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The Volume Effect and Safety of 6% Hydroxyethyl Starch 130/0.4 in Patients Undergoing Major Elective Surgery: An Uncontrolled, Open-Labeled, Multi-Center Study

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ABSTRACT

Purpose: The primary aim of this study was to investigate volume effect and safety of up to 50 mL/kg BW 6% hydroxyethyl starch (HES) 130/0.4 in adult and pediatric patients undergoing major elective surgery. The need to infuse human albumin may be reduced or avoided in Japan if these large doses 6% HES 130/0.4 can be infused. **Methods:** The study was an uncontrolled, open-labeled, multi-center trial. Fifteen adult and 5 pediatric patients undergoing major elective surgery received 6% HES 130/0.4 (Voluven®) with a maximum dose of 50 mL/kg from the start of surgery until 2 hours after the end of surgery according to a treatment algorithm. The primary efficacy endpoint was the volume effect of 6% HES 130/0.4 determined by the volume of saved albumin during the investigational period and the time course of hemodynamic stability in adult and pediatric patients. Safety parameters were fluid balance, hemodynamic and laboratory parameters ECG, local and systemic tolerance and adverse events. **Results:** Adult patients received a mean of 32.0 mL/kg of 6% HES 130/0.4. For 12 out of 15 adult patients an average amount of 1033.8 mL (18.6 mL/kg) albumin could be saved. The other 3 adult patients did not receive more than 1000 mL of HES 130/0.4. All pediatric patients received approximately 50 mL/kg of HES 130/0.4; for these patients an average amount of 39.9 mL/kg body weight albumin could be saved. The majority of adult patients, and all pediatric patients were hemodynamically stable at all 3 time points. The observed changes of the assessed laboratory parameters including hematological and coagulation parameters or in any other safety parameter determined did not reveal any safety concern related to the administration of 6% HES 130/0.4 up to doses of 50 mL/kg body weight. **Conclusion:** The study results indicate that 6% HES 130/0.4 has a reliable volume effect, could contribute to significant human albumin savings and was safe and well tolerated up to a maximum dose of 50 mL/kg body weight in adult and pediatric patients undergoing major elective surgery.

Keywords: High Dose; Volume Effect; Safety; 6% Hydroxyethyl Starch 130/0.4; Elective Surgery; Multi-Center Study

1. Introduction

Colloid solutions are indicated for the treatment of hypovolemia and to maintain adequate circulating blood volume in patients undergoing surgery, experiencing trauma, or in intensive care. Among the available synthetic colloids, hydroxyethyl starch (HES) has been shown to have the lowest incidence of anaphylactoid reactions [1]. With the latest third generation, so called tetrastarches or HES 130/0.4, a major advancement particularly in respect of safety issues has been achieved over recent years. This advancement leads to a more rapid metabolization and degradation of HES molecules and thus to a minimal plasma accumulation even after repeated administration of HES 130/0.4 [2]. In addition, the influence on the coagulation system has been minimized [3]. Several studies confirmed that HES 130/0.4

does not result in deterioration in kidney function [4] in surgery even in those patients who are prone to acute renal failure [5]. Interestingly, despite the more rapid metabolization and the higher urinary excretion rate of HES 130/0.4 the duration of volume effect has been preserved comparable to that of pentastarches, such as HES 200/0.5 [6].

The usage of the currently available HES 70/0.5 solution in Japan is limited to doses up to 20 mL/kg body weight (adult patients) or up to 10 mL/kg body weight (pediatric patients). In patients exceeding this dose limitation and requiring additional colloid loading, human albumin is recommended according to Japanese guidelines for transfusion (2007-revised 2005 guideline for usage of blood products by the Japanese Ministry of Health, Labor and Welfare). Consequently, the need to infuse human albumin may be reduced or avoided once the current dose limitation of HES 70/0.5 is reached if the infusion of larger volumes of HES 130/0.4 up to doses of 50 mL/kg BW would be possible in Japan like in most other countries worldwide. Consequently the reduction or avoidance of albumin infusions may also lead to considerable cost-savings.

Therefore, the aim of this study was to show the volume effect of 6% HES 130/0.4 and to demonstrate the safety of doses up to 50 mL/kg body weight in Japanese patients undergoing major elective surgery with an expected blood loss ≥ 1000 mL in adults and 15 mL/kg body weight in pediatric patients, respectively.

