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CLINICAL TRIAL REPORT

Up-and-Down Determination of Different Crystalloid Coload Volumes on the ED 90 of Prophylactic Norepinephrine Infusion for Preventing Postspinal Anesthesia Hypotension During Cesarean Section

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Background: Fluid loading improves hemodynamic stability and reduces the incidence rate of post-spinal anesthesia hypotension when prophylactic vasopressors are administered. We investigated the impact of different crystalloid coload volumes on the 90% effective dose (ED) of prophylactic norepinephrine infusion for preventing post-spinal anesthesia hypotension in non-hypertensive patients undergoing cesarean section.

Methods: Patients were randomly allocated to receive one of the different crystalloid coload volumes (0mL/kg [0mL/kg Group], 5mL kg [5mL/kg Group], and 10mL kg [10mL/kg Group]) in combination with prophylactic norepinephrine infusion immediately after the induction of spinal anesthesia. The prophylactic norepinephrine infusion doses were determined using the up-and-down sequential allocation methodology, with an initial dose of 0.025 μg/kg/min and a gradient of 0.005 μg/kg/min. The primary endpoint was the effective dose at which 90% (ED 90) of patients responded to prophylactic norepinephrine infusion for preventing post-spinal anesthesia hypotension.

Results: The estimated effective dose of norepinephrine infusion, at which 90% (ED 90) of patients responded, was found to be 0.084 (95% CI, 0.070 to 0.86), 0.074 (95% CI, 0.059 to 0.077), and 0.063 (95% CI, 0.053 to 0.064) μg/kg/min in the three groups, respectively.

Conclusion: A crystalloid coload of 5 mL/kg or 10 mL/kg, as opposed to the groups receiving 0 mL/kg crystalloid coloads, resulted in a reduction of approximately 11.9% and 25.0%, respectively, in the ED90 of prophylactic norepinephrine infusion for preventing post-spinal anesthesia hypotension during cesarean section.

Keywords: crystalloid, coload, norepinephrine, postspinal anesthesia hypotension, cesarean section

Introduction

As a common and high-frequency complication, post-spinal anesthesia hypotension during cesarean section warrants attention due to its contribution to a series of maternal and neonatal pathophysiological changes, including maternal organ hypoperfusion and fetal acidosis.[1,2] Vasopressors are deemed as the foremost strategy to cope with post-spinal anesthesia hypotension during cesarean section, both in terms of prevention and treatment.[3] Due to the extensive blockade of thoracolumbar sympathetic nerves and accompanying dilation of arteries in the lower limbs, vasopressors, particularly potent α-receptor agonists, can directly counteract dilated arteries as well as decreased peripheral vascular

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resistance.[4] This stabilizes both maternal blood pressure and cardiac output, while also preventing insufficient placental perfusion induced by maternal hypotension.[5] Currently, norepinephrine is being considered as an alternative to phenylephrine for obstetric anesthesia due to its potent α-receptor agonist and weak β-receptor agonist properties, which help avoid bradycardia and maintain cardiac output.[6]

Fluid loading is recommended by an international consensus statement to improve hemodynamic stability and reduce the incidence rate of post-spinal anesthesia hypotension when prophylactic vasopressors are administered, in combination with the removal of inferior vena cava compression to optimize venous return in non-hypertensive parturients undergoing cesarean section.[7] The optimal timing for fluid loading is crucial in maximizing these effects. Preloading (15–30 minutes prior to spinal anesthesia) was previously a common practice for cesarean section.[8] However, it has been found that a crystalloid preload of 30mL/kg alone is insufficient in preventing post-spinal anesthesia hypotension.[9] The practice has thus shifted towards coload, which involves the immediate administration of fluids loading following the induction of spinal anesthesia. Coload is a more effective approach to augment intravascular volume at the time of maximum arterial expansion (during the period of maximum arterial expansion) caused by sympathetic blockade.[10]

The administration of a 10 mL/kg crystalloid coload combined with prophylactic vasopressor infusion has been observed in several studies.[11,12] It is still unknown whether the use of a relatively higher dose of crystalloid coload has an impact on the 90% effective dose (ED) of prophylactic norepinephrine infusion, and if a relatively smaller dose, such as 5 mL/kg, is inferior to a 10 mL/kg crystalloid coload. An up-and-down sequential allocation approach was employed to investigate the impact of different crystalloid coload volumes (0mL/kg, 5mL/kg, and 10mL/kg) on the ED 90 of prophylactic norepinephrine infusion for preventing post-spinal anesthesia hypotension in non-hypertensive patients undergoing cesarean section.

