A Randomized Controlled Trial of Variable Rate Phenylephrine Infusion With Rescue Phenylephrine Boluses Versus Rescue Boluses Alone on Physician Interventions During Spinal Anesthesia for Elective Cesarean Delivery

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BACKGROUND: Phenylephrine infusion is used to reduce hypotension during spinal anesthesia for cesarean delivery. A prophylactic fixed rate infusion regimen may not improve hemodynamic control; a variable rate regimen adjusted in response to changes in arterial blood pressure and heart rate may allow more accurate maintenance of baseline blood pressure. We hypothesized that a combination of crystalloid solution coload with a variable rate phenylephrine infusion and phenylephrine rescue boluses may be associated with fewer physician interventions needed to maintain maternal systolic blood pressure within 20% of baseline and greater hemodynamic stability than crystalloid solution coload with phenylephrine rescue boluses alone.

METHODS: In this prospective, double-blind study, 80 patients received a coload with 15 mL/kg lactated Ringer's solution immediately after the initiation of spinal anesthesia. Patients were randomized to receive a prophylactic variable rate phenylephrine infusion starting at 0.75 μg/kg/min (group P) or infusion of normal saline (group S). Maternal systolic blood pressure was maintained within 20% of baseline with rescue phenylephrine boluses using a preset algorithm. During the predelivery period, the number of physician interventions (primary outcome), hemodynamic performance, nausea/vomiting, and umbilical cord blood gas values were compared between the groups.

RESULTS: One patient from group S was excluded due to protocol violation. Therefore, group P included 40 patients and group S 39 patients. The median (range) number of physician interventions needed to maintain maternal hemodynamics within the target range (0 [0–6] vs 3 [0–9], difference in median: 3, 95% confidence interval of difference: 2–4) and incidence of hypotension (8/40 [20%] vs 35/39 [90%]) were lower in group P compared with group S ($P < 0.001$). Group P had a higher incidence of hypertension compared with group S (6/40 [15%] vs 0/39 [0%], $P = 0.026$). The median performance error was closer to baseline ($P < 0.001$) with a smaller median absolute performance error ($P = 0.001$) in group P versus group S. In group P, 4/40 (10%) patients had nausea/vomiting compared with 17/39 (44%) in group S ($P = 0.001$). The number needed to treat was 1.4 women to prevent 1 case of hypotension, and 3 women to prevent 1 case of nausea/vomiting; the rate of hypertension was 1 case per 6.7 women treated. Neonatal outcomes were not different between the 2 groups.

CONCLUSION: Prophylactic variable rate phenylephrine infusion and rescue phenylephrine bolus dosing is more effective than relying on rescue phenylephrine bolus dosing with respect to limiting clinician workload and maternal symptoms during spinal anesthesia for cesarean delivery. (Anesth Analg 2014;118:611–8)

Phenylephrine infusion is a safe and effective way to reduce the incidence and severity of hypotension and nausea during spinal anesthesia for cesarean delivery,[1–4] despite animal data suggesting an adverse effect on uteroplacental perfusion.[5,6] A recent meta-analysis clearly demonstrated a decreased risk of fetal acidosis associated with phenylephrine use compared with ephedrine.[7] Hypotension was virtually eliminated by using a prophylactic phenylephrine infusion at a fixed rate of 100 μg/min and rapid crystalloid solution coload of up to 2 L.[2] However, reactive hypertension was frequent with a decrease in maternal heart rate, indicating a decrease in cardiac output. This may raise concern in patients in whom an increase of arterial blood pressure may be detrimental, for example, patients with chronic hypertension, preeclampsia, and those with compromised uteroplacental blood flow.

In a recent study, prophylactic fixed-rate phenylephrine infusions (on/off) reduced the incidence and severity of maternal predelivery hypotension compared with placebo.[8] There was greater hemodynamic stability using the low-dose infusion rates, namely the 50 μg/min, compared with

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the high-dose infusion rates (75–100 μg/min). However, this fixed regimen did not significantly reduce the number of physician interventions needed to maintain maternal systolic blood pressure (SBP) within 20% of baseline or the accuracy of hemodynamic control compared with placebo. Of note, many of the interventions in the high-dose infusion rates were necessary to manage reactive hypertension and bradycardia (incidence of 80% and 30%, respectively). Therefore, in clinical practice, the simple fixed-rate infusion regimen may not improve hemodynamic control; a variable rate regimen, that is, titrated in response to changes in arterial blood pressure and heart rate may more accurately maintain blood pressure near baseline. The bolus administration of phenylephrine to treat hypotension is commonly used and is still considered standard practice. However, this technique requires multiple interventions from the anesthesia provider, which might be time consuming.

