J Anesth (2010) 24:418–425
DOI 10.1007/s00540-010-0914-5

ORIGINAL ARTICLE

Fluid therapy with hydroxyethyl starch for massive blood loss during surgery

Toshinari Suzuki · Hideki Miyao · Katsuo Terui · Kaoru Koyama · Michio Shiibashi

Received: 3 December 2009 / Accepted: 1 February 2010 / Published online: 26 March 2010

Abstract
Purpose This clinical trial reports the use of hydroxyethyl starch (HES70/0.55/4) at very high dosages during surgery. HES70/0.55/4 has the lowest molecular weight among all HES products, and thus may have the least side effects. This observational retrospective study clarified the effects of high-dose HES70/0.55/4 on coagulation and renal function up to 1 month after massive bleeding during surgery.
Methods Of 20875 patients on our surgical database, 31 patients were identified who had lost more than 5000 ml of blood during surgery and had survived for more than 1 month. The fluid balance, and pre- and postoperative laboratory data were analyzed. Patients were assessed using acute kidney injury (AKI) criteria. AKI and non-AKI groups were compared regarding volume of HES70/0.55/4 infused and serum creatinine (Cr) levels before surgery and until 1 month after surgery.
Results The mean volumes of blood loss, total transfusions, HES70/0.55/4, and urine output during surgery were 8051 ml; 5765 ml; 3085 ml (54 ml/kg); and 1338 ml (2.7 ml/kg/h), respectively. Cr increased, and activated partial thromboplastin time, prothrombin time and international normalized ratio were prolonged postoperatively (0.77–0.9 mg/dl, 34–52 s, and 1.1–1.7, respectively). Of the 31 patients, 13 developed AKI, and 10 of the 13 had recovered at 1 month. Renal impairment due to HES70/0.55/4 was not evident, as shown by the finding that the HES70/0.55/4 amount infused in the AKI patients (53 ml/kg) did not differ from that in the nonAKI patients (55 ml/kg), and there was no relationship between the amount of HES infused and Cr changes.
Conclusion High-dose HES70/0.55/4 could be safely used in massive bleeding during surgery. HES70/0.55/4 may affect coagulation, but renal impairment was not evident 1 month after surgery.

Keywords HES70/0.55/4 · Massive bleeding · Adverse effects · Renal complications · Coagulation disorders

T. Suzuki (✉) · H. Miyao · K. Terui · K. Koyama
Department of Anesthesiology, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama 350-8550, Japan
e-mail: tsuzuki@saitama-med.ac.jp

M. Shiibashi
Information Technology Center, Saitama Medical University, 38 Morohongo, Moroyama, Saitama 350-0495, Japan

Introduction

Lactated, acetated, or bicarbonated Ringer's solution has been used as the first-line choice in the fluid management of surgical operations. However, the infusion of crystalloids does not increase blood volume adequately and is associated with an increased risk of interstitial edema and pulmonary complications. Colloids are used as a means of supplementing the plasma volume in cases of massive bleeding, although the colloid-versus-crystalloid controversy is still present. Albumin solutions are associated with resource problems and with the potential risk of infection (with hepatitis A virus [1], human parvovirus B19 [2], and prions [3]), and have not yet been demonstrated to be superior to saline in Cochrane's metaanalysis [4] or in a multicenter study [5]. Issues remain to be addressed regarding the use of albumin solutions. Moreover, Japan has been criticized with regard to its use of large amounts of albumin.

Hydroxyethyl starch (HES) is used worldwide as a plasma substitute. The HES product used in Japan has the lowest molecular weight among all of these products (average molecular weight (Mw): 70000; degree of substitution: 0.55; C_2/C_6 ratio: 4; herein HES70/0.55/4). As no large-scale and high-dose studies of HES70/0.55/4 have been carried out in Japan so far, we have had to cite evidence from studies of HES other than HES70/0.55/4 performed in other countries concerning renal impairment and hemostasis/coagulation disorder, which are claimed to be typical adverse effects of HES. A prospective high-dose HES study, however, is thought to be difficult because massive bleeding occurs incidentally. As our hospital has been using higher dosages of HES70/0.55/4 (Salinehes; Fresenius Kabi Japan, Tokyo, Japan) than those recommended if clinically indicated, we felt obligated to report clinical data and, consequently, the present retrospective observational study was carried out after approval was obtained from our institutional ethics committee.

The objectives of this study were as follows: (1) to investigate issues retrospectively concerning the dosage and adverse effects of HES, particularly in relation to renal and hemostasis/coagulation functions, in patients with massive bleeding (5000 ml or more) immediately after surgery; and (2) to determine whether HES altered the incidence of acute kidney injury (AKI) for 1 month postoperatively.

Materials and methods

Of 20875 patients on our surgical database (January 2004 to October 2007), we searched for patients who had an intra-operative bleeding volume of 5000 ml or more, and survived for more than 1 month after surgery (that is, death is not associated with surgery [6]) to distinguish the renal effects of HES infusion from those of surgery itself or primary disease such as multiple trauma. The patients who had missing laboratory data during study period were excluded. Postoperative laboratory data were compared against baseline preoperative data. The laboratory data included blood urea nitrogen (BUN), serum creatinine (Cr), albumin (Alb), activated partial thromboplastin time (APTT), prothrombin time-international normalized ratio (PT-INR), platelet count, hemoglobin (Hb), lactate, Na, Cl, arterial pH, and base excess (BE), and were documented preoperatively (within 3 days before surgery) and postoperatively (on the day of surgery or 1 day after surgery). The volumes of HES70/0.55/4 used, intraoperative blood loss, volume of other replacement fluids, transfusion volumes (concentrated human red blood cells [MAP]), and amounts of fresh frozen plasma (FFP), and concentrated human blood platelets (PC), and urine output were documented. In the present study, AKI was classified according to the serum creatinine criteria column in Table 1 (Acute Kidney Injury Network [AKIN] staging system [7, 8]), but not according to the urine output criteria column, because precise urine output could not be checked for 1 month after surgery. All patients were analyzed with respect to changes in Cr from baseline, and the need for dialysis until 1 month after surgery. Of the postoperative Cr data for each patient (on the day of surgery, at 2 days, at 1 week, etc.), the maximum value within 1 month after surgery was adopted for comparison with the baseline. Patients in AKIN stages 1, 2, and 3 were classified into the AKI group; the rest were classified as the non-AKI group. The two groups were statistically compared in terms of age, blood loss, the total amount of HES used, urine output during surgery, pre- and post-operative Cr levels, maximum Cr level within 1 month after surgery, and Cr level 1 month after surgery. We also investigated the correlation between the amount of HES infused during surgery and the maximumΔCr (maximum Cr–preoperative Cr) or 1 monthΔCr (1 month Cr–preoperative Cr) in all patients. To elucidate a link between the AKI group and the pre- and intraoperative factors described below, logistic regression analysis using an SAS statistical package (SAS Institute, NC, USA) was performed. The primary endpoint was AKI, and the explanatory variables were age, body weight, preoperative Cr level, anesthetic time, blood loss, amount of HES used, amount of albumin used, amount of crystalloids used, transfusion volume, and urine output during surgery.

Data were expressed as means ± standard deviation (M ± SD). The paired *t*-test was used for comparisons of all preoperative and postoperative values, and the unpaired

Table 1 Acute Kidney Injury Network (AKIN) stage [5]

AKIN stage	Serum creatinine criteria	Urine output criteria
1	↑SCr ≥ 0.3 mg/dl from baseline or ↑SCr > 1.5–2-fold from baseline	<0.5 ml/kg/h for >6 h
2	↑SCr > 2–3-fold from baseline	<0.5 ml/kg/h for >12 h
3	↑SCr > 3-fold from baseline or SCr ≥ 4 mg/dl with an acute rise of ≥0.5 mg/dl in ≤24 h or initiated on RRT (irrespective of stage at time of initiation)	<0.3 ml/kg/h for 24 h or anuria for 12 h

Only one criterion (serum creatinine or urine output) needs to be fulfilled to qualify for a stage. *SCr* serum creatinine (mg/dl), *↑SCr* change of serum creatinine from the baseline, *RRT* renal replacement therapy

t-test was used for the comparison of laboratory data between the non-AKI and AKI groups. All statistical significance levels were set at 5%.

Results

Fifty patients were identified who had had a blood loss of more than 5000 ml during surgery. Of these 50, 2 had missing data, 3 may have had low estimated blood loss because a large amount of ascites or exudate was counted in the blood loss, 2 died immediately after surgery, and 12 died within 1 month after surgery. Consequently, 31 patients met the search criteria and their demographic and operative data are listed in Table 2. Four patients died postoperatively from 1 month to 3 months after surgery. The remaining 27 patients recovered fully and were discharged from the hospital.

Table 2 shows that the blood loss of the entire population of 31 patients was 8051 ± 5358 ml, ranging from 5150 to 34150 ml. The HES volume infused was 3085 ± 1623 ml (54 ± 30 ml/kg), ranging from 750 ml (10 ml/kg) to 6500 ml (120 ml/kg). Regarding other replacement fluids, the total volume of fluids infused was 7352 ± 3529 ml (17 ml/kg/h), the volume of crystalloids infused was 2865 ± 2144 ml (6 ml/kg/h), and that of albumin was 1331 ± 1717 ml; the volumes of crystalloids and albumin used were less than that of HES. The volumes of each blood product transfused were as follows: 3378 ± 2660 ml for MAP, 2181 ± 2326 ml for FFP and 206 ± 274 ml for PC. The patients showed adequate urinary flow, with a mean urine output of 1338 ± 955 ml (2.7 ml/kg/h).

Comparison of preoperative and postoperative laboratory data for all patients (Table 3) showed no significant changes in BUN; increases in Cr, lactate, Na and Cl levels; prolongation of APTT and PT-INR; and decreases in Hb, Alb, platelet count, BE, and pH. Although serum creatinine increased slightly from the baseline postoperatively (0.77–0.9 mg/dl), its level was within the normal range.

Thirteen patients were classified into the AKI group according to change in maximum Cr level during the follow-up 1 month—0.3 mg/dl or more than the baseline preoperative Cr, or above 1.5-fold the baseline preoperative Cr (Table 4; the asterisks in Table 4 indicate fulfillment of the AKI criteria (listed in Table 1). Four patients were in stage 3 of AKI, of whom 3 were initiated on renal replacement therapy indicating stage 3 per se (Table 1). The remaining 18 patients were classified as the non-AKI group. Table 4 shows that there were no significant differences in age, body weight, anesthesia time, blood loss, or HES volume infused (53 vs. 55 ml/kg) during surgery between the AKI and non-AKI groups, but significant changes were observed in pre- and postoperative Cr, urine output during surgery, maximum Cr during follow up 1 month after surgery and Cr at 1 month. No correlations were found between HES infused during surgery and

Table 3 Comparison of preoperative and postoperative data for all 31 patients

	Pre	Post	*t*-test
BUN	17.5 ± 11.0	15.8 ± 10.7	NS
Cr	0.77 ± 0.26	0.9 ± 0.4	$p < 0.05$
Alb	3.5 ± 0.6	2.5 ± 0.6	$p < 0.01$
APTT	34.2 ± 9.3	51.9 ± 22.4	$p < 0.01$
PT-INR	1.06 ± 0.13	1.72 ± 0.69	$p < 0.01$
Plt	24.0 ± 10.4	9.6 ± 4.9	$p < 0.01$
Hb	11.7 ± 2.1	9.1 ± 2.0	$p < 0.01$
Lac	1.54 ± 1.33	4.84 ± 2.70	$p < 0.01$
Na	138.1 ± 4.6	140.1 ±4.0	$p < 0.01$
Cl	105.9 ± 5.8	110.3 ± 4.9	$p < 0.01$
pH	7.45 ± 0.09	7.37 ± 0.07	$p < 0.01$
BE	2.1 ± 4.5	−0.4 ± 4.0	$p < 0.01$

Data are expressed as means ± standard deviation (SD). Preoperative values were obtained within 3 days before surgery. Postoperative values were obtained on the day of surgery or 1 day after surgery. Paired *t*-test was used to determine differences between pre- and postoperative data

BUN blood urea nitrogen, *Cr* creatinine, *Alb* albumin, *APTT* activated partial thromboplastin time, *PT-INR* prothrombin time-international normalized ratio, *Plt* platelets, *Hb* hemoglobin, *Lac* lactate, *Na* sodium, *Cl* chloride, *BE* base excess, *NS* not significant

Table 2 Patient demographic data, volumes infused, and urine output

	Age (years)	BW	Ane time	Blood loss	HES	Alb	Cryst	Total fluid	FFP	MAP	PC	UO
Mean	55.8	59.0	9.1	8051	3085	1331	2865	7352	2181	3378	206	1338
SD	19.2	10.2	4.4	5358	1623	1717	2144	3529	2326	2660	274	955
Max	89	82	20	34150	6500	8750	9450	16750	13440	15400	1200	4250
Min	19	37	2	5150	750	0	0	2100	320	1120	0	110

BW body weight (kg), *Ane time* anesthesia time (h), *HES* hydroxyethylstarch (HES70/0.55/4) infused during surgery (ml), *Alb* albumin infused (ml), *Cryst* crystalloid (ml), *Total fluid* total infusion volume of HES, crystalloid, and albumin during surgery (ml), *FFP* fresh frozen plasma (ml), *MAP* concentrated red blood cells (ml), *PC* platelet concentrate (ml), *UO* urine output (ml)

Table 4 Data of AKI group and non-AKI group

Diagnosis	Age	BW	Ane time	Blood loss	HES/kg	UO/kg/h	Pre Cr	Post Cr	Max Cr	1 m Cr	RRT	AKI stage	Outcome
AKI group ($n = 13$)													
Acute epidural hematoma	55	53	2.5	7000	66.0	2.26	0.62	1.38*	5.8*	0.72	No	3	Rec and Disc
Malig pleur mesothelioma	73	63	8.5	6400	12.7	0.21	1.02	1.69*	3.88*	3.88*	Yes*	3	Died 1 month
Marfan's syndrome	41	54	12.5	6720	46.3	2.61	0.56	1.09*	3.07*	1.14*	Yes*	3	Rec and Disc
Liver Ca	67	69	12	5210	43.5	2.08	1.4	1.64	2.58*	1.13	No	1	Rec and Disc
Liver Ca	72	52	14.5	8600	105.8	1.37	1.07	0.89	1.99*	1.06	Yes*	3	Died 1 month
Duodenal Ca	71	72	9.5	7450	10.4	1.36	1.04	1.2	1.67*	1.22	No	1	Rec and Disc
Retroperitoneal Ca	38	56	12.5	5430	35.7	1.46	1.45	2*	2.06*	1.54	No	1	Rec and Disc
Liver Ca	57	60	11	7580	66.7	2.8	1.1	0.82	1.6*	1.29	No	1	Rec and Disc
Head trauma	27	60	2	5970	21.6	3.33	0.59	1.24*	1.08*	0.66	No	1	Rec and Disc
Pancreatic Ca	60	72	12	5750	90.3	1.01	0.98	1.34*	1.38*	1.02	No	1	Rec and Disc
Multiple trauma	83	50	3.5	15000	120.0	1.71	0.83	0.74	1.17*	0.96	No	1	Died 2 months
Colorectal perforation	40	82	6.5	8100	26.8	1.67	0.81	0.98	1.15*	0.88	No	1	Rec and Disc
Liver Ca	70	50	7.5	5970	48.0	1.04	1.01	0.87	1.34*	1.34*	No	1	Rec and Disc
Mean	58	61	8.81	7322	53.4	1.76	0.96	1.22	2.21	1.30			
SD	16.9	10.1	4.15	2529	34.9	0.84	0.28	0.38	1.36	0.81			
P value of unpaired *t*-test	0.6	0.36	0.76	0.53	0.89	0.01	<0.01	<0.01	<0.01	<0.01			
Non-AKI group ($n = 18$)													
Brain A–V malformation	33	65	14.5	5800	38.5	2.65	0.62	0.7	0.87	0.64	No	–	Rec and Disc
Pancreatic Ca	77	49	15	5800	71.4	4.01	0.51	0.68	0.71	0.6	No	–	Rec and Disc
Prostatic Ca	64	72	8	8753	41.7	0.73	0.79	0.93	0.96	0.84	No	–	Rec and Disc
Placenta previa	31	42	4.5	9500	97.6	7.3	0.35	0.35	0.51	0.52	No	–	Rec and Disc
BPH	81	60	5	5230	16.6	7.47	0.53	0.58	0.68	0.68	No	–	Rec and Disc
Placenta previa	35	65	5.5	5250	23.0	3.75	0.5	0.5	0.64	0.64	No	–	Rec and Disc
Ovarian tumor	51	47	4	6560	21.3	0.85	0.54	0.65	0.66	0.47	No	–	Rec and Disc
Uterine Ca	39	52	8.5	5475	76.9	2.34	0.67	0.74	0.79	0.69	No	–	Rec and Disc
Placenta previa	37	54	4	5600	46.3	2.82	0.4	0.37	0.52	0.52	No	–	Rec and Disc
Liver Ca	82	37	13.5	5150	75.0	3.1	0.46	0.44	0.58	0.4	No	–	Rec and Disc
Giant hemangioma	39	72	11.5	12800	77.5	3.14	0.67	0.9	0.73	0.73	No	–	Rec and Disc
Lung suppuration	68	67	12.5	9120	52.2	2.84	0.72	0.61	0.77	0.74	No	–	Rec and Disc
Hemorrhagic ulcer	64	50	4	5410	40.0	3.6	0.91	0.8	0.92	0.73	No	–	Rec and Disc
Malig pleur mesothelioma	56	65	20	34150	84.6	3.27	0.68	0.68	0.69	0.64	No	–	Died 3 months
Liver trauma	19	63	5	6000	31.7	6.98	0.66	0.51	0.56	0.5	No	–	Rec and Disc
Bladder Ca	72	54	12	7890	92.6	1.7	0.92	0.92	0.82	0.82	No	–	Rec and Disc
Colorectal perforation	40	69	9	10165	21.7	1.14	0.88	0.73	0.76	0.61	No	–	Rec and Disc
Bile duct Ca	89	52	11	5760	78.8	3.08	1.05	0.67	0.57	0.57	No	–	Rec and Disc
Mean	54.3	57.5	9.31	8579	54.9	3.38	0.66	0.65	0.71	0.63			
SD	21	10.4	4.72	6741	27.0	2.02	0.19	0.17	0.13	0.12			

Unpaired *t*-test was used to determine differences between AKI and non-AKI group data (age, BW, Ane time, blood loss, HES/kg, UO/kg/h, pre Cr, post Cr, max Cr, 1 m Cr)

Ca, carcinoma; *BPH*, benign prostatic hypertrophy; *Malig*, malignant; *Pleur*, pleural; *BW*, body weight (kg); *Ane time*, anesthesia time (h); *HES/kg*, hydroxyethyl starch (HES) infused during surgery per body weight (kg); *UO/kg/h*, urine output per body weight per hour during surgery; *pre*, preoperative values (obtained within 3 days before surgery); *post*, postoperative values (obtained the day of surgery or one day after surgery); *max*, maximum values within 1 month postoperatively; *1 m*, at 1 month; *RRT*, renal replacement therapy; *Rec and Disc*, recovered and was discharged from the hospital; *Died 1 month*, died after 1 month

Asterisks indicate fulfillment of AKI criteria (Table 1)

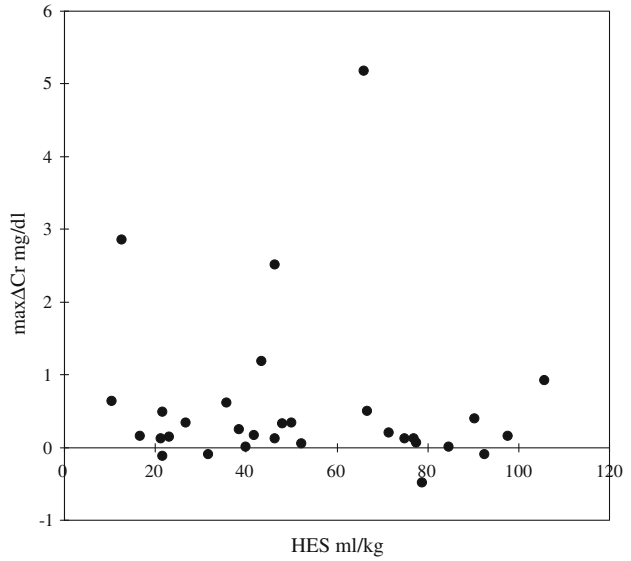

Fig. 1 Relationship between hydroxyethyl starch (*HES*) infused during surgery and *maxΔCr* (difference of maximum creatinine [*Cr*] level during 1 month after surgery from the preoperative baseline Cr) in all the patients

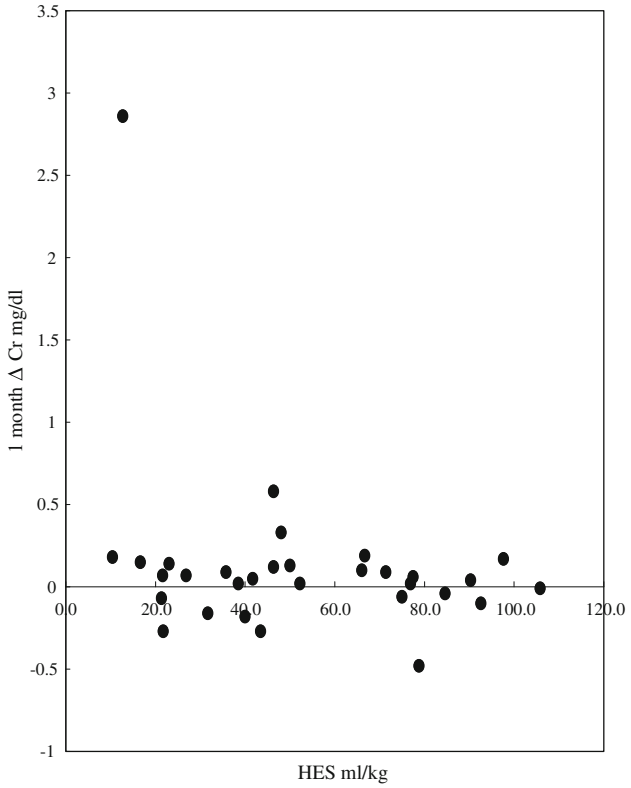

Fig. 2 Relationship between HES infused during surgery and *1 monthΔCr* (difference of 1-month Cr level after surgery from the preoperative baseline Cr) in all the patients

maximum change of Cr during the follow-up 1 month, or between the amount of HES infused and 1-month change of Cr (Figs. 1, 2). Three patients in the AKI group died. One patient with malignant pleural mesothelioma died of metastasis to the heart after more than 1 month without weaning from dialysis. One patient who underwent extended hepatectomy for hepatocellular carcinoma died of hepatic failure after more than 1 month without weaning from dialysis. One patient with multiple trauma recovered from AKI at 1 month but died of respiratory failure 2 months postoperatively. One patient with malignant pleural mesothelioma in the non-AKI group died of the original disease. The remaining 27 patients in the two groups recovered fully and were discharged from the hospital. The amounts of MAP, FFP, PC, albumin, and total fluid infused in the two groups were not significantly different.

The p value of this regression analysis model was significant ($p = 0.0204$) and the contribution ratio (R^2) of the explanatory variables to the AKI group was 0.5003. Table 5 shows the results of logistic regression analysis, revealing that the preoperative Cr level was the only factor linked to AKI ($p = 0.046$). It should be noted that the amount of HES used was not significant ($p = 0.84$) to account for the development of AKI.

Table 5 The results of logistic regression analysis

	Estimate	Standard error	χ^2	P value (Prob > χ^2)
Intersection	5.93645353	6.5958224	0.81	0.3681
Age	0.00918804	0.0493748	0.03	0.8524
BW	−0.0433578	0.0981197	0.20	0.6586
Ane ime	0.03171976	0.2896904	0.01	0.9128
Blood loss	0.00005924	0.0005983	0.01	0.9211
HES	−0.000103	0.0005209	0.04	0.8433
Alb	0.00089787	0.0007278	1.52	0.2173
Cryst	0.00027049	0.0006459	0.18	0.6754
Transfusion	−0.0004606	0.0006413	0.52	0.4726
UO	0.0023176	0.0016354	2.01	0.1564
Pre-Cr	−7.5066002	3.7626327	3.98	0.0460*

The primary endpoint (AKI) was 42% (13/31) with the use of the AKI criteria. Pre-Cr was the only factor accounting for AKI. *P value <0.05

Discussion

To summarize and simplify the above results, MAP (3400 ml), FFP (2200 ml), PC (200 ml), HES (3100 ml), albumin (1300 ml), and crystalloid (2900 ml) were given to patients whose mean blood loss was 8000 ml during surgery. Hemostasis/coagulation disorders emerged immediately after surgery, but renal impairment caused by HES70/0.55/4 was not evident 1 month after surgery.

Table 6 Characteristics of different HES products

Property	70/0.55	130/0.4	200/0.5	200/0.5; 260/0.5	200/0.62	670/0.75
Concentration	6%	6%	6%	10%	6%	6%
Volume efficacy (%)	80–90	100	100	130–150	100	100
Volume effect (h)	1–2	3–4	3–4	3–4	5–6	5–6
Mean molecular weight (Mw)	70000	130000	200000	200000	200000	670000
Degree of substitution	0.55	0.4	0.5	0.5	0.62	0,75
C2/C6 ratio	4	9	6	6	9	4.6
Max dose (ml/kg)	20	33–50	33	20	33	20

The present study is the first report of a reasonable-scale observational study of intraoperative high-dose use of HES70/0.55/4 in patients with massive bleeding. A study from the United States used a mean amount of 1596 ml of HES with a molecular weight of 450000 Da [9]; it was a high-dose study (although the dose was half the dose used in the present study) of the highest molecular weight HES product. In Europe, the officially approved dose of HES with a molecular weight of 130000 Da is 50 ml/kg [10]. Thus, there are many kinds of HES products in the world (Table 6) and a recent review noted: "Different Product–Different Effect" [11]. That review did not devote sufficient space to HES70 because of the lack of English-language references to the product.

Issues related to the structure of HES

The structure of HES is characterized by its molecular weight, degree of substitution, and C_2/C_6 ratio, and the HES product we used is described as HES70/0.55/4. The degree of substitution represents the number of substituted hydroxyethyl groups per glucopyranose unit (glucose ring). The C_2/C_6 ratio is the ratio of molecules with a hydroxyl substitution at the C_2 position to those with a hydroxyl substitution at the C_6 position. High molecular weight and a high degree of substitution can be associated with a longer half-life and an increased intensity of adverse effects. Table 6 shows the characteristics of many kinds of HES products. The HES product used in Japan, labeled as 6% HES70/0.55/4, has the lowest molecular weight, a low degree of substitution, and a low C_2/C_6 ratio.

Issues related to the effect of HES on renal function

Yamazaki reported that HES70 was unlikely to be toxic to the kidney [12]. Mishler [13] reported that even if the renal tissue appears to be grossly abnormal, renal function remains essentially normal. To maintain renal blood flow and normal renal function, it is important to maintain an adequate circulating blood volume, which we believe can be facilitated by the active use of HES. The package insert of HES in Japan does not specify renal impairment as an adverse event.

On the other hand, Brunkhorst et al. [14] and Schortgen et al. [15] examined HES efficacy in patients with severe sepsis and demonstrated a significantly high incidence of acute renal failure when using 10% HES200/0.5/6 and 6% HES200/0.62/9, respectively. Both studies indicate that repeated HES infusions for several days increase the risk of acute renal failure. However, these studies differ from the present study in terms of the pathological condition of the patients (i.e., severe sepsis vs. acute intraoperative massive bleeding), the property and concentration of HES used (i.e., 10% HES200/0.5/6 and 6% HES200/0.62/9 vs. 6% HES70/0.55/4), and the mode of infusion (i.e., chronic infusion vs. intraoperative infusion). Boldt et al. [16] reported that HES130/0.4/9 maintained proximal tube function (as albumin did) and had more beneficial effects regarding renal impairment than albumin. The most recent review of HES stated: "… there are differences between the older and newer generations of HES and the reports of adverse effects on renal function should not be extrapolated to newer HES products" [11].

In the present results, Table 3 shows that postoperative serum Cr level increased. Table 4 shows, however, that preoperative Cr level was significantly higher in the AKI group than in the non-AKI group. The logistic regression analysis revealed that the preoperative creatinine level, not the amount of HES used, was the only factor accounting for AKI. Urine output during surgery was not a factor accounting for AKI, although it was significantly lower in the AKI group by Student's *t*-test (Tables 4, 5). That is, the AKI group potentially had some renal problems before surgery. In addition, it should be noted that the volumes of HES infused were not different between the two groups. These findings indicate that the increase in postoperative serum Cr would have resulted from the originalunderlying renal problems in the AKI group patients and, consequently, renal impairment would emerge due to surgical stress and massive bleeding. The decrease in urine output during surgery in the AKI group shown by Student's *t*-test can be explained in the same way, because the fluid and transfusion volumes were not different in the two groups.

During follow up for 1 month, 13 patients were classified into the AKI group by comparing the maximum Cr within 1 month to the preoperative baseline Cr (max Cr in Table 4). Three of these patients received renal replacement therapy. If postoperative Cr were to have been adopted to classify AKI, only 6 patients (denoted by asterisks in the "post Cr "column in Table 4) would have been classified into the AKI group. This finding may indicate that inadequate postoperative management for the other 7 patients in the AKI group may have induced AKI. Assessment of Cr at 1 month (Table 4) indicated that the AKI group no longer had AKI at 1 month, except for 3 patients. Figures 1 and 2 also show that there were no correlations between HES volumes and Cr changes. Thus, the present results show that HES70/0.55/4 did not adversely affect renal function.

Issues related to HES effects on hemostasis/coagulation systems

In the present study, comparison of preoperative and postoperative values showed a significant prolongation of APTT and PT-INR and a significant decrease in platelet count (Table 3). Several mechanisms by which HES causes such coagulation disorders have been suggested by Treib et al. [17]. They concluded that HES affected the coagulation system by reducing the concentration of factor VIII/vWF complex, but HES70 had the least effects among the HES products that they studied. The mechanism of coagulation disorder thus appears to be attributable to a decrease in factor VIII/vWF complex, although the detailed mechanism of the decrease has not been elucidated [18, 19]. Regarding the effects on platelets and their function, a decrease in factor VIII/vWF complex is considered to be associated with inhibition of platelet aggregation. In any case, the involvement of both dilution-mediated coagulation disorder and loss of platelets due to bleeding cannot be ruled out in explaining how HES affects coagulation and platelet functions. Given that the HES product used in Japan has the lowest molecular weight among all HES products, a low degree of substitution, and a low C_2/C_6 ratio, its effect on the hemostasis/coagulation systems is expected to be limited [20]. However, it is still important to monitor platelet count and coagulation function using laboratory tests or even thromboelastography, and appropriately replace coagulation factors via platelet concentrate and FFP administration.

The limitations of the present study include the following:

1. This was a retrospective observational study.

Massive bleeding of more than 5000 ml can only occur following severe trauma or accidental vascular rupture during surgery, making it difficult to select patients to be included in a prospective study. This is why no large-scale study of fluid therapy for massive bleeding has been reported. The present study, although retrospective and with an insufficient number of cases (31), is the first report of very high-dosage use of HES70/0.55/4, and can propose some useful information about fluid management for massive bleeding. The results in the present study, however, should be carefully assessed because each anesthesiologist followed his/her own algorithm for using HES, and many factors, such as preoperative complications, the anesthetics used, anesthetic methods, perioperative administration of antibiotics, and the administration of many other drugs may have influenced the present results.

2. The present study excluded nonsurvivors within 1 month after surgery

Massive bleeding of more than 5000 ml may generally become a lethal complication of surgery and it, per se, would influence the renal function to a greater degree than HES infusion. As operative mortality is defined as death within 1 month after surgery [6], the 1-month survivor is thought to have surmounted surgical stress. To make a clear distinction between the influence of the primary disease or surgical stress and the effect of HES infusion on renal function, we excluded the patients who died within 1 month after surgery. Although nonsurvivors within 1 month after surgery had no effect on the present main results in our preliminary analysis, we had excluded them for assessing the long-term effect of HES infusion. It cannot be denied that the excluded patients may have affected the problems focused on in the present study if they had been included.

3. Urine output was not used to classify AKI stages.

Checking intervals of urine output differs depending on each ward and the intervals are gradually prolonged day by day after surgery. And, as the urine criteria were adopted originally for the early diagnosis of AKI by the AKI Network, we thought that the choice of the urine criteria was inappropriate and difficult to employ in this study. We may therefore have missed some information about classifying AKI stages.

HES70/0.55/4 has the lowest molecular weight among HES product groups and had not yet been investigated in a large-scale clinical study. This material may be locally used, especially in Japan, but could have the potential to spread through a wide area because of its safety. We believe that the present study can shed some light on operative fluid management in Japan and can present the safety of the Japanese HES product to the world.

In summary, HES70/0.55/4 can be safely used even in very high dosages above the recommended maximum dose,

but a sufficient amount of platelet concentrates and FFP should be used to replenish platelets and coagulation factors in patients with massive bleeding. In the present study, renal impairment caused by infusing even a large amount of HES70/0.55/4 was not recognized 1 month after surgery, but the potential for HES70/0.55/4 to impair renal function may not be excluded.

Conflict of interest HES70 is a product of Fresenius Kabi Inc. As we found that the second author, Dr. Miyao, had been the medical consultant of this company, we changed the COI form to a new version.

References

1. Adcock WL, MacGregor A, Davies JR, Hattarki M, Anderson DA, Goss NH. Chromatographic removal and heat inactivation of hepatitis A virus during manufacture of human albumin. Biotechnol Appl Biochem. 1998;28:85–94.
2. Blümel J, Schmidt I, Willkommen H, Löwer J. Inactivation of parvovirus B19 during pasteurization of human serum albumin. Transfusion. 2002;42:1011–8.
3. Thyer J, Unal A, Thomas P, Eaton B, Bhashyam R, Ortenburg J, Uren E, Middleton D, Selleck P, Maher D. Prion-removal capacity of chromatographic and ethanol precipitation steps used in the production of albumin and immunoglobulins. Vox Sang. 2006;91:292–300.
4. Roberts I. (Cochrane Injuries Group Albumin Reviewers) Human albumin administration in critically ill patients: systematic review of randomized controlled trials. Br Med J. 1998;317:235–9.
5. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–56.
6. Johnson ML, Gordon HS, Petersen NJ, Wray NP, Shroyer AL, Grover FL, Geraci JM. Effect of definition of mortality on hospital profiles. Med Care. 2002;40:7–16.
7. Molitoris BA, Levin A, Warnock DG, Joannidis M, Mehta RL, Kellum JA, Ronco C, Shah SV. Improving outcomes of acute kidney injury: report of an Initiative. Nat Clin Pract Nephrol. 2007;3:439–42.
8. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:31.
9. Gan T, Bennett GE, Phillips BB, Wakeling H, Moskowitz DM, Olufolabi Y, Konstadt SN, Bradford C, Glass PS, Machin SJ, Mythen MG. Hextend®, a physiologically balanced plasma expander for large volume use in major surgery: a randomized Phase III clinical trial. Anesth Analg. 1999;88:992–8.
10. Gallandat HRCG, Siemons AW, Bauss D, Rooyen-Butijn WT, Haagenaars JAM, Oeveren W, Bepperling F. A novel hydroxyethyl starch (Voluven®) for effective perioperative plasma volume substitution in cardiac surgery. Can J Anaesth. 2000; 47:1207–15.
11. Westphal M, Jame MFM, Kozek-Langenecker S, Stocker R, Guidet B, Aken HV. Hydoroxyethyl starches. Anesthesiology. 2009;111:187–202.
12. Yamazaki H. Effects of low-molecular weight HES on kidney—comparison with low-molecular weight dextran (in Japanese with English abstract). Jpn J Anesthesiol. 1975;24:26–43.
13. Mishler JM. Synthetic plasma volume expanders—their pharmacology, safety and clinical efficacy. Clin Haematol. 1984; 13:75–92.
14. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358:125–39.
15. Schortgen F, Lacherade JC, Bruneel F, Cattaneo I, Hemery F, Lemaire F, Brochard L. Effects of hydroxyethyl starch and gelatin on renal function in severe sepsis: a multicentre randomised study. Lancet. 2001;357:911–6.
16. Boldt J, Brosch C, Rohm K, Lehmann A, Mengistu A, Suttner S. Is albumin administration in hypoalbuminemic elderly cardiac surgery patients of benefit with regard to inflammation, endothelial activation, and long-term kidney function? Anesth Analg. 2008;107:1496–503.
17. Treib J, Haass A, Pindur G. Coagulation disorder caused by hydroxyethyl starch. Thromb Haemost. 1997;78:974–83.
18. Yamakage M, Sato J, Namiki A. Further potential of hydroxyethyl starch-based plasma substitute (in Japanese with English abstract). J Clin Anesth (Japan). 2005;29:61–73.
19. Yuasa H, Koga Y. Effects of hydroxyethyl starch on hemostasis system (in Japanese with English abstract). J Clin Anesth (Japan). 1998;22:204–8.
20. Dalrymple-Hay M, Aitchison R, Collins P, Sekhar M, Colvin B. Hydroxyethylstarch induced acquired von Willebrand's disease. Cin Lab Haematol. 1992;14:209–11.