



Norepinephrine intravenous prophylactic bolus versus rescue bolus to prevent and treat maternal hypotension after combined spinal and epidural anesthesia during cesarean delivery: a sequential dose-finding study

Tao Xu^{1,2,3}, Jing Zheng^{1,2,3}, Xiao-Hu An^{1,2,3}, Zi-Feng Xu^{1,2,3}, Fang Wang⁴

¹Department of Anesthesiology, the International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200030, China; ²Shanghai Key Laboratory of Embryo Original Diseases, Shanghai 20030, China; ³Shanghai Municipal Key Clinical Specialty, Shanghai 20030, China; ⁴Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN, USA

Contributions: (I) Conception and design: XH An, ZF Xu; (II) Administrative support: XH An, ZF Xu; (III) Provision of study materials or patients: J Zheng; (IV) Collection and assembly of data: T Xu, J Zheng, F Wang; (V) Data analysis and interpretation: T Xu, J Zheng, F Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jing Zheng, MD. Department of Anesthesiology, the International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, Henshan Road 910, Shanghai 200030, China. Email: Sukura5203yy@sjtu.edu.cn.

Background: As a relatively new drug in obstetrical anesthesia, norepinephrine is less likely to induce bradycardia and decrease cardiac output, which makes it a potential alternative to phenylephrine. The purpose of this study was to determine the optimal norepinephrine bolus dose needed to either prevent or reverse hypotension after the use of combined spinal and epidural (CSE) anesthesia in 90% of women during elective cesarean delivery (CD).

Methods: Eighty women undergoing elective CD were randomly allocated into either a prophylactic group or a rescue group in this dose finding study. If the women's systolic blood pressure (SBP) was maintained above 80% of their baseline, the next patient had an 8/9th chance of receiving the same dose or a 1/9th chance of receiving a lower dose. If the patient's SBP was not maintained, a higher dose was used for next patient. The primary outcome was the successful use of the norepinephrine bolus dose to maintain SBP above 80% of the baseline until after delivery. Secondary outcomes included nausea, vomiting, breathlessness, dizziness, hypertension, bradycardia due to hypotension and supplemental use of atropine and norepinephrine, upper sensory level of anesthesia, umbilical vein (UV) blood gases, and 1- and 5-minute Apgar scores. The 90% effective dose (ED₉₀) and 95% confidence interval (95% CI) were estimated using isotonic regression methods.

Results: The estimated ED₉₀ of the norepinephrine prophylactic bolus was 10.85 µg (95% CI, 9.20–11.67 µg) and that of the norepinephrine rescue bolus was 12.3 µg (95% CI, 10.0–12.8 µg) using isotonic regression methods.

Conclusions: For norepinephrine, either a prophylactic bolus dose of 11 µg or a rescue bolus dose of 12 µg was recommended for clinical practices.

Keywords: Norepinephrine; prophylactic bolus; rescue bolus; 90% effective dose (ED₉₀); maternal hypotension; cesarean delivery (CD)

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Introduction

Norepinephrine, as a relatively new drug in obstetric anesthesia, has α -adrenergic and weak β -adrenergic effects. Compared with phenylephrine, it is less likely to induce bradycardia and decreased cardiac output (1-3), which makes it a potential alternative to phenylephrine.

Prophylactic use of vasopressors is increasingly considered to be a standard measure during spinal anesthesia (SA) for cesarean delivery (CD) (4-7). However, few developing countries incorporate prophylactic vasopressors into their delivery management guidelines (8).

This prospective, double-blind, randomized, sequential dose finding study aims to identify the 90% effective dose (ED₉₀) value of norepinephrine for both prophylactic and rescue bolus doses by using the biased coin up-and-down (BCUD) design.

Methods

Materials and methods

After obtaining approval from the Research Ethics Committee of the International Peace Maternity and Child Health Hospital and registering at <http://www.chictr.org.cn> (INR-1800016213), we began a prospective, double-blind, randomized, sequential dose-finding study, using a BCUD design to estimate ED₉₀. A total of 109 women aged 18–40 years, with a full-term (>37 weeks' gestation) singleton pregnancy, ASA score II, and undergoing an elective CD were recruited during the study period from January 2018 to August 2018. After providing signed informed consent, the women were randomly allocated into two groups according to the randomized numbers generated by a research assistant using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA): the prophylactic bolus group (Group P) and the rescue bolus group (Group R). Exclusion criteria for the study were as follows: allergy to norepinephrine, preexisting or pregnancy-induced hypertension, preeclampsia, cardiovascular or cerebrovascular disease, fetal distress or fetal abnormalities, multiple gestations, patient refusal, and emergent CD.

