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A Study of Plasma Substitutes for Volume Replacement in Intraoperative Hemodilution Technique

—Estimation of Circulating Blood Volume by Pulse Dye-Dentistometry—

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Abstract

The purpose of this study was to experimentally compare the hemodynamic variables, plasma colloidal and crystalloidal osmotic pressure (Pcop and Posm), and circulating blood volume (CBV), under normovolemic hemodilution in isoflurane-anesthetized dogs. We divided anesthetized dogs into two groups: a HES 70 group (hydroxyethyl starch, MW=70 kDa, 6 % in saline), and a HES 200 groups (hydroxyethyl starch, MW=200 kDa, 6% in saline). Hemodilution was produced by exchanging blood (25 mℓ/kg) with isovolemic artificial colloid of either HES 70 or HES 200. Measurements and sampling were taken before hemodilution, at the end of hemodilution, and 30, 60, 120, 180, 240, and 300 min after hemodilution. CBV was measured by pulse-dye densitometry (PDD) method. A significant increase in mean pulmonary arterial pressure (mPAP), cardiac index (CI), left ventricular stroke work index (LVSWI), and maximum rate of left ventricular pressure change (LV dp/dt max), and a significant decrease in systemic vascular resistance (SVR) values occurred after hemodilution in both groups. However, mAP, mPAP, pulmonary artery wedge pressure (PAWP) and LV dp/dt max values in group HES 70 decreased significantly over time compared with the pre-hemodilution condition. On the other hand, mPAP, CI, LVAWI and LV dp/dt max values in group HES 200 increased significantly. After hemodilution, CBV and Pcop increased significantly compared with the pre-hemodilution condition in both groups. In group HES 70, CBV and Pcop decreased from the pre-hemodilution condition over time, but not in group HES 200. Moreover, CBV and Pcop in group HES 200 significantly greater than those in group HES 70. On the other hand, Posm did not change significantly during any of the experimental periods compared to the pre-hemodilution condition in both groups.

These results suggest that HES 200 may be more effective than HES 70 for the normovolemic hemodilution. This is due to an improvement and a maintainance in hemodynamic variables, CBV and Pcop.

Key word : Plasma substitute, Molecular weight, Hemodilution, Circulating blood volume, Pulse dye-dentistometry method

Introduction

Hemodilution method avoids the need for homologous blood transfusion, thus eliminating the risk of hepatitis, acquired immunodifficiency syndrome (AIDS), and graft versus host disease (GVHD). Although hemodilution can also be performed with crystalloid solutions, it has to be noted that in this case the patients blood has to be exchanged in a 1 : 2.5～4.0 ratio for crystalloids to ensure normovolemia. Colloid solution composed of dextran or hydroxyethyl starch has already been introduced and found to be

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safe and effective in reducing blood loss in the majority of surgical procedures. The physiologic colloid albumin is very popular, but, albumin is very expensive and also may be associated with side effects. Hydroxyethyl starch including oncotic properties, half-life in circulation, essential absence of risk of infections disease transmission, low incidence of anaphylactic reactions and low cost compared to using albumin, make it almost ideal for this purpose.

The purpose of this study was to assess the hemodynamic effects of postoperative normovolemic hemodilution. Blood loss and replacement therapy with two hydroxyethyl starch groups were simulated experimentally. The efficacy of the two hydroxyethyl starch groups in maintaining hemodynamics was investigated in mongrel dogs with normovolemic hemodilution during a 300 min period.

Materials and Methods

Twenty adult male mongrel dogs weighing 15 to 20 kg were randomly allocated into two groups of animals: an HES 70 group (hydroxyethyl starch of 6% weight/volume, average molecular weight of 70 kDa, molar substitution of 0.57 [ratio hydrxyethlyl groups/glucose units] in 0.9% sodium chloride) and an HES 200 group (hydroxyethyl starch of 6% weight/volume, average molecular weight of 200 kDa, molar substitution of 0.62 in 0.9% sodium chloride). The animals were anesthetized with pentobarbital (30 mg/kg i.v.). Pancuronium (0.2 mg/kg) was administered after an endotracheal tube was inserted. The animals were ventilated with 0.5% isoflurane in 60% nitrous oxide using a Harvard respirator. The tidal volume was monitored with an infrared CO_2 analyzer and adjusted to maintain end expiratory $ETCO_2$ of 40 mmHg. The animals were maintained in the supine position under anesthesia.

