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# Effects of Crystalloid and Colloid Preload on Blood Volume in the Parturient Undergoing Spinal Anesthesia for Elective Cesarean Section

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**Background:** The role of crystalloid preloading to prevent hypotension associated with spinal anesthesia in parturients during cesarean section has been challenged. Direct measurement of blood volume should provide insight regarding the volume-expanding effects. The aim of the current study was to clarify the effects of volume preload with either crystalloid or colloid solution on the changes in blood volume of parturients undergoing spinal anesthesia for cesarean section.

**Methods:** Thirty-six healthy parturients scheduled for elective cesarean section during spinal anesthesia were allocated randomly to one of three groups receiving 1.5 l lactated Ringer's solution (LR; n = 12), 0.5 l hydroxyethylstarch solution, 6% (0.5 l HES; n = 12), and 1.0 l hydroxyethylstarch solution, 6% (1.0 l HES; n = 12), respectively. Blood volume and cardiac output were measured before and after volume preloading with indocyanine green (ICG), and the indocyanine green blood concentrations were monitored by noninvasive pulse spectrophotometry.

**Results:** After volume preload, the blood volume significantly increased in all three groups ( $P < 0.01$ ). The volume of infused solution remaining in the vascular space in the LR, 0.5-l HES, and 1.0-l HES groups were  $0.43 \pm 0.20$  l,  $0.54 \pm 0.14$  l, and  $1.03 \pm$

$0.21$  l, respectively, corresponding to 28% of lactated Ringer's solution and 100% of hydroxyethylstarch solution infused. Significant increases in cardiac output were observed in the 0.5-l and 1.0-l HES groups ( $P < 0.01$ ). A significant correlation between the percentage increase in blood volume and that of cardiac output was observed by volume preloading ( $r^2 = 0.838$ ;  $P < 0.001$ ). The incidence of hypotension was 75% for the LR group, 58% for the 0.5-l HES group, and 17% for the 1.0-l HES group, respectively.

**Conclusions:** The incidence of hypotension developed in the 1.0-l HES group was significantly lower than that in the LR and 0.5-l HES groups, showing that greater volume expansion results in less hypotension. This result indicates that the augmentation of blood volume with preloading, regardless of the fluid used, must be large enough to result in a significant increase in cardiac output for effective prevention of hypotension. (Key words: Cardiac output; hydroxyethylstarch solution; indocyanine green; lactated Ringer's solution; pulse spectrophotometry.)

ACUTE administration of crystalloid solution to parturients undergoing spinal anesthesia for cesarean section has been recommended to reduce the incidence and severity of hypotension before the induction of spinal anesthesia.<sup>1-3</sup> However, several investigations have recently shown that increasing the amount of crystalloid does not eliminate the incidence of hypotension or ephedrine requirements after spinal anesthesia.<sup>4-7</sup> Colloid solutions, such as 5% albumin, 6% hydroxyethylstarch (HES), and gelatin, are also used for preventing the hypotension associated with spinal anesthesia.<sup>8,9</sup> Preloading the circulation with crystalloids or colloids is aimed at the volume expansion that alleviates the vasodilation induced by spinal anesthesia. Most of the previous investigations of the effects of preloading with a variety of fluids have focused on the incidence and severity of hypotension and some vital signs, such as systolic blood pressure (SBP) and heart rate. These variables do not directly reflect the volume expansion effect because they are not only influenced by the volume status, but also by many other factors, such as cardiac function, vascular tone, and aortocaval compres-

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sion.<sup>7,10-12</sup> Direct measurement of blood volume (BV) should provide insight regarding the volume-expanding effects of crystalloid or colloid solutions. Until now, no investigation of the changes in BV after crystalloid or colloid preloading has been performed because BV measurement is a time-consuming and complicated procedure that necessitates blood sampling and indicator concentration measurement at the laboratory level. A sophisticated system that can noninvasively measure the blood concentration of indocyanine green (ICG) using pulse spectrophotometry, based on the same principle as oximetry, recently was developed. The accuracy and reproducibility of measuring BV and cardiac output (CO) using this system have been investigated.<sup>13-15</sup> The current study was designed to clarify the effects of volume preload, with either crystalloid or colloid solutions, on the changes both in BV and CO of parturients undergoing spinal anesthesia for cesarean section.

