



Comparison between Twin and Singleton Pregnancies on the Incidence of Hypotension and Vasopressor Requirement during Spinal Anesthesia for Cesarean Delivery

제왕절개 수술을 받는 쌍태임신 산모와 단태임신 산모 간 척추 마취 중 저혈압 발생율 및 승압제 요구량의 비교

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이 논문을 의학박사 학위 논문으로 제출함

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Abstract

Comparison between Twin and Singleton Pregnancies on the Incidence of Hypotension and Vasopressor Requirement during Spinal Anesthesia for Cesarean Delivery

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Introduction: Spinal anesthesia (SA) is a preferred and widely used anesthetic method for cesarean delivery (CD). However, maternal hypotension is a common side effect during SA. With the development of assisted reproductive technologies, the number of multifetal pregnancies has recently increased. Nevertheless, there are only a few studies investigating complications including hypotension associated with SA during CD for multifetal pregnancy. The aim of our study is to compare hypotension incidence and vasopressor requirement in parturients with twin versus singleton pregnancies during SA for elective CD.

Methods: Pregnant women undergoing SA for elective CD between June 2022 and December 2022 were enrolled in this study. On arrival in the operating room, all parturients underwent standard monitoring. Their baseline parameters were recorded in the supine position before SA. SA was performed using hyperbaric 0.5% bupivacaine 8 mg with fentanyl 15mcg. The blood pressure was automatically measured non-invasively at 1-minute intervals as the established protocol after SA. If hypotension, defined as a drop in systolic blood pressure (SBP) to <80% of baseline SBP, occurred, intravenous (IV) phenylephrine 100 mcg was administered. If the blood pressure did not increase to \geq 80% of the baseline SBP despite repeated administration of 100 mcg of phenylephrine, the dose of phenylephrine was increased to 200 mcg.

Results: We analyzed 111 parturients with singleton pregnancy and 55 parturients with twin pregnancy. There was no significant difference between the two groups in the patient characteristics except for two variables, gestational age and the sum of total birth weight of the newborns. There was a significant difference in SBP between the two groups over time (p

= 0.023), namely, SBP 5 minutes after SA was significantly lower in the singleton group than in the twin group (100 \pm 17 vs. 108 \pm 19, p = 0.014). Hypotension immediately before delivery was observed in 77 of 111 (69.4%) women with singleton pregnancy and in 35 of 55 (63.6%) women with twin pregnancy (p = 0.458). No differences in the use of phenylephrine were observed between the two groups.

Conclusions: The incidence of hypotension and the amount of vasopressor required during SA in twin pregnancies were not significantly different from those of singleton pregnancies. There are few studies related to the use of vasopressors in twin pregnancy during SA. Our findings could help develop a strategy for preparing for hypotension while supporting the appropriate use of limited medical resources.

Key words: Cesarean Delivery, Hypotension, Spinal Anesthesia, Twin, Vasopressor

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Introduction

Spinal anesthesia (SA) is a preferred and widely used anesthetic method for cesarean delivery (CD) because it has several advantages over other anesthetic methods.¹⁾ However, maternal hypotension is a common side effect during SA undergoing CD.²⁾ When hypotension occurs, the parturient develops symptoms such as nausea, vomiting, and dizziness, and the fetus may develop acidosis due to a decrease in placental blood flow. Therefore, when spinal hypotension occurs, it is necessary to normalize blood pressure by using a vasopressor. Hypotension can be prevented through continuous infusion of vasopressors during SA.^{3,4)}

Meanwhile, with the development of assisted reproductive technologies, the number of multifetal pregnancies has recently increased.^{5, 6)} The majority of multifetal pregnancies are twin pregnancies.^{6, 7)} Although the optimal mode of delivery in twin pregnancies remains controversial, it is not uncommon for the second twin to need to be delivered by CD after vaginal birth of the first twin.^{8, 9)} The rising incidence of multifetal pregnancies induced by the increased use of assisted reproductive technology has led to higher rates of CDs.¹⁰⁾ Nevertheless, there are only a few studies on SA during CD for multifetal pregnancy because the aortocaval compression is greater than that of singleton pregnancy and the extent of its blockage during SA can spread upward.¹¹⁾ However, despite widespread acceptance of this view, few quantitative data are available to support it.^{12, 13)}

The aim of our study was to compare (1) the hypotension incidence and (2) the vasopressor requirement between parturients with twin and singleton pregnancies during SA for elective CD.

