COMPARISON BETWEEN TWO PHENYLEPHRINE INFUSION RATES WITH MODERATE CO-LOADING FOR THE PREVENTION OF SPINAL ANAESHTESIA- INDUCED HYPOTENSION DURING ELECTIVE CAESAREAN SECTION*

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Abstract

Background: Phenylephrine induces maternal bradycardia in 50% of mothers when used for prevention and treatment of spinal anaesthesia-induced hypotension during caesarean delivery. Rapid fluid administration immediately after initiation of the spinal block (co-loading) may have a vasopressor sparing effect. The aim of this study was to evaluate the hypothesis that when using rapid crystalloid co-loading, an infusion of 50 mcg/minute of PE could be as effective as 100 mcg/minute in preventing maternal hypotension but with minimal maternal bradycardia and an acceptable fetal outcome.

Methods: 117 mothers scheduled for elective caesarean section were recruited in this randomized controlled trial. Co-loading with 10 ml/kg of Hartmann's solution started immediately after a standard spinal anaesthesia. Parturients were then randomly allocated into two groups. Group 50 (n = 54) received phenylephrine infusion at 50 μg/min, and group 100 (n = 63) 100 μg/min. Rescue phenylephrine boluses (50 mcg) were administered if needed to maintain systolic blood pressure between 80-100% of its baseline values.

Results: Systolic blood pressure was not different between mothers in both groups during the study period. All neonatal Apgar scores at 1 minute were ≥7 and at 5 minutes were ≥ 9. No mother had umbilical arterial pH <7.2. Umbilical arterial and venous blood gas and acid base values were not different between both groups except the umbilical arterial PCO_2 that was significantly higher in group 100. There were more frequent episodes of maternal bradycardia in Group 100 than in Group 50 (eleven and one parturients respectively). There was no difference in the incidence of nausea and vomiting in both groups.

Conclusion: In combination with rapid co-loading, an infusion rate of 50 μg/min of PE is as adequate as 100 μg/min in prevention of spinal anaesthesia-induced hypotension during elective caesarean section. Both infusions are associated with a similar neonatal outcome. PE infusion of 50 μg/min is associated with significantly less maternal bradycardia than 100 μg/min.

Keywords: Phenylephrine, Spinal Aneasthesia, Caesarean section, Hypotension, Co-loading.

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Introduction

During elective caesarean section, maternal hypotension is the most frequent complication of spinal anaesthesia with an incidence approaching 100%[1]. Among its multifactorial aetiology is profound vasodilatation secondary to complete sympathetic denervation that is often accentuated by a variable degree of aortocaval compression. Many strategies are currently used to minimize hypotension including maternal left tilt, leg wrappings[2], sympathomimetic drugs[3], and intravenous fluid loading whether before (pre-loading)[4] or with (co-loading) induction of spinal anaesthesia. Co-loading may be more effective than preloading in terms of reducing the dose of vasopressor prior to delivery[5].

Recent work suggests that prophylactic continuous infusion of the <alpha>-adrenergic agonist phenylephrine (PE) is superior to ephedrine in prevention of spinal anaesthesia induced hypotension. Major postulated benefits are a reduction in the incidence of nausea and vomiting, and less fetal acidosis[6,7]. But when PE was used on its own to maintain maternal systolic blood pressure at 100% of baseline, the incidence of hypotension was still 29%[8]. A Cochrane systematic review concluded that no one method on its own is effective, and that combining more than one measure should be investigated[9].

PE induces bradycardia in up to 50% of mothers, in a dose-related manner, via a secondary baroreceptor response to induced-hypertension[11]. The aim of the study was to evaluate the hypothesis that when using rapid crystalloid co-loading, PE infusion of 50 mcg/minute could be as effective as 100 mcg/minute in preventing maternal hypotension with similar foetal outcome but with minimal maternal bradycardia.

Methods

Following Corniche hospital Ethics Committee approval (Abu Dhabi United Arab Emirates) and informed written consent, 117 mothers scheduled for elective caesarean section were recruited. All mothers had normal singleton pregnancy at 37 week gestation or more. Exclusion criteria were American Society of Anaesthetists (ASA) Class 3 or more, height <150 or >180 cm, or body mass <60 or >100 kg, pre-eclampsia, known fetal abnormality, or any contraindication to spinal anaesthesia.

Oral ranitidine (150 mg) was given on the evening before and the morning of surgery. In the preparation room, oral sodium citrate 0.3 M (30 ml) was given. Three measurements of non-invasive blood pressure at one minute interval were taken after the mothers were allowed a 5 minute rest period in the supine position with left lateral tilt. The average of the 3 readings of systolic blood pressure (SBP) was used as a baseline.