## Materials and Methods

### *Parturients*

This study was approved by the Institutional Review Board, Osaka University Medical School, Osaka, Japan, and informed consent was obtained from 36 healthy, full-term parturients scheduled for elective cesarean section during spinal anesthesia. Patients with abruptio placenta, placenta previa, multiple gestation, and pre-eclampsia, or who were receiving ritodrine or other  $\beta$ -tocolytic agents were excluded from the current study. Only an H<sub>2</sub> blocker (ranitidine hydrochloride, 100 mg) was administered orally the night before, and no other medicine was administered. Parturients were allocated randomly to one of three groups: the lactated Ringer's solution (LR) group received 1.5 l LR solution (n = 12), the 0.5-l hydroxyethylstarch solution (HES) group received 0.5 l hydroxyethylstarch solution, 6% (saline HES; Kyorin Pharmaceutical Inc., Tokyo, Japan), with an average molecular weight of 70,000 d and a substitution ratio of 0.55 (n = 12), and the 1.0-l HES group received 1.0 l of the same HES solution (n = 12), respectively. The LR and the HES solutions each were infused over a 30-min period before the induction of spinal anesthesia.

### *Study Design*

An intravenous catheter was inserted into a peripheral vein and 5% glucose solution was infused at a rate of 100 ml/h. The BV and CO measurements were performed

with the patient in the right lateral position to avoid aortocaval compression by fixing the probe to the left index finger. The first measurement of BV, which was regarded as the baseline value, was performed in the obstetric ward before the volume preload, approximately 1 h before the induction of spinal anesthesia. After the volume loading, BV was again measured using the same device. Spinal anesthesia was undertaken during the infusion of an additional 500 ml LR solution in all groups. Lumbar punctures were performed by using a 25-gauge spinal needle at the L3-L4 intervertebral space with patients in the right lateral position. Spinal anesthesia was achieved by administering 8.0 mg tetracaine hydrochloride and 100  $\mu$ g preservative-free morphine hydrochloride in 10% dextrose.

After spinal block, parturients were placed in the supine position with a wedge placed under the right hip to obtain a 15° left uterine displacement. Maternal blood pressure and heart rate were monitored at 1-min intervals from the induction of spinal anesthesia to delivery, and every 5 min thereafter (M2360A; Hewlett Packard, Andover, MA). Hypotension was defined as a decrease in SBP to less than 100 mmHg and less than 80% of the baseline value. Hypotension was treated with 10 mg ephedrine at 2-min intervals. Oxytocin was administered to all parturients at a rate of 2 to 3 U/h after delivery. Methyl ergonovine or prostaglandin F<sup>2</sup> $\alpha$ , or both, were administered when necessary to prevent the parturients from postpartum hemorrhage.

### *Measurement of Blood Volume*

Blood volume was estimated using ICG as an indicator. Ten milligrams of ICG was administered in an intravenous bolus dose within 1 s *via* a cannula placed in the peripheral vein, and the blood ICG concentration was monitored *via* pulse spectrophotometry using a probe fixed on the patient's left index finger. The measurement of blood ICG concentrations by pulse spectrophotometry operates by the same principle as the monitoring of oxygen saturation measured by pulse oximetry (SpO<sub>2</sub>). It is designed using the principles of light absorbency and pulse detection, in which endogenous hemoglobin is used as the reference material.<sup>16</sup> The integrated pulse spectrophotometry monitoring system is composed of a finger probe, a monitoring device, and a computer for recording and printing the results (DDG1001; Nihon Kohden Inc., Tokyo, Japan). Before injection of ICG, approximately 0.5 ml of blood was drawn and placed in a heparinized syringe to measure the hemoglobin concentration (ABL601; Radiometer, Copenhagen, Den-

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**Table 1. Maternal Characteristics and Hemodynamics in Response to Volume Preload with either LR or HES**

