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Prevention of Hypotension during Spinal Anesthesia for Cesarean Delivery

An Effective Technique Using Combination Phenylephrine Infusion and Crystalloid Cohydration

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Background: **Many methods for preventing hypotension during spinal anesthesia for cesarean delivery have been investigated, but no single technique has proven to be effective and reliable. This randomized study studied the efficacy of combining simultaneous rapid crystalloid infusion (cohydration) with a high-dose phenylephrine infusion.**

Methods: **Nonlaboring patients scheduled to undergo elective cesarean delivery received an intravenous infusion of 100 μg/min phenylephrine that was started immediately after spinal injection and titrated to maintain systolic blood pressure near baseline values until uterine incision. In addition, patients received infusion of lactated Ringer's solution that was given either rapidly (group 1, n = 57) or at a minimal maintenance rate (group 0, n = 55). Maternal hemodynamic changes and neonatal condition were compared.**

Results: **Six patients were excluded from analysis. Only 1 of 53 patients (1.9% [95% confidence interval, 0.3–9.9%]) in group 1 experienced hypotension *versus* 15 of 53 patients (28.3% [95% confidence interval, 18.0–41.6%]) in group 0 ($P = 0.0001$). Compared with group 0, patients in group 1 had greater values for the following: serial measurements of systolic blood pressure ($P = 0.02$), minimum recorded systolic blood pressure ($P = 0.0002$), and minimum recorded heart rate ($P = 0.013$). Total phenylephrine consumption was smaller in group 1 compared with group 0 ($P = 0.008$). Neonatal outcome and maternal side effects were similar between groups.**

Conclusions: **Combination of a high-dose phenylephrine infusion and rapid crystalloid cohydration is the first technique to be described that is effective for preventing hypotension during spinal anesthesia for cesarean delivery.**

DESPITE more than three decades of research, hypotension during spinal anesthesia for cesarean delivery remains a common clinical problem that is associated with morbidity for both mother (nausea and vomiting) and fetus (fetal acidosis). An effective method for preventing hypotension has been referred to as the "Holy Grail" of obstetric anesthesia[1] and has yet to be described. Techniques currently in use for preventing hypotension include intravenous fluid prehydration,[2] sympathomimetic drugs,[3] and physical methods such as leg bindings and compression stockings.[4] However, a Cochrane review concluded that none of these techniques alone was effective in eliminating hypotension and suggested that future research be directed toward investigation of combinations of interventions.[5]

In previous studies, we found that use of a high-dose prophylactic phenylephrine infusion to maintain maternal blood pressure near baseline values reduced maternal symptoms without adverse effects on the fetus.[6,7] However, despite aggressive infusion regimens, approximately one fourth of patients still experienced one or more episodes of hypotension. Of note, in these studies, we did not use intravenous prehydration, based on recent evidence that showed that crystalloid prehydration has poor efficacy for preventing hypotension,[8–11] probably because it undergoes rapid distribution.[12] As an alternative, administration of a fluid bolus starting at the time of intrathecal injection (cohydration) may be more physiologically appropriate because the maximum effect can be achieved during the time the block and the consequent vasodilatation are evolving. However, experience with this approach is limited.[13,14]

The aim of the current study was to investigate whether the combination of rapid crystalloid cohydration with a high-dose phenylephrine infusion would be more effective at preventing hypotension than a phenylephrine infusion alone and whether this technique would prove to be an effective method for eliminating hypotension.

This article is featured in "This Month in Anesthesiology." Please see this issue of Anesthesiology, page 5A.

Materials and Methods

After obtaining institutional approval from the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee, Shatin, Hong Kong, China, we recruited 112 women with American Society of Anesthesiologists physical status of I or II and term singleton pregnancies who were scheduled to undergo elective cesarean delivery during spinal anesthesia. All patients gave written informed consent. We excluded patients who had preexisting or pregnancy-induced hypertension, cardiovascular or cerebrovascular

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disease, known fetal abnormalities, contraindications to spinal anesthesia, or any signs of onset of labor.

