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Changes in acid-base, electrolyte and hemoglobin concentrations during infusion of hydroxyethyl starch 130/0.42/6 : 1 in normal saline or in balanced electrolyte solution in children

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Summary

Introduction: A balanced volume replacement strategy is a well established concept for correcting hypovolemia using plasma adapted isotonic crystalloid solutions with a physiological electrolyte pattern and acetate as bicarbonate precursor. Recently, third-generation hydroxyethyl starch (HES) has also become available in a balanced electrolyte solution instead of normal saline. Therefore, in this prospective non-interventional clinical study, the perioperative administration of HES 130/0.42/6 : 1 in normal saline (ns-HES) and in balanced electrolyte solution (bal-HES) was evaluated in children with a focus on acid-base, electrolyte and hemoglobin changes.

Methods: Following local ethics committee approval, pediatric patients aged up to 12 years with an ASA risk score of I–III undergoing perioperative administration of HES (ns-HES from May 2006 to December 2007, bal-HES from January 2008 to January 2009) were included. Patient demographics, the performed procedure, adverse drug reactions, hemodynamic data and the results of blood gas analysis were documented with a focus on changes in acid-base, electrolyte and hemoglobin concentrations.

Results: Of 396 enrolled patients (ASA I–III; age 2.3 ± 3, range day of birth – 12 years; body weight 10.8 ± 9, range 0.9–52 kg), 249 received ns-HES and 147 bal-HES (mean volume infused 9.9 ± 4 and 9.4 ± 6.9 $ml \cdot kg^{-1}$, respectively). After HES infusion, hemoglobin decreased in both groups, whereas bicarbonate and base excess (BE) decreased only with ns-HES and remained stable with bal-HES (BE before infusion: ns-HES −1.8 ± 2.8, bal-HES −1.7 ± 2.7 $mmol \cdot l^{-1}$; after infusion: ns-HES −2.6 ± 2.4; bal-HES −1.6 ± 2.6 $mmol \cdot l^{-1}$, $P < 0.05$). Chloride (Cl) concentrations increased in both groups and were significantly higher with ns-HES (Cl before infusion: ns-HES 105.6 ± 3.7, bal-HES 105.1 ± 2.8 $mmol \cdot l^{-1}$; after infusion: ns-HES

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107.7 ± 3.2, bal-HES 106.3 ± 2.9 mmol·l^{-1}, $P < 0.01$). No serious adverse drug reactions were observed.
Conclusion: Infusion related iatrogenic acid-base and electrolyte alterations can be minimized by using hydroxyethyl starch in a balanced electrolyte solution instead of normal saline.

Keywords: hydroxyethyl starch; normal saline; balanced electrolyte solution; neonates; children

Introduction

A balanced volume replacement strategy is a well established concept for correcting hypovolemia using plasma adapted isotonic crystalloid solutions with a physiological electrolyte pattern and acetate as bicarbonate precursor (1–3). Presently, most hydroxyethyl starch solutions (HES) are still dissolved in normal saline which contains unphysiologically large amounts of sodium (154 mmol·l^{-1}) and chloride (154 mmol·l^{-1}) and therefore may cause hyperchloremic acidosis. 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) were designed to improve safety while maintaining efficacy (4). Third generation HES 130/0.42 is now approved for children, but published data on the use in children is still limited and the Summary of Product Characteristics (SPC) recommends the use only after careful benefit/risk assessment, and with caution. Therefore we joined an international multicentric prospective observational post-authorization safety study (PASS) for evaluation of the perioperative use of HES 130/0.42/6 : 1 (M_w/MS/C_2 : C_6) in 1130 children with a particular focus on possible serious adverse drug reactions. This study started using HES 130/0.42/6 : 1 dissolved in normal saline (ns-HES) and the preliminary results have been published recently (5). The data showed that third generation HES 130/0.42/6 : 1 is safe and effective even in neonates and small infants. After 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 (2,4) this bal-HES was investigated in a second study phase. Therefore, in this study, we compared the cohort that received HES 130/0.42/6 : 1 in normal saline and the cohort that received HES 130/0.42/6 : 1 in balanced electrolyte solution with a focus on acid-base, electrolyte and hemoglobin changes.