Patients were instructed to fast after midnight on the day of surgery. After entering the operating room, an intravenous (IV) line was established with an 18-G IV catheter in the left forearm, and lactated Ringer's solution was infused at a rate of 1 mL/min to maintain the vein open. Routine monitoring, including electrocardiography, non-invasive blood pressure, and pulse oximetry, was performed

continuously. Systolic blood pressure (SBP), mean arterial pressure (MAP), heart rate (HR), and pulse oximetry were assessed once a minute (min). The first two resting SBP, MAP, and HR measurements in a supine position were recorded, and their average values were treated as the baseline pressure and HR. If the baseline SBP was above 140 mmHg, the patient was excluded from the study due to hypertension. The combined spinal and epidural (CSE) anesthesia was performed by experienced anesthesiologists. The CSE puncture was performed routinely at the level of L3–4 with the patient in the right lateral decubitus position. A 17G Tuohy needle was used to perform the epidural puncture with a paramedian approach. After identifying entrance into the epidural space, a 27-G Whitacre needle was then inserted through the epidural needle. As soon as the cerebrospinal fluid was detected, 10.5 mg (9) of 0.75% isobaric ropivacaine was injected through the Whitacre needle. After injecting the ropivacaine, an epidural catheter was inserted into the epidural space by advancing it 3 cm through the Tuohy needle. After the patient was moved to a supine position with left uterine displacement created by placing a wedge under the right hip, 5 mL of 2% lidocaine was administered through the epidural catheter. In addition, an infusion of 1 mL/kg/min lactated Ringer's solution was administered until delivery. Another 5 mL of 2% lidocaine was administered through the epidural catheter 3 min after the initial dose if the patient could still feel the cold sensation of ice being placed on the skin below the level of T6. Patients who still had a sensory response to ice below the level of T6 at the beginning of surgery were excluded from the study. Immediately after delivery, 1 mL of umbilical vein (UV) blood was collected by the obstetrician, and blood gas assessments were performed using a blood gas analyzer (iSTAT1 Analyzer MN:300-G, Abbott Point of Care Inc., USA) with an iSTAT CG7+ test cartridge.

In Group P, a 5-mL prophylactic dose of norepinephrine in a 5-mL syringe prepared by a research assistant was administered via the IV catheter immediately after the patient was moved to a supine position. An additional 5-mL syringe with a rescue bolus of 6 μ g of norepinephrine was prepared by the research assistant, and the patient received the rescue norepinephrine bolus of 6 μ g immediately after the first episode of hypotension was detected. In Group R, 5 mL of normal saline in a 5-mL syringe prepared by the research assistant was administered immediately after the patient was moved to a supine position. Then, the rescue dose of norepinephrine in a 5-mL syringe prepared by the research assistant was administered immediately after the

first episode of hypotension was detected. The research assistant was the only person who knew which drugs and doses were in which syringes. All anesthesiologists and patients were blinded to the drugs and doses. Hypotension was defined as having a SBP <80% of the baseline value. If the SBP of patients in either group could not be maintained at 80% of the baseline after the initial drug administration, then the additional rescue norepinephrine bolus of 6 µg in a 2-mL syringe would be administered by the anesthesiologist. To differentiate from the initial drugs, the additional rescue norepinephrine boluses of 6 µg were prepared in 2-mL syringe by anesthesiologist. If bradycardia, defined as HR below 50 beats per minute (BPM), was detected, then 0.5 mg atropine was administered to increase HR. The atropine and norepinephrine were given separately. Hypertension was defined as a SBP >120% of the baseline value.