	LR	0.5L HES	1.0L HES
N	12	12	12
Age (yr)	32 ± 0.3	30 ± 5.3	32 ± 3.6
Weight (kg)	60.6 ± 3.7	61.3 ± 5.3	62.4 ± 7.5
Height (cm)	156 ± 6.4	157 ± 5.8	160 ± 4.5
Gestational age (wk)	39 ± 0.3	39 ± 0.5	39 ± 0.3
Blood volume (l)			
Baseline	5.33 ± 0.46	5.28 ± 0.59	5.30 ± 0.55
After volume preload	5.76 ± 0.52*	5.82 ± 0.63*	6.33 ± 0.67*†‡
Cardiac output (l/min)			
Baseline	5.4 ± 1.0	5.4 ± 1.0	5.10 ± 1.0
After volume preload	6.0 ± 1.0	6.2 ± 0.6*	7.3 ± 1.1*†‡
Level of anesthesia	T4 (2-6)	T4 (1-5)	T4 (2-4)
Systolic blood pressure (mmHg)			
Baseline	117 ± 7	114 ± 9	116 ± 7
After volume preload	119 ± 7	121 ± 12	118 ± 9
Lowest following spinal anesthesia	88 ± 10*	92 ± 10*	102 ± 10*†‡
Incidence of hypotension (%)	75	58	17§
Heart rate (beats/min)			
Baseline	74 ± 11	73 ± 7	72 ± 8
After volume preload	80 ± 9	78 ± 8	78 ± 11
Lowest following spinal anesthesia	78 ± 12	77 ± 7	79 ± 9
Hemoglobin concentration (mg/dl)			
Baseline	10.9 ± 0.7	11.0 ± 0.8	11.0 ± 0.9
After volume preload	9.8 ± 0.8*	9.9 ± 1.0*	8.9 ± 0.7*†‡

Values are mean ± SD.

\*  $P < 0.01$  versus baseline.

†  $P < 0.01$  versus LR.

‡  $P < 0.01$  versus 0.5L HES.

§  $P < 0.05$  versus LR.

||  $P < 0.05$  versus 0.5L HES.

HES = hydroxyethylstarch; LR = lactated Ringer's.

mark), which is necessary for calculating ICG blood concentration. Blood ICG concentration was measured immediately after the administration of ICG. The BV and CO were estimated based on the ICG blood concentration time courses as follows:

$$BV = \frac{\text{Dose}}{C_{\text{MTT}}} \quad (1)$$

where  $C_{\text{MTT}}$  is the blood concentration of ICG at the mean transit time (MTT) calculated from the first dilution curve.

$$CO = \frac{\text{Dose}}{AUC_{\text{first}}} \quad (2)$$

where  $AUC_{\text{first}}$  is the area under the first dilution curve calculated based on the trapezoidal rule.

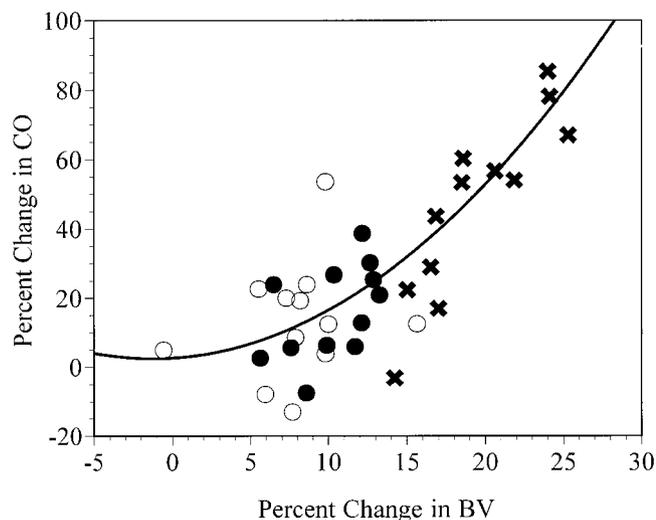
### Statistical Analysis

Data are represented as the mean ± SD. The differences for age, weight, height, and gestational age among

the three groups were studied using the Kruskal-Wallis rank test. Two-way analysis of variance and the Newman-Keuls test were used for the comparisons of BV, CO, SBP, and hemoglobin concentration among the three groups. For each group, values before and after volume preload were compared using a paired  $t$  test, and Bonferroni correction was conducted to evaluate the  $P$  value. The incidence of spinal hypotension was compared using the chi-square test. The coefficient of correlation between percent change in CO and in BV were analyzed by using polynomial regression. A value of  $P < 0.05$  was considered statistically significant.

