Hemodilution with Hydroxyethyl Starch During Cardiopulmonary Bypass: Review of a Multi-Institutional Study

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ABSTRACT

Three colloidal plasma expanders for use during cardiopulmonary bypass were compared in 85 patients treated at four Japanese hospitals. Patients were randomly allocated to receive: Hydroxyethyl Starch (HES) 5 ml/kg, HES 10 ml/kg, gelatin (Haemacel 10 ml/kg), or a mixture of HES 5 ml/kg and low viscosity dextran (LVD) 5 ml/kg, in addition to the usual priming dose of 1000-1500 ml Lactated Ringer's solution, 20 gm/dl mannitol, and heparinized whole blood. These colloidal plasma expanders appeared equivalent in safely replacing whole blood. Following surgery, urine outputs increased slightly, there were transient elevations of SGOT, LDH, and serum bilirubin, and transient decrements in serum alkaline phosphatase, Na, K, and Cl concentrations. Serum protein, one week following surgery was decreased, possibly reflecting persistence of the plasma expanders. There was no increased bleeding or prolongation of clotting times, bleeding times, or prothrombin times, even though platelet counts were low following surgery. Plasma hemoglobin concentrations were greater in patients receiving gelatin as compared with those given HES. Hydroxyethyl Starch (6 gm/dl), a new plasma expander, appears to be efficacious and nontoxic in hemodilution extracorporeal perfusion.

The priming solution employed in the extracorporeal circuit has undergone refinement to limit denaturation of blood and consequent clinical sequelae.[5,29,30,40] Initially, heparinized whole blood primed the circuit, but the possibility of incompatible blood administration, transmission of viral hepatitis, and nonhemolytic reactions of a febrile or allergic nature became apparent with the use of homologous blood.[10,23] Development and improvement of colloidal and crystalloid solutions for hemodilution, has conserved blood and prevented adverse effects attendant upon blood transfusion.[12,19,21,24] The use of hemodilution has allowed prolongation of the perfusion period, expanding the application of open heart surgery.[21]

The present study compares the efficacy and toxicity of hydroxyethyl starch (HES) and gelatin in 85 patients during open heart surgery.

METHODS

Eighty-five patients at four Japanese hospitals undergoing open heart surgery between July 10, 1970 and November 18, 1971, were assigned randomly to four experimental treatment regimens.[16,31,34,38]

TABLE 1. CASES OF OPEN HEART SURGERY

Priming Colloid Component	Diagnosis VSD	ASD	PS	T-F	MS	Other	Total Number of Patients	Mean Duration of Bypass Procedure (Min.)
HES 5 ml/kg	1	1	1	1	2	3	9	113.3
HES 10 ml/kg	17	18	6	2	3	3	49	48.5
Haemacel 10 ml/kg	3	8		1		6	18	60.7
HES (5 ml/kg) + LMWD (5 ml/kg)	3		1		2	3	9	64.5

Nine patients were given HES (6 gm/dl) 5 ml/kg. Forty-nine patients were given HES (6 gm/dl) 10 ml/kg. Eighteen patients were given gelatin (Haemacel® 2.2 gm/dl) 10 ml/kg., and the remaining nine patients received HES (6 gm/dl) 5 ml/kg in addition to low viscosity dextran (40,000 MW, 10 gm/dl) 5 ml/kg. Each colloid was suspended in 0.9% NaCl and added to 1000-1500 ml of Lactated Ringer's solution with 20 gm/dl mannitol and 400-600 ml heparinized whole blood in the extracorporeal circulation.

The patient population (Table 1) consisted of 27 patients with atrial septal defect (ASD), 24 patients with ventricular septal defect (VSD), 7 patients with mitral stenosis (MS), 8 patients with pulmonary stenosis (PS), 4 patients with Fallot's tetralogy (FT), and 15 other patients.

Hematocrit values during hemodilution in the extracorporeal circuit varied from 23 to 38 per cent. Extracorporeal perfusion lasted 18 to 179 minutes, using hypothermia (30-34° C), with bubble[16,31,34,38] and disc-type[34] oxygenators.

Clinical efficacy of HES was assessed by pre and postoperative hepatic, renal, and hematological parameters.

