

RANDOMIZED STUDY COMPARING THE EFFECT OF HYDROXYETHYL STARCH HES 130/0.4, HES 200/0.5 AND MODIFIED FLUID GELATIN FOR PERIOPERATIVE VOLUME REPLACEMENT IN THORACIC SURGERY: GUIDED BY TRANSESOPHAGEAL DOPPLER

Maged S. Abdallah, MD.* Osama M. Assad, MD*

**From department of anesthesia, Faculty of Medicine, Cairo University, Egypt.*

Background:

Plasma volume expansion is of great importance during major surgery. To achieve this goal, colloids may be preferred to crystalloids, as they more effectively increase blood volume and consequently, cardiac output. The aim of this study was to assess whether using the new hydroxyethyl starch with a lower molecular weight (HES 130/0.4) will be as effective as standard HES 200/0.5 and Gelatin in restoring the hemodynamics guided by trans-esophageal doppler monitor (EDM).

Methods:

Sixty adult patients scheduled for major thoracic surgery were randomized to receive either 6% HES 130/0.4 (HES 130/0.4 group) or 3% modified fluid gelatin (Gelatin group) or 6% HES 200/0.5 (HES 200/0.5 group) as their colloid during the intraoperative period. The maximum dosage of all colloids was 33 mL/kg. Each group has 20 patients. Hemodynamic data and Doppler derived measurements; Cardiac index (CI), Systolic flow time corrected for heart rate (FTc) and Stroke Volume Index (SVI) were recorded serially at 5 time points during the operation. Laboratory Measurements were recorded at baseline and every day postoperative for five days.

Main Result:

The mean volume of gelatin 3% given was significantly more than the amount of HES 130/0.4 and HES 200/0.5 given ($p < 0.05$). Volume of colloids infused in HES 130/0.4 was higher than HES 200/0.5 without statistical significance. Doppler derived measurements were comparable in all groups throughout the whole procedure. Platelet count was significantly lower in the Gelatin group in comparison to the other HES groups in the five PODs ($p < 0.05$). The two HES treated groups were comparable to each other. INR was significantly higher for Gelatin group in comparison to HES 130/0.4 group in the second and third PODs ($p < 0.05$) but in comparison to HES 200/0.5 group the higher level did not reach statistical significance. Serum creatinine was significantly higher and Creatinine clearance was significantly lower in the Gelatin than in the HES-treated patients on the first and second PODs ($p = 0.004$) with no difference between the two starches.

Conclusions:

The new HES 130/0.4 were as effective as HES 200/0.5 and modified fluid gelatin in intravascular volume expansion in major thoracic surgery. Also administration of the new HES 130/0.4 has more favorable effect on hemostasis and on renal and platelet than Gelatin.

Key Words: *Hydroxyethyl starch; Gelatin; Esophageal doppler monitor.*

Introduction:

ARTIFICIAL colloids, particularly hydroxyethyl starch solutions (HES) with a favorable benefit-risk profile and duration of action, are increasingly used for the compensation of surgical blood loss.¹ While commonly used pentastarches like HES 200/0.5 have a prolonged effect on hemodynamic stabilization, a certain risk of accumulation and side-effects is to be expected.² However, short-acting preparations may bear the risk of an inadequate circulatory volume effect.³ The degree of substitution and the C2/C6 hydroxyethylation ratio, in combination with the molecular weight, are responsible for the pharmacokinetic characteristics of HES solutions. Side-effects like haemostatic interaction and renal dysfunction were found to be associated with increasing values for these pharmacokinetic characteristics.^{4,5}

Gelatins with average molecular weight (MW) of 30–35 K dalton have the advantage of their unlimited daily dose recommendation and minimal effect on hemostasis.³ However, they are associated with a more frequent incidence of allergic reaction.⁴ A new Hydroxyethyl starch (Voluven®) with a lower in vivo molecular weight, HES 130/0.4, has been introduced and it has the advantage of a higher plasma-expanding effect and fewer effects on hemostasis.^{6,7}

Esophageal Doppler monitoring (EDM) measures blood flow velocity in the descending thoracic aorta. When combined with a nomogram-based estimate of aortic cross sectional area, it allows hemodynamic variables, including stroke volume, cardiac output, and index to be calculated. The monitor, however, does not provide direct measurement of pulmonary artery occlusion pressure, although changes in the corrected systolic flow time have been shown to reflect qualitative changes in pulmonary artery occlusion pressures, allowing optimization in left ventricular filling.⁸ Several studies demonstrated the importance of the use of EDM to direct intraoperative fluid administration.^{9,10}

The aim of this study was to assess whether using the new 6% HES 130/0.4 solution will be as effective as gelatin and 6% HES 200/0.5 solutions in restoring the hemodynamics guided by trans-esophageal Doppler during thoracic surgery. Our hypothesis is that the HES (130/0.4) are more effective than Gelatin and 6% HES 200/0.5 in restoring the hemodynamics.

