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

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Summary

Background: Several clinical studies have shown that hydroxyethyl starch (HES) may be as effective and safe as, but less expensive than, albumin when used for perioperative plasma volume replacement (PVR) in children. The new third generation HES 130/0.42 solution was designed to reduce adverse drug reactions (ADRs) and improve safety while maintaining efficacy. Therefore, the objective of this prospective multicenter observational postauthorization safety study (PASS) was to evaluate the perioperative use of HES 130/0.42 in 1000 children with a particular focus on possible ADRs.

Methods: Approximately 300 of 1000 pediatric patients aged up to 12 years with ASA risk scores of I–III receiving perioperative HES 130/0.42 (Venofundin 6%; Braun, Melsungen, Germany) should be enrolled for interims analysis in the first year. The statistical sample size calculation showed that this number of patients would be sufficient to detect a 1% incidence of ADRs. Following approval by local ethics committee, patient demographics, data relating to HES 130/0.42 use, the procedures performed, anesthesia, and ADRs were documented with a particular focus on cardiovascular stability, hemodilution, acid–base balance, renal function, blood coagulation, and hypersensitivity.

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Results: Three hundred and sixteen children (ASA I–III, age 3 ± 3.4 [range, day of birth–12 years], body weight 13 ± 10.5 [range, 1.1–60 kg]) were studied at five centers in Germany, Austria, and Italy from May 2006 until August 2007. Forty-five percent of the patients underwent abdominal surgery, 12.4% urologic procedures, 11.4% thoracic surgery, 7.6% orthopedic procedures, and 7% cardiovascular surgery. The mean volume of infused HES 130/0.42 was 11 ± 4.8 $ml \cdot kg^{-1}$ (range, 5–42). Cardiovascular stability was maintained in all cases. After HES infusion, hemoglobin (11.5 vs 10.25 $g \cdot dl^{-1}$), base excess (−2 vs −2.7 $mmol \cdot l^{-1}$), anion gap (12.9 vs 11.2 $mmol \cdot l^{-1}$), and strong ion difference (34.3 vs 31.4 $mmol \cdot L^{-1}$) decreased, and chloride (105.7 vs 107.8 $mmol \cdot l^{-1}$) increased significantly ($P < 0.05$). No serious ADRs (i.e., anaphylactoid reaction, renal failure, clotting disorders) were observed.
Conclusion: Moderate doses of HES 130/0.42 help to maintain cardiovascular stability and lead to only moderate changes in hemoglobin concentration and acid–base balance in children. The probability of serious ADRs is lower than 1%. Therefore, HES 130/0.42 for PVR seems to be safe and effective even in neonates and small infants with normal renal function and coagulation.

Keywords: hydroxyethyl starch; safety; adverse drug reactions; neonates; children

Introduction

The use of colloid plasma replacement fluids for correction of absolute or relative volume deficiency is a standard procedure for children during major pediatric surgery, intensive care or medical emergencies. For traditional reasons, perioperative plasma volume replacement has mainly been performed by using human albumin (HA) (1). Artificial colloids like hydroxylethyl starch (HES) or modified fluid gelatin are associated with no infection risk and a reduced risk of allergic reactions, and are less expensive. During the past few years, a number of HES solutions have been shown to be as effective and safe as HA when administered to children in clinical studies (2–6). The therapeutic and adverse effects of HES depend mainly on molecular weight, the C2/C6 ratio of hydroxyethylation, and the degree of hydroxyethyl substitution. Molecular weight determines colloidal activity, and the degree of substitution is the major determinant of circulating half-life. While molecules smaller than the renal threshold are eliminated by glomerular filtration, larger molecules are digested by α-amylase first. Hydrolysis is rapid with minimal substitution, and starch metabolism increases as the C2/C6 ratio decreases (7). The new third generation HES 130/0.42 was designed to reduce adverse drug reactions (ADRs) and improve safety while maintaining efficacy. HES 130/0.42 is also approved for children, but the Summary of Product Characteristics (SPC) recommends the use only after careful benefit/risk assessment, and with caution, because clinical data in a large number of pediatric patients are missing. Therefore, the objective of this prospective multicenter observational postauthorization safety study (PASS) was to evaluate the perioperative use of HES 130/0.42 in a large number of children with a particular focus on possible serious ADRs.