The left femoral vein was cannulated for infusion of lactated Ringer's solution (maintenance dose of 10 mℓ/kg/h) and for withdrawal of blood and volume replacement with a plasma substitute for induced hemodilution. The left femoral artery was cannulated for the continuous monitoring of systemic arterial pressure and for blood samplings. Left ventricula pressure (LVP) was monitored with a 7-French pigtail catheter cannulated via the right femoral artery. The maximum rate of the left ventricular pressure change (LV dp/dt max) was measured electrically deriving a LVP wave using an electric differentiator. A 7.5-French ballon-tipped triple-lumen pulmonary catheter was inserted via the right external jugular vein and its top was positioned in a branch of the pulmonary artery for circulatory parameter measurements. Cardiac output (CO) was determined by the thermodilution method using 5 mℓ of 0.9% saline at 0℃ injected into the right atrium at the end of expiration. Heart rate (HR) was monitored using a cardiotachometer from lead Ⅱ of an electrocardiograph.

Circulating blood volume (CBV) was measured by pulse-dye densitometry(PDD) method. PDD is a newly developed technique for monitoring the arterial concentration of indocyanine green (ICG). PDD was performed using a DDG analyzer (DDG-2001 Nihon Kohden Corp, Japan). A nostrial probe which is connected to the integrated pulse-spectrophotometry monitoring system was fixed on the tongue to detect the blood concentrations of ICG based on pulse-spectophotometry. In a preliminary experiment, the tongue probe was found to direct pulsation better than probes placed on the finger, ear, and nostril. Twenty-five milligrams of ICG in 10 mℓ saline were injected as a bolus followed by a flush of 0.16 mℓ/kg into the right atrium at the end of expiration. The arterial dye concentration was continuously computed by reference to the previously measured blood hemoglobin (Hb) concentration.

The dogs were allowed to stabilize for at least 60 minutes after the surgical procedure, and baseline measurements were taken (pre-hemodilution). Hemodilution was produced by exchanging blood (25 mℓ/kg) with isovolemic artificial colloid of either HES 70 or HES 200. Measurements and sampling were taken at baseline, end of hemodilution, 30, 60, 120, 180, 240, and 300 min.

HR, mean arterial pressure (mAP), mean pulmonary arterial pressure (mPAP), pulmonary arterial wedge pressure (PAWP), left ventricular pressure (LVP), cardiac output (CO), arterial partial oxygen pressure

(Pa_{O_2}), arterial partial carbon dioxide pressure (Pa_{CO_2}), CBV, plasma crystalloidal osmotic pressure (Posm), and plasma colloidal osmotic pressure (Pcop) were measured. The cardiac index (CI), systemic vascular resistance (SVR), left ventricular stroke work index (LVSWI) and LV dp/dt max, were calculated using standard formulas. Blood samples were drawn at the point of the experimental measurements for analysis of Posm, and Pcop. Blood samples were kept on ice and centrifuged at 2,000 g for 10 minutes at 4℃. The plasma was removed and analyzed for Posm using a cryoscope (Osmotic Pressure AUTO & STAT OM-6030, Kyoto Daiichi Kagaku Corp., Japan). Pcop was measured by an osmometer(Colloid Osmometer 4400, WESCOR Corp., USA). Date are expressed by mean ±SEM. The date were analyzed for significant differences within groups between the baseline values and those for the subsequent phases (HD;30～300 min), using Student's paired t-test, with $p<0.05$ considered as statistically significant. Differences between the two groups were analyzed using Student's unpaired t-test. Values of $p<0.05$ were considered statistically significant.

Results

Hb values did not differ significantly between the HES 70 and HES 200 groups under pre-hemodilution conditions (HES 70 group 11.8±0.7 g/dℓ; HES 200 group 10.9±0.4 g/dℓ) or hemodilution conditions (HES 70 group 7.3±0.5 g/dℓ; HES 200 group 7.2±0.3 g/dℓ).

Hemodynamic variables are shown in Table 1. Under baseline and hemodilution conditions, there was no significant difference in the hemodynamic variables between the two groups. A significant increase in mPAP, CI, LVSWI and LV dp/dt max and a significant decrease in SVR values occurred after hemodilution in both groups. However, mAP, mPAP, PAWP, CI, LVSWI, and LV dp/dt max values in group HES 70 decreased significantly with the lapse of time as compared with the baseline condition. On the other hand, mPAP, CI, LVSWI and LV dp/dt max values in

Table 1 Hemodynamic Variables in Response to Hemodilution with 6% hydroxyethyl starch 70(HES 70) or 6% hydoxyethyl starch 200 (HES 200).

