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Effect of Phenylephrine vs Ephedrine on Cardiac Output for Treatment of Spinal Hypotension during Cesarean Section: a Retrospective Non-Inferiority Analysis

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Abstract

Objective: As the first study to evaluate maternal cardiac output in Thai parturients, we compared the hemodynamic effects of phenylephrine and ephedrine during the management of spinal-induced hypotension for elective cesarean delivery.

Materials and methods: This study was a secondary analysis of a previously published randomized controlled multi-centered trial. Data from 33 parturients experiencing spinal hypotension during cesarean section was analyzed retrospectively; 19 received phenylephrine (group P) and 14 received ephedrine (group E). Case enrollment was done from December 2019 to September 2020. The primary aim was to compare alterations in maternal cardiac output between before and after vasopressor administration of phenylephrine and ephedrine treatment group, in healthy parturients undergoing an elective cesarean section. The secondary outcomes were to assess the changes in maternal cardiac output and systolic blood pressure, as well as to determine correlation between cardiac output and heart rate after vasopressor administration.

Results: The maternal cardiac output change between pre- and post-vasopressor treatment in group P, -0.08 l/min (95%CI -0.44, 0.28), is non-inferior to group E, -0.01 l/min (95%CI -0.44, 0.41). The change in cardiac output in the phenylephrine group did not cross the pre-specified non-inferior margin of -1.17 l/min. There were no significant differences in changes of heart rate and cardiac output before after vasopressor administration between and two groups. In addition, it is found that cardiac output is positively correlated with heart rate (Pearson correlation = 0.512) after vasopressor administration.

Conclusion: Cardiac output difference after vasopressor administration in the phenylephrine was non-inferior to ephedrine. Heart rate, rather than choice of vasopressor, might have a role on maternal cardiac output. Additional research focusing on high-risk pregnancies is necessary to gain insights into specific patient populations.

Keywords: cesarean section, cardiac output, ephedrine, hypotension, phenylephrine, spinal anesthesia

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Introduction

While ephedrine and phenylephrine both may be used for neuraxial-induced hypotension in pregnancy[1], in the absence of bradycardia, phenylephrine remains a preferred agent as it can effectively increase blood pressure and has minimal placental transfer resulting in improved fetal acid-base status compared to ephedrine.[1,2] Nevertheless, phenylephrine can frequently cause maternal bradycardia. In our institution, some anesthesiologists preferentially use ephedrine as an initial treatment for hypotension. One study demonstrated a strong association between slower maternal heart rate and reduced cardiac output following phenylephrine administration; however, this resulted in no adverse effect on umbilical arterial pH.[3] In contrast, patients receiving ephedrine exhibited lower umbilical pH and base excess despite higher cardiac output. Given that there were no significant differences in maternal blood loss, complications, or fetal Apgar scores between the two groups, the clinical significance of these hemodynamic changes remains unclear. Phenylephrine is an alpha-1 selective agonist but may affect beta-adrenergic receptors in high doses. Its main effect is vasoconstriction which leads to increases in arterial pressure, systemic vascular resistance, and ventricular afterload. Patient may exhibit phenylephrine-induced decrease in stroke volume caused by a rise in systemic vascular resistance and reflex bradycardia. Consequently, there is concern that phenylephrine's mechanism of action may contribute to a decrease in cardiac output. On the contrary, ephedrine is an indirect alpha and beta-adrenergic agonist which also enhances the release of endogenous catecholamines from adrenergic nerve terminals. Repeating administration of ephedrine may lead to tachyphylaxis due to intrinsic catecholamine depletion. The overall hemodynamic effect of ephedrine is elevation in mean arterial pressure through increase in systemic vascular resistance and increase in heart rate and cardiac output.[4] For cesarean section, systolic blood pressure has been widely used as a surrogate for maternal cardiac output. A previous study suggested that correlation between uteroplacental blood flow and cardiac output is stronger than that with systolic blood pressure.[5] Significant associations were observed between the maximum change in maternal cardiac output and umbilical artery pulsatility index (PI) as well as umbilical arterial pH during delivery. This implies that cardiac output serves as a more reliable predictor of uteroplacental blood flow compared to arterial pressure. Additionally, supporting evidence from Skjoldebrand and coworkers revealed no correlation between maternal arterial pressure and placental blood flow based on placental scintigraphy.[6] Therefore, it is vital to maintain maternal cardiac output under spinal anesthesia during cesarean section as the fetus depends on uteroplacental blood flow for its supply of oxygen and nutrients.