RESULTS

Renal Function

Twenty-nine patients (Kurume University) underwent treatment with HES 10 ml/kg, Haemacel or HES-LVD 5 ml/kg, and following surgery had similar urinary outputs (Figure 1).[31] Patients (Tokyo University) receiving either HES 10 ml/kg or Haemacel, had normal urine outputs and specific gravity postoperatively (Figure 2).[38] No significant increases in BUN post surgery were reported for patients (Nagoya University) receiving HES 5 or 10 ml/kg (Figure 3).[34] Normal BUN values were observed on the second postoperative day, in patients given HES 10 ml/kg.

High concentrations of plasma hemoglobin have caused renal damage.[7,27] Patients (Toyko University) given HES 10 ml/kg had significantly lower plasma hemoglobin concentrations ($p = 0.05$) than Haemacel-treated patients (Figure 4).[38]

In 29 patients (Kurume University), the mean rate of hemolysis during hemodilution with HES 10 ml/kg, Haemacel or HES-LVD 5 ml/kg was 0.20, 0.32 and 0.44 mg/dl/minute, respectively.[31] Immediate postoperative plasma hemoglobin values ranged from 18-76, 18-76 and 15-50 mg/dl for patients receiving HES 10 ml/kg, Haemacel, and HES-LVD 5 ml/kg, respectively. These differences were not highly significant.

Hepatic Function

In patients (Nagoya University) given HES 5 or 10 ml/kg, LDH increased following surgery, alkaline phosphatase decreased briefly, and total serum protein decreased 15 per cent after surgery (Figure 5). Total serum bilirubin and SGOT increased significantly but returned to normal within two weeks (Figure 6), and SGPT remained unchanged.

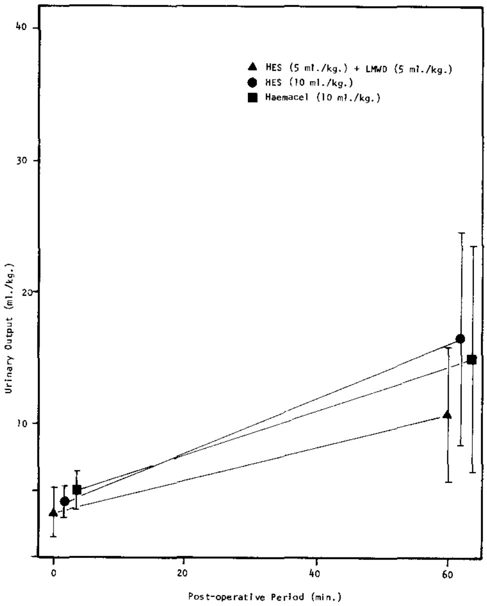

Fig. 1. Urine output determinations conducted before and following the first post-operative hour of perfusion in 29 patients receiving HES 10ml/kg, Haemacel 10ml/kg and 5ml/kg HES-LVD.

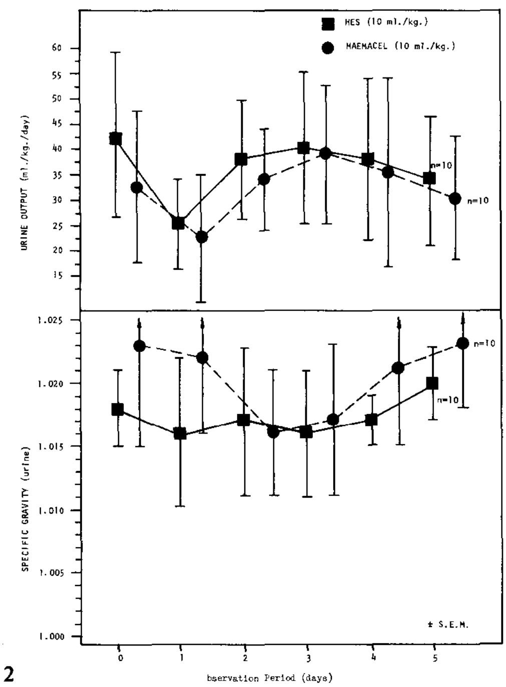

Fig. 2

Fig. 2. Urine output and specific gravity parameters during the first five post-operative days in 20 patients given HES 10ml/kg and Haemacel 10ml/kg.