2. Materials and Methods

2.1. Study Design

In this prospective, uncontrolled, open-labeled, multicenter trial a total of 20 patients were screened and enrolled into the study. All 20 patients were treated with 6% HES 130/0.4 and analyzed for efficacy and safety variables. Inclusion criteria were patients undergoing major elective surgery, with an expected blood loss of ≥1000 mL in the case of adults (≥20 years of age) or ≥15 mL/kg (pediatric patients <20 years of age), a routine measurement of CVP (adult patients only) and a written informed consent and assent, if applicable. No restriction was placed on surgical procedures. Patients were excluded if they fulfilled the following exclusion criteria: participation in a clinical trial within the last 4 months from the day of administration of HES 130/0.4, known or suspected allergy to hydroxyethyl starch including its ingredients and related drugs, American Society of Anesthesiologists (ASA) classification ≥IV, (in the case of adults) renal failure with oliguria (<400 mL urine/24 hours) and anuria or (in the case of pediatric patients) renal failure with oliguria and anuria not related to hypovolemia, receiving dialysis treatment, known bleeding disorders, fluid overload, intracranial bleeding, severe hypernatremia, severe hyperchloremia, known pregnancy, ineligibility at the discretion of the investigator.

6% HES 130/0.4 (Voluven®, Fresenius Kabi, Bad Homburg, Germany) was administered intravenously to maintain or restore hemodynamic parameters up to a maximum dose of 50 mL/kg body weight. Before skin incision, no colloid solutions were to be used. Following a treatment algorithm (**Figure 1**) HES 130/0.4 was administered during the investigational period with an infusion rate of 250 to 500 mL in about 15 to 30 minutes, from the start of surgery (skin incision) until 2 h (±15 min) after end of surgery. After reaching the dose limit of 50 mL/kg BW of HES 130/0.4, human albumin 4.4% or 5% was used exclusively as colloid in case the patient required additional colloids. In addition, a sufficient fluid therapy had to be administered as basic infusion of crystalloids .During the whole study period, transfusion requirements for blood products followed 2007-revised 2005 Guideline for usage of blood products by MHLW.

2.2. Investigations and Assessments

Hemodynamic stability was defined as a systolic blood pressure of not more than 30% below the baseline value and evaluated by end of surgery, 2 hours after surgery and 24 hours after surgery.

Systolic/diastolic blood pressure (SBP/DBP), mean arterial pressure (MAP), heart rate (HR) and central venous pressure (CVP, in adults and preferable in pediatric patients) were measured immediately before induction of anesthesia, in the case of adults, and the day before induction of anesthesia, in the case of pediatric patients, until 48 h after the end of surgery.

Fluid balance was determined by fluid input categorized as HES 130/0.4, 4.4% human albumin, 5% human albumin, commercial colloid, crystalloids, predeposit autologous blood, salvaged autologous blood, homologous packed red blood cells, fresh frozen plasma, platelets, and other minus fluid output categorized as urine output, blood loss [suction], and blood loss [from clothweight calculation]).

Laboratory parameters were measured at baseline, at end of surgery as well as 2 and 24 hours after surgery, and also as last value available and included following parameters: hematology (hematocrit, hemoglobin, and platelets), serum clinical chemistry (creatinine, blood urea nitrogen (BUN), total bilirubin (only adult patients), glucose, total protein, albumin, sodium, potassium, chloride, GOT/AST, GPT/ALT, lactate dehydrogenase (LDH, only adult patients), γ-GT (only adult patients), and amylase), and hemostasis (international normalized ratio (INR), activated partial thromboplastin time (aPTT), fi-