Materials and Methods

Trial design and ethics

This prospective observational study was conducted in a large tertiary single center. The study protocol was approved by our institutional review board (protocol number 2022-0598) and was registered with the Clinical Research Information Service (KCT0007389; principal investigator: W-JC; date of first registration: June 14, 2022). The study was conducted from June 2022 to December 2022. Written informed consent was obtained from every participant.

Study population

Pregnant women undergoing SA for elective CD between June 2022 and December 2022 were enrolled in this study. Healthy parturients with an American Society of Anesthesiologists (ASA) physical status class 2 with singleton or twin pregnancies aged >20 and \leq 45 years old were included. Pregnant women with known cardiovascular disease, hypertensive disorders, diabetes mellitus, or placenta previa were excluded. Patients with inadequate sensory block level below T6 were excluded from the analysis.

Monitoring and data collection

On arrival in the operating room, all parturients underwent standard monitoring, including 3lead electrocardiography (ECG), non-invasive blood pressure (NIBP), and pulse oximetry. After a brief resting period, baseline values for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and heart rate (HR) were determined by calculating the mean of 3 consecutive measurements at 1-minute intervals. Through lead Π , continuous ECG waveforms were observed, with the values obtained from ECG analysis before anesthesia set as the baseline values. The baseline parameters were recorded in the supine position before anesthetic induction. All parameters were monitored by one anesthesiologist during CD. NIBP was measured automatically in 1-minute intervals to treat spinal hypotension as the established protocol after SA. In brief, when maternal hypotension occurs, vasopressor is administered intravenously, and the vasopressor requirement is measured. While collecting factors that may affect the occurrence of hypotension during SA, QT interval (QTI) data from the ECG monitoring was also collected. The QTI and corrected QTI (QTc) were measured automatically as 1-minute average values from the patient monitor (IntelliVue MP70, Philips Medizin Systeme Boeblingen GmbH, Boeblingen 71034, Germany) connected to the parturient with an ECG lead. The QTI measured via the patient monitor was corrected for HR using Bazett's formula (QTc = QTI/RR interval^{1/2}).

Spinal anesthesia (SA) and management of hypotension

SA was performed according to the following protocol. In all cases, SA was performed at the L3-4 or L4-5 vertebral interspaces with the patient in the left lateral decubitus position using combined spinal epidural anesthesia. After skin infiltration with lidocaine, an 18-gauge Tuohy needle was placed in the epidural space using the loss of resistance technique. Once a free flow of clear cerebrospinal fluid was observed in the 27-gauge Sprotte spinal needle inserted through the Tuohy needle using the needle-through-needle technique, hyperbaric 0.5% bupivacaine 8 mg with fentanyl 15 mcg was administered intrathecally. After placement and fixation of an epidural catheter, the patients were immediately turned supine from the left lateral decubitus position. Administration of local anesthetic via the epidural catheter was done only for postoperative analgesia. Oxygen was administered via a nasal prong at 2 L/min. The upper sensory level of the block to cold was measured using alcohol swabs 10 minutes after spinal injection and surgery only began when the sensory block reached the T6 level. To prevent maternal hypotension, crystalloid was infused rapidly (16-20 ml/kg/h) and the uterus was displaced to the left. Hypotension was defined as (1) a drop in SBP to <80% of baseline SBP and/or (2) complaints of symptoms (nausea, vomiting, dizziness, and restlessness) related to hypotension even if the symptoms were not accompanied by hypotension.⁴⁾ Hypotension was treated with intravenous phenylephrine 100 mcg as required. If the decreased SBP did not increase to $\geq 80\%$ of the baseline SBP in two consecutive measurements despite two bolus administration of phenylephrine 100 mcg, the dose of administered phenylephrine was increased to 200 mcg. If after two consecutive administrations of 200 mcg phenylephrine the SBP did not increase to \geq 80% of the baseline SBP, ephedrine 5 mg was administered. If there was a successful increase in SBP \geq 80% of the baseline SBP with the increased dose of phenylephrine, the increased dose of phenylephrine was administered if maternal hypotension occurred again. After newborn delivery, intravenous carbetocin of 100 mcg for uterine contraction was administered slowly for 1 minute. The primary outcome of this study was the incidence of hypotension and the secondary outcome was the vasopressor requirement before delivery. The total dose of vasopressor given until this endpoint was measured as the vasopressor requirement. The protocol continued until the end of the surgery when data collection stopped.

