

BMJ Open Height-based dosing algorithm of bupivacaine in spinal anaesthesia for decreasing maternal hypotension in caesarean section without prophylactic fluid preloading and vasopressors: study protocol for a randomised controlled non-inferiority trial

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ABSTRACT

Introduction Effectively preventing or treating spinal-induced maternal hypotension is considered to be the Holy Grail of obstetric anaesthesia. Prophylactic fluid preloading and vasopressors decrease hypotension but may aggravate heart load, induce fetal acidosis or maternal bradycardia. Using low-dose local anaesthetic decreases hypotension but may cause insufficient anaesthesia. Whether there is a height-based dosing algorithm of local anaesthetic in spinal anaesthesia for caesarean section that can provide sufficient anaesthesia with less hypotension without prophylactic fluid preloading and vasopressors is unclear. This study was designed to investigate a height-based dosing algorithm of bupivacaine in spinal anaesthesia for caesarean section.

Methods and analysis This single-centre, double-blinded, prospective, non-inferiority, randomised controlled trial will include 264 parturients (between 18 and 45 years of age) who are scheduled for caesarean section. All participants will not receive prophylactic fluid preloading. The participants will be randomly divided into two groups: the test group or conventional group. For parturients in the test group, 0.5% isobaric bupivacaine (1.15–1.70 mL) will be injected into the subarachnoid space without prophylactic vasopressors. The bupivacaine dose depends on the height of subjects. For parturients in the conventional group, 0.5% bupivacaine (1.8 mL) will be injected into the subarachnoid space along with prophylactic vasopressors. The primary outcome is the incidence of maternal hypotension. The secondary outcomes include the failure rate of spinal anaesthesia, level of sensory block, degree of motor block, other complications in parturients, time of operation, neonatal outcome and quality of anaesthesia.

Ethics and dissemination This study was approved by the Ethics Committee of Shenzhen People's Hospital of Jinan University (Permit No. SZY-00251, chairperson Xiaofang Yu) on 8 February 2018. The study results will be disseminated through peer-reviewed journals, professional societies and meetings.

Strengths and limitations of this study

- This study is the first to investigate spinal anaesthesia for caesarean section without prophylactic fluid preloading and vasopressors.
- This study will clarify the relationship between the height of parturients and the dose of local anaesthetic
- Compared with parturients in China, the optimum dose for parturients in Europe and America should be different but may also be adjusted in the same manner (0.05 mL/2–3 cm).
- In a portion of parturients, timely supply of local anaesthetic through the epidural space or an analgesic through a vein may be necessary.

Trial registration number NCT03497364; Pre-results.

INTRODUCTION

Spinal anaesthesia can provide high-quality anaesthesia without any inhibitory effects on the fetus from general anaesthetics and is a popular anaesthetic technique for caesarean sections.^{1 2} Unfortunately, maternal hypotension frequently occurs due to sympathetic blockade¹ and special physiological changes in parturients.³ Mild hypotension may cause impaired fetal oxygenation and fetal acidosis,⁴ as well as unpleasant maternal complications (eg, nausea, vomiting and dizziness).⁵ Severe hypotension may threaten the life of the parturient and fetus.⁶ Effectively preventing or treating spinal-induced maternal hypotension is considered to be the Holy Grail of obstetric anaesthesia.²

The prophylactic use of fluid (crystalloid⁷ or colloid⁸) and/or vasopressors (phenylephrine⁹ or ephedrine⁷) is usually applied to decrease maternal hypotension. However, the blood volume of the parturient is obviously increased in the later trimesters of pregnancy. The heart load is further aggravated by fluid preloading. The use of ephedrine may be associated with fetal acidosis,¹⁰ which may influence the neonatal outcome.¹¹ The use of phenylephrine increases the incidence of bradycardia¹² and decreases cardiac output in the parturient.¹³ Therefore, avoiding prophylactic fluid preloading and vasopressors may be advantageous to the parturient or fetus.