While cardiac output monitoring is not routinely utilized at our institution, its application is reserved for high-risk parturients presenting with severe cardiac diseases, mostly using invasive modalities, such as pulmonary artery thermodilution and arterial waveform analysis. For the purposes of this

study, electrical cardiometry (EC) was selected for the assessment of stroke volume and cardiac output, due to its non-invasive nature and clinical accessibility. Multiple investigations have shown that electrical cardiometry is reliable in comparison to established methods such as thermodilution[7], transesophageal doppler echocardiography[8], and direct Fick-oxygen principle.[9] Nevertheless, a study conducted by Feng et al[10] revealed contradictory findings suggesting that electrical cardiometry might have restricted accuracy, precision, and interchangeability with transthoracic echocardiography. Despite this limitation, electrical cardiometry can still be employed to track the trend of cardiac output peri-operatively. In the obstetric population, EC via the ICON® monitor has been validated as a reliable hemodynamic monitoring tool. It demonstrates high accuracy for heart rate and a robust capability for trending cardiac output, though absolute stroke volume measurements exhibit greater variance when compared to transthoracic echocardiography.[11]

This is the first study that compare the effect of ephedrine and phenylephrine on maternal cardiac output in Thai parturients. The primary aim was to compare alterations in maternal cardiac output before and after vasopressor administration during elective cesarean section of parturients in phenylephrine group (group P) and ephedrine group (group E), with the hypothesis that cardiac output change in phenylephrine group is above the non-inferiority margin. The secondary outcomes were changes in maternal cardiac output and systolic blood pressure, as well as correlation between cardiac output and heart rate after vasopressor treatment.

Material and methods

This retrospective non-inferiority analysis is a secondary analysis of previously published randomized controlled multi-centered trial[12] conducted at the Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Chiang Mai University, Samutprakarn Hospital, and Chaophrayayommarat Hospital between December 2019 and September 2020. This randomized controlled trial focused on comparing the incidence of abnormal heart rate after phenylephrine and ephedrine administration after spinal hypotension during cesarean section. The author enrolled singleton, 37-42-week pregnant women aged >18 yr who had elective cesarean section under spinal anesthesia and had American Society of Anesthesiologist physical status II without potential fetal compromise or any underlying disorders. Patients were excluded if they had emergency cesarean sections, complicated pregnancies that involved maternal hemodynamic conditions, such as multiple pregnancies, placenta previa, abruptio placenta, and maternal co-morbidities, which included cardiovascular, infectious, hepatic, renal, endocrine, or psychiatric problems. Upon the institutional board review approval of the study protocol (IRB No 486/62), data from 33 healthy parturients experiencing spinal hypotension during elective caesarean section was anonymously analyzed. Among them, 19 were in phenylephrine group (group P) and 14 were

in ephedrine group (group E).

Maternal heart rate (HR) and systolic blood pressure (SBP) were measured in a supine position at the night before surgery (T0), and the baseline values were defined as the average of three measurements. All participants started to fast at midnight, and no routine premedication was administered on the day of the operation. Hypotension prompted treatment with 100 mcg in 10 ml of phenylephrine for group P and 6 mg of ephedrine for group E. However, parturients in group P with heart rate < 60 beats/min were instead treated with 6 mg of ephedrine, as phenylephrine may exacerbate bradycardia and pose a potential risk. Following treatment, the same vasopressor was administered if two consecutive systolic blood pressure measurements every minute reach hypotension criteria (Figure 3). When a participant developed bradycardia, 0.6 mg of atropine was administered.