Sample size

The sample size was based on recent historical data obtained from clinical cases in our department for which we had used a similar anesthetic and vasopressor regimen. Using the software package PASS 15.0 (NCSS, LLC., Kaysville, UT, USA. www.ncss.com), a study with 55 in the twin group and 110 in the singleton group achieved 80.04% power to detect a difference in hypotension incidence between the group proportions of 0.20. It was assumed that the incidence of hypotension was higher in twins than in singletons. The proportion in the twin group was assumed to be 0.60 under the null hypothesis and 0.80 under the alternative hypothesis. The proportion in the singleton group was 0.60. The test statistic used was the two-sided Z-Test with unpooled variance. The significance level of the test is 0.05. Unequal sample sizes according to the group were chosen deliberately because, in the planning of this study, we anticipated that recruitment of patients with twin pregnancy would be slow due to the limited number of suitable and consenting patients present in our center.

Statistical analysis

Data are expressed as means \pm standard deviation (SD) or medians (interquartile range) for continuous variables and as numbers (percentage) for categorical variables. We compared the patient characteristics and baseline hemodynamic data between groups using independent t-tests for continuous variables and chi-squared for categorical variables. Two-way repeated measures analysis of variance (ANOVA) was used for inter-group comparisons. When there were significant differences, Bonferroni correction was applied to detect the exact difference between groups. All statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). P <0.05 was considered statistically significant.

Results

A total of 167 parturients undergoing elective CD under SA were assessed for eligibility (Fig. 1). CD was completed under SA for 166 patients except for one parturient with twin pregnancy following conversion to general anesthesia. Finally, a total of 166 patients were enrolled in the current study: 111 parturients with singleton pregnancy and 55 parturients with twin pregnancy. The upper sensory level of the block was measured over T6 for all the patients. Table 1 lists the maternal and neonatal demographic data, and the anesthetic data. There was no significant difference between the two groups in the patient characteristics except for two variables, gestational age (singleton: 38 weeks [38–38] vs. twin: 36 weeks [36–37], p < 0.001) and the sum of the total birth weight of the newborns (singleton: $3.2 \pm 0.4 \text{ kg vs. twin: } 5.1 \pm 0.5 \text{ kg, p} < 0.001$).

Hemodynamic data of the two groups are listed in Table 2. Hypotension immediately before delivery was observed in 77 of 111 (69.4%) women with singleton pregnancy and in 35 of 55 (63.6%) women with twin pregnancy (p = 0.458). One parturient with singleton pregnancy complained of nausea and was defined as hypotension.

Statistically significant differences between the two groups appeared in the SBP during CD (p = 0.023). SBP was significantly higher in the twin group (108 ± 19) compared with the singleton group (100 ± 17) at 5 minutes after SA (p = 0.014) (Fig. 2).

The vasopressor requirements are summarized in Table 2. No differences in the use of phenylephrine were observed between the two groups before delivery (100 mcg [0 mcg–200 mcg] vs. 100 mcg [0 mcg–200 mcg], p = 0.791). No ephedrine was used in iether groups. Spearman's rank correlation analysis to investigate the relationship between the sum of the total birth weight of the newborns and the total amount of phenylephrine showed no significant correlation (correlation coefficient = 0.045, p = 0.567). In the patients with hypotension, only one bolus administration of phenylephrine was the most common, and the number of doses was the same in both groups.

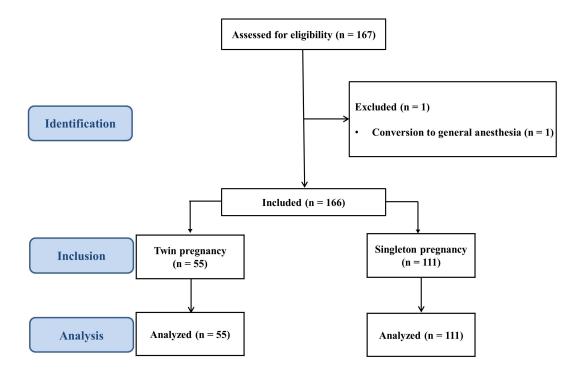


Fig. 1. STROBE study flow diagram.

