[Original]

Plasma Colloidal Solution for Volume Replacement in Hemorrhagic Shock-Comparison of 6 % and 12 % 200 kDa Hydroxyethyl Starch Solution-

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INTRODUCTION

Plasma substitutes are used for the prevention and treatment of hemorrhagic shock. The main reason for using colloidal volume replacements is to maintain the circulating blood volume by stabilizing plasma oncotic pressure.

This study was undertaken to compare the effects of iso-oncotic and hyper-oncotic colloidal solution on hemodynamic variables and circulating blood volume under experimental conditions of hemorrhagic shock.

MATERIALS AND METHODS

Sixteen adult male mongrel dogs weighing 11 to 19 kg were assigned randomly to receive a 6 % 200 kDa hydroxyethyl starch (HES) in saline (A group) or a 12 % 200 kDa HES in saline (B group). The dogs were sedated initially with pentobarbital sodium 30 mg/kg administered intravenously. Pancuronium bromide 0.2 mg/kg was administered to facilitate tracheal intubation. The dogs were placed in a supine position under anesthesia with continuous intravenous infusion of ketamine chloride at 5 mg/kg/h. The dogs were ventilated with oxygen using a Harvard respirator (DOG Respirator Model 613, Harvard Apparatus, USA). The respiratory tidal volume was adjusted to maintain an end-expiratory carbon dioxide pressure of 30 to 40 mmHg and was monitored with an infrared carbon dioxide analyzer.

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 for volume resuscitative therapy with a plasma substitute. The left femoral artery was cannulated for the continuous monitoring of systemic arterial pressure and for blood samplings. Left ventricular pressure (LVP) was monitored with a 7-French pigtail catheter introduced through the right femoral artery. The maximum rate of left ventricular pressure change (LV dp/dt max) was measured by electrically deriving a LVP wave using an electric differentiator. A 7.5-French balloon-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 measurement of circulatory parameters. 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 densitomerty (PDD). PDD was performed using a DDG analyzer (DDG-2001 Nihon Kohden Corp, Tokyo, Japan). A nostril probe which is connected to the integrated pulse-spectrophotometry monitoring system was fixed on the tongue to detect the blood concentrations of indocyanine green (ICG) based on pulse-spectophotometry. In a preliminary experiment, the tongue probe was found to detect pulsation better than probes on the finger, ear or nostril. Twenty-five milligrams of ICG in 10 ml of 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 (min) after the surgical procedure before the physiological measurements were taken (baseline values). Thereafter, hemorrhagic shock was induced by withdrawal of blood. The mean arterial pressure

(mAP) decreased to approximately 50 mmHg within 10 min and then stabilized at this level for 20 min on further withdrawal or retransfusion of blood.

Thirty minutes after induction of hemorrhagic hypotension, resuscitation was started within 2 min by an intravenous bolus injection of either group A or group B in a volume equivalent to the amount of blood lost. Measurements were taken at baseline, end of hypotensive shock (Shock), 5 (5R), 30 (30R), 60 (60R), 120 (120R), and 180 (180R) min after bolus resuscitation.

The following variables were measured in all dogs: Hb, HR, mean arterial pressure (mAP), mean pulmonary arterial pressure (mPAP), pulmonary arterial wedge pressure (PAWP), LVP, CO, partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), plasma colloidal osmotic pressure (Pcop), plasma crystalloidal osmotic pressure (Posm), and CBV. 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 mesurements for analysis of Pcop and Posm. Blood samples were kept on ice and centrifuged at 2,000 g for 10 min at 4 ℃. The plasma was removed and analyzed for Pcop using an osmometer (Colloid Osmometer 4400, WESCOR Corp., USA). The Posm was measured by a cryoscope (Osmotic Pressure AUTO & STAT OM-6030, Kyoto Daiichi Kagaku Corp., Japan).

Data are expressed as mean ± standard error (SE). The data were analyzed for significant differences within groups between the baseline values or Shock values and those for the subsequent phases (5R~180R), using the Student's paired t-test, with $P<0.05$ considered as statistically significant. Differences between the two groups were analyzed using the Student's unpaired t-test. Values of $P<0.05$ were considerd statistically significant.