Methods

After obtaining approval from the Ethics Committees of General Hospital of Ningxia Medical University, Yinchuan, China (No. KYLL-2023-0118) on 27 February 2023 and The Fifth People's Hospital of Huaian, Huaian, China (No. 2023001) on 5 January 2023, as well as written informed consent from patients, this up-and-down sequential allocation study was conducted in compliance with the Declaration of Helsinki between March 2023 and June 2023 and registered at clinicaltrials.gov (NCT05690334).

Healthy ASA II patients (either primaparous or multiparaous) with a singleton full-term pregnancy aged between 18 and 40 years, scheduled for an elective cesarean section under spinal anesthesia were included in this study. Patients having height less than 150 cm, body mass index (BMI) greater than 35 kg/m^2, coexisting chronic hypertension (baseline systolic blood pressure [SBP] greater than 160 mmHg) or pregnancy-induced hypertension, known abnormal fetal development and fetal distress were excluded in this study.

During the resting state in the operating room prior to spinal anesthesia, patients were positioned supine with left displacement of the uterus. Three consecutive readings of non-invasive SBP and heart rate (HR) were taken at 3-minute intervals to obtain the mean value, with a maximum difference of less than 10%, as baseline values. SBP and HR were measured at 1-minute intervals following induction of spinal anesthesia until fetal delivery, and subsequently at 5-minute intervals until the completion of the procedure. An 18-gauge intravenous (IV) catheter was inserted into the upper arm for norepinephrine (Batch No. 2301043, Jinyao Pharmaceutical, Tianjin, China) and crystalloid (Ringer's lactate) infusion. No pre-medication drugs and a crystalloid preload of 5 mL/kg were administered. Patients received a 12.5 mg (2.5 mL) dose of hyperbaric bupivacaine via a 25-gauge spinal needle at the estimated L3-4 vertebral interspace in the lateral decubitus position for spinal anesthesia, and subsequently positioned supine with left displacement of the uterus. After achieving a sensory blockade level of at least T6, as determined by loss of pinprick sensation with the use of a sterile needle, cesarean section was allowed to be performed.

The random sequences were enclosed within opaque containers. Immediately after the induction of spinal anesthesia, patients randomly received one of the different crystalloid coload volumes (0mL/kg [0mL/kg Group], 5mL/kg [5mL/kg Group], and 10mL/kg [10mL/kg Group]) over a period of 10–15 minutes using a pressure bag combined with prophylactic norepinephrine infusion based on a computer-generated randomization sequence. Patients and investigators involved in data recording and group assignment, rather than anesthesiologists involved in intraoperative patient

management, were blinded to the volumes of crystalloid coload. The crystalloid infusion rate was maintained at 6 mL/kg/h for fluid management up to a total volume of 2000 mL following fetal delivery until the completion of the procedure.

The prophylactic norepinephrine infusion doses were determined using the up-and-down sequential allocation methodology, with an initial dose of 0.025 μg/kg/min and a gradient of 0.005 μg/kg/min. If the current dose did not show an efficacy in preventing post-spinal anesthesia hypotension, the norepinephrine gradient was increased by 0.005 μg/kg/min. If three consecutive doses showed efficacy, the norepinephrine gradient was decreased by 0.005 μg/kg/min.

The primary endpoint was the effective dose at which 90% (ED 90) of patients responded to prophylactic norepinephrine infusion for preventing post-spinal anesthesia hypotension. Secondary endpoints, including baseline values (SBP and HR), anesthetic and surgical characteristics (block height, consumption of norepinephrine, volume of coload, anesthesia - delivery interval, skin incision - delivery interval, and length of postoperative hospital stay), the incidence of post-spinal anesthesia hypotension, severe post-spinal anesthesia hypotension (defined as a decline in SBP to >20% and 40% of baseline, respectively; managed with a 6-μg IV norepinephrine bolus), bradycardia (defined as a HR < 60 beats/min, managed with a 0.5 mg IV atropine bolus), nausea or vomiting, and reactive hypertension (defined as an increase in SBP > 20% of baseline; managed by discontinuing norepinephrine infusion until recovery), Apgar scores (1 and 5 min; with a ratio of <7), and umbilical artery blood gas (pH, PCO_2, PO_2, and base excess [BE]).