Following skin infiltration with 2% lidocaine, a 16G IV catheter was inserted and intravenous fluid was started at a minimal rate to keep the vein open. Mothers were randomized into Group 50 (PE 50 µg/ml) or Group 100 (PE 100 µg /ml) using closed similar envelops labeled with either of the two designated concentration of PE. An anaesthetist, who was not involved in the case management, prepared a 20 ml syringe for PE infusion with the designated concentration. Both the patient and the anaesthetist in charge of the case were blinded to the concentration of PE in the syringe.

In the operating theatre, after the skin was infiltrated with 2% lidocaine, subarachnoid injection of 3 ml (15 mg) hyperbaric bupivacaine 0.5% and preservative-free fentanyl 20 µg was performed in the sitting position using a 26G atraumatic spinal needle (Rapid™, Portex, UK) at the L3-4 or L4-5 interspace. With the operating table leveled, mothers were positioned supine with left lateral tilt and 2 pillows supporting the head and shoulders. Monitoring consisted of a continuous 3 lead electrocardiograph, noninvasive blood pressure measurement every minute, and pulse oximetry. Intraoperative haemodynamic data, from the time of induction of spinal anaesthesia until the delivery of the baby, were downloaded from the monitor (IntelliVue MP70, Phillips Medical Ltd, Germany) for off-line analysis. Five minutes after induction of anaesthesia, the upper sensory level of anaesthesia was assessed using loss of cold stimulus discrimination. Oxygen (5 L/min) by a clear facemask was given only if pulse oximetry reading was less than 95%.

Immediately after spinal anaesthesia, both PE infusion and co-loading were commenced. An intravenous bolus of warm Hartmann's solution (10 ml/kg) was administered as rapidly as possible, with the aid of a pressure bag inflated at 200 mmHg, followed by a reduction of the rate to a minimal flow. PE infusion was commenced at a rate of 60 ml/h for the first three minutes and stopped if SBP was greater than 120% of the baseline. After the first three minutes, the infusion was continued at the same rate if SBP was between 80-100% of baseline, until the time of delivery. PE infusion was discontinued if the SBP was more than 100% of the baseline value. A rescue dose of PE (50 μg) was given if blood pressure decreased to below 80% of the baseline for two consecutive readings despite PE infusion. If bradycardia (heart rate <50/min) developed without hypotension, PE infusion was discontinued for one minute. Intravenous glycopyrronium (200 μg) was used to treat bradycardia associated with hypotension (SBP<80% of baseline). After delivery, an intravenous bolus of oxytocin (5 IU) was slowly administered. Apgar score was assessed at 1 and 5 minutes after delivery by the attending paediatrician, who was unaware of the dose of PE used. With the umbilical cord double clamped, umbilical venous and arterial blood samples were drawn for gas and acid base analysis.

The primary outcome of the study was the incidence of maternal hypotension, defined as a drop in SBP to less than 80% of baseline. The incidence of hypotension was 29% in a previous study[8]. A priori sample size of 58 mothers in each group was deemed sufficient to detect a 5% difference ($\alpha = 0.05$, $\beta = 0.8$). Another 10% was added to compensate for drop outs. Secondary outcomes were maternal bradycardia, the total dose of PE used pre-delivery, the incidence of nausea and vomiting, Apgar scores at 1 and 5 minutes, and umbilical arterial and venous blood gases and base deficits. Normally distributed numerical data were described in terms of mean and standard deviation and compared using unpaired t-test and one way ANOVA. Non-normally distributed data were compared using Mann-Whitney test. Categorical data were analysed using Chi square and Fischer Exact tests where appropriate. Statistical analysis was performed using SPSS 14.0 for windows (Statistical Package for Social Sciences). Statistical significance was assumed at a P value of <0.05.

Results

One hundred and twenty eight mothers were originally enrolled in this trial with eleven dropouts due to different reasons. Two mothers had inadequate block and subarachnoid injection was repeated. Trial design was not strictly followed in four mothers. Five umbilical blood gas results had technical problems. One hundred and seventeen full-term parturients undergoing elective caesarean section completed the study. None of them complained of intraoperative pain nor was intraoperative supplementation with analgesics or sedatives required (Table 1).