We designed a prospective, randomized, double-blind study to test the hypothesis that crystalloid solution coload combined with a variable rate phenylephrine infusion (started initially at 0.75 μg/kg/min) and rescue phenylephrine boluses are associated with fewer interventions needed to maintain maternal SBP within 20% of baseline and to treat bradycardia than crystalloid solution coload with rescue phenylephrine boluses only. We decided to base our phenylephrine dose on body weight because it reduces variability in dosing due to variability in body weight. We set our starting dose at 0.75 μg/kg/min because it is equivalent to the low-dose fixed-rate infusion of 50 μg/min in a parturient weighing 75 kg. The primary outcome was the number of physician interventions needed. Secondary outcomes included effects on arterial blood pressure, heart rate, and the need for vasopressors, as well as the incidence of nausea and/or vomiting and neonatal outcomes.

METHODS

This study was conducted with IRB approval and was registered with the www.clinicaltrials.gov protocol registration system (NCT01378325). Written informed consent was obtained from 80 nonlaboring parturients >37 weeks' gestation, ASA physical status I or II scheduled for elective cesarean delivery. Exclusion criteria were allergy or hypersensitivity to phenylephrine, hypertension, multiple gestation, known fetal abnormalities, diabetes mellitus, polyhydramnios, body weight less than 50 and more than 100 kg, height less than 150 and more than 180 cm, major systemic disease, anemia (hemoglobin concentration <10 g/dL), or clotting diathesis.

Patients were randomly assigned using a computer-generated table of random numbers to receive crystalloid solution coload with lactated Ringer's solution combined with either prophylactic variable rate phenylephrine infusion started at 0.75 μg/kg/min (group P) or prophylactic variable rate saline infusion (initial rate, 0.0075 mL/kg/min) (group S). Group allocations were placed in sealed, opaque envelopes on initial simple randomization. An anesthesia resident not involved in anesthetic management prepared either a phenylephrine 100 μg/mL or saline in 50-mL syringe according to instructions contained within each sealed envelope and gave it to the attending anesthesiologist. The patient, the attending anesthesiologist performing the spinal block, collecting the data, and treating the side effects, and the pediatrician assessing neonatal outcome were unaware of the patient's group assignment.

In the preoperative holding area, an 18-gauge IV cannula connected to a 3-way stopcock was placed in a peripheral vein in the patient's upper limb, and the initial infusion rate of lactated Ringer's solution was to keep the vein open.

In the operating room, the patients were placed comfortably in the left supine wedged position and were monitored by automated noninvasive arterial blood pressure monitoring (placed on the upper limb without the IV line), electrocardiogram, and pulse oximetry. Baseline arterial blood pressure was the mean of 3 consecutive readings at 3-minute intervals during which the SBP did not vary by >10% from the average value. When the SBP did vary by >10%, we continued to record until 3 readings in a row were consistent; 80% and 120% of the baseline mean value were calculated.

Spinal anesthesia was initiated in the sitting position at the estimated L2-L3 or L3-L4 interspace with 0.75% hyperbaric bupivacaine (Marcaine® Spinal; bupivacaine hydrochloride in dextrose injection, USP, Lake Forest, IL) 12.75 mg (1.7 mL) combined with morphine (Laboratoire Renaudin, Itxassou, France) 0.2 mg (0.2 mL). Parturients were placed promptly in the supine position with left uterine displacement, and supplemental oxygen was delivered through a facemask at 5 L/min. Blood pressure was measured every minute until delivery and every 3 minutes thereafter.

Immediately after the injection of the intrathecal medication, the patients received a coload of 15 mL/kg lactated Ringer's solution administered by gravity at a wide-open rate over a period of approximately 10 to 15 minutes, then the rate of administration of IV fluid was reduced to keep the vein open until delivery. At the same time, the infusion of the study drug (either phenylephrine or saline) was started at a rate of 0.75 μg/kg/min via a 3-way stopcock connected directly to the IV cannula. The primary end point was the number of physician interventions needed to maintain SBP within 20% of baseline and to treat bradycardia during the study period. Physician interventions were triggered in both groups by the presence of any of the following hemodynamic values (Fig. 1):

1. Hypertension defined as an increase of SBP >20% of baseline: the infusion was stopped and was restarted at a rate reduced by 0.25 μg/kg/min when the SBP decreased to below the upper limit of the target range.
2. Hypotension defined as a decrease in SBP to <80% of baseline and <100 mm Hg: a rescue IV bolus of phenylephrine 100 μg was administered from another syringe. The infusion rate was also immediately increased by 0.25 μg/kg/min. Smaller decreases in blood pressure (SBP below baseline measurement) were similarly treated if accompanied by nausea, vomiting, or dizziness.
3. Bradycardia defined as heart rate < 50 bpm: if bradycardia was not accompanied by hypotension, the infusion was stopped and was restarted at a rate reduced by 0.25 μg/kg/min when the heart rate was >50 bpm. Bradycardia accompanied by hypotension