The bolus dose of 4 µg was used for the first patient of both groups. The dose for subsequent patients was determined by the response of each previous patient. In Group P, if the SBP decreased below 80% of the baseline, the bolus dose was considered failed and the dose for the following patient was increased by 1 µg. If the SBP was maintained to at least 80% of the baseline, the dose used was considered a success, and the next patient was randomly assigned a dose with a 1/9th chance of receiving a lower dose (decreased by 1 µg) or an 8/9th chance of receiving the same dose as the previous patient. In Group R, if the SBP remained below 80% of the baseline for 2 successive 2 minutes blood pressure cycles after the bolus dose was given, or could be not maintained above 80% of the baseline until delivery, the dose was considered to have failed, and the dose for the following patient was increased by 1 µg. If the SBP was maintained above 80% of the baseline, the dose was considered to be a success and the next patient was randomly assigned a dose with a 1/9th chance of receiving a lower dose level (decreased by 1 µg) or an 8/9th chance of receiving the same dose level. This was implemented using the BCUD scheme prepared by a study statistician in Microsoft Excel 2016, and was used by the research assistant, who was the only person with access to this software, maintaining the double-blind nature of the study.

The primary outcome was the success of both the prophylactic bolus dose and the rescue bolus dose to maintain the SBP above 80% of the baseline until delivery. Secondary outcomes included both maternal and fetal

observations. Maternal observations included dizziness, breathlessness, nausea (spontaneous complaints from patients recorded by anesthesia providers), vomiting, bradycardia requiring the use of atropine, use of additional rescue norepinephrine doses, hypertension, upper sensory level of anesthesia to ice cold, total co-load IV fluid, total consumption of norepinephrine. Neonatal observations included induction-delivery interval, uterine incision-delivery interval, UV blood gases [including pH, pO₂, pCO₂, base excess (BE), pHCO₃, and SO₂], neonatal weight, and Apgar scores measured at 1 and 5 min post-delivery. Maternal demographics such as age, weight, height, gestational weeks, gravida, para, baseline SBP, baseline MAP, and baseline HR were also recorded.

Statistical analysis and sample size calculation

This dose finding study based on BCUD design and simulation studies suggests that the stopping rule of enrolling 20–40 patients will provide stable estimates of the target dose for most realistic cases (10). In this study, the sample size of each group was 40 patients.

The ED₉₀, defined as the bolus dose of norepinephrine at which the primary outcome of success was observed in 90% of the patients in the study population, was estimated by isotonic regression method (10,11). The isotonic regression estimator of ED₉₀ is the linear interpolated dose between $p^*(r)$ and $p^*(r+1)$: $\hat{U}_3 = \frac{0.9 - p^*(r)}{p^*(r+1) - p^*(r)}(x(r+1) - x(r)) + x(r)$, where

$x(r) = \max(x(i): p^*(i) \leq 0.9)$ and $p^*(i)$ is the adjusted rate of the primary outcome of success at dose $x(i)$, $i=1, 2, 3, \dots, k$, estimated by the pooled-adjacent-violators algorithm (PAVA). Because the observed rate of $p = \{p(1), p(2), \dots, p(k)\}$ might not be increased with respect to the dose level, which is the implicit assumption of a dose-finding study, the PAVA algorithm was first used in isotonic regression to obtain an increase adjusted rate $p^* = \{p^*(1) \leq p^*(2) \leq \dots, \leq p^*(k)\}$ based on p . The 95% confidence interval (CI) of isotonic regression estimator of ED₉₀ was obtained by a bias-corrected percentile method (12,13) using 2,000 bootstrap replications of \hat{U}_3 . Each replication was obtained by drawing a bootstrap data set with sample size of 40 and BCUD design, assuming that the true dose-response rate at each dose is $p^*(i)$, $i=1, 2, 3, \dots, k$, estimated based on the original data. We then estimated \hat{U}_3 , the isotonic regression estimator of ED₉₀ based on the bootstrap data. The isotonic regression and bootstrapping were performed