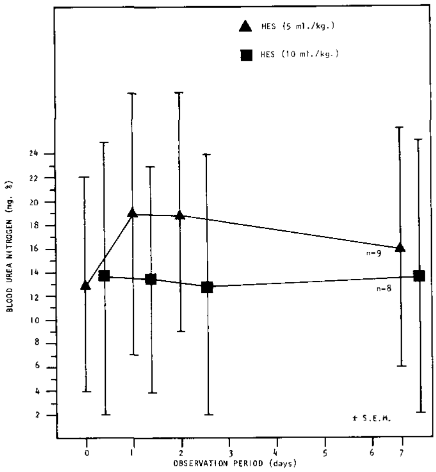

Fig. 3

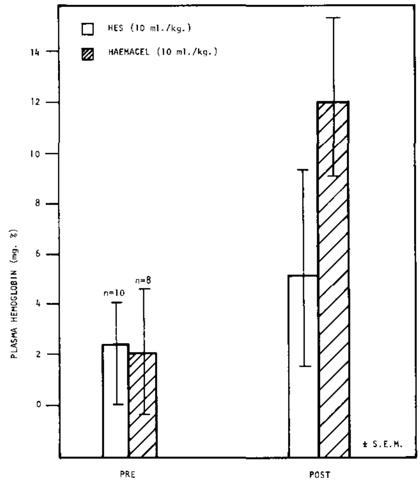

Fig. 4

Fig. 3. Post-operative blood urea nitrogen values in 17 patients receiving HES 10ml/kg and Haemacel 10ml/kg.

Fig. 4. Pre- and post-operative plasma hemoglobin levels in 18 patients given HES 10ml/kg and Haemacel 10ml/kg as part of their extracorporeal perfusion solution.

Serum protein reductions were equivalent in patients (Kurume University) given HES 10 ml/kg, Haemacel or HES-LVD 5 ml/kg and reflected at most, a 24 per cent decrease (Figure 7). Total serum protein did not fall below 4 gm/dl, and recovery to normal values occurred within one week.

Serum Electrolytes

In patients (Nagoya University) given HES 5 or 10 ml/kg, serum Na, K, Cl decreased slightly following surgery (Figure 8). Similar changes were observed in 29 patients (Kurume University) given HES 10 ml/kg, Haemacel or HES-LVD 5 ml/kg and 18 patients (Toyko University) treated with HES 10 ml/kg or Haemacel.

Coagulation Studies

In patients (Nagoya University) given HES 5 or 10 ml/kg, platelet counts decreased significantly ($p = 0.05$) following surgery, but major changes were not observed in bleeding time, clotting time, or prothrombin time (Table 2). The thromboelastogram (TEG) values were not significantly altered in these patients.

Bleeding volumes following surgery were similar in patients given HES 10 ml/kg or Haemacel (Figure 9).

Blood Studies

Figure 10 summarizes blood studies on patients (Nagoya University) given HES 5 or 10 ml/kg. Red cell counts decreased slightly during the first 24-hour postoperative period in both experimental groups. Patients receiving HES 10 ml/kg experienced recovery of preoperative red cell levels during the one week observation period. A moderate leukocytosis occurred in patients receiving HES 5 ml/kg. Leukocytosis (immature granulocytes) occurs in response to the mechanical trauma of the perfusion process.[18] Leukocytosis will persist in the absence of sepsis for periods approaching a week or more. White cell increases, in the absence of infection, were observed in both experimental groups. Hemoglobin and hematocrit values returned to relatively normal levels in the one week observation period.

Patients (Kurume University) receiving HES 10 ml/kg, Haemacel or HES-LVD 5 ml/kg, had increases in blood glucose postoperatively (Figure 11). Elevated glucose levels were in part due to degradation products of the infused synthetic starch colloids.