Table 1
Mothers' characteristics, block height and surgical times in both groups

	Group 50 (n = 54)	**Group 100 (n = 63)**	***P***
Age (years)	32.7 (4.6)	32.8 (5.3)	0.92
Weight (Kg)	74.0 (9.1)	75.5 (9.9)	0.41
Height (cm)	158.4 (4.8)	159.0 (6.6)	0.56
Gestational age (weeks)	38.4 (1.0)	38.2 (0.9)	0.26
Block height at 5 minutes (dermatome)	T4 (T2-T6)	T4 (T2-T6)	1.0
Induction to delivery time (minutes)	14.5 (2.7)	14.0 (3.5)	0.35
Uterine incision to delivery time (seconds)	65.5 (36.9)	72.0 (55.8)	0.47

All values are mean (SD) except block height: median (range).

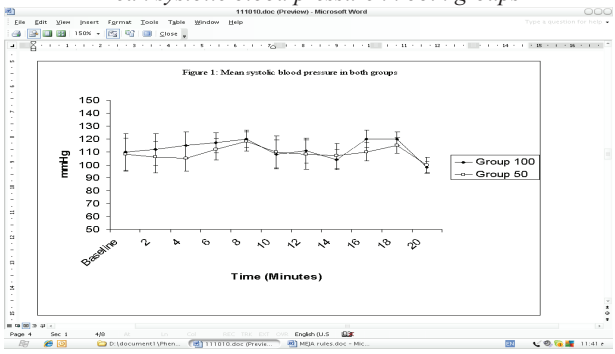
Table 2
Intraoperative haemodynamic data and side effects

	Group 50 (n = 54)	**Group 100 (n = 63)**	***P***
Incidence of hypotension (systolic blood pressure less than 80% of baseline)	8 (14.8)	3 (4.7)	0.12
Incidence of hypertension (systolic blood pressure more than 120%)	2 (3.7)	10 (15.8)	0.063
Phenylephrine dose used (micrograms)	546.9 (211.3)	913.5 (361.4)	<0.001*
Number of mothers that received at least one rescue dose of phenylephrine	7 (12.9)	1 (1.5)	0.023*
Incidence of bradycardia (heart rate less than 50/min)	1 (1.8 %)	11 (17.4 %)	0.005*
Number of mothers that received glycopyrronium	0	1 (1.5 %)	0.46
Co-loading volume (ml)	759 (95)	775 (107)	0.39
Incidence of nausea and vomiting	3 (5.5)	1 (1.5)	0.33

Values are number (%) except phenylephrine dose and co-loading volume: mean (SD).
* denotes a significant difference (p<0.05).

Intraoperative haemodynamic data and side effects are shown in table 2. Systolic blood pressure was not different statistically at any time during the study period (Fig. 1).

Fig. 1
Mean systolic blood pressure in both groups



None of the neonates in both groups had an umbilical artery pH <7.2 (Table 3). All neonatal Apgar scores at 1 minute were ≥7 and at 5 minutes were ≥9. All umbilical arterial and venous blood gas values were not different between neonates in both groups except the umbilical arterial PCO_2 that was significantly higher in neonates in group 100 (p<0.05).

Discussion

In this trial, we found that when using rapid crystalloid co-loading, PE infusion of 50 mcg/min would maintain SBP at near normal values, similar to PE infusion of 100 mcg/min that was suggested in previous trial.[10] This trial failed to detect a difference in the incidence of hypotension although it was powered to detect it. Also, there was no difference in the incidence of hypertensive episodes between both groups. Blood pressure was measured non-invasively every minute in this study. Invasive arterial blood pressure monitoring would have been more sensitive but it lacks clinical justification. There was no significant difference in

Table 3
Neonatal outcome in both groups

	Group 50 (n = 54)	**Group 100 (n = 63)**	***P***
Umbilical arterial blood gases			
pH	7.31 (0.04)	7.30 (0.04)	0.14
PCO_2 (mmHg)	52.5 (6.7)	55.4 (7.1)	0.02*
PO_2 (mmHg)	13.8 (5.0)	12.7 (5.4)	0.24
Base excess (mmol Litre^{-1})	-0.15 (2.5)	0.26 (1.9)	0.26
Umbilical venous blood gases			
pH	7.36 (0.03)	7.35 (0.03)	0.29
PCO_2 (mmHg)	43.1 (4.2)	44.4 (5.2)	0.13
PO_2 (mmHg)	23.8 (5.5)	24.4 (6.1)	0.64
Base excess (mmol Litre^{-1})	-1.5 (1.6)	-1.3 (1.6)	0.29

Values are mean (SD), * denotes a significant difference (p<0.05).

the incidence of nausea and vomiting between both groups.

