

ORIGINAL ARTICLE

Hydroxyethyl starch 130/0.42/6:1 for perioperative plasma volume replacement in 1130 children: results of an European prospective multicenter observational postauthorization safety study (PASS)

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Summary

Introduction: Third-generation hydroxyethyl starch (HES) is now approved also for the use in children, but safety studies including large numbers of pediatric patients are still missing. Therefore, we performed an European multicentric prospective observational postauthorization safety study (PASS) to evaluate the use of HES 130/0.42/6:1 in normal saline (ns-HES) or a balanced electrolyte solution (bal-HES) in children undergoing surgery.

Methods: Children aged up to 12 years with ASA risk scores of I–III receiving ns-HES (Venofundin 6%; Braun) or bal-HES (Tetraspan 6%; Braun) were followed perioperatively. Demographic data, surgical procedures performed, anesthesia, hemodynamic and laboratory data, adverse events (AE), and adverse drug reactions (ADR) were documented using a standardized case report form.

Results: Of 1130 children studied at 11 European pediatric centers from 2006 to 2009 (ns-HES, 629 children; bal-HES, 475 children; mean age, 3.6 ± 3.8 [range, day of birth–12 years]; and body weight, 15.4 ± 13 [0.9–90 kg]), 1104 were included for analysis. The mean infused HES volume was 10.6 ± 5.8 (0.83–50) $\text{ml} \cdot \text{kg}^{-1}$. In the 399 (36.1%) cases with blood gas analysis before and after HES infusion, hemoglobin and strong ion difference decreased significantly in both groups, whereas bicarbonate and base excess (BE before infusion: ns-HES -1.8 ± 3.1 , bal-HES -1.2 ± 3.3 mm; after infusion: ns-HES -2.5 ± 2.8 ; bal-HES -1.1 ± 3.2 mm, $P < 0.05$) decreased only with ns-HES but remained stable with bal-HES. Chloride concentrations increased in both groups and were significantly higher with ns-HES (Cl before infusion: ns-HES 105.5 ± 3.6 , bal-HES 104.9 ± 2.9 mm; Cl after infusion: ns-HES 107.6 ± 3.4 , bal-HES 106.3 ± 2.9 mm, $P < 0.05$). For the AE/ADR rates, dose–response but no age relationships could be demonstrated. No serious and no severe ADR directly related to HES (i.e. anaphylactoid reaction, clotting disorders, renal failure) were observed.

Conclusion: Moderate doses of HES 130/0.42/6:1 for perioperative plasma volume replacement seem to be safe even in neonates and small infants. The probability of serious ADR is lower than 0.3%. Changes in acid–base balance may be decreased when HES is used in an acetate-containing balanced electrolyte solution instead of normal saline. Caution should be exercised in patients with renal function disturbances and those with an increased bleeding risk.

Introduction

Hypovolemia is the most common cause of decreased tissue perfusion during the perioperative period in children. Appropriate fluid management is therefore essential for maintaining or restoring circulatory function in children intra- and postoperatively. Solutions available for intravenous fluid management during major pediatric surgery may be either crystalloid or colloid. Although the relative merits of the two methods of fluid management remain controversial, the use of colloid solutions seems to be more effective with regard to stabilizing the intravascular blood volume and avoiding interstitial fluid overload (1–3). In the past, human albumin (HA) was frequently used in pediatric anesthesia (4), but recently, a number of hydroxyethyl starch solutions (HES) have been shown to be as effective and safe and less costly as HA in several clinical studies in children (review in Ref. (5)). Generally, HES preparations are defined by mean molecular weight (M_w), molar substitution (MS), and the C_2/C_6 ratio of substitution. The first generation of HES with $M_w > 450$ kDa was associated with negative side effects with regard to coagulation, organ function, and accumulation. The second and the new third generation of HES (M_w 200 and 130 kDa, respectively) have been developed to improve safety while maintaining efficacy (review in Ref. (6)). Third-generation HES 130/0.42/6:1 ($M_w/MS/C_2:C_6$) is now approved also for children, but the summary of product characteristics (SPC) recommends the use only after careful benefit/risk assessment, and safety studies with large numbers of pediatric patients are still missing (7). We, therefore, performed an European multicentric prospective observational postauthorization safety study (PASS) to evaluate the perioperative use of HES 130/0.42/6:1 in children, particularly focusing on possible serious adverse drug reactions (ADR). This study started in 2006 using HES 130/0.42/6:1 dissolved in normal saline (ns-HES), and the preliminary results have been published recently (8). The data showed that this HES solution was safe and effective in a cohort of 316 patients including neonates and small infants. After the marketing authorization of HES 130/0.42/6:1 in a balanced electrolyte solution (bal-HES) with a more physiological electrolyte pattern and acetate as bicarbonate precursor, this bal-HES was investigated in a second study phase, and preliminary results comparing a cohort with ns-HES or bal-HES, respectively (composition of both preparations see Table 1), were published thereafter (9). The data showed that infusion-related iatrogenic acid–base and electrolyte alterations could be minimized by using HES in a balanced