Fibrinogen levels in patients (Nagoya University) receiving HES 5 or 10 ml/kg,

TABLE 2. RESULTS OF COAGULATION STUDY

Coagulation Studies	Number of Patients	Observation Period (Days)			
		0	1	2	7
Platelet Counts ($x10^4$/cu. mm.)					
HES (5 ml./kg.) mean	9	28.0	16.4	12.3	17.1
HES (10 ml./kg.) mean	8	25.7	8.8	12.1	20.8
Bleeding Time (min.)					
HES (5 ml./kg.) mean	9	4'4"	3'48"	3'41"	3'5"
HES (10 ml./kg.) mean	8	5'24"	6'36"	5'48"	4'6"
Whole Blood Clotting Time (min.)					
HES (5 ml./kg.) mean	9	6'51"	6'40"	6'48"	6'21"
HES (10 ml./kg.) mean	8	9'0"	9'24"	7'6"	8'12"
Prothrombin Time (sec.)					
HES (5 ml./kg.) mean	9	13.1	15.0	14.3	13.5
HES (10 ml./kg.) mean	8	15.4	16.7	15.9	16.1
Thrombo Test (sec.)					
HES (5 ml./kg.) mean	9	42.6	45.0	42.5	42.0
HES (10 ml./kg.) mean	8	46.5	52.0	47.0	46.0
TEG - r value (min.)					
HES (5 ml./kg.) mean	9	4.4	5.1	4.7	3.3
HES (10 ml./kg.) mean	8	6.4	5.6	5.8	7.07
TEG - k value (min.)					
HES (5 ml./kg.) mean	9	4.6	6.2	4.8	3.6
HES (10 ml./kg.) mean	8	6.2	8.2	5.0	3.9
TEG - ma value (mm.)					
HES (5 ml./kg.) mean	9	48	48.5	50	53
HES (10 ml./kg.) mean	8	41.5	33.5	41.6	53.5

increased post surgery. In patients given HES 5 ml/kg, fibrinogen levels increased from 260 mg/dl (control) to 454 mg/dl one week postoperatively. In patients given HES 10 ml/kg, a mean preoperative fibrinogen level of 225 mg/dl increased to 507 mg/dl, one week post surgery.

Blood viscosity measurements on 29 patients (Kurume University) given HES 10 ml/kg, Haemacel or HES-LVD 5 ml/kg, revealed viscosity was reduced in all patients one hour following surgery. No significant differences existed between experimental groups.

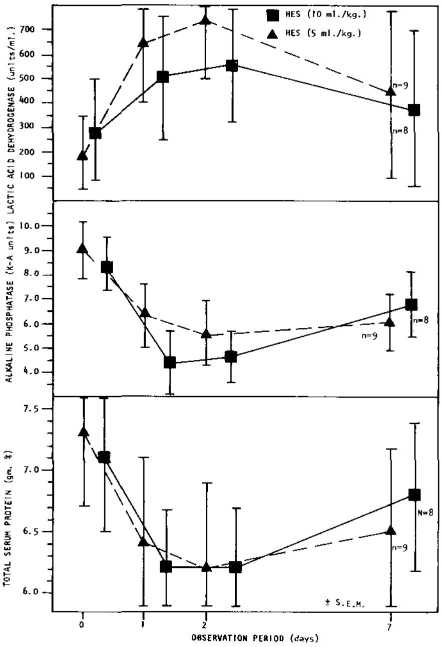

Fig. 5

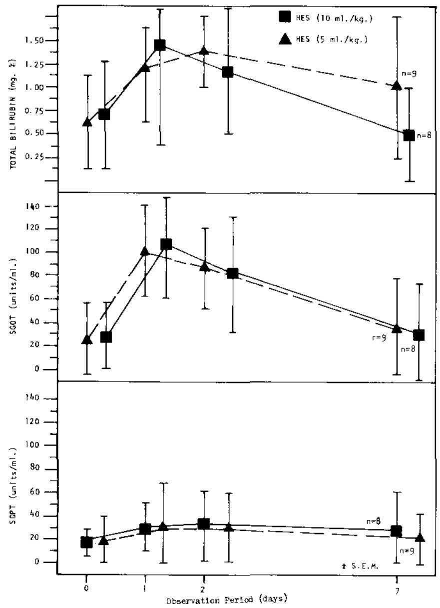

Fig. 6

Fig. 5. Total serum protein, alkaline phosphatase and lactic acid dehydrogenase determinations in 17 patients administered HES 5 or 10ml/kg.

Fig. 6. One week post-operative total bilirubin, SGOT and SGPT levels in 17 patients receiving HES 5 or 10 ml/kg.