		Base line	HD	30min	60min	120min	180min	240min	300min
HR	HES 70	155±6	137±4	157±4	158±7	156±6	145±6	136±5	139±5
	HES 200	155±7	145±8	154±8	157±8	154±8	146±8	144±9	143±8
mAP	HES 70	109±2	105±2	104±2	90±3[ab]	85±3[ab]	79±3[ab]	68±3[ab]	52±3[ab]
	HES 200	108±2	106±2	108±2	105±2	105±3	108±2	108±2	107±2
mPAP	HES 70	16±1	18±1[a]	19±1[a]	17±1	17±1	17±1	16±1[b]	14±1[ab]
	HES 200	17±1	18±2[a]	20±1[a]	20±1[a]	19±1[a]	19±1[a]	19±1[a]	19±1[a]
PAWP	HES 70	10±1	11±1	10±1	10±1	9±1	8±1[ab]	8±1[ab]	8±1[ab]
	HES 200	10±1	11±1	11±1	11±1	11±1	11±1	11±1	11±1
CI	HES 70	1.6±0.1	2.3±0.3[a]	2.3±0.3[a]	2.0±0.3	1.7±0.2	1.5±0.2[b]	1.2±0.1[ab]	0.9±0.1[ab]
	HES 200	1.6±0.1	2.0±0.1[a]	2.1±0.1[a]	2.1±0.1[a]	2.1±0.1[a]	2.0±0.1[a]	1.9±0.1[a]	1.8±0.1[a]
SVR	HES 70	7584±491	5835±515[a]	5460±452[a]	5522±545[a]	5904±519[a]	6264±623[a]	6810±882[b]	6901±862[b]
	HES 200	7412±324	5791±274[a]	5825±298[a]	5589±254[a]	5573±225[a]	5871±210[a]	6130±240[a]	6338±248[a]
LVSWI	HES 70	14±1	21±2[a]	18±2[a]	13±2	11±1[ab]	10±1[ab]	7±1[ab]	4±1[ab]
	HES 200	14±1	18±1[a]	17±1[a]	17±1[a]	17±1[a]	18±1[a]	18±1[a]	16±1[a]
LV dp/dt max	HES 70	2150±208	2340±214[a]	2880±263[a]	2740±294[a]	2510±275	2190±249	1680±207[ab]	1180±152[ab]
	HES 200	2050±145	2260±210[a]	2840±270[a]	2970±259[a]	2900±269[a]	2850±273[a]	2790±285[a]	2740±291[a]

Data are expressed as mean±SEM. (n=10)

HR: heart rate (beat/min) ; mAP: mean arterial pressure (mmHg) ; mPAP: mean pulmonary arterial pressure (mmHg).
PAWP: pulmonary arterial wedge pressure (mmHg) ; CI: cardiac index (ℓ/min/m^2). SVR: systemic vasucular resistance (dyne sec/cm^5).
LVSWI: left ventricular stroke work index (g m/beat m^2). LV dp/dt max: the maximum rate of the left ventricular pressure change (mmHg/sec).
Baseline: pre-hemodilution ; HD: after hemodilution.
30 min, 60 min, 120 min, 180 min, 240 min, 300 min: 30, 60, 120, 180, 240,300 minutes after hemodilution.
[a] : $P<0.05$ from control. [b] : $P<0.05$ between HES 70 and HES 200.

group HES 200 increased significantly, while mAP and PAWP did not differ significantly compared with the baseline condition during any of the experimental periods. After induction of hemodilution, mAP, mPAP, PAWP, CI, LVSWI and LV dp/dt max in group HES 200 were significantly greater than those in group HES 70. SVR in group HES 200 was significantly lower than that in group HES 70.

Respiratory variables are shown in Table 2. After hemodilutional induction, Pa_{O_2} and Pa_{CO_2} did not change significantly campared to the pre-hemodilution condition in both groups. The respiratory variables of Pa_{O_2} and Pa_{CO_2} during all the experimental periods, did not differ significantly between the two groups.

CBV, Posm and Pcop are shown in Table 3. CBV values did not differ significantly between the two groups under baseline conditions. After hemodilution, CBV values increased significantly compared with the baseline condition in both groups. However, CBV values in group HES 70 decreased significantly over time. Moreover, CBV in group HES 200 was significantly greater than those in group HES 70. After hemodilutional induction, Posm did not change significantly compared to the baseline condition in both groups. However, a significant increase in Pcop values occurred after hemodilution in both groups. In group HES 70, Pcop values was decreased significantly as compared with the baseline condition over time, but not in group HES 200. Pcop in group HES 70 was significantly lower than that in group HES 200.

