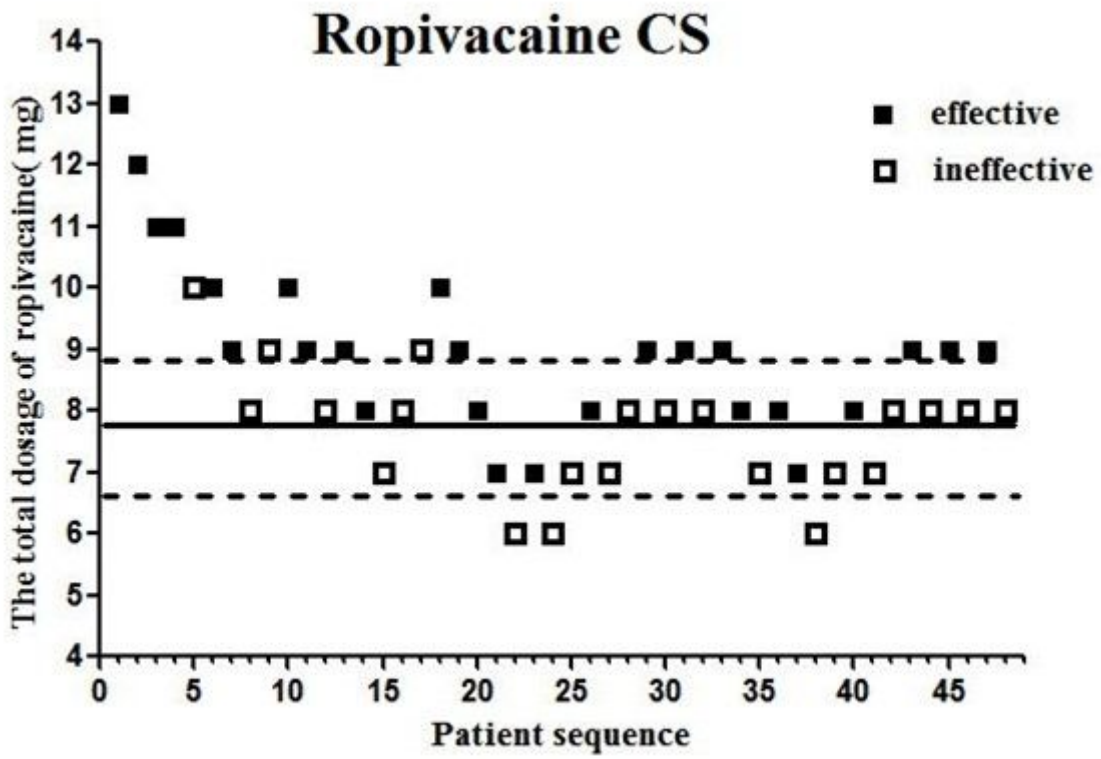

Figure 2

Calculation of ropivacaine ED50 and 95% confidence interval. Sequential study of 0.5% ropivacaine under spinal anesthesia for cesarean section after failed vaginal delivery by epidural analgesia. EC50=8.2985mg. 95%CI(8.0795mg, 8.5235mg) Sm=0.05*0.11854=0.005927