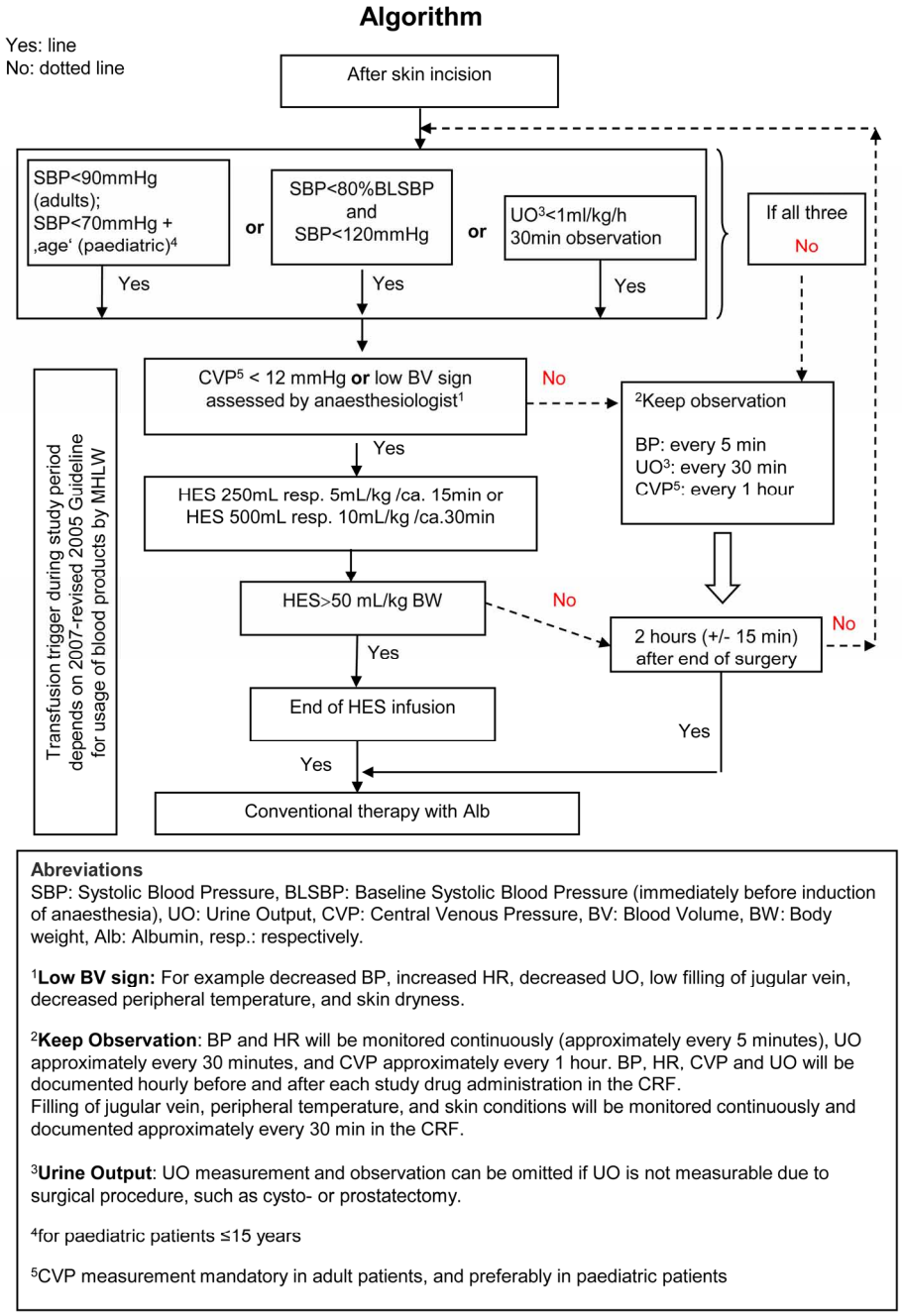

Figure 1. Algorithm for 6% HES 130/0.4 administration.

brinogen, factor VIII activity (only adult patients), and von Willebrand factor antigen (only adults patients).

ECG was determined until 24 hours after surgery. Local and systemic tolerance was evaluated as good, moderate or poor until 2 hours after surgery, and adverse events were followed-up for 28 days after surgery.

2.3. Statistics

The primary efficacy endpoint was the volume effect of 6% HES 130/0.4 determined by 1) the volume of the saved albumin during the investigational period and 2) the time course of hemodynamic stability stratified by adult and pediatric patients. Saved albumin was defined as the amount of HES 130/0.4 administered during the investigational period after 1000 mL for adults and 10 mL/kg for pediatric patients had been reached The definition was based on the assumption that 1 mL administered HES would save 1 mL human albumin that would have been used once the dose limit for HES had been

reached. Saved albumin was only analyzed in patients receiving more HES 130/0.4 than the current dose limitation of 6% HES 70/0.5.

Only descriptive methods were used. The variables were summarized by age (adult and pediatric patients) with the number of non-missing observations (n), arithmetic mean, standard deviation (SD), median and ranges. Changes from baseline were calculated and summarized by time point for all post-baseline values and the individually determined last available post-baseline value.

3. Results

3.1. Efficacy

Fifteen adult and 5 pediatric Japanese patients were assessed for both efficacy and safety. The demographic data for the adult and pediatric patient populations treated with HES 130/0.4 are shown in **Table 1**, information on individual type and time of surgery and presented in **Table 2**. Adult patients underwent different types of abdominal surgery, with a majority of patients undergoing liver surgery (7 patients). All pediatric patients were liver transplanted (living donor transplantation).

All patients received % HES 130/0.4. For 12 out of 15 adult patients an average amount of 1033.8 mL (18.6 ml/kg) albumin was saved, whereas 3 adult patients did not receive more than 1000 mL of 6% HES 130/0.4. All pediatric patients received about 50 mL/kg of HES 130/0.4; for these 5 pediatric patients a mean volume of 652.7 ml (39.9 mL/kg body weight) albumin was saved (**Table 3**).

The summary of hemodynamic stability is shown in **Table 4**. Overall, the majority of adult patients and all pediatric patients were hemodynamically stable at all time points.

Table 1. Demographic data.

