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Effect of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride (Voluven®) on complications after subarachnoid hemorrhage: a retrospective analysis

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Abstract

Background: 6% Hydroxyethyl Starch 130/0.4 in 0.9% Sodium Chloride (Voluven®; 6% HES 130/0.4) is a colloid often used for fluid resuscitation in patients with subarachnoid hemorrhage (SAH), despite a lack of safety data for this use. The purpose of our study was to evaluate the effect of 6% HES 130/0.4 on major complications associated with SAH.

Methods: Medical records of all patients presenting between May 2010 and September 2012 with aneurysmal SAH were analyzed. Patients were divided in two groups based on the administration of 6% HES 130/0.4; HES group (n=57) and Non-HES group (n=72). The primary outcome included a composite of three major complications associated with SAH: Delayed Cerebral Ischemia (DCI), Hydrocephalus (HCP) requiring cerebrospinal fluid (CSF) shunting, and Rebleeding.

Results: The study groups were similar with respect to most characteristics except the incidences of hypertension, ischemic heart disease, Fisher grade and lowest hemoglobin during stay. The odds of developing the primary composite outcome was higher in the HES group [OR= 3.1(1.30-7.36), p=0.01]. The patients in the HES group had a significantly longer median duration of hospital (19 vs 14 days) and Neurointensive Care Unit stay (14 vs 10 days) compared to the Non HES group.

Conclusion: We observed increased complications after SAH with 6% HES 130/0.4 (Voluven®) administration. An adequately powered prospective randomized controlled trial into the safety of 6% HES 130/0.4 in this patient population is warranted.

Keywords: Subarachnoid hemorrhage; Hydroxyethyl starch; 6% HES 130/0.4; Voluven; Fluid therapy; Delayed cerebral ischemia; Hydrocephalus; Rebleeding; Mortality

Background

Aneurysmal Subarachnoid hemorrhage (SAH) has an incidence of nine cases per 100,000 patient years (de Rooij et al. 2007), with 65% survival after the initial hemorrhage (Lovelock et al. 2010; Nieuwkamp et al. 2009). Most fatality occurs within 2 weeks after ictus, with 10% occurring

before receiving medical care and 25% within 24 hours of the event (Broderick et al. 1994). Initial management after resuscitation and stabilization is the prevention of re-bleeding, prevention and management of vasospasm, and the treatment of other complications like hydrocephalus (HCP) (Solenski et al. 1995; van Gijn et al. 1985).

Maintenance of euvolemia remains a mainstay of treatment of these patients during their initial stay (Storrow and Wrenn 2006). Clinicians have used several different fluid regimens and formulations to achieve this goal. Hydroxyethyl Starch (HES) based resuscitation fluids

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have been available for several years, with subsequent generations of HES differing in their mean molecular weight (Mw), Molar substitution (MS), C2/C6 hydroxyethylation ratio and solvent (saline or balanced salt solution). The current generation HES are more rapidly degradable with a lower Mw (130 kDa) and a lower MS (<0.5). Voluven® (Fresenius Kabi, Bad Homburg, Germany) is a colloid solution which consists of a maize derived 6% HES (Mw: 130 kDa, MS: 0.40, C2/C6 ratio 9:1) suspended in normal saline, which has been available in the United States since 2007. Despite its contraindication for use in patients with intracranial hemorrhage (Anonymous 2013), it is used fairly commonly in many neuro-intensive care units including our own once the aneurysm has been secured. Moreover, recently there have been a number of publications in literature which describe the use of 6% HES 130/0.4, in patients which have had SAH (Lehmann et al. 2013; Anonymous 2012; Moretti and Pizzi 2010).

Recent publications with regards to the use of HES in the critically ill patients have indicated a tendency toward harm (Perner et al. 2012; Myburgh et al. 2012). To the best of our knowledge there are currently no safety data with regards to the use of 6% HES 130/0.4 in patients with SAH. We therefore conducted a retrospective observational study to assess the impact of 6% HES 130/0.4 administration on the incidence of complications in patients admitted for aneurysmal subarachnoid hemorrhage. Our a priori defined primary outcome was a composite of serious complications associated with SAH (Delayed Cerebral Ischemia (DCI), Rebleeding, and HCP requiring CSF shunting).

