

Hemodynamic Effects of 6% Hydroxyethyl Starch Infusion in Sevoflurane-Anesthetized Thoroughbred Horses

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ABSTRACT. To determine hemodynamic effects of hydroxyethyl starch (HES) infusion during anesthesia in horses, incremental doses of 6% HES were administered to 6 healthy Thoroughbred horses. Anesthesia was induced with xylazine, guaifenesin and thiopental and maintained with sevoflurane at 2.8% of end-tidal concentration in all horses. The horses were positioned in right lateral recumbency and administered 3 intravenous dose of 6% HES (5 ml/kg) over 15 min with 15-min intervals in addition to constant infusion of lactated Ringer's solution at 10 ml/kg/hr. Hemodynamic parameters were measured before and every 15 min until 90 min after the administration of 6% HES. There was no significant change in heart rate and arterial blood pressures throughout the experiment. The HES administration produced significant increases in mean right atrial pressure, stroke volume, cardiac output (CO) and decrease in systemic vascular resistance (SVR) in a dose-dependent manner. There was no significant change in electrolytes (Na⁺, K⁺, Cl⁻) throughout the experiment, however, packed cell volume, hemoglobin concentration, and total protein and albumin concentrations decreased in a dose-dependent manner following the HES administration. In conclusion, the HES administration provides a dose-dependent increase in CO, but has no impact upon arterial blood pressures due to a simultaneous decrease in SVR.

KEY WORDS: equine, hemodynamic effect, hydroxyethyl starch, sevoflurane.

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Anesthetic-induced hypovolemia and hypotension reduce blood flow to peripheral tissues [11], which increases the risk of postanesthetic complications and death [5, 17, 18]. Intravenous administration of fluids is a useful method for the treatment of hypovolemia and hypotension during anesthesia in horses. Crystalloid solutions, in particular lactated Ringer's solution (LRS), are frequently administered for the improvement of anesthetic-induced hypovolemia and hypotension. It is reported that less than 33% of the infused volume of a crystalloid solution is retained within the vascular compartment during infusion, and less than 20% of the infused volume is retained after 30 min [6, 10, 13]. Therefore, large volumes of crystalloids must be required to treat hypovolemia and hypotension. However, it is clinically difficult to administer large volumes of fluids in a short duration in large animals. Moreover, rapid administration of large volumes of crystalloids can result in hemodilution of blood constituents and increase the risk of interstitial and pulmonary edema [7, 15].

The administration of colloidal solutions, in particular 6% hydroxyethyl starch (HES) solution, for the treatment of hypovolemia and hypotension is becoming increasingly popular in veterinary practice. Colloid solutions are retained within the vascular compartment after administration, thereby reducing the total fluid requirement, prolonging volume expansion and improving peripheral blood flow [3, 13]. It is

reported that the administration of colloid fluid, compared with administration of LRS, is significantly effective in expanding the intravascular volume in isoflurane-anesthetized dogs with hypotension induced via blood withdrawal [14]. Other study indicates that administration of colloid fluid rather than LRS is recommended for the treatment of isoflurane-induced hypotension in dogs [1].

The efficacy of HES solution in anesthetized horses has not been well investigated in a prospective manner. The purpose of this study is to determine the hemodynamic effects of 6% HES solution in sevoflurane-anesthetized Thoroughbred horses and to evaluate the clinical usefulness and safety of HES.

MATERIALS AND METHODS

Animals: Six Thoroughbred horses (1 female and 5 males) were used in this study. Mean age was 4.2 ± 1.6 years (range, 2 to 6 years), and mean body weight was 458 ± 9 kg (range, 446 to 470 kg). All horses were considered healthy on the basis of preanesthetic physical examination, CBC and ECG. Food, but not water, was withheld for 12 hr prior to anesthesia. This study was carried out according to the Guidelines for Animal Experiments at Equine Research Institute, Japan Racing Association.