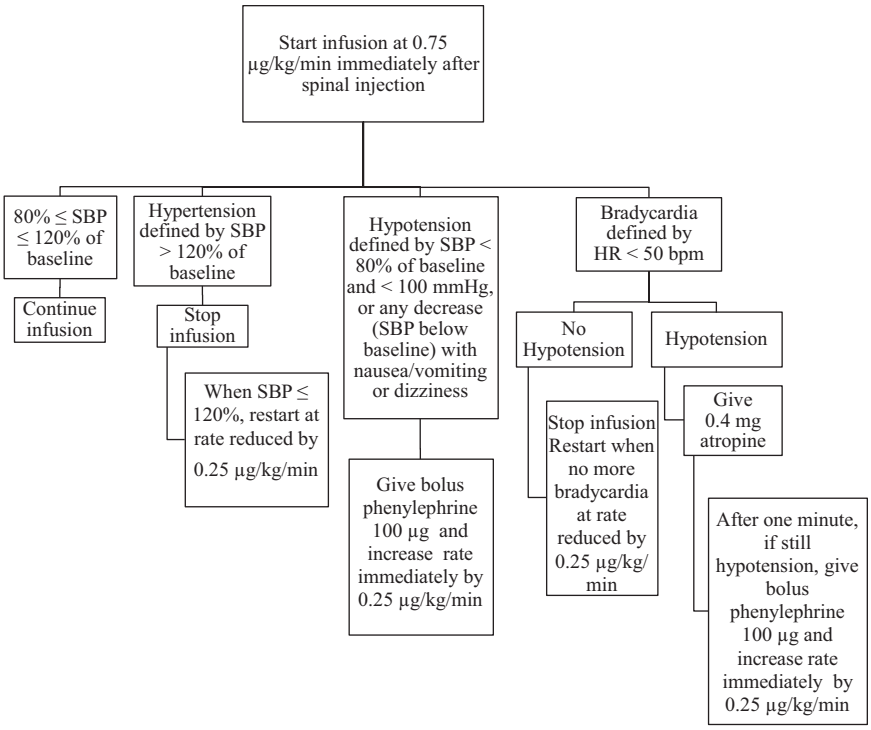

Figure 1. Algorithm describing study protocol. SBP = systolic blood pressure; HR = heart rate.

was treated with 0.4 mg atropine. After 1 minute, if the patient was still hypotensive, a rescue IV bolus of phenylephrine 100 µg was administered from another syringe. At the same time, the infusion rate was immediately increased by 0.25 µg/kg/min.

Stopping, increasing, decreasing, or restarting the phenylephrine infusion and administration of a bolus of phenylephrine or atropine for the same event were all considered 1 physician intervention. For the saline group, manipulations of the syringe pump were performed as per protocol to preserve blinding but were discarded during data entry. Therefore, only the administration of a bolus of phenylephrine or atropine was counted as interventions in the saline group. The number of physician interventions in both groups was recorded.

To compare the accuracy of blood pressure control between the 2 groups, we reported the maximum, median, minimum, and median absolute values for performance error (PE) (%) for SBP (calculated as previously described).[8,9] The following definitions were used:

1. PE: the percentage change in SBP from baseline during spinal anesthesia. It is a measure of accuracy that can be positive or negative. It was calculated for each SBP reading from the induction of anesthesia until delivery, as follows:

PE_{ij} (%) = ($meaSBP_{ij}$ – $basSBP_i$)/$basSBP_i$ × 100, where PE_{ij} is the PE for the *i*th patient at the *j*th minute, meaSBP*ij* is the measured SBP for the *i*th patient at the *j*th minute, and basSBP*i* is the baseline SBP for the *i*th patient.

2. Median performance error (MDPE): the median value for PE for each patient during anesthesia. It is an overall measure of bias of SBP control, which can be positive or negative. It was calculated as follows:

MDPE*i* (%) = median {PE*ij*, j = 1; . . .;N*i*}, where MDPE*i* is the MDPE for the *i*th patient, and N*i* is the number of values for PE obtained for the *i*th patient.

3. Absolute performance error (APE): the absolute percentage change in individual SBP readings from baseline during anesthesia and is, therefore, ≥ 0%.
4. Median absolute performance error (MDAPE): the median value for APE for each patient during anesthesia. It is an overall measure of inaccuracy of control. It is increased by greater overall positive or negative bias. It is also increased by greater instability of control (imprecise control). It was calculated as follows:

MDAPE*i* (%) = median {|PEij|, j = 1; . . .;N*i*}, where MDAPE*i* is the MDAPE for the *i*th patient, and N*i* is the number of values for PE obtained for the *i*th patient.

5. Maximum PE: the maximum value for PE for each patient during anesthesia.
6. Minimum PE: the minimum value for PE for each patient during anesthesia.