For spinal anaesthesia, whether the height of the patient influences the block level is controversial. Several studies have reported no statistical correlation between height and block level.^{14–16} In many studies, the dose of the local anaesthetic is not adjusted according to height.^{14–17–19} However, the block level is related to vertebral column length.²⁰ Although the height accounts for only 10.6% of the variation in vertebral column length, a statistically significant correlation exists between height and vertebral column length.¹⁶ Therefore, the block level should be related to height, which has been supported by two studies.^{21–22} With a low dose of local anaesthetic, our preliminary data also showed that the block level was highly dependent on the parturient's height. For spinal anaesthesia, a decreased dose of local anaesthetic induces a lower block level and decreases the incidence of hypotension but may cause incomplete analgesia and muscle relaxation.²³ Therefore, we hypothesise that for spinal anaesthesia, there is a height-based dosing algorithm of local anaesthetic that can provide sufficient anaesthesia

with a low incidence of hypotension during caesarean sections even without prophylactic fluid preloading and vasopressors. This randomised controlled trial (RCT) is designed to investigate a height-based dosing algorithm of bupivacaine in spinal anaesthesia for caesarean section.

METHODS AND ANALYSIS

Study design

This single-centre, double-blinded, prospective, non-inferiority, RCT was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (for details, see online supplementary additional file 1).^{24–25} This study will be performed in compliance with International Conference on Harmonization (ICH)-Good Clinical Practice (GCP) and the Declaration of Helsinki at the Department of Anesthesiology of Shenzhen People's Hospital of Jinan University. Figure 1 shows the schedule of enrol, interventions and assessments, and figure 2 provides the trial flow chart.

Participants

Parturients (aged 18–45 years) who are scheduled for elective caesarean section will be recruited for this study. All parturients will fast for 2–3 hours for clear liquids and 6–8 hours for non-fatty solids. Ana will be free for all recruited parturients. To avoid incomplete analgesia and muscle relaxation, we will perform combined spinal-epidural anaesthesia (CSE) instead of spinal anaesthesia in this study. Written informed consent will be obtained

TIMEPOINT	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Follow-up & Close-out
	Outside OR	Outside OR	Entering OR-to-Anesthesia	Anesthesia-to-delivery	Delivery -to- end of surgery	After surgery
Enrolment:						
Eligibility screen	x					
Informed consent	x					
Allocation		x				
INTERVENTIONS						
Test dose of bupivacaine			x			
Conventional dose of bupivacaine			x			
ASSESSMENTS						
Demographic data	x					
Baseline data			x			
General data	x	x		x	x	x
Primary outcome						
Incidence of hypotension				x		
Secondary outcomes						
Failure rate of spinal anesthesia				x		
Sensory block				x		
Motor block				x		
Other complications				x		
Time of operation					x	x
Neonatal outcome					x	x
Quality of anesthesia						x

Figure 1 The schedule of enrolment, interventions and assessments. OR, operation room.