Statistical Analysis

The statistical methodology Review suggests that, due to the non-independence and uncertain arrangement of response sequence data, it is advisable to include 20–40 patients in most trials using the up-and-down sequential allocation methodology.[13] Moreover, to enhance the overall performance in the up-and-down sequential allocation methodology, it is recommended to adjust the step size and boundaries while ensuring a sample size of 30–60 and avoiding a sample size less than 20.[14] Thus, the determination of 30 patients for each of the three groups was based on a stable estimation of ED 90 in our study.

The data analysis was conducted using the SPSS software, version 23.0 for Microsoft Windows (SPSS, Inc., Chicago, IL, USA). The Shapiro–Wilk test was used to assess the normality of continuous data, which were presented as either mean ± SD and analyzed using an ANOVA test with a post hoc Bonferroni test for multiple comparisons or median (interquartile range, IQR) and analyzed using Kruskal–Wallis test with a post hoc Dunn test for multiple comparisons as appropriate. Chi-squared tests were used for both overall and pairwise comparisons, and the results were presented as numbers (%). The ED90 of prophylactic norepinephrine infusion was calculated using the isotonic regression model. A P value <0.05 was considered to indicate statistical significance.

Results

Ninety patients were randomly assigned to three groups of 30 each and subsequently included in the final analysis. The CONSORT flow diagram shows patient recruitment (Figure 1). Patient demographics and surgical characteristics were comparable among the groups (Table 1).

The sequences of responses and response rates to varying rates of norepinephrine infusion among the groups are shown in Figure 2A-C and Table 2. The estimated effective dose of norepinephrine infusion, at which 90% (ED 90) of patients responded, was found to be 0.084 μg/kg/min (95% CI, 0.070 to 0.86), 0.074 μg/kg/min (95% CI, 0.059 to 0.077), and 0.063 μg/kg/min (95% CI, 0.053 to 0.064) in the three groups, respectively.

The observed outcomes, including maternal adverse events and neonatal Apgar scores and umbilical artery blood gas values, were comparable among the three groups (Table 3).

Discussion

In our study, we observed that crystalloid coload (5 mL/kg and 10 mL/kg) combined with prophylactic norepinephrine infusion were efficacious in preventing post-spinal anesthesia hypotension during cesarean section. Administration of