Methods

After obtaining Institutional Review Board approval, all patients who had SAH at Duke University Hospital between May 2010 (when we implemented use of 6% HES 130/0.4) and September 2012 were identified using the appropriate International Classification of Diseases (ICD 9) code. The list of patients was further checked manually by the authors using electronic records (eBrowser, version 7.07, Pegasus Imaging Corporation, Tampa, FL, USA). Patients were excluded from analysis if they were incorrectly coded by ICD 9 classification, had SAH secondary to trauma or anticoagulation, if they had an SAH that was non-aneurysmal in nature, or where the source of SAH was not apparent. Baseline hospital admission characteristics including preexisting medical problems, home medication use, SAH severity, and admission laboratory values were obtained for each eligible patient. This information was obtained by manual searching of electronic medical records and by an automated search of Duke University hospital's Decision Support Repository (DSR) using the Duke Enterprise Data Unified Content Explorer (DEDUCE) portal. The

DSR is a quality assured custom-built data warehouse containing integrated clinical and financial data of all patients admitted to the Duke health care system (Horvath et al. 2011). Individual values which deviated noticeably from the normal or any missing data points were further cross checked manually by a separate investigator after completion of the preliminary data collection. Medical conditions and medication used at the time of admission were considered to be present if they were recorded in the electronic medical records.

Clinical management

All patients with a presumptive diagnosis of SAH presenting to our institution are admitted to the Neurosciences Intensive Care Unit (NICU) after undergoing confirmatory radiological investigations. All patients receive a normal saline infusion supplemented with colloids including 5% Human Plasma Protein Fraction (Plasmanate®, Talecris Biotherapeutics, Research Triangle Park, NC, USA) or 6% HES 130/0.4 (Voluven®) to maintain a positive daily fluid balance and adequate urine output. All patients undergo daily transcranial Doppler ultrasound and routine laboratory investigations (blood counts and electrolytes) for 14 days. Blood pressure is maintained below a systolic blood pressure (SBP) of 140 mmHg until the aneurysm is secured (using appropriate medications if necessary), following which the blood pressure targets are relaxed to a SBP < 160 mmHg. Patients undergo frequent neurological assessments during their stay; any deterioration in the exam is aggressively investigated with appropriate tests (CT angiography and/or conventional angiography). Hypertensive euvolemic therapy is initiated in response to suspected cerebral ischemia due to vasospasm. Refractory symptomatic vasospasm is treated with intra-arterial vasodilators and/or angioplasty. External ventricular drains (EVD) are placed to treat HCP. Patients unable to tolerate drain weaning and removal are given ventriculoperitoneal shunts. Intracranial hypertension is treated with repeated boluses of 20% mannitol (0.25–1.5 g/kg) or 23.4% hypertonic saline targeted to serum osmolality of < 330 mOsm/L. Red blood cell transfusion is targeted to a hemoglobin to >8 g/dl (>9 g/dl in patients with significant heart disease).

We studied the effect of 6% HES 130/0.4 administration on complication rates in patients with aneurysmal SAH. Patients were classified into the 6% HES 130/0.4 group (HES) if they received any amount of 6% HES 130/0.4 during their hospital stay for SAH, while all others were classified into the Non-HES group.

The primary outcome was a priori defined composite of three major complications (Delayed Cerebral Ischemia, Rebleeding, & HCP requiring permanent CSF shunting) (Defined in Appendix 1). We also compared Modified Rankin scores on discharge, blood product

utilization, change in serum creatinine (Δ Cr), 30 day mortality and durations of hospital and ICU stay between the two groups.