Anesthesia and instrumentation: A 14-G catheter was placed in the left external jugular vein for LRS administration and venous blood sample collection. A 12-G catheter was placed in the right external jugular vein for HES administration. Horses were premedicated with xylazine 1.0 mg/kg (Celactar; Bayer, Osaka, Japan) and induced anesthesia by a rapid injection of 5% guaifenesin 2.0 ml/kg (Shinyo Pure Chemicals Co., Ltd., Osaka, Japan) containing thiopental

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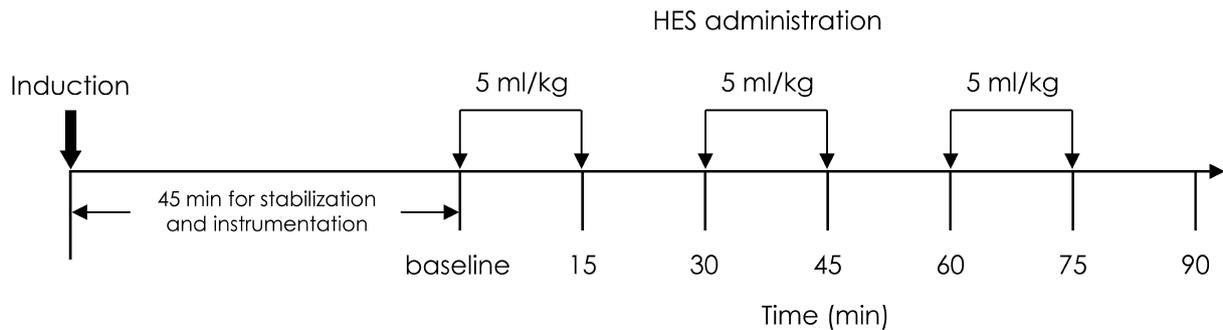


Fig. 1. The schematic diagram of the experiment protocol for six sevoflurane-anesthetized horses administered 6% hydroxyethyl starch (HES).

sodium 2.0 mg/ml (Ravonal; Mitsubishi Tanabe Pharma Co., Osaka, Japan). After induction of anesthesia, the horses were intubated endotracheally and positioned in right lateral recumbency on a padded surgical table. Anesthesia was maintained with sevoflurane (Sevofrane; Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) and oxygen (approximately 5 l/min) delivered via a large-animal rebreathing circle system (MOK 94; Silver Medical Co., Tokyo, Japan). The horses were mechanically ventilated at a rate of 8 to 12 breaths/min with peak airway pressure of 25 cmH₂O to maintain arterial carbon dioxide tension (PaCO₂) between 45 and 55 mmHg.

A base-apex lead electrocardiogram was used to monitor heart rate (HR) and rhythm. A 20-G catheter was placed in the facial artery for measurement of systemic arterial blood pressure and for arterial blood sample collection. A Swan-Ganz catheter (93A-191-8F; Baxter, Co., Tokyo, Japan) was introduced into right atrium via the left jugular vein for measurement of mean right atrial pressure (MRAP). These catheters were connected to the pressure transducers. Respiratory gas was collected continuously from the circuit end of the endotracheal tube. End-tidal sevoflurane concentration (ET_{SEVO}) HR, systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial blood pressure (MAP) and MRAP were recorded every 5 min by an anesthesia monitoring system (BP608; Omron Colin Co., Ltd., Tokyo, Japan).

Left ventricular internal diameter in diastole (LVIDd) and left ventricular internal diameter in systole (LVIDs) were measured according to the M-mode echocardiographic imaging method as previously described [12]. Images were obtained using an ultrasound machine (Apron EUB-7000HV, Hitachi Medical Co., Tokyo, Japan) with a 2.0 MHz transducer with 30 cm maximum depth of penetration. All measurements were made by the same operator to reduce variability between investigators. Left ventricular end-diastole volume (LVEDV) and left ventricular end-systole volume (LVEsV) were calculated by Pombo's method [16]. Stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR) were calculated as follows; $SV (ml) = LVEDV (ml) - LVEsV (ml)$, $CO (l/min) = SV (ml) \times HR (beats/min) / 1,000$ and $SVR (dynes \cdot sec/cm^5) = 60 \times [MAP (mmHg) - MRAP (mmHg)] \times 1,332 / [CO (l/min) \times 1,000]$. Fractional

shortening of the left ventricle (FS%) was calculated as the percentage change in LVID between diastole and systole as follows; $FS\% = (LVIDd - LVIDs) / LVIDd \times 100$.

