Comparison of HES 130/0.42 and HES 200/0.5 for hemodynamic stabilisation in major urological surgery

H. Heinze[1], K. Hage[1], F. Hackmann[1], R. Schäfer[1], R. Zulkowski[2], K.-F. Klotz[1]

[1]Department of Anesthesiology, University of Luebeck, Luebeck, Germany; [2]Department of Plastic Surgery, Clinic Wels, Wels, Austria

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Abstract

Purpose: Different hydroxyethyl starches (HES) may lead to different volume effects. We compared a new HES130/0.42 with an established HES200/0.5 with respect to perioperative volume requirements, hemodynamic effects, safety and tolerability.
Methods: After approval of the local ethics committee we investigated in a prospective, randomized double-blinded clinical trial 100 adult patients scheduled for elective major urological surgery. The study fluids were administered according to patients´ individual need from induction of anesthesia until 12:00 midnight on the day of surgery. Infusion trigger were mean arterial pressure, central venous pressure, heart rate, or other clinical reasons. The required volume of study medication served as primary endpoint. Secondary endpoints were safety and tolerability. Equivalence was tested using the confidence interval inclusion method. A $p < 0.05$ indicates a high probability of equivalence. Hemodynamic and laboratory data were compared with the t-test, Mann-Whitney U-test or χ^2-test as appropriate. In this case a probability value of less than 0.05 was considered as statistically significant.
Results: Groups did not differ at baseline. Intraoperatively and during ICU stay equivalent amounts of HES were administered [mean ± SD] (HES 130/0.42: 1150 ± 574mL vs. HES 200/0.5: 1070 ± 572mL, p = 0.0002 (OP); HES 130/0.42: 1390 ± 955 mL vs. HES 200/0.5: 1245 ± 715 mL, p = 0.0196 (ICU)). Statistical equivalence over the whole observation period could not be achieved (HES 130/0.42: 2540 ± 1232 mL, HES 200/0.5: 2290 ± 1040mL, p = 0.1379). There was no difference in total fluid requirements, hemodynamics, routine chemistry, and blood coagulation parameters. Intraoperatively red blood cells were administered more frequently in group HES 200/0.5 (HES 130/0.42: 4/50 patients; HES200/0.5: 11/50 patients; p = 0.0499). Over the entire observation period no serious adverse events occurred.
Conclusions: HES 130/0.42 can be used as safely and efficiently for perioperative plasma volume expansion to maintain hemodynamic stability during major urological surgery as a standard HES 200/0.5 formulation.

Implication statement

A new HES130/0.42 solution is compared with an established HES200/0.5 in 100 patients undergoing major urological surgery. HES 130/0.42 can be used safely and efficiently for perioperative plasma volume expansion to maintain hemodynamic stability.

Introduction

Hydroxyethylstarch (HES) is increasingly used as colloidal volume replacement in anesthesiology and critical care medicine for treatment of hypovolemia (1,2). The effectiveness and tolerability of HES formulations depend mostly on the mean molecular weight and the degree of molar substitution, i.e. the ratio of hydroxy-

ethyl groups to glucose residues (3). Side-effects like hemostatic interaction, renal dysfunction and the risk of accumulation were found to be associated with increasing values of these pharmacokinetic characteristics (2). To reduce these side-effects, efforts have been made to develop new HES solutions with a smaller molecular weight and a lower degree of substitution. Indeed fewer side effects – especially on coagulation parameters – have been reported with the use of HES 130 when compared to HES with higher molecular weight and degree of molar substitution (4-6). The novel potato starch-based HES solution (Venofundin®, B.Braun Melsungen AG, Germany) is characterized by an average molecular weight of 130 ± 15 kD, a degree of substitution of 0.42, and a C2/C6 ratio of 6:1. The molecular weight distribution is the narrowest of all available HES types, i.e., the proportion of very large and very small molecules was significantly reduced. In addition, the lower C2/C6 hydroxyethylation ratio may lead to further reduced side-effects. It is known that lower molecular weight starch preparations may be less effective in restoring plasma volume, as they have shorter half-life times (7), therefore more volume may be needed compared to HES with a higher molecular weight (8). In addition, the low C2/C6 ratio may increase the metabolic degradation and subsequent renal excretion.

Venofundin® was compared with a HES 200/0.5 solution in a clinical trial in women undergoing major gynecological surgery (9). It demonstrated therapeutic equivalence in maintaining hemodynamic stability. The mean volume administered was 1224 ± 544 mL (9). As much larger doses are frequently infused during surgery and intensive care therapy volume requirements may increase to achieve hemodynamic stability. But side-effects may increase and tolerability decrease with increasing volume.