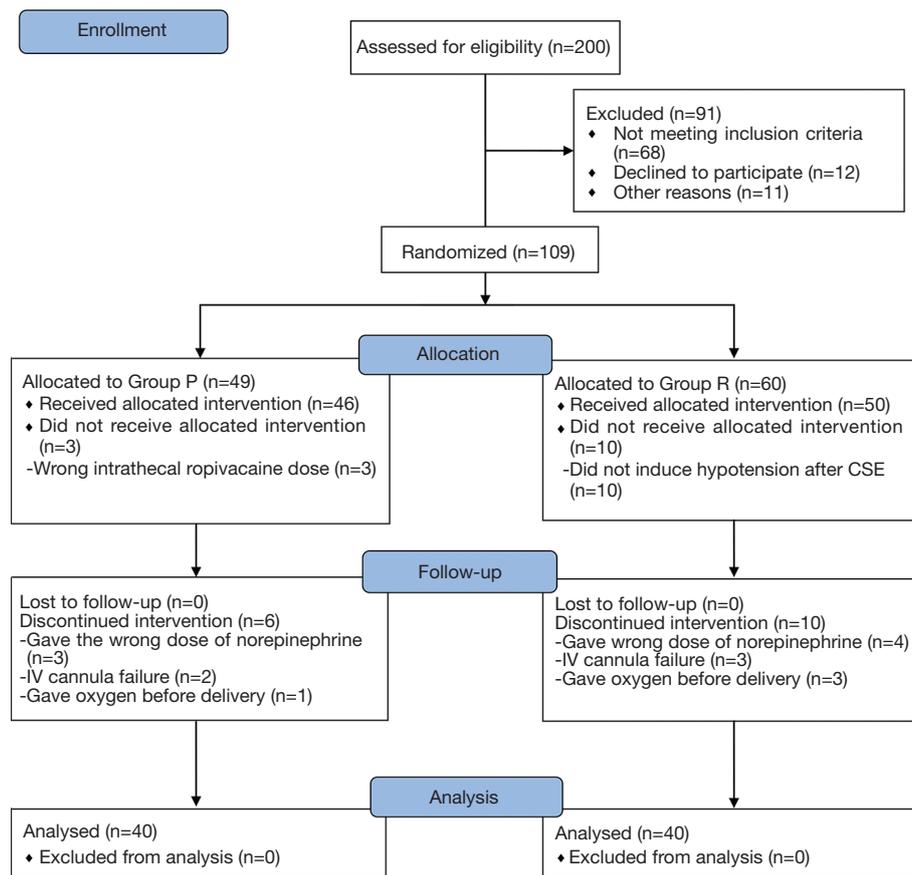


Figure 1 Flow diagram. IV, intravenous; CSE, combined spinal and epidural.

by the study statistician using R version 3.4.4.

The data composed of demographic variables and secondary outcomes were summarized as mean \pm standard deviations (SD), median, range, numbers, and proportions. Parametric data were analyzed with the *t*-test and nonparametric data were analyzed with the Mann-Whitney test. Comparison of proportions was performed using Chi-square test and Fisher exact tests as appropriate. Statistical comparisons were made using SPSS for Windows version 18.0 (SPSS Inc., IL, USA). Statistical significance was assumed if $P < 0.05$.

Results

Two hundred women who underwent elective CSE for CD were selected for the study during January 2018 to August 2018. Data used for patient recruitment are shown in the *Figure 1*. Forty patients from each group were included in

final data analysis. Maternal characteristics are shown in *Table 1*.

The sequence of effective and ineffective responses at each prophylactic norepinephrine and rescue norepinephrine bolus dose for forty successive patients are shown in *Figures 2,3*. *Tables 2,3* show the observed and PAVA-adjusted response rates for each prophylactic norepinephrine and rescue norepinephrine bolus dose level, respectively. The ED₉₀ value of norepinephrine prophylactic bolus was 10.85 μg (95% CI, 9.20–11.67 μg) and the ED₉₀ value of norepinephrine rescue bolus was 12.3 μg (95% CI, 10.0–12.8 μg) as determined using isotonic regression methods.