Four skin sensors for the ICON® monitor were placed on the neck and left side of the thorax to record cardiac output data (Figure 4). The ICON® monitor (Osypka Medical GmbH, Berlin, Germany), an electrical cardiometry, was employed to non-invasively measure maternal cardiac output at two time points: initially at baseline before spinal anesthesia, and subsequently after vasopressor administration during cord clamping. Attending anesthesiologists placed four sensors to the neck and the left side of the thorax, adhering to the standardized electrode configuration specified by the manufacturer (ICON® User Guide). EC analyzes the rate of change in thoracic conductivity before and after aortic valve opening to determine stroke volume, which is then used to calculate cardiac output. The data collected in this study included heart rate, systolic blood pressure, and cardiac output at baseline before spinal anesthesia and during cord clamping (after vasopressor administration).

Spinal anesthesia was performed using 2.2 or 2.4 mL of 0.5% hyperbaric bupivacaine (depending on the participant's height of less or more than 160 cm) with 0.2 mg of morphine via a 27-gauge Quincke spinal needle at the L3-4 or L4-5 intervertebral space. The highest level of sensory anesthesia assessed using ice was recorded 5 min after intrathecal injection. To avoid hypotension, IV co-loading with 500 mL of Ringer acetate solution was administered during the spinal block, and left uterine displacement was performed until delivery. After the spinal block, HR and SBP were recorded every minute until delivery and every 5 min thereafter until the operation was completed. Hypotension was defined as a reduction in SBP to <80% of baseline SBP before surgery. When hypotension was detected, the treatment allocation concealed in a sealed envelope was revealed, and vasopressor administration for Groups P/E or C was administered according to the allocated protocol. Tachycardia was defined as heart rate > 120% of baseline value and > 100 beats/min. Bradycardia was defined as heart rate < 50 beats/min or < 60 beats/min comorbid with hypotension. When a participant developed bradycardia, 0.6 mg of atropine was administered intravenously when HR was <50 beats/min after ephedrine or sustained bradycardia (for >1 min) after phenylephrine. And if the participant

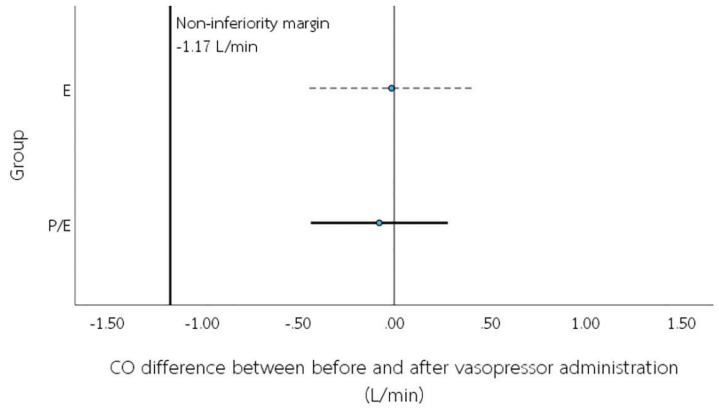


Figure 1 Difference in cardiac output (CO) between before and after vasopressor administration of group P and group E, with non-inferior margin at -1.17 l/min

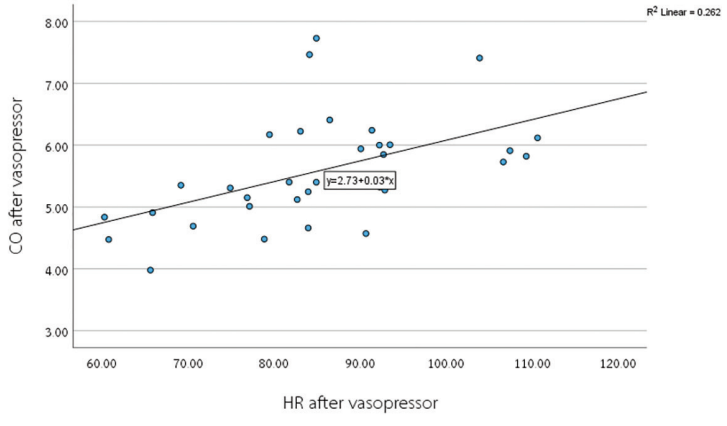


Figure 2 Correlation between cardiac output (CO) and heart rate (HR) following vasopressor administration (n=33). A significant positive correlation was observed (Pearson correlation = 0.512, P = 0.002, R2 = 0.262)