### Results

Details of the maternal characteristics and various hemodynamic values are summarized in table 1. There were no significant differences among the three groups with regard to age, weight, height, and gestational age. In addition, there also were no differences observed in



**Fig. 1.** The relation between percent change in blood volume and cardiac output after volume preload with 1.5 l lactated Ringer's solution (○), 0.5 l hydroxyethylstarch solution, 6% (●), and 1.0 l hydroxyethylstarch solution, 6% (×).

the baseline values of BV, CO, SBP, heart rate, and hemoglobin concentration among the three groups. The BV measured with ICG before and after preloading the circulation with LR, 0.5 l HES, 6%, or 1.0 l HES, 6%, were significantly increased ( $5.33 \pm 0.46$  l vs.  $5.76 \pm 0.52$  l;  $5.28 \pm 0.59$  l vs.  $5.82 \pm 0.63$  l;  $5.30 \pm 0.55$  l vs.  $6.33 \pm 0.67$  l;  $P < 0.01$  for all comparisons). The volumes remaining in the vascular space after administration of 1.5 l LR, 0.5 l HES, 6%, or 1.0 l HES, 6%, over 30 min were  $0.43 \pm 0.20$  l,  $0.54 \pm 0.14$  l, and  $1.03 \pm 0.21$  l, respectively, which correspond to 28% of the LR solution and 100% of the HES solution infused. The BV in the 1.0-l HES group after volume preload ( $6.33 \pm 0.67$  l) was significantly greater than that in the LR and 0.5-l HES groups ( $5.76 \pm 0.52$  l and  $5.82 \pm 0.63$  l;  $P < 0.01$ ). Cardiac output in the 0.5-l and 1.0-l HES groups was significantly increased by volume preloading (table 1;  $P < 0.01$ ), and the CO for the 1.0-l HES group showed a significantly higher value than that for the LR and 0.5-l HES groups ( $P < 0.01$ ). The relation between the percent change in BV and that in CO by volume preloading is shown in figure 1. A significant curvilinear correlation was observed between the percentage change in BV and that in CO ( $r^2 = 0.838$ ;  $P < 0.001$ ). The mean values of SBP remained unchanged after preloading with the LR solution or either HES solution (table 1). As the lowest values recorded within 10 min after spinal anesthesia indicated, the mean values of SBP were decreased significantly by spinal anesthesia in all three groups. Irrespective of the

similar level of spinal anesthesia for all three groups (table 1), the lowest SBP after spinal anesthesia observed in the 1.0-l HES group ( $102 \pm 10$  mmHg) was maintained at a significantly higher level than that of the LR and 0.5-l HES groups ( $88 \pm 10$  mmHg and  $92 \pm 10$  mmHg, respectively;  $P < 0.01$ ). Spinal anesthesia-induced hypotension was observed in 75% of parturients in the LR group, in 58% of parturients in the 0.5-l HES group, and in 17% of parturients in the 1.0-l HES group. The incidence of hypotension was significantly lower in the 1.0-l HES group than in the LR and 0.5-l HES groups ( $P < 0.05$ ). Heart rate was not influenced by volume preloading in all three groups. Hemoglobin concentrations were decreased significantly by volume preload in all three groups ( $P < 0.01$ ).

## Discussion

Because Wollman and Marx<sup>1</sup> proposed the importance of fluid infusion to counteract the relative hypovolemia induced by spinal anesthesia, various fluids, including crystalloids and colloids, have been used for preloading before spinal anesthesia for cesarean section. Many studies have been reported<sup>1-9</sup> regarding the effects of volume preload, using various fluids, on the incidence and severity of hypotension induced by spinal anesthesia; however, no investigations have been conducted to directly clarify the effects of volume preload on BV because of the difficulty in measuring the BV of parturients. In this study, we directly measured BV and CO at the bedside by administering an intravenous injection of ICG that was monitored noninvasively using the newly developed approach of pulse spectrophotometry.<sup>13,16,17</sup> Preloading with 1.5 l LR solution, which corresponds to approximately 30% of the basal BV before preloading circulation, resulted in only an 8% increase in the BV of parturients. The finding that only 28% of infused LR remained in the vascular space after infusion over 30 min is not surprising because crystalloid solution, such as LR, has a short intravascular half-life because of its rapid distribution into the interstitial space. We observed a high incidence of hypotension of 75% for this group, which was comparable to that found in the previous studies by Robson *et al.*<sup>18</sup> and Riley *et al.*<sup>19</sup> The BV of parturients preloaded with 0.5 l HES, 6%, increased by 10%, and the incidence of hypotension was 58%, which was not significantly different from the LR group. Although 100% of infused 6% HES remained in the vascular space, the volume of 0.5 l or the resultant 10% increase

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in BV were ineffective in preventing the hypotension associated with spinal anesthesia. A 20% increase in BV was achieved by preloading the circulation with 1.0 l HES, 6%, and the incidence of hypotension was significantly decreased to 17%, as compared with the LR and 0.5-l HES groups ( $P < 0.05$ ). Therefore, a greater increase in BV may be necessary to prevent the hypotension associated with spinal anesthesia.