The cephalad extent of sensory blockade was assessed every 5 minutes after intrathecal injection using loss to pinprick sensation. Surgery was allowed to proceed after T6 sensory blockade had been established. The extent of the sensory blockade assessed at 20 minutes was recorded. Before the start of the study, patients were asked to report to the anesthesiologist any symptoms of nausea if they occurred. During the study period, the presence of nausea and/or vomiting was recorded whenever the patient complained of feeling sick or vomited. The severity of nausea (nausea score) was not documented, and retching was considered vomiting. Metoclopramide 10 mg IV was administered if nausea and/or vomiting were unrelated to hypotension

or not corrected by vasopressor bolus alone. The number needed to treat (NNT) for hypotension and nausea/vomiting, and the number needed to harm for hypertension were calculated.

The study ended at delivery, and the patient's management was continued by the attending anesthesiologist according to his or her discretion. The induction-skin incision, induction-delivery, and uterine incision-delivery intervals, and Apgar scores at 1 and 5 minutes were recorded. Also, umbilical venous and arterial blood gas measurements were obtained from a double-clamped segment of the umbilical cord.

The sample size was computed after calculating Δ as follows: $\Delta = \mu_0 - \mu_1/\gamma$ (μ_0 = mean number of interventions in control group, μ_1 = mean number of interventions in study group, and γ = standard deviation [SD]). The mean number of interventions and SD were derived from median, range, and interquartile range values obtained from a pilot study; the following values were obtained: $\mu_0 = 3$, $\mu_1 = 1$, $\gamma = 3$. Therefore, with β of 0.2 and α of 0.05 and 2-sided test for comparing 2 means (http://www.stat.ubc.ca/~rollin/stats/ssize/n2.html), the calculated number of patients was 37 in each group. The sample size was increased to 40 per group to compensate for potential subject loss that may occur during the course of the study.

Continuous data were reported as mean ± SD and were analyzed using Student *t* test. Serial changes in SBP and heart rate were analyzed using a 2-factor (treatment and time) repeated measures analysis of variance model. Because the time from induction to delivery varied among patients, serial data were compared only up to 15 minutes. Data were tested for homogenicity of between-group variance using the Levene test and for sphericity using the Mauchly test. If the Mauchly test was significant, we used the Greenhouse-Geisser epsilon adjustment. If there was significant interaction between groups, we performed simple comparisons between groups for all time levels with Bonferroni adjustments. Categorical data were reported as numbers and percentages and were analyzed using χ^2 or Fisher exact test as appropriate. Nonparametric data were reported as median and range and were analyzed using Mann-Whitney *U* test. $P < 0.05$ was considered significant. For each outcome, 95% confidence intervals of the difference were calculated assuming equal variances for continuous factors, using Wilson's procedure without continuity correction for differences in proportion, and based on the method proposed by Bonett and Price[10] for differences of 2 medians. The incidence and timing of hypotension were analyzed using Kaplan–Meier survival analysis, with comparison between groups using log-rank test. Survival time was defined as the time from induction to the first episode of hypotension, with the censoring of patients who did not become hypotensive. All analyses were performed using SPSS (version 19; Chicago, IL).

RESULTS

Eighty patients were enrolled in the study (Fig. 2). One patient from group S was excluded due to protocol violation. Therefore, group P included 40 patients and group S 39 patients. There was no significant difference in patient

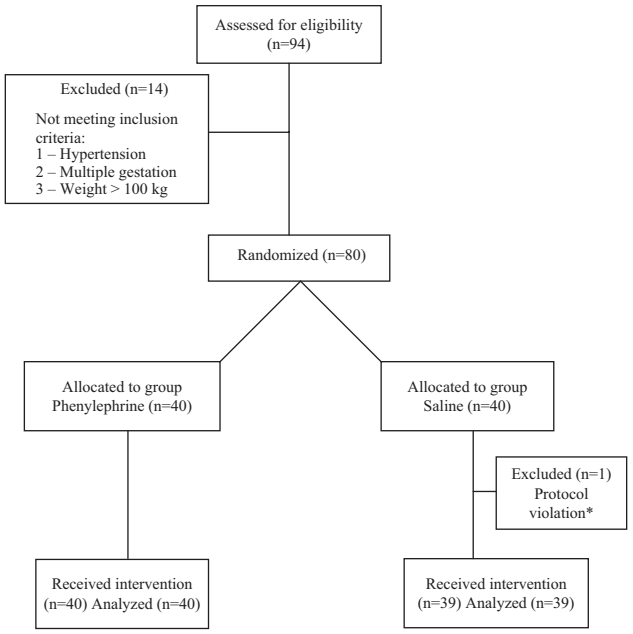

Figure 2. Consort flow diagram. *Phenylephrine administered with smaller decrease in systolic blood pressure than set by study protocol.