Crystalloid preloading before spinal anaesthesia for caesarean section, as a sole measure, is not effective in preventing hypotension[12]. This is probably due to its rapid redistribution and the stimulation of atrial natriuretic peptide secretion that lead to peripheral vasodilatation and diuresis[13]. Starting fluid loading immediately after induction of spinal anaesthesia (co-loading) is a more rational approach as intravascular volume expansion coincides with sympathetic blockade-associated vasodilatation[5,14]. Rapid crystalloid co-loading with 20 ml/kg was associated with less ephedrine requirement than with preloading suggesting that co-loading has a vasopressor-sparing effect[5]. In non-obstetric patients, co-loading, with 12 ml/kg, was associated with a significant increase in cardiac output as compared to preloading and no loading, with no difference in the incidence of hypotension[15].

In a recent Cochrane systematic review, no conclusions were reached with respect to the optimum intravenous fluid loading volume[9]. In this trial, co-loading relied on a body weight-based moderate volume of Hartmann's solution (10 ml/kg). This moderate co-loading would minimize any deleterious effect of sudden intravascular volume expansion. This volume was used previously in a similar study[16]. To achieve an optimum response to co-loading, the preset Hartmann's volume was infused as rapidly as possible, aided with a pressure bag inflated at 200 mmHg, through a standard 16 gauge venous catheter. Gravity was the driving force in previous co-loading trials[5,10]. Further studies are needed to quantify the vasopressor-sparing effect of different co-loading volumes.

All vasopressors share the same adverse effects that include anaphylaxis, hypertension and cardiac dysrhythmia[17]. There is also a potential for impaired utero-placental perfusion secondary to vasoconstriction. Among the currently used vasopressors, PE is gaining popularity in preventing spinal anaesthesia-induced hypotension in mothers undergoing caesarean section. Contrary to previous beliefs, it is now suggested that maintaining utero-placental perfusion pressure by PE outweigh its potential utero-placental vasoconstriction effect[18]. This is evident by higher UApH in mothers receiving PE as compared to ephedrine[19].

Although some studies showed that PE was not associated with maternal or foetal morbidity, the high incidence of maternal bradycardia is still a concern[20]. The recommended infusion dose of PE ranges from 30 to 180 mcg/min. according to blood pressure response[21]. This wide dose range may precipitate high plasma concentrations that might precipitate hypertension and bradydysrhythmia. Ventricular bigeminy was previously reported in a mother having a caesarean section under spinal anaesthesia while receiving PE boluses of 100 μg/min[22]. We believe that a user-friendly infusion regimen that can be adopted easily even by less experienced practitioners is needed. PE infusion protocol in this study was simple. PE infusion (60 ml/h) commenced immediately after subarachnoid injection for 3 minutes. After 3 minutes, the anaesthetist will either discontinue or continue PE infusion at the same rate to maintain maternal SBP within 20% of its baseline. If maternal SBP dropped below 80% of baseline, PE infusion will restart at the same rate (60 ml/h).

In this trial, only one mother in group 50 developed one or more episodes of sinus bradycardia (1.8%) as compared to eleven mothers in group 100 (17.4%). The difference was highly significant ($p = 0.005$). The incidence of bradycardia in group 100 is comparable to that of Ngan kee et al, 16.9% when used a similar dose of PE[10]. Two different mechanisms could instigate sinus bradycardia during spinal anaesthesia; sympathetic cardiac denervation and baroreceptor response to PE induced hypertension. In this trial, the technique of spinal anaesthesia was the same in all mothers. The dose of bupivacaine used (15 mg) was within the recommended dose range[18,23]. As there was no detectable difference in block height between both groups, we can assume that the difference in the incidence of sinus bradycardia is attributed to the significant difference between the doses of PE. In this trial, glycopyrrolate was given if bradycardia persists despite PE discontinuation or if bradycardia was associated with hypotension. There was no difference in the use of glycopyrrolate between both groups as apparently discontinuation of PE infusion promptly eliminated sinus bradycardia.

All babies in both groups had an Apgar score

of >7 at one minute and >9 at 5 minutes. The UA pH was ≥7.3 for all babies in both groups. There was no statistical significant difference between both groups' UA and UV blood gas and acid-base values except UA PCO_2. The UA PCO_2 was significantly higher in group 100 as compared to group 50. Although the difference in UA PCO_2 was statistically significant, it was not clinically relevant. It was previously suggested that a higher UA PCO_2 might indicate foetal respiratory acidaemia secondary to acute utero-placental insufficiency[24]. We believe that any attempt to associate this with the higher dose of PE (100 mcg/minute) would be speculative.

We conclude that, in combination with rapid co-loading, an infusion rate of 50 µg/min of PE is as adequate as 100 µg/min in prevention of spinal anaesthesia-induced hypotension during elective caesarean section. PE infusion of 50 µg/min is associated with significantly less maternal bradycardia than 100 µg/min. Both infusions are associated with a similar neonatal outcome.

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