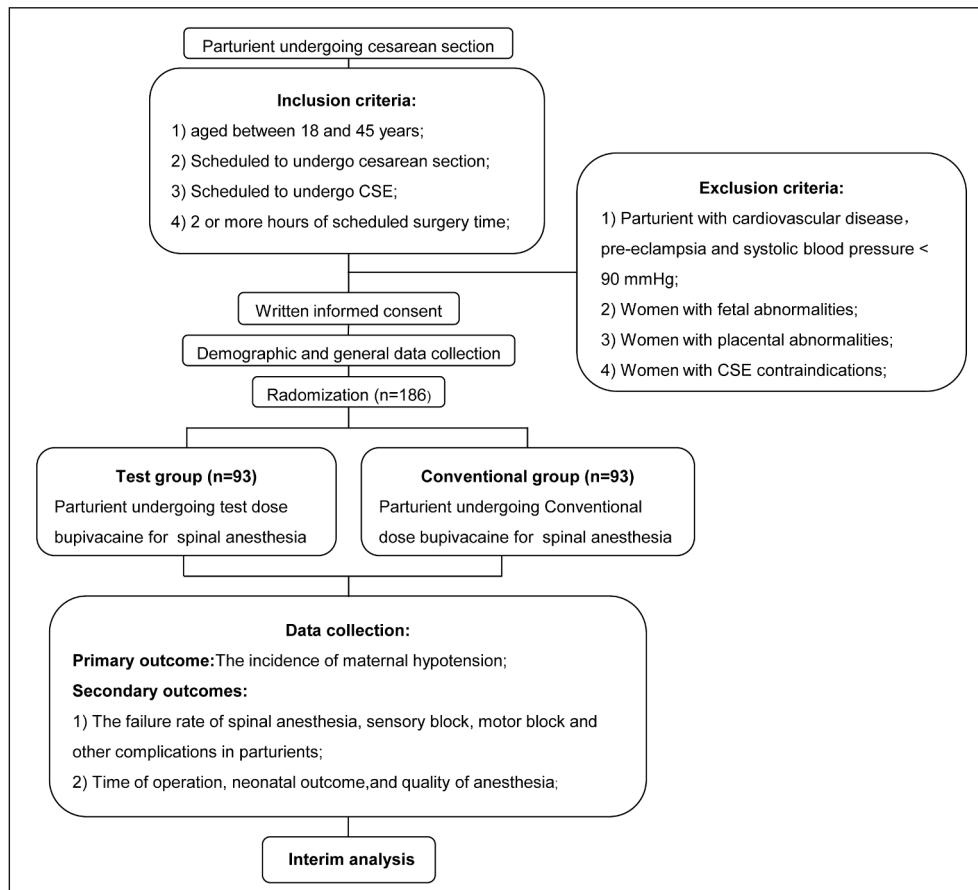


Figure 2 Study flow chart. CSE, combined spinal-epidural.

from all parturients. Parturients with cardiovascular disease, pre-eclampsia, systolic blood pressure (SBP) <90 mm Hg, fetal abnormalities, placental abnormalities and CSE contraindications are excluded from the study.

Randomisation and blinding

For blocked randomisation, all participants will be given a serial number (1–520) according to the time and date of surgery and be divided into 65 blocks. Eight participants with adjacent time and date of surgery will be put into a block. For each block, from a random number table, eight participants will be allocated a group of random number, which is different for any two blocks. Then, the random numbers of each block will be sorted from small to large, and be respectively gave another serial number (1–8) to label the participants. The participants with odd number will be assigned to test group. The participants with even number will be assigned to conventional group. The random serial numbers of each subject will be placed in a sealed envelope. Before conducting this study, the randomisation will be performed by a research assistant, who will open the sealed envelope, and allocate a random serial number to a new recruited subject, then prepare the study drugs (bupivacaine, phenylephrine and normal saline) out of the operation room (OR) without presence of other persons (parturients, outcomes assessors and surgical team), but will not participate in outcome assessments and statistical analyses. Outcome assessments and

statistical analyses will be performed by an and another research assistant. The parturients, outcomes assessors and surgical team will be blinded to the information concerning randomisation, group allocation and study drug preparation.

Intervention

Before entering the OR, the parturient will be placed supine with a left lateral tilt (15°), and blood pressure and heart rate (HR) will be measured three times at 1 min intervals. The arithmetic average of the three measured values will be regarded as the basal blood pressure and HR of the parturient. After entering the OR, ECG, blood pressure, HR and saturation of pulse oximetry will be monitored. Supplementary oxygen will be given through a face. Venipuncture will be performed in the forearm vein. Then, 1000 mL Ringer's lactate will be slowly administered to subjects in both groups (2 mL/kg/hour).