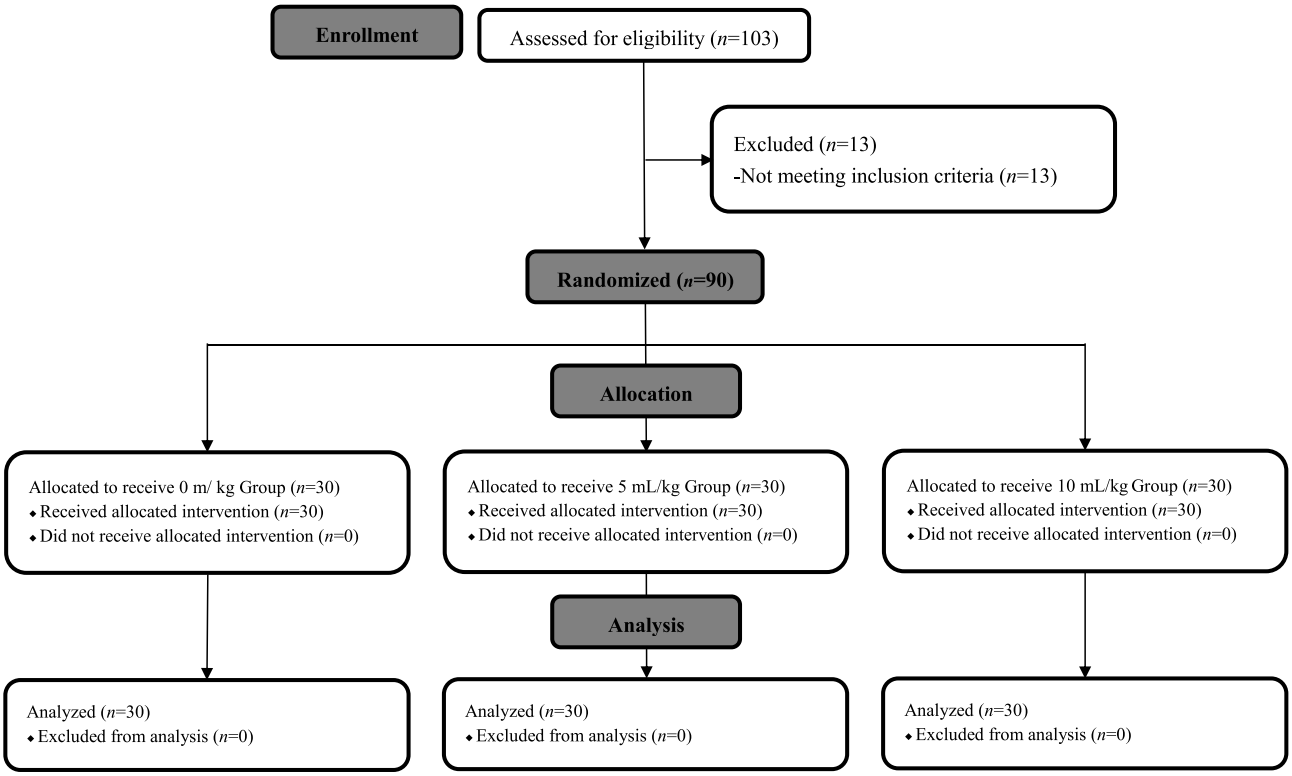

Figure 1 The CONSORT flow diagram.

both 5mL/kg and 10mL/kg of crystalloid coload reduced ED90 of prophylactic norepinephrine infusion when compared to no crystalloid coload.

Qian et al[11] conducted an up-and-down sequential allocation method and probit regression analysis to determine an ED90 of 0.080 (95% CI, 0.069–0.120) μg/kg/min for preventing post-spinal anesthesia hypotension with a crystalloid coload of 10 mL/kg in combination with prophylactic norepinephrine infusion. Our findings suggest that the ED90 was comparatively lower, which may be attributed to a lesser block height (average T6 vs T4) during spinal anesthesia. Despite administering a higher dose of bupivacaine (12.5 mg) compared to Qian et al (10 mg), we intentionally and habitually maintained a lower block height in order to prevent significant changes in maternal hemodynamics. A higher block height leads to a more extensive sympathetic blockade, which increases the likelihood of inducing maternal

Table 1 Patient Demographics, Baseline Values, Anesthetic and Surgical Characteristics

	0 mL/kg Group (n=30)	5 mL/kg Group (n=30)	10 mL/kg Group (n=30)	*P* value
Age (yr),	30.6 (4.2)	32.6 (4.6)	30.5 (4.6)	0.127
BMI (kg/m)	29.7 (3.9)	28.1 (3.1)	28.2 (2.8)	0.113
Baseline values				
Systolic blood pressure (mmHg)	122.1 (10.8)	123.1 (10.7)	122.0 (10.9)	0.912
Heart rate (beats/min)	89.8 (15.3)	95.4 (15.9)	96.8 (13.1)	0.162
Block height (T)	T5 (T4 to T6)	T6 (T5 to T6)	T6 (T5 to T6)	0.260
Consumption of norepinephrine (μg)	70.4 (32.6)	62.2 (19.0)	59.0 (17.0)	0.012
Volume of coload (mL)	0.0 (0.0)	368.8 (43.9)	754.7 (73.9)	< 0.001
Anesthesia - delivery interval (min)	14.4 (2.3)	13.9 (2.8)	14.5 (2.2)	0.546
Skin incision - delivery interval (min)	3.1 (1.1)	2.6 (1.0)	2.8 (1.2)	0.185
Length of postoperative hospital stay (days)	3.6 (0.9)	3.3 (0.5)	3.4 (0.7)	0.148

Note: Data are presented as mean (SD) and median (IQR).
Abbreviation: BMI, body mass index.