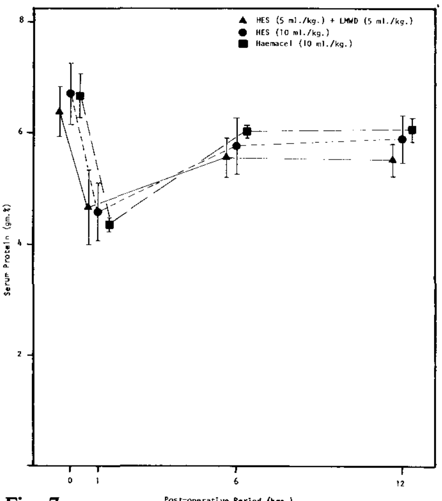

Fig. 7

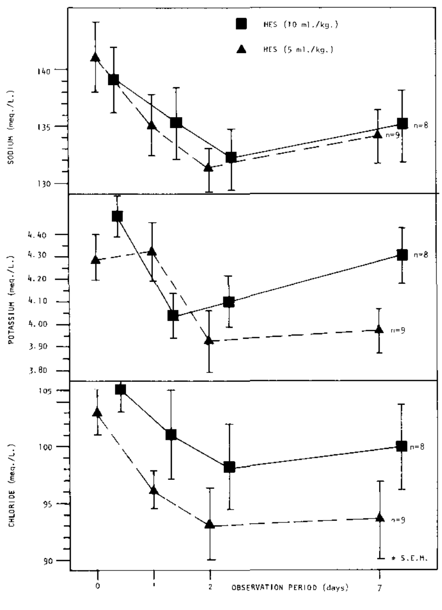

Fig. 8

Fig. 7. Serum protein levels monitored during the first 12 post-operative hours in 29 patients given HES 10ml/kg, Haemacel 10ml/kg and 5ml/kg HES-LVD.

Fig. 8. Seven day post-operative sodium, potassium and chloride ion levels in 17 patients administered HES 5 or 10ml/kg.