Then, with the subjects in left lateral position, CSE will be performed as follows: skin will be infiltrated with lidocaine at the L3–4 interspace; a 16-gauge Tuohy epidural puncture needle will be slowly perpendicularly advanced until the tip passes through the ligamentum flavum and reaches the epidural space, which will be verified by the loss of resistance with identical air volume; then an intrathecal injection will be administered with a 27-gauge pencil-point spinal needle, and the epidural catheter will be inserted 4 cm. Then, subjects will be immediately

Table 1 The relationship between the height of the parturient and dose of 0.5% bupivacaine

Height of parturient (cm)	Dose of 0.5% bupivacaine (mL)
173–174	1.70
170–172	1.65
168–169	1.60
165–167	1.55
163–164	1.50
160–162	1.45
158–159	1.40
155–157	1.35
153–154	1.30
150–152	1.25
148–149	1.20
145–147	1.15

placed the supine position with a left lateral tilt (15°). In the test group, 0.5% isobaric bupivacaine (1.15–1.7 mL) (ChaoHui drug company, ShangHai, China) will be injected by the research assistant who prepares study drugs. The bupivacaine dose will depend on the height of the subjects (table 1, 0.05 mL/2–3 cm). In the conventional group, 0.5% isobaric bupivacaine (1.8 mL) will be injected in all subjects by the research assistant who prepares study drugs.²⁶ Immediately after the intrathecal injection, the infusion rate of Ringer's lactate will be increased to 10 mL/kg/hour in both groups.²⁷ In the conventional group, by the research assistant who prepares study drugs, phenylephrine will be continuously infused at an infusion rate of 0.25 µg/kg/min (ie, 2.5 mL/hour)²⁸ to maintain SBP at ≥ 90 mm Hg or 70%–100% of the baseline value. In the test group, by the research assistant who prepares study drugs, normal saline (2.5 mL/hour) will be applied. All participants will not receive prophylactic fluid preloading.

The SBP < 90 mm Hg or 70% of baseline value will be defined as maternal hypotension. During time from anaesthesia initiation to delivery, if the SBP is less than 90 mm Hg or 70% of baseline value at any time point, this parturient will be defined as a parturient with hypotension. For all subjects, by the outcomes assessors, when the SBP is less than 90 mm Hg or 70% of baseline value, then 100 µg phenylephrine will be given and every 1 min until the SBP returns to normal. When the HR is less than 60 beat/min, then 0.5–1 mg atropine will be given to maintain normal HR. Nausea and vomiting will be treated with metoclopramide (10 mg intravenous). The sensory block level after the intrathecal injection will be assessed with a 20-gauge hypodermic needle (hypoalgesia to pinprick). When the sensory block level is lower than dermatome level dominated by the eighth thoracic nerve (T8) at 10 min after anaesthesia, spinal anaesthesia will be considered a failure. The unsuccessful parturients

will be excluded from the study. For unsuccessful parturients, an epidural injection of 2% lidocaine (3 mL, test dose) + 0.75% ropivacaine (12 mL) will be given (3 mL/5 min) until the sensory block level is higher than T8 (total volume will be less than 15 mL)^{7 29} or the anaesthetic technique will be changed into general anaesthesia.

Data acquisition

Before anaesthesia, demographic data, general data and baseline data will be collected by a research assistant. After an intrathecal injection, the blood pressure, HR, respiratory rate and saturation of pulse oxygen (SpO_2) and will be recorded every 1 min until delivery and then every 3 min.

After anaesthesia, the level of sensory block, defined as hypoalgesia to pinprick at the midclavicular level, is measured every 1 min until 10 min, then every 15 min until the block has receded to T8. Anaesthesia is considered to be adequate for surgery if the hypoalgesia level reaches T8.^{7 29} Motor block will be assessed every 1 min using the modified Bromage scale (0=no motor block; 1=unable to raise extended leg; 2=unable to flex knee; 3=unable to flex ankle)³⁰ until 10 min after anaesthesia.