Table 1 Composition of hydroxyethyl starch in normal saline (ns-HES) or balanced solution (bal-HES)

	ns-HES	bal-HES
Sodium (mm)	154	140
Potassium (mm)	–	4
Calcium (mm)	–	2.5
Magnesium (mm)	–	1
Acetate (mm)	–	24
Malate (mm)	–	5
Chloride (mm)	154	118
Osmolarity (mOsmol·l ⁻¹)	308	296

electrolyte solution instead of normal saline. In March 2009, the study was closed after enrolling 1130 pediatric patients, and we here present the final results with a special focus on possible adverse drug reactions and acid–base, electrolyte, and hemoglobin changes.

Methods

Following local ethics committee announcement, the study was carried out in European countries where either HES is nationally approved for general use or a EU registration is accepted, and in pediatric centers where HES 130/0.42/6:1 was already introduced and used for plasma volume replacement in children. Pediatric patients aged up to 12 years with ASA risk scores of I–III undergoing perioperative administration of HES 130/0.42/6:1 during major pediatric surgery were enrolled. From May 2006 to December 2007, only HES in normal saline (Venofundin 6%; Braun, Melsungen, Germany) was used, and from January 2008 until March 2009, HES in balanced electrolyte solution (Tetraspan 6%; Braun; composition of both preparations see Table 1) was also used. Exclusion criteria (according to the SPC) were hyperhydration, renal failure, intracranial bleeding, severe hyponatremia or hyperchloremia, hypersensitivity to HES, severely impaired hepatic function, and congestive cardiac failure. Adverse events (AE) were defined as any untoward occurrence with or without causal relationship to the study drug, which were observed during the clinical courses of the patients by the investigators. ADRs were defined as all untoward and unintended responses to the investigational medicinal product related to any dose administered. Patient demographics, the surgical procedures performed, anesthesia, hemodynamic and laboratory data, AE, and ADR were documented using a standardized case report form with particularly focusing on cardiovascular stability, hemodilution, acid–base balance, renal function, blood coagulation, and hypersensitivity, documented from induction of anesthesia

until discharge from the recovery room or intensive care unit to a normal ward. Results of blood gas analysis were included when blood samples were collected routinely before and within 1 h after HES infusion. The anion gap was calculated as the sum of sodium and potassium concentrations minus the sum of bicarbonate and chloride concentrations. For the calculation of the strong ion difference, the sum of chloride and lactate concentrations was subtracted from the sum of sodium and potassium concentrations. Because the estimated probability of ADR for N patients with a confidence interval of 95% is less than $3/N$, in the case of the present observational study, 1000 patients were planned to be treated to detect an ADR with an incidence of 0.3%. All captured data were analyzed using the SAS statistics software (SAS System for Windows, Version 9.1.3; SAS Institute Inc., Cary, NC, USA) and presented as mean $\pm$ standard deviation (range) or frequency, and Wilcoxon and Mann–Whitney U tests were performed for quantitative parameters with a pre-specified significance level of $\alpha = 0.05$.