Methods

Following local ethics committee approval, the study was carried out as part of an international multicenter prospective observational PASS. The data presented are obtained from one pediatric center in Germany, where blood gas analysis including chloride and base line values was performed routinely in regular time intervals during major pediatric surgery. Pediatric patients aged up to 12 years with an ASA risk score 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, HES in normal saline (Venofundin; Braun, Melsungen, Germany) was used and from January 2008 to January 2009 HES in balanced electrolyte solution (Tetraspan; Braun; for compositions of both see Table 1). Exclusion criteria were hyperhydration, renal failure, intracranial bleeding, severe hypernatremia or hyperchloremia, hypersensitivity to HES, severely impaired hepatic function and congestive cardiac failure. Patient data and those relating to the administration of HES 130/0.42/6 : 1, the performed surgical procedure, anesthesia related data and adverse drug reactions were documented using a standardized case report form with a focus on acid-base balance, hemodilution, cardiovascular stability, renal function, blood coagulation

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

	ns-HES	*bal-HES*
Sodium, mmol·l^{-1}	154	140
Potassium, mmol·l^{-1}	–	4
Calcium, mmol·l^{-1}	–	2.5
Magnesium, mmol·l^{-1}	–	1
Acetate, mmol·l^{-1}	–	24
Malate, mmol·l^{-1}	–	5
Chloride, mmol·l^{-1}	154	118
Osmolarity, mosmol·l^{-1}	308	296

and hypersensitivity from induction of anesthesia until discharge from the recovery room or intensive care unit to the ward. Results of blood gas analysis (Rapidlab 860; Siemens, Eschborn, Germany) 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. All collected data were analyzed using the statistical analysis systems software (SAS 9.2; SAS Institute Inc., Cary, NC, USA) and presented as mean ± standard deviation (range), and two-tailed *t*-tests and linear regression analysis were performed for metric data with a prespecified significance level of $\alpha = 0.05$.

Table 2
Demographic data [mean ± SD (range)]

	ns-HES	*bal-HES*
Sex, % M/F	58/42	57/43
Age, year	2.1 ± 2.8 (0–11.8)	2.7 ± 3.4 (0–11.6)
Weight, kg	9.9 ± 7.8 (1–48)	12.6 ± 10.9 (0.9–52)
Height, cm	77 ± 28 (33–161)	82 ± 31 (34–150)
Duration of surgery, min	136 ± 72 (25–415)	130 ± 61 (25–308)

Results

Of 396 enrolled patients (58% male, 42% female) 54.5% underwent major abdominal surgery, 13.6% urological, 11.6% thoracic, 7.3% cardiovascular, and 12.1% other surgery, respectively. ns-HES was used in 249 children, and bal-HES in 147 children. Demographic data and results of hemodynamic, acid-base and electrolyte values before and after HES infusion are given in Tables 2 and 3, and Figures 1 and 2. The mean volume of infused HES was 9.86 ± 4 ml·kg^{-1} in ns-HES and 9.41 ± 6.9 ml·kg^{-1} in bal-HES. Before HES infusion, all variables were comparable between the groups. During the study, cardiovascular stability was maintained in all cases. After HES infusion, hemoglobin, hematocrit and strong ion difference decreased significantly