Patients were premedicated orally with 20 mg famotidine the night before and on the morning of surgery and 30 ml sodium citrate, 0.3 M, at arrival in the operating room. Standard monitoring was attached, including noninvasive blood pressure measurement, electrocardiography, and pulse oximetry. Fetal heart rate was monitored by external cardiotocography until the time of surgical preparation. We allowed patients to rest undisturbed in the tilted supine position for several minutes, during which blood pressure was measured every 1–2 min. Blood pressure measurements were continued until they became consistent (three successive measurements of systolic blood pressure [SBP] that had a difference of no more than 10%). Baseline SBP and heart rate (HR) were calculated as the mean of the three recordings.

We then inserted a 16-gauge intravenous cannula into a forearm vein under local anesthesia and connected this using a wide-bore infusion administration set to a 1-l bag of warmed lactated Ringer's solution that was suspended at a height of 1.5 m above the operating table. The infusion was initially adjusted to provide a minimal rate to maintain vein patency. No intravenous prehydration was given. We then turned the patient to the right lateral position and induced spinal anesthesia. After skin infiltration with lidocaine, a 25-gauge pencil-point needle was inserted at what was estimated to be the L2–L3 or L3–L4 vertebral interspace and 2.0 ml hyperbaric 0.5% bupivacaine (10 mg), and 15 μg fentanyl was injected intrathecally. We then immediately returned the patient to the tilted supine position. Blood pressure was measured at 1-min intervals beginning 1 min after spinal injection. Hemodynamic data were downloaded to a computer from the anesthetic machine at 5-s intervals using software developed within our department.

Patients were allocated to one of two groups according to computer-generated randomization codes contained in sealed, sequentially numbered envelopes that were opened after the recording of baseline blood pressure values. In group 1, rapid crystalloid infusion was given by fully opening the clamp of the infusion administration set at the start of intrathecal injection and continuing the infusion to a maximum of 2 l until uterine incision. After the first 2 l of fluid had been given, the infusion was adjusted to a minimal rate to maintain vein patency. In group 0, the infusion was continued at a minimal rate to maintain vein patency. Patients and investigators were not blinded to group allocation.

Maternal blood pressure was maintained using a protocol similar to that used in our previous studies.[6,7] We prepared a solution of 100 μg/ml phenylephrine, which we infused using a syringe pump (Graseby 3500 Anesthesia Pump; Graseby Medical Ltd., Watford, Herts, United Kingdom). To minimize dead space, the infusion was connected directly to the intravenous cannula using a three-way stopcock. We started the infusion at 100 μg/min (60 ml/h) immediately after completion of intrathecal injection. For the first 2 min, the infusion was continued unless SBP was greater than 120% of baseline, in which case it was stopped. Subsequently, until the time of uterine incision, we adjusted the infusion according to the value of SBP measured at 1-min intervals; we continued the infusion if SBP was less than or equal to baseline and stopped the infusion if SBP was greater than baseline. We recorded any incidences of hypotension, which was defined as SBP less than 80% of baseline. If there were three successive episodes of hypotension, we administered a "rescue" intravenous bolus of 100 μg phenylephrine from a separate syringe.

Five minutes after intrathecal injection, we measured the upper sensory level of anesthesia by assessing loss of pinprick discrimination and then invited the surgeon to scrub. Further checks of the block height were made as required before the start of surgery, but these levels were not recorded as part of the study. We recorded the times of skin incision, uterine incision, and delivery with a stopwatch. We continued the phenylephrine infusion protocol until the time of uterine incision. After this, the study was terminated and further management was at the discretion of the attending anesthesiologist. We recorded the total dose of phenylephrine given up to the time of uterine incision as measured by the syringe pump.

We did not routinely give oxygen unless the arterial oxyhemoglobin saturation decreased to less than 95%, when we gave 5 l/min oxygen by clear facemask. Bradycardia was defined as HR less than 50 beats/min and was treated by stopping the phenylephrine infusion or, if accompanied by hypotension, with 0.6 mg intravenous atropine. We recorded any incidences of nausea (reported by patients) or vomiting (observed by investigators), the total amount of intravenous fluid given up to the time of uterine incision, and the incidence of reactive hypertension, which was defined as SBP greater than 120% of baseline.

After delivery, we administered 5 U oxytocin by slow intravenous injection. The attending pediatrician assessed Apgar scores at 1 and 5 min after delivery. We took arterial and venous blood samples from a double-clamped segment of umbilical cord for immediate measurement of blood gases using a Rapid Point 400 analyzer (Bayer Diagnostics Mfg. [Sudbury] Ltd., Sudbury, United Kingdom).