Table 1. Demographic Data

	Group phenylephrine (*n* = 40)	Group saline (*n* = 39)
Age (y)	32 ± 5	33 ± 5
Height (cm)	163 ± 6	163 ± 5
Weight (kg)	79 ± 10	76 ± 8
Gestational age (wk)	39 ± 1	39 ± 1
Nulliparous (*n*)	2 (5)	6 (15)
Induction-skin incision (min)	13 ± 4	12 ± 4
Induction-delivery (min)	25 ± 6	24 ± 6
Uterine incision-delivery (min)	1 ± 1	1 ± 1
Sensory block level	T4 (T2-T6)	T4 (T3-T6)

Data are presented as mean ± SD, number (%), and median (range). There were no differences between the groups.

demographic characteristics, extent of sensory blockade, induction-skin incision, induction-delivery, and uterine incision-delivery intervals between the 2 groups (Table 1).

Both groups had similar baseline SBP and heart rate. The median (range) number of physician interventions needed to maintain maternal hemodynamics within the target range (0 [0–6] vs 3 [0–9]) and incidence of hypotension (8/40 [20%] vs 35/39 [90%]) were lower in group P compared with group S ($P < 0.001$). Group P had a higher incidence of hypertension compared with group S (6/40 [15%] vs 0/39 [0%], $P = 0.026$) (Table 2). All nausea/vomiting episodes coincided with hypotension and were successfully treated by correcting hypotension. None of the patients received rescue antiemetic. The NNT for the prophylactic phenylephrine infusion was 1.4 women to prevent 1 case of hypotension, and 3 women to prevent 1 case of maternal nausea/vomiting; the rate of hypertension (number needed to harm) was 1 case per 6.7 women treated.

Serial changes of SBP and heart rate over time are shown in Figures. 3 and 4. SBP was higher over time in

Table 2. Hemodynamic Variables and Vasopressor Requirements

	Group phenylephrine (n = 40)	Group saline (n = 39)	95% confidence interval of the difference	P
Physician interventions	0 (0–6)	3 (0–9)	3 (2 to 4)	< 0.001
Patients where no interventions needed	22 (55)	4 (10)	−45 (−60 to −25)	< 0.0001
Incidence of hypotension	8 (20)	35 (90)	70 (50 to 81)	< 0.001
Incidence of severe hypotension[a]	3 (8)	17 (44)	36 (17 to 52)	0.001
Number of hypotensive episodes	0 (0–3)	3 (0–9)	3 (2 to 4)	< 0.001
Incidence of hypertension	6 (15)	0 (0)	−15 (−29 to −3)	0.03
Number of hypertensive episodes	0 (0–2)	0 (0–0)	0 (0 to 0)	0.01
Incidence of bradycardia	7 (18)	6 (15)	−2 (−19 to 15)	0.8
Number of bradycardia episodes	0 (0–5)	0 (0–4)	0 (0 to 0)	0.79
Phenylephrine infusion pump (μg)	1501 ± 516	0	−1503 (−1667 to −1338)	< 0.001
Phenylephrine cumulative dose (μg)	1533 ± 519	313 ± 214	−1220 (−1398 to −1041)	< 0.001
Number of phenylephrine boluses	0 (0–2)	3 (0–9)	3 (2 to 4)	< 0.001
Receiving atropine	1 (3)	1 (3)	0 (0 to 0)	0.1
Nausea/vomiting	4 (10)	17 (44)	34 (14 to 50)	0.001

Data are presented as number (%), mean ± SD, and median (range).
[a]Systolic blood pressure <80 mm Hg.

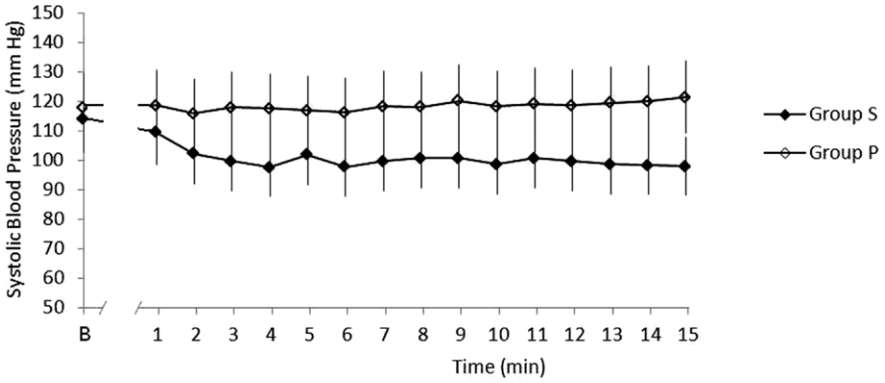

Figure 3. Serial changes in systolic blood pressure for the first 15 minutes, with B representing baseline blood pressure. Data are presented as mean and SD. There was significant treatment by time interaction and significant between-groups effect ($P < 0.001$ for both groups). Statistical significance was found between the 2 groups at each time interval with all $P < 0.001$ except for systolic blood pressure at first minute. Group S = saline, group P = phenylephrine.