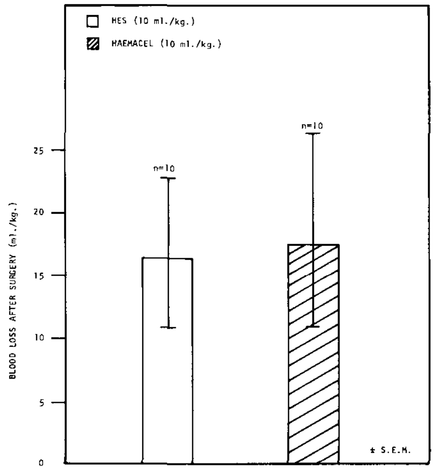

Fig. 9

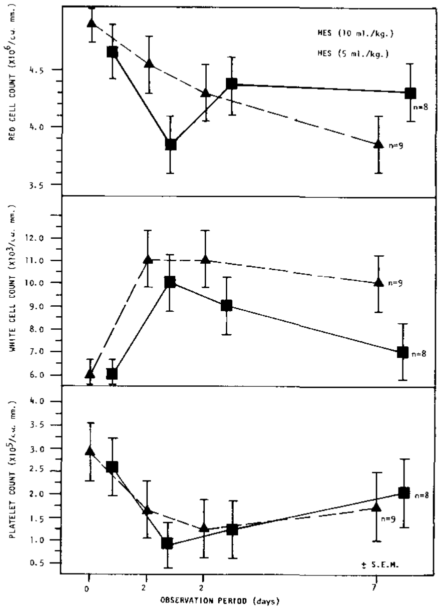

Fig. 10

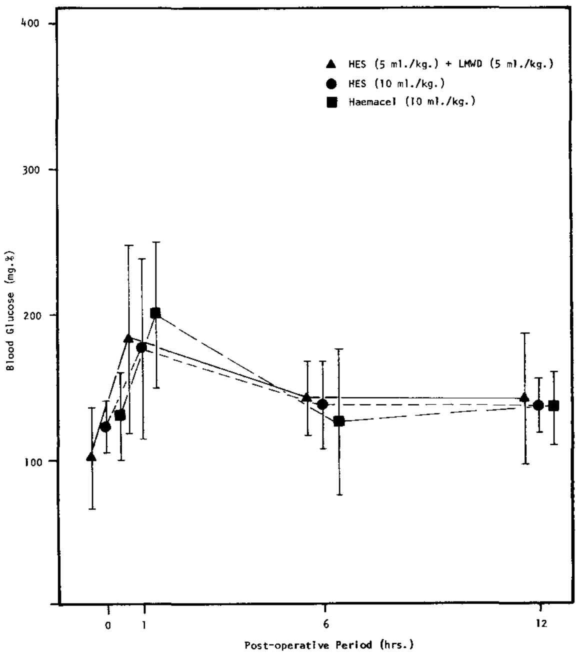

Fig. 11

Fig. 9. Blood loss after surgery monitored in 20 patients given HES 10ml/kg and Haemacel 10ml/kg.

Fig. 10. One week post-operative red cell, white cell and platelet counts in 17 patients given HES 5 or 10ml/kg.

Fig. 11. Twelve hour post-operative blood glucose levels monitored in 29 patients receiving HES 10ml/kg, Haemacel 10ml/kg and 5ml/kg HES-LVD.

DISCUSSION

The continued technical refinement of the extracorporeal circuit has resulted in the increasing application of total body perfusion.[4, 5, 6, 8, 40] However, denaturation of blood and consequent clinical sequelae still exist and continue to limit the usefulness of extracorporeal perfusion.[13, 14, 17, 20, 28, 32, 33, 35, 39] Redesigning of pumps, oxygenators, and accessory equipment has been directed toward eliminating mechanical trauma. Hemodilution with colloidal[2, 12, 15, 19, 21, 24] and crystalloid[5, 29, 30, 40] solutions has decreased denaturation of plasma and of the formed elements subjected to the mechanical trauma of the extracorporeal circuit. Currently, Dextran-40, gelatin, Mannitol and albumin are used as colloidal components of the electrolyte priming solution. However, Dextran-40 has been associated with bleeding episodes in open heart surgery[2, 15, 35] and in the occurrence of renal failure.[25]

The objectives of the present review were to: 1) document the efficacy of colloidal priming solutions and 2) review 58 patients given HES as the colloidal pump priming component.

Previous studies[12, 19, 21] employing HES during hemodilution have reported efficacy and absence of toxic effects. In the present study, HES has been shown useful in reduction of renal, hepatic and hematological alterations occurring as the result of extracorporeal perfusion.

The effectiveness of HES in doses of 10 ml/kg has been shown by three institutions to be associated with better results, in comparison with the other three treatment regimens. The use of HES 10 ml/kg (Figure 1) increased urinary output slightly more than either Haemacel or HES-LVD. Urine output was higher in HES 10 ml/kg-treated patients following surgery than patients treated with Haemacel (Figure 2). Blood urea nitrogen (Figure 3) decreased insignificantly in patients given HES 10 ml/kg, in comparison to HES 5 ml/kg-treated patients.

The use of HES 10 ml/kg normalized more rapidly, hepatic enzyme levels one week postoperatively, in direct contrast to HES 5 ml/kg-treated patients (Figures 5 and 6). Total serum protein levels (Figure 5) returned to control values sooner in HES 10 ml/kg-treated patients. Serum protein levels (Figure 7) approached control levels 12-hours postoperatively, regardless of colloidal component used.

Postoperative return of platelet, white and red cell counts, was not significantly different in patients given either HES 5 or 10 ml/kg (Figure 10). White cell counts remained elevated in HES 5 ml/kg-treated patients, possibly due to increased trauma as the result of a lesser degree of hemodilution.

Significant differences in blood losses were not observed in HES 10 ml/kg or Haemacel-treated patients (Figure 9).

Significant differences ($p = 0.05$) occurred in plasma hemoglobin levels postoperatively (Figure 4). In the HES 10 ml/kg and Haemacel-treated patients, the mean postoperative plasma hemoglobin level was 7 and 14 mg/dl, respectively.

In summary, colloidal agents were effective in reducing renal, hepatic and hematological alterations occurring as the result of extracorporeal perfusion. In addition, HES in a dosage of 10 ml/kg was associated with better results when compared to other experimentally treated patients.

ACKNOWLEDGEMENT

The authors wish to thank W. Leigh Thompson, M.D., Ph.D., for his valuable review of the clinical data, and Rosemary Harmon and Carolyn King, M.A., for their patience in preparing this manuscript.

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