Experimental protocol: The schematic diagram of the experiment protocol is shown in Fig 1. ET_{SEVO} was adjusted to reach 2.8% (approximately 1.2 times of minimum alveolar concentration [MAC] of sevoflurane for horses [2]) within 15 min after induction of anesthesia and then maintained constantly at the same level throughout the experiment. LRS (Hartmann's solution; Nipro Pharma Co., Osaka, Japan) was administered at a rate of approximately 10 ml/kg/hr throughout anesthesia. Each horse was allowed 45 min of anesthesia after induction for stabilization and instrumentation prior to baseline measurements (the baseline measurement period was designated as the 0-min time point). After the baseline data were collected, 6% HES (Hespander fluid solution; Fresenius Kabi Japan, Tokyo, Japan) 5 ml/kg was administered over 15 min. HES 5 ml/kg administrations were repeated three times with 15-min intervals.

Data collection and analysis: HR, SAP, DAP, MAP, MRAP and echocardiographic variables were measured and recorded at the baseline (45 min after induction of anesthesia), and at 15 (the end of 1st HES administration), 30, 45 (the end of 2nd HES administration), 60, 75 (the end of 3rd HES administration) and 90 min after the baseline. Arterial and venous blood samples were also collected at the same time points. PaCO₂, arterial oxygen tension (PaO₂) and pH were immediately analyzed by a blood-gas analyzer (ABL800 FLEX, Radiometer Co., Ltd., Tokyo, Japan). Packed cell volume (PCV) and hemoglobin concentrations (Hb) were analyzed by a hematology analyzer (K-4500, Sysmex Co., Hyogo, Japan), and serum concentrations of total protein, albumin and electrolytes (Na⁺, K⁺, Cl⁻) were analyzed by an automatic blood biochemical analyzer (7700 Clinical Analyzer, Hitachi High-Technologies Co., Tokyo, Japan).

Statistical analysis: Statistical analysis of data was carried out using JMP v6.0.3 (SAS Institute Inc., Cary, NC, U.S.A.). Hemodynamic variables and blood sample data were analyzed by one-way repeated-measures analysis of variance (ANOVA). Tukey's post-test for multiple comparisons was applied, when significant differences were identified. Values are given as mean \pm SD, and statistical significance was ac-

Table 1. Changes in heart rate (HR), systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial blood pressure (MAP), mean right atrial pressure (MRAP), stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR) and fractional shortening of the left ventricle (FS%) in sevoflurane-anesthetized horses administered 6% hydroxyethyl starch (HES)

	Time Point (min)													
	Baseline	15		30		45		60		75		90		
HES Administration	← 5 ml/kg →				← 5 ml/kg →				← 5 ml/kg →					
HR (beats/min)	31±3	32±3		33±2		33±2		34±2		34±2		33±3		
SAP (mmHg)	75±12	76±13		76±14		77±12		79±12		81±11		83±13		
DAP (mmHg)	41±12	42±12		41±12		40±10		42±9		45±12		45±13		
MAP (mmHg)	54±11	55±11		54±11		55±9		56±8		60±11		60±12		
MRAP (mmHg)	6±5	A	8±5	AB	8±5	AB	10±6	BC	10±6	BC	12±6	C	11±7	C
SV (ml)	765±117	A	832±159	AB	931±147	ABC	973±142	BC	975±149	BC	982±188	BC	1,063±300	C
CO (l/min)	24±3	A	26±5	AB	30±6	BC	33±6	C	33±6	C	33±6	C	35±8	C
SVR (dyne•s/cm ⁵)	165±40	A	148±49	AB	124±30	BC	113±29	C	113±26	C	118±25	BC	116±33	C
FS% (%)	25±5	25±4		27±4		28±4		27±4		27±4		26±4		

Data are presented as mean ± SD.