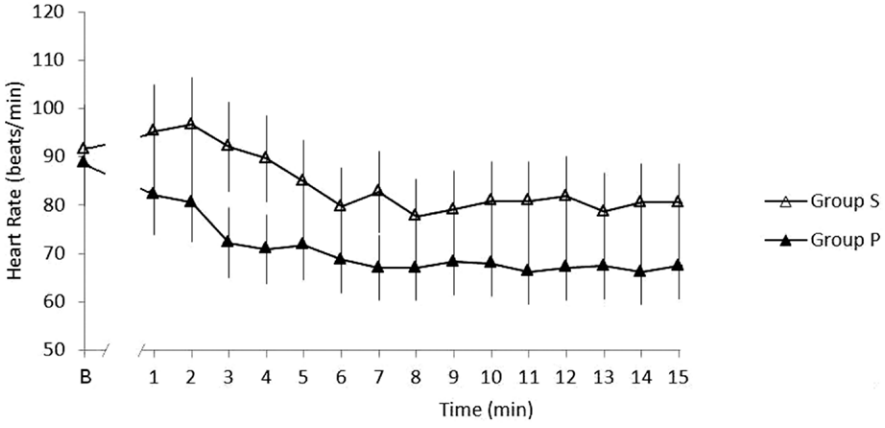

Figure 4. Serial changes in heart rate for the first 15 minutes, with B representing baseline heart rate. Data are presented as mean and SD. There was no significant treatment by time interaction ($P = 0.05$), but a significant between-groups effect was present ($P < 0.001$). Statistical significance was found between the 2 groups at each time interval (all $P \leq 0.01$). Group S = saline, group P = phenylephrine.

group P compared with group S, and heart rate was slower over time in group P compared with group S. No major violations of assumptions of homogeneity of between-groups variance were found; Levene test showed equality of error variances between the 2 groups. Mauchly test of sphericity was significant for both SBP and heart rate. Therefore, the Greenhouse-Geiser epsilon was used. For SBP, there was significant treatment by time interaction and significant between-groups effect ($P < 0.001$ for both). Statistical significance was found between the 2 groups at each time interval with all $P < 0.001$ except SBP at the first minute. For heart rate, there was no significant treatment by time interaction ($P = 0.05$), but a significant between-group effect was present ($P < 0.001$). Statistical significance was found between the 2 groups at each time interval (all $P \leq 0.01$).

The median values of maximum, median, minimum, and median absolute for PE were significantly different between the 2 groups (Table 3). The MDPE was closer to baseline ($P < 0.001$) with a smaller MDAPE ($P < 0.001$) in group P versus group S. Results of the Kaplan–Meier survival analysis are shown in Figure 5. The proportion of patients who did not become hypotensive (from initiation of spinal anesthesia to delivery) was significantly different between the

Table 3. Performance Error for Systolic Blood Pressure Control During Spinal Anesthesia

Performance error	Group phenylephrine (n = 40)	Group saline (n = 39)	95% confidence interval of the difference	*P*
Minimum (%)	−9.2 (−47.4 to +8.6)	−26.3 (−48.3 to 0)	−17.1 (−22.5 to −11.7)	< 0.001
Median (%)	+0.2 (−13 to 16.8)	−11.2 (−20.3 to 0)	−11.4 (−15.9 to −7)	< 0.001
Maximum (%)	+11.5 (−3.6 to +48)	+3.6 (−6.2 to +19)	−8 (−12.4 to −3.5)	< 0.001
Median Absolute (%)	+7.2 (0 to +26.3)	+11.2 (0 to +20.3)	4 (1.5 to 6.4)	0.001

Data are presented as median (range). The percentage performance error is a measure of the patient's systolic blood pressure distance form baseline expressed as a percentage of that baseline