Discussion

Hemodilution is a well-accepted technique during surgery because it reduces the need for homologous

Table 2 Respiratory Variables in Response to Hemodilution with 6% hydroxyethyl starch 70 (HES 70) or 6% hydoxyethyl starch 200 (HES 200).

		Baseline	HD	30min	60min	120min	180min	240min	300min
Pa_{O_2}	HES 70	222±19	220±19	223±17	229±19	235±19	232±21	217±22	227±24
	HES 200	257±12	250±8	247±8	259±8	250±8	257±11	259±11	265±10
Pa_{CO_2}	HES 70	35±1	38±2	40±2	39±3	40±3	41±4	40±4	41±5
	HES 200	34±1	36±2	38±2	38±1	38±2	38±2	37±2	38±2

Data are expressed as mean±SEM. (n=10)

Pa_{O_2}: arterial partial oxygen pressure (mmHg); Pa_{CO_2}: arterial partial carbon dioxide pressure (mmHg).
Baseline: pre-hemodilution ; HD: after hemodilutin.
30 min, 60 min, 120 min, 180 min, 240 min, 300 min: 30, 60, 120, 180, 240, 300 minutes after hemodilution.

Table 3 Circulating Blood Volume and Plasma Osmotic Pressure in Response to Hemodilution with 6% hydroxyethyl starch 70(HES 70) or 6% hydoxyethyl starch 200 (HES 200).

		Baseline	HD	30min	60min	120min	180min	240min	300min
CBV	HES 70	1.3±0.1	1.6±0.1[a]	1.7±0.1[a]	1.6±0.1[a]	1.6±0.1[a]	1.4±0.1	1.2±0.1[ab]	1.0±0.1[ab]
	HES 200	1.3±0.1	1.6±0.1[a]	1.7±0.1[a]	1.7±0.1[a]	1.8±0.1[a]	1.7±0.1[a]	1.8±0.1[ab]	1.8±0.1[ab]
Posm	HES 70	311±4	320±3	318±3	318±2	317±2	317±2	319±2	320±1
	HES 200	309±2	315±1	312±1	313±1	313±1	314±1	313±1	316±2
Pcop	HES 70	10±1	13±1[a]	11±1[a]	10±1[a]	9±1[ab]	8±1[ab]	8±1[ab]	8±1[ab]
	HES 200	10±1	13±1[a]	11±1[a]	11±1[a]	10±1[a]	10±1[a]	10±1[a]	9±1[a]

Data are expressed as mean±SEM. (n=10)

CBV: circulating blood volume (1).
Posm: plasma crystalloidal osmotic pressure (mmHg); Pcop: plasma colloidal osmotic pressure (mmHg).
Baseline: pre-hemodilution ; HD: after hemodilutin.
30 min, 60 min, 120 min, 180 min, 240 min, 300 min: 30, 60, 120, 180, 240, 300 minutes after hemodilution.
[a] : $P<0.05$ from control.
[b] : $P<0.05$ from between HES 70 and HES 200.

blood transfusion. Furthermore, blood lost during surgery contains fewer cells and plasma factors, and hence the hemodiluted patient loses fewer blood constituents as compared to unhemodiluted patients. However, hemodilution is contraindicated in patients with anemia, myocardial dysfunction, coronary heart disease, liver cirrhosis and blood clotting deficiencies. Preoperative blood withdrawal by an isovolemic exchange with colloids, in order to maintain a constant circulating volume, is offset by an adequate increase of cardiac output and unchanged systemic oxygen transport capacity despite a decreased oxygen content. In the present study, after induction of hemodilution, a significant increase in CI was observed in both groups.

The basic mechanism that compensates for the decrease in oxygen-carrying capacity of diluted blood is the rise in cardiac output[1,2] and increased organ blood flow, factors that result from the improved fluidity of blood viscosity at lower Ht values, cardiac sympathetic activity, and increased myocardial contractility. Particularly, many investigators[3~6] had suggested that the myocardial blood flow increased proportionally more than the cardiac output. The augmented coronary flow resulted from a fall in vascular resistance caused by both coronary vasodilution and lowered blood viscosity. However, Doss et al[7] reported that the systemic vasodilator response to hemodilution is abolished after inhibition of endogenous nitric oxide (NO) synthesis in rats. Further detailed studies must be made in a large number of fundamental studies in animals.