Table 4 shows maternal outcomes. The occurrences of unpleasant symptoms, such as dizziness (2.5% vs. 42.5%, $P=0.000$), breathlessness (7.5% vs. 70.0%, $P=0.000$), bradycardia (0.0% vs. 15.0%, $P=0.026$), and nausea (10.0% vs. 50.0%, $P=0.000$) related to hypotension were much

Table 1 Maternal Characteristics

Characteristics	Group P (n=40)	Group R (n=40)	P value
Age, years	32.1±3.5	33.5±4.1	0.108
Weight, kg	69.7±7.4	70.7±8.7	0.600
Height, cm	162.6±5.1	160.7±4.7	0.082
Gestational weeks, weeks	38.8±0.9	38.5±0.9	0.138
Gravida, n	1.85±0.9	1.92±1.0	0.090
Para, n	1.35±0.5	1.5±0.6	0.136
Baseline HR, bpm	79.5±14.1	81.8±10.3	0.407
Baseline SBP, mmHg	122.7±8.5	119.6±10.8	0.157
Baseline MAP, mmHg	87.8±8.7	88.5±7.4	0.680

Values are mean ± SD. HR, heart rate; SBP, systolic blood pressure; MAP, mean arterial pressure; SD, standard deviation.

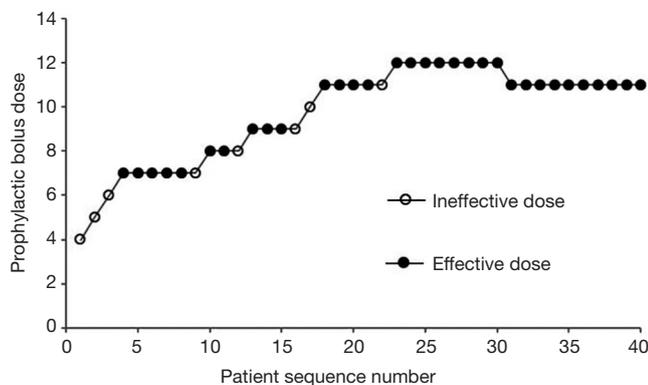


Figure 2 The patient allocation sequence and the response to the assigned dose of Group P. The patient sequence number (X-axis) is the order of patient exposures using the BCUD design. The assigned dose levels are presented on y-axis. An effective dose is denoted by a solid circle, while an ineffective one is denoted by a hollow circle. BCUD, biased coin up-and-down.

lower in Group P. The number of patients who needed atropine (0.0% vs. 15.0%, P=0.026) was less in Group P. Fewer patients in Group P needed additional rescue norepinephrine boluses (5.0% vs. 25.0%, P=0.025) to maintain normal blood pressure.

Table 5 shows neonatal outcomes. The results of UV blood gases were not obtained in one patient from Group P and four patients from Group R due to technical problems. The PO₂ values of UV (24.5±6.7 vs. 20.1±7.1 mmHg,

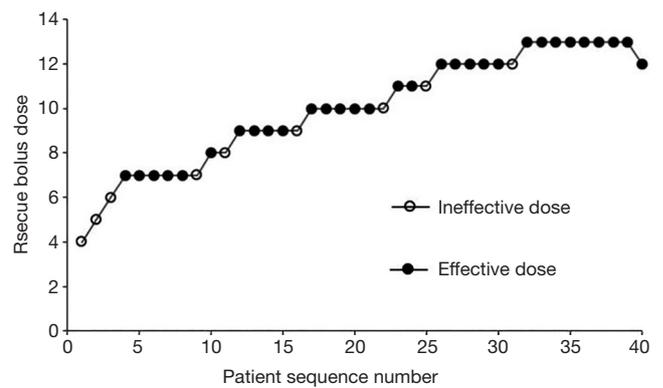


Figure 3 The patient allocation sequence and the response to the assigned dose of Group R. The patient sequence number (X-axis) is the order of patient exposures using the BCUD design. The assigned dose levels are presented on y-axis. An effective dose is denoted by a solid circle, while an ineffective one is denoted by a hollow circle. BCUD, biased coin up-and-down.

Table 2 Observed and PAVA-adjusted response in Group P

Assigned dose, ug	Number of successes, n	Number of patients, n	Observed response rate, %	PAVA-adjusted response rate, %
4	0	1	0.00	0.000
5	0	1	0.00	0.000
6	0	1	0.00	0.000
7	5	6	0.83	0.714
8	2	3	0.67	0.714
9	3	4	0.75	0.714
10	0	1	0.00	0.714
11	14	15	0.93	0.933
12	8	8	1.00	1.000

PAVA-adjusted response rates were estimated using the weighted isotonic regression method. PAVA, pooled-adjacent-violators algorithm.