Methods

Following approval by local ethics committee, the study was carried out in European countries where HES is either nationally approved for general use or

a EU registration is accepted, and in pediatric centers where HES 130/0.42 was already introduced and used for plasma volume replacement in children. Approximately 300 pediatric patients aged up to 12 years with ASA risk scores of I–III receiving perioperative HES 130/0.42 in normal saline (Venofundin 6%; Braun) were to be enrolled in the first year for interims analysis (study goal 1000 patients). Exclusion criteria (according to the SPC) were hyperhydration, renal failure, intracranial bleeding, severe hypernatriemia or hyperchloremia, hypersensitivity to HES, severely impaired hepatic function, and congestive cardiac failure. Patient demographics, the surgical procedures performed, anesthesia, hemodynamic, and laboratory data and ADRs were documented using a standardized case report form with a particular focus on cardiovascular stability, hemodilution, acid–base balance, renal function, blood coagulation, and hypersensitivity. Data were collected from induction of anesthesia until discharge from the recovery room or intensive care unit to the 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 calculation of 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 ADRs for N patients with a confidence interval of 95% is less than $3/N$, in the case of the present observational study 300 patients were sufficient to detect an ADR with an incidence of 1%. All captured data were analyzed using the SPSS software package, presented as mean ± standard deviation (range) or frequency, and two-tailed t-tests were performed for metric data with a prespecified significance level of $\alpha = 0.05$.

Results

Three hundred and sixteen children were studied at five pediatric centers in Germany, Austria, and Italy. Demographic data, details of the surgical procedures, and results of hemodynamic, acid–base and electrolyte values before and within 1 h after HES infusion are given in Table 1 and Figure 1. The mean volume of infused HES was 11 ± 4.8 ml·kg^{-1} (range per day 5–42). Cardiovascular stability was maintained in all cases. In 111 (35%) cases, results of blood gas analysis were available before and within 1 h after HES infusion. After HES infusion, hemoglobin (11.5 ± 2.1 vs 10.3 ± 2.8 g·dl^{-1}), base excess (−2 ± 2.3 vs −2.7 ± 3.4 mmol·l^{-1}), anion gap (12.9 ± 3.8 vs 11.2 ± 3.6 mmol·l^{-1}), and strong ion difference (34.3 ± 3.6 vs 31.4 ± 3.8 mmol·l^{-1}) decreased, and chloride (105.7 ± 3.7 vs 107.8 ± 3.6 mmol·l^{-1}) increased significantly (Table 2 and Figure 2). No serious ADRs directly related to HES (i.e., anaphylactoid reaction, renal failure, clotting disorders) were reported.

Table 1
Demographic data (mean ± SD [range])

Gender (M/F)	187 (59.4%)/128 (40.6%)
Age (year)	3 ± 3.4 (0–12)
Weight (kg)	13 ± 10.4 (1.1–60)
Height (cm)	85 ± 30 (33–161)
Duration of surgery (h)	2.36 ± 2.17 (0.42–8.5)

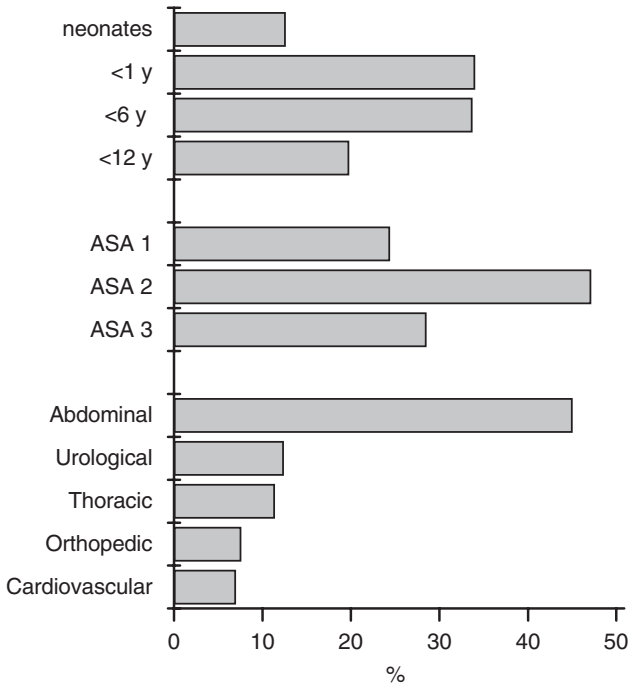

Figure 1
Age, ASA classification, and type of surgery.