continued to have hypotension after receiving three consecutive doses of the study vasopressor, 5-10 mcg of norepinephrine was administered. The total doses of the vasopressor, atropine, or any vasoactive drugs were recorded.

Sample size calculation and data analysis

The sample size was calculated to define the adequate number of participating parturients in the study. As the administration of phenylephrine was not expected to increase cardiac output compared to ephedrine, non-inferiority analysis was used. The formula for comparing two means in non-inferiority or superiority study is as followed[13] and the calculated sample size is 30 people in each group. However, as the ICON® monitor was only available in one of four centers, King Chulalongkorn Memorial Hospital, only 33 parturients had available cardiac output measurements, 19 in the phenylephrine group and 14 in the ephedrine group.

$$n_2 = \frac{(z_{1-\alpha} + z_{1-\beta})^2 \sigma^2 \left(1 + \frac{1}{k}\right)}{(\epsilon - \delta)^2}$$

$$\epsilon = \mu_2 - \mu_1$$

$$k = \frac{n_1}{n_2}$$

Z (0.95) = 1.64, Z (0.8) = 0.84

Mean CO in ephedrine group (μ_1) = 6.2 and mean CO in phenylephrine group (μ_2) = 5.8[3]

SD. = 1.2, Margin (δ) = 1.17

Ratio (k) = 1.0,

n_2 = 29.88

The primary outcome variable was the change in cardiac output before and after vasopressor administration, reported as mean and standard deviation (SD). A non-inferiority analysis was employed in this study to evaluate whether the cardiac output in group P was lower than group E. We expect that cardiac output change between pre- and post-vasopressor treatment in Phenylephrine group (P) should not be less than the non-inferiority margin, -1.17 l/min, which is calculated based on a study by Dyer and colleagues.[3] It was determined by using the point estimate of the observed difference between these two groups and was set at 40%. However, in our study, we opted for 20% instead of 40% to align it more closely with a null effect. As a result, the non-inferiority margin for cardiac output alteration applied in this research stands at -1.17 l/min. The clinical significance of this specific margin has yet to be fully established.

The secondary outcomes were changes in maternal cardiac output and systolic blood pressure, as well as a correlation between cardiac output and heart rate after vasopressor administration. Statistical analysis included Student's T-test and Pearson correlation. Categorical variables were expressed as percent. Statistical analysis was performed using SPSS version 29 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was performed to assess the distributional characteristics of the data.

Results

Among thirty-three parturients who developed hypotension following spinal anesthesia, 19 were in phenylephrine group (group P) while 14 were in ephedrine group (group E). Table 1 illustrates maternal characteristics such as age, gestational age, weight, height, total average dose of vasopressors, and anesthetic levels of both groups. Baseline demographic characteristics were similar between two groups. Among the 19 parturients in Group P, 17 received phenylephrine exclusively. One received a combination of 6 mg ephedrine and 100 mcg phenylephrine, while another was given 18 mg ephedrine and 300 mcg phenylephrine. The use of ephedrine in the phenylephrine group adhered to the study protocol[9], which specified that ephedrine was administered instead of phenylephrine when the heart rate fell below 60 beats/min, to avoid potentially harmful bradycardia. The median dose of phenylephrine given in group P was 100 mcg (IQR 100-200) whereas the median dose of

ephedrine administered in group E was 12 mg (IQR 6-18). Most parturients had an anesthetic level of T4 or above, except for one parturient in group P who had an anesthetic level below T4. Table 2 displays hemodynamic parameters at baseline, prior to and after vasopressor administration, as well as the incidence of bradycardia and tachycardia.

