Safety of Phenylephrine in Antihypotensive Treatment during Spinal Anesthesia for Cesarean Section

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Objective: *In Thailand, hypotension after spinal anesthesia for cesarean section is routinely treated by ephedrine. As incidence of fetal acidosis reportedly increases resulting from placental transfer of ephedrine, phenylephrine, an alpha-1 agonist with less lipid solubility, becomes an alternative. However, the potential development of serious bradycardia after phenylephrine is a concern. The objectives of this study were to investigate the incidence of serious bradycardia and identify risk factors associated with phenylephrine-induced serious bradycardia and other side effects of phenylephrine.*

Material and Method: *This descriptive cross-sectional study was conducted between July 1, 2014 and March 15, 2015 on 509 parturients undergoing cesarean section under spinal anesthesia. Predelivery hypotension was treated by intravenous phenylephrine 100 mcg and pretherapeutic heart rate (pHR) was recorded. If serious bradycardia (HR <60 bpm and hypotension or HR <45 bpm) developed, atropine 0.6 mg was administered intravenously. Data were analyzed using multivariable logistic regression and AuROC.*

Results: *Incidence of serious bradycardia was 11% (95% CI: 8.0-14.0). A one bpm increment increase in pHR reduced this incidence by 4% (adjusted OR: 0.96; 95% CI: 0.94-0.98, p<0.001; AuROC: 0.76). As compared to a pHR greater than 80 bpm, a pHR of 61 to 80 bpm and a pHR of 60 bpm or lower increased the risk of serious bradycardia by 3.55 times and 12.81 times, respectively. Other risk factors were height (adjusted OR: 0.94; 95% CI: 0.89-0.98, p = 0.015), baseline DBP (adjusted OR: 0.97; 95% CI: 0.94-0.99, p = 0.03), and anesthetic level at first minute (adjusted OR: 1.13; 95% CI: 1.02-1.23, p = 0.02). Benign and temporary abnormal ECG readings were noted.*

Conclusion: *Phenylephrine for antihypotensive treatment in spinal anesthesia induces bradycardia. Findings indicate an association between slower HR at time phenylephrine is administered and serious bradycardia. Close ECG monitoring and prompt treatment are required.*

Keywords: *Phenylephrine, Spinal anesthesia, Antihypotensive treatment, Cesarean section, Bradycardia*

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Ephedrine is currently used to maintain blood pressure during spinal anesthesia for cesarean section[1]. Many studies have reported a preference for phenylephrine over ephedrine, notwithstanding ephedrine's influence on materno-fetal transfer and increased risk of fetal acidosis[2,3]. A recent systematic review and cumulative meta-analysis found the use of ephedrine to be associated with lower pH and base excess (BE) in neonates[4]. However, because phenylephrine contains a potent α-adrenergic (without β-adrenergic receptor activity at normal clinical doses), its use is often associated with a dose-related reflexive slowing of maternal heart rate (HR) and a corresponding decrease in cardiac output (CO)[5-7].

Based on our review of the literature, no previous study has investigated factors associated with phenylephrine-induced serious bradycardia. A specific point of interest centered on maternal heart rate just before phenylephrine administration (hereafter referred to as pretherapeutic heart rate (pHR)) and whether pHR is an explanatory factor that limits the safe use of phenylephrine.

The primary objective of this descriptive cross-sectional study was to determine the incidence of phenylephine-induced serious bradycardia. Secondary objectives include identification of risk factors associated with phenylephrine-induced serious bradycardia, exploration of the potential diagnostic utility of identified risk factors, and identification of other side effects of phenylephrine use in the treatment of spinal anesthesia-induced hypotension among patients undergoing cesarean section.

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Material and Method

Approval for this study was obtained from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital and from Chaoprayayomraj Hospital, Suphanburi Province, Thailand. The study protocol was registered in the Thai Clinical Trials Registry (TCTR). All patients gave written informed consent to participate in the study and data collection was performed between July 1, 2014 and March 15, 2015.