After delivery, umbilical blood samples will be taken for blood gas analysis. APGAR scores at 1 and 5 min will be evaluated. The complications (hypotension, nausea, vomiting, dizziness, bradycardia and dyspnoea), total dose of phenylephrine and total volume of fluid before delivery will be noted.

After surgery, the time from anaesthesia initiation to skin incision, time from skin incision to delivery and operation duration will be calculated. The quality of analgesia (judged by the anaesthetist), the quality of muscle relaxation (judged by the surgeon) and the degree of intraoperative comfort (judged by the patient via asking how you feel during operation) will be recorded as excellent, good, fair or poor.

Study outcomes

Primary outcome measure

Incidence of maternal hypotension (cumulative incidence) during time from anaesthesia initiation to delivery.

Secondary outcomes

1. Failure rate of spinal anaesthesia, time for sensory block to reach T8, sensory level at 10 min after anaesthesia, time for sensory block to recede to T8, time to complete motor block, number of parturients with complete motor block at 10 min after anaesthesia, other complications in parturients.
2. Time from anaesthesia initiation to skin incision, time from skin incision to delivery, operation duration.
3. APGAR scores at 1 and 5 min of newborn, blood gas analysis (PH, partial pressure of oxygen, $[PO_2]$, partial pressure of carbon dioxide $[PCO_2]$ and base excess [BE]) of newborn.
4. Quality of analgesia, quality of muscle relaxation, degree of intraoperative comfort.

The incidence of maternal hypotension is very high after spinal anaesthesia and maternal hypotension may be disadvantageous to fetal and maternal outcomes. In this study, the incidence of maternal hypotension will be confirmatory outcome, the other measured variables will be exploratory outcomes.

Adverse events

Following the SPIRIT recommendations, serious adverse events that require hospitalisation, are life-threatening, or result in death will be collected. All adverse events will be registered and actively treated until stabilisation or resolution, or until it has been proved that the study treatment is not related with the event. Treatment will be free for these parturients. Once any serious adverse event in any participant is found, this participant will be unblinded, the chief investigator (in cooperation with the treating medical practitioners) will determine the causality and seriousness of these events. The serious adverse events due to study treatment will be reported to the research ethics committee as part of the report. Unexpected serious adverse events will be reported to the research ethics committee within the relevant time frames. All adverse events will be reported by the chief investigator. Before study initiation, every site staff will be appropriately trained in the procedures to follow and the forms to use during the study protocol. Once serious adverse events occur, the chief investigator can then unblind the participant and give the participant post-trial care.

Withdrawal and drop

The recruited parturients in the study can end at any time if consent is withdrawn, the study protocol is violated, the inclusion and exclusion criteria are not met, or the participant refuses to continue. Ana will not be free for all exited parturients. This study will be ceased if there are unacceptable risks of serious adverse events. Interim analysis will not be performed. However, to avoid differences in the rate of hospitalisation or exacerbation in each group, the data safety and monitoring committee (DSMC) will regularly review all study outcomes and adverse event data. The study may also be ceased early by the DSMC if there is clear evidence of worsened safety during the study or an effect size has been obtained, which would change clinical practice in the presence of the current literature or understanding of the disease area.

Confidentiality

At recruitment, a unique scrambled study number is allocated to each participant by a research assistant. The participants will only be identified by the study number. Data collection sheets and all printouts of electronic files will be kept in a locked filing cabinet in a secure office with limited access. The master list of participants and informed consent forms will be securely stored separately from de-identified participant records. The digital files will be password protected and stored in a firewall-protected secure environment. Only the study sponsor has

access to the final study dataset. A signed consent must be obtained from every participant in the ancillary study, if the data collection/request is not covered in the original informed consent process for the main clinical trial.