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

	Before			*After infusion*		
	ns-HES	*bal-HES*	P^a	*ns-HES*	*bal-HES*	P^b
pH	7.36 ± 0.06	7.37 ± 0.06	ns	7.37 ± 0.07	7.37 ± 0.07	ns
Bicarbonate, mmol·l^{-1}	23 ± 3	23.6 ± 2.9	ns	22.6 ± 2.9*	23.6 ± 2.3	<0.05
Base excess, mmol·l^{-1}	−1.8 ± 2.8	−1.7 ± 2.7	ns	−2.6 ± 2.4*	−1.6 ± 2.6	<0.05
Sodium, mmol·l^{-1}	137 ± 3.4	136.9 ± 2.8	ns	137.1 ± 3.4	135.4 ± 3*	<0.01
Potassium, mmol·l^{-1}	4 ± 0.5	4 ± 0.5	ns	4 ± 0.5	4.1 ± 0.5	ns
Chloride, mmol·l^{-1}	105.6 ± 3.7	105.1 ± 2.8	ns	107.7 ± 3.2*	106.3 ± 2.9*	<0.01
Lactate, mmol·l^{-1}	1.5 ± 0.7	1.7 ± 1.1	ns	1.7 ± 0.8*	1.7 ± 1.2	ns
Anion gap, mmol·l^{-1}	12.9 ± 4.4	12.2 ± 2.8	ns	10.8 ± 3.1*	9.6 ± 3*	<0.05
Strong ion difference, mmol·l^{-1}	34.3 ± 4.2	34 ± 3.4	ns	31.8 ± 3.2*	31.6 ± 3.3*	ns
Hemoglobin, g·dl^{-1}	11.5 ± 2.2	11.7 ± 2.3	ns	10.2 ± 1.6*	10 ± 2*	ns
Hematocrit, %	34 ± 6.5	34 ± 6.7	ns	30 ± 4.9*	29.6 ± 5.8*	ns
Mean arterial pressure, mmHg	55 ± 13	55 ± 12	ns	55 ± 11	56 ± 11	ns

ns, not significant.
*$P < 0.05$ before vs. after HES infusion.
[a]ns-HES vs. bal-HES before infusion.
[b]ns-HES vs. bal-HES after infusion.

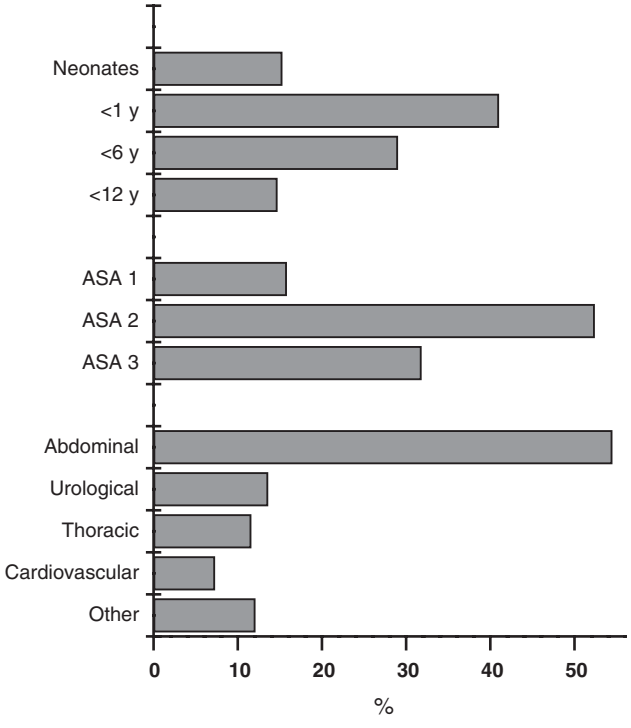

Figure 1
Age, ASA classification and type of surgery.