RESULTS

Hb did not differ significantly between the A and B groups under the baseline condition (11.9 ± 0.4 and 11.8 ± 0.6 g/dl). Similarly, the volume of blood withdrawn did not differ significantly between the 2 groups (A group= 33.5 ± 4.2 ml/kg, B group= 32.3 ± 3.5 ml/kg).

Hemodynamic variables are shown in Table. Under the baseline and hemorrhagic conditions, there

Table 1
Hemodinamic variables in response to Shock and at 15, 30, 60, 120, and 180 min often resuscitation

Variable	Group	Baseline	Shock	5R	30R	60R	120R	180R
HR	A	156±7	162±9	140±8	150±7	152±8	147±8	145±9
	B	148±10	158±9	122±7	138±7	142±6	136±5	132±5
mAP	A	133±4	50±1[a]	125±6[b]	132±5[b]	131±4[b]	135±4[b]	135±4[b]
	B	130±8	50±1[a]	137±7[b]	133±6[b]	132±5[b]	132±5[b]	137±6[b]
mPAP	A	17±1	11±1[a]	24±2[ab]	23±2[ab]	22±2[ab]	21±1[ab]	19±1[ab]
	B	17±1	12±1[a]	25±1[ab]	24±1[ab]	22±1[ab]	21±1[ab]	19±1[ab]
PAWP	A	11±1	6±1[a]	14±1[ab]	14±1[ab]	14±1[ab]	13±1[ab]	14±1[ab]
	B	12±1	8±1[a]	16±1[ab]	15±1[ab]	15±1[ab]	15±1[ab]	14±1[ab]
CI	A	1.5±0.1	0.5±0.1[a]	2.5±0.2[ab]	2.5±0.2[ab]	2.5±0.2[ab]	2.4±0.2[ab]	2.2±0.3[ab]
	B	1.6±0.1	0.5±0.1[a]	2.3±0.2[ab]	2.5±0.2[ab]	2.5±0.2[ab]	2.4±0.2[ab]	2.3±0.2[ab]
SVR	A	8417±556	9295±298[a]	5115±740[ab]	5240±719[ab]	5296±681[ab]	5827±772[ab]	6343±807[ab]
	B	8501±766	10043±488[a]	6354±587[ab]	5694±511[ab]	5789±469[ab]	6043±470[ab]	6376±532[ab]
LVSWI	A	17.5±0.9	2.1±0.2[a]	26.0±1.9[ab]	26.3±2.3[ab]	26.4±2.8[ab]	26.6±2.6[ab]	25.2±3.1[ab]
	B	17.8±0.9	1.9±0.1[a]	29.6±0.9[ab]	29.3±0.8[ab]	28.4±0.9[ab]	28.7±1.0[ab]	29.5±1.2[ab]
LV dp/dt max	A	2250±172	950±105[a]	2938±471[ab]	2750±295[ab]	2963±322[ab]	2800±295[ab]	2700±276[ab]
	B	2250±287	925±111[a]	2888±408[ab]	3138±388[ab]	3025±257[ab]	2888±229[ab]	2775±248[ab]
Pcop	A	13.9±0.5	11.2±0.3[a]	16.7±0.4[abc]	15.0±0.7[abc]	14.0±0.4[bc]	13.8±0.8[bc]	12.8±0.4[bc]
	B	14.0±0.7	12.3±0.6[a]	28.0±2.1[ab]	21.6±1.4[ab]	19.4±1.1[ab]	17.7±1.0[ab]	16.9±0.9[ab]
Posm	A	308±2	309±3	317±3	314±2	309±2	310±2	311±2
	B	306±2	306±2	314±3	310±2	310±4	312±2	312±3
CBV	A	1.35±0.08	0.89±0.03[a]	1.85±0.11[ab]	1.90±0.13[ab]	1.81±0.10[ab]	1.80±0.10[ab]	1.85±0.15[ab]
	B	1.36±0.15	0.89±0.09[a]	1.90±0.18[ab]	2.20±0.27[ab]	2.41±0.37[ab]	2.07±0.25[ab]	2.09±0.27[ab]