This prospective descriptive cross-sectional study enrolled 509 pregnant women undergoing elective and emergency cesarean section who matched the following inclusion criteria, ASA physical status I or II, age ≥18 years, singleton baby, and term pregnancy (gestational age ≥37 weeks). Exclusion criteria were as follows, chronic hypertension, gestational hypertension or preeclampsia, cardiovascular disease, cerebrovascular disease, complicated obstetrics (abruptio placentae, placenta previa), known fetal abnormalities, history of monoamine oxidase inhibitor (MAOI) use or other drugs that prolong heart conduction (PR or QT interval), and contraindications to spinal anesthesia (e.g., coagulopathy, intracranial space occupying lesion, or patient refusal).

Demographic data was obtained at the wards on the evening before the day of surgery. A nurse anesthetist recorded the non-invasive blood pressure (NIBP) and heart rate (HR) of the parturient at rest in a tranquil environment in three positions. Averaged systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) from three consecutive readings taken in the supine position with left uterine displacement for five minutes before readings were taken were defined as baseline values. The same measurements were repeated in the left lateral and supine positions to determine supine hypotensive syndrome of pregnancy (SHSP). In emergency cases, average NIBP and HR were recorded only in supine position with left uterine displacement due to time limitation.

On the day of surgery, fluid preload of 0.9% NaCl solution 10 ml/kg IV was given over a 15 to 20-minute period before performing spinal anesthesia. After standard monitoring instruments were applied, parturient was positioned in the left lateral position and spinal anesthesia was performed with a 27-gauge Quincke spinal needle at the L2 to L3 or L3 to L4 vertebral interspace. After confirmation of free flow of cerebrospinal fluid, 2.2 ml of 0.5% hyperbaric bupivacaine and 0.2 mg of preservative free morphine were injected intrathecally. The patient was then positioned in the supine position with left uterine displacement at 15 degrees.

One-minute automatic interval NIBP, HR, and SpO_2 were monitored immediately after administration of spinal medication (defined as Time 0), with continuous monitoring until the baby was delivered. Oxygen 6 L/min was given via face mask from induction of spinal anesthesia until delivery. Dermatomal level of anesthesia was assessed by loss of cold sensation discrimination at first and fifth-minute after administration of spinal anesthesia. Sensory block to T5 level was determined as adequate anesthesia for cesarean section.

Incidence of hypotension (SBP <80% of baseline or <90 mmHg), reactive hypertension (SBP >120%), and serious bradycardia (HR <60 bpm and hypotension or HR <45 bpm) were recorded. If hypotension occurred, phenylephrine 100 mcg/1 ml was administered via intravenous bolus. Patient pHR was recorded immediately preceding administration of phenylephrine. Additional phenylephrine doses were given every minute if hypotension persisted. Serious bradycardia was treated by atropine 0.6 mg IV with doses repeated every two minutes, as needed. An external pacemaker was prepared and ready for use if serious bradycardia did not respond to maximum dose of atropine (3 mg).

After delivery, oxytocin 20 units in 0.9% NaCl 1,000 ml was given via intravenous infusion. Cases with heart block, arrhythmia, and/or cardiac arrest were recorded and prompt treatment was given. The following times were recorded, administration of spinal anesthesia, skin incision, uterine incision and baby delivery. Baby birth weight and Apgar scores at first and fifth-minute were also recorded.

Statistical analysis

For a confidence level of 95%, α was 0.05, $Z\alpha/2$ was 1.96, and d was 0.026. The required sample size was 509. Continuous data were presented as mean (SD) and median (IQR) and analyzed using either unpaired t-test or Mann-Whitney U test, where appropriate. Categorical data were presented as number and percentage and analyzed using Chi-square test or Fisher exact test, where appropriate. Possible risk factors were analyzed by univariable and multivariable logistic regression and reported as crude and adjusted odds ratio (OR) with 95% confidence interval (CI) and the area under the curve (AuROC). All were calculated by

Stata version 12 (StataCorp, College Station, TX, USA). A *p*-value less than 0.05 was considered statistically significant.

Results

Five hundred nine participants inluding 150 parturients from King Chulalongkorn Memorial Hospital and 359 parturients from Chaoprayayomraj Hospital were included during the study period. The incidence of phenylephrine-induced serious bradycardia was 11% (n = 56, 95% CI 8.0-14.0). Incidence of bradycardia (HR <60 bpm) was 28.88% (n = 147, 95% CI 24.9-32.83). Four parturients had pHR <60 bpm (bpm results: 58, 57, 56, 54) while phenylephrine was being given for treatment of hypotension. One parturient (pHR 57 bpm) developed serious bradycardia and received atropine 0.6 mg IV bolus for rescue treatment. Demographic and relevant data pertaining to anesthesia, surgery, and neonatal outcome are shown in Table 1. Comparing between the serious bradycardia and non-serious bradycardia groups, there were statistically significant differences in height, anesthetic level at first minute, duration of induction-to-uterine incision, and induction-to-delivery between the two groups.