Statistical Analysis

The primary outcome of the study was defined as the incidence of hypotension. We made an *a priori* decision to define an effective method as one that would reduce the incidence of hypotension to 5% or less. Power analysis was based on data from our previous studies,[6,7] from which we estimated that the incidence of hypotension

in group 0 would be approximately 23%. We calculated that a sample size of 53 patients per group would have 80% power (two tailed) to detect a reduction in the incidence of hypotension to 5% or less in group 1. To allow for a possible dropout rate of 5%, a total of 112 patients were recruited.

Secondary outcomes that we compared included serial changes in blood pressure and HR, the incidence of reactive hypertension, bradycardia, nausea or vomiting, umbilical cord blood gases, and Apgar scores.

We compared data using the Student *t* test, the Mann–Whitney U test, the chi-square test, and the Fisher exact test. Serial changes in SBP, diastolic blood pressure (DBP), and HR were analyzed using two-way analysis of variance for repeated measures. Because the time from induction to delivery varied among patients, serial data were compared only up to 12 min, which was the time of uterine incision of the patient with the smallest induction-to-uterine incision interval. In this analysis, the independent (qualitative) variable was defined as patient group, and the dependent (quantitative) variable was defined as SBP, DBP, or HR, measured repeatedly over time for each subject. Data were tested for normality using the Kolmogorov-Smirnov test, for homogeneity of between-groups variance using the Levene test, and for sphericity using the Mauchly test. If the Mauchly test was significant, indicating violation of the assumption of sphericity, we used the Greenhouse-Geisser ε adjustment. We used the univariate approach to analyze within-subjects effects. If there was a significant interaction between the between-groups and within-subjects factors (significant treatment $\times$ time interaction), we performed simple effects analysis of between-groups factors for all time levels, with Bonferroni adjustments, using a multivariate analysis of variance model.

The incidence and timing of hypotension were further analyzed using Kaplan-Meier survival analysis, with comparison between groups using the log-rank test. Survival time was defined as the time from the induction of anesthesia to the first episode of hypotension. Patients who delivered without any incidence of hypotension were considered "censored."

All analyses were performed using Statview for Windows 5.0.1 (SAS Institute Inc., Cary, NC), SPSS for Windows 10.1.4 (SPSS Inc., Chicago, IL), and Confidence Interval Analysis 2.0.0 (T. Bryant, University of Southampton, United Kingdom). $P < 0.05$ was considered significant.

Results

Fifty-five patients were randomly assigned to group 0, and 57 patients were randomly assigned to group 1. Two patients in group 0 were excluded (1 because of inadequate spinal block and 1 because severe shivering prevented accurate measurement of blood pressure), and 4 patients in group 1 were excluded (2 because of inadequate spinal block, 1 because of severe shivering, and 1 because the intravenous cannula required replacement during the study period). Patient characteristics and surgical times were similar between groups (table 1). Insufficient umbilical arterial blood was obtained for analysis in 1 patient in group 0 and 1 patient in group 1, and insufficient umbilical venous blood was obtained for analysis in 1 patient in group 0. One patient in group 1 required supplemental oxygen.

Table 1. Patient Characteristics and Surgical Times

	Group 0 (n = 53)	Group 1 (n = 53)	*P* Value
Age, yr	31 (5.7)	32 (4.4)	0.63
Weight, kg	65 (7.9)	68 (9.5)	0.10
Height, cm	156 (5.0)	157 (6.2)	0.13
Block height, dermatome	T4 [T4–T6]	T5 [T4–T6]	0.96
Induction to delivery time, min	27.3 [23.5–32.0]	27.1 [24.0–31.6]	0.91
Incision to delivery time, min	8.4 [6.0–12.8]	8.5 [6.3–10.8]	0.75
Uterine incision to delivery time, s	73 [50–123]	84 [56–133]	0.53

Values are mean (standard deviation) or median [interquartile range].