Patients and Methods:Patient Population & Study design:

After obtaining ethics Committee approval and written informed consent from each patient, 60 patients scheduled for elective major thoracic surgery (such as lobectomy or pleural decortications) were included after they satisfied the exclusion criteria. This prospective, randomized, double blinded study was conducted between May 2009 and April 2010 in the cardiothoracic surgical unite in Kasr El-Aini hospital. We excluded patients with history of allergy to HES or Gelatin, decompensated cardiac or pulmonary diseases, pregnancy, esophageal pathology, significant liver disease (liver enzymes > 2.5 times normal), significant kidney disease (creatinine clearance (CrCl) < 80 mL/min or plasma creatinine concentration >1.5 mg/dl), significant coagulopathy (international normalized ratio (INR) or activated partial thromboplastin time (aPTT) > 1.5 times normal), preoperative anticoagulants or NSAID (within 5 days prior to randomization).

Patients were randomly allocated to receive either 6% HES 130/0.4 (Voluven®) (HES 130/0.4 group: n = 20) or 3% modified fluid gelatin (Plasmion®) (Gelatin group: n = 20) or 6% HES 200/0.5 (HAES-steril®) (HES 200/0.5 group: n = 20) (all products from Fresenius Kabi, Bad Homburg, Germany) as their colloid during the intraoperative period. The maximum dosage of all colloids was 33 mL/kg body weight. Randomization was done by the attending physician opening a sealed envelope. All solutions were supplied in identical-looking, sequentially numbered plastic bags according to the random code.

Anesthesia technique:

Two hours preoperatively, each patient received 0.15 mg/kg diazepam orally for premedication. Before anesthesia, a thoracic epidural catheter was inserted at the level of the thoracic segments T4-5 to T6-7 and a test dose (3 mL bupivacaine 0.5% with epinephrine, 5µg/mL) was given to exclude intrathecal or intravascular position of the catheter. General anesthesia was induced IV with propofol (1-1.5 mg/kg), cisatracurium (0.1-0.15 mg/kg), and fentanyl (3 µg/kg). Anaesthesia was maintained with isoflurane 0.4 – 1.0 % and additional doses of fentanyl and cisatracurium were given as appropriate. After tracheal intubation with a left- or right-sided standard double-lumen tube (DLT) and during one lung ventilation (OLV), the ventilatory

setting changed to keep inspiratory pressure limited to 35 cm H₂O. Respiratory frequencies were adjusted to achieve a PaCO₂ of 35–45 mm Hg. All patients were monitored for temperature, noninvasive and invasive arterial blood pressure, electrocardiogram (ECG), peripheral oxygen saturation, end-tidal carbon dioxide tension (ETCO₂), urinary output, and central venous pressure (CVP). At end of surgery, all patients were extubated and admitted to the intensive care unit (ICU) for at least 24 h.

Esophageal Doppler monitoring (EDM)

The CardioQ (Deltex Medical, Chichester, UK) EDM display a wave form of the velocity plotted against time. The systolic portion is typically triangular and its base represents the flow time (= systolic ejection time). Because flow time depends on the heart rate, it is usually corrected by a modification of Bazett's equation (flow time divided by the square root of the cycle time), which is used to correct the QT interval of an electrocardiogram. The resulting flow time corrected (FTc) represents the systolic ejection time adjusted to one cardiac cycle per second. The peak of the waveform depicts the peak velocity in the descending aorta. The area under the systolic portion of the curve (AUC) represents the stroke distance. The stroke distance is proportional to the stroke volume under the assumption that aortic diameter and distribution of blood flow between the supra-aortic vessels and the descending aorta remains constant. Descending aortic stroke volume (cm³) can then be determined by multiplying the stroke distance (cm) with the aortic cross-sectional area (cm²) (Fig.1).¹¹

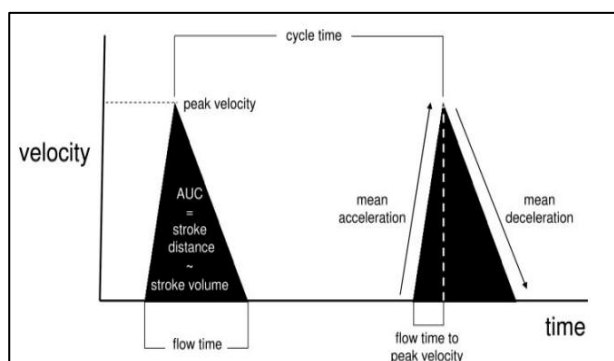


Fig. 1: Velocity-time plot.¹¹

After induction of anesthesia, the EDM probe was inserted orally and positioned approximately 35–40 cm from the teeth. The CardioQ EDM measures the velocity of blood flow in the descending thoracic aorta. Integrating the velocity–time curve gives the distance traveled by the blood following

cardiac systole and multiplying this by the cross-sectional area (estimated by a nomogram based on the patient's age, height, and weight.) derives stroke volume and cardiac output.