Variable	Adult patients (N = 15)	Pediatric patients (N = 5)
Age (years)		
N	15	5
Mean (SD)	71.0 (7.2)	4.8 (4.4)
Range	57 - 80	0 - 11
Sex, n (%)		
Male	11 (73.3)	1 (20.0)
Female	4 (26.7)	4 (80.0)
Height (cm)		
N	15	5
Mean (SD)	161.72 (9.25)	100.24 (30.90)
Range	145.1 - 177.1	66.2- 135.8
Weight (kg)		
N	15	5
Mean (SD)	59.24 (12.63)	16.33 (8.26)
Range	40.1 - 85.0	7.3 - 28.8
Blood group, n (%)		
A	4 (26.7)	1 (20.0)
B	2 (13.3)	1 (20.0)
AB	2 (13.3)	0 (0.0)
0	7 (46.7)	3 (60.0)
ASA classification, n (%)		
I	3 (20.0)	0 (0.0)
II	11 (73.3)	3 (60.0)
III	1 (6.7)	2 (40.0)

3.2. Safety

3.2.1. Fluid Input and Output

The data for fluid input and output are shown in **Table 5**. When expressed in terms of mL/kg body weight, adult patients received a mean of 32.0 mL/kg of 6% HES 130/0.4. All pediatric patients received about 50 mL/kg 6% HES 130/0.4. Five adult patients and 3 pediatric patients required additional colloids for hemodynamic stabilization, which was 5% human albumin in all cases. Mean total input was 12,091 mL for the adult patients and 7584 mL for the pediatric patients. Total overall fluid output had a mean value of 7860 mL in adult patients and 5600 mL in the pediatric patients. Overall, fluid balance was positive in all patients.

3.2.2. Laboratory Parameters

Tables 6-8 summarize the data for the laboratory parameters monitored during the investigational period.

Regarding hematology parameters (**Table 6**) median values for hematocrit, hemoglobin, and platelets showed major decreases from baseline for adult and pediatric patients and were still below baseline values at 24 hours.

The analysis of hemostasis parameters (**Table 7**) revealed increases of INR and aPTT for both patient groups, which was even stronger for pediatric than for adult patients. For adults, the strongest increase for both parameters occurred at the end of surgery followed by a decrease until 2 h after surgery whereas for pediatric patients the strongest increase was observed 2 hours after the end of surgery. In pediatric patients, values nearly returned to baseline level for the last available value.

Fibrinogen showed strong decreases in the median for

Table 2. List of individual surgeries.

Patient	Age	Sex	Weight (kg)	Type of surgery	Duration of surgery (min)
1	79 years	Male	53.7	Total pelvic exenteration with Urethrectomy Ileal conduit diversion Colostomy	705
2	59 yeasr	Male	85.0	Laparoscopic Rt radical nephroureterectomy Radical cystectomy Ileal neobladdar reconstruction	563
3	62 years	Male	70.9	Radical cystectomy Ileal conduit diversion	485
4	72 years	Male	53.3	Total gastrectomy Patial resection of jejunum Constrution of the tube jejunostomy Splenectomy, chole	430
5	80 years	Male	51.4	Left partial nephrectomy	203
6	67 years	Female	46.6	Segmentectomy (Segmentum posterius hepatitis) Partial gastrectomy	245
7	57 years	Female	44.4	Partial Liver resection (S1, S2)	240
8	70 years	Male	53.6	caudate lobectomy, extra hepatic bile duct resection Splenectomy, left hepatectomy	480
9	76 years	Male	66.2	Partial hepatic Resection (S4)	161
10	74 years	Female	40.1	Biliary reconstruction Partial hepatic resection	630
11	79 years	Male	63.1	Hepatectomy	498
12	75 years	Female	49.9	Total cystectomy, Ileal conduit.	526
13	69 years	Male	66.7	Left lateral segmentectomy	182
14	71 years	Male	70.2	Pancreaticoduodenectomy	387
15	75 years	Male	73.5	Pancreaticoduodenectomy	421
16	1 year 3 months (481 days)	Female	10.8	Living donor liver transplantation	467
17	11 years 5 months (4177 days)	Male	28.8	Living donor liver transplantation	550
18	0 years 7 months (222 days)	Female	7.3	Living donor liver transplantation	420
19	6 years 10 months (2496 days)	Female	16.3	Living donor liver transplantation	380
20	6 years 10 months (2498 days)	Female	18.5	Living donor liver transplantation	451

Table 3. Volume of Saved Albumin* in Patients Receiving more than 1000 mL (adults) or 10 mL (pediatrics) of 6% HES 130/0.4.

Unit	Statistic	Adult patients (N = 12)	Pediatric patients (N = 5)
mL	Mean (SD)	1033.8 (499.7)	652.7 (331.3)
	Median	1000.0	652.0
	Range	500 - 2000	287.5 - 1152.0
mL/kg body weight	Mean (SD)	18.6 (9.7)	39.9 (0.2)
	Median	17.1	40.0
	Range	6.8 - 31.7	39.7 - 40.0

*Saved albumin was calculated as the volume of study drug administered during the investigational period minus the dose limit.

