대한마취과학회지 2007; 53: S 14～21
Korean J Anesthesiol Vol. 53, No. 3, September, 2007

□ 영문논문 □

The Effect of 6% Hydroxyethyl Starch 130/0.4 on Hemostasis and Hemodynamic Efficacy in Off-pump Coronary Artery Bypass Surgery: a Comparison with 6% Hydroxyethyl Starch 200/0.5

Department of Anesthesiology and Pain Medicine, Anesthesia and Pain Research Institute, Yonsei University College of Medicine, Seoul; *Department of Anesthesiology and Pain Medicine, Gachon University of Medicine and Science, Incheon, Korea

Ji Young Kim, M.D.*, **Jong Wha Lee,** M.D., **Tae Dong Kweon,** M.D., **Young Lan Kwak,** M.D., **Ji Ho Kim** M.D., and **Sou Ouk Bang,** M.D.

Background: This study was designed to compare the effect of low-molecular 6% hydroxyethyl starch (HES) 130/0.4 on hemostasis and hemodynamic efficacy with that of medium-molecular 6% HES 200/0.5 in patients undergoing off-pump coronary artery bypass surgery.

Methods: Forty-eight patients were randomized to receive up to 33 ml/kg of either 6% HES 130/0.4 or 6% HES 200/0.5. Hemodynamic variables and blood tests including thromboelastography were measured 10 min after induction (baseline value, T0), 5 min after acute loading of HES 10 ml/kg (T1) in hypovolemic patients, after sternum closure (T2), and 16 hr after intensive care unit (ICU) arrival (T3). Chest tube drainage was recorded until 16 hours after ICU arrival.

Results: Hemodynamic variables were similar in both groups. Chest tube drainage at 16 hr after surgery was higher in HES 200/0.5 group than that in HES 130/0.4 group. Maximum clot firmness was decreased in HES 200/0.5 group at sternal closure but not in HES 130/0.4 group.

Conclusions: Both HES 200/0.5 and HES 130/0.4 were equally efficient in maintaining stable hemodynamics during off-pump coronary artery bypass surgery. However, HES 130/0.4 may reduce postoperative blood loss compared to that of HES 200/0.5 at the same dose of 33 ml/kg. **(Korean J Anesthesiol 2007; 53: S 14～21)**

Key Words: blood coagulation, fluid therapy, off-pump coronary artery bypass surgery, thromboelastography.

INTRODUCTION

Hydroxyethyl starch (HES) solutions are widely used for intravascular volume replacement. They are effective in volume therapy but they may cause coagulopathy when administered in large doses. High-molecular weight (MW) HES was reported to adversely affect on coagulation.[1,2] On the other hand, many studies confirmed that newly developed low to medium MW, low-substituted HES such as 6% HES 130/0.4 (Voluven®, Fresenius Kabi, Bad Homburg, Germany) and 6% HES 200/0.5 (HAES-steril Inj 6%®, Fresenius Kabi, Bad Homburg, Germany) affect less on coagulation compared to that of high molecular HES solutions.[3-5] When these two HES solutions were compared during cardiac surgery under cardiopulmonary bypass, both colloids have demonstrated similar effect on coagulation and volume expansion.[6-9] However, since cardiopulmonary bypass compromises coagulation system, the effect of a volume expander on coagulation profile would be better studied during off-pump coronary artery bypass surgery (OPCAB). This study was designed to compare the effect of low-molecular 6% HES 130/0.4 on hemostasis and hemodynamic efficacy with that of medium-molecular 6% HES 200/0.5 in patients undergoing OPCAB.

MATERIALS AND METHOS

After obtaining the approval of the Institutional Review Board, written informed consent for the study was obtained from all patients. Forty-eight patients undergoing elective OPCAB were randomly divided into either the HES 130/0.4 group or the

Received : March 27, 2007
Corresponding to : Sou Ouk Bang, Department of Anesthesiology and Pain Medicine, Severance Hospital, 134, Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea. Tel: 82-2-2228-8500, Fax: 82-2-364-2951, E-mail: sokbang@yumc.yonsei.ac.kr

HES 200/0.5 group using a computer-generated randomized table. Patients and anesthesiologists were blinded to the treatment group and an independent researcher transferred the maximum amount of study solution (33 ml/kg/d) into a collection bag, which was marked with patient's name and identification number. Patients who had medical histories of valvular heart disease, myocardial infarction within the previous 3 months, congestive heart failure (left ventricular ejection fraction < 40%), anemia (hemoglobin [Hb] < 10.0 g/dl), renal insufficiency (serum creatinine [Cr] > 1.2 mg/dl), liver dysfunction (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 40 U/L), uncontrolled diabetes mellitus, chronic obstructive pulmonary disease and/or an allergy to HES were excluded from this study. Patients who had coagulopathy (platelet count < 100×10^9/L, activated partial thromboplastin time [aPTT] > 70 s, fibrinogen < 200 mg/dl, antithrombin-III < 40 %) and/or recent (< 3 days) or current medication with any drugs known to affect blood coagulation were also excluded.