Cardiac output measured at baseline and after vasopressor were 5.45 l/min (95% CI 4.95, 5.95) and 5.37 l/min (95% CI 4.98, 5.76) in group P, and 5.88 l/min (95% CI 5.37, 6.39) and 5.87 l/min (95% CI 5.34, 6.39) in group E. The cardiac output changes between pre- and post-vasopressor treatment were -0.08 l/min (95% CI -0.44, 0.28) in group P and -0.01 l/min (95%CI -0.44, 0.41) in group E. The lower limits of 95%CI in both groups were above the non-inferiority margin. The difference in heart rate before and after vasopressor administration was -8.19 (95% CI -14.59, -1.79) in group P and -0.31 (95% CI -9.57, 8.96) in group E. There was a positive correlation observed between post-vasopressor cardiac output and heart rate (correlation = 0.512). One parturient in group P received Atropine as a treatment for bradycardia and none received Norepinephrine. Nausea and vomiting were found in 9 parturients in group P and 4 in group E. All infants from both groups had APGAR scores of 9 at minute 1 and 10 at minute 5.

Table 1 General demographic

Variables	Group P (n=19)	Group E (n=14)	*P*-value
Maternal characteristics			
Age (yr), mean (SD)	34.2 (5.8)	33.5 (5.3)	0.725
Weight (kg), mean (SD)	73.5 (9.3)	69.0 (13.9)	0.276
Height (cm), mean (SD)	157.9 (3.6)	157.3 (4.9)	0.685
Gestational age (wk), mean (SD)	38.6 (0.8)	38.3 (0.4)	0.198
Supine hypotension, n (%)	2 (10.5)	0	0.500
Total phenylephrine (mcg), median (IQR)	100 (100, 200)	0 (0, 0)	<0.0001*
Total ephedrine (mg), median (IQR)	0 (0, 0)	12 (6, 18)	<0.0001*
Anesthetic level			
Above T4, n (%)	2 (10.5)	1 (7.1)	>0.999
T4, n (%)	16 (84.2)	13 (92.9)	0.620
Below T4, n (%)	1 (5.3)	0	>0.999

Values are expressed as mean (SD) and median (interquartile range; IQR).

Table 2 Cardiac output, heart rate, and systolic blood pressure

Variables	Baseline (Before spinal anesthesia)		Before vasopressor		After vasopressor (During cord clamping)	
	P	E	P	E	P	E
Cardiac output (l/min)	5.45 (4.95-5.95)	5.88 (5.37-6.39)			5.37 (4.98-5.76)	5.87 (5.34-6.39)
Cardiac output difference[a]					-0.08 (-0.44, 0.28)	-0.01 (-0.44, 0.41)
Heart rate (beats/min)	80.76 (76.17-85.35)	89.36 (83.90-94.81)	77.87 (70.82-84.91)	89.11 (79.97-98.24)	79.71 (73.64-85.77)	92.55 (86.33-98.77)
Heart rate difference[a]					-8.19 (-14.59, -1.79)	-0.31 (-9.57, 8.96)
Systolic blood pressure (mmHg)	117.37 (112.89-121.86)	115.61 (106.66-124.55)	103.16 (99.37-106.94)	104.26 (100.91-107.62)	104.48 (99.98-108.99)	103.85 (100.21-107.48)
Bradycardia, n (%)			3 (15.8)	0	3 (15.8)	0
Tachycardia, n (%)			12 (63.2)	6 (42.9)	10 (52.6)	5 (35.7)

Independent t-test was used for all calculations. a = difference between before and after vasopressor administration

Table 3 The incidences of medical resuscitation requirement, and intraoperative nausea and vomiting