Hemodynamic changes are summarized in table 2. Only one patient (1.9% [95% confidence interval, 0.3–9.9%]) in group 1 experienced hypotension (three episodes). In contrast, 15 patients (28.3% [95% confidence interval, 18.0–41.6%]; $P = 0.0001$) in group 0 experienced hypotension (one to nine episodes). Compared with group 0, patients in group 1 had greater minimum recorded SBP and greater minimum recorded HR. The total dose of phenylephrine was smaller in group 1 (median, 1,160 μg [interquartile range, 753–1,568 μg]) compared with group 0 (1,400 μg [1,145–1,818 μg]; $P = 0.008$), and the rate of phenylephrine infusion was smaller in group 1 (median, 42.1 [interquartile range, 30.4–52.3 μg/min]) compared with group 0 (55.9 μg/min [46.3–63.6 μg/min]; $P < 0.0001$).

Serial changes of SBP, DBP, and HR over time are shown in figures 1 and 2. Analysis showed no major violations of assumptions of normality and homogeneity of between-groups variance. However, for each of SBP, DBP, and HR, the Mauchly test of sphericity was significant ($P < 0.05$), and therefore, the Greenhouse-Geisser ε adjustment was applied. For both SBP and DBP, there was no significant treatment $\times$ time interaction ($P > 0.05$). For SBP, there was a significant between-groups (treatment) effect (SBP averaged across time was greater in group 1 *vs.* group 0; $P = 0.02$). However, for DBP, the between-groups effect was not significant ($P = 0.11$). For HR, there was a significant treatment $\times$ time interaction ($P < 0.001$). Analysis of between-groups factors for all time levels showed that HR was significant greater

Table 2. Hemodynamic Changes, Fluid, and Vasopressor Requirement

	Group 0	Group 1	*P* Value
Total intravenous fluid, ml	50 [40–60]	1,975 [1,609–2,010]	< 0.0001
Rate of intravenous fluid infusion, ml/min	1.7 [1.5–2.4]	63.5 [53.7–74.4]	< 0.0001
Total phenylephrine dose, μg	1,400 [1,145–1,818]	1,160 [753–1,568]	0.008
Rate of phenylephrine administration, μg/min	55.9 [46.3–63.6]	42.1 [30.4–52.3]	< 0.0001
Incidence of hypotension	15 (28.3%)	1 (1.9%)	0.0001
Minimum recorded SBP, mmHg	95 [89–106]	107 [98–110]	0.0002
Incidence of hypertension	25 (47%)	25 (47%)	1.0
Maximum recorded SBP, mmHg	139 [129–147]	140 [128–149]	0.83
Incidence of bradycardia (HR < 50 beats/min)	13 (24.5%)	9 (1.8%)	0.34
Minimum recorded HR, beats/min	53 [50–58]	58 [52–63]	0.013
Atropine required	0	0	1.0

Values are median [interquartile range] or number (%).

HR = heart rate; SBP = systolic blood pressure.

in group 1 *versus* group 0 at 4 min ($P = 0.013$), 5 min ($P = 0.026$), 9 min ($P = 0.04$), 10 min ($P = 0.003$), 11 min ($P = 0.04$), and 12 min ($P = 0.001$).

Results of the survival analysis are shown in figure 3. The proportion of patients remaining not hypotensive until uterine incision was significantly different between groups ($P = 0.0002$).

Bradycardia was recorded in 13 patients in group 0 and 9 patients in group 1 ($P = 0.34$), but no patient required atropine. Twenty-five patients (47%) in each group had one or more transient episodes of reactive hypertension. Two patients in group 0 and 1 patient in group 1 required a single rescue bolus of phenylephrine. Two patients in each group experienced nausea, of whom 1 patient in each group vomited. For both patients in group 0 and 1 patient in group 1, this was associated with hypotension. There was no difference in neonatal outcome between groups (table 3).

Discussion

This is the first description of an effective, safe, and reliable technique for preventing hypotension during spinal anesthesia for elective cesarean delivery. Our results showed that hypotension was virtually eliminated by the combination of a high-dose phenylephrine infusion and rapid intravenous crystalloid cohydration. Patients who received cohydration with the phenylephrine infusion had greater hemodynamic stability compared with patients who received maintenance fluid, as evidenced by greater values for serial measurements of SBP and greater minimum values of SBP and HR. Furthermore, patients who received cohydration required less phenylephrine to maintain their blood pressure. Our technique had no adverse effect on neonatal outcome and a low incidence of maternal nausea and vomiting.