It was the aim of this clinical trial to compare the new HES 130/0.42 formulation (Venofundin®, B.Braun Melsungen AG, Germany) with an established HES 200/0.5 (Infukoll® HES, Serumwerk Bernburg, Germany) with respect to perioperative volume requirements, hemodynamic effects, safety and tolerability in patients scheduled for major urological surgery with an expected fluid requirement of more than 3 L during the perioperative period. The primary goal was to show equivalence of perioperative need of both HES to achieve hemodynamic stability. As secondary objectives safety and tolerability were investigated by comparing clinical and laboratory parameters.

Methods

This prospective, randomized, double-blinded, parallel-group, single-centre clinical phase III trial was carried out at the clinic for urology, University of Luebeck. It was approved by the local ethics committee. After written informed consent 100 patients scheduled for major urological surgery with an expected fluid requirement of more than 3 L were included into the study. They were randomly assigned to receive either HES 200/0.5 or HES 130/0.42 coded as treatment A or treatment B, respectively. Block randomization each 8 was computerized using Rancode® by an employee of B.Braun Melsungen AG, Germany. The main conductor of the trial (K.-F. K.) received blinded envelops containing the code "A" or "B" to be opened only after inclusion of each patient into the study. Decoding envelops were deposited by K.-F. K. to be opened in case of emergencies. After completion of the study no envelope had been opened.

Exclusion criteria were emergency surgery, increased anesthetic risk (ASA>III), myocardial insufficiency (NYHA>III), myocardial infarction in the last 3 months, renal insufficiency with serum creatinine > 150 µmol L^{-1}, known liver insufficiency or liver transplantation, blood coagulation disorders, preoperative HES infusion (within 48 hours prior to randomization), known HES allergy, and general contraindication to volume replacement therapy.

General anesthesia was induced intravenously with propofol, sufentanil, and rocuronium in doses adapted for the patient's need. Maintenance of anesthesia was achieved by use of propofol and intermittent boli of sufentanil as appropriate. Ventilation was adjusted to achieve normocapnia ($etCO_2$ 35 – 40 mmHg). A heat blanket was used to prevent hypothermia. After induction of anesthesia patients received a 4-F thermistor-tipped arterial catheter (4-Fr Pulsiocath, Pulsion Medical Systems, Munich, Germany) inserted to the femoral artery and an 8-F central venous catheter inserted into the internal jugular vein.

After compensation of preoperative fasting with 1 L of Ringer solution, crystalloids were infused at a constant rate of 5 – 10 mL $kg^{-1}\,h^{-1}$. The hydroxyethyl starch study solution could be administered from induction of anesthesia until 12:00 midnight of the operation day according to individual requirements of the patients. One unit (500 mL) of the study medication was infused if one or more of the following infusion triggers was observed for more than 5 minutes.

– Mean arterial pressure (MAP) < 80 % of the individual value measured on the day before surgery
– Stroke volume (SV) < 60 mL
– Central venous pressure < 5 mmHg
– Other clinical reasons, e.g. reduced cardiac output (CO) (< 4 L min^{-1}), increased stroke volume variability (> 20%), and reduced diuresis (< 0.5 mL kg^{-1}).

Blood loss was estimated by measuring blood volume in suction containers from the surgical field and in drainages postoperatively. Vasoconstrictors were given if MAP was below 60 mmHg despite adequate volume replacement. Triggers for transfusion of packed red blood cells were hemoglobin < 90 g L^{-1} and for platelets a platelet count < 60000 μL^{-1}.

Study medications contained either a test substance of HES 130/0.42 with an average mean molecular weight of 130 kD, a molar substitution of 0.42 and a C2/C6 ratio of 6:1 or the reference solution of HES 200/0.5 with an average mean molecular weight of 200 kD, a molar substitution of 0.5 and a C2/C6 ratio of 6:1. Test and reference preparations were equally 6 % concentrated HES dissolved in 0.9 % sodium chloride. Solutions were isooncotic, isotonic and indistinguishably blinded. Randomization was concealed until end of the study.

For efficacy measurements the primary variable was defined as the volume of the study medication infused from induction of anesthesia until 12 pm to maintain hemodynamic stability. Secondary variables comprised: Suitability of the substance for postoperative volume replacement, hemodynamics including arterial blood pressure, intrathoracic blood volume (ITBV), extravascular lung water (EVLW), cardiac output (CO), stroke volume variability (SVV), central venous pressure (CVP), and heart rate (HR); hematology and coagulation including hemoglobin, hematocrit, platelet count, prothrombin time, partial thromboplastin time, thrombin time, fibrinogen; clinical chemistry including total protein, albumin, creatinine, sodium, potassium, calcium, glucose; overall requirements of fluid replacement and transfusion, separated by study medication, crystalloids, blood and blood derivates; volume of perioperative blood and fluid loss via drainage and urinary output; and finally acid-base-balance parameters like pH, pCO_2, pO_2, base excess (BE), and bicarbonate. In addition, adverse events were recorded.