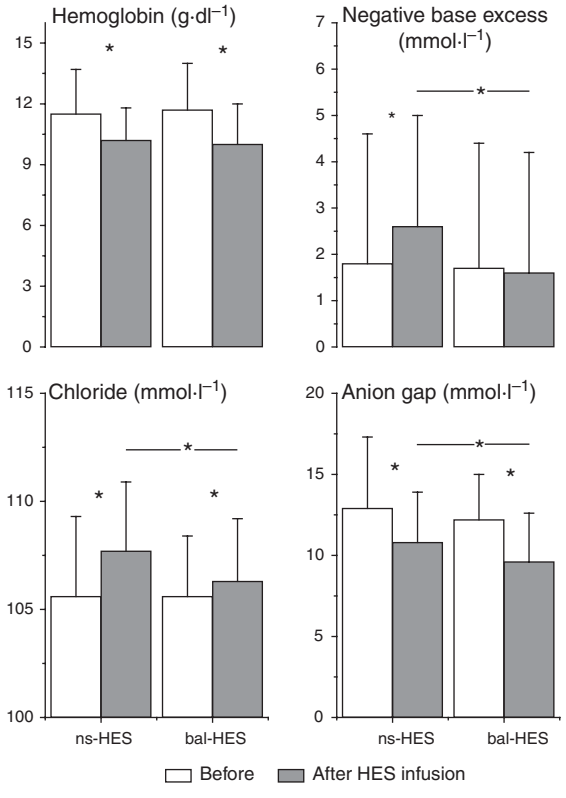

Figure 2
Hemoglobin and acid-base values before and after infusion of hydroxyethyl starch in normal saline (ns-HES) and balanced solution (bal-HES) (mean ± SD, *$P < 0.05$).

in both groups, whereas bicarbonate and base excess (BE before infusion: ns-HES −1.8 ± 2.8, bal-HES −1.7 ± 2.7 mmol·l^{-1}; after infusion: ns-HES −2.6 ± 2.4; bal-HES −1.6 ± 2.6 mmol·l^{-1}, $P < 0.05$) decreased only with ns-HES and remained stable with bal-HES. Chloride concentrations increased in both groups and were significantly higher with ns-HES (Cl before infusion: ns-HES 105.6 ± 3.7, bal-HES 105.1 ± 2.8 mmol·l^{-1}; after infusion: ns-HES 107.7 ± 3.2, bal-HES 106.3 ± 2.9 mmol·l^{-1}, $P < 0.01$). After HES infusion, chloride concentrations correlated significantly with dose per body weight with ns-HES but not with bal-HES. Anion gaps decreased in both groups and were significantly lower with bal-HES. No serious adverse drug reactions were observed.

Discussion

The main findings of this study were firstly that HES 130/0.42/6 : 1 in normal saline leads to a significant increase in chloride concentration and a concomitant decrease in bicarbonate and BE, and secondly that this can be attenuated when using HES 130/0.42/6 : 1 in a balanced electrolyte solution.

The decrease in hemoglobin concentration after HES infusion indicates effective plasma expansion (6). HES infusion decreases the anion gap and strong ion difference and increases the chloride concentration because HES molecules are electroneutral. 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 (7,8). When compared to extracellular fluid or plasma, the composition of HES in normal saline is not physiological because it contains too much sodium (154 mmol·l^{-1}) and chloride (154 mmol·l^{-1}). In addition, normal saline contains no bicarbonate precursor, i.e. lactate or acetate, and therefore dilutes the bicarbonate con-

tent of the entire extracellular space. Based on the Henderson–Hasselbalch equation, this will lead to metabolic acidosis when partial pressure of carbon dioxide remains constant. Using Stewart's approach (9,10), the decrease of the strong ion difference is caused by the normal saline induced increase in chloride concentration leading to hyperchloremic acidosis. In animal experiments, hyperchloremic acidosis was associated with reduced renal blood flow and glomerular filtration rate (11), less hypercoagulability and increased blood loss (12), and worsened outcome (13). Results from adult human studies showed an increased time to first urination (14), a lower urine output (15) and a greater need for blood products (16). In this study, the mean acid-base and electrolyte changes found were small and clinically not harmful, and this may be due to the fact that firstly the extracellular space and the bicarbonate buffer capacity are relatively larger in pediatric patients compared to adults, and secondly the mean hydroxyethyl starch dose of approximately 10 $ml \cdot kg^{-1}$ used was low in both groups. Theoretically, the acidotic effect of normal saline is dose dependent and significant hyperchloremic acidosis may occur when using higher volumes of ns-HES close to the maximum daily dose of 50 $ml \cdot kg^{-1}$. The concept of balanced fluid resuscitation (1,3) includes the use of isotonic solutions with a nearly physiological electrolyte pattern and acetate as a bicarbonate precursor in order to prevent these iatrogenic acid-base and electrolyte imbalances. Because the composition of extracellular fluid or plasma of children and adults is comparable, this concept should benefit both children and adults, especially when high volumes of crystalloid or colloid solutions are applied.

In conclusion, infusion related iatrogenic acid-base and electrolyte alterations can be minimized by using hydroxyethyl starch in a balanced electrolyte solution instead of normal saline.

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