(n=7)
Data are expressed as mean ± standard error (SE)
HR: heart rate (beats·min^{-1}); mAP: mean arterial pressure (mmHg); mPAP: mean pulmonary arterial pressure (mmHg); PAWP: pulmonary arterial wedge pressure (mmHg); CI: cardiac index (l·min^{-1}·m^{-2}); SVR: systemic vascular resistance (dyn·sec·cm^{-5}); LVSWI: left ventricular stroke work index (g·m·beat^{-1}·m^{-2}); LV dp/dt max: maximum rate of left ventricular pressure change (mmHg·sec^{-1}); Pcop: plasma colloid osmotic pressure (mmHg); Posm: plasma crystalloid osmotic pressure (mOsm·kg^{-1}·H_2O^{-1}); CBV: circulating blood volume (litter)
A: prostaglandin E_1 group,
B: saline group
Baseline: after surgical procedure. Shock: end of hemorrhagic hypotensive shock.
5R, 30R, 60R, 120R, and 180R: 15, 30, 60, 120, and 180 min after resuscitation.
[a]$P<0.05$: from Baseline
[b]$P<0.05$: between group A and B

was no difference in the hemodynamic variables between the two groups. After hemorrhagic shock, a significant decrease in mAP, mPAP, PAWP, CI, LVSWI and LV dp/dt max and an increase in SVR values occurred as compared with baseline values in both groups. After induction of resuscitation, HR and mAP did not differ significantly as compared with the baseline values. However, a significant increase in mPAP, PAWP, CI, LVSWI and LV dp/dt max and a decrease in SVR values occurred as compared with the baseline condition during any of the experimental periods in both groups. After resuscitation, all the hemodynamic variables did not differ significantly between the two groups.

With regard to the respiratory variables, PaO_2 and $PaCO_2$ under the baseline condition did not differ between the two groups: In the group A, PaO_2 was 562 ± 12 mmHg and $PaCO_2$ was 37.3 ± 2.5 mmHg, whereas in the group B, the corresponding values were 586 ± 9 mmHg and 36.1 ± 1.1 mmHg, respectively.

Pcop, Posm and CBV are shown in Table. Pcop, Posm and CBV values did not differ significantly between the two groups under the baseline and hemorrhagic condition. After hemorrhagic shock, a significant decrease in Pcop and CBV occurred as compared with baseline values in both groups. After resuscitation, CBV increased significantly as compared with the baseline condition during all the resuscitative periods in both groups. CBV did not differ significantly between the two groups. In the group B, after resuscitation, Pcop values were increased significantly as compared with the baseline condition during all the resuscitative period. On the other hand, in the group A, Pcop values showed a significant increase during 5R~30R following resuscitation. Moreover, the Pcop values in the group B were significantly greater than those in the group A during all the resuscitative periods. On the other hand, the Posm did not differ throughout the experimental period as compared with the baseline conditionin both group.

DISCUSSION

Plasma expansion after infusion of crystalloidal solution was relatively short-lived. Hauser et al.(1) have suggested that aggressive use of crystalloid extracellular fluid expantion to expand the plasma volume is contraindicated. On the other hand, plasma substitutes, such as hydroxyethyl starch, are commonly used as a plasma volume expander, in part because of thrapeutic safety, its stable effect on plasma volume, and its association with a low incidence of anaphylactic reactions (2). In the present study, the authors compared the effects of either iso- or hyper-oncotic colloidal solution used as treatment for experimental hemorrhagic condition.

Many investigators (1,3-5) reported that volume replacement with artificial colloid yielded hemodynamic stability, whereas administration of crystalloids alone jeopardized tissue perfusion and oxygenation. In constant, crystalloids are equally capable of achieving hemodynamic stability, provided sufficient volumes are infused (6). However, fluid overload may become a problem. The increased blood volume after colloids and the decreased blood volume after crystalloids suggests that the escape of fluid from plasma is greater after the latter. For reason of safety, efficiency and practicability colloid solutions rather than crystalloid solutions should be used for volume replacement therapy.