Arterial blood pressure and heart rate was recorded on the day before surgery, intraoperatively after induction of anesthesia every 10 minutes and postoperatively during intensive care treatment every 30 minutes. Hemodynamic parameters like ITBV, EVLW, SVV, CO, and CVP were recorded intraoperatively every 20 minutes and postoperatively every 60 minutes till 12:00 midnight of the operative day. Blood samples for evaluation of laboratory parameters were taken before induction of anesthesia, after surgery and every four hours postoperatively. Study ended at 12:00 midnight on the day of surgery.

For measurements the arterial thermodilution catheter was connected to the monitor for pulse contour analysis and transpulmonary thermodilution (PICCO, Pulsion Medical Systems, Munich, Germany). Three consecutive measurements of CO by transpulmonary thermodilution were performed by injecting 10 – 15 mL iced saline 0.9 % randomly across the respiratory circle into the distal port of the central venous catheter. CO, ITBV, EVLW, SVV were recorded.

Statistics

The sample size was calculated prospectively before beginning of the study assuming a mean amount of infused volume of 1920 ± 799 mL, an equivalence bound of 500 mL, a two-tailed type 1 error of $\alpha = 0.05$ and a type 2 error of $\beta = 0.2$ with a minimum of 45 patients in each group. Calculating a drop out rate of 10 %, 2 x 50 patients were enrolled into the study. The test of equivalence between the test and the reference solution was based on the required volume of study medications in each treatment arm. The equivalence bounds were defined as the mean infused volume of the reference solution ± 500 mL. Equivalence was tested using the confidence interval inclusion method. A $p < 0.05$ indicates a high probability of equivalence. Hemodynamic and laboratory data were compared with the t-test, Mann-Whitney U-test or χ^2-test as appropriate. A probability value of less than 0.05 was considered as statistically significant. Data are presented as mean ± standard deviation (SD) or number (n). Analysis was done using the intention to treat method. Each significant result was confirmed with the analysis of the per protocol set. The statistical software SAS® Version 8.02 was used for statistical analyses.

Results

From 27th of February 2001 until 2nd of December 2003 one hundred patients were enrolled in this study and randomized either to the reference treatment (HES 200/0.5) or to the test treatment (HES 130/0.42) (figure 1). Demographic data of the two groups are summarized in table 1. More patients in group HES 130/0.42 had the diagnosis of carcinoma of the prostate (p = 0.024) and needed a radical prostatectomy, and more patients in group HES 200/0.5 had other diagnosis (p = 0.021). Other parameters did not differ (see table 1). Perioperative data were without any significant differences in both groups (see table 2). Observation time did not differ between the two groups (HES 130/0.42: 15.5 ± 1.25 h, range: 11.5 – 17.25 h; HES 200/0.5: 15.3 ± 2.22 h, range 2.42 – 16.25 h; p = 0.98).

Adverse events with a questionable relationship to the HES solutions occurred in six patients, four patients in group HES 130/0.42 (three times hypertension, one time hypotension) and two patients in group HES 200/0.5 (one time bleeding, one time acidosis) (p = 0.40). No adverse events with causal relationship to the investigational products occurred during the study. One patient in group HES 200/0.5 died on the 30th postoperative day due to a pulmonary artery embolism, which was not related to the study medication.

In both groups intraoperatively and postoperatively during ICU stay equivalent volumes [mean±SD] of the study medications were infused to maintain or achieve hemodynamic stability (HES 130/0.42: 1150 ± 574 mL vs. HES 200/0.5: 1070 ± 572 mL, p= 0.0002 (OP); HES 130/0.42: 1390 ± 955 mL, HES 200/0.5: 1245 ± 715 mL, p= 0.0196 (ICU)). Perioperative need of HES showed, that more HES130/0.42 was needed compared to HES200/0.5: 2540 ± 1232 mL vs. 2290 ± 1040 mL, p = 0.1379 (see figure 2). Equivalent amounts of crystalloids were infused (HES 130/0.42= 3714 ± 579 mL, HES 200/0.5= 3728 ± 685 mL, p = 0.0001, confidence interval inclusion method). Total fluid balance did not differ between both groups (HES 130/0.42: 2824 ± 1643 mL, HES 200/0.5: 2866 ± 1564 mL, p = 0.705). Intraoperatively a significantly higher number of patients in group HES 200/0.5 received red blood cell transfusion in comparison to the patients in the group HES 130/0.42 (HES 130/0.42: 4 of 50 patients; HES 200/0.5: 11 of 50 patients; p = 0.0499).