Statistical analysis

Data are presented as median [interquartile range (IQR)] or mean (standard deviation) for continuous variables and as count (percentage) for categorical variables. Mann–Whitney U test, Fisher exact or Chi-square tests were used for intergroup comparisons as appropriate. Co-variables that were significantly different between the two study groups were tested in a multivariate logistic regression model with HES use, and non-significant variables were sequentially removed. Interactions between HES use and the significant variables were also tested. Statistical significance was defined as a $P < 0.05$. All analysis was done using SAS statistical software version 9.3 (SAS Institute, Cary, NC).

Results

There were 544 cases with an ICD 9 diagnosis code of SAH identified from the database during the study period. After removal of cases meeting the exclusion criteria, 129 cases of SAH in 129 patients were included in the final analysis. 57 patients (44.2%; HES group) had 6% HES 130/0.4 administered during their hospital stay while 72 patients (55.8%; Non-HES group) did not. Baseline demographics, medical conditions, home medication, and laboratory values on admission are presented in Table 1.

In our study population SAH occurred more commonly in females (67.4% vs. 32.6% males) with an average age of 56.3 yr (SD \pm 13). Racially, aneurysmal SAH was most frequent in Caucasian patients compared to African American and other groups (54.3%, 35.7% and 10%, respectively). Aneurysms were located (in decreasing order of frequency) in the posterior communicating artery (35.7%), anterior communicating artery (32.5%), middle cerebral artery (17%), basilar artery (10.9%) and other sites (3.9%). Overall 30-day mortality was 13.9%. The overall median durations of hospital and NICU stays were found to be 15 days (IQR: 13 to 23) and 12 days (IQR: 8.50 to 16), respectively. The aneurysm was secured in 63 patients by craniotomy with clip ligation and in 57 patients by endovascular coiling. In 9 patients (3 in the HES group, 6 in the Non HES group) the aneurysm was not treated.

A comparison of outcomes of interest between the study groups is described in Tables 2 & 3. The composite primary outcome occurred in 19 (33.3%) and 10 (13.8%) patients in the HES and non-HES groups, respectively ($p = 0.01$). The odds of the primary composite outcome were more in the HES group [OR=3.1(95CI: 1.30-7.36), $p = 0.01$] Figure 1. The Median amount of 6%

HES 130/0.4 administered to the HES group was 1250 ml (IQR: 500–2500). The median 6% HES 130/0.4 doses in the patients in the HES group and in those which suffered the primary outcome were 15.63 ml/kg (IQR: 6.62-26.60) and 16.26 ml/kg (IQR: 8.33-27.16), respectively. We found that the nadir hemoglobin level was significantly lower in the HES compared to the Non HES group during the hospital stay [8.3 (IQR: 7.6 to 9.4) and 9.5 (IQR: 8.3 to 10.7), respectively].

Patients in the HES group received significantly more red blood cell transfusion than the Non HES group. There was no statistically significant difference in the amount of 5% Plasma Protein Fraction (Human), platelets, or fresh frozen plasma between the study groups (Table 3). Median creatinine rise (Δ Cr) in patients which had the primary outcome in the HES and Non HES groups were 12.5% (IQR: 0–37.5) & 7.1% (IQR: 0–27), $p = 0.74$, respectively.

Multivariate analysis

Covariates tested with HES use in the multivariable logistic model included lowest hemoglobin during stay (LHB), Fisher Grade, Ischemic heart disease, and Hypertension. Of these, only LHB showed a significant association with the outcome in an interaction with HES (interaction $p = 0.0085$). The model predicted an increased risk of the primary outcome with HES use at higher levels of LHB (see Figure 2). Estimated odds ratios of primary outcome with HES use were 3.55 (95CI: 1.32- 9.60) at LHB=9 gdl^{-1} , compared to 5.84 (95CI: 1.78-19.1) at LHB=9.5 gdl^{-1} . The model c-index (ROC area) was 0.729.

Discussion

We found that there was a statistically significant increased incidence of the primary outcome in patients who received HES. Patients in the HES group also had significantly longer durations of hospital and NICU stay compared to the Non-HES group (Table 3). However, there was no statistically significant difference in the overall 30-day mortality between the study groups (Table 3).