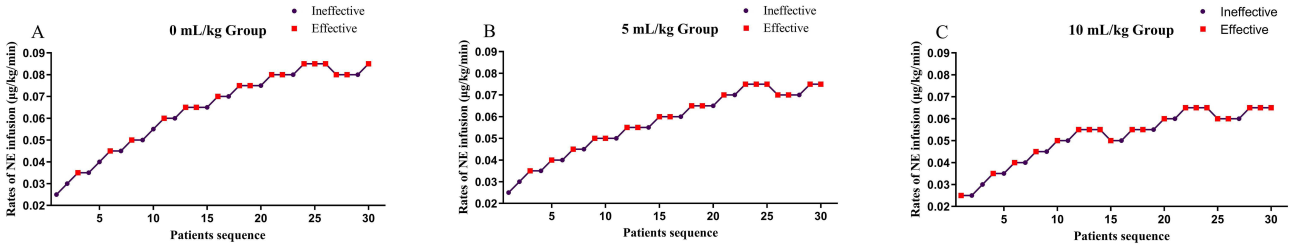

Figure 2 The sequence of effective or ineffective responses to varying rates of norepinephrine infusion in the 0mL/kg (**A**), 5mL/kg (**B**), and 10mL/kg (**C**) groups, respectively. NE, norepinephrine.

hypotension and poses challenges for correction. Xu et al[12] conducted an investigation into the ED95 of varying doses of prophylactic norepinephrine infusion (0, 0.025, 0.05, 0.075 and 0.1 μg/kg/min) combined with a crystalloid coload of 10 mL/kg; their findings revealed that the ED95 was estimated at 0.097 (95% CI, 0.072 to 0.157) μg/kg/min though probit regression analysis. It should be noted that the higher ED95 may be attributed to different research and statistical methodologies, which can impact the final results. The probit regression method is well-suited for conducting

Table 2 Response Rates to Varying Rates of Norepinephrine Infusion

Assigned Dose of Noradrenaline (μg/kg/min)	0 mL/kg Group (*n*=30)			5 mL/kg Group (*n*=30)			10 mL/kg Group (*n*=30)		
	Number of Successes	Number of Patients	Response Rate (%)	Number of Successes	Number of Patients	Response Rate (%)	Number of Successes	Number of Patients	Response Rate (%)
0.025	0	1	0.0%	0	1	0.0%	1	2	50.0%
0.030	0	1	0.0%	0	1	0.0%	0	1	0.0%
0.035	1	2	50.0%	1	2	50.0%	1	2	50.0%
0.040	0	1	0.0%	1	2	50.0%	1	2	50.0%
0.045	1	2	50.0%	1	2	50.0%	1	2	50.0%
0.050	1	2	50.0%	2	3	66.7%	2	4	50.0%
0.055	0	1	0.0%	2	3	66.7%	5	6	83.3%
0.060	1	2	50.0%	2	3	66.7%	3	5	60.0%
0.065	2	3	66.7%	2	3	66.7%	6	6	100.0%
0.070	1	2	50.0%	3	5	60.0%	–	–	%
0.075	2	3	66.7%	5	5	100.0%	–	–	%
0.080	4	6	66.7%	–	–	%	–	–	%
0.085	4	4	100.0%	–	–	%	–	–	%