Fluid management:

In all groups, Ringer lactate solution was administered routinely at 8-10 mL/kg/h to cover fluid deficit from the starving period and basal fluid requirements. In addition, 200 cc of colloid solution were given guided by EDM to maximum volume recommended before. Ringer lactate solution was given if additional fluid replacement was required to compensate for surgical loss. Volume replacement was guided as follows¹²; Colloid was infused when the systolic flow time corrected for heart rate (FTc) is less than 0.35 second. If the stroke volume is maintained or increased by the fluid challenge and the FTc remains below 0.35 second, the fluid challenge will be repeated. If the stroke volume rise by more than 10% but the FTc exceeded 0.35 second, the fluid challenge will be repeated until no further rise in stroke volume occurred. If the FTc rise above 0.40 second with no change in stroke volume, indicating that intravascular volume is optimized, further fluid will not then be administered until the FTc or stroke volume fall by 10%.

Blood transfusion was done based on hemoglobin level (less than 7 g/dL). In the presence of abnormal clinical bleeding, transfusion of platelet was done if platelet count < 50,000 /dl and fresh-frozen plasma (FFP) was done if INR > 1.5 or abnormal bleeding in the surgical field.

Measured Hemodynamic and oxygenation Variables

Heart rate (HR), Mean arterial pressure (MAP), Central Venous Pressure (CVP), Central venous oxygen saturation (ScvO₂) and Oxygen delivery index (DO_{2i}) (calculated according to standard formula) were recorded after induction of anesthesia and before any colloid administration T1; after skin incision T2; 2 hours after skin incision T3; and at the end of surgery T4.

Doppler derived Measurements:

Cardiac index (CI), Systolic flow time corrected for heart rate (FTc), Stroke Volume (SV) and Stroke Volume Index (SVI) were recorded at same time points like hemodynamic data.

Laboratory Measurements:

Hemoglobin Concentration (Hg), Hematocrite (Ht), Platelet Count, activated partial thromboplastin time (aPTT), International Normalized Ratio (INR), plasma fibrinogen concentration, serum creatinine and calculating creatinine clearance (CrCl) using a complete 24-h urine collection. All laboratory works were recorded before induction of anesthesia, and at the morning of every postoperative day (PODs) for 5 days.

Other Variables:

Intravascular volume replacement therapy, including crystalloid and colloid infusion, and blood and plasma transfusion in addition to urine output were recorded in the intraoperative period. The duration ICU stay, and hospital stay were documented

For efficacy measurements the primary variable was defined as the volume of study medication infused from induction of anaesthesia until end of surgery to maintain haemodynamic stability. Secondary variables comprised: haemodynamics; haematology and blood coagulation; renal functions; overall requirements of fluid substitutes and transfusions, volume of perioperative blood loss, fluid loss via drainages.

Statistical Analysis:

Results were expressed as mean \pm standard deviation or number (%). Comparison of quantitative variables among the study groups was done using one way ANOVA for independent samples in comparing 3 groups when normally

distributed and Kruskal Wallis for independent samples when not normally distributed. For comparing categorical data, Chi square (χ^2) test was performed. Fischer Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, and USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows)

Sample size calculation was done using mean volume of infused colloids as it was considered the primary outcome of our study. The hypothesis was that the volume need in all groups would be equivalent within a range of \pm 500 mL. If the true difference in the experimental and control means is 200, we will need to study less than 20 experimental subjects in each group with 80% power. Type I error probability associated with this test of this null hypothesis is 0.05. Calculations were done using PS Power and Sample Size Calculations software, version 2.1.30 for MS Windows (William D. Dupont and Walton D. Vanderbilt, USA).

Results:

All 60 enrolled patients completed the study. The groups were well matched as regard to demographics, as well as perioperative data. No postoperative pulmonary complications were recorded between the study groups (Table-1).