Voluven® (Fresenius Kabi, Bad Homburg, Germany), a colloid solution consisting of a maize derived 6% HES (Mw: 130 kDa, MS: 0.40, C2/C6 ratio 9:1) suspended in normal saline, has been available in the United States since 2007. Similar to the earlier HES based fluids, it has a longer intravascular half-life (compared to isotonic crystalloids) and is therefore considered a suitable resuscitation fluid in hypovolumic states (Guidet et al. 2012). 6% HES 130/0.4 is not recommended for use in patients with intracranial hemorrhage due to its possible effects on coagulation. 6% HES 130/0.4 is used in many patients with SAH around the world, with several studies also

Table 1 Demographics and laboratory values between the study groups

	Non-HES group (n=72)	HES group (n=57)	p value
<i>Demographic characteristics</i>			
Age (years)	57 (48–63)	57 (46–65)	0.58
Weight (kilogram)	75 (62.5–87)	79 (63.5–97.5)	0.18
Male	24 (33.3%)	18 (31.6%)	0.83
Female	48 (66.4%)	39 (68.4%)	
Caucasian	38 (52.8%)	32 (56.1%)	0.88
African-American	27 (37.5%)	19 (33.3%)	
Others	7 (9.7%)	6 (10.5%)	
<i>Pre-existing medical conditions at admission</i>			
No past medical history	7 (9.7%)	3 (5.3%)	0.34
Ischemic heart disease	4 (5.6%)	10 (17.5%)	0.03
Congestive heart failure	4 (5.6%)	4 (7%)	0.73
Cerebro-vascular accident-stroke	2 (2.8%)	2 (3.5%)	0.81
Cerebro-vascular accident-transient ischemic attack	0 (0%)	2 (3.5%)	0.11
Previous history of Subarachnoid Hemorrhage	0 (0%)	0 (0%)	NA
Epilepsy	1 (1.4%)	1 (1.8%)	0.86
Hypertension	40 (55.6%)	43 (75.4%)	0.02
Chronic renal failure- no dialysis	2 (2.8%)	3 (5.3%)	0.46
Chronic renal failure- Peritoneal or Hemodialysis	0 (0%)	0 (0%)	NA
Diabetes- not on insulin	2 (2.8%)	3 (5.3%)	0.47
Diabetes- treated with insulin	3 (4.2%)	5 (8.8%)	0.28
COPD (no home oxygen)	3 (4.2%)	4 (7%)	0.48
COPD (home oxygen)	0 (0%)	0 (0%)	NA
Smoker	22 (30.6%)	11 (19.3%)	0.14
Family history of Subarachnoid Hemorrhage	6 (8.3%)	2 (3.5%)	0.26
<i>Home medication at admission</i>			
Patient not on any home medications	18 (25%)	10 (17.5%)	0.31
Aspirin	17 (23.6%)	20 (35%)	0.15
Clopidogrel	0 (0%)	2 (3.5%)	0.11
Statin	22 (30.6%)	12 (21%)	0.22
<i>Subarachnoid Hemorrhage grading at admission</i>			
<i>Hunt-Hess grade</i>			
Hunt-Hess grade 1	6 (8.3%)	4 (7%)	
Hunt-Hess grade 2	36 (50%)	32 (56.1%)	
Hunt-Hess grade 3	17 (23.6%)	13 (22.8%)	
Hunt-Hess grade 4	6 (8.3%)	2 (3.5%)	

Table 1 Demographics and laboratory values between the study groups (Continued)