Hemodynamic parameters are documented in figure 3 and 4. There were no differences between the groups with the exception of more patients showing HR values > 100 b min^{-1} in group HES 200/0.5 (HES

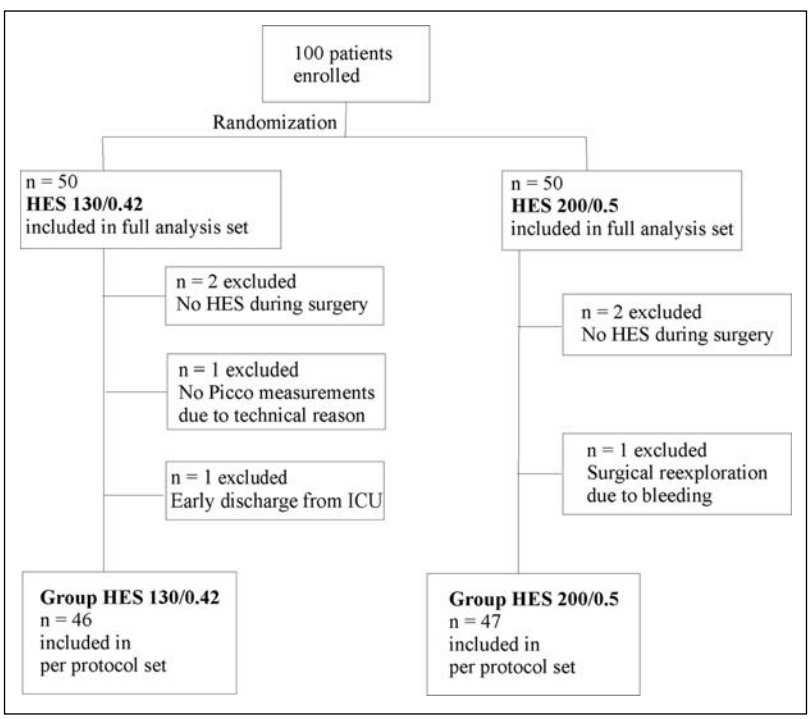

Figure 1: Study flow

Table 1: Demographic data

Parameter	**HES 130/0.42**	**HES 200/0.5**
Gender (m/f)	46/4	42/8
Age (years)	65 ± 7	66 ± 6
Height (cm) Male Female	 176 ± 6 160 ± 7	 176 ± 6 162 ± 6
Weight (kg) Male Female	 83 ± 13 78 ± 13	 83 ± 12 66 ± 13
ASA Grade I II III	 2 44 4	 3 40 7
MAP (mmHg) evening before surgery	100 ± 10	99 ± 9
Main diagnosis Carcinoma of prostate Carcinoma of urinary bladder or tract Renal carcinoma Others	 36 12 2	 25* 17 7 1

m: male, f: female. Data are presented as mean ± SD or number (n), * $p < 0.05$ between groups.

Table 2. Perioperative data

Parameter	**HES 130/0,42**	**HES 200/0,5**
Duration of surgery (h)	3.1 ± 1.2	3.5 ± 1.6
Duration of ventilation (h)	4.6 ± 3.4	6.1 ± 5.0
Duration of hospital stay (d)	18 ± 8	18 ± 10
Non-survivor	0	1

Data are presented as mean ± SD or n.