Table 1: Demographic and perioperative data

Each group = 20	HES 130/0.4	HES 200/0.5	Gelatin
Age (yrs.)	52.6 \pm 12.7	50.4 \pm 11.6	59.1 \pm 13.5
Gender (F/M)	5/15	3/17	4/16
Weight (Kg)	65.4 \pm 6.5	63.3 \pm 5.4	67.3 \pm 11.2
Height (cm)	167.6 \pm 5.3	164.5 \pm 4.3	165.8 \pm 4.3
Right/Left sided lobectomy	4/14	3/13	5/12
Decortication	2	4	3
Operation time (min)	196 \pm 30	201 \pm 23	193 \pm 25
ICU stay (days)	1 \pm 0.5	1 \pm 0.4	1 \pm 0.5
Hospital stay (days)	8 \pm 3	9 \pm 2	8 \pm 2

Data were expressed as mean \pm SD or number (%).

* $p < 0.05$ = significance between groups.

Haemodynamic variables (MAP, HR and CVP) displayed similar changes between successive observation time points during anesthesia in different treatments groups except CVP was significantly higher in gelatin

group than other groups at T3 ($p < 0.05$). Central venous oxygen saturation (ScvO₂) and Oxygen delivery index (DO_{2i}) results were comparable in the three groups throughout the whole procedure (Table-2). As regards Doppler derived data (cardiac index, stroke volume, stroke volume index, and systolic flow time corrected for heart rate) the results were comparable in three groups throughout the whole procedure with no significant difference ($p > 0.05$) (Table -3).

Table 2: Hemodynamic and oxygenation data

	Each group = 20	T 1	T 2	T 3	T 4
HR (beat/min)	HES 130/0.4	75 ± 11	82 ± 8	79 ± 9	83 ± 8
	HES 200/0.5	77 ± 12	85 ± 7	77 ± 11	82 ± 12
	Gelatin	74 ± 9	85 ± 14	84 ± 10	85 ± 8
MAP (mmHg)	HES 130/0.4	90 ± 17	103 ± 16	87 ± 9	94 ± 10
	HES 200/0.5	90 ± 15	101 ± 13	85 ± 12	90 ± 7
	Gelatin	87 ± 7	108 ± 9	94 ± 9	92 ± 10
CVP (mmHg)	HES 130/0.4	5.5 ± 2.8	5.6 ± 2.5	5.2 ± 1.6	6.5 ± 1.2
	HES 200/0.5	6.4 ± 2.8	5.8 ± 2.5	6.0 ± 1.6	6.4 ± 1.3
	Gelatin	6.1 ± 3.2	6.2 ± 2.3	7.9 ± 1.3*	7.1 ± 1.4
ScvO ₂ %	HES 130/0.4	89.4 ± 3.7	92.3 ± 3.2	88.4 ± 5.4	89.7 ± 5.4
	HES 200/0.5	90.3 ± 2.5	91.2 ± 4.3	89.3 ± 5.3	89.6 ± 4.3
	Gelatin	88.3 ± 2.4	92.1 ± 3.8	87.3 ± 6.1	88.7 ± 6.5
DO _{2i} (ml/min/m ²)	HES 130/0.4	517 ± 164	554 ± 159 ⁺	506 ± 183	514 ± 153
	HES 200/0.5	510 ± 134	543.2 ± 137 ⁺	513 ± 173	513 ± 143
	Gelatin	485 ± 165	508.3 ± 164	532 ± 84 ⁺	511 ± 204

Values are expressed as mean ± SD.

* $P < 0.05$ = significance between groups.

⁺ $P < 0.05$ relative to preoperative time within the same group

T1; after induction, T2; after skin incision, T3; two hours after skin incision, T4; end of surgery

HR: heart rate, MAP; mean blood pressure, CVP; central venous pressure, ScvO₂; Ccentral venous oxygen saturation, DO_{2i}; Oxygen delivery index.

Table 3: Doppler derived data

	Each group =20	T 1	T 2	T 3	T 4
CI (L/min/m ²)	HES 130/0.4	3.3 ± 1.2	3.7 ± 1.2	2.7 ± 1.4	4.5 ± 1.3
	HES 200/0.5	3.5 ± 1.3	3.6 ± 1.2	2.8 ± 1.5	4.4 ± 1.2
	Gelatin	2.8 ± 1.2	3.4 ± 1.1	2.8 ± 0.9	4.07 ± 1.3
SV (ml)	HES 130/0.4	71.3 ± 21.2	74.6 ± 25.6	81.2 ± 24.4	84.3 ± 14.7
	HES 200/0.5	73.2 ± 20.3	73.6 ± 23.5	84.2 ± 23.4	83.2 ± 16.7
	Gelatin	69.1 ± 23.7	75.7 ± 19.3	83.2 ± 22.5	78.2 ± 22.7
SVI (ml/ m ²)	HES 130/0.4	41.5 ± 12.7	41.4 ± 14.3	48.1 ± 17.3	49.6 ± 12.1
	HES 200/0.5	37.1 ± 11.6	44.2 ± 9.5	46.2 ± 12.2	43.5 ± 10.5
	Gelatin	38.1 ± 12.8	43.2 ± 9.4	44.3 ± 11.1	44.5 ± 9.4
FTc (msec)	HES 130/0.4	364.8 ± 32.7	397.4 ± 54.4	416.7 ± 23.7	417.2 ± 24.2
	HES 200/0.5	345.4 ± 6.6	417.1 ± 33.1	409.2 ± 19.8	409.4 ± 16.7
	Gelatin	358.5 ± 7.6	422.3 ± 35.2	407.1 ± 18.3	410.4 ± 15.13

Data were expressed as mean ± SD.

⁺ $p < 0.05$ relative to preoperative time within the same group.

* $P < 0.05$ = significance between both groups.

T1: after induction, T2; after skin incision, T3; two hours after skin incision, T4; end of surgery

CI; cardiac index, SV; stroke volume, SVI; stroke volume index, FTc; systolic flow time corrected for heart rate

The mean (sd) volume of gelatin 3% given in the study period was significantly more than the amount of HES 130/0.4 and HES 200/0.5 given in the same period ($p < 0.05$). Volume of colloids infused in HES 130/0.4 was higher than HES 200/0.5 without statistical significance. The use of crystalloids did not differ between the three groups. Perioperative packed RBCs, Fresh-frozen plasma and platelets transfusion were similar in all groups. Blood loss, Chest tube drainage and urine output showed insignificant difference between three studied groups (Table -4).

Table 4: Total fluid intake and output

Each group = 20	HES 130/0.4	HES 200/0.5	Gelatin
Crystalloid (mL)	3703 ± 1441	3600 ± 1328	3610 ± 1431
Colloid (mL)	1106 ± 367	924 ± 268	1396 ± 467*
Blood loss (mL)	1210 ± 335	1102 ± 140	1190 ± 319
PRBCs (total number of units/group)	7	6	7
FFP (total number of units/group)	4	4	6
Platelets (total number of units/group)	0	0	4
Chest tube drainage (ml)	660 ± 120	705 ± 132	710 ± 122
Urine output (ml)	896 ± 117	986 ± 115	835 ± 262

Data were expressed as mean ± SD or number

* $P < 0.05$ difference between the groups

FFP; fresh frozen plasma, PRBCs; packed red blood cell

Regarding hemoglobin and hematocrite levels (which reflect the degree of hemodilution), there were no significant differences between the three groups in the five PODs except in day five where the hematocrite level was significantly lower in the Gelatin group compared to other groups. In day one, the HES 200/0.5-treated patients were lower than the others ($p < 0.05$). Within each group, hemoglobin and hematocrite levels were significantly lower in most of PODs compared to the baseline ($p < 0.01$).

Platelet count was significantly lower in the Gelatin group in comparison to the other HES groups in the five PODs ($p < 0.05$). The two HES treated groups were comparable to each other. Within each group, in the Gelatin group the platelets count was significantly lower in the all PODs compared to the baseline ($p < 0.05$).

The results of INR were significantly higher in most of PODs when compared to the baseline ($p < 0.01$). INR was significantly higher for Gelatin group in comparison to HES 130/0.4 group in the second and third PODs ($p < 0.05$) but in comparison to HES 200/0.5 group the higher level did not reach statistical significance. Fibrinogen level had slightly decreased in the HES groups in second and third PODs and in Gelatin group in first and second PODs as compared with baseline but without any significance. The difference between groups was insignificant ($p > 0.05$). aPTT levels were insignificant between all groups (Table-5).

Serum creatinine was significantly higher and Creatinine clearance was significantly lower in the Gelatin than in the HES-treated patients on the first and second PODs ($p=0.004$) with no difference between the two starches (Table-5).

Table 5: Laboratory Measurements

	Group	Baseline	POD - 1	POD - 2	POD - 3	POD - 4	POD - 5
Hg (g/dl)	HES 130/0.4	12.3±1.3	10.1±1.5+	9.6±1.1+	10.9±0.9	9.7±0.8+	10.4±1.2+
	HES 200/0.5	13.3±1.2	9.2±1.3+	10.1 ±1.3+	9.6±0.8+	11.2±1.3	10.5±1.1+
	Gelatin	12.4± 2.2	10.7± 1.7+	9.5 ± 2.2+	9.7±2.4+	9.8±2.2+	9.8±1.8+
Ht (%)	HES 130/0.4	35.5±3.4	30.2±3.7+	28.5±3.3+	31.4±2.2	29.6 ±1.2+	33.2±1.7
	HES 200/0.5	37.7±3.3	27.2±3.3 ⁺ *	29.9 ± 4.2+	28.8±2.2+	28.6 ±2.2+	32.2±1.6+
	Gelatin	35.6±5.3	29.8±4.7+	28.7±5.3 +	28.5±5.8+	29.3 ±6.3+	29.1±4.6+*
Platelets x 10 ³	HES 130/0.4	234 ± 126	224 ± 78	202 ± 51 ⁺	217 ± 35	214 ± 83	264 ± 49
	HES 200/0.5	237 ± 126	194 ± 71+	203 ± 54	213 ± 34	205 ± 82	255 ± 38
	Gelatin	214 ± 57	158 ± 45+*	148 ± 43+*	143 ± 42+*	169 ±58+*	194 ± 47+*
INR	HES 130/0.4	1.08±0.1	1.34 ±1.13+	1.22±0.11+	1.18± 0.09	1.24±0.1+	1.23±0.3+
	HES 200/0.5	1.09±0.1	1.28 ±0.15+	1.25±0.19 +	1.26±0.17+	1.19±0.1	1.22±0.2+
	Gelatin	1.09±0.06	1.38±0.26 +	1.37±0.15+*	1.32±0.18+*	1.15±0.1	1.12±0.1
aPTT (seconds)	HES 130/0.4	28 ± 13	33 ± 3	34 ± 5	34 ± 6	34 ± 3	34 ± 2
	HES 200/0.5	28 ± 2	32 ± 3	35 ± 5	35 ± 6	37 ± 7	35 ± 6
	Gelatin	26 ± 4	35 ± 27	35 ± 11	36 ± 4	36 ± 4	36 ± 4
Fibrinogen [1.5–4.5 g/ L]	HES 130/0.4	3.52 ±1.32	3.55± 1.23	2.38± 0.72	2.91± 1.02	3.42 ± 0.96	3.25 ± 1.43
	HES 200/0.5	3.60± 0.9	3.43± 1.45	2.47± 1.55	2.61± 1.48	3.41 ± 0.61	3.23 ± 1.36
	Gelatin	3.73 ± 15	2.97 ± 1.65	2.61 ± 1.48	3.12 ± 0.71	3.53 ± 0.14	3.73 ± 0.14
Creatinine (mg/dl)	HES 130/0.4	1.44±0.9	1.18±0.11	1.16±0.8	1.23±0.7 +	1.21±0.5+	1.1±0.56 +
	HES 200/0.5	1.31±0.8	1.15 ± 0.12	1.18±0.7	1.32±0.6	1.02±0.1+	1.2±0.66
	Gelatin	1.38±0.5	1.40±0.38*	1.4 ±0.5*	1.34±0.6	1.15±0.5+	1.17±0.4 +
CrCl (mL/min)	HES 130/0.4	95.3±15.3	84.1 ± 24.7	78.4 ± 21.0+	89.1 ± 21.4	106.8 ± 21.3	107.4 ± 22.3
	HES 200/0.5	96.2 ±14.2	80.1 ± 12.7+	84.4 ± 26.0	88.1 ± 11.3	102.8 ± 31.3	105.4 ± 21.3
	Gelatin	92.3±21.4	68.5±22.2*+	71.4±28.1*+	85.7 ± 32.4	98.2 ± 32.2	102.2 ± 30.2

Data were expressed as mean ± SD.

⁺ P < 0.05 relative to preoperative time within the same group.

* P < 0.05= significance between both groups.

Hg; hemoglobin, Ht; Hematocrite, aPTT; activated partial thromboplastin time, INR; International Normalized Ratio., Cr Cl; creatinine clearance. POD; postoperative day

Discussion:

This study was designed to investigate the clinical efficacy and safety between a novel 6% HES 130/0.4 (Voluven®) and a standard 6% HES 200/0.5 (HAES-steril®) and modified fluid gelatin with respect to correction of intraoperative hypovolaemia and maintenance of haemodynamic stability. The primary efficacy endpoint was the colloid volume infused. Mean volumes of HES 200/0.5 and HES 130/0.4 infused were comparable but significantly less than Gelatin. Safety evaluation focused on coagulation, estimated blood loss, and blood transfusion requirements.

Plasma expanding effect of any colloids depends primarily on the number of osmotically active molecules. For a similar concentration, HES 130 contains a higher number of osmotically active molecules than with HES 200. The number of molecules above the renal threshold of HES 130/0.4 is higher while the amount of large molecules is reduced. This leads to a lower initial renal elimination rate, so that the immediate plasma substitution effect appeared similar with the two starches.¹³

Modified fluid GEL is expected to have a lower and shorter plasma-expanding effect than HES 130/0.4 based on its pharmacodynamic data. Haisch et al.¹⁴ demonstrated that a similar volume of 4% modified fluid GEL and 6% HES 130/0.4 was required to maintain CVP between 10 and 14 mm Hg. In contrast, Boldt et al.¹⁵ stated that more gelatin than HES 130/0.4 was required to keep CVP between 12 and 14 mm Hg. In our study, significantly more gelatin than starches was required to reach our target for volume therapy, which means HES colloids may display a better intravascular volume effect than gelatin 3%. Other papers also found a better volume effect with HES 130/0.4 in an animal study, HES 130/0.4 6% resulted in higher CO, oxygen delivery, and lower blood lactate levels than similar volumes of gelatin 3%.¹⁶

In the present study, the two HES treated groups and modified fluid GEL (up to 33 mL/kg) were associated with similar perioperative blood losses. This result contrasts with previous data reporting larger blood losses with HES 200/0.5 than with GEL.¹⁷ Gallandat et al,¹⁸ in his study of volume replacement with 6% HES 130/0.4, versus 6% HES 200/0.5 revealed that HES 130/0.4 can reduce

blood loss in cardiac surgery compared with HES 200/0.5.

Regarding platelet count in our study, it was significantly lower in the Gelatin group in comparison to the other HES groups in the five PODs and it was significantly lower in the all PODs compared to the baseline ($p < 0.05$). The two HES treated groups were comparable to each other. HES solutions have been shown to directly compromise platelet contribution to hemostasis by reducing the availability of the functional receptor for fibrinogen on the platelet surface.¹⁹ In addition, a decrease in von Willebrand factor may contribute to the decreased platelet responsiveness.²⁰ These different effects appear closely related to intrinsic properties of the different solutions, such as the in vitro molecular weight and the degree of hydroxyethyl substitution.^{6,21} HES 130/0.4 exhibits a lower in vitro molecular weight and a lower degree of hydroxyethyl substitution than HES 200/0.5. Therefore it could have less impact on hemostasis, in particular on the factor VIII-von Willebrand factor complex and on platelet aggregability.²²

In our study, plasma coagulation parameters (INR, aPTT and Fibrinogen) between two HES groups were comparable but in Gelatin group, INR was significantly higher than HES groups postoperatively. These data were in contrast with results of a previous study that demonstrated HES 130/0.4 interfering significantly less than HES 200/0.5 with coagulation parameters.²³ In one high-dose study, Ellger et al.²⁴ found that 6% HES 130/0.4, when given up to 50 ml/kg, had similar effects on coagulation as 30 ml/kg HES 200/0.5. Similar results were found in a study by Neff et al.²⁵ who infused very high doses of HES 130/0.4 to 31 patients with severe head injury, up to 70 ml/kg/day or a control 6% HES 200/0.5 up to a limit of 33 ml/kg/day. The authors reported no major differences in coagulation variables.

Again, our results were in contrast with Haisch et al,¹⁴ who stated that infusion of HES 130/0.4 in patients undergoing cardiac surgery was not associated with side effect on hemostasis when compared with patients receiving gelatin. Also, Jungheinrich et al,²¹ found that urea-linked gelatins appear to inhibit in vitro platelet aggregation induced by activators of the platelet receptor GPIIb/IIIa. In their study, Alexander et al,

²⁶ and Martin et al, ²⁷ they compared the effect of different types of HES on hemostasis using rotational thromboelastogram (ROTEG). Similar findings were observed in the study of Shan-liang and Bu-Wei, ²⁸ on gastric cancer patients using thromboelastogram (TEG) and they documented that, Gelatin reduced clot quality associated with derangements of fibrin polymerization. HES 130/0.4 delayed initiation of sufficient thrombin generation to convert fibrinogen to fibrin and impaired platelet function to lesser extent than Gelatin.

Niemi and colleagues, ²⁹ compared the use of 4% succinylated gelatin solution, 6% HES 200/0.5, and 4% albumin solutions on hemostasis after cardiac surgery and reported that much impairment of coagulation was seen with HES. However, the newer starch formulation of 6% HES 130/0.4 has been shown to be safe and comparable to gelatin-based colloids in cardiac surgery.^{30, 31}

In contrary to our study, Mortelmans et al, ³² found that higher post operative blood loss with HES 130/0.4 was more than Gelatin in orthopedic and cardiac surgeries. Also, the results of Shramko et al, ³³ were not in accordance with us as their study revealed that by using TEG, both HES 130/0.4 and Gelatin impaired clot formation and firmness shortly after cardiac surgery. This effect became more pronounced as the doses increase. Osthau et al, ³⁴ studied the effects of Gelatin and HES 130/0.4 on modified TEG in children. The study concluded that there is no difference in coagulation in both colloids. Petroianu et al, ³⁵ showed that global tests of coagulation (PT and aPTT) and platelet aggregation were only slightly influenced by Gelatin used in orthopedic patients undergoing acute normovolemic hemodilution when compared to patients received High MW-HES preparation. This significant difference may be explained by the pharmacokinetic differences between the high MW HES which is used in this study as compared to HES 130/0.4 which is used in our study.

The other important finding in our study was the negative effect of Gelatin on renal functions expressed in serum creatinine and creatinine clearance levels. Both parameters were significantly different in the Gelatin than in the HES-treated patients on the first and second PODs.

($P=0.004$) with no difference between the two starches.

A large-scale retrospective study of the effects of HES on renal function done by Sakr et al. ³⁶ in critically ill patients, it was found that HES per se was not an independent risk factor for adverse effects on renal function. Another recent reports preliminary results of an observational study of pediatric patients undergoing different types of surgery while receiving 6% HES 130/0.42. The study evaluated the perioperative use of HES 130/0.42 in 1,000 children, with a particular focus on cardiovascular stability, acid-base balance, renal function, blood coagulation, and hypersensitivity. Reports on the first 300 children have shown no serious effects on renal function.³⁷

Potential adverse renal outcome after HES infusion has been reported for slowly metabolizable HES formulations such as HES 200/0.62, which has been compared to gelatin.²³ Also, high doses of HES 130/0.4 (70mL/kg/ day) did not influence Cr Cl and serum creatinine in craniocerebral trauma patients.²⁵

These findings were coinciding with the previous study of Mahmood et al, ³⁸ who demonstrated that HES 130/0.4 maintained glomerular and tubular functions throughout the postoperative period more than Gelatin in patients undergoing abdominal aortic aneurysm surgery. The explanation may be due to improving the microcirculation and renal tissue oxygenation. In his study he used more sensitive biochemical markers for renal functions like urinary α -glutathione transferase, Neutrophil Gelatinase Associated Lipocalin. Another study done by Boldt et al, ³⁹ (2008) on cardiac patients over 80 years, found that volume replacement with HES 130/0.4 was associated with less marked changes in kidney functions and endothelial inflammatory response than Gelatin. Also the study done by Mills, ⁴⁰ showed that HES 130/0.4 when administered to patients with stable renal impairment did not accumulate and there was no evidence of a subsequent worsening of creatinine clearance.

Contrary to our results, was the data revealed from the study done by Goldet et al, ⁴¹ who compared HES 130/0.4 with Gelatin in abdominal aortic aneurysm surgery patients concluding that both colloids are equally safe regarding renal functions. However administration of HES 130/0.4 did not

cause deterioration of renal functions in patients with pre-existing renal impairment compared to Gelatin. Again, data from studies done by Franziska et al,⁴² and Christiane et al,⁴³ showed that moderate cumulative doses of modern HES and Gelatin solutions are associated with higher risks of acute renal failure.

Doppler derived data in our study showed no significant difference between all groups, which renders the three replacement therapies equally efficient. The EDM is a minimally invasive method for continuous monitoring of the circulation. There is good agreement between measures of cardiac output made simultaneously with the esophageal Doppler and a thermodilution pulmonary arterial catheter.⁴⁴ Sinclair et al.⁴⁵ investigated the use of EDM to guide intraoperative plasma volume expansion, and they demonstrated significant improvement in postoperative recovery and shortened hospital stay in patients undergoing proximal femoral neck fracture repair.

One limitation to our study is that, additional tests should have been used to ensure optimal evaluation of organ function. More sensitive biochemical markers for renal functions like urinary α -glutathione transferase, Neutrophil Gelatinase Associated Lipocalin, and urinary immunoglobulin G. These biochemical markers are more sensitive than creatinine and are able to detect early changes in renal functions before changes in serum creatinine. Also additional tests for coagulation and platelet function are recommended to be used in future studies like thromboelastogram (TEG).

Ultimately, we conclude that using the new HES 130/0.4 was as effective and safe as HES 200/0.5 and modified fluid gelatin in intravascular volume expansion in major thoracic surgery. Also administration of the new HES 130/0.4 has more favorable effect on hemostasis and on renal and platelet than Gelatin in major thoracic surgery.

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