Discussion

The main finding of this study was that moderate doses of HES 130/0.42/6:1 help to maintain cardio-

Table 2
Hemodynamic, acid–base, and electrolyte values before and after HES infusion (mean ± SD)

HES infusion	*Before*	*After*	*P-value*
Heart rate ($1 \cdot min^{-1}$)	115 ± 24	111 ± 22	<0.001
Mean arterial pressure (mm Hg)	56 ± 13	57 ± 12	ns
Hemoglobin ($g \cdot dl^{-1}$)	11.5 ± 2	10.3 ± 2.8	<0.0001
Hematocrit (%)	34 ± 6	31 ± 7	<0.0001
pH	7.38 ± 0.07	7.36 ± 0.07	<0.01
Bicarbonate ($mmol \cdot l^{-1}$)	22.7 ± 2.5	22.4 ± 2.3	ns
Base excess ($mmol \cdot l^{-1}$)	−1.96 ± 3	−2.7 ± 3.4	<0.01
Sodium ($mmol \cdot l^{-1}$)	138 ± 3.7	137 ± 3.7	ns
Potassium ($mmol \cdot l^{-1}$)	4.1 ± 0.6	4.1 ± 0.8	ns
Calcium ($mmol \cdot l^{-1}$)	1.2 ± 0.1	1.2 ± 0.1	ns
Chloride ($mmol \cdot l^{-1}$)	105.7 ± 3.7	107.8 ± 3.6	<0.0001
Anion gap ($mmol \cdot l^{-1}$)	12.9 ± 3.8	11.2 ± 3.6	<0.001
Strong ion deficit ($mmol \cdot l^{-1}$)	34.3 ± 3.6	31.4 ± 3.8	<0.0001

ns, not significant.

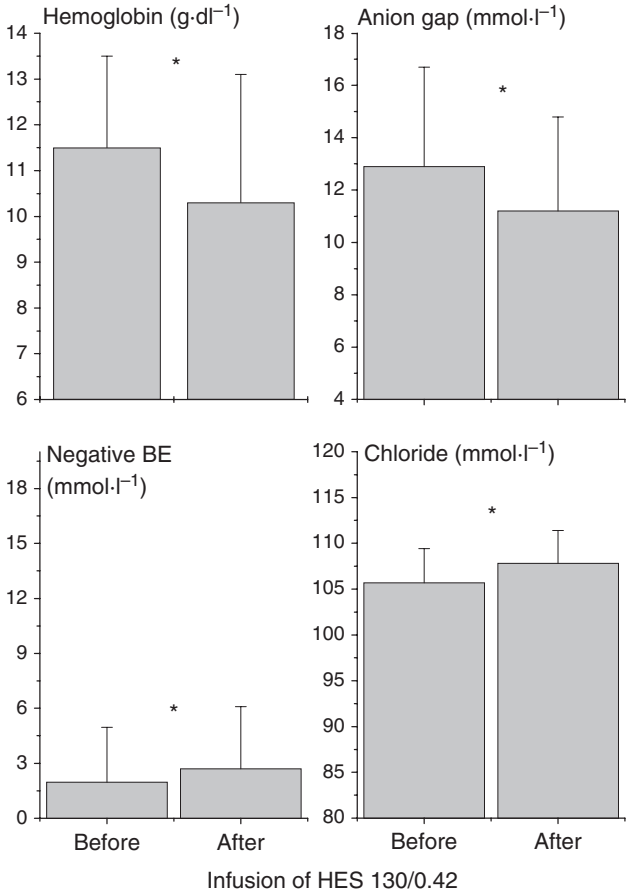

Figure 2
Hemoglobin and acid–base values before and after infusion of HES 130/0.42 (mean ± SD, *$P < 0.001$).

vascular stability and lead to only moderate changes in hemoglobin concentration and acid–base balance in children. The probability of serious ADRs (i.e., anaphylactoid reaction, renal failure, clotting disorders) is lower than 1%.

The decrease in hemoglobin concentration after HES infusion indicates effective plasma expansion (6). HES in normal saline decreases the anion gap and strong ion difference and increases the chloride concentration because of the electroneutrality of HES molecules and the unbalanced saline solution. The anion gap reflects the presence of negatively charged particles, mainly proteins, organic (i.e., lactate), or inorganic acid anions. Therefore, the replacement of negatively charged plasma proteins by electroneutral HES decreases the value of unmeasured negative charges and the chloride concentration increases in order to maintain electroneutrality (8). The moderate changes in anion balance found in this study were tolerated well even in neonates and small infants, but they can be misleading when they are used for the differential diagnosis of metabolic acidosis. Probably the acid–base balance is more stable when HES is used in an acetate-containing balanced electrolyte solution.

In this study, only patients with normal renal function were included and no serious ADRs regarding renal function were reported. Davidson (9) stated in a review that randomized trials have demonstrated adverse renal effects of HES in sepsis and surgery regardless of molecular weight, substitution or C2/C6 ratio. Liet *et al.* (3) found in 13 healthy neonates that 10 $ml \cdot kg^{-1}$ HES 200/0.5 does not increase serum creatinine. Jungheinrich *et al.* (10) concluded in a study including 19 adult volunteers with renal dysfunction that 500 ml of HES 130/0.4 can be safely administered even to 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 (2–6) that HES can be used safely even in small children with normal renal function but is probably not the colloid of first choice for children with significant renal dysfunction.