Variables	Group P (n=19)	Group E (n=14)	*P*-value
Atropine, n (%)	1 (5.3)	0	>0.999
Norepinephrine, n (%)	0	0	1.000
Nausea, n (%)	9 (47.4)	4 (21.4)	0.259
Vomiting, n (%)	0	1 (7.1)	0.424
APGAR 9, 10	19 (100)	14 (100)	>0.999

Discussion

For this research, we established a non-inferiority margin of a 1.17 l/min decrease in cardiac output, based on the observed differences between phenylephrine and ephedrine in a study by Dyer.[2] The maximal decrements in both group P (-0.44 l/min) and group E (-0.44 l/min) remained well within this margin. While no statistically significant differences were observed in cardiac output or heart rate alterations between the two groups, we noted a positive correlation between cardiac output and heart rate following vasopressor administration in both cohorts, aligning with previous literature.[2] Ultimately, both ephedrine and phenylephrine effectively managed spinal hypotension in this study, with no incidence of birth asphyxia in either group. Contrary to previous studies reporting increased cardiac output following ephedrine administration[1,2], our study exhibited a decrease in cardiac output in both groups relative to baseline. This discrepancy may stem from several unmeasured data inherent to this retrospective design, including maternal blood loss prior to cord clamping and the total volume of fluid co-loading. Furthermore, electrical cardiometry may possess limited accuracy and precision in capturing acute cardiac output dynamics when compared to gold-standard techniques.

As the first study to evaluate maternal cardiac output specifically among Thai parturients, a key strength lies in its use of data from a previously published multi-center randomized controlled trial, ensuring high baseline data quality. However, several limitations must be acknowledged. First, due to the limited availability of EC monitors, this analysis was restricted to a single center from the original trial, introducing potential selection bias where local demographics may not reflect the broader trial population or all Thai healthcare settings. Crucially, this single-center restriction severely compromised our statistical power. The study enrolled only 33 participants instead of the targeted 60. Assuming the original sample size of 60 was calculated to detect a standard large effect (d = 0.74), this drop to 33 participants reduced the trial's statistical power to just 52.5%, heavily increasing the risk of a Type II error. A sensitivity power analysis (alpha = 0.05, power = 0.80) confirms that this final sample distribution was only equipped to detect a large effect size (Cohen's d = 1.02). Consequently, our non-significant findings regarding changes in cardiac output must be interpreted with caution, as the study was underpowered to detect clinically meaningful, moderate differences between the two vasopressors.

Second, the exclusive inclusion of healthy parturients limits the generalizability of these findings to high-risk populations, such as those with obesity, pregnancy-induced hypertension, or cardiomyopathy. Third, the study lacked data on potential confounders during measurement at cord clamping, such as maternal blood loss, the total volume of fluid administered prior to delivery, and the amount and timing of uterotonic agent administration. Finally, because fetal blood sampling for acid-base status and base excess was not collected,

we could not confirm whether the observed reduction in cardiac output adversely affected uteroplacental blood flow; thus, the clinical relevance of this non-inferiority margin remains to be fully validated.

Conclusion

Within the constraints of this single-center study, our findings offer valuable insights for healthcare providers managing spinal anesthesia-induced hypotension. Our data highlight that maternal heart rate may exert a more influence on cardiac output than the specific choice of vasopressor, emphasizing the critical importance of heart rate maintenance at the bedside. Furthermore, providing the first specific hemodynamic data within a Thai cohort offers local clinicians a reassuring baseline of clinical safety for both phenylephrine and ephedrine, ultimately contributing to more tailored and safer perioperative care for obstetric patients. Future prospective, multi-center studies utilizing larger, adequately powered sample sizes are required to validate these hemodynamic trends.