P=0.008) were higher in Group P. The SO₂ values of UV (41.6%±17.2% vs. 30.2%±13.3%, P=0.002) were higher in Group P.

Discussion

In this sequential dose-finding study, the ED₉₀ value of norepinephrine for both prophylactic and rescue bolus doses to prevent hypotension after CSE during CD were

Table 3 Observed and PAVA-adjusted response in Group R

Assigned dose, ug	Number of successes, n	Number of patients, n	Observed response rate, %	PAVA-adjusted response rate, %
4	0	1	0.00	0.000
5	0	1	0.00	0.000
6	0	1	0.00	0.000
7	5	6	0.83	0.750
8	1	2	0.50	0.750
9	4	5	0.80	0.786
10	5	6	0.83	0.786
11	2	3	0.67	0.786
12	6	7	0.86	0.857
13	8	8	1.00	1.000

PAVA-adjusted response rates were estimated using the weighted isotonic regression method. PAVA, pooled-adjacent-violators algorithm.

Table 4 Maternal outcomes

Outcomes	Group P (n=40)	Group R (n=40)	P value
Hypertension	0 (0.0)	0 (0.0)	1.000
Bradycardia	0 (0.0)	6 (15.0)	0.026
Dizziness	1 (2.5)	17 (42.5)	0.000
Atropine use	0 (0.0)	6 (15.0)	0.026
Breathlessness	3 (7.5)	28 (70.0)	0.000
Nausea	4 (10.0)	20 (50.0)	0.000
Vomiting	0 (0.0)	1 (2.5)	1.000
Additional norepinephrine bolus use	2 (5.0)	10 (25.0)	0.025
Upper sensory level	T3 [T1–T6]	T3 [T1–T6]	0.131
Total co-load IV fluid, mL	830±194	849±221	0.679
Total norepinephrine consumption, ug	11 [7–17]	12 [7–20]	0.267

Values are mean ± SD, n (%) or median [range]. IV, intravenous; SD, standard deviation.

estimated. The results showed that the ED₉₀ value of prophylactic norepinephrine bolus was 10.85 µg (95% CI, 9.20–11.67 µg) and the ED₉₀ value of rescue norepinephrine bolus was 12.3 µg (95% CI, 10.0–12.8 µg) using isotonic

regression methods. The occurrences of unpleasant symptoms, such as dizziness, breathlessness, bradycardia, and hypotension related nausea were much lower in Group P. Fewer patients needed atropine or additional norepinephrine boluses in Group P. The PO₂ and SO₂ values of the UV blood gases were higher in Group P.

The latest study by Onwochei *et al.* (14) showed the ED₉₀ for prophylactic intermittent bolus doses of norepinephrine, aimed at maintaining patients' blood pressure at their baseline, was 5.8 µg (95% CI, 5.01–6.59 µg). Intermittent use of this bolus dose was proven to be safe and effective to prevent hypotension after SA. According to Onwochei's (14) and Ngan Kee's study (15), a dose of 4 µg was cautiously chosen for the first patient of this sequential study. In Onwochei's study, the total consumption of norepinephrine ranged from 6 to 78 µg, which was much higher when compared to the current study (11 µg, 7–17 µg). This may partly due to the difference in the study methods. In the Onwochei's study, the target for the patients' blood pressure was set as the baseline and the patients were intermittently given a bolus dose of norepinephrine when BP fell below the baseline. To some extent, their treatment of hypotension after SA more approximated a rescue therapy, although it aimed to estimate the ED₉₀ dose of prophylactic norepinephrine. In this study, a real sense of the ED₉₀ of prophylactic norepinephrine was estimated, which caused the increased ED₉₀ value and decreased the total consumption of norepinephrine.

Ngan Kee *et al.* (15) designed a dose-response study to estimate ED₅₀ and ED₉₀ of norepinephrine to treat the first episode of hypotension after SA. The resulting ED₉₀ dose of norepinephrine was 18 µg, which was higher than that in the current study (12.3 µg). The target BP was also set to 80% of the baseline, the same as in the current study. However, the patients in that study were divided into six different dose groups (4, 5, 6, 8, 10, and 12 µg), and adopted a dose-response method, which was different from the current study. More importantly, the response rate of the 12 µg group was above 95%, which was similar to the result of the current study (12.3 µg). In the dose-response study, the estimated ED₉₀ dose of norepinephrine was 18 µg and this result was based on their special statistic method; however, the dose groups above 18 µg were absent from that study.