Plasma substitutes are used for the prevention and treatment of hypovolemia after the loss of blood and plasma through surgical procedures. Hydroxyethyl starch (HES), a highly branched polysaccharide, is commonly used as a plasma volume expander. Generally, HES is a safe and effective colloid for intravascular blood volume replacement within a daily dose of 20~30 mℓ/kg. In the present study, hemodilution was performed by replacing blood (25 mℓ/kg) with isovolemic hydroxyethyl starch solution. For reasons of safety, efficiency and practicability, colloid solutions rather than crystalloid solutions should be used for intentional hemodilution. Many investigators[8~12] suggest that hemodynamic and oxygen transport responses are greater and more prolonged after colloid than after crystalloid solution. These responses are related to concomitant improvement in blood volume and colloidal osmotic pressure. The main reason for using colloidal volume replacements is to maintain the circulating blood volume by stabilizing plasma oncotic pressure in the perioperative period. In our study, Pcop values significantly increased after hemodilution in both groups. However, Pcop values in group HES 70 were decreased as compared with the pre-hemodilution condition over time.

CBV has been measured previously using radioactive isotopes. However, this approach is not suitable for routine monitoring of CBV because the method is complex and carries the potential biohazard of a radioactive indicator. Some investigators[13~15] have reported methods of CBV measurement using ICG and indicated that they have good accuracy compared with other standard methods. However, the method has not been widely adopted because it necessitates intermittent blood sampling to determine the time course of ICG concentration. At present, the ICG blood concentration is monitored noninvasively with pulse-spectrophotometry, which is based on the same principle as pulse oximetry. Some investigators[16,17] have suggested that the CBV estimation with a bolus injection of ICG and pulse-spectrophotometry is reliable. Moreover, Iijima et al[18] reported that pulse dye-densitometry can measure CBV with an imprecision, and thus is also as accurate as the conventional radioisotope method. In the present study, CBV in group HES 200 was significantly greater than those in group HES 70. The implication is that the increased blood volume after HES 200 solution and the decreased blood volume after HES 70 solution suggests that the escape of fluid from plasma is greater after the latter. Plasma expansion after infusion of HES 70 solution was relatively short-lived and was associated with significant mean decrease in CBV.

In the present study, decreases in CBV after administration of HES 70 paralleled the decrease in PAWP and Pcop over time, compared with those

before the hemodilution. CBV is one of the most important factors that affect cardiac preload. Because directly measuring CBV usually necessitates tracer injection, the adequacy of CBV is clinically estimated in other ways, such as by monitoring CVP or PAWP. Such estimates may be misleading because CVP and PAWP depend not only on CBV, but also on other factors, such as intrathoracic pressure, cardiac function, and compliance of the vein.

In this study, PDD method could be useful in permitting subsequent measures within relatively short intervals. This is probably because the short half-life of ICG which is within 3 minutes makes it a useful indicator for repetitive measurement of CBV at an interval of as short as 30 minutes with little problem of dye accumulation. Haruna et al reported that the estimation of CBV by the pulse method can be repeated at 20 min intervals.

Hydroxyethyl starch, a synthetic colloidal glycogen-like polysaccharide, frequently used as a plasma expander, is available in high, medium, and low molecular weight types. A potential side effect of HES treatment is the inhibition of the coagulation system. Boldt et al[19] reported that volume replacement with high molecular weight hydroxyethyl strach (MW＝400 kDa) resulted in the most pronounced impairment of platelet aggregation associated with the highest postoperative blood loss compared with that of medium molecular weight (MW＝200 kDa). In addition, Kapiotis et al[20] reported that the medium molecular weight of HES does not specifically influence the activity of the fibrinolytic system. Generally, a high molecular weight of HES was suggested to specifically influence blood coagulation and fibrinolysis parameters. The reason for small starch molecules excreted rapidly via the kidney may be clear. In the present study, small volumes (25 mℓ/kg) of 6 % HES may cause no clinically relevant disturbances of the coagulation and fibrinolysis system in both two groups. However, Mc Loughlin et al[21] reported that normovolemic hemodilution may be more limited by preservation of normal coagulation than of global oxygen delivery and consumption.

In conclusion, HES 200 may be more effective than HES 70 for the normovolemic hemodilution. This is due to an improvement and maintenance in hemodynamic variables, circulating blood volume, and colloidal osmotic pressure.

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