Hunt-Hess grade 5	7 (9.7%)	6 (10.5%)	0.82
<i>Fisher grade</i>			
Fisher grade 1	4 (5.5%)	1 (1.8%)	0.04
Fisher grade 2	12 (16.7%)	2 (3.5%)	
Fisher grade 3	45 (62.5%)	47 (82.4%)	
Fisher grade 4	11 (15.3%)	7 (12.3%)	
<i>Treatment of aneurysm during this hospital stay</i>			
Open Craniotomy and aneurysm clipping	31 (43%)	32 (56.1%)	0.14
Endovascular coil embolization	35 (48.6%)	22 (38.5%)	0.25
<i>Laboratory investigation during hospital stay</i>			
Hemoglobin at admission (g.dl ⁻¹)	13 (11.6-14)	12.7 (11.5-14.3)	0.84
Lowest Hemoglobin during hospital stay (g.dl ⁻¹)	9.5 (8.3-10.7)	8.3 (7.6-9.4)	0.001
Platelet count at admission (× 10 ⁹ /L)	243 (206–283)	235 (194–272)	0.59
Prothrombin Time at admission (sec)	11.9 (11.1-12.8)	12.2 (11.6-13)	0.16
Partial Thromboplastin Time at admission (sec)	26.8 (24–28.8)	25.7 (23.5-27.6)	0.26
Serum Creatinine at admission (mg.dl ⁻¹)	0.8(0.6-1)	0.8(0.7-0.9)	0.46
Highest Serum Creatinine during hospital stay (mg.dl ⁻¹)	0.9 (0.8-1.2)	0.9 (0.75-1.1)	0.70

Median (Interquartile Range) was reported for continuous variables and count (%) for categorical variables. Mann–Whitney U test was used to compare continuous variables and chi-square test for categorical variables. COPD Chronic obstructive pulmonary disease. ARB/ACEI Angiotensin receptor blocker/Angiotensin converting enzyme inhibitor. NA Not applicable.

attesting to this. Most of these studies are small sized (Moretti and Pizzi 2010; Lehmann et al. 2013; Anonymous 2012) (largest being 36 patients) and have not evaluated the effect of 6% HES 130/0.4 on complications associated with SAH like DCI, rebleeding, HCP, or death. This is of concern because recent large randomized control trials (RCTs) have shown that use of Voluven® and similar HES solutions have been associated with poor outcomes and increased mortality (Perner et al. 2011; Myburgh et al. 2012; Estrada and Murugan 2013) in patients with sepsis. Recently, the Surviving Sepsis campaign recommended against the use of HES in patients with severe sepsis (Dellinger et al. 2013). Although potato-derived and maize-derived HES have certain structural differences due to differences in the C2/C6 ratios and percentage of amylopectin content (Westphal et al. 2009), ex vivo studies have demonstrated no

Table 2 Clinical outcomes between study groups

	Non HES group (n=72)	HES group (n=57)	Odds ratio (95%CI)	p value
Primary outcome	10 (13.8%)	19 (33.3%)	3.1 (1.30-7.36)	0.01
Rebleeding	4 (5.6%)	0 (0%)	0.54 (0.06-0.64)	0.13
HCP requiring CSF shunting	3 (4.2%)	12 (21%)	6.1 (1.63-22.95)	0.004
Delayed cerebral ischemia	5 (6.9%)	10 (17.5%)	2.86 (0.91-8.88)	0.09

Data reported as count (%).
 HCP Hydrocephalous.
 CSF Cerebrospinal fluid.
 CI Confidence interval.

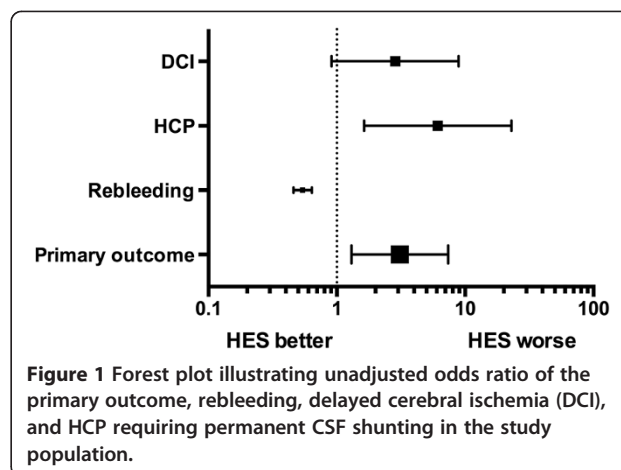
difference between the two with respect to bleeding (Godier et al. 2010). This may suggest a class effect by HES on outcomes like bleeding and acute kidney injury (AKI) (National Heart L and Blood Institute NHLBI and Food and Drug Administration FDA Public Workshop National Heart, Lung, and Blood Institute NHLBI and