In this study, only patients with intact coagulation system were included and no serious ADRs regarding coagulopathy or bleeding events were reported. Hausdorfer *et al.* (2) found no differences in routine

coagulation tests and native thrombelastography in children with HES 40/0.5. Boldt *et al.* (5) also reported comparable results of routine coagulation tests in children with HES 200/0.5 or albumin after cardiac surgery. In the study of Liet *et al.* (3), no bleeding duration >3 min after venous prick or prolongation of activated partial thromboplastin time (aPTT) occurred after infusion of 10 $ml \cdot kg^{-1}$ HES 200/0.5. Simbruner (11) stated in an editorial that HES infused in newborn infants is not a higher risk than 5% albumin in respect to renal function and hemorrhagic diathesis. Also Lochbühler *et al.* (4) 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.* (12) showed that the administration of 10 $ml \cdot kg^{-1}$ HES 130/0.4 to children undergoing cardiac surgery does not cause more bleeding or a higher transfusion requirement than fresh frozen plasma infusion. In own studies (W.A. Osthaus unpublished data), values of activated modified thrombelastography were comparable after infusion of 10 $ml \cdot kg^{-1}$ HES 130/0.42 or modified fluid gelatin. Using a higher infusion volume of 15 $ml \cdot kg^{-1}$, Haas *et al.* (13) found that activated modified thrombelastography values were significantly more impaired after HES 130/0.4 than after albumin or gelatin in children weighing 3–15 kg. Van der Linden and Ickx (14) concluded in a review that in most cases the clinical effects of colloids on hemostasis are limited, provided that safety considerations are observed (i.e., maximum daily dosage, patient's hemostatic status). Therefore, this study shows in accordance with previous studies (2–6,12,13) that HES can be used safely even in small children with an intact coagulation system but is probably not the colloid of first choice for children with an increased risk of bleeding (i.e., hemostatic disorders or corrective heart surgery).

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

References

1 Soderlind M, Salvignol G, Izard P *et al.* Use of albumin, blood transfusion and intraoperative glucose by APA and ADARPEF members: a postal survey. *Paediatr Anaesth* 2001; **11:** 685–689.

2 Hausdorfer J, Hagemann H, Heine J. Comparison of volume substitutes 5 percent human albumin and 6 percent hydroxyethyl starch (40,000/0.5) in pediatric anesthesia. *Anasth Intensivther Notfallmed* 1986; **21:** 137–142.

3 Liet JM, Bellouin AS, Boscher C *et al.* Plasma volume expansion by medium molecular weight hydroxyethyl starch in neonates: a pilot study. *Pediatr Crit Care Med* 2003; **4:** 305–307.

4 Lochbühler HGC, Hagemann H. Hydroxyethyl starch HES 130/0,4 in paediatric surgery. *Crit Care* 2003; **7**(Suppl. 2)**:** P107.

5 Boldt J, Knothe C, Schindler E *et al.* Volume replacement with hydroxyethyl starch solution in children. *Br J Anaesth* 1993; **70:** 661–665.

6 Paul M, Dueck M, Joachim Herrmann H *et al.* A randomized, controlled study of fluid management in infants and toddlers during surgery: hydroxyethyl starch 6% (HES 70/0.5) vs lactated Ringer's solution. *Paediatr Anaesth* 2003; **13:** 603–608.

7 Treib J, Baron JF, Grauer MT *et al.* An international view of hydroxyethyl starches. *Intensive Care Med* 1999; **25:** 258–268.

8 Sümpelmann R, Schurholz T, Marx G *et al.* Alteration of anion gap during almost total plasma replacement with synthetic colloids in piglets. *Intensive Care Med* 1999; **25:** 1287–1290.

9 Davidson IJ. Renal impact of fluid management with colloids: a comparative review. *Eur J Anaesthesiol* 2006; **23:** 721–738.

10 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:** 544–551.

11 Simbruner G. The safety of hydroxyethyl starch use in newborns and its short- and long-term benefits in hypovolemic patients. *Pediatr Crit Care Med* 2003; **4:** 388.

12 Chong Sung K, Kum Suk P, Mi Ja Y *et al.* Effects of intravascular volume therapy using hydroxyethyl starch (130/0.4) on post-operative bleeding and transfusion requirements in children undergoing cardiac surgery: a randomized clinical trial. *Acta Anaesth Scand* 2006; **50:** 108–111.

13 Haas T, Preinreich A, Oswald E *et al.* Effects of albumin 5% and artificial colloids on clot formation in small infants. *Anaesthesia* 2007; **62:** 1000–1007.

14 Van der Linden P, Ickx BE. The effects of colloid solutions on hemostasis. *Can J Anaesth* 2006; **53:** S30–S39.

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