Results

A total of 1130 children were studied at 11 pediatric centers in Germany (803 cases), Austria (140 cases), Czech Republic (80 cases), the Netherlands (67 cases) and Italy (40 cases). Because of the high number of countries and study sites and the different modes of recruitment, it was not possible to terminate the study after exactly 1000 children. Deviations from the observational plan occurred in 8 patients with regard to age, and in 18 patients with regard to the ASA risk score, 26 cases were therefore excluded from analysis except for the presentation of AE and ADR. The mean duration of observation was 6.2 ± 14.1 (0.1–216) h. Demographic data, details of the surgical procedures, total HES doses, and results of hemodynamic, acid–base, and electrolyte examinations before and within 1 h after HES infusion are given in Tables 2 and 3 and Figures 1, 2, and 3. The ns-HES was used in 629 children, and bal-HES, in 475 children. The mean infused HES volume was 10.6 ± 5.8 (0.83–50) $\text{ml}\cdot\text{kg}^{-1}$ (ns-HES 10.4 ± 5.9 (1.2–50), and bal-HES, 10.9 ± 5.7 (0.83–47) $\text{ml}\cdot\text{kg}^{-1}$). In 399 (36.1%) cases, there were

results of blood gas analyses before and within 1 h after HES infusion available. Before the HES infusion, the groups were comparable in all variables. During the HES infusion, heart rate decreased and mean arterial pressure increased within the physiological ranges. After the HES infusion, hemoglobin, hematocrit, and strong ion difference decreased significantly in both groups, whereas bicarbonate and base excess (BE before infusion: ns-HES -1.8 ± 3.1 , bal-HES -1.2 ± 3.3 mm; BE after infusion: ns-HES -2.5 ± 2.8 ; bal-HES -1.1 ± 3.2 mm, $P < 0.05$) decreased only with ns-HES but remained stable with bal-HES. Chloride concentrations increased in both groups and were significantly higher with ns-HES (CI before infusion: ns-HES 105.5 ± 3.6 , bal-HES 104.9 ± 2.9 mm; CI after infusion: ns-HES 107.6 ± 3.4 , bal-HES 106.3 ± 2.9 mm, $P < 0.05$). Anion gaps decreased in both groups and were significantly lower with bal-HES. In the total population of 1130 children, 49 AEs were reported in 31 patients with ns-HES, and 11 AEs, in 9 patients with bal-HES. One neonate with ns-HES developed a generalized erythema, which was evaluated as nonserious with an unlikely causal relation to the study drug. Serious AE occurred in three patients receiving ns-HES (surgical bleeding, blood pressure abnormal, pulmonary edema after laryngospasm) and one patient receiving bal-HES (blood pressure abnormal). In these cases, a causal relationship to the study drug was ruled out by the investigators. One of these serious AE – namely hypotension and low hemoglobin concentration because of massive surgical bleeding – was reported by the manufacturer to the authorities as serious adverse reaction. All cases resolved until the end of the study. Mild to moderate ADRs were reported in 13 patients in the ns-HES group (hemodilution $n = 11$, acid–base balance abnormal $n = 2$, blood pressure abnormal $n = 1$) and in one patient in the bal-HES group (blood pressure abnormal). The differences in AE and ADR between ns-HES and bal-HES were statistically significant ($P < 0.05$). For both the AE and ADR rates, dose–response relationships could be demonstrated. Comparatively higher rates of AEs/ADRs were observed in the high-dose group ($>20 \text{ ml}\cdot\text{kg}^{-1}$) with ns-HES ($P < 0.0001$). The AE/ADR rates stratified by age-groups were not different. No serious and no severe ADRs directly related to HES (i.e., anaphylactoid reaction, clotting disorders, and renal failure) were reported.

Table 2 Demographic data (mean $\pm$ sd [range])

Gender (M/F)	58.4%/41.6%
Age (years)	3.6 ± 3.8 (0–12)
Body weight (kg)	15.4 ± 13 (0.9–90)
Body height (cm)	89 ± 33 (30–179)
Duration of the surgical procedure (h)	2.42 ± 1.44 (0.33–12.5)

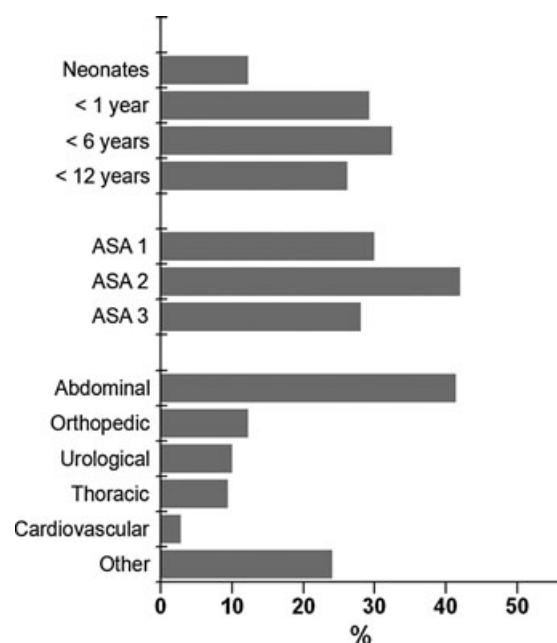
Discussion

The main finding of this study was that the probability of serious ADRs (i.e., anaphylactoid reaction, renal

