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EPINEPHRINE;
A VASOCONSTRICTOR OR A UTERINE RELAXANT? A CASE SERIES

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ABSTRACT: The most common complication of spinal anesthesia for cesarean section is hypotension. Ephedrine is the most commonly used vasopressor that increases blood pressure with minimal impact on uteroplacental blood flow. An alpha-1 adrenergic receptor agonist may need to be administrated when ephedrine is ineffective. Unavailability of alpha-1 receptor agonists in a period of time in our center leads to administration of epinephrine as the second drug. In the present study, the data of 14 patients with ephedrine resistant hypotension during spinal anesthesia for cesarean section were reviewed. Increase in maternal blood pressure was recorded one minute after epinephrine administration in all patients. Surprisingly, this medication also causes uterine relaxation after one to five minutes. Ease of fetal extraction was noticed in 13 patients. All patients achieved adequate uterine contraction after delivery. Epinephrine helped regulate blood pressure and surprisingly facilitate uterine relaxation in patients with emergency cesarean section with spinal anesthesia.

Key words: Hypotension; Epinephrine; Anesthesia, Spinal; Cesarean Section; Tocolytic

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INTRODUCTION

Spinal anesthesia has become preferred choice for anesthesia in emergency cesarean delivery. In obstetrics, regional anesthesia particularly spinal block, eliminate the need for general anesthesia. However, hypotension is commonly found after performing of spinal anesthesia and continues hypotension can have detrimental maternal and fetal effects.[1,2] Therefore it is crucial to prevent and treat induced hypotension. Many strategies have been developed to minimize the impact of hypotension but if occurs, use of vasopressors are needed.[3]

Ephedrine that its action is considered to be indirect is the most commonly used vasopressor. Repeated doses of ephedrine may be needed to induce maternal dynamic stability but it should be noted that tachyphylaxis can occur following repeated use of this drug.[4] So an alpha-1 adrenergic receptor agonist may require to be added when ephedrine is inefficient. Epinephrine is not ordinary used as an agent to treat spinal hypotension. But in the present study because of restriction on access to other drugs and the availability of epinephrine, therefore it is reasonable for epinephrine administration to treat hypotension. As well, epinephrine acts as an agonist for smooth muscle beta2-adrenoceptors activation.[5] Beta2-adrenoceptors are found abundantly in the smooth muscle of uterine that mediating relaxation.[6]

In this case series, we present 14 patients with ephedrine resistant hypotension during spinal anesthesia for emergency cesarean delivery that all of them were treated with low dose of epinephrine.

CASE REPORT

In this case series, the medical records of patients with emergency cesarean delivery at Alzahra hospital between 2007 and 2011, who underwent spinal anesthesia, were reviewed. During study period, 14 patients with ephedrine resistant hypotension were identified. The mean age of patients was 25.3 years (range from 16 to 35). Demographic and anesthetic data are

summarized in table-I and II. Neonatal outcome are shown in table-III.

Briefly, on arrival at the operating room, basal monitoring (including non-invasive blood pressure measurement, heart rate, respiratory rate, arterial oxygen saturation) were started. Sixteen or eighteen gauge intravenous cannula was used for administration of normal saline (5 cc/kg).

Spinal anesthesia was performed with hyperbaric 5% lidocaine (70 mg) in the sitting position with 25 G Quincke needle. Patients were then immediately returned to the supine position. Systolic blood pressure was measured at 2-3 min intervals. If blood pressure fell below 100 mmHg, ephedrine (10mg) was administrated intravenously. Further ephedrine blouses (10 mg) were given when systolic blood pressure remains low. Epinephrine (10μg) was administered for treating of ephedrine resistant hypotension. All patients received intravenous oxytocin (30IU) infusion over 1 hour period. If uterine atony persisted after the administration of oxytocin, methylergonovine (0.2 mg) was administrated intramuscularly. Anesthesiologist provided neonatal resuscitation when it was required. After delivery, apgar scores were determined at 1^{th}, 5^{th} and 10^{th}min.

Repeated dose of ephedrine displayed tachyphylaxis in all patients so epinephrine were given as the second drug for treating hypotension induced by spinal anesthesia. Increase in maternal blood pressure was recorded 1 min after epinephrine administration. Surprisingly, this medication also causes uterine relaxation in all patients after 1 to 5 min. Ease fetal extraction was indicated in thirteen patients. Neonates were delivered in case of multiple gestations, dystocia and fetal distress, had low apgar scores at first minute and after resuscitation, apgar scores increase at fifth minute after birth.

Three of fourteen patients required more than 30 unit of oxytocin infusion to achieve uterine contraction. All patients achieved adequate uterine contraction after delivery. Methylergonovine was given to four patients (including previous cesarean, multiple gestation, breech presentation and IUFD) because of uterine atony persists after the administration of oxytocin.

There was no sign of massive uterine bleeding and blood transfusion wasn't required. There were no cases of emergency hysterectomy due to persistent uterine atony unresponsive to medication.

Patient	Age (yrs)	Weight (kg)	Obstetrics records					Gestational age(weeks)	Fetal presentation	Reason for cesarean	Current medication
			D	L	Ab	P	G				
1	34	79	-	-	-	1	1	34	Breech	Premature rupture of membranes	-
2	31	75	-	1	-	2	2	39	Cephalic	Previous cesarean	
3	35	96	0	0	0	0	0	37	Cephalic	Fetal distress	Insulin
4	17	75	0	0	0	1	1	40	Cephalic	Dystocia	-
5	22	70	0	0	0	0	1	28	Cephalic	Multiple gestation	-
6	16	50	0	0	0	0	1	36	Breech	Premature rupture	-
7	18	60	0	0	0	0	1	39	Cephalic	Fetal distress	-
8	33	70	0	0	0	0	1	30	Transverse	Multiple gestation-Prematurity-preterm Labor	Levothyroxine
9	27	60	0	0	0	0	1	34	Breech	Oligohydramnios	-
10	23	68	0	0	0	1	1	26	Breech	Footling	Levothyroxine
11	23	67	0	1	2	2	4	38	Breech	Previous cesarean	-
12	19	65	0	0	0	0	1	41	Cephalic	Fetal distress	
13	22	60	0	0	0	2	2	34	Cephalic	Previous cesarean	Smoking and addiction
14	34	80	0	1	0	1	2	37	Cephalic	IUFD	

Table-I. Demographic data of 14 patients with ephedrine resistant hypotension during spinal anesthesia for emergency cesarean delivery.

D, dead; L, live; Ab, abortion; P, para; G, gravid; IUFD, intrauterine fetal death

	Preoperative		induction													
			1th min of anesthesia		3th min of anesthesia		5th min of anesthesia		10th min of anesthesia		Immediately before epinephrine administration		1th min after epinephrine administration		5th min after epinephrine administration	
Patient	BP(mmHg)	HR(bpm)	BP(mmHg)	HR(bpm)	BP(mmHg)	HR(bpm)	BP(mmHg)	HR(bpm)	BP(mmHg)	HR(bpm)	BP(mmHg)	HR(bpm)	BP(mmHg)	HR(bpm)	BP(mmHg)	HR(bpm)
1	120/80	60	90/60	65	80/60	60	90/60	70	90/60	75	85/60	90	100/70	100	120/70	120
2	120/80	70	100/70	80	90/60	80	90/60	80	90/60	80	90/60	80	100/70	90	110/70	95
3	110/70	90	90/60	85	80/60	85	80/60	85	100/70	92	90/60	90	110/70	100	100/65	94
4	130/70	90	120/70	80	110/70	80	100/70	75	90/60	75	90/60	75	110/70	85	140/80	90
5	120/75	130	110/70	120	85/65	120	95/75	115	90/80	110	80/70	120	110/85	130	100/80	120
6	110/80	80	70/50	90	90/60	90	80/60	95	100/75	90	80/60	95	110/80	112	100/75	110
7	120/80	70	110/80	80	95/80	85	110/75	80	110/75	75	90/65	80	120/80	85	125/80	100
8	120/80	80	100/70	80	100/70	80	100/70	85	100/70	85	85/60	85	110/70	90	120/70	90
9	110/70	70	100/70	75	100/70	75	100/70	75	100/70	75	90/65	75	110/70	85	110/70	90
10	110/70	90	100/70	95	100/70	95	100/70	95	100/70	95	90/65	95	106/70	105	105/70	105
11	110/70	70	100/70	60	100/70	70	120/80	75	120/80	75	95/65	70	120/80	75	120/80	80
12	120/80	70	100/70	100	100/70	100	90/70	105	90/70	105	85/50	100	110/80	110	115/80	105
13	120/80	70	100/70	75	90/70	80	100/70	75	95/75	80	85/55	70	120/80	80	140/80	90
14	100/60	95	90/50	90	100/50	85	100/60	85	110/60	85	90/65	85	110/50	95	110/60	95

Table-II. Anesthetic data of 14 patients with ephedrine resistant hypotension during spinal anesthesia for emergency cesarean delivery.

BP, blood pressure; HR, heart rate

Patient	Onset of tocolysis after epinephrine administration(min)	Fetal extraction (difficult, normal,easy)	Apgar score at 1 min	Apgar score at 5 min	Apgar score at 10 min	Total dose of oxytocin (IU) (infusion)	Administered methylergonovine (mg)	Uterine Contraction after delivery
1	2	Easy	8	9	9	30		good
2	2	Easy	1	7	8	30	0.2	good
3	1	Easy	5	8	8	30		good
4	4	easy	5	7	8	30		good
5	3	easy	5-5-5-4	7-7-7-6	7-7-7-7	30	0.2	good
6	2	easy	7	8	9	30		good
7	1	normal	7	9	9	30		good
8	2	easy	2-5-5	5-7-7	6-8-8	50		good
9	1	easy	7	8	9	50	0.2	good
10	1	easy	5	7	7	30		good
11	5	difficult	7	8	8	30		good
12	5	normal	4	6	8	30		good
13	3	easy	4	8	8	30		good
14	2	normal	0	0	0	40	0.2	Good

Table-III. Neonatal outcome of 14 patients with ephedrine resistant hypotension during spinal anesthesia for emergency cesarean delivery.

DISCUSSION

The findings of the present case series include that epinephrine helped regulate blood pressure and also induced uterine relaxation in patients with emergency cesarean section with spinal anesthesia. Surgeon admitted ease of fetal extraction and no patients experienced unusual severe bleeding, resistant uterine atony and emergency hysterectomy.

Spinal anesthesia is an effective technique whereas preventing general anesthesia and related risks in cesarean section. However, spinal anesthesia for cesarean section is not without risk, because of induced maternal hypotension which can cause maternal detrimental effects and fetal distress. Spinal anesthesia-induced hypotension is triggered by sympathetic blockade which leads to reduction in peripheral vascular resistance and venous return.[7] Many strategies have been developed to minimize the impact of hypotension. In the present case series, we used ephedrine as the first line vasopressor for management of maternal spinal hypotension but after three 10 mg doses, tachyphylaxis was induced. Epinephrine 5-10 μg was injected intravenously when ephedrine was ineffective. Epinephrine isn't the preferred vasopressor for treating hypotension during spinal anesthesia for cesarean section, but should be available in operating room. In the present study, because of limited access to an alpha-1 adrenergic receptor agonist, in a period of time, epinephrine was used as the second line vasopressor. Surprisingly, epinephrine resulted uterine relaxation within 1 to 5 min and fetal were extracted easily. Emergent uterine relaxation is required for situations like internal podalic version, retained placenta, inverted uterus and breech delivery during cesarean section.[8] Halogenated anesthetics were used traditionally for smooth muscle uterine relaxation in emergency situation, but it is required endotracheal intubation using rapid sequence induction of anesthesia and can be a very risky option. However, a way of avoiding general anesthesia and providing transient uterine relaxation for full stomach patients would be beneficial.

Nitroglycerin, as a short acting smooth muscle relaxant acts via increase in synthesis of cyclic guanosine monophosphate (cGMP) and induction cGMP-mediated dephosphorylation of myosin light chain.[9] Mayer[10] discuses a case of cesarean section for twin pregnancy at 30 weeks. After initiation of spinal anesthesia, systolic blood pressure decreased from 120 to 95 mmHg. Following the request for uterine relaxation, nitroglycerin was administrated to facilitate fetal extraction. Systolic blood pressure also reduced to 85 mmHg but increased after ephedrine administration.

Despite tocolytic (uterine relaxant) effect, hypotensive properties of nitroglycerin during general anesthesia have been described.[11-13] As a result, an important concern about this drug in spinal anesthesia for cesarean section has been the excessive induced hypotension. So it can be assumed that nitroglycerin is not good selection for uterine relaxation in patients with hypotension due to sympathetic block after spinal anesthesia.

In general, drugs with myometrial beta-2 adernoreceptor agonist activity have been used for uterine relaxation.[14] Intravenous epinephrine, at low and high doses, can respectively stimulate beta 2, beta 1 and alpha 1 adrenoceptors . It relaxes the smooth muscles by activating beta-2 adrenoceptors and enhances the rate and force of heart contraction through beta-1 adrenoceptors.[15] The combination of these effects of epinephrine is desirable during spinal anesthesia for cesarean section. Beyond the effect on hypotension treatment, epinephrine is a surprisingly a cause of uterine relaxation in this study. The findings, generate hypothesis that epinephrine is a suitable choice, not only for regulation of blood pressure but also surprisingly for facilitation of uterine relaxation in patients with emergency cesarean section with spinal anesthesia induced hypotension needed uterine relaxation for fetal extraction delivery.

So in summary, the present case series provided information to introduce epinephrine, for treatment of ephedrine resistant hypotension and providing

adequate uterine relaxation in spinal anesthesia for cesarean section. However the findings should be expounded discreetly and considered as basic step that will inform subsequent studies on administration of epinephrine as a uterine relaxant. Until completion of studies, the usage of epinephrine should be avoided in hypertensive pregnant patients (preeclampsia and eclampsia).

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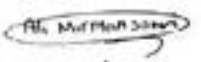
1	Ali Mirmansouri M.D	Study design, Data analysis	
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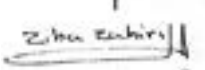
4	Ziba Zahiri Sorouri M.D	Data collection	
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