Table 3 Maternal Adverse Events and Neonatal Outcomes

	0 mL/kg Group (n=30)	5 mL/kg Group (n=30)	10 mL/kg Group (n=30)	*P* value
Postspinal anesthesia hypotension, *n* (%)	12 (40.0)	11 (36.7)	10 (33.3)	0.866
Severe postspinal anesthesia hypotension, *n* (%)	1 (3.3)	1(3.3)	1 (3.3)	1.000
Bradycardia, *n* (%)	3 (10.0)	2 (6.7)	2 (6.7)	0.856
Nausea or vomiting, *n* (%)	5 (16.7)	3 (10.0)	3 (10.0)	0.661
Intraoperative hypertension, *n* (%)	2 (6.7)	1 (3.3)	1 (3.3)	0.770
Birth weight (g)	3082 (553)	3175 (439)	3209 (626)	0.651
Umbilical arterial pH	7.35 (0.04)	7.35 (0.04)	7.34 (0.04)	0.741
Umbilical arterial PCO_2 (mmHg)	42.4 (6.6)	40.6 (5.2)	41.9 (5.8)	0.460
Umbilical arterial PO_2 (mmHg)	23.0 (6.8)	24.9 (6.4)	23.6 (5.5)	0.498
Umbilical arterial BE (mmol/L)	−3.0 (1.4)	−3.0 (1.6)	−2.8 (1.5)	0.794
Apgar score at 1 min, *n* (%)	9 (8 to 9)	9 (9 to 9)	9 (9 to 9)	0.486
Apgar score < 7 at 1 min, n (%)	0 (0)	0 (0)	0 (0)	–
Apgar score at 5 min, *n* (%)	10 (9 to 10)	10 (10 to 10)	10 (10 to 10)	0.442
Apgar score <7 at 5 min, n (%)	0 (0)	0 (0)	0 (0)	–

Note: Data are presented as number (%), mean (SD) or median (IQR).
Abbreviation: BE, base excess.

probabilistic analysis on primary endpoint, such as the incidence of post-spinal anesthesia hypotension. However, the assessment of ED90 using isotonic regression analysis, which provides more accurate ED90 and a smaller 95% CI, is more appropriate for the up-and-down sequence allocation methodology employed in our study, despite logistic or probit regression methods being more commonly utilized prior to the introduction of isotonic regression analysis.[14]

Ngan Kee et al[15] compared the efficacy of a minimal crystalloid infusion rate for maintaining vein patency with that of rapid crystalloid coload (up to 2000 mL until uterine incision) combined with prophylactic phenylephrine infusion (100 μg/min). They found that the latter approach reduced the incidence of post-spinal anesthesia hypotension (1.9% vs 28.3%; $P = 0.001$), while neonatal outcomes, including pH and BE, were similar in both groups despite different crystalloid infusion rates. Buthelezi et al[16] added the initial 1000 mL crystalloid with 500 μg of phenylephrine (20–50 μg/min) as a coload (approximately 10mL/kg in their report) in resource-limited settings, resulting in a reduction in the incidence of post-spinal anesthesia hypotension (37% vs 51%; $P = 0.011$) and lower lowest SBP (94.6 vs 89.0 mmHg; $P < 0.01$) compared to no prophylactic phenylephrine infusion. In addition, Ngan Kee et al[17] employed a maximal 2000 mL crystalloid coload in combination with prophylactic norepinephrine infusion (5μg/mL; 2.5 μg/min). They observed a reduction in patients with one or more episodes of post-spinal anesthesia hypotension among patients who received this combination therapy compared to those who only received crystalloid coload (17% vs 66%; $P < 0.001$), as well as more stable hemodynamics (MDPE: −2.99 vs −11.15; $P < 0.001$; MDAPE: 4.97 vs 11.33; $P < 0.001$). In our study, no significant difference in the incidence of post-spinal anesthesia hypotension was observed when crystalloid coload was not administered for preventing post-spinal anesthesia hypotension as compared to the administration of either 5 mL/kg or 10 mL/kg of crystalloid coload in combination with a prophylactic norepinephrine infusion. However, a crystalloid coload of either 5 mL/kg or 10 mL/kg resulted in a reduction of ED90 of the prophylactic norepinephrine infusion in comparison to no crystalloid coload. This also helps clarify the initial dose of prophylactic norepinephrine infusion with different crystalloid coload doses. For instance, when administering higher doses of crystalloid coload, it is advisable to avoid an elevated initial infusion dose of prophylactic norepinephrine in order to minimize maternal exposure to exogenous catecholamines. Once again, it is recommended that vasopressors remain the primary strategy for managing post-spinal anesthesia hypotension during cesarean section, while fluid loading may further enhance hemodynamic stability when prophylactic vasopressors are administered.