Table 3 Changes in acid-base, electrolyte, and hemoglobin concentrations during infusion of hydroxyethyl starch in normal saline (ns-HES) or in a balanced electrolyte solution (bal-HES)

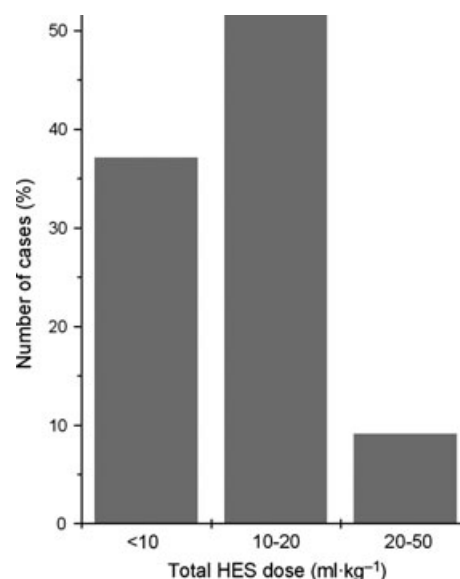
	Before infusion				After infusion			
	All	ns-HES	bal-HES	<i>P</i> -value ^a	All	ns-HES	bal-HES	<i>P</i> -value ^b
pH	7.38 ± 0.07	7.37 ± 0.07	7.38 ± 0.07	n.s.	7.37 ± 0.07*	7.36 ± 0.07	7.38 ± 0.07	n.s.
Bicarbonate (mm)	23.3 ± 3	23 ± 2.8	23.7 ± 3.3	n.s.	23.2 ± 3*	22.5 ± 2.8*	23.9 ± 3	<0.001
Base excess (mm)	-1.6 ± 3.2	-1.8 ± 3.1	-1.2 ± 3.3	n.s.	-1.9 ± 3.1*	-2.5 ± 2.8*	-1.1 ± 3.2	<0.0001
Sodium (mm)	137.5 ± 3.2	137.5 ± 3.3	137.5 ± 3.1	n.s.	137.2 ± 3.5*	137.4 ± 3.6	137 ± 3.4*	n.s.
Potassium (mm)	4.1 ± 0.6	4 ± 0.6	4.2 ± 0.6	n.s.	4.1 ± 0.6	4 ± 0.5	4.2 ± 0.5	n.s.
Chloride (mm)	105.3 ± 3.4	105.5 ± 3.6	104.9 ± 2.9	n.s.	107.2 ± 3.3*	107.6 ± 3.4*	106.3 ± 2.9*	<0.05
Lactate (mm)	1.6 ± 0.8	1.5 ± 0.8	1.6 ± 0.9	n.s.	1.6 ± 0.9*	1.7 ± 0.8*	1.6 ± 0.9	n.s.
Anion gap (mm)	12.5 ± 3.4	12.7 ± 3.7	12 ± 2.8	n.s.	10.1 ± 3.3*	10.5 ± 3.5*	9.4 ± 2.9*	<0.05
SID (mm)	34.3 ± 3.6	34.4 ± 3.7	34 ± 3.3	n.s.	31.5 ± 3.3*	31.5 ± 3.4*	31.6 ± 3.2*	n.s.
Hemoglobin (g·dl ⁻¹)	11.3 ± 2.2	11.3 ± 2.1	11.3 ± 2.3	n.s.	10 ± 2*	10 ± 1.8*	9.92 ± 2.2*	n.s.
Hematocrit (%)	33.7 ± 6.5	33.6 ± 6.4	33.7 ± 6.7	n.s.	29.5 ± 5.6*	29.6 ± 5.3*	29.5 ± 6*	n.s.

SID, strong ion difference; n.s., not significant.