The main reason for using colloidal volume replacements is to maintain the circulating blood volume by stabilizing plasma oncotic pressure (7). This study was carried out in order to find out whether hyper-oncotic colloidal solution has a beneficial effect on restoration of circulating blood volume in hypovolemic condition. After resuscitation, Pcop in group B were significantly greater than that in group A. On the other hand, CBV did not differ significantly between two groups. Moreover, all the hemodynamic variables did not differ significantly. In group B, high and prolonged colloidal osmotic pressure levels in blood were noteworthy. However, treatment with group B was made with little or no improvement in clinical symptoms as compared to that with group A.

A potential side effect of HES treatment is the in-

hibition of the coagulation system. In particularly, high molecular weight hydroxyethyl starch was reported to specifically influence blood coagulation and fibrinolysis parameters (8,9). On the other hand, hydroxyethyl starch, used as a plasma expander in the present study, was in medium molecular weight type. Some investigators (9,10) reported that medium molecular weight hydroxyethyl starch does not influence the function of platelet aggregation and fibrinolytic system. However, after repeated administration, there was a more pronounced increase in partial thromboplastin time and a factor of 2 large decrease of factor VIII/von Willebrand factor-complex, which exceed the dilution effect (11). Vogt et al.(12) reported that with respect of efficacy and side effects on coagulation and renal function, medium molecular HES is an appropriate and economic alternative to alubumin at daily doses of up to at least 36 ml/kg.

PDD method is a technique for monitoring the arterial concentration of ICG. Using this method, CBV can be calculated without using radioisotopes. The CBV estimation with the method is reliable, as reflected by the reproducible CBV estimated in the same subject (13,14). One potential pitfall of this PDD method is the variation of the hematocrit value (or blood hemoglobin concentration) within the body. In the present study, Hb obtain from a peripheral artery. In certain pathologic conditions, the difference in the hematocrit between the central and peripheral circulation becomes larger, and this ratio is called the F-cell ratio. For instance, hypovolemia creates a lower F-cell ratio when erythrocytes become heterogeneous within the body. A varying F-cell ratio may produce a large error in the estimates of CBV value. Further detailed studies must be made in a large number of experiments.

CONCLUSION

The results of this study suggest that hemodynamic variables and CBV did not differ significantly between two groups as volume replacement therapy in a canine model of hemodynamic shock. However, Pcop in group B were significantly greater than that in group A. Treatment with group B was made with little or no improvement in clinical symptoms as compared to that with group A.

ACKNOWLEDGMENT

The authors thank Doctor Akiyoshi Hosoyamada for his valuable comments on the contents of his manuscript.

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ABSTRACT

Objective: The aim of this study was to assess the relative efficacy of 2 volume replacement therapies in a canine model of induced hemorrhagic shock.

Methods: Anesthetized dogs were bled to maintain a mean arterial pressure (mAP) at 50 mmHg for 30 minutes and then administered a single bolus injection of 6 % hydroxyethyl starch (HES) with a molecular weight of 200 kDa (A group) or 12 % HES (B group) at a volume equivalent to the blood withdrawn. The efficacy of both therapies in maintaining the hemodynamic variables, the plasma colloidal and crystalloidal osmotic pressure (Pcop and Posm), and the circulating blood volume (CBV) were investigated.

Results: After resuscitation, hemodynamic variables were improved in both groups. All the hemodynamic variables did not differ signifacantly between two groups. While CBV decreased significantly after hemorrhagic shock, subsequent increased after volume replacement resuscitation in both groups. After resuscitation, CBV did not differ significantly between the two groups. However, plasma colloidal osmotic pressure (Pcop) in group B were significantly greater than that in group A.

Conclusion: The results of this study suggest that hemodynamic variables and CBV did not differ significantly between two groups as volume replacement therapy in a canine model of hemodynamic shock. However, Pcop in group B were significantly greater than that in group A. Treatment with group B was made with little or no improvement in clinical symptoms as compared to that with group A.

Key Words: hydroxyethyl starch, hemorrhagic shock, colloidal osmotic pressure (Posm), circulating blood volume (CBV), plasma colloidal osmotic pressure(Pcop).