Table 1. Patient characteristics

	Singleton pregnancy (n = 111)	Twin pregnancy (n = 55)	<i>P</i> value
Age (years)	35 ± 4	36 ± 3	0.719
Weight (kg)	70.2 ± 9.9	71.8 ± 8.8	0.307
Height (cm)	162.0 ± 5.5	163.1 ± 4.8	0.198
Gestational age (weeks)	38 (38–38)	36 (36–37)	< 0.001
Induction to delivery time (min)	22.2 ± 4.3	22.7 ± 4.7	0.512
Total birth weight of newborns (kg)	3.2 ± 0.4	5.1 ± 0.5	< 0.001
Apgar score at 1 min	9 (8–9)	1 st 9 (8–9) 2 nd 9 (8–9)	
Apgar score at 5 min	9 (9–10)	1 st 9 (9–10) 2 nd 9 (9–10)	

Data are presented as mean \pm SD, or median (IQR).

Abbreviations: SD, standard deviation; IQR, interquartile range.

Table 2. Comparison of hemodynamic data between two groups

	Singleton pregnancy		Twin pregnancy		<i>P</i> value	
	Total (n = 111)	Hypotension $(n = 77)$	Total (n = 55)	Hypotension $(n = 35)$	Total	Hypotension
Baseline SBP (mmHg)	120 ± 11	120 ± 11	122 ± 10	120 ± 10	0.325	0.968
Baseline DBP (mmHg)	79 ± 8	79 ± 8	82 ± 9	81 ± 9	0.017	0.400
Baseline MBP (mmHg)	92 ± 8	92 ± 8	95 ± 9	93 ± 8	0.033	0.585
Baseline HR (beast/min)	84 ± 14	85 ± 14	85 ± 14	87 ± 15	0.708	0.568
Baseline QTI (ms)	383 ± 32	379 ± 30	378 ± 28	376 ± 28	0.304	0.575
Baseline QTc (ms)	440 ± 22	440 ± 22	440 ± 21	443 ± 21	0.890	0.454
Dose of phenylephrine (mcg)	100 (0-200)	200 (100-300)	100 (0-200)	200 (100-300)	0.791	0.751
Hypotension, n (%)	77 (69.4)		35 (63.6)		0.458	

Table 2. continued

	Singleton pregnancy			Twin pregnancy			<i>P</i> value	
	Total (n = 111)	Hypotension $(n = 77)$		Total ($n = 55$)	Hypotension $(n = 35)$		Total	Hypotension
The lowest SBP among hypotension (mmHg)		83 ± 12			84 ± 12			0.687
		1	32 (41.6)		1	14 (40.0)		
Numbers of phenylephrine administration,		2	21 (27.3)		2	9 (25.7)		
n (%)		3	11 (14.3)		3	6 (17.1)		
		≥4	13 (16.9)		≥4	6 (17.1)		

Values are expressed as mean ± SD, median (IQR), or number (percentage).

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; QTI, QT interval; QTc,

corrected QT interval; ms, milliseconds; SD, standard deviation; IQR, interquartile range.

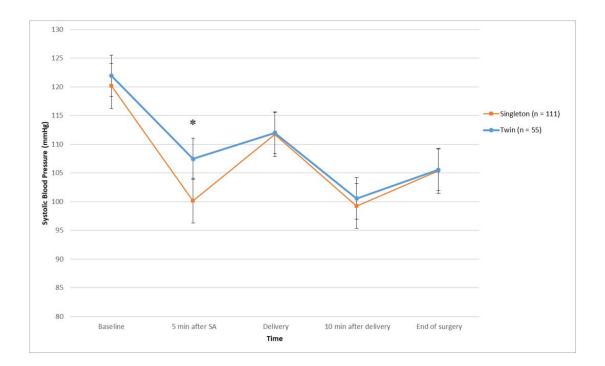


Fig. 2. Changes in systolic blood pressure (SBP) during cesarean delivery.

SBP was recorded at baseline, 5 minutes after spinal anesthesia (SA), delivery, 10 minutes after delivery, and at the end of surgery. Data are shown as mean \pm standard deviation. *P <0.05, singleton vs. twin group.

Discussion

This prospective observational study found significant changes in SBP over time after spinal anesthetic drug injection between singleton and twin pregnancies during CD. There was a significant difference in SBP between the two groups at 5 minutes after SA. However, we did not observe a difference in the incidence of hypotension or vasopressor requirements between the two groups before delivery.

Our results call into question the theory in the literature suggesting that multiple gestation is associated with a higher incidence of maternal hypotension than singleton pregnancy during SA for CD.¹¹⁾ Despite being theoretically based, there is an absence of quantitative data to support this theory. Studies that do not support the theory have been published, but they are not quantitatively sufficient to disprove the theory.