Table 3 Length of hospital stay, percent creatinine rise, modified Rankin score at discharge and blood product utilization between the study groups

	Non-HES group (n=72)	HES group (n=57)	*p value
Length of ICU stay [†]	10 (8–13)	14 (11–19.5)	0.001
Length of hospital stay [†]	14 (12–17)	19 (14–26)	0.001
30 day mortality	11 (15.3%)	7 (12.2%)	0.79
Percentage ΔCr in patients with primary outcome [‡]	7.1 (0–27)	12.5 (0–37.5)	0.74
Modified Rankin score (discharge)			
0	8 (11.1%)	2 (3.5%)	0.38
1	26 (36.1%)	30 (52.6%)	
2	14 (19.4%)	7 (12.3%)	
3	7 (9.7%)	4 (7%)	
4	5 (6.9%)	6 (10.5%)	
5	1 (1.4%)	1 (1.7%)	
death	11 (15.3%)	7 (12.3%)	
Blood product usage [‡]			
5% PPF	24.31 (119.85)	26.32 (102.25)	0.51
PRBC	184.65 (428.64)	388.12 (610.98)	0.006
FFP	30.67 (131.42)	82.84 (299.60)	0.43
Platelet	34.04 (105.06)	109.30 (445.32)	0.57

*Mann–Whitney U test was used to compare continuous variables and chi-square test for categorical variables. Data reported as †Median (Interquartile range) ‡Mean (Standard deviation) for continuous variables and count (%) for categorical variables.

ICU Intensive care unit.
 ΔCr Creatinine rise.
 PPF Plasma protein fraction (Human).
 PRBC Packed red blood cells.
 FFP Fresh frozen plasma.



Food and Drug Administration FDA Public Workshop 2013).

The mechanism by which 6% HES 130/0.4 would increase SAH associated complications remains uncertain and under-researched. Only a handful of small studies (Hwang et al. 2007; Dieterich et al. 2003; Feng et al. 2010; Chen et al. 2009) have studied HES with respect to neurological pathophysiology. In a small study of 8 patients (Dieterich et al. 2003), it was found that higher molecular weight HES (Mw: 200 kDa) was not present in the CSF of patients who were given moderate amounts (500–1000 ml). The authors conceded in their study that the accumulation of HES in the brain interstitium could not be ruled out. Accumulation of HES in endothelial cells has been studied previously (Nohe et al. 2002), and it can be hypothesized that a similar accumulation of 6% HES 130/0.4 in the endothelium of the arachnoid villi might effect CSF absorption and promote hydrocephalus. Other mechanism by which HES could affect complications like DCI could be via inhibition of endothelium derived relaxation of blood vessels (Dagtekin et al. 2008; Dagtekin et al. 2010), which could have potentiated microcirculatory consequences.

We found that patients in our HES group with the primary composite outcome had a median rise in serum creatinine (ΔCr) of 12.5% during their hospital stay compared to a rise of 7.1% in the Non HES group. None of the patients required renal replacement therapy during their hospitalization. Although, the clinical significance of this rise is uncertain, retrospective data suggests that a decrease in creatinine clearance of as little as 25% can be associated with poor outcomes at 3 months following SAH (Zacharia et al. 2009). The increased risk of AKI with HES has been found previously by several studies (Estrada and Murugan 2013; Perner et al. 2012), and may be independent of molecular weight and substitution (National Heart L and Blood Institute NHLBI and Food and Drug Administration FDA Public Workshop