Data with no superscript or with the same superscript are not significantly different from each other within the same row.

Table 2. Changes in arterial carbon dioxide tension (PaCO₂), arterial oxygen tension (PaO₂), pH, packed cell volume (PCV), hemoglobin concentrations (Hb) and serum concentrations of total protein, albumin and electrolytes (sodium, potassium and chloride) in sevoflurane-anesthetized horses administered 6% hydroxyethyl starch (HES)

	Time Point (min)													
	Baseline	15		30		45		60		75		90		
HES Administration	← 5 ml/kg →				← 5 ml/kg →				← 5 ml/kg →					
PaCO ₂ (mmHg)	49±3	50±3		50±3		51±3		51±4		51±2		51±2		
PaO ₂ (mmHg)	397±101	398±72		387±66		392±68		386±68		379±65		360±64		
pH	7.392±0.016	7.388±0.017		7.390±0.019		7.384±0.024		7.388±0.026		7.389±0.022		7.394±0.020		
PCV (%)	32±4	A	29±4	B	28±4	B	26±5	C	26±5	C	24±5	D	24±5	D
Hb (g/dl)	11.6±1.3	A	10.3±1.3	B	10.2±1.4	B	9.4±1.5	C	9.3±1.6	C	8.5±1.6	D	8.5±1.6	D
Total Protein (g/dl)	5.7±0.4	A	5.1±0.4	B	5.0±0.4	B	4.6±0.4	C	4.6±0.4	C	4.3±0.4	D	4.3±0.4	D
Albumin (g/dl)	3.1±0.2	A	2.8±0.2	B	2.8±0.2	B	2.6±0.2	C	2.6±0.2	C	2.5±0.2	D	2.5±0.2	D
Sodium (mmol/l)	136±2	135±2		135±2		135±2		135±2		134±2		134±2		
Potassium (mmol/l)	4.1±0.2	4.1±0.2		4.1±0.2		4.1±0.2		4.1±0.2		4.1±0.3		4.1±0.3		
Chloride (mmol/l)	99±1	99±2		99±2		99±2		99±2		99±2		99±2		

Data are presented as mean ± SD.

Data with no superscript or with the same superscript are not significantly different from each other within the same row.

cepted when $P < 0.05$.

RESULTS

The results of the changes in hemodynamic variables during the experiment are shown in Table 1. There were no significant changes in HR, SAP, DAP, MAP and FS% throughout the experiment. MRAP was significantly increased ($P < 0.0001$), and there were significant differences between the baseline value and the values at 45 to 90 min. SV was significantly increased ($P = 0.0004$), and there were significant differences between the baseline value and the values at 45 to 90 min. CO was significantly increased ($P < 0.0001$), and there were significant differences between the baseline value and the values at 30 to 90 min. SVR was significantly decreased ($P < 0.0001$), and there were significant differences between the baseline value and the values at 30 to 90 min.

The results of the changes in blood gas, hematologic

and serum biochemical variables during the experiment are shown in Table 2. There were no significant changes in PaCO₂, PaO₂ and pH throughout the experiment. PaCO₂ values were maintained within the target values at all the measurement points. PCV, Hb, and total protein and albumin concentrations were significantly decreased ($P < 0.0001$) in a dose-dependent manner. These variables significantly decreased with each increase in infusion dosage of HES. There were no significant changes in electrolyte concentrations (Na⁺, K⁺, Cl⁻) throughout the experiment.

Recovery from anesthesia was calm and smooth with minimal ataxia in all horses. No apparent complications were observed after standing in all cases.

DISCUSSION

In this study, the administration of 5 to 15 ml/kg of 6% HES significantly increased CO in sevoflurane-anesthetized

horses. Therefore, the administration of HES solution was considered to be effective for the improvement of sevoflurane-induced hypovolemia.