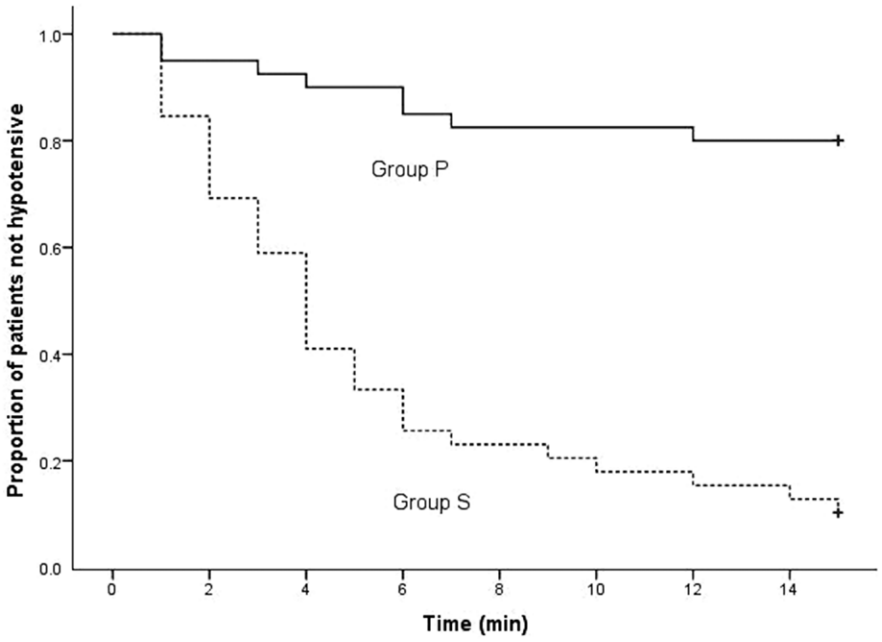

Figure 5. Kaplan–Meier survival curves showing proportion of patients whose systolic blood pressure remained higher than 80% above baseline from the initiation of spinal anesthesia to uterine incision. There was a significant difference between the groups ($P < 0.001$).

Table 4. Neonatal Data

Umbilical sample	Group phenylephrine (n = 40)	Group saline (n = 39)	95% confidence interval of the difference	*P*
Arterial pH	7.3 ± 0.1	7.3 ± 0.1	0 (−0.0 to 0.0)	1.00
Arterial Po_2 (mm Hg)	17.5 ± 6	18.9 ± 5.4	1.4 (−1.6 to 4.5)	0.35
Arterial Pco_2 (mm Hg)	54.5 ± 7.5	52.9 ± 6.7	−1.6 (−5.5 to 2.3)	0.41
Arterial base excess (meq/L)	−2.4 ± 2.6	−3.1 ± 1.5	−0.7 (−1.9 to 0.6)	0.28
Venous pH	7.3 ± 0.1	7.3 ± 0.0	0 (−0.0 to 0.0)	0.60
Venous Po_2 (mm Hg)	28.8 ± 6.7	28.4 ± 6.7	−0.4 (−3.8 to 3.1)	0.82
Venous Pco_2 (mm Hg)	44.0 ± 7.2	43.6 ± 5.2	−0.4 (−3.6 to 2.8)	0.80
Venous base excess (meq/L)	−2.4 ± 3.9	−3.1 ±1.4	−0.7 (−2.2 to 0.9)	0.40
Apgar score at 1 min	9 (6–10)	9 (8–9)	0 (0 to 0)	0.66
Apgar score at 5 min	10 (9–10)	10 (9–10)	0 (0 to 0)	0.31

Data are presented as mean ± SD and median (range).

groups ($P < 0.001$). Neonatal outcomes were not different between the 2 groups (Table 4).

DISCUSSION

The findings support the prophylactic variable rate infusion strategy based on reduced number of interventions (less labor intensive) and also based on reduced maternal hypotension and nausea, with NNTs of 1.4 women to prevent 1 case of hypotension, and 3 women to prevent 1 case of maternal nausea, at the same time causing hypertension that was mild at a rate of 1 case per 6.7 women treated. These interventions are a surrogate of inaccuracy of blood pressure control. In fact, there was a bias (MDPE) toward maintaining SBP very close to baseline in the phenylephrine group (+0.2%) and below baseline in the saline group (−11.2%). In addition, the phenylephrine group had a lower degree of inaccuracy (MDAPE) for SBP control than the saline group (+7.2% and +11.2%, respectively).

In a previous study, Allen et al.[8] compared 4 prophylactic fixed regimens of phenylephrine versus placebo with regard to hemodynamic stability in patients receiving 12 mg spinal bupivacaine and 2 L coload. Similar to our study, the primary outcome was the number of physician interventions triggered by an increase or a decrease in SBP by >20% of baseline and bradycardia. The 50, 75, and 100 μg/min infusion rates each had fewer incidences of hypotension than

the placebo group. The lower infusion rates (25 and 50 μg/min) caused less reactive hypertension than the higher rates (75 and 100 μg/min) and fewer interventions to maintain target blood pressure compared with the 100 μg/min dose. In contrast to the results of our study, prophylactic fixed-rate infusions did not reduce the number of interventions needed to maintain SBP within target range or improve the accuracy of hemodynamic control when compared with placebo. The authors recommended titrating the infusion rate in response to changes in blood pressure.