All patients received an intramuscular injection of morphine 0.05 mg/kg for premedication. Aspirin and antiplatelet agents were discontinued three days before the procedure. The right radial artery was cannulated and a pulmonary artery catheter (Vigilance Swan-Ganz Combo, Baxter Healthcare Co, USA) was inserted through the right internal jugular vein to monitor hemodynamic variables. Anesthesia was induced with midazolam 2.0－3.0 mg, sufentanil 1.5－2.0μg/kg and vecuronium 8 mg. Anesthesia was maintained with a continuous infusion of sufentanil 0.05－0.1μg/kg/h, vecuronium 5－7 mg/h and isoflurane (0.3－0.5%). Ventilation was adjusted to keep the $P_{ET}CO_2$ between 35 mmHg and 40 mmHg with an oxygen- air mixture (FiO_2 = 0.6).

After anesthesia induction, patients with pulmonary capillary wedge pressures (PCWP) equal to or less than 10 mmHg were considered hypovolemic and 10 ml/kg of the HES solution was infused over 30 min period. During the study period, maximum dosage of either 6% HES 130/0.4 or 200/0.5 was infused according to their group to maintain the cardiac index above 2.2 L/min/m^2, the PCWP between 8－14 mmHg and the urine output above 0.5 ml/kg/h. Volume requirements in excess of the maximum dose of the HES solution were treated with crystalloid solutions. Activated clotting time was kept above 250 s with heparin throughout the anastomosis and reversed with protamine 0.5 mg per 100 units. A cell saver was used and salvaged blood from the cell saver was transfused during surgery in all cases.

Hemodynamic variables including heart rate, mean arterial blood pressure, pulmonary artery pressure, PCWP, central venous pressure, and cardiac output (CO) were measured 10 min after induction (baseline value, T0), 5 min after acute loading of HES 10 ml/kg (T1) in hypovolemic patients, after sternum closure (T2), and 16 hr after intensive care unit (ICU) arrival

Table 1. Patient Characteristics and Data from the Perioperative Period

	HES 200/0.5 (n = 24)	HES 130/0.4 (n = 24)
Gender (M/F)	18/6	15/9
Age (yr)	61 (53－67 [42－77])	66 (56－70 [46－81])
Weight (kg)	66.6 ± 11.1	64.9 ± 8.8
Preoperative EF (%)	62.2 ± 8.5	61.1 ± 7.8
Diabetes mellitus	7 (29)	7 (29)
Hypertension	11 (46)	14 (58)
Preoperative LVEDD (mm)	48.0 ± 5.4	48.5 ± 3.2
Preoperative medication		
Beta-blockers	15 (62)	19 (79)
Ca^{2+} channel blockers	8 (33)	15 (62)
ACE-I	10 (42)	10 (42)
Diuretics	1 (4)	3 (12)
Grafts (number)	3 (3－4 [2－5])	3 (3－4 [2－5])
Operation time (min)	322 ± 27.4	324 ± 66.5

Data are mean ± SD, median (IQR [range]) or number of patients (%). EF: ejection fraction, LVEDD: left ventricular end diastolic dimension, ACE-I: angiotensin converting enzyme inhibitors.

(T3). Left ventricular end diastolic dimensions at the mid-papillary level were measured with transesophageal echocardiography at T0, T1 and T2. To obtain oxygen profiles, arterial and mixed venous blood gas analyses were performed at T0, T2 and T3. Hematologic parameters (Hb and hematocrit [Hct]), biochemical variables (blood urea nitrogen, Cr, AST and ALT) and coagulation profiles (thromboelastrography [TEG], prothrombin time [PT], aPTT, antithrombin-Ⅲ, fibrinogen and platelet count) were recorded simultaneously. Using blood gas analysis results such as partial arterial oxygen pressure (PaO_2), arterial oxygen saturation (SaO_2), partial mixed venous oxygen pressure (PvO_2) and mixed venous oxygen saturation (SvO_2), the oxygen profiles were calculated according to following formulae: arterial oxygen content (CaO_2) = 1.39 × Hb × SaO_2 + 0.0031 × PaO_2; mixed venous oxygen content (CvO_2) = 1.39 × Hb × SvO_2 + 0.0031 × PvO_2; oxygen delivery (DO_2) = 10 × CO × CaO_2; oxygen extraction ratio = 10 × CO × (CaO_2 − CvO_2)/DO_2. The TEG was measured with a 2-channel coagulation analysis system (TEG model 3000, Haemoscope Corp., Niles, IL, USA).