Table 4. Hemodynamic stability*.

	Adult patients (N = 15)		Pediatric patients (N = 5)	
Time point	n	(%)	N	(%)
End of surgery	10	(66.7)	5	(100.0)
2 h after end of surgery	15	(100.0)	5	(100.0)
Follow-up 24 hours after end of surgery	13	(86.7)	5	(100.0)
At exactly 1 time point	2	(13.3)	0	(0.0)
At exactly 2 time points	3	(20.0)	0	(0.0)
At all 3 time points	10	(66.7)	5	(100.0)

*Hemodynamic stability is defined as a systolic blood pressure of not more than 30% below baseline.

Table 5. Fluid input and output (mL).

	Adult patients				Paediatric patients			
	N	Mean	SD	Range	N	Mean	SD	Range
Including only components > 0 mL								
Fluid input								
6% HES 130/0.4	15	1794	675	500 - 3000	5	816	414	360 - 1440
4.4% human albumin	0				0			
5% human albumin	5	1000	884	250 - 2500	3	407	121	270 - 500
Commercial colloid (25% albumin)	1	100		100 - 100	5	81	43	44 - 149
Crystalloids	15	8113	2375	4350 - 12,134	5	6256	2070	4167 - 9401
Predeposit autologous blood	1	650		650 - 650	0			
Salvaged autologous blood	1	1200		1200 - 1200	0			
Homologous packed red blood cells	9	1602	1207	260 - 3780	4	208	159	60 - 430
Fresh frozen plasma	8	1294	938	240 - 3360	1	107		107 - 107
Platelets	2	525	177	400 - 650	0			
Total other input	0				0			
Study drug plus rescue colloid	15	2127	1099	750 - 4500	5	1060	340	810 - 1440
Total colloid input	15	2134	1095	750 - 4500	5	1141	377	859 - 1574
Total input	15	12,091	4691	5350 - 22,754	5	7584	2308	5336 - 10,933
Fluid output								
Urine output	15	4624	1506	2015 - 6909	5	3696	1728	1417 - 5719
Blood loss (suction)	15	2854	2209	300 - 8810	5	315	197	20 - 535
Blood loss (from cloth-weight calculation)	4	650	597	180 - 1485	5	188	235	20 - 595
Total blood loss	15	3027	2390	300 - 8810	5	503	393	100 - 1130
Total other output	5	627	684	158 - 1837	5	1400	606	748 - 2367
Total output	15	7860	2905	3351 - 14,286	5	5600	1902	3144 - 7092
Balance								
Fluid balance	15	4231	2528	672 - 10,174	5	1984	1190	591 - 3842

both patient subgroups at the end of surgery and 2 hours later. For adult patients, the median decrease was less pronounced at 24 hours, while for pediatric patients there was still a major decrease at 24 hours which, however, returned to nearly the baseline level for the last available value.

Compared to baseline, Factor VIII activity was strongly decreased at the end of surgery, still slightly decreased 2 hours later and slightly increased at 24 hours. Von Willebrand factor antigen was strongly decreased at the end of surgery. The median values were nearly back to baseline values 2 hours after surgery and increased from baseline at 24 hours after surgery.

The analysis of clinical chemistry parameters indicated that median creatinine and BUN values basically remained stable from baseline to the end of surgery and at 24 hours for adult and pediatric patients. Total bilirubin was nearly unchanged at the end of surgery and increased at 24 hours. Glucose showed increases in the median for adult patients and stronger increases for pediatric patients after surgery. Median total protein and albumin showed decreases for each patient group at all post-baseline time points. In pediatric patients, the decrease was smaller for the last available value. Sodium and potassium showed only small median changes in adults. Transiently, there was a significant increase in sodium in pediatric patients

Table 6. Summary of hematology parameters.

	Adult patients (N = 15)				Pediatric patients (N = 5)			
Parameter (unit)	**Absolute values**		**Change from baseline**		**Absolute values**		**Change from baseline**	
Time point	**N**	**Median**	**N**	**Median**	**N**	**Median**	**N**	**Median**
Hematocrit (%)								
Baseline	15	39.30			5	33.90		
1 h after start of surgery	15	26.50	15	−6.40				
2 h after start of surgery	15	24.80	15	−8.50				
End of surgery	15	26.30	15	−11.60				
2 h after end of surgery	15	31.60	15	−9.50	5	30.30	5	−3.50
Follow-up 24 hours	15	31.60	15	−6.90	5	30.40	5	−7.60
Last available value	15	31.60	15	−6.90	5	29.20	5	−7.80
Hemoglobin (g/dL)								
Baseline	15	13.20			5	11.70		
1 h after start of surgery	15	8.80	15	−2.30				
2 h after start of surgery	15	8.20	15	−3.10				
End of surgery	15	9.10	15	−4.00				
2 h after end of surgery	15	10.30	15	−2.60	5	10.50	5	−1.20
Follow-up 24 hours	15	10.50	15	−1.80	5	9.90	5	−1.70
Last available value	15	10.50	15	−1.80	5	9.80	5	−1.80
Platelets (10^4/µL)								
Baseline	15	18.50			5	31.40		
End of surgery	15	12.60	15	−8.00				
Follow-up 24 hours	15	11.80	15	−6.60	5	12.00	5	−11.70
Last available value	15	11.80	15	−6.60	5	12.00	5	−11.70

2 hours after end of surgery. Median chloride increased at the end of surgery (adult patients) and 2 hours after end of surgery (pediatric patients), and returned close to the baseline values at 24 hours.

Both GOT/AST and GPT/ALT showed strong median increases after surgery, in particular in pediatric patients with very high median values for GOT/AST and GPT/ALT two hours post-surgery and the next 24 h. This observation should be regarded in the context that all pediatric patients had a liver transplantation and an increase of transaminases may be seen as a normal physiological adaptation after surgery. For the last available value, which includes additional follow-up measureements, GOT/AST and GPT/ALT levels of the transplanted livers were within the normal ranges in pediatric patients. Seven adult patients underwent a liver surgery during this study. Due to the type of surgery, high GOT/AST and GPT/ALT values occurred particularly in these patients, as well as in two patients with pancreaticoduodenectomy. Median LDH (only adult patients) slightly increased at the end of surgery and more pronounced at 24 hours. Median γ-GT (only adult patients) decreased at the end of surgery, whereas the values were slightly increased at 24 hours. Median value of amylase was nearly unchanged at the end of surgery. Thereafter it strongly increased in both patient groups, mainly at 24 hours and decreased thereafter. Overall, the analyzed laboratory parameters did not reveal any safety concern with regard to the administration HES 130/0.4.

The analysis of ECG parameters did not reveal important changes and local and systemic tolerance of HES 130/0.4 was always assessed as good (data not shown).

3.3. Adverse Events

No adverse event led to discontinuation of the administration of 6% HES 130/0.4. The most frequent reported

Table 7. Summary of hemostasis parameters.

	Adult patients (N = 15)				Pediatric patients (N = 5)			
Parameter (unit)	**Absolute values**		**Change from baseline**		**Absolute values**		**Change from baseline**	
Time point	**N**	**Median**	**N**	**Median**	**N**	**Median**	**N**	**Median**
INR (1/1)								
Baseline	15	1.010			5	1.060		
End of surgery	14	1.230	14	0.225				
2 h after end of surgery	15	1.180	15	0.120	4	2.020	4	0.890
Follow-up 24 hours	15	1.140	15	0.160	5	1.940	5	0.840
Last available value	15	1.140	15	0.160	5	1.150	5	0.080
aPTT (sec)								
Baseline	15	33.50			5	29.30		
End of surgery	15	40.60	15	9.10				
2 h after end of surgery	15	33.90	15	1.90	5	70.40	5	41.20
Follow-up 24 hours	15	35.30	15	1.00	5	49.50	5	20.30
Last available value	15	35.30	15	1.00	5	31.60	5	2.00
Fibrinogen (mg/dL)								
Baseline	15	350.0			5	226.0		
End of surgery	15	184.0	15	−152.0				
2 h after end of surgery	15	219.0	15	−130.0	5	67.0	5	−153.0
Follow-up 24 hours	15	329.0	15	−20.0	5	144.0	5	−93.0
Last available value	15	329.0	15	−20.0	5	205.0	5	−16.0
Factor VIII activity (%)								
Baseline	15	155.90						
End of surgery	15	90.00	15	−71.20				
2 h after end of surgery	15	126.70	15	−17.50				
Follow-up 24 hours	15	158.90	15	6.30				
Last available value	15	158.90	15	6.30				
von Willebrand fact. antigen (%)								
Baseline	15	168.0						
End of surgery	15	114.0	15	−52.0				
2 h after end of surgery	15	158.0	15	0.0				
Follow-up 24 hours	15	201.0	15	33.0				
Last available value	15	201.0	15	33.0				

adverse event for adults was “blood amylase increased”, which occurred in all 7 adult patients with adverse events related to the study medication and is an established and well-known effect of the administration of starches. In pediatric patients, the most common reported adverse event was an abnormality in serum electrolytes. All 5 pediatric patients had an increased blood chloride level, 4 patients had abnormal or increased sodium levels, and 2

Table 8. Summary of clinical chemistry parameters.

	Adult patients (N = 15)				Pediatric patients (N = 5)			
Parameter (unit)	**Absolute values**		**Change from baseline**		**Absolute values**		**Change from baseline**	
Time point	**N**	**Median**	**N**	**Median**	**N**	**Median**	**N**	**Median**
Creatinine (mg/dL)								
Baseline	15	0.80			5	0.24		
End of surgery	15	0.80	15	−0.04				
2 h after end of surgery					5	0.25	5	0.02
Follow-up 24 hours	15	0.96	15	0.08	5	0.18	5	−0.02
Last available value	15	0.96	15	0.08	5	0.18	5	−0.02
BUN (mg/dL)								
Baseline	15	15.00			5	7.00		
End of surgery	15	14.00	15	−1.30				
2 h after end of surgery					5	7.30	5	0.70
Follow-up 24 hours	15	18.40	15	2.00	5	6.30	5	−0.70
Last available value	15	18.40	15	2.00	5	6.30	5	−0.70
Total bilirubin (mg/dL)								
Baseline	15	0.89						
End of surgery	15	1.00	15	−0.10				
Follow-up 24 hours	15	1.50	15	0.58				
Last available value	15	1.50	15	0.58				
Glucose (mg/dL)								
Baseline	15	114.0			5	99.0		
End of surgery	15	128.0	15	17.0				
2 h after end of surgery					5	181.0	5	90.0
Follow-up 24 hours	15	142.0	15	28.0	5	161.0	5	61.0
Last available value	15	138.0	15	23.0	5	161.0	5	61.0
Total protein (g/dL)								
Baseline	15	6.60			5	6.30		
End of surgery	15	3.80	15	−2.90				
2 h after end of surgery					5	3.40	5	−2.70
Follow-up 24 hours	15	4.60	15	−1.80	5	3.90	5	−2.20
Last available value	15	4.60	15	−1.80	5	5.60	5	−0.70
Albumin (g/dL)								
Baseline	15	3.70			5	3.80		
End of surgery	15	2.20	15	−1.40				
2 h after end of surgery					5	2.90	5	−1.00
Follow-up 24 hours	15	2.70	15	−1.00	5	2.70	5	−1.10
Last available value	15	2.70	15	−1.00	5	3.70	5	−0.30

Continued

Sodium (mEq/L)								
Baseline	15	140.0			5	139.0		
End of surgery	15	141.0	15	1.0				
2 h after end of surgery					5	148.0	5	9.0
Follow-up 24 hours	15	138.0	15	−1.0	5	138.0	5	0.0
Last available value	15	138.0	15	−1.0	5	139.0	5	0.0
Potassium (mEq/L)								
Baseline	15	4.20			5	4.50		
End of surgery	15	4.10	15	−0.10				
2 h after end of surgery					5	4.00	5	−0.40
Follow-up 24 hours	15	4.10	15	0.00	5	4.10	5	−0.40
Last available value	15	4.10	15	0.00	5	4.10	5	−0.40
Chloride (mEq/L)								
Baseline	15	106.0			5	107.0		
End of surgery	15	112.0	15	6.0				
2 h after end of surgery					5	119.0	5	14.0
Follow-up 24 hours	15	108.0	15	3.0	5	105.0	5	0.0
Last available value	15	108.0	15	3.0	5	105.0	5	0.0
GOT/AST (U/L)								
Baseline	15	28.0			5	64.0		
End of surgery	15	78.0	15	44.0				
2 h after end of surgery					5	761.0	5	727.0
Follow-up 24 hours	15	89.0	15	63.0	5	584.0	5	434.0
Last available value	15	89.0	15	63.0	5	34.0	5	−39.0

patients had increased blood amylase. None of these adverse events was serious. One adult patient died 12 days after surgery, but the death was assessed as being unrelated to the administration of 6% HES 130/0.4.

4. Discussion

In this study, the infusion of high volumes of up to 50 mL/kg BW of 6% HES 130/0.4 was shown to be efficacious and safe in adult and pediatric patients undergoing major elective surgery.

Based on the obtained findings it is assumed that considerable potential savings of human albumin are possible if the internationally approved maximum dose of 50 mL/kg BW of 6% HES 130/0.4 would also be possible in Japan. For 12 of the 15 adult patients in need of additional colloid solution, approximately 1000 mL albumin could be saved, and about 650 mL in pediatric patients. In the present study the savings of human albumin are based on the assumption that 6% HES 130/0.4 and 5% human albumin have the same volume effect in adults and children. Comparable efficacy of both colloids has been previously demonstrated in several studies among different age groups of patients and clinical settings. In a study by Standl *et al*. (2008) [7] comparable volumes of 6% HES 130/0.4 and 5% human albumin were infused in 82 small infants (<2 years) undergoing non-cardiac surgery to restore or maintain hemodynamic stabilization. Hanart *et al*. (2009) [8] compared the effects of 6% HES 130/0.4 and 4% human albumin on perioperative blood loss and intraoperative volume requirements in 119 pediatric patients undergoing cardiac surgery. Both groups received comparable high volumes of both colloids (50 ml/kg), and measured or calculated blood losses were similar between both groups. A recent study [9] con-

firmed these results comparing 6% HES 130/0.4 and 5% human albumin in 60 patients undergoing cardiac surgery. Both groups received similar volumes for intraoperative volume requirements (mean in both groups 36 ml/kg), and no differences in transfusion requirements or blood loss were found.

Almost all patients were hemodynamically stable at all time points. Direct comparison of 6% HES 130/0.4 and 5% human albumin in adult surgical patients is scarce. Gondos *et al*. (2010) [10] compared the hemodynamic effects of 6% HES 130/0.4, 5% human albumin, 4% gelatin and Ringer's lactate in a fluid challenge with 10 ml/kg infused within 30 minutes in postoperative hypovolemic patients. They concluded that the hemodynamic effects of 6% HES 130/0.4 were at least similar to 5% human albumin. Langeron *et al*. (2001) [11] and Gandhi *et al*. (2007) [12] could demonstrate equivalence of 6% HES 130/0.4 with 6% HES 200/0.5 or 6% HES 450/0.7 in volume needed to restore or maintain hemodynamics during orthopedic surgery. Vogt *et al*. (1996) [13] compared 6% HES 200/0.5 with 5% human albumin and demonstrated similar volume needs to stabilize hemodynamics. Thus, it can be assumed that the volume effects of 6% HES 130/0.4 and 5% human albumin are similar, and a 1:1 exchange of volumes as calculated in our trial seems to be a reasonable calculation. However, a larger study directly comparing the volumes of 6% HES 13/0.4 with 5% human albumin needed to restore or maintain hemodynamics is missing so far to confirm this assumption.

With regard to safety, laboratory parameters as well as the type, frequency, maximal intensity and outcome of adverse events were consistent with what would be expected for a patient population undergoing major elective surgery as in this study. No adverse event led to a discontinuation of HES 130/0.4 administration. In all pediatric and 7 adult patients, there was a moderate to very high increase in parameters associated with liver function; in particular, transaminases. These individuals underwent liver transplantation (all pediatric patients), partial hepatictomy/lobectomy/segmentectomy or pancreaticoduodectomy. Accordingly, the elevated liver function parameters are to be interpreted as a reflection of the type and extent of surgery carried out in these patients and do not reveal any safety concern related to the administration of HES 130/0.4. The hemodilution effect of HES 130/0.4 associated with its mode of action was reflected by significant changes in hematological and coagulation parameters. The quick recovery of Factor VIII and vWF in adults after surgery is in line with other findings [3,11,12].

However, it is not possible to separate the effects of profound bleeding from those attributable to hemodilution in an uncontrolled trial. Previous studies have shown that at high dosages, dilution effects may result in a corresponding dilution of blood components such as coagulation factors and other plasma proteins, and in a decrease of hematocrit [6,14]. It is known that various disturbances of blood coagulation can occur depending on the dosage of non-sanguineous fluid infused. Despite the influence on coagulation of HES 130/0.4 has been significantly reduced compared to other HES preparations with regard to bleeding complications [15], the dilution of blood and plasma factors must be taken into account for any fluid therapy when large volumes (e.g. in cases of massive traumatic or surgical blood loss) are administered.

Overall, neither the laboratory parameters analyzed nor the incidence of adverse events did reveal any new or unexpected safety concern with regard to the administration of HES 130/0.4 in doses up to 50 mL/kg BW. James *et al*. (2011) [16] reported that renal injury was lower in the 6% HES 130/0.4 group as compared to normal saline, though very high volumes (approx. 70 ml/kg) were infused in trauma patients during initial resuscitation. Further studies confirm the safe use of 6% HES 130/0.4 [17-20].

However, when interpreting results of this study some limitations also have to be taken into account such as the low patient number and the missing control group. Thus, data can only be considered as explorative with respect to volume effect and human albumin savings, and safety conclusions are limited. In conclusion, in this trial it was demonstrated that doses of up to 50 mL/kg BW 6% HES 130/0.4 are safe and well tolerated in adult and pediatric patients undergoing major elective surgery. 6% HES 130/0.4 showed the expected and reliable volume effect in all evaluable adult and pediatric patients and could contribute to potential savings of human albumin infusion.

5. Conflict of Interest

Voluven® is a product of Fresenius Kabi. Dr. Frank Bepperling is an employee of this company, and Dr. Mi-yao is a Medical Consultant to this company.

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