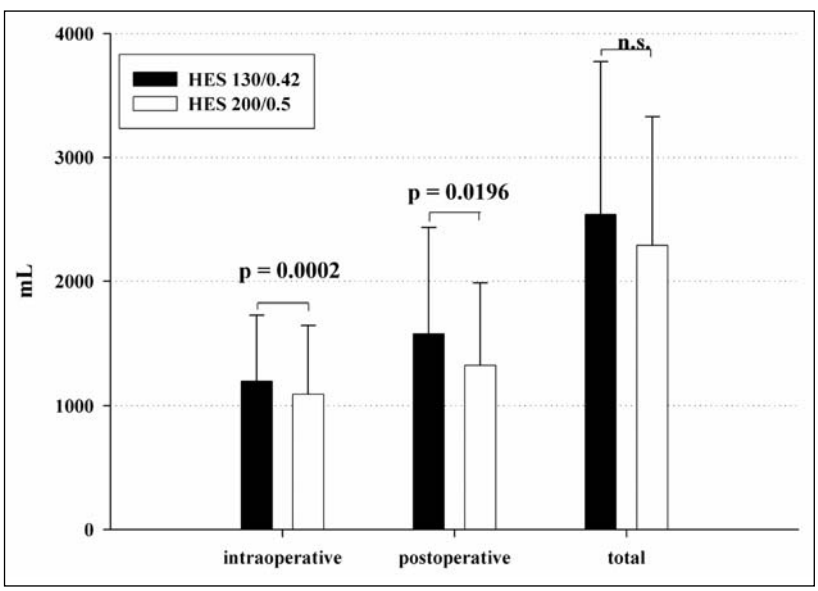

Figure 2. Intraoperative, postoperative until 12 pm, and total amount of administered hydroxyethyl starch (HES) (mean ± SD) in the test group (HES 130/0.42; n = 50) marked in solid bars and the reference group (HES 200/0.5; n = 50) marked with open bars. Equivalence was tested using the confidence interval inclusion method.

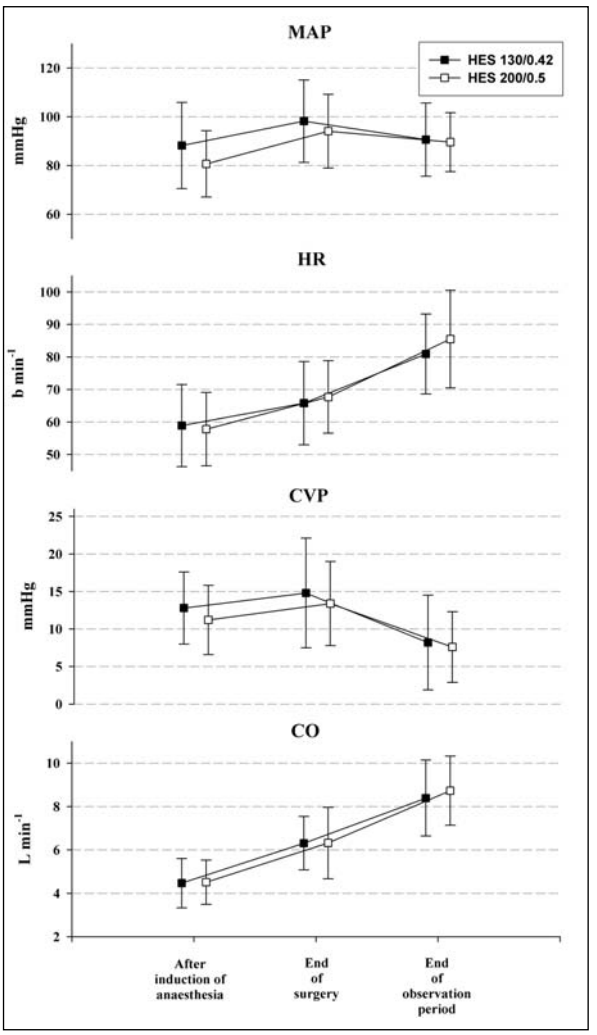

Figure 3. Values (mean ± SD) of mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), and cardiac output CO) before induction of anaesthesia, at the end of surgery, and at the end of the observation period in the test group (HES 130/0.42; n = 50) marked with solid squares and the reference group (HES 200/0.5; n = 50) marked with open squares.

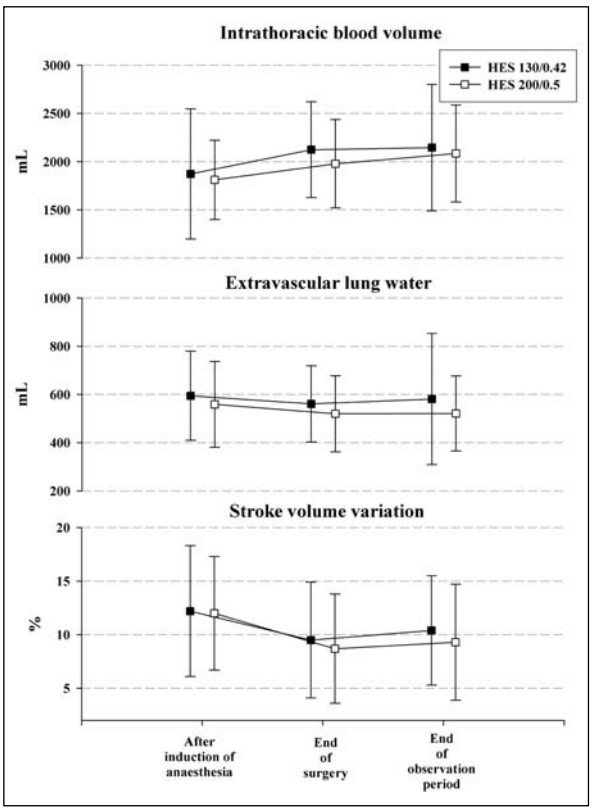

Figure 4. Values (mean ± SD) of intrathoracic blood volume, extravascular lung water, and stroke volume variation before induction of anaesthesia, at the end of surgery, and at the end of the observation period in the test group (HES 130/0.42; n = 50) marked with solid squares and the reference group (HES 200/0.5; n = 50) marked with open squares.

130/0.42: 4.0 ± 12.1 %; HES 200/0.5: 11.6 ± 21.1 %; p = 0.0367).

Routine chemistry including electrolytes, total protein, and albumin did not vary considerably. No differences between groups could be detected for mean values of Hb, creatinine, and coagulation parameters (table 3). At the end of the operation more patients in group HES 200/0.5 showed abnormal low values for PT (HES 130/0.42: n = 2 of 47; HES 200/0.5: n = 7 of 49; p = 0.16) and two patients in group HES 200/0.5 showed abnormally increased creatinine values. Although no differences between groups concerning mean values of acid-base-balance could be detected (data not shown), during surgery group HES 200/0.5 showed lower minimal values of pH (HES 130/0.42: 7.34 ± 0.05, HES 200/0.5: 7.32 ± 0.06, p = 0.0141), bicarbonate (HES 130/0.42: 21.3 ± 1.9 mmol L^{-1} , HES 200/0.5: 20.4 ± 2.1 mmol L^{-1}, p = 0.043) and base ex-

Table 3. Hemoglobin, Creatinine, and coagulation parameters over time

Parameter	Group	After induction of anesthesia	End of surgery	End of observation period
Hb (g dL^{-1})	HES 130/0.42	12.7 ± 1.6	10.4 ± 1.5	9.8 ± 1.7
	HES 200/0.5	12.3 ± 1.8	10.5 ± 1.7	9.7 ± 1.8
Creatinine (µmol L^{-1})	HES 130/0.42	75 ± 17	78 ± 17	75 ± 19
	HES 200/0.5	73 ± 23	76 ± 25	76 ± 26
PT (%)	HES 130/0.42	93 ± 6	83 ± 8	89 ± 11
	HES 200/0.5	92 ± 9	83 ± 10	87 ± 10
PTT (s)	HES 130/0.42	27 ± 3	35 ± 17	33 ± 9
	HES 200/0.5	29 ± 11	34 ± 16	34 ± 7
TT (s)	HES 130/0.42	18 ± 2	19 ± 2	18 ± 2
	HES 200/0.5	19 ± 5	22 ± 15	17 ± 3
Fibrinogen (g L^{-1})	HES 130/0.42	2.6 ± 0.7	2.3 ± 0.7	2.7 ± 0.6
	HES 200/0.5	3.0 ± 1.1	2.5 ± 1.0	3.0 ± 1.0

Hb: Hemoglobin; PT: Prothrombin time; PTT: Partial thromboplastin time; TT: Thrombin time. Data are presented as mean ± SD.

cess (HES 130/0.42: -3.9 ± 2.3 mmol L^{-1}, HES 200/0.5: -5.0 ± 2.7 mmol L^{-1}, p = 0.0325).

Discussion

This prospective, randomized, double-blinded study in major urological surgery was designed to investigate the clinical efficacy, safety, and tolerability of the new potato-based HES 130/0.42. We could show in this investigation that the new HES 130/0.42 can be used as effectively and safely for hemodynamic stabilization over a period of 16 hours as the standard HES 200/0.5 formulation.

We choose to study the effects of HES in urological patients scheduled for major surgery, as they frequently exhibit a need for large plasma volume replacement due to bleeding, urine loss, and surgical tissue trauma, leading to tissue edema. If not corrected adequately, persistent hypovolemia may occur. This has been shown to be associated with organ dysfunction and subsequent organ failure and death (10). In fact, measures to correct hypovolemia have been shown to reduce cost, morbidity, and mortality (11,12). But there is an ongoing discussion concerning the optimal criteria for volume replacement. Different parameters have been studied as to their ability to give information about the volume responsiveness of surgical and critically ill patients. Beside more sophisticated parameters mean arterial pressure and heart rate are the most often used parameters in clinical routine. Therefore, we decided to use the individual MAP measured in rest on the day before surgery minus 20% as an infusion trigger for colloidal volume replacement therapy. In addition, a low SV, a low CVP, and different other clinical reasons, e.g. reduced diuresis, served as triggers. Using this combination of triggers we tried to administer volume according to the individual requirement. In this way we indeed optimized the macro-hemodynamic circulation, which can be seen by the optimized PICCO values as ITBV, EVLW, and CO in both groups. As we did not measure parameters of regional or micro-circulation we cannot rule out differences of the two study medications concerning this issue. Recently, in an animal model of fecal peritonitis HES 130/0.42 in comparison to HES 200/0.5 has been shown to significantly attenuate systemic capillary leakage and therefore might have improved microcirculation (13).