^ans-HES vs bal-HES before infusion.^bns-HES vs bal-HES after infusion.**P* < 0.05 before vs after infusion.**Figure 1** Age distribution, ASA classification, and types of surgical procedure.

failure, and clotting disorders) after infusion of HES 130/0.42/6:1 is extremely low and that the use of HES in a balanced electrolyte solution instead of normal saline leads to less acid-base changes in children.

Third-generation tetrastarches have a lower mean molecular weight, a lower MS, and a higher C_2/C_6 ratio than the older first- and second-generation

**Figure 2** Distribution of total doses of infused hydroxyethyl starch (HES).

products, and this altogether is leading to more rapid degradation, higher clearance, and less retention in blood circulation and tissues (10). The colloid oncotic pressure depends on the number of oncologically active molecules available. Low molecular weight HES solutions contain more macromolecules per volume than the higher molecular weight HES solutions and are, therefore, likely to exert greater colloid osmotic pressure at similar plasma concentrations (6). Colloids

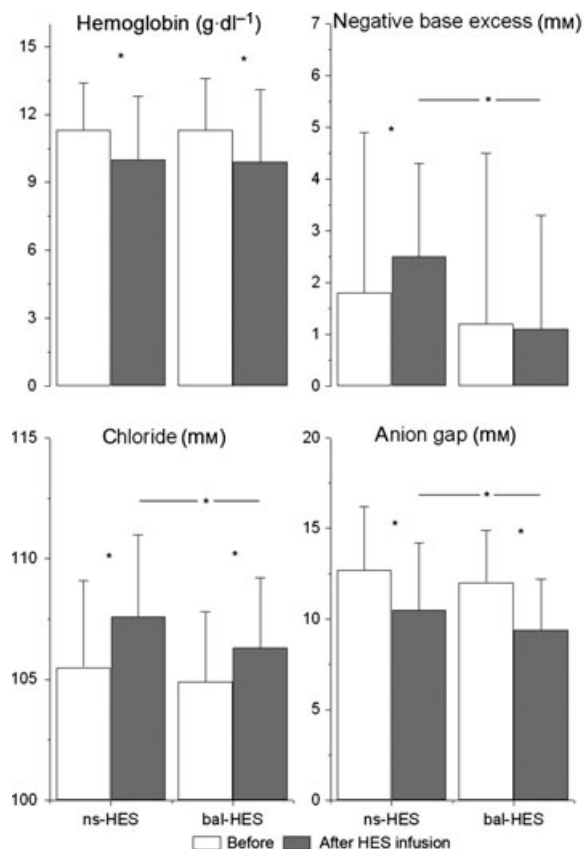


Figure 3 Hemoglobin and acid-base values before and after infusion of hydroxyethyl starch in normal saline (ns-HES) and balanced electrolyte solution (bal-HES) (mean ± SD).

retain within the intravascular space, whereas crystalloids are distributed within the extracellular space (which is the sum of the intravascular and interstitial space), and as a consequence, higher volumes of crystalloid solution are needed for replacing plasma deficits as compared to colloids (3). Chappell *et al.* (2) stated that when using crystalloids as a substitute of significant acute blood losses, interstitial fluid edema is the obligatory consequence. As interstitial fluid overload may be related to postoperative complications, the authors recommended to use crystalloids only to replace losses because of urine production and insensible perspiration and to use colloids for the substitution of acute blood loss or when the patient's circulation is in need of additional volume. Iatrogenic acute hypervolemia may damage the endothelial surface layer of the capillaries; thus, carefully maintaining intravascular volume without hypervolemic peaks was hypothesized to be the most promising concept. Accordingly, we found in a previous animal experimental study (3) with almost total plasma replacement in piglets that body