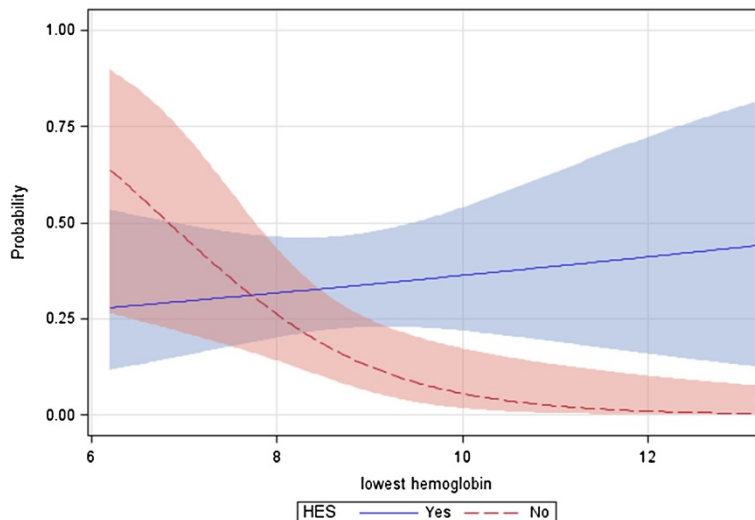


Figure 2 Probability of primary composite outcome with HES use at different levels of lowest hemoglobin.

National Heart, Lung, and Blood Institute NHLBI and Food and Drug Administration FDA Public Workshop 2013). It has been suggested that HES induced AKI may be due to HES accumulation in the proximal renal epithelial cells inducing an “osmotic nephrosis like lesion” leading to tubular obstruction and renal interstitial inflammation (Claus et al. 2010).

In our study, we found that patients in the HES group had more red blood cells transfused compared to the Non HES group. This result is similar to that of other studies (Myburgh et al. 2012; Estrada and Murugan 2013), where more blood product transfusions occurred in the 6% HES 130/0.4 group. HES has been found to be associated with platelet dysfunction, decrease in coagulation factors (like factor VIII and von Willebrand factor) and fibrin polymerization (Westphal et al. 2009; Godier et al. 2010). Although the effects on coagulation and bleeding are greater with higher molecular weight HES, even low molecular weight HES has been found to effect bleeding (Navickis et al. 2012). It is uncertain in our study whether increased red blood cell administration is a simple association with 6% HES 130/0.4 use or a result of it. It is well known that anemia commonly occurs after SAH in 39 to 57% patients (Giller et al. 1998; Kramer et al. 2008). Previous studies have found that lower levels of hemoglobin have been associated with poor outcomes in patients with SAH, including a higher rate of cerebral infarction (Naidech et al. 2006; Naidech et al. 2007; Kramer et al. 2009). This anemia is likely to reflect a suppression of bone marrow activity and response to erythropoietin (Corwin and Krantz 2000; Rodriguez et al. 2001) mediated by increased inflammatory cytokines such as interleukin-1 and tumor necrosis

factor associated with SAH (Fink 2004; Gruber et al. 2000; Naredi et al. 2006). It can be further hypothesized that in patients with SAH, higher degree of anemia may represent a greater systemic inflammatory response (SIRS) and a greater likelihood of poor outcomes like cerebral ischemia and infarction (Naidech et al. 2006). Indeed 65.5% of the primary outcome (19 of 29 events) in our study occurred in patients which had a LHB of less than 9gdl^{-1} . On analysis of the interaction between LHB and HES, we found an increased association between HES use and the primary outcome at higher levels of LHB. This relationship suggests that the effect of HES on the primary outcome is confounded by severity of SIRS at lower hemoglobin levels and unmasked only in patients where SIRS is less severe (as in patients with higher LHB levels).

Our study has several strengths. It is the first study that examines the safety of the use of 6% HES 130/0.4 (Voluven®) in patients with SAH. Secondly, we measure clinically important outcomes in our study, which are defined based on expert consensus and objective criteria (Naidech et al. 2005; Vergouwen et al. 2010). Thirdly, our data and outcomes represent real world practice because it is obtained from routinely collected clinical data.

Our study also has limitations. It is not a prospective trial. Therefore, the presence of unbalanced confounders and lack of randomization could have influenced the outcomes despite our efforts to measure and account for multiple important covariