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Original Research Paper

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THE ROLE OF AUTONOMIC FUNCTION TEST FOR PREDICTION OF HYPOTENSION IN PATIENTS UNDERGOING CESAREAN SECTION UNDER SPINAL ANESTHESIA

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ABSTRACT Maternal hypotension is common complication during obstetric spinal anesthesia. We investigated the role of autonomic function test for predicting maternal hypotension during spinal anesthesia for cesarean section. Thirty two parturients undergoing cesarean section under spinal anesthesia were enrolled. Sympathetic function test included diastolic blood pressure changes response to hand grip and systolic blood pressure changes response to postural change(supine to standing position). Parasympathetic function test included heart rate responses to deep breathing and heart rate responses to postural change(supine to standing position). Hypotension occurred in 22/32 parturients. There was not correlation in sympathetic dysfunction and hypotension incidence. But the incidence of hypotension in parasympathetic dysfunction positive group and negative group was 12/12(100%) and 10/20(50%) respectively, and there was significant difference (p=0.004). This study suggested that the autonomic function test may be useful methods to predict maternal hypotension during spinal anesthesia for cesarean section.

KEYWORDS : Autonomic nervous system, Cesarean section, Hypotension, Spinal anesthesia

INTRODUCTION

Spinal anesthesia is used as the standard anesthetic technique for Cesarean sections (C-section) to prevent complications related to airway management during general anesthesia, such as intubation failure or airway aspiration (Algert et al., 2009). Spinal anesthesia lowers peripheral vascular resistance by blocking sympathetic nerves, which can cause maternal hypotension (Miller et al., 2009; Langesæter, Rosseland, & Stubhaug, 2008).

Maternal hypotension induces unpleasant symptoms, such as dyspnea, nausea, and vomiting caused by reduced blood flow to the brain. When severe hypotension persists, it may lead to serious complications, such as loss of consciousness, cardiovascular collapse, and ischemia in organs. Furthermore, prolonged maternal hypotension may cause reduced uterine placental blood flow and fetal distress, which may result in bradycardia, hypoxia, and acidosis in the fetus (Ebner, Barcohana, & Bartoshuk, 1960; Zilianti, Salazar, Aller, & Agoero, 1970). Therefore, it is important to predict and prevent maternal hypotension.

Studies have reported that heart rate variability (Sakata et al., 2017; Hanss et al., 2005), pleth variability index (Sun & Huang, 2014), baseline heart rate (HR) (Yokose, Mihara, Sugawara, & Goto, 2015; Frölich & Caton, 2002), cerebral oxygen saturation (Sun, Liu, & Huang, 2016), and pulse transit time (Sharwood-Smith, Bruce, & Drummond, 2005) can be used to predict maternal hypotension during C-sections under spinal anesthesia. However, it is difficult to measure these indices in the recovery or operating rooms immediately before surgery because of the required programs and instruments. It was hypothesized that the incidence of maternal hypotension during C-sections under spinal anesthesia was associated with autonomic nervous system function, so this study investigated the correlation between autonomic dysfunction and incidence of maternal hypotension using an autonomic function test, which can be performed by simply monitoring maternal blood pressure and heart rate.

METHODS

This study was approved by the Institutional Review Board at Daegu Fatima Hospital and informed consent was obtained from all participants (Reg. No. DFH17MRIO355).

The subjects in this study were patients undergoing non-urgent C-sections under spinal anesthesia who were American Society of Anesthesiology physical status class I or II and who had gestational ages of 36 to 41 weeks. Patients undergoing emergency surgery, with twins, who had pre-eclampsia, or who took steroids, diuretics, anticholinergic agents, cholinergic agents, antidepressants, or antihistamines were excluded from the study. The participants fasted for 8 hours prior to the autonomic function test and urinated naturally.

Of the 35 pregnant women examined in this study, 3 were withdrawn as they were converted to general anesthesia after spinal anesthesia failed before C-section was resumed.

First, patients rested in a supine position for 20 minutes. Then their systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure were measured noninvasively from the right upper arm and HR was measured using an electrocardiograph. These values were used as controls for the measurements taken during the autonomic function test.

Parasympathetic functions were evaluated by testing HR changes while taking a deep breath and after standing up. The Valsalva maneuver was not performed to prevent fetal hypoxia. Sympathetic functions were evaluated by observing DBP changes during a hand grip test and SBP changes after standing up. Tests were performed in order to observe HR changes during deep breathing, DBP changes during a handgrip test, and HR and blood pressure changes after standing up (Kim et al., 2006; Miller et al., 2009). Patients rested for 10 minutes in a supine position between tests.

Sympathetic function test

- **Hand grip test**

During the hand grip test, the difference between peak DBP and DBP immediately before gripping was evaluated. Patients who had a difference of 16 mmHg or less were determined to have tested positive for sympathetic abnormality.

- **Supine-to-standing-position test**

Patients were instructed to stand without assistance within four seconds. Patients who had a difference of 10 mmHg or more between supine and standing position SBP ([redacted]

Parasympathetic function test

- **Deep breathing test**

For the deep breathing test, patients were instructed to breathe six times per minute. Each breath was to be a slow inhalation for five seconds and a slow exhalation for five seconds. They were told not to stop, cough, laugh, talk, or move while breathing and were asked to breathe strongly to reach maximum tidal volume. Patients who had a heart rate variability between inhalation and exhalation, which was the difference between maximum and minimum HR, of 15 or less were considered to have tested positive for parasympathetic abnormality.

- **Supine-to-standing-position test**

Patients were instructed to stand up without assistance within four seconds. HRs were compared using the 30/15 ratio in which the longest R-R interval was at beat 30 and the shortest R-R interval was at beat 15. Patients with ratios of 1.04 or less were considered to have tested positive for parasympathetic abnormality R-R intervals were measured to within 0.1 mm by using an ECG patient monitoring device (Anesthesia V24C, Agilent, Germany).

Autonomic tests were performed in the recovery room immediately before surgery. Patients who had positive results for both sympathetic function tests were defined as having sympathetic dysfunction and those who had positive results for both parasympathetic function tests were defined as having parasympathetic dysfunction. After the tests, patients were moved to the operating room and spinal anesthesia was induced by inserting a 25-gauage pencan needle into the intrathecal space in the left lateral position through the L3-4 vertebra to inject a mixture of 9 mg of heavy Marcaine (bupivacaine) and 20 mcg of fentanyl, after which oxygen was supplied at 5 L/min through an oxygen mask with the patient in the supine position. A crystalloid solution was injected at 10 mg/kg/h from the induction of anesthesia until delivery. The dose was reduced to a maintenance dose after delivery.

Until delivery of the neonate or until 20 minutes after induction of spinal anesthesia, patient HR and blood pressure were measured in one-minute intervals. The interval was increased to five minutes once blood pressure stabilized after delivery. After delivery, the neonate's 5-minute APGAR score was recorded.

A total of 100 mcg of phenylephrine (George, McKeen, Columb, & Habib, 2010) was intravenously administered when hypotension occurred, which was defined as SBP decreasing 20% or more below the initial SBP prior to spinal anesthesia (KlÖHR, Roth, Hofmann, Rossaint, & Heesen, 2010), and 0.5 mg of atropine was intravenously administered when bradycardia, which was defined as HR falling to 50 bpm or less, occurred. The presence of symptoms such as nausea, vomiting, dizziness, and headache were recorded.

The sensory block level was checked five minutes after induction using an alcohol rub. Length of surgery, duration of anesthesia, and volume of intraoperative blood loss were recorded.

STATISTICAL ANALYSIS

Normally distributed data were analyzed with a student t-test and non-normal data were analyzed with a Mann-Whitney test. All statistical analysis was performed using IBM SPSS version 21.0 (IBM Co., USA). All data were expressed as mean ± SD or median [interquartile range]

The area under the receiver operating characteristic curve (AUC) in each of the two parasympathetic tests and two sympathetic tests, the cut-off value, sensitivity, and specificity were analyzed.

The correlations between parasympathetic dysfunction, sympathetic dysfunction, and hypotension were analyzed using cross correlation analysis. The same analysis was used to examine the correlation between the incidence of side effects and use of vasopressor agents. The significance level was set to $p < 0.05$.

RESULT

Of the remaining 32 participants, 9 tested positive for sympathetic dysfunction while 23 did not and 12 tested positive for parasympathetic dysfunction while 20 did not. A total of 22 patients (68.7%) developed hypotension (Fig. 1).

The AUC of the supine-to-standing test as a predictor of hypotension was below 0.5 (Fig. 2).

The AUC of the deep breathing test as a predictor of hypotension was 0.664 with a cut-off value of 10.50, a sensitivity of 59%, and a specificity of 60% (Fig. 2). The AUC of the hand grip test as a predictor of hypotension was 0.539 with a cut-off value of 7.5, a sensitivity of 45.5%, and a specificity of 40% (Fig. 2).

There were no significant differences in the demographic data between the patients that showed sympathetic dysfunction and those that did not (Table 1). The incidence of hypotension in these two groups was 55.6% (5/9) and 73.9% (17/23), respectively, showing that the incidence of hypotension was not significantly correlated with the incidence of sympathetic dysfunction (Table 2).

There were no significant differences in the demographic data between the patients that showed parasympathetic dysfunction and those that did not (Table 3). However, the incidence of hypotension in these groups was 100% (12/12) and 50% (10/20), respectively, showing that the incidence of hypotension was significantly correlated with the incidence of parasympathetic dysfunction. The phenylephrine use frequency significantly differed but it had no effect on neonates' 5-minute APGAR scores (Table 4).

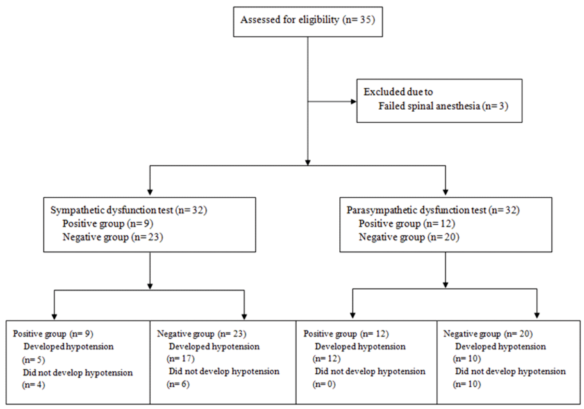

Fig. 1. Flow diagram of the Autonomic function test & developed hypotension

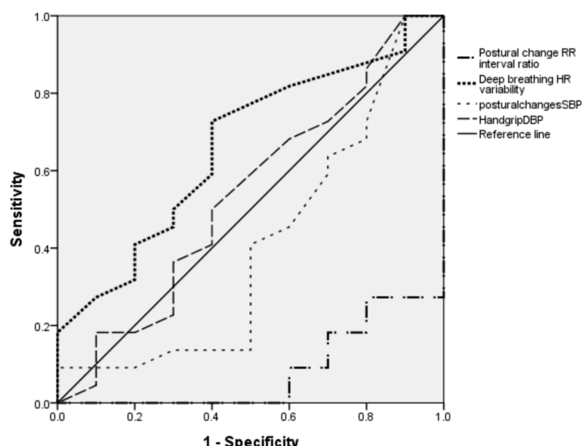

Figure 2. Receiver operating characteristic curve for each autonomic function tests.

Value for area under the ROC curve ;

RR interval ratio in postural change : 0.082 (95% CI 0 to 0.176)

Heart rate variability when deep breathing : 0.664 (95% CI 0.462 to 0.865)

Systolic blood pressure in postural changes : 0.405 (95% CI 0.173 to

0.636)

Diastolic blood pressure in handgrip test : 0.539 (95% CI 0.312 to 0.765)

Table 1. Patient characteristics (Sympathetic dysfunction test Positive group vs. Negative group).

	Sympathetic dysfunction test	
	Positive (N=9)	**Negative (N=23)**
Age (years)	32.33 ± 4.87	34.48 ± 3.99
Height (cm)	161.72 ± 7.28	161.53 ± 6.73
Weight (kg)	78.98 ± 12.00	76.11 ± 14.16
Gestational age (weeks)	38.40 (38.00, 38.92)	38.10 (37.60, 38.38)
Sensory block level	8 [6 - 8]	6 [6 - 8]
Surgical time (min)	40.11 ± 9.33	37.87 ± 8.18
Anesthesia time (min)	56.78 ± 8.50	55.83 ± 9.04
Intravenous fluid (mL)	614.44 ± 287.19	506.52 ± 207.18
Estimated blood loss (mL)	468.89 ± 156.00	386.96 ± 183.26
Urine output (mL)	116.67 ± 89.03	110.43 ± 78.30

Data are mean ± SD or median [IQR]. N : number

Table 2. Hemodynamic data (Sympathetic dysfunction test Positive group vs. Negative group).

	Sympathetic dysfunction test		P value
	Positive (N = 9)	**Negative (N =23)**	
Hypotension before delivery (%)	4 (44.4%)	12 (52.2%)	1.000
Hypotension after delivery	4 (44.4%)	12 (52.2%)	1.000
Hypotension during operation	5 (55.6%)	17 (73.9%)	0.407
Phenylephrine use	4 (44.4%)	17 (73.9%)	0.703
Frequency of Phenylephrine	1 [0 - 2]	2 [0 - 3]	0.247
Apgar score	10 [9 - 10]	10 [9 - 10]	0.681

Data are mean ± SD or median [IQR]. N : number

Table 2. Hemodynamic data (Sympathetic dysfunction test Positive group vs. Negative group).

	Parasympathetic dysfunction test	
	Positive (N = 12)	**Negative (n = 20)**
Age (years)	35.25 ± 4.92	33.05 ± 3.75
Height (cm)	163.30 ± 5.41	130.55 ± 7.342
Weight (kg)	80.7 ± 14.36	76.62 ± 12.72
Gestational age (weeks)	38.20 (37.70,39.88)	38.20 (37.60, 38.58)
Sensory block level	6 [6 - 8]	8 [6 - 8]
Surgical time (min)	38.08 ± 7.97	38.75 ± 8.88
Anesthesia time (min)	56.92 ± 8.81	55.60 ± 8.93
Intravenous fluid (mL)	487.50 ± 109.72	566.50 ± 269.08
Estimated blood loss (mL)	372.50 ±121.30	432.50 ± 203.67
Urine output (mL)	89.17 ± 72.25	126.00 ± 81.59

Data are mean ± SD or median [IQR]. N : number

Table 4. Hemodynamic data (Parasympathetic dysfunction test Positive group vs. Negative group).

	Parasympathetic dysfunction test		P value
	Positive (N = 12)	**Negative (N = 20)**	
Hypotension before delivery (%)	9 (75%)	7 (35%)	0.066
Hypotension after delivery	9 (75%)	7 (35%)	0.066
Hypotension during operation	12 (100%)	10 (50%)	0.004
Phenylephrine use	12 (100%)	9 (45%)	0.002
Frequency of Phenylephrine	2.5 [1.25 – 3.75]	0.5 [0 – 2]	0.003
Dose of Phenylephrine	266.67 ± 143.55	105.0 ± 123.44	0.004
Apgar score	10 [9 – 10]	10 [9 – 10]	1.000

Data are mean ± SD or median [IQR]. N : number

DISCUSSION

Pregnancy induces hemodynamic changes in the mother. During pregnancy, hormonal effects lead to reduced systemic vascular tone and increased vascular volume, which in turn causes a reduction in cardiac afterload and an increase in cardiac preload, thereby increasing cardiac output. Compared to non-pregnant women, women experiencing normal pregnancy show elevated levels of sympathetic activity. This activity is greater in women with gestational hypertension. Unlike sympathetic activity, peripheral vascular resistance decreases. In late pregnancy, the baroreflex function decreases as a result of increased hormones and blood volume. The consequent weakening of the inhibitory regulation of the baroreflex against the sympathetic nervous system is believed to be one of the factors that increases sympathetic activity (Fu & Levine, 2009).

In the present study, the AUCs for all of the autonomic function tests were below 0.7, which suggests that they were not adequate predictors of hypotension after spinal anesthesia in pregnant women.

The incidence of hypotension was not significantly correlated with sympathetic dysfunction. Of the 32 patients, 11 (34.4%) tested positive during the supine-to-standing test and 17 (53.1%) actually showed an elevation, rather than a decline, in SBP upon standing from a supine position. This result may have been the result of the fact that, compared to non-pregnant women, pregnant women show elevated sympathetic activity and vascular capacitance (Frölich & Caton, 2002) smaller reductions of cardiac output upon standing (Pyörälä, 1966). Furthermore, sympathetic activity may have been more elevated due to tension and anxiety as the tests were performed immediately before the C-section.

In the hand grip test, DBP was elevated as a result of the baroreflex control and sympathetic activity (Kamiya et al., 2001). A DBP increase less than the normal level (> 16 mmHg) in the hand grip test was accepted as an indicator of sympathetic abnormality (Ewing, Irving, Kerr, Wildsmith, & Clarke, 1974). In the present study, 29 of the 32 patients (90.6%) showed a DBP increase of less than 16 mmHg. This result is inconsistent with the fact that pregnant women show elevated sympathetic activity, which may have been the result of the fact that, compared to non-pregnant women, pregnant women have a reduced sympathetic regulation of vascular resistance due to the effects of estrogen, though this mechanism is still unclear (Fu & Levine, 2009). It was hypothesized that most of the participants tested positive in the hand grip test because the sympathetic regulation of vascular resistance was reduced even in pregnant women without sympathetic activity problems, which hindered an appropriate rise in DBP after the patients conducted the hand grip test. Furthermore, the fact that pregnant women have reduced baroreflex sensitivity may have been another cause of these results (Greenwood, Scott, Stoker, Walker, & Mary, 2001).

Unlike the incidence of sympathetic dysfunction, the incidence of hypotension was correlated with the presence of parasympathetic dysfunction. The incidence of hypotension was higher in the parasympathetic dysfunction group than in the non-parasympathetic dysfunction group.

Sun et al. (2014) reported that hypotension after spinal anesthesia is affected by preoperative sympathetic activity and effective circulating blood volume. They explained that hypotension is developed as the reduced systemic vascular resistance, arterial and venous blood pooling.

In a study analyzing the correlation between hypotension and autonomic dysfunction during C-sections under spinal anesthesia using heart rate variability, Robert et al. (2005) reported that the group of pregnant women who developed moderate to severe hypotension showed a significantly higher sympathetic and lower parasympathetic drives than those the group of pregnant women who only had mild hypotension. This result reflects the fact that sympathetic and parasympathetic activity critically affects hypotension during C-section under spinal anesthesia.

In the present study, patients' sympathetic drives could not be accurately calculated using autonomic function tests, as the hand grip test was believed to be inadequate at showing actual patient sympathetic activity. However, the incidence of hypotension was substantially higher among mothers with parasympathetic dysfunction, and the frequency and average dose of phenylephrine were also significantly higher in the same group (2.5 times /0.5 times, 266.67 ± 143.55 mcg / 105.0 ± 123.44 mcg). Furthermore, two patients in the parasympathetic dysfunction group were administered phenylephrine five times due to severe hypotension. This can be explained by the correlation between parasympathetic and sympathetic nerve function. The sympathetic activity increased in normal pregnant women compared with non-pregnant women, and the presence of parasympathetic dysfunction in the hemodynamic state can lead to a relative large increase of sympathetic activity. This may explain the markedly higher incidence of hypotension caused by sympathetic nervous block after spinal anesthesia.

Wamalwa et al. (2012) and Corke et al. (1982) reported that short maternal hypotension that persisted for less than two minutes did not have a significant impact on neonates' 5-minute APGAR scores and the incidence of neonatal acidemia. These findings highlight the importance of the prediction and early discovery of maternal hypotension.

Limitation

Autonomic tests were conducted immediately before entering the operating room, so the participants may have had more autonomic activity than pregnant women at rest due to the anxiety and tension from the impending C-section. Further, this was a pilot test with an insufficient number of cases to achieve normal distribution, so subsequent studies need to have greater sample sizes. Finally, a significant association between parasympathetic activity and incidence of hypotension during C-section under spinal anesthesia was confirmed based on autonomic function tests, but it was difficult to accurately examine the degree to which each patient's sympathetic functions decreased.

CONCLUSION

In conclusion, maternal hypotension after spinal anesthesia during C-section may induce maternal complications, and fetal distress syndrome, so it is critical to be able to predict and quickly correct the condition. This study's findings suggest that parasympathetic function tests can be used as predictors of maternal hypotension.

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