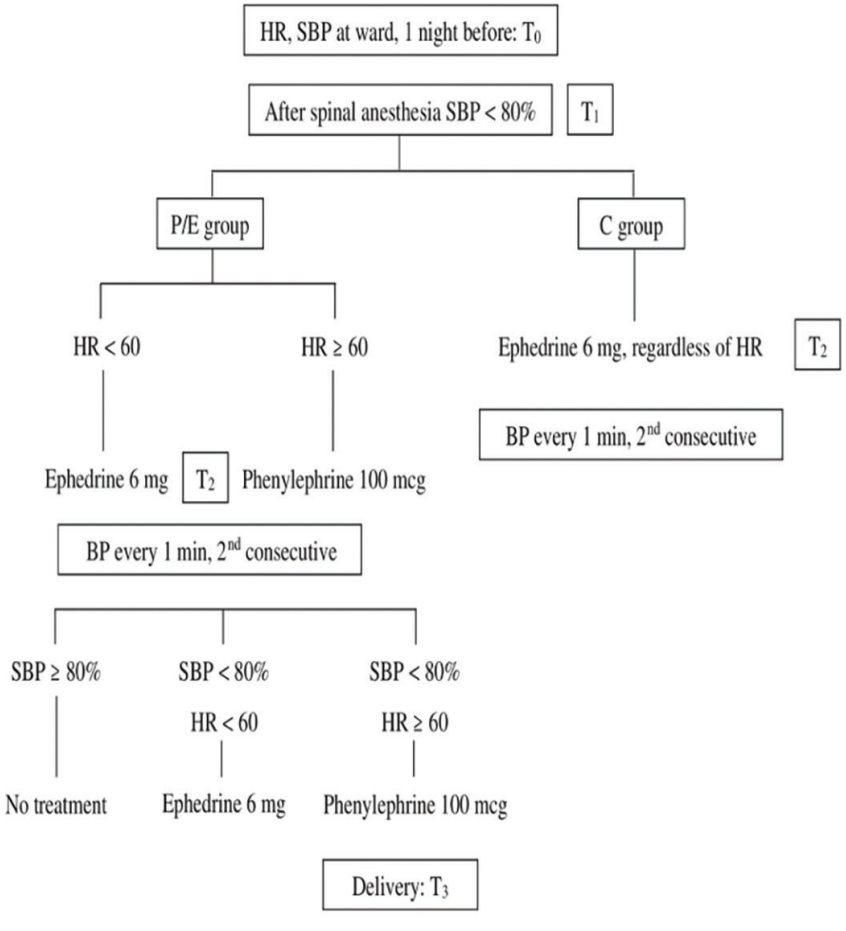


FIGURE 1 Description of the two-protocol design for managing hypotension

Figure 3 Description of the two-protocol design for managing hypotension

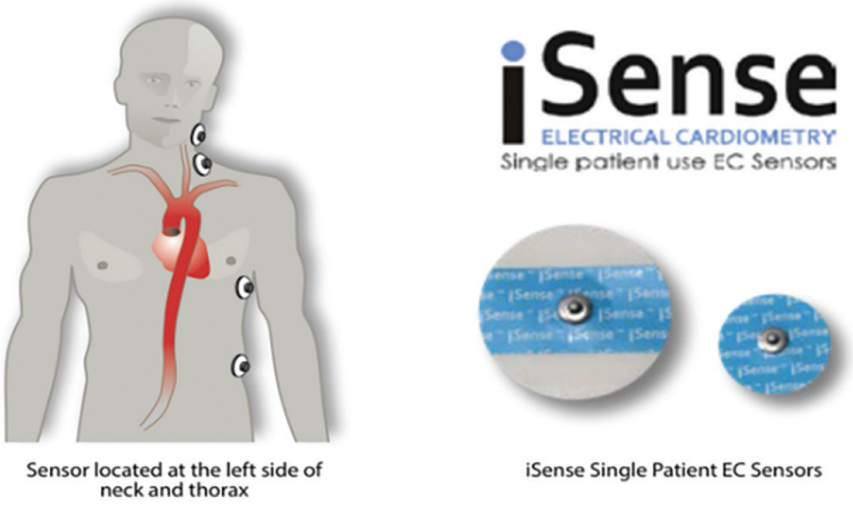


Figure 4 ICON® monitor

Conflict of interest statement

The authors declare no conflicts of interest regarding the publication of this paper.

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