Fluid loading is a highly effective supplement strategy that plays a crucial role in managing post-spinal anesthesia hypotension. This technique involves the administration of fluids to increase venous return, which helps counteract hypovolemia.[18] By replenishing the body's fluid levels, fluid loading can help stabilize blood pressure and prevent complications associated with spinal anesthesia. Both coload and preload are commonly used methods for fluid loading in clinical practice. The preload strategy alone has not proved effective for preventing post-spinal anesthesia hypotension during cesarean section.[19] A large volume of intravenously administered preload, especially crystalloid, will rapidly redistribute into the extracellular space thus decreasing the colloid oncotic pressure.[20] Additionally, with crystalloid preloading, atrial natriuretic peptide release is stimulated by atrial stretching resulting in diuresis and peripheral vasodilation, thus reducing intravascular fluid volume and pressure.[21] In our study, a crystalloid preload of 5mL/kg was administered to avoid preoperative dehydration and compensate for apparent body fluid loss when coload was not administered. Coload is superior to preload and its superiority lies in the fact that the increased fluid volume administered coincides with peak arterial dilation, so excessive fluid redistribution is avoided because hydrostatic pressure is decreased with spinal-induced vasodilation. It should be noted that a large volume of coload may increase this associated risk. The superiority of coload, however, lies in its ability to avoid excessive fluid redistribution resulting from the increased fluid volume that coincides with peak arterial dilation.[22] Crystalloid is an economical option with minimal adverse effects. When administered intravenously, it serves as a potent volume expander in clinical settings. However, due to its small molecules, it remains in the intravascular space for a shorter period of time and may readily diffuse into the extravascular space, potentially leading to edema.[23]

Referring to both practice guidelines for obstetric anesthesia and an international consensus statement, the administration of α-receptor agonists is recommended as a primary strategy of managing post-spinal anesthesia hypotension during cesarean section.[7,24] Ephedrine, with its ability to effortlessly cross the placental barrier, is a contributing factor to neonatal acidosis caused by direct fetal β-receptor agonists.[25] It has been replaced with norepinephrine and

phenylephrine. Because it is a potent α-adrenergic agonist with weak β-adrenergic receptor agonist activity, norepinephrine may be more suitable for maintaining hemodynamic stability with minimal cardiac depression and lower incidence of bradycardia than phenylephrine.[26] Ngan Kee et al[27] conducted a randomized non-inferiority study and found that the use of norepinephrine for blood pressure maintenance did not exhibit any deleterious impact on the pH of the umbilical artery. Furthermore, it was determined to be non-inferior to phenylephrine in terms of efficacy. Owing to its rapid onset and short duration of action, as well as its restricted ability to cross the placental barrier, norepinephrine may facilitate maternal hypotension correction and maintain optimal fetal acid-base status.[26] In accordance to the aforementioned results, our study, using a combination of prophylactic norepinephrine infusion and crystalloid coload, demonstrated that active management of maternal hypotension and hemodynamic stability effectively maintained neonatal outcomes within normal range, as evidenced by umbilical artery blood gas values and Apgar scores, while minimizing maternal adverse effects such as nausea and vomiting.

This study is subject to certain limitations. A higher volume of coload, such as 15 mL/kg or 20 mL/kg, was not explored in our study to further determine the ED90 for preventing post-spinal anesthesia hypotension, so as to preclude an increased risk of tissue and pulmonary edema. Loubert et al[8] have indicated that administering crystalloid fluid volumes ranging from 500 to 1000 mL can effectively achieve optimal hemodynamic status, and increasing fluid volumes does not offer any additional benefits. A subsequent meta-analysis has similar results.[18] However, the optimal volume of coload remains to be explored. Uteroplacental blood perfusion primarily relies on maternal cardiac output, with blood pressure serving as a surrogate marker for cardiac output. Therefore, hemodynamic indices such as cardiac output, cardiac index, and stroke volume variation may be more desirable for guiding fluid loading.

Conclusion

A crystalloid coload of 5 mL/kg or 10 mL/kg was found to decrease the ED 90 of prophylactic norepinephrine infusion for preventing post-spinal anesthesia hypotension during cesarean section by approximately 11.9% and 25.0%, respectively, compared to no crystalloid coload.

Data Sharing Statement

The data that support the study findings are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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