We showed equivalence of both HES solutions with respect to maintenance of hemodynamic stability during the intraoperative and postoperative period, which is consistent with previous studies (4,9). Considering the perioperative period the need of HES130/0.42 was slightly higher than that of HES200/0.5. The effect on plasma volume expansion of HES 130 solutions is 1 – 2h shorter than that of HES 200 solutions (3). In contrast to the studies by Langeron (4) and Sander (9), where the effect of HES 130 was investigated during surgery and until 5h and 6h after surgery, our study lasted until the end of the operation day with a mean time of investigation of 16

hours. Our data indicate the more rapid renal elimination of HES 130/0.42 compared to larger molecular HES preparations, as has been shown by others (14). This shows the reduced risk of accumulation of HES 130/0.42 and in consequence the improved possibility to control the volume therapy.

HES solutions, especially the first generation with high molecular weight and high degree of substitution (e.g. HES 450/0.7), have been suspected of impairing the coagulation system (15) by increased bleeding (16). In contrast, the latest third generation of HES with low molecular weight and low degree of substitution only shows minimal or even no influence on coagulation (4,17-19). The results of our clinical trial confirm these previous data showing no negative effects on standard laboratory coagulation parameters, blood loss or transfusion requirements. Additionally, we observed a significantly lower transfusion rate of red blood cells in group HES 130/0.42 in comparison to the HES 200/0.5 group. With our data we cannot explain this positive result/observation. Whether more sensitive measures of coagulation parameters like activated thrombelastography would have revealed differences between the groups remains speculative. Recently, HES 130 has been shown to have favourable effects on these coagulation parameters in comparison to human albumin (20).

With respect to safety, there is an ongoing discussion concerning effects of HES, especially HES 200 solutions, on renal function (21-24). In our clinical trial we could not find any evidences for negative influence of HES 130 on renal function. Two patients in the HES 200/0.5 showed new abnormally increased creatinine values, but this was not statistically significant. Whether more sensitive measures, as kidney specific proteins would have revealed differences cannot be answered. We could not demonstrate any renal impairment in both groups as judged by normal postoperative creatinine values consistent with the literature (25). But as patients with a preoperative plasma creatinine value of more than 150 µmol L^{-1} were excluded from our study, we do not know whether the results would have been different in patients with chronic renal deficiency. In the safety assessment, both groups did not show any differences in the number or cause of observed adverse events. All observed events had no or a questionable relation to the study medications. This confirms the results by Sander et al., who demonstrated that the new HES 130/0.42 can be used safely during major gynaecological surgery (9).

Saline based unbalanced volume replacement solutions have been accused to contribute to metabolic (hyperchloremic) acidosis by increasing plasma levels of sodium and chloride (26). Although the exact consequences of such acid-base-disturbances are not clear it may interfere with organ perfusion, e.g. splanchnic perfusion (27). 72 patients in our study showed abnormal low values of BE, 48 abnormal low pH-values during intensive care treatment. Whether this may have been different using a balanced HES solution, as has been shown in a small investigation (28), should be evaluated in further studies.

In conclusion, this clinical trial demonstrated that HES 130/0.42 can be used as safely and efficiently for perioperative plasma volume expansion to maintain hemodynamic stability during major urological surgery as a standard HES 200/0.5 formulation.

References

1. Treib J, Baron J-F, Grauer MT, Strauss RG. An international view of hydroxyethyl starches. Intensive Care Med 1999; 25: 258-68
2. Boldt J. New light on intravascular volume replacement regimens: what did we learn from the past three years? Anesth Analg 2003; 97: 1595-604
3. Boldt J. Hydroxyethylstarch (HES). Wien Klin Wochenschr 2004; 116: 159-69
4. Langeron O, Doelberg M, Ang ET et al. Voluven, a lower substituted novel hydroxyethyl starch (HES 130/0.4), causes fewer effects on coagulation in major orthopedic surgery than HES 200/0.5. Anesth Analg 2001; 92: 855-62
5. Franz A, Braunlich P, Gamsjager T et al. The effects of hydroxyethyl starches of varying molecular weights on platelet function. Anesth Analg 2001; 92: 1402-7
6. Ickx BE, Bepperling F, Melot C et al. Plasma substitution effects of a new hydroxyethyl starch HES 130/0.4 compared with HES 200/0.5 during and after extended acute normovolaemic haemodilution. Br J Anaesth 2003; 91: 196-202
7. Jungheinrich C, Scharpf R, Wargenau M et al. The pharmacokinetics and tolerability of an intravenous infusion of the new hydroxyethyl starch 130/0.4 (6%, 500 mL) in mild-to-severe renal impairment. Anesth Analg 2002; 95: 544-51
8. Boldt J, Haisch G, Suttner S et al. Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend) on measures of coagulation. Br J Anaesth 2002; 89: 722-8
9. Sander O, Reinhart K, Meier-Hellmann A. Equivalence of hydroxyethyl starch HES 130/0. 4 and HES 200/0. 5 for perioperative volume replacement in major gynaecological surgery. Acta Anaesthesiol Scand 2003; 47: 1151-8
10. Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost. Intensive Care Med 1994; 20: 99-104
11. Gan TJ, Soppitt A, Maroof M et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002; 97: 820-6

12. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg 1995; 130: 423-9
13. Marx G, Pedder S, Smith L et al. Attenuation of capillary leakage by hydroxyethyl starch (130/0.42) in a porcine model of septic shock. Crit Care Med 2006; 34: 3005-10
14. Madjdpour C, Dettori N, Frascarolo P et al. Molecular weight of hydroxyethyl starch: is there an effect on blood coagulation and pharmacokinetics? Br J Anaesth 2005; 94: 569-76
15. Wiedermann CJ. Hydroxyethyl starch – can the safety problems be ignored? Wien Klin Wochenschr 2004; 116: 583-94
16. Wilkes MM, Navickis RJ, Sibbald WJ. Albumin versus hydroxyethyl starch in cardiopulmonary bypass surgery: a meta-analysis of postoperative bleeding. Ann Thorac Surg 2001; 72: 527-33
17. Haisch G, Boldt J, Krebs C et al. The influence of intravascular volume therapy with a new hydroxyethyl starch preparation (6% HES 130/0.4) on coagulation in patients undergoing major abdominal surgery. Anesth Analg 2001; 92: 565-71
18. Jamnicki M, Bombeli T, Seifert B et al. Low- and medium-molecular-weight hydroxyethyl starches: comparison of their effect on blood coagulation. Anesthesiology 2000; 93: 1231-7
19. Kasper SM, Meinert P, Kampe S et al. Large-dose hydroxyethyl starch 130/0.4 does not increase blood loss and transfusion requirements in coronary artery bypass surgery compared with hydroxyethyl starch 200/0.5 at recommended doses. Anesthesiology 2003; 99: 42-7
20. Boldt J, Scholhorn T, Mayer J et al. The value of an albumin-based intravascular volume replacement strategy in elderly patients undergoing major abdominal surgery. Anesth Analg 2006; 103: 191-9
21. Schortgen F, Lacherade JC, Bruneel F et al. Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. Lancet 2001; 357: 911-6
22. Sakr Y, Payen D, Reinhart K et al. Effects of hydroxyethyl starch administration on renal function in critically ill patients. Br J Anaesth 2007; 98: 216-24
23. Zander R, Boldt J, Engelmann L et al. The design of the VISEP trial: Critical appraisal. Anaesthesist 2007; 56: 71-7
24. Brunkhorst FM, Engel C, Bloos F et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358: 125-39
25. Neff TA, Doelberg M, Jungheinrich C et al. Repetitive large-dose infusion of the novel hydroxyethyl starch 130/0.4 in patients with severe head injury. Anesth Analg 2003; 96: 1453-9
26. Gan TJ, Bennett-Guerrero E, Phillips-Bute B et al. Hextend, a physiologically balanced plasma expander for large volume use in major surgery: a randomized phase III clinical trial. Hextend Study Group. Anesth Analg 1999; 88: 992-8
27. Wilkes NJ, Woolf R, Mutch M et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg 2001; 93: 811-6
28. Boldt J, Schollhorn T, Munchbach J, Pabsdorf M. A total balanced volume replacement strategy using a new balanced hydoxyethyl starch preparation (6% HES 130/0.42) in patients undergoing major abdominal surgery. Eur J Anaesthesiol 2007; 24: 267-75

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Address for corresponding: Hermann Heinze, M.D., Department of Anesthesiology, University of Luebeck, Ratzeburger Allee 160, 23538 Luebeck, Germany, E-Mail: Hermann.heinze@uk-sh.de