Spinal block causes peripheral vasodilation and venous pooling, which may result in maternal hypotension. Investigations regarding the effects of fluid preloading on maternal hemodynamic factors such as CO and systemic vascular resistance (SVR) would be helpful for discussion of the meaning and usefulness of volume preloading. Park *et al.*<sup>7</sup> measured the cardiac index and systemic vascular resistance index in parturients undergoing spinal anesthesia for cesarean section using noninvasive thoracic impedance monitoring. They observed a similar and significantly decreased systemic vascular resistance index among groups receiving 10, 20, or 30 ml/kg LR and an unchanged cardiac index. Wennberg *et al.*<sup>12</sup> measured cardiac index in parturients preloaded with dextran (15 ml/kg) using a similar technique to that of Park and *et al.*<sup>7</sup> and observed no significant changes in maternal heart rate and cardiac index until induction of extradural anesthesia. Conversely, Robson *et al.*<sup>18,20</sup> measured the CO using Doppler flow combined with cross-sectional echocardiography at the aortic valve in parturients undergoing spinal or extradural anesthesia for cesarean section, demonstrating that CO increased after preloading the circulation with 1000–2200 ml LR solution. Several studies<sup>18,20,21</sup> have reported the decreased CO in parturients after spinal or epidural anesthesia and suggested that the hypotension induced by spinal or epidural anesthesia is associated with a marked decrease in CO. It seems that the effects of crystalloid and colloid preload on CO vary in different studies, depending on the variations in fluids infused, the prophylactic or simultaneous administration of ephedrine, and the approaches of measuring CO.<sup>7,12,18</sup>

In the current study, CO was measured noninvasively with ICG using pulse spectrophotometry. This new method has been shown to have the same degree of accuracy as the conventional thermodilution method for measuring CO.<sup>17</sup> We observed a significant curvilinear correlation between the percent change in BV and CO by volume preload. The conflicting results reported from many studies of the preventive effects of volume preload based on the incidence and severity of hypotension might be attributed to the insufficient augmentation of

BV to result in a significant change in maternal CO because of the variety in the volumes and fluids used. As relative hypovolemia associated with spinal anesthesia reduces CO by lowering venous return, effective volume expansion with crystalloid or colloid will certainly augment the venous return. Volume preloading with either 0.5-l or 1.0-l HES, 6%, induced significant increases in CO in parturients. Because no significant change was found in heart rate before or after volume preload, the significant increase in CO after volume preload with 6% HES solution can be attributed to the increase in stroke volume. The percentage increases by volume preload relative to the baseline CO in the 0.5-l HES and 1.0-l HES groups were 14% and 43%, respectively. Measurement of BV and CO after spinal anesthesia would have provided valuable information regarding the relation between BV and CO and the relation between the incidence of hypotension and CO. However, this measurement could not be performed. For subsequent measurements (at least a 40-min interval is necessary), the period between establishment of spinal anesthesia and the birth of the infant was less than 40 min.

Riley *et al.*<sup>19</sup> compared the effectiveness of preloading the circulation with either 2 l LR or 1 l LR plus 0.5 l HES, 6%. They observed spinal hypotension in 45% of patients who received HES (0.5 l) plus LR (1 l) *versus* 85% of those who received LR (2 l) only. They concluded that 6% HES plus LR is more effective than LR alone. Although Martho *et al.*<sup>8</sup> reported complete prevention of spinal hypotension by preloading the circulation of parturients with approximately 1 l albumin, 5%; HES, which is cheaper than albumin, seems to be more practical. Our results support the opinion of Riley *et al.*,<sup>19</sup> who advocated the routine use of 6% HES solution before spinal anesthesia for cesarean section, based on several years of routine use in their obstetric service.

In summary, BV was significantly increased by volume preload with 1.5 l LR or 0.5 l or 1.0 l HES, 6%, solutions, and the percentage increments relative to the basal BV were 8%, 10%, and 20%, respectively. A significantly lower incidence of hypotension associated with spinal anesthesia in the 1.0-l HES group was observed as compared with the LR and 0.5-l HES groups. The significant correlation between the percent change in BV and CO suggests that the augmentation of BV with volume preload must be great enough to result in a significant increase in CO.

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