It should be noted that the spinal drugs and doses were not same in both studies above (13,14), although the same anesthesia method for the patient of SA was adopted. The CSE was adopted in the current study, which was different from the studies above. The difference of the rate and

Table 5 Neonatal outcomes

Outcomes	Group P (n=40)	Group R (n=40)	P value
Induction-delivery interval, minutes	12.0±2.9	12.0±2.6	1.000
Uterine incision-delivery interval, seconds	89±59	99±74	0.511
UV, pH	7.36±0.03	7.36±0.11	0.722
PO ₂ , mmHg	24.5±6.7	20.1±7.1	0.008
PCO ₂ , mmHg	41.1±5.8	43.7±6.5	0.079
BE, mEq/L	-2.0±1.6	-1.9±1.6	0.816
SO ₂ , %	41.6±17.2	30.2±13.3	0.002
HCO ₃ , mmHg	23.3±1.0	24.1±2.1	0.116
Neonatal weight, g	3,438±507	3,367±379	0.483
Apgar Scores at 1 min	10 [10–10]	10 [8–10]	0.494
Apgar Scores at 5 min	10 [10–10]	10 [10–10]	1.000

Values are mean ± SD or median [range]. UV, umbilical vein; BE, base excess; SD, standard deviation.

degree of hypotension in patients was difficult to evaluate due to the prophylactic drug use method, but the median upper anesthetic levels of patients were close (T2 to T4) between the current study, Onwochei's study, and Ngan Kee's study. The increasing incidence of hypotension after SA for CD with higher analgesic levels above T4 was proven by several studies (16,17); therefore, we can reasonably infer that the hypotension rates were not much different among three studies.

In the current study, the prophylactic use of a small bolus of norepinephrine was employed in an attempt to prevent the hypotension after SA during CD. It may have more advantages in reduction of unpleasant symptoms related to hypotension and the total consumption of rescue dose of vasopressors, increasing oxygen supplementation for fetuses.

The ED₉₀ dose of norepinephrine in the current study had been proven to be safe by the studies of Onwochei and Ngan Kee. Side effects such as maternal tissue ischemia on hands and forearms, severe maternal hypertension, severe maternal tachycardia, and adverse effect to fetuses and neonates were absent. Only one patient in Group R and two patients in Group P encountered hypertension soon after norepinephrine was given, and all patients' blood pressures

came back to baseline in 3 min. None of them complained about hypertension related side effects such as headaches and nausea. Furthermore, all three patients were more tolerant to anesthesia and had their upper sensory level below T6; therefore, they were excluded from the study. This suggests that identifying the anesthetic effect or upper sensory level before using a bolus of norepinephrine may reduce the occurrence of hypertension.

The current study further proves the effectiveness and safety of prophylactic use of norepinephrine in preventing hypotension after SA during CD. It also provides a new clinical idea of reducing the rate of hypotension, maintaining hemodynamic stability, and reducing the necessary dose of vasopressors by prophylactic use of a small bolus norepinephrine.

Conclusions

The ED₉₀ of a norepinephrine bolus to prevent hypotension and as a rescue bolus for hypotension after CSE during CD was determined to be 10.85 µg (95% CI, 9.20–11.67 µg) and 12.3 µg (95% CI, 10.0–12.8 µg), respectively, using isotonic regression methods. A norepinephrine prophylactic bolus dose of 11 µg or a rescue bolus dose of 12 µg was recommended for clinical practice. Both methods appear to either prevent hypotension or act as a rescue medication for hypotension after CSE, and adverse outcomes were not observed. Furthermore, the prophylactic use of norepinephrine may have more advantages in the reduction of unpleasant symptoms related to hypotension, reducing the likelihood of using rescue drugs, and increasing oxygen supplementation for fetuses than when using a rescue bolus of norepinephrine.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The present study obtained signed informed consent, and the research plan obtaining approval from the Research Ethics Committee of the International Peace Maternity and Child Health Hospital and registering at <http://www.chictr.org.cn> (INR-1800016213).

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