Jawan et al.¹²⁾ found that the maximum cephalic spread during SA in parturients was higher in twin pregnancy compared to singleton pregnancy. However, there was no difference in the incidence of hypotension requiring ephedrine administration between the two groups (singleton group, 20/35 [57%] vs. twin group, 13/20 [65%]). It is known that there is no association between the occurrence of hypotension and the level during SA.¹⁴⁾ Although this previous study reported the number of parturients who needed ephedrine, they did not investigate the vasopressor requirement to treat spinal hypotension. In addition, they had a limitation of a small study population. We set our primary outcome as the incidence of hypotension and calculated the sample size per group necessary to achieve sufficient statistical power. Therefore, a larger sample size was recruited for this study than in the previous study.¹²

Warwick et al.¹³⁾ compared vasopressor requirements and hemodynamic changes during SA for CD between women with multiple gestation and singleton pregnancy. Their results showed that the total dose of metaraminol and the rate of metaraminol consumption until uterine incision were similar between the two groups. For the treatment of hypotension, bolus and infusion of metaraminol were used in parallel when the SBP decreased to <90% of the baseline value. The incidence of hypotension, defined as a decrease in SBP by more than 20% below baseline, was measured at a time when a vasopressor was already being

administered.

a -agonists drugs are known to be the most appropriate agents to treat or prevent hypotension caused by SA.⁴⁾ Several vasopressors, including ephedrine and metaraminol, have been studied and used.^{4, 13, 15, 16)} Recently, research on norephinephrine has been active,¹⁷⁻¹⁹⁾ and among these drugs, phenylephrine is currently recommended due to the amount of supporting data.^{15, 20, 21)} With regard to the treatment or prevention of spinal hypotension, when comparing the effects and doses of vasopressors on hypotension, and studying the effects of drugs on the fetus, many studies used a continuous infusion of vasopressors before hypotension occurs, as recommended by the guidelines.⁴⁾ Prophylactic infusion of a vasopressor before the occurrence of hypotension may affect the incidence of hypotension due to the effect of the vasopressor. Our study has the significance of being the first study to investigate the incidence of actual hypotension, not affected by vasopressors, between twin and singleton pregnancies.

In the current study, the incidence of hypotension after regional anesthesia was not significantly increased in twin pregnancies compared with in singleton pregnancies. First, it is considered that the increase in cardiac output (CO) from the mid-trimester in twin pregnancies compared with singleton pregnancies may have an effect in compensating for hypotension. In several studies that measured echocardiographic variables using twodimensional and/or M-mode echocardiography of the left ventricle in the second and third trimesters between twin and singleton pregnancies, a significant increase in maternal CO was reported in twin compared with singleton pregnancies.²²⁻²⁴⁾ Another study using the impedance cardiography measured the variation of impedance in the thorax due to the physical contractile activity of the heart, and the CO was also found to be increased in twins relative to singletons.²⁵⁾ In most studies, the increase in maternal CO was mostly due to a significantly increased HR in twin compared with singleton pregnancies.^{22, 24, 25)} In studies using a bioimpedance device to compare maternal cardiac parameters in singleton and twins before and during CD, there were no significant hemodynamic changes intraoperatively, but they showed that the HR increased during SA in parturients with twin pregnancies compared to those with singleton pregnancies.^{26, 27)} In our study, in twin pregnancies rather than singleton pregnancies, the HR before delivery was significantly increased compared to the baseline HR, which is not considered to make a difference in the incidence of hypotension. Standard textbooks state that multiple gestation pregnancies are more prone to hypotension during regional anesthesia than singleton pregnancies.¹¹⁾ This was thought to be due to greater aortocaval compression and cephalic spread of the block in twin pregnancies relative to singleton pregnancies.²⁸⁾ In a study directly comparing the spread of the spinal block in parturients with singleton and twin pregnancy, although they found a significant difference in the level of the block, they failed to demonstrate a significant difference in the incidence of hypotension between the two groups. Nevertheless, they noted that the absence of a significant difference in the incidence of hypotension does not imply that the compression of the inferior vena cava was the same.¹²⁾ Aya et al.²⁹⁾ compared the spinal hypotension risk between healthy women with preterm pregnancies and patients with severe preeclampsia. They concluded that the incidence of hypotension during SA for CD was primarily attributable to preeclampsia-associated factors rather than the uterine mass (the total fetal weight) and aortocaval compression. In our study, there was a significant difference in fetal weight between the two groups, but there was no difference in the incidence of hypotension, and there was no association between the total fetal weight and the vasopressor requirement.