weight and hemodynamic conditions were stable when using HES and that body weight increased and tissue oxygenation was impaired when using crystalloids. Generally, the intravascular volume effect of crystalloids depends on the ratio between the intravascular and the extracellular space. The extracellular space of neonates and infants is larger than in adults (11), and the intravascular volume effect of crystalloids is, therefore, in theory lower in the younger age-group. Accordingly, Li *et al.* (12) found less pronounced plasma dilution after infusion of crystalloids in pediatric patients than in adults, and Paul *et al.* (13) reported a more effective plasma expansion after HES infusion in children as compared to crystalloids. Currently, there is a strong trend toward a more restrictive use of blood products perioperatively to decrease transfusion-associated morbidity (14,15), and perioperative stabilization of the plasma volume is, therefore, of paramount importance especially in patients with low hemoglobin concentrations. Although the current evidence on the choice of fluids for resuscitation in children is weak (16), our study showed that the perioperative use of moderate doses of HES 130/0.42/6:1 seems to be safe even in neonates and small infants. Possible ADRs of HES include anaphylactoid reactions, coagulation disorders, renal function impairment, and tissue accumulation. Studies investigating the incidence of anaphylactoid reactions of colloids are rare and included mainly the use of older HES generations in adult populations. Ring *et al.* (17) found that the rate of severe reactions (shock, cardiac, and/or respiratory arrest) was 0.003% for plasma protein solutions, 0.006% for HES, and 0.038% for gelatin (total infusions registered = 200 906). Laxenaire *et al.* (18) reported a slightly higher incidence of anaphylactoid reactions of 0.345% for gelatin, 0.099% for albumin, and 0.058% for HES in 19 593 patients. Studies investigating the incidence of anaphylactoid reactions in children are missing, but in our study, we observed only one nonserious case of a skin reaction in a neonate with an unlikely relationship to the HES infusion. Therefore, the probability of severe anaphylactoid reactions after HES 130/0.42/6:1 in children seems to be as low as in adults.

The effects of the different HES products on coagulation parameters closely depend on their physicochemical properties. The older HES generations are known to decrease the plasma concentrations of factor VIII and von Willebrand factor and to affect fibrin polymerization, platelet aggregation, and endothelial adhesion more than by dilution alone (review in Ref. (19)). Tetrastarches with a lower molecular weight and MS are hypothesized to have less impact on hemostasis.

In a meta-analysis in adults, Kozek-Langenecker *et al.* (20) found that blood loss and transfusion requirements can be significantly reduced in major surgery when using third-generation HES instead of second-generation HES products. Standl *et al.* (21) found no clinically significant changes in platelet count, prothrombin time (PT), or aPTT after infusion of HES 130/0.4 in neonates and infants. Chong Sung *et al.* (22) showed that the use of $10 \text{ ml}\cdot\text{kg}^{-1}$ HES 130/0.4 in children undergoing cardiac surgery did not cause more bleeding events or higher transfusion requirements than fresh-frozen plasma infusion. In a study performed by Osthaus *et al.* (23), values of activated modified thrombelastography were comparable after infusion of $10 \text{ ml}\cdot\text{kg}^{-1}$ HES 130/0.42 or modified fluid gelatin. Using a higher infusion volume of $15 \text{ ml}\cdot\text{kg}^{-1}$, Haas *et al.* (24) found that activated modified thrombelastography values were significantly more impaired after use of HES 130/0.4 than after albumin or gelatin in children weighing 3–15 kg. Hanart *et al.* (25) compared the infusion of high doses of up to $50 \text{ ml}\cdot\text{kg}^{-1}$ of albumin or HES 130/0.4 for intraoperative volume replacement and bypass priming in children undergoing cardiac surgery and found higher transfusion requirements and intraoperative fluid balance in the albumin group. James (10) concluded in a review that the risk of coagulation disorders with HES 130 is similar to that of albumin or gelatin and significantly smaller than with older HES products. Therefore, our study shows in accordance with previous studies (21–25) that HES 130 in a maximum daily dose of $50 \text{ ml}\cdot\text{kg}^{-1}$ can be used safely even in small children with an intact coagulation system but is probably not the first-choice colloid for children with hemostatic disorders.

In the study presented here, only patients with normal renal function were included, and no serious ADRs as regards renal function were observed. Neonates are a particularly vulnerable group with respect to renal function, and possible adverse renal effects may have been concealed by the short follow-up and the small number of neonates and other patients with an increased risk of renal failure. In an animal experimental study comparing the renal effects of HES 200/0.5, HES 130/0.42, and lactated Ringer's solution (LR), Hüter *et al.* (26) found osmotic nephrosis-like lesions of the tubuli in all groups but in a significantly lesser degree after LR. Impaired diuresis and sodium excretion were observed more frequently after use of HES, and renal interstitial proliferation, macrophage infiltration, and tubular damage were identified as potential pathological mechanisms of HES-induced adverse effects on renal function. The proinflammatory