In our study, we used a variable rate infusion regimen started at 0.75 μg/kg/min which is close to the fixed-rate dose of 50 μg/min used in the Allen et al.[8] study. The incidence of hypotension in the phenylephrine group was similar to that achieved in the 50 μg/min group in the Allen et al.[8] study (20% vs 15%, respectively); however, the incidence of reactive hypertension was much lower (15% vs 40%, respectively). The explanation is that we stopped the phenylephrine infusion in the presence of reflex bradycardia and gave atropine only if bradycardia was associated with hypotension. In addition, we decreased the infusion rate of phenylephrine when hypertension occurred.

Doherty et al.[11] found no clinical benefits to administering phenylephrine as a high-dose fixed-rate infusion compared with a bolus phenylephrine regimen. In addition to using a much higher dose of phenylephrine infusion (120 μg/min), the bolus administration in that study was prophylactic and not in response to a decrease in blood pressure as in our study. Their bolus regimen maintained maternal arterial blood pressure closer to baseline in the initial minutes after spinal injection. In our study, the infusion regimen was superior because it resulted in more patients remaining normotensive until uterine incision. Also, it resulted in a milder degree of hypotension. Only 3 patients developed severe hypotension defined as SBP <80 mm Hg in the phenylephrine group versus 17 patients in the saline group, indicating the advantage of a phenylephrine infusion that restores the decrease in systemic vascular resistance induced by spinal anesthesia. In addition, in contrast to Doherty et al.'s[11] results, the variable rate infusion in our study maintained SBP closer to baseline than bolus administration of phenylephrine in the saline group as evidenced by PE values in both groups.

In an observational study, Cooper et al.[9] assessed the incidence of hypotension and nausea using a variable phenylephrine infusion rate regimen, but the study lacked a control group. More patients developed hypertension in Cooper et al.[9] study (35% vs 15% in our study); a possible explanation is a higher starting phenylephrine dose of 67 μg/min (approximately 0.96 μg/kg/min, given the median body weight was 70 kg).

More recently, Ngan Kee et al.[12] have shown that closed-loop feedback computer-controlled phenylephrine infusion provided better arterial blood pressure control with fewer interventions required compared with manual-controlled infusion. However, this technique is complicated and still experimental, while our technique is simple and requires an infusion pump only.

The incidence of bradycardia was similar in both the phenylephrine infusion group and saline group (15% and 17.5%, respectively). In the saline group, most of the bradycardia was associated with a decrease of blood pressure, and thus was related to the inhibition of cardiac nerves by sympathetic blockade, or to increasing vagal tone in response to decreased venous return (the reverse Bainbridge reflex and Bezold-Jarish reflex).[13] In the phenylephrine group, bradycardia occurred in response to a baroreceptor-mediated reflex after an increase in arterial blood pressure. Some investigators suggested that cardiac output correlates more with uterine perfusion than arterial pressure, and that heart rate is a good surrogate of cardiac output during spinal anesthesia for cesarean delivery.[14,15] Therefore, they recommended low-dose phenylephrine, insufficient to cause mean arterial blood pressure increases above baseline associated with sinus bradycardia, for the initial management of spinal-induced hypotension.

Nausea is thought to be secondary to brainstem ischemia or reflex response to decreased venous return. In our study, nausea occurred less frequently in the infusion group than the saline group and was obviously in relation to hypotension. Umbilical cord blood gas values and Apgar scores were similar between the 2 groups. The total phenylephrine dose was higher in the infusion group (1532 μg) than the saline group (313 μg) but less than that used in many other studies (exceeding 2000 μg with infusion rates at 100 to 120 μg/min).[8,11] Using a similar high dose of phenylephrine to maintain maternal blood pressure, Ngan Kee et al.[16] observed no adverse effect on neonatal outcome as measured by Apgar scores and umbilical cord blood gas values.

One limitation of the study is the likely impossibility of blinding clinicians effectively and the limitation inherent in a necessarily predefined regimen. The hemodynamic trajectories were so different that clinician blinding may have been compromised. The second limitation impacts generalizability: in clinical practice, clinicians using a bolus strategy may be more likely to recognize trends in heart rate and blood pressure and to treat at higher thresholds if a trend becomes apparent. However, treating at higher thresholds might well cause reactive hypertension and bradycardia and affect hemodynamic accuracy.

In conclusion, our regimen of prophylactic variable rate phenylephrine infusion initially started at 0.75 μg/kg/min combined with a crystalloid solution coload of 15 mL/kg and rescue phenylephrine boluses in parturients undergoing cesarean delivery with spinal bupivacaine 12.75 mg is more reliable than crystalloid coload and rescue phenylephrine boluses. It is associated with fewer physician interventions, less hypotension and nausea/vomiting, minimal incidence of hypertension, as well as greater hemodynamic stability, all of which lead to increased maternal comfort. Further studies comparing fixed to variable rates or the use of variable rates in the setting of fetal compromise are required.

DISCLOSURES

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Attestation: This author has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

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