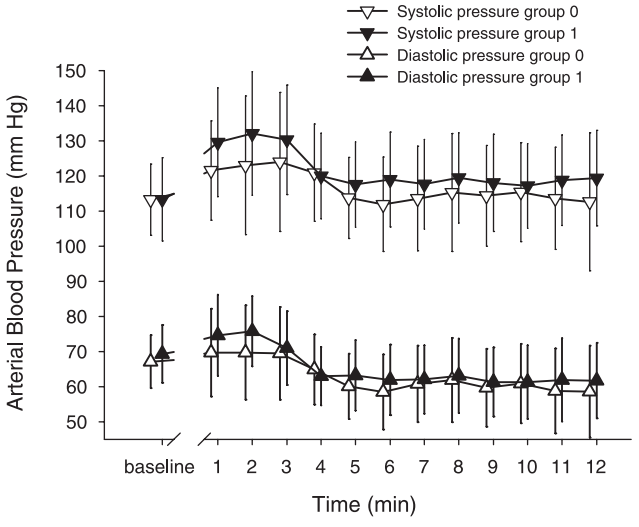

Fig. 1. Serial changes in systolic blood pressure and diastolic blood pressure. Data are presented as mean and SD. For both systolic blood pressure and diastolic blood pressure, there was no significant treatment × time interaction ($P > 0.05$). For systolic blood pressure, there was a significant between-groups effect (systolic blood pressure averaged across time was greater in group 1 *versus* group 0; $P = 0.02$). For diastolic blood pressure, the between-groups effect was not significant ($P = 0.11$).

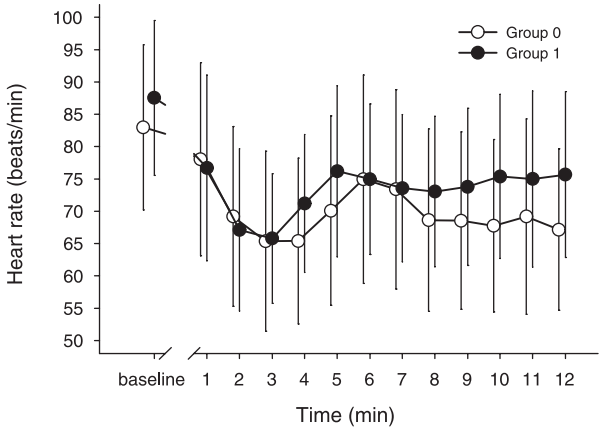

Fig. 2. Serial changes in heart rate. Data are presented as mean and SD. There was a significant treatment × time interaction ($P < 0.001$). Analysis of between-groups factors for all time levels showed that heart rate was significant greater in group 1 *versus* group 0 at 4 min ($P = 0.013$), 5 min ($P = 0.026$), 9 min ($P = 0.04$), 10 min ($P = 0.003$), 11 min ($P = 0.04$), and 12 min ($P = 0.001$). Baseline values were not significantly different ($P = 0.06$).

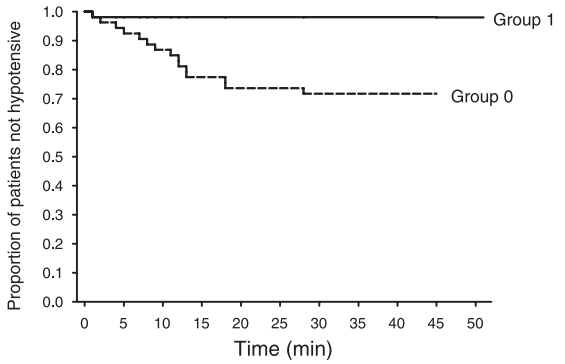

Fig. 3. Kaplan-Meier survival curves showing proportion of patients remaining not hypotensive until uterine incision. There was a significant difference between groups ($P = 0.0002$).