effects and the tubular damage were more pronounced after HES 200/0.5 than after HES 130/0.42. Liet *et al.* (27) found in 13 healthy neonates that $10 \text{ ml}\cdot\text{kg}^{-1}$ HES 200/0.5 did not increase serum creatinine concentrations. In the study of Hanart *et al.* (25), diuresis and both urea and creatinine concentrations after $50 \text{ ml}\cdot\text{kg}^{-1}$ of HES 130/0.4 were comparable to the findings after use of albumin in children undergoing cardiac surgery. Jungheinrich *et al.* (28) concluded in a study including 19 adult volunteers with renal function disorders that 500 ml of HES 130/0.4 can be safely administered even to adult patients with severe renal impairment as long as urine flow is preserved. Studies investigating HES infusion in children with impaired renal function are still missing. Therefore, the results of this study suggest in accordance with previous studies (21,22,25) that HES 130 can be used safely even in small children with normal renal function but is probably not the first-choice colloid for children with significantly impaired renal function.

Several studies and case reports in adults showed a correlation between administration of slow-degradable HES products and pruritus (review in Ref. (29)). The pathophysiological basis of the pruritus observed are HES tissue deposits within perineural cells and endoneurial connective tissue cells that were observed in light and electron microscopy, and this effect was judged as dose dependent and time related (30). In an animal experimental study, the tissue storage was significantly lower with rapidly degradable HES 130/0.4 than with slower-degradable HES 200/0.5 (31). In our study, the follow-up was too short to detect HES-related pruritus, but a Medline search produced no published articles reporting on cases of HES-related pruritus in children. Although there is currently no evidence available, the risk of skin itching and other consequences of tissue accumulation should be low when using moderate doses of rapid-degradable HES products in children (10).

In the study presented here, moderate HES doses ($<20 \text{ ml}\cdot\text{kg}^{-1}$) were used more frequently than high HES doses ($>20 \text{ ml}\cdot\text{kg}^{-1}$). The possible HES-related ADRs (i.e., coagulation disorders, renal function impairment, and tissue storage) are dose dependent, and the lack of serious ADR observed may, therefore, be due to the low number of patients receiving high HES volumes. Hanart *et al.* (25) used high HES doses of up to $50 \text{ ml}\cdot\text{kg}^{-1}$ in 60 children and did not observe severe ADRs. Generally, moderate HES doses are sufficient in most pediatric patients undergoing major surgery procedures. High HES doses close to the maximum daily dose of $50 \text{ ml}\cdot\text{kg}^{-1}$ should be used with

caution to avoid critical hemodilution, dilutional coagulopathy, or iatrogenic hypervolemia.

In previous studies (32,33), we found that HES in normal saline decreases the anion gap and the strong ion difference and increases the chloride concentration because of the electroneutrality of the HES molecules and the high chloride concentration and the lack of metabolizable anions of the saline solution. Infusions of high normal saline volumes may lead to the development of hyperchloremic acidosis, which is possibly associated with reduced renal and splanchnic perfusion as indicated by reduced urine flow (34). In accordance with our previous report (9), we found less negative BE and lower chloride concentrations in the cohort receiving HES in a balanced electrolyte solution containing less chloride (118 mm instead of 154 mm) and acetate and malate as bicarbonate precursors as compared to the cohort receiving HES in normal saline. Although the mean acid–base and electrolyte changes observed were only small and possibly clinically not harmful, the incidence of significant

acid–base disorders after high doses ($> 20 \text{ ml} \cdot \text{kg}^{-1}$) was lower when using HES in a balanced electrolyte solution instead of normal saline. Generally, it seems to be advantageous to use crystalloid solutions with a physiological electrolyte pattern and a bicarbonate precursor to prevent possible iatrogenic acid–base and electrolyte disturbances and to increase the intrinsic safety (35).

In conclusion, moderate doses of HES 130/0.42 for plasma volume replacement seem to be safe even in neonates and small infants. Changes in acid–base balance may be decreased when HES in an acetate-containing balanced electrolyte solution is used instead of normal saline. Caution should be exercised in patients with renal function disturbances and those with an increased bleeding risk.

Conflict of interest

RS has received fees for speaking and funding for research carried out in this work.

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