Study oversight

The chief investigator, data manager, study statistician, study coordinator and study manager constitute a study management group, which will maintain contact with one another every week. A study steering committee will meet at least two times every month over the internet and more frequently if required to review the study progress and ensure that it is being performed in accordance with the study protocol, relevant regulations and the principles of GCP. Study progress and safety data will be routinely reviewed by the DSMC, which is independent of the study investigators and will include three independent members (two clinical specialists and a study statistician).

Protocol amendments

Protocol amendments will be agreed on with sponsor, DSMC, study steering committee and funding body before submission for ethical approval. After ethical approval, protocol amendments will be communicated with relevant parties, such as the study investigators, study registry and, if required, the study participants.

Patient and public involvement

The development of current research question and outcome measures was informed by patients' priorities, experience and preferences in a way that this height-based dosing algorithm of bupivacaine in spinal anaesthesia may be more suitable for parturients who are scheduled for caesarean section. Parturients were not involved during the phase of study design; however, parturients' concerns and questions were addressed during parturient recruitment and study implementation. The results will be disseminated to study participants through email. Indicators of intervention burden will be partially parturient self-reported, such as level of sensory block, degree of motor block, complications (nausea, dizziness and dyspnoea) and degree of intraoperative comfort, while the other outcomes will be assessed by the research investigators.

Dissemination policy

The results of the trial will be widely disseminated to health professionals, commissioners, policy-makers, parturients and the general public. The study results will be disseminated to a wide clinical audience through publication in a high-impact international scientific journal. All professionals who have participated in the study for a minimum of 6 months will be listed as authors.

Statistical analysis

Sample size calculation

The incidence of hypotension ranges from 7.4% to 74.1%.¹ For parturients in China, SBP<90 mm Hg or 70% of the baseline value is defined as hypotension; in the study by

Geng *et al* in *Chin Med J (Engl)* magazine, the incidence of hypotension was 30%,³¹ and we considered a $\geq 10\%$ difference in the incidence of hypotension to be of clinical significance. In this study, if the incidence of hypotension in the test group is similar to it in the conventional group, this height-based dosing algorithm of bupivacaine will be of clinical significance. For sample size calculation by hand, a non-inferiority one-sided test will be carried out with this equation ($n = \frac{2 \cdot p \cdot (1-p) \cdot (z_{(1-\alpha)} + z_{(1-\beta)})^2}{\Delta^2}$), where p is the incidence of hypotension in other study, Z is the corresponding value from table of the normal distribution, α and β are the probabilities of type I and II errors, Δ is the cut-off value of difference.³² Assuming a type I error protection of 0.05 and a power of 0.80, each group requires 260 subjects. In this study, we plan to include a total of 520 parturients.

Outcome analysis

Statistical analysis will be performed at the Clinical Research Institute of Shenzhen People's Hospital by blinded biostatisticians using SPSS V.13.0 software package. All continuous data are recorded as the mean \pm SD and 95% CI. For comparing the primary outcome measure (ie, incidence of maternal hypotension), χ^2 tests will be used. For secondary outcomes, the continuous data (time for sensory block to reach T8, time for sensory block to recede to T8, time to complete motor block, time from anaesthesia initiation to skin incision, time from skin incision to delivery, operation duration, APGAR scores at 1 and 5 min, blood gas analysis (PH, PO₂, PCO₂ and BE) of newborn) will be compared by Student's t-test (normally distributed data) or Mann-Whitney U-test (non-normally distributed data), the ranked data (sensory block level at 10 min after anaesthesia, quality of analgesia, quality of muscle relaxation, degree of intraoperative comfort) will be compared by Mann-Whitney U-test, and the other enumeration data (failure rate of spinal anaesthesia, number of parturients with complete motor block at 10 min after anaesthesia, other complications in parturients) will be compared by χ^2 tests. $P < 0.05$ indicates that the differences have statistical significance.