This work is the continuation of a series of investigations we have performed over several years in an attempt to delineate a reliable method to prevent hypotension in obstetric spinal anesthesia. In initial work, we investigated the efficacy of prophylactic ephedrine for prevention of hypotension.[15,16] We found that prophylactic ephedrine has poor efficacy and demonstrated that large doses of ephedrine are associated with a high incidence of fetal acidosis. In contrast, in other studies we showed that the use of α agonists such as metaraminol and phenylephrine is associated with a low incidence of fetal acidosis.[17–19] The advantage of phenylephrine over ephedrine has also been shown in other clinical studies[20,21] and contradicts early animal studies that cautioned against the use of α agonists in obstetrics.[22,23] The availability of clinical data from humans has provided a basis for renewed investigation of α agonists in obstetrics. We believe that the use of potent vasoconstrictors such as phenylephrine is more physiologically appropriate to treat the vasodilatation-induced hypotension of spinal anesthesia compared with ephedrine, the action of which is mainly mediated by cardiac stimulation.

In recent studies, we have described the use of high-dose phenylephrine infusions for maintaining maternal blood pressure.[6,7] The advantages of this technique include efficacy, ease of titration, and the important observation that even with very large doses ($> 2{,}000$ μg), there was no adverse effect on neonatal outcome as measured by Apgar scores and umbilical cord blood gases. However, despite using liberal phenylephrine infusion regimens, in our previous studies, we found that approximately one fourth of patients still experienced one or more episodes of hypotension. The current study shows that this is virtually eliminated by the addition of a simultaneous rapid cohydration. Our findings are consistent with a recent Cochrane review that suggested that combination techniques might be more effective than use of single interventions.[5]

We believe that the technique of rapid intravenous crystalloid infusion after spinal injection (cohydration or coload) is more physiologically appropriate than the practice of giving large volumes before spinal injection (prehydration or preload) for decreasing hypotension during spinal anesthesia for cesarean delivery. Several recent reports have shown that prehydration using crystalloids has poor efficacy.[8–11] For example, we previously investigated the use of prehydration with 20 ml/kg lactated Ringer's solution in combination with a metaraminol infusion for maintaining maternal blood pressure.[11] In that study, we found that prehydration had minimal effect on the incidence of hypotension and vasopressor requirement. This is explained by the rapid distribution into the interstitial space that occurs after infusion of crystalloids, which limits the effective augmentation of intravascular volume that is achieved.[12] In comparison, crystalloid given as cohydration also undergoes rapid redistribution, but by timing administration with the induction of anesthesia, the maximum augmentation of intravascular volume coincides with the time that the block and consequent vasodilatation are evolving, thus maximizing effect. In addition, rapid cohydration may also have the simple beneficial effect of facilitating rapid circulation of the vasopressor. An alternative

Table 3. Neonatal Outcome

	Group 0	Group 1	*P* Value
Apgar scores at 1 min < 7	1	1	1.0
Apgar scores at 5 min < 7	0	0	1.0
Umbilical arterial blood gases			
pH	7.29 [7.26 to 7.31]	7.28 [7.27 to 7.30]	0.88
P_{CO_2}, mmHg	56 [51 to 62]	54 [50 to 60]	0.28
P_{O_2}, mmHg	15 [11 to 17]	15 [12 to 18]	0.26
Base excess, mM	−1.9 [−3.0 to −0.7]	−2.4 [−3.2 to −1.2]	0.13
Umbilical venous blood gases			
pH	7.34 [7.31 to 7.36]	7.34 [7.32 to 7.36]	0.41
P_{CO_2}, mmHg	46 [43 to 51]	45 [41 to 48]	0.08
P_{O_2}, mmHg	25 [21 to 29]	27 [23 to 33]	0.08
Base excess, mM	−1.8 [−2.6 to −0.7]	−2.5 [−2.9 to −1.6]	0.06

Values are number or median [interquartile range].

P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen.

approach is to consider use of colloid solutions. Infusion of colloids results in greater expansion of intravascular volume, and thus, colloids seem to be more effective than crystalloids at preventing hypotension.[12,24,25] However, greater cost and potential risk of allergic reactions are disadvantages of colloids.