Baseline hemodynamics, intraoperative HR changes, and administered phenylephrine doses are presented in Table 2. There were statistically significant differences in baseline DBP, baseline HR, and pHR between the serious bradycardia and non-serious bradycardia groups. The dose range of phenylephrine administration among all study parturients was 100 to 700 mcg, with no statistically significant differences between the two groups. No statistically significant difference was found in the incidence of SHSP between the serious bradycardia and non-serious bradycardia groups (7.32% and 5.49%, respectively). Incidence of HR <60 bpm before phenylephrine administration was 3.57% and 0.44% in the serious and non-serious bradycardia groups, respectively ($p = 0.06$).

Univariable logistic regression showed

Table 1. Demographic and relevant data pertaining to anesthesia, surgery, and neonatal outcome

Variables	Serious bradycardia group (n = 56)		Non-serious bradycardia group (n = 453)		*p*-value
	Mean/median	SD/IQR	Mean/median	SD/IQR	
Demographic data					
Age (year)	30.4	6.5	29.4	5.9	NS[a]
Body weight (kg)	68.4	10.9	72.2	13.2	NS[a]
Height (cm)	156.4	6.1	158.2	5.9	0.01[a]
Gestation age (week)	38	38-39	38	38-38	NS[b]
ASA physical status	1	1-1	1	1-1	NS[c]
I - n (%)	56 (100)		438 (97.1)		
II - n (%)	-		13 (2.9)		
Relevant data pertaining to anesthesia and surgery					
Anesthetic level (dermatome)					
At 1st min	T6	T4-T10	T8	T6-T10	<0.001[b]
At 5th min	T4	T4-T4	T4	T3-T4	NS[b]
Incision interval (min)					
Induction-skin	4	3-5	4	3-5	NS[b]
Induction-uterine	8	6-11	7	6-9	0.03[b]
Induction-delivery	9	8-13	9	7-10	0.01[b]
Neonatal outcome					
Apgar score					
At 1st min	9	9-9	9	9-9	NS[b]
At 5th min	10	10-10	10	10-10	NS[b]
Birth weight (g)	3,040	2,810-3,265	3,130	2,905-3,410	NS[b]

a = unpaired t-test; b = Mann-Whitney U test; c = Fisher exact test
NS = no statistical significance

association between serious bradycardia and the following factors, pHR, height, baseline DBP, anesthetic level at first minute, and baseline HR ($p<0.05$) (Table 3). No multicollinearity (VIF: 1.00-1.41) was found among these factors. Multivariable logistic regression demonstrated that pHR was significantly associated with serious bradycardia after adjusting for height, baseline DBP, and anesthetic level at first minute (adjusted OR 0.96, 95% CI 0.94-0.98, $p<0.001$, AuROC 0.76). A one bpm increment increase in pHR reduced the incidence of serious bradycardia by 4%. This result demonstrated that pHR is a predictor of serious bradycardia after phenylephrine administration.

The incidence of serious bradycardia in various ranges of five bpm pHR intervals also demonstrated association, which confirmed the results from multivariable logistic regression analysis (Fig. 1, Table 4). The incidence of serious bradycardia in parturients with pHR greater than 80 (about 10%) was the half that of parturients with pHR in the range of 61-80 bpm (about 20%). Parturients in the pHR range equal to or below 60 bpm showed a higher incidence of up to 50% (Table 4). Compared with pHR >80 bpm group, the incidence of serious bradycardia increased with lower pHR (adjusted OR 3.55, 95% Cl 1.86-6.93 in pHR 61-80 bpm group and adjusted OR 12.81, 95% Cl 4.40-37.30 in pHR ≤60 bpm group, respectively).

The incidence of reactive hypertension was 5.7% (n = 29, 95% CI 3.68-7.71). There was a statistically significantly higher incidence in the serious bradycardia group than in the non-serious bradycardia group (16.07% and 4.42%, respectively; $p = 0.002$). This difference was associated with and attributable to the administration of atropine. However, no clinically significant differences in hypertensive crisis symptoms were found between the two groups.

The number and incidence of atrioventricular block (AVB) was 7 and 1.38% (95% CI 0.4-2.4),

Table 2. Baseline hemodynamics, intraoperative HR change data, and amount of phenylephrine administration

Variables	Serious bradycardia group (n = 56)		Non-serious bradycardia group (n = 453)		*p*-value
	Median	IQR	Median	IQR	
Baseline SBP (mmHg)	120	110-125.3	119	111-128.7	NS
Baseline DBP (mmHg)	70	62.7-75	73.3	67-80.7	0.002
Baseline HR (bpm)	82.9	74-89	86.3	80.3-95	0.003
Pretherapeutic HR (bpm)	79.5	67-95.5	95	82-113	<0.001
HR difference at 1 minute after phenylephrine administration	13	6-27	12	5-22	NS
Total amount of phenylephrine (mcg)	200	100-200	100	100-200	NS

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure

Table 3. Univariable and multivariable logistic regression evaluating factors associated with phenylephrine-induced serious bradycardia

	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
pHR	0.96 (0.95-0.98)	<0.001	0.96 (0.94-0.98)*	<0.001
Height	0.94 (0.90-0.99)	0.014	0.94 (0.89-0.98)	0.015
Baseline DBP	0.95 (0.93-0.98)	0.002	0.97 (0.94-0.99)	0.030
Anesthetic level at 1st min	1.18 (1.07-1.29)	0.001	1.13 (1.02-1.23)	0.020
Baseline HR	0.96 (0.93-0.99)	0.030	0.98 (0.95-1.01)**	0.285

* Adjusted for height, baseline DBP, and anesthetic level at 1st min
** Adjusted for pHR, height, baseline DBP, and anesthetic level at 1st min
pHR = pretherapeutic heart rate

Table 4. Univariable and multivariable logistic regression evaluating the association between pHR (interval) and phenylephrine-induced serious bradycardia

	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
pHR >80 bpm	-	-	-	-
pHR 61-80 bpm	2.42 (1.34-4.36)	0.003	3.55 (1.81-6.93) *	<0.001
pHR ≤60 bpm	9.45 (3.58-24.96)	<0.001	12.81 (4.40-37.30) *	<0.001

* Adjusted for height, baseline DBP, and anesthetic level at 1st min

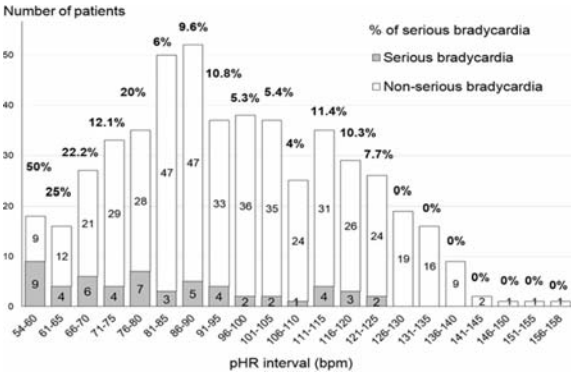

Fig. 1 Incidence of serious bradycardia (%) and number of serious and non-serious bradycardia patients in 5 bpm pHR intervals.

Table 5. Intraoperative side effects of phenylephrine administration

Side effects	n = 509 n (%)
Reactive hypertension	29 (5.70)
AV block	7 (1.38)
1st degree	4 (0.79)
2nd degree (Mobitz I)	3 (0.59)
Premature ventricular contraction	3 (0.59)
Premature atrial contraction	7 (1.38)
Sinus arrhythmia	6 (1.19)
Supraventricular tachycardia	1 (0.19)

respectively. Four cases were first degree AVB and three cases were second degree AVB (Mobitz I). One AVB case showed asymptomatic ECG change to sinus bradycardia with junctional rhythm and then to Mobitz I. Duration of this abnormality lasted one to two minutes and then returned to normal sinus rhythm after IV administration of 0.6 mg atropine. The other six cases developed within minutes and then spontaneously returned to normal.

One case of supraventricular tachycardia was found. After one minute of phenylephrine administration, the patient developed one premature ventricular contraction and one premature atrial contraction. After two minutes of phenylephrine administration, supraventricular tachycardia (117 bpm) developed, but spontaneously resolved within 10 seconds without any hypoperfusion symptoms. During the study, no external pacemaker was used and no severe abnormal ECG or cardiac arrest occurred.

Discussion

The ideal vasopressor for antihypotensive treatment during cesarean section would be one that is effective and easy to use, has rapid onset, short duration of action, easy titration, has prophylactic use, and absent of any adverse maternal or fetal impact[8]. Despite evidence in favor of phenylephrine as a superior antihypotensive treatment option, there remains widespread variation in dosing and method of administration of vasopressors[2]. Previously, both ephedrine and phenylephrine were recommended as equally efficacious vasopressors in obstetric anesthesia[9]. As a consequence of improved fetal acid-base status, the ASA Task Force on Obstetric Anesthesia and Canadian guidelines declared phenylephrine preferable to ephedrine[10].

According to a previous study, different initial phenylephrine bolus doses of 100, 125, and 150 mcg did not significantly differ in efficacy in the treatment of post-spinal hypotension in patients undergoing elective caesarean delivery[11]. The authors used 100 mcg intravenous bolus titration, given that blood pressure can be stabilized within the first six minutes and method of administration is practical and simple and does not involve the set-up of a syringe pump[12]. Therapeutic indication was considered, because some studies reported a higher incidence of hypertension and bradycardia after prophylactic administration[13]. Some evidence showed a decrease in cardiac output

after phenylephrine that was correlated with reduced heart rate, emphasizing the importance of heart rate as a surrogate indicator of cardiac output[6].

The present study found the incidence of phenylephrine-induced serious bradycardia to be 11%, which was similar to that of a previous report[14]. In addition, lower pHR increased the incidence of serious bradycardia. Lower height, baseline DBP, and higher anesthetic level after one minute of spinal anesthesia also increased incidence. These findings might result from rapid sympathetic blockade. The results show the association and direction of the pHR interval to predict the risk of serious bradycardia, which may help to guide physician for clinical judgement when using phenylephrine. The present study also supports some clinical protocols regarding the recommended use of phenylephrine in the presence of maternal tachycardia (heart rate >110 bpm)[15].

Bradycardia was mediated via non-vagal component[16-18] and a reflex increase in vagal activity[19]. The non-vagal component is characterized as a consequence of reduced sympathetic activity. Increasing arterial blood pressure from phenylephrine caused a baroreflex-mediated inhibition of sympathetic nerve activity in conscious[20-22] and anesthetized rabbits[23]. This action would reduce the release of endogenous noradrenaline and adrenaline, thus reducing stimulation of β1-adrenoceptors on SA nodal cells and resulting in a lowered HR[19]. This might be the main mechanism in this setting. Some reports described an association between phenylephrine and torsade de pointes (TdP)[19].

Furthermore, bradycardia is a risk factor for the development of torsade de pointes (TdP), but TdP was not found in this study.

Abnormal ECGs showed benign AVB, premature atrial contraction, premature ventricular contraction, sinus arrhythmia, and short run SVT. These findings agreed with the literature, which describes events that occur over a short period of time and then spontaneously recover[24]. An excess of vagotonia resulting from the higher site of the block might cause Mobitz I from AV node blockade. The likelihood of development of complete AVB is very low[25]. Lai FM et al reported ventricular bigeminy and suggested that this was most probably a stretch-induced ventricular arrhythmia due to increased ventricular afterload caused by phenylephrine[26]. In addition to the direct effect of α-1 adrenergic activity, a previous study reported that phenylephrine also has β-adrenergic effects like tachycardia and supraventricular arrhythmia when administered at high doses[27].

The incidence of reactive hypertension was found to be dose dependent, ranging from 25% to 82% in prophylactic phenylephrine infusions of 25, 50, 75, and 100 mcg/min. The administration of glycopyrrolate for management of bradycardia may also have contributed to incidence of reactive hypertension[13]. George et al[28] found no reactive hypertension in an up-down determination of the ED90 study of phenylephrine in the treatment of spinal anesthesia-induced hypotension. Of note, the initial dose of phenylephrine in the George et al study (100 mcg) was the same as the amount used in our study. The reported higher incidence of reactive hypertension (SBP >20% baseline) in the serious bradycardia group might be attributable to effect of atropine administration, but none of these patients presented with any symptoms of hypertensive crisis. The authors recommend careful observation of phenylephrine-induced bradycardia, as opposed to early treatment by atropine.

To protect both mother and baby, all parturients with serious bradycardia received atropine 0.6 mg intravenous bolus. This emphasizes the importance of careful monitoring of patients and early management of side effects[29]. This protocol may facilitate the prevention of advanced heart block.

Conclusion

Phenylephrine for antihypotensive treatment in spinal anesthesia induces bradycardia. Findings indicate an association between slower heart rate at time phenylephrine is administered and serious bradycardia. If serious bradycardia develops, close ECG monitoring and prompt treatment are required.

Limitations

The present study demonstrated the possible diagnostic utility of pHR to predict serious bradycardia after phenylephrine administration. However, further study is required to identify the optimal cut-off point of pHR for the safe use of phenylephrine.

What is already known on this topic?

Phenylephrine induces serious bradycardia.

No severe adverse events can normally be expected from phenylephrine administration.

What this study adds?

Higher pHR reduces the incidence of serious bradycardia. If pHR is >80 bpm, incidence of serious

bradycardia is less than 10%. If pHR is 61 to 80 bpm, incidence of serious bradycardia increases 3.55 times. In cases where pHR is ≤60 bpm, incidence of serious bradycardia increases 12.81 times.

Lower height, baseline DBP, and higher anesthetic level at first minute increase the incidence of serious bradycardia.

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Potential conflicts of interest

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

References

1. Allen TK, Muir HA, George RB, Habib AS. A survey of the management of spinal-induced hypotension for scheduled cesarean delivery. Int J Obstet Anesth 2009; 18: 356-61.
2. Habib AS. A review of the impact of phenylephrine administration on maternal hemodynamics and maternal and neonatal outcomes in women undergoing cesarean delivery under spinal anesthesia. Anesth Analg 2012; 114: 377-90.
3. Dyer RA, Biccard BM. Ephedrine for spinal hypotension during elective caesarean section: the final nail in the coffin? Acta Anaesthesiol Scand 2012; 56: 807-9.
4. Veeser M, Hofmann T, Roth R, Klohr S, Rossaint R, Heesen M. Vasopressors for the management of hypotension after spinal anesthesia for elective caesarean section. Systematic review and cumulative meta-analysis. Acta Anaesthesiol Scand 2012; 56: 810-6.
5. Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M. The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. Anesth Analg 2010; 111: 1230-7.
6. Dyer RA, Reed AR, van Dyk D, Arcache MJ, Hodges O, Lombard CJ, et al. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. Anesthesiology 2009; 111: 753-65.
7. Langesaeter E, Rosseland LA, Stubhaug A. Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery: a randomized, double-blind comparison of low-dose versus high-dose spinal anesthesia with intravenous phenylephrine or placebo infusion. Anesthesiology 2008; 109: 856-63.
8. Nag DS, Samaddar DP, Chatterjee A, Kumar H, Dembla A. Vasopressors in obstetric anesthesia: A current perspective. World J Clin Cases 2015; 3: 58-64.
9. Soltanifar S, Russell R. The National Institute for Health and Clinical Excellence (NICE) guidelines for caesarean section, 2011 update: implications for the anaesthetist. Int J Obstet Anesth 2012; 21: 264-72.
10. Practice guidelines for obstetric anesthesia: an updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. Anesthesiology 2007; 106: 843-63.
11. Mohta M, Harisinghani P, Sethi AK, Agarwal D. Effect of different phenylephrine bolus doses for treatment of hypotension during spinal anaesthesia in patients undergoing elective caesarean section. Anaesth Intensive Care 2015; 43: 74-80.
12. Ngan Kee WD. Phenylephrine infusions for maintaining blood pressure during spinal anesthesia for cesarean delivery: finding the shoe that fits. Anesth Analg 2014; 118: 496-8.
13. Allen TK, George RB, White WD, Muir HA, Habib AS. A double-blind, placebo-controlled trial of four fixed rate infusion regimens of phenylephrine for hemodynamic support during spinal anesthesia for cesarean delivery. Anesth Analg 2010; 111: 1221-9.
14. Prakash S, Pramanik V, Chellani H, Salhan S, Gogia AR. Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anaesthesia for caesarean delivery: a randomised study. Int J Obstet Anesth 2010; 19: 24-30.
15. Tulane Department of Anesthesiology. Obstetric anesthesia guidelines [Internet]. 2009 [cited 2014 Jul 19]. Available from: http://www.tulaneanesthesiology.com/web/data/documents/

Jul2009%20TulOBAnesGuidelines.pdf
16. Dukes ID, Vaughan Williams EM. Effects of selective alpha 1-, alpha 2-, beta 1-and beta 2-adrenoceptor stimulation on potentials and contractions in the rabbit heart. J Physiol 1984; 355: 523-46.
17. Fedida D, Shimoni Y, Giles WR. Alpha-adrenergic modulation of the transient outward current in rabbit atrial myocytes. J Physiol 1990; 423: 257-77.
18. Thomas D, Kiehn J, Katus HA, Karle CA. Adrenergic regulation of the rapid component of the cardiac delayed rectifier potassium current, I(Kr), and the underlying hERG ion channel. Basic Res Cardiol 2004; 99: 279-87.
19. Farkas A, Dempster J, Coker SJ. Importance of vagally mediated bradycardia for the induction of torsade de pointes in an in vivo model. Br J Pharmacol 2008; 154: 958-70.
20. Weinstock M, Rosin AJ. Relative contributions of vagal and cardiac sympathetic nerves to the reflex bradycardia induced by a pressor stimulus in the conscious rabbit: comparison of 'steady state' and 'ramp' methods. Clin Exp Pharmacol Physiol 1984; 11: 133-41.
21. Dorward PK, Riedel W, Burke SL, Gipps J, Korner PI. The renal sympathetic baroreflex in the rabbit. Arterial and cardiac baroreceptor influences, resetting, and effect of anesthesia. Circ Res 1985; 57: 618-33.
22. Undesser KP, Pan JY, Lynn MP, Bishop vs. Baroreflex control of sympathetic nerve activity after elevations of pressure in conscious rabbits. Am J Physiol 1985; 248: H827-34.
23. Thames MD, Ballon BJ. Occlusive summation of carotid and aortic baroreflexes in control of renal nerve activity. Am J Physiol 1984; 246: H851-7.
24. Atlee JL. Perioperative cardiac dysrhythmias: diagnosis and management. Anesthesiology 1997; 86: 1397-424.
25. Narula OS, Samet P. Wenckebach and Mobitz type II A-V block due to block within the His bundle and bundle branches. Circulation 1970; 41: 947-65.
26. Lai FM, Jenkins JG. Ventricular bigeminy during phenylephrine infusion used to maintain normotension during caesarean section under spinal anaesthesia. Int J Obstet Anesth 2007; 16: 288-90.
27. Collins V. Physiologic and pharmacologic bases of anesthesia. Pennsylvania: Williams & Wilkins press; 1996.
28. George RB, McKeen D, Columb MO, Habib AS. Up-down determination of the 90% effective dose of phenylephrine for the treatment of spinal anesthesia-induced hypotension in parturients undergoing cesarean delivery. Anesth Analg 2010; 110: 154-8.
29. Shen CL, Ho YY, Hung YC, Chen PL. Arrhythmias during spinal anesthesia for Cesarean section. Can J Anaesth 2000; 47: 393-7.

ความปลอดภัยในการใช้ยาฟีนิลเอฟรินรักษาภาวะความดันโลหิตต่ำจากการได้รับการระงับความรู้สึกทางช่องน้ำไขสันหลังในการผ่าตัดคลอดทางหน้าท้อง

รติกร อนุสรธนาวัฒน์, เกศชาดา เอื้อไพโรจนกิจ, ณัฐณิชา ทองทวีภรณ์, สมรัตน์ จารุลักษณานันท์

วัตถุประสงค์: *ในประเทศไทยใช้ยาอีฟีดรีนในการรักษาภาวะความดันโลหิตต่ำจากการได้รับการระงับความรู้สึกทางช่องน้ำไขสันหลังในผู้ป่วยที่มาผ่าตัดคลอดทางหน้าท้อง ต่อมาพบภาวะเลือดเป็นกรดในทารกเพราะยาอีฟีดรีนสามารถผ่านรกได้ จึงมีการใช้ยาฟีนิลเอฟรินซึ่งกระตุ้นแอลฟาวันละลายในไขมันได้น้อยเข้ามาแทนที่ แต่ผลข้างเคียงที่สำคัญคือ ทำให้อัตราการเต้นของหัวใจมารดาช้าลง ดังนั้น วัตถุประสงค์ของการศึกษาคือ การหาอุบัติการณ์การเกิดภาวะหัวใจเต้นช้า ระบุปัจจัยที่มีผลต่อการเกิดภาวะหัวใจเต้นช้าและผลข้างเคียงอื่นๆ หลังจากได้ยาฟีนิลเอฟริน*

วัสดุและวิธีการ: *การวิจัยเชิงพรรณนาแบบตัดขวางเก็บข้อมูลตั้งแต่วันที่ 1 กรกฎาคม พ.ศ. 2557 ถึงวันที่ 15 มีนาคม พ.ศ. 2558 ในหญิงตั้งครรภ์ที่ได้รับการระงับความรู้สึกทางช่องน้ำไขสันหลังในการผ่าตัดคลอดทางหน้าท้อง 509 คน บันทึกข้อมูลพื้นฐาน ระดับการชา ความดันโลหิตและอัตราการเต้นของหัวใจทุก 1 นาที รักษาภาวะความดันโลหิตต่ำด้วยยาฟีนิลเอฟริน 100 ไมโครกรัม ทางหลอดเลือดดำและบันทึก อัตราการเต้นของหัวใจขณะให้ยาถ้ามีภาวะหัวใจเต้นช้า (<60 ครั้ง/นาที พร้อมกับความดันโลหิตต่ำ หรือ <45 ครั้ง/นาที) รักษาด้วยยาอะโทรปีน 0.6 มิลลิกรัม ทางหลอดเลือดดำ วิเคราะห์ข้อมูลโดยใช้การวิเคราะห์ถดถอยแบบหลายตัวแปรและหาพื้นที่ใต้กราฟ*

ผลการศึกษา: *พบอุบัติการณ์ภาวะหัวใจเต้นช้าจากยาฟีนิลเอฟรินร้อยละ 11 (ช่วงเชื่อมั่นร้อยละ 95 คือร้อยละ 8.0-14.0) ถ้าอัตราการเต้นของหัวใจขณะให้ยาเพิ่มขึ้น 1 ครั้ง/นาที อุบัติการณ์ภาวะหัวใจเต้นช้าลดลงร้อยละ 4 โดยมีนัยสำคัญทางสถิติ (adjusted OR 0.96; 95% CI 0.94-0.98, p<0.001) และพื้นที่ใต้กราฟเท่ากับ 0.76 เมื่อเปรียบเทียบกับอัตราการเต้นของหัวใจขณะให้ยาในช่วงมากกว่า 80 ครั้งต่อนาที พบว่าช่วง 61-80 ครั้งต่อนาที และช่วงน้อยกว่าหรือเท่ากับ 60 ครั้งต่อนาที จะเพิ่มความเสี่ยงในการเกิดภาวะหัวใจเต้นช้า 3.55 เท่า (ช่วงเชื่อมั่นร้อยละ 95 คือ 1.81-6.93 เท่า) และ 12.81 เท่า (ช่วงเชื่อมั่นร้อยละ 95 คือ 4.40-37.30 เท่า) ตามลำดับ โดยมีนัยสำคัญทางสถิติ ปัจจัยอื่นที่มีผลคือ ความสูง (adjusted OR 0.94; 95% CI 0.89-0.98, p = 0.015), ความดันไดแอสโตลิกพื้นฐาน (adjusted OR 0.97; 95% CI 0.94-0.99, p = 0.03) และระดับการชาที่ 1 นาที (adjusted OR 1.13; 95% CI 1.02-1.23, p = 0.02) นอกจากนี้พบภาวะหัวใจเต้นผิดปกติแบบไม่รุนแรงและชั่วคราว*

สรุป: *ฟีนิลเอฟรินทำให้เกิดภาวะหัวใจเต้นช้า ซึ่งสัมพันธ์กับอัตราการเต้นของหัวใจที่ช้าลงขณะให้ยาฟีนิลเอฟริน ควรมีการเฝ้าระวังผู้ป่วยอย่างใกล้ชิด ตรวจคลื่นไฟฟ้าหัวใจ และให้การรักษาภาวะแทรกซ้อนอย่างทันท่วงที*