DISCUSSION

The quality of anaesthesia and incidence of maternal hypotension are related to block level, which depends on the dose of local anaesthetic injected into the subarachnoid space.²³ The volume of the subarachnoid space is decreased in parturients due to high abdominal pressure.^{33 34} When using a low dose of local anaesthetic, the block level of the local anaesthetic may also depend on the height of the parturient.^{21 22} This single-centre, double-blinded, prospective, non-inferiority RCT was designed to test the hypothesis that 1.15–1.7 mL of 0.5% isobaric bupivacaine, varying with the height of parturient, is the optimal dose of bupivacaine in spinal anaesthesia for caesarean section and provides sufficient anaesthesia with

a low incidence of maternal hypotension and that prophylactic fluid preloading and vasopressors are unnecessary in spinal anaesthesia for caesarean section. Our previous data from a small cohort of parturients have preliminarily supported this hypothesis. The results of this study will obviously increase the safety of parturients and fetuses with fewer complications and decrease the stress of the anaesthetist.

The study has some strengths. First, in obstetric anaesthesia, the question of how to prevent or treat spinal-induced hypotension has been extensively investigated, and the answer has been considered to be the Holy Grail of obstetric anaesthesia.² In previous studies, prophylactic fluid preloading or vasopressor is usually used, even while using an ultra-low dose of local anaesthetic.²⁶ This study is the first to investigate spinal anaesthesia for caesarean section without prophylactic fluid preloading and vasopressors. Our preliminary data showed that the incidence of spinal-induced hypotension is 10%, which is lower than when using prophylactic fluid preloading or vasopressors. Second, although several studies show that the height is not related to the block level and the dose of local anaesthetic for spinal anaesthesia,^{14–17 19} our preliminary study showed that the dose of local anaesthetic must vary with the height of the parturient, which is consistent with previous studies.^{21 22} This study will clarify the relationship between the height of parturient and the dose of local anaesthetic for spinal anaesthesia without prophylactic fluid preloading and vasopressors. Third, in many studies, the sensory block level is usually tested using loss of pinprick or cold sensation,^{19 26 30 35} which may underestimate the sensory block level because many subjects cannot differentiate pain, cold or tactile sensation due to nervousness. In this study, we will use hypoalgesia to test the sensory block level because we found many subjects are able to differentiate the degree of pain sensation.

This study has some limitations. First, in previous studies, the dose of local anaesthetic was not associated with the height of the parturients,^{14–16} and adjustments of the dose based on height were unnecessary.^{17–19} However, our preliminary study has shown that the dose of local anaesthetic depends on the height of parturients when using small doses. Compared with women in Europe and America, women in China are shorter. Therefore, the optimum dose for parturients in Europe and America should be different but may also be adjusted in the same manner (0.05 mL/2–3 cm). Second, because a small dose of local anaesthetic is used, the level of sensory block is low and may regress faster to $<T8$.²⁶ In a portion of parturients, timely supply of local anaesthetic through the epidural space or an analgesic through a vein may be necessary, which will be routinely performed in this study. Third, we included all kinds of parturients (eg, parturients who are not full term). The fetal weight may aggravate compression of the subarachnoid space^{33 34} and inferior vena cava³ and increase the incidence of hypotension. For special parturients with macrosomia and two

or more pregnancies, the incidence of hypotension may differ.

Trial status

This study is currently at the patient enrolment and data collection stage.

Trial sponsor

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Contributors ZZ and BH conceived and designed the experiments. BH, QH, CH and ZZ performed the experiments. QH and YL analysed the data. CH contributed reagents/materials/analysis tools. BH wrote the paper.

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Disclaimer The sponsors have no role in the study design and conduct; the collection, management, analysis and interpretation of the data; or the preparation and approval of the manuscript.

Competing interests None declared.

Ethics approval This study was approved by the Ethics Committee of Shenzhen People's Hospital of Jinan University (Permit No. SZY-00251, chairperson Xiaofang Yu) on 8 February 2018.

Provenance and peer review Not commissioned; externally peer reviewed.

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