There was no increase in HR during anesthesia in spite of the hypotensive condition. Under hypotension, baroreceptor reflex is known to increase HR in normal animals. This reflex might have been blunted by 1.2 MAC of sevoflurane in this study. Although CO was significantly increased by the administration of HES, increases in SAP, DAP and MAP were not significant. Significant decrease in SVR may have limited the drastic increases in SAP, DAP and MAP in this study. The previous study in isoflurane-anesthetized dogs showed the similar results to this study, in which colloid (hetastarch) fluid administration increased cardiac index and decreased SVR [1]. It was considered that atrial distention by the administration of HES increased release of atrial natriuretic peptide, which resulted in vasodilation. MRAP is the common index of changes in cardiac preload when cardiopulmonary organs are free from disease. Dose-dependent increase in MRAP may have represented the intravascular volume expansion by the administration of HES. FS% is calculated as a percent change in left ventricular size between filling and emptying and is one of the common measurements of left ventricular function. Because both HR and FS% were stable during the experiment, it was considered that the administration of HES could increase blood flow without increasing myocardial oxygen consumption in sevoflurane-anesthetized horses.

Measurement of SV or CO during surgery is unrealistic in equine practice. Therefore, direct measurement of arterial blood pressure is routine for monitoring cardiovascular condition during surgery. However, arterial blood pressure may not be the best indicator of blood flow, because it will be affected by the modulation of SVR. In fact, no apparent changes were observed in arterial blood pressures in this experiment in spite of significant increase in CO. When applying HES in clinical cases, it must be kept in mind that arterial blood pressure measurements have limitations for estimating the cardiovascular condition.

Dose-dependent decrease in PCV, Hb, and total protein and albumin concentrations may also have represented the intravascular volume expansion by the administration of HES. Fluid overload could result in marked hemodilution which leads to interstitial and pulmonary edema [7, 10, 15]. However, no apparent clinical signs associated with fluid overload, such as nasal discharge or chemosis, were developed in any horses. As the volume of HES is increased, the total protein concentration should come close to the value of HES itself (approximately 4.5 g/dl). In fact, the administration of HES did not decrease the total protein concentration excessively in this study, indicating that a large volume of administered fluids was retained within the vascular compartment.

On the other hand, it is reported that administration of a large volume of colloid fluids is associated with coagulopathies, renal failure and allergic reactions [8]. To minimize the adverse effects of colloid fluids, low molecular weight HES which has a mean molecular weight of 70 kD and molar

substitution of 0.5 was used in this study. Compared to the commonly used HES solution in the U.S.A. (hetastarch), which has a mean molecular weight of 550 kD and molar substitution of 0.7, HES used in this study has a relatively low mean molecular weight. It is known that the lower the mean molecular weight is, the shorter the effective period is [9]. At the dosage of HES administered in this study, sevoflurane-induced hypovolemia was improved without remarkable side effects, indicating that the applied dosage in this study was considered to be appropriate and safe for clinical use in sevoflurane-anesthetized horses.

A certain amount of fluid is lost from the body by respiration and sweating under general anesthesia. To compensate for these insensible fluid losses, most guidelines for routine fluid administration during anesthesia recommend the administration of balanced electrolyte solutions at a rate of 10 to 15 ml/kg/hr [4, 10]. In this study, LRS was administered at a rate of approximately 10 ml/kg/hr throughout anesthesia to maintain intravascular volume. Thus, it was considered that the significant increase in blood flow observed in this study was mainly caused by the administration of HES. The influence of premedication and induction drugs also should be taken into consideration. In this study, each horse was allowed 45 min of anesthesia after induction for stabilization prior to the baseline measurements. Under this condition, the influence of premedication and induction drugs on measurements must have been presumably small.

In conclusion, the HES administration provides a dose-dependent increase in CO, but has no impact upon arterial blood pressures due to a simultaneous decrease in SVR. To prevent postanesthetic complications, adequate MAP (65 to 70 mmHg or more) is necessary for perfusion of peripheral tissues. For this reason, the use of low-dose inotropic agents (e.g. dobutamine) or vasoconstrictive agents (e.g. phenylephrine) in combination with HES is recommended for the treatment of hypovolemia and hypotension in sevoflurane-anesthetized horses.

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