All patients were transferred to the ICU after surgery. Packed red blood cells were transfused when the Hb fell below 8 g/dl. Fresh frozen plasma was transfused to correct microvascular bleeding (chest tube drainage > 200 ml/h for two consecutive hours) in the presence of abnormal coagulation

Table 2. Fluid Balance

	HES 200/0.5 (n = 24)	HES 130/0.4 (n = 24)
Study drug (L)	2.3 ± 0.6	2.4 ± 0.5
Crystalloids (L)	6.7 ± 1.4	7.2 ± 1.5
Transfusion requirements (U)		
Packed red blood cell	1 (0−2 [0 − 3])	1 (0−1 [0−4])
Fresh-frozen plasma	0 (0−2 [0−6])	0 (0−0 [0−4])
Cell saver blood (ml)	339 ± 192	344 ± 295
Chest tube drainage (ml)	713 ± 263	530 ± 247*
Urine output (ml)	2,500 ± 800	2,400 ± 900

Data are mean ± SD or median (IQR [range]). *: P < 0.05, vs. HES 200/0.5 group.

Table 3. Hemodynamic Variables before and after Hydroxyethyl Starch Loading in Hypovolemic Patients

	Group	T0	T1
Heart rate (beats/min)	HES 200/0.5	63.1 ± 8.4	56.2 ± 3.4*
	HES 130/0.4	63.9 ± 7.0	60.7 ± 5.2†
MBP (mmHg)	HES 200/0.5	71.7 ± 10.5	78.1 ± 13.4
	HES 130/0.4	75.7 ± 7.9	75.0 ± 7.9
PCWP (mmHg)	HES 200/0.5	8.2 ± 1.4	13.3 ± 2.7*
	HES 130/0.4	7.3 ± 0.6	14.2 ± 2.6*
Cardiac index (L/min/m^2)	HES 200/0.5	2.7 ± 0.5	2.6 ± 0.3
	HES 130/0.4	2.9 ± 0.5	3.1 ± 0.4†
RVEF (%)	HES 200/0.5	35.7 ± 9.3	32.3 ± 5.5
	HES 130/0.4	30.3 ± 6.7	34.5 ± 7.4
LVEDD (mm)	HES 200/0.5	32.4 ± 7.6	36.3 ± 5.4*
	HES 130/0.4	32.2 ± 6.7	36.6 ± 4.9*
DO_2 (ml O_2/min)	HES 200/0.5	831 ± 173	628 ± 133*
	HES 130/0.4	838 ± 209	784 ± 167†
O_2 extraction ratio (%)	HES 200/0.5	22 ± 3	23 ± 2
	HES 130/0.4	20 ± 3	21 ± 3
PaO_2/FiO_2 ratio	HES 200/0.5	400 ± 82	401 ± 97
	HES 130/0.4	339 ± 89	401 ± 84
Pulmonary shunt ratio	HES 200/0.5	0.12 ± 0.04	0.17 ± 0.06
	HES 130/0.4	0.16 ± 0.04	0.18 ± 0.09

Data are mean ± SD. T0: ten minutes after induction of anesthesia (baseline), T1: five minutes after loading 10 ml/kg of HES solutions, MBP: mean arterial blood pressure, PCWP: pulmonary capillary wedge pressure, RVEF: right ventricular ejection fraction, LVEDD: left ventricular end diastolic dimension, DO_2: oxygen delivery. *: P < 0.05, vs. T0, †: P < 0.05, vs. HES 200/0.5 group.

values (PT > 15 s, aPTT > 60 s, and/or fibrinogen concentration < 1 g/dl). Platelet concentrate was transfused when the platelet count was less than 80 × 10^9/L. The amount of chest tube drainage, infused fluid and homologous transfusions throughout the study period were recorded. The length of the stay in the ICU was also recorded.

Statistical analyses were performed with SPSS 11.5 (SPSS 11.5 for Windows, SPSS Inc., Chicago, IL, USA). All data are expressed as mean ± standard deviation unless otherwise indicated. The sample-size calculation was performed based on the Ruttmann's Study with the following assumptions:[10] clinical significance α at 0.05 with a paired t-test and power to expect a significant result = 0.85, the mean difference between groups = 10% with a standard deviation at 12% of the mean value of the maximal amplitude. This generates an estimate of 24 patients. Demographic data and ICU data between the groups were compared using Chi-square test, Fisher's Exact Test or independent t-test where appropriate. Mann-Whitney U Test was used when the variables did not have a normal distribution. Paired t-test with Bonferroni Correction was used for multiple comparisons between baseline values and the values at each time point within each group. Independent t-test for comparisons between the groups was also used. A P-value of less than 0.05 was considered as statistically significant.

RESULTS

Patient characteristics and data from the perioperative period are listed in Table 1 and they were comparable. Fluid balance is listed in Table 2. There were no differences in total amounts of HES and fluid infused between the two groups. The chest tube drainage in the ICU was higher in the HES 200/0.5 group than in the HES 130/0.4 group (P = 0.016) but the amount of cell saver blood and the use of allogenic blood products were similar between the two groups. The frequency of transfusions and the length of ICU stay were not different between the two groups. The length of the stay in the ICU was 1.9 ± 0.7 d in the HES 200/0.5 group and 2.4 ± 2.1 d in the HES 130/0.4 group.

Twelve patients from each group were hypovolemic after the

Table 4. Changes in Hemodynamic Variables and Oxygenation Profiles

	Group	T0	T2	T3
Heart rate (beats/min)	HES 200/0.5	65.7 ± 9.6	76.5 ± 12.0*	78.1 ± 7.1*
	HES 130/0.4	65.0 ± 8.3	74.1 ± 9.9*	82.0 ± 10.1*
MBP (mmHg)	HES 200/0.5	75.6 ± 12.3	78.7 ± 10.3	77.9 ± 8.9
	HES 130/0.4	76.3 ± 9.6	77.1 ± 10.6	74.2 ± 9.4
PCWP (mmHg)	HES 200/0.5	9.9 ± 3.6	13.2 ± 3.3*	11.9 ± 3.4
	HES 130/0.4	9.7 ± 3.2	12.8 ± 3.0*	10.7 ± 2.2
Cardiac index (L/min/m^2)	HES 200/0.5	3.0 ± 0.6	2.7 ± 0.5	3.5 ± 0.6*
	HES 130/0.4	3.1 ± 0.6	2.6 ± 0.8*	3.5 ± 0.8*
RVEF (%)	HES 200/0.5	37.0 ± 10.6	32.1 ± 7.7	
	HES 130/0.4	36.7 ± 8.4	33.2 ± 6.9	
LVEDD (mm)	HES 200/0.5	33.9 ± 6	30.2 ± 6	
	HES 130/0.4	33.8 ± 6	33.7 ± 6	
DO_2 (ml O_2/min)	HES 200/0.5	998 ± 295	649 ± 214*	
	HES 130/0.4	984 ± 288	606 ± 169*	
O_2 extraction ratio (%)	HES 200/0.5	21 ± 3	29 ± 6*	
	HES 130/0.4	20 ± 2	30 ± 6*	
PaO_2/FiO_2 ratio	HES 200/0.5	383 ± 89	314 ± 92*	
	HES 130/0.4	346 ± 86	317 ± 96	
Pulmonary shunt ratio	HES 200/0.5	0.14 ± 0.05	0.18 ± 0.08	
	HES 130/0.4	0.16 ± 0.05	0.18 ± 0.08	

Data are mean ± SD. T0: ten minutes after induction of anesthesia (baseline), T2: after sternum closure, T3: 16 hr after arrival at the intensive care unit. MBP: mean arterial blood pressure, PCWP: pulmonary capillary wedge pressure, RVEF: right ventricular ejection fraction, LVEDD: left ventricular end diastolic dimension, DO_2: oxygen delivery. *: P < 0.05, versus T0.

Table 5. Laboratory Data

	Group	T0	T2	T3
PT (s)	HES 200/0.5	11.8 ± 0.8	14.9 ± 1.2*	14.9 ± 1.1*
	HES 130/0.4	11.7 ± 0.8	14.6 ± 1.7*	14.8 ± 1.4*
aPTT (s)	HES 200/0.5	38.0 ± 9.9	44.7 ± 15.9	46.4 ± 16.5
	HES 130/0.4	45.3 ± 22.1	40.9 ± 9.2	42.9 ± 13.1
Platelet ($\times 10^9$/L)	HES 200/0.5	242 ± 80.4	152 ± 46.6*	149 ± 58.0*
	HES 130/0.4	239 ± 71.2	155 ± 65.9*	133 ± 46.7*
Fibrinogen (mg/dl)	HES 200/0.5	358 ± 81.9	191 ± 61.0*	
	HES 130/0.4	373 ± 101.0	235 ± 79.7*	
AT-III (%)	HES 200/0.5	93.9 ± 8.9	56.1 ± 11.6*	
	HES 130/0.4	94.9 ± 17.5	59.9 ± 17.7*	
BUN (mg/dl)	HES 200/0.5	15.4 ± 4.5	12.0 ± 2.9*	12.6 ± 4.1*
	HES 130/0.4	15.2 ± 2.9	11.7 ± 2.5*	14.7 ± 3.7
Creatinine (mg/dl)	HES 200/0.5	1.00 ± 0.2	0.8 ± 0.2*	0.9 ± 0.2*
	HES 130/0.4	0.96 ± 0.2	0.8 ± 0.3*	1.0 ± 0.2
AST (U/L)	HES 200/0.5	25.1 ± 11.3	30.3 ± 12.3	46.1 ± 23.3*
	HES 130/0.4	34.0 ± 28.4	31.8 ± 17.8	48.2 ± 34.0
ALT (U/L)	HES 200/0.5	28.2 ± 17.7	25.1 ± 16.6	27.1 ± 14.2
	HES 130/0.4	32.3 ± 28.0	26.0 ± 25.3	27.8 ± 20.2
Hematocrit (%)	HES 200/0.5	38.2 ± 4.5	28.2 ± 4.3*	24.3 ± 4.1*
	HES 130/0.4	37.3 ± 4.5	28.6 ± 4.4*	24.7 ± 2.5*

Data are mean ± SD. T0: ten minutes after induction of anesthesia (baseline), T2: after sternum closure, T3: 16 hr after arriving at the intensive care unit. PT: prothrombin time, aPTT: activated partial thromboplastin time, AT-III: antithrombin-III, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase. *: $P < 0.05$, vs. T0.

induction of anesthesia and hemodynamic data before (T0) and after (T1) HES loading are listed in Table 3. The PCWP and left ventricular end diastolic dimension significantly increased in both groups compared to their baseline values at T1. Heart rate and DO_2 at T1 significantly decreased in the HES 200/0.5 group but not in the HES 130/0.4 group. Heart rate, cardiac index and DO_2 were significantly higher in the HES 130/0.4 group than in the HES 200/0.5 group at T1. There were no significant differences in TEG parameters after HES loading both within the group and between two groups.

The changes in hemodynamic variables and oxygenation profiles throughout the study period are listed in Table 4. At sternal closure (T2), heart rate and PCWP significantly increased in both groups. At T2, the decrease in DO_2 and the increase in oxygen extraction ratio were significant in both groups compared to baseline values. In the ICU (T3), the heart rate and cardiac index significantly increased in both groups compared to the baseline values.

Laboratory data are presented in Table 5. There were no significant differences in the hematologic variables and coagulation profiles between the two groups. Fibrinogen and antithrombin-III were significantly decreased at T2 compared to the baseline values in both groups. The increase in PT and the decrease in Hct, platelet count were statistically significant at T2 and T3 compared to the baseline values in both groups. Biochemical variables were within normal limits throughout the study period in both groups. There were no differences in TEG parameters within the group and between two groups except maximum amplitude in HES 200/0.5 group, which was significantly decreased at T2 compared to the baseline value (Fig. 1).

DISCUSSION

The present study demonstrated that in patients undergoing OPCAB, HES 130/0.4 showed similar hemodynamic efficacy with 200/0.5. Biochemical data representing liver and kidney function remained within normal limit after the surgery in both groups. On the other hand, the amount of postoperative bleeding, which was measured as chest tube drainage, was less in

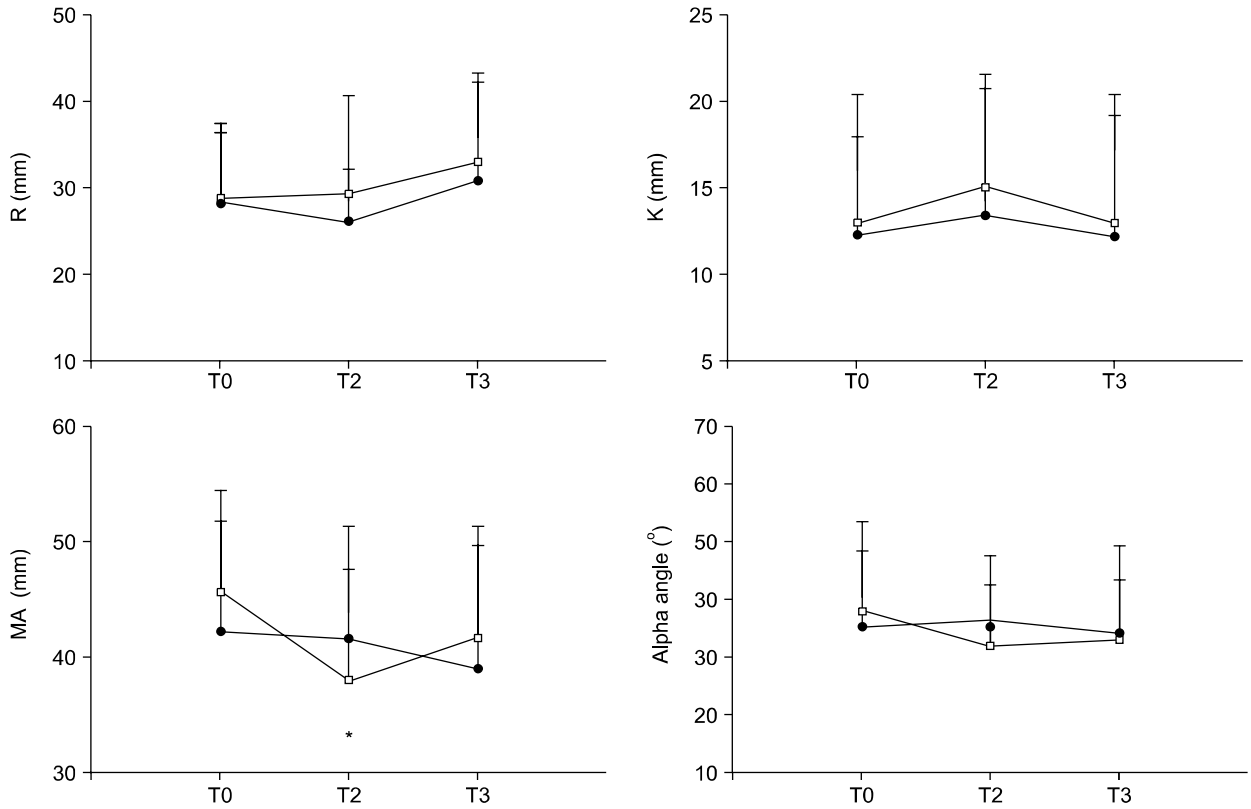

Fig. 1. Changes in Thromboelastography Data. Data are mean ± SD. T0: ten minutes after induction of anesthesia (baseline), T2: after sternum closure, T3: 16 hr after arriving at the intensive care unit. R: reaction time, K: kinetic time, MA: maximal amplitude. Open squares: HES 200/0.5 group, Filled circles: HES 130/0.4 group. *: $P < 0.05$, vs T0. Horizontal dotted line: normal range.

the HES 130/0.4 group than in the HES 200/0.5 group. Although maximum amplitude in TEG demonstrated HES 130/0.4 to have less effect on platelet function compared to HES 200/0.5, other changes in TEG data were too sporadic to conclude this result as favorable effect on coagulation.

High molecular weight HES with high degree of substitution and high C2 to C6 ratio is reported to impair hemostasis.[1,2] Although several human studies confirmed that medium molecular weight HES (MW 200,000 to 250,000) with a lower degree of substitution does not have same negative effect on hemostasis, medium MW HES also compromises platelet contribution to hemostasis by reducing the availability of fibrinogen binding sites on activated platelets.[11-13] On the other hand, recent studies on the effect of HES specifications on hemostasis report that HES 130/0.4 has smallest effect compared to other HES specifications and similar with gelatin, which has minimal effect on coagulation.[3,14,15] In this study, TEG data in the HES 130/0.4 group were similar within the group except maximum amplitude (Fig. 1). The decrease in maximum amplitude compared to the baseline value at sternal closure (T2) in the HES 200/0.5 group was statistically significant, which was consistent with previous study.[10] Alpha angle was also decreased at sternal closure in the HES 200/0.5 group but the value did not reach statistical significance. Maximum amplitude and alpha angle are two variables that are significantly influenced by platelet function. However, although chest tube drainage was less with HES 130/0.4 than with 200/0.5, clinical significance could not be determined because other clinical outcome variables such as amount of cell saver blood, total units of packed red blood cells and fresh frozen plasma per group and the number of patients transfused with allogenic blood product during the study period were comparable between the two groups. In addition, although statistically not significant, the amount of crystalloid was lower and the urine output was higher in HES 200/0.5 group compared to those in HES 130/0.4 group. Further study with large dose HES 130/0.4 (50 ml/kg) may confirm the clinical significance since Kasper et al.[16] reported that large dose HES

130/0.4 dose not increase blood loss and transfusion requirement in patients undergoing cardiopulmonary bypass compared with HES 200/0.5 at recommended doses. Hemodynamic variables were similar in the ICU. This may have resulted from difference in the use of vasopressors and inotropic drugs.

Although HES 130/0.4 has an increased metabolic turnover and enhanced plasma elimination, its volume expanding efficacy was reported to be comparable to that of HES 200/0.5 in several studies.[4,8,9] Likewise, there was no significant difference in the amount of crystalloid solution after the maximum dose of HES solution to maintain hemodynamics within the predetermined level between the two groups in this study. This is because the water binding effect of different HES types primarily depends on the number of molecules rather than on their size. The number of molecules in HES 130/0.4 is relatively high due to its lower average MW and narrow MW distribution. The greater number of osmotically effective molecules in HES 130/0.4 is thought to counterbalance its more rapid elimination. This also explains in higher cardiac index shortly after loading of HES 130/0.4 compared to that of HES 200/0.5 in hypovolemic patients. Decrease in heart rate, which was significantly lower in HES 200/0.5 group after loading when compared to that in HES 130/0.4, seemed to be associated with this difference in cardiac index after loading. Although the reason could not be clarified in this study, this minimal effect of HES 130/0.4 on heart rate can be beneficial in patients with coronary artery disease because the heart rate is already reduced with preoperative cardiac medication. Further decrease may result in decreased CO and cardiac distension.

After acute volume loading in hypovolemic patients, DO_2 was significantly reduced only in HES 200/0.5 group, which was significantly lower than in HES 130/0.4 group. This different effect on DO_2 was also reported from the result of a previous study that DO_2 was increased immediately after the infusion of HES 130/0.4 but not with HES 200/0.5.[9] A higher CO in the HES 130/0.4 group seemed to be responsible for this result because Hb, SaO_2 and PaO_2 values were similar between the two groups. The PaO_2/FiO_2 ratio increased after acute loading in the HES 130/0.4 group, although it did not reach statistical significance. An improved oxygen exchange with volume expansion in the ventilaion-perfusion mismatching area of the lung was considered as a possible mechanism.

Many *in vivo* studies on volume expanders are performed during cardiac surgery because clinically relevant bleeding is anticipated and maintenance of adequate volume is critical in patients undergoing cardiac surgery. This permits assessment of outcome variables and optimal hemodynamic efficacy of various colloids as well as their effect on coagulation. However, cardiac operations with long duration of cardiopulmonary bypass cause dilution of blood component and compromise platelet function, which may markedly affect the result of the study regarding hemostasis. On the other hand, OPCAB has the advantage of avoiding cardiopulmonary bypass while necessitating optimal volume therapy to maintain stable hemodynamics, which is affected by cardiac manipulation and considerable amount of bleeding due to the use of anticoagulant. Lo et al.[17] compared the activation of hemostasis after coronary artery bypass surgery with or without cardiopulmonary bypass. They reported that immediately after OPCAB, there is much less hemostatic activation and therefore less consumption of clotting factors that leads to reduced postoperative blood loss. Therefore, the effect of a volume expander on hemostasis is more accurately assessed with OPCAB. Since HES 130/0.4 resulted in decreased postoperative blood loss, HES 130/0.4 would be preferred in high risk patients and especially, in those who could not stop antiplatelet drug before surgery.

In conclusion, both HES 200/0.5 and HES 130/0.4 were equally efficient in terms of hemodynamic efficacy in patients undergoing OPCAB. However, HES 130/0.4 may reduce postoperative blood loss compared to that of HES 200/0.5 at the same dose of 33 ml/kg.

REFERENCES

1. Strauss RG, Stansfield C, Henriksen RA, Villhauer PJ: Pentastarch may cause fewer effects on coagulation than hetastarch. Transfusion 1988; 28: 257-60.
2. Treib J, Haass A, Pindur G: Coagulation disorders caused by hydroxyethyl starch. Thromb Haemost 1997; 78: 974-83.
3. Franz A, Braunlich P, Gamsjager T, Felfernig M, Gustorff B, Kozek-Langenecker SA: The effects of hydorxyethyl starches of varying molecular weights on platelet function. Anesth Analg 2001; 92:1402-7.
4. Boldt J, Haisch G, Suttner S, Kumle B, Schellhaass A: Effects of a new modified, balanced hydroxyethyl starch preparations (Hextend®) on measures of coagulation. Br J Anaesth 2002; 89: 722-8.
5. Konrad CJ, Markl TJ, Schuepfer GK, Schmeck J, Gerber HR: In vitro effects of different medium molecular hydroxyethyl starch solutions and lactated Ringer's solution on coagulation using SONOCLOT. Anesth Aanalg 2000; 90: 274-9.

6. Waitzinger J, Bepperling F, Pabst G, Opitz J: Hydroxyethyl starch (HES) [130/0.4], a new HES specification: pharmacokinetics and safety after multiple infusions of 10% solution in healthy volunteers. Drugs R D 2003; 4: 149-57.
7. Haisch G, Boldt J, Krebs C, Suttner S, Lehmann A, Isgro F: Influence of a new hydroxyethyl starch preparation (HES 130/0.4) on coagulation in cardiac surgical patients. J Cardiothorac Vasc Anesth 2001; 15: 316-21.
8. Gallandat Huet RC, Siemons AW, Baus D, van Rooyen-Butijn WT, Haagenaars JA, van Oeveren W, et al: A novel hydroxyethyl starch (Voluven®) for effective perioperative plasma volume substitution in cardiac surgery. Can J Anaesth 2000; 47: 1207-15.
9. Boldt J, Lehmann A, Rompert R, Haisch G, Isgro F: Volume therapy with a new hydroxyethyl starch solution in cardiac surgical patients before cardiopulmonary bypass. J Cardiothrac Vasc Anesth 2000; 14: 264-8.
10. Ruttmann TG, James MF, Aronson I: In vivo investigation into the effects of haemodilution with hydroxyethyl starch (200/0.5) and normal saline on coagulation. Br J Anaesth 1998; 80: 612-6.
11. Treib J, Haass A, Pindur G, Grauer MT, Wenzel E, Schimrigk K: All medium starches are not the same: influence of the degree of hydroxyethyl substitution of hydroxyethyl starch on plasma volume, hemorrheologic conditions, and coagulation. Transfusion 1996; 36: 450-5.
12. Boldt J, Knothe C, Zickmann B, Andres P, Dapper F, Hempelmann G: Influence of different intravascular volume therapies on platelet function in patients undergoing cardiopulmonary bypass. Anesth Analg 1993; 76: 1185-90.
13. Stogermuller B, Stark J, Willschke H, Felfernig M, Hoerauf K, Kozek-Langenecker SA: The effect of hydroxyethyl starch 200 kD on platelet function. Anesth Analg 2000; 91: 823-7.
14. Felfernig M, Franz A, Braunlich P, Fohringer C, Kozek-Langenecker SA: The effects of hydroxyethyl starch solutions on thromboelastography in preoperative male patients. Acta Anaesthesiol Scand 2003; 47: 70-3.
15. Van der Linden PJ, De Hert SG, Deraedt D, Cromheecke S, De Decker K, De Paep R, et al: Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for volume expansion in cardiac surgery patients: the effects on perioperative bleeding and transfusion needs. Anesth Analg 2005; 101: 629-34.
16. Kasper SM, Meinert P, Kampe S, Gorg C, Geisen C, Mehlhorn U, et al: Large-dose hydroxyethyl starch 130/0.4 does not increase blood loss and transfusion requirements in coronary artery bypass surgery compared with hydroxyethyl starch 200/0.5 at recommended doses. Anesthesiology 2003; 99: 42-7.
17. Lo B, Fijnheer R, Castigliego D, Borst C, Kalkman CJ, Nierich AP: Activation of hemostasis after coronary artery bypass grafting with or without cardiopulmonary bypass. Anesth Analg 2004; 99: 634-40.