A number of other recent studies have also investigated the use of intravenous cohydration. Dyer *et al.*[13] randomly assigned patients to receive 20 ml/kg modified Ringer's lactate solution either before or immediately after induction of spinal anesthesia for elective cesarean delivery. They found that patients who received fluid after induction had a smaller requirement for ephedrine. Similarly, Mercier *et al.*[14] randomly assigned parturients to receive 1 l crystalloid before or after induction. They found no difference in vasopressor requirement between groups. However, vasopressor requirement was inversely correlated with the speed of crystalloid administration in patients who received fluid after induction; therefore, they concluded that fluid should be given as quickly as possible. In nonobstetric patients, Mojica *et al.*[26] reported that rapid infusion of 20 ml/kg lactated Ringer's solution did not reduce the incidence of hypotension compared with a control group, although patients who received rapid fluid after induction had a lower incidence of hypotension-related symptoms. Differences among these studies may be explained in part by differences in methodology, such as volume and rate of infusion, intrathecal drug doses, vasopressor regimens, and definitions of hypotension.

We used doses of phenylephrine that were greater than those that have been reported by other investigators.[21,27,28] However, our technique was based on our previous reports in which we used similar infusion regimens,[6,7] and in none of these studies did we observe adverse neonatal effects despite similarly large doses of phenylephrine. For example, in a previous comparison of different phenylephrine infusion regimens, we found that the incidence of nausea and vomiting was smallest and values for umbilical arterial pH were greatest when we maintained the maternal SBP closest to baseline values, despite this group receiving the largest total dose of phenylephrine.[7] However, it should be noted that in our studies, we have specifically excluded patients with chronic hypertension and preeclampsia. In our normal clinical practice, when we use phenylephrine infusions in these patients, we often start with a lower infusion rate and subsequently titrate the rate according to response.

A large proportion of patients in both groups had transient episodes of reactive hypertension (defined in our study as an increase in SBP by $>$ 20% above baseline), and this was commonly associated with decreases in maternal heart rate. This always corrected rapidly after turning off the phenylephrine infusion, and there was no evidence of any adverse neonatal effect. Nonetheless, some caution is necessary when applying our technique, particularly in patients in whom an increase in blood pressure may be detrimental. The high incidence of reactive hypertension in our study may be partly related to the limitations of only measuring blood pressure noninvasively at 1-min intervals and the fact that, being part of a randomized clinical trial, our infusion protocol was fixed and inflexible. In clinical practice, when it is possible to be more flexible with titration of the infusion, we have found that by occasionally adjusting it according to changes in heart rate, which is measured continuously, it is possible to anticipate increases in blood pressure and thus reduce the incidence of hypertension. Similarly, we have found that use of direct intraarterial pressure monitoring facilitates very accurate maintenance of blood pressure without major fluctuations, but this is difficult to justify in routine clinical cases. In our study, the phenylephrine infusion rate was chosen empirically. Further investigation, including dose–response studies and studies of variable dose regimens would be of interest and might facilitate better hemodynamic stability.

When designing this study, we decided that it was not practical to attempt blinding. In retrospect, it is possible that a tall screen or barrier could have been used to blind the investigator administering the phenylephrine infusion and the patient from the rate of intravenous fluid infusion, although this would have been cumbersome. Moreover, many patients who received cohydration would probably have been aware of the sensation of rapid fluid infusion. Nonetheless, the unblinded methodology is a weakness of our study. However, because titration of phenylephrine was performed according to a rigid objective protocol, we do not believe that this weakness impacted significantly on our results.

How practical is our technique for normal clinical practice? Our protocol requires the use of a syringe pump and frequent measurements of maternal blood pressure with corresponding frequent review of the syringe pump setting. However, our infusion protocol uses a basic on–off algorithm that was designed to be simple and easy to use. As an alternative, phenylephrine can also be administered by intermittent boluses. Although this requires less equipment, we have found that an infusion system, once set up, is no more difficult to use. We have previously compared phenylephrine administration by infusion *versus* bolus[6] and found that, compared with intermittent boluses, the use of an infusion was associated with lower incidence, frequency, and magnitude of hypotension, and there was a trend toward less nausea and vomiting (4% *vs.* 21%). We chose to administer the intravenous fluid from a fixed height using passive gravity-driven flow. Although the use of a pressurized bag may have resulted in more rapid or more consistent flow rates, we believe that this would have detracted from the simplicity of our technique and its

application to everyday practice. We use our technique regularly in our normal clinical practice and have found it easy to use and easy to teach, and the low frequency of maternal symptoms is a particular advantage.

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