This study has some limitations. First, the patient groups had different numbers of patients. Although this aspect was considered at the time of study design and the number of participants per group was adjusted, data collection of the parturients with single pregnancy was completed first, which could potentially affect the conclusion. Second, although there was no significant difference in the time from induction to delivery between each group, it is considered that the difference in the time from the end of anesthetic induction to the start of the surgery could be a significant confounding factor. Third, as in most studies investigating the incidence of hypotension during SA, our study focused on hypotension until the time of newborn delivery. There was no significant difference in the results between the two groups until the time of delivery; however, since the risk of postpartum bleeding is greater in multiple pregnancies, additional studies are needed.

Conclusions

In conclusion, the incidence of hypotension and the amount of vasopressor required during SA in twin pregnancies were not significantly different from those of singleton pregnancies. Quantitative studies on the incidence of hypotension in twin pregnancy are still scarce, and there are no guidelines, even in the international consensus statements on the management of hypotension with vasopressors for multiple pregnancies. We believe that the findings of our study could help develop a strategy for preparing for hypotension while supporting the appropriate use of limited medical resources. Although the results of our study will help control the hemodynamic status of parturients with twin pregnancy during SA, more studies are required to confirm our findings.

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국문 요약

제왕절개 수술을 받는 쌍태임신 산모와 단태임신 산모 간 척추 마취 중 저혈압 발생율 및 승압제 요구량의 비교

연구 목적 및 배경: 척추 마취는 제왕절개 수술에 널리 이용하고 있는 마취 방법이지 만 산모의 저혈압이 흔하게 동반된다. 보조생식기술의 발전과 더불어 최근 다태임신 의 수는 증가하였다. 그렇지만 다태임신의 제왕절개 수술에서 척추 마취로 인한 저혈 압을 포함한 합병증에 대한 정량적인 연구는 부족하다. 본 연구는 정규 제왕절개 수술 을 위한 척추 마취 중 쌍태임신 산모와 단태임신 산모의 저혈압 발생율과 승압제 요구 량을 비교하고자 하였다.

연구 대상 및 방법: 2022 년 6 월부터 12 월까지 정규 제왕절개 수술을 받는 산모를 대 상으로 하였다. 수술장에 도착한 모든 산모에게 일반적인 모니터링을 적용하였다. 마 취 전 앙와위에서 측정한 지표를 기준으로 하였다. 척추 마취는 고비중의 0.5% 부피바 케인 8 mg 과 펜타닐 15 mcg 를 이용하여 시행하였다. 마취제 투입 후 분만 전까지 정 해진 프로토콜에 따라 저혈압을 치료하기 위해 1 분 간격으로 비침습적인 혈압을 자동 으로 측정하였다. 기준 수축기 혈압 값의 80% 미만 값의 발생시 저혈압으로 정의하였 고, 페닐에프린 100 mcg 를 투여하였다. 100 mcg 의 페닐에프린을 반복적인 투여에도 불구하고 혈압이 기준 수축기 혈압의 80% 이상으로 상승하지 않으면 페닐에프린의 투 여량을 200 mcg 로 증량하였다.

연구 결과: 단태임신 산모 111 명과 쌍태임신 산모 55 명을 분석하였다. 환자의 기본 특 성 중 재태 연령과 신생아의 총 출생 체중의 합을 제외하고 유의한 차이는 없었다. 시 간에 따라 두 군의 수축기 혈압은 유의하게 차이가 있었는데 (p = 0.023), 척추 마취 5 분 후 수축기 혈압이 쌍태임신 군에 비해 단태임신 군에서 유의하게 낮았다 (100 ± 17 vs. 108 ± 19, p = 0.014). 분만 전 저혈압은 단태임신 산모 111 명 중 77 명 (69.4%), 그리 고 쌍태임신 산모 55 명 중 35 명 (63.6%)에서 발생하였고 유의한 차이를 보이지는 않 았다 (p = 0.458). 두 군 간 저혈압 발생시 투여한 승압제의 사용량도 유의한 차이를 보 이지 않았다.

결론: 쌍태임신 산모에서 단태임신 산모에 비해 척추 마취 중 저혈압이 더 흔히 발생하

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거나 승압제의 요구량이 더 높지 않았다. 척추 마취 중 쌍태임신 산모의 승압제 관리에 대한 연구는 거의 없다. 의료 자원 및 비용이 제한적이기 때문에, 우리 연구의 결과가 쌍태임신 산모의 저혈압에 대비한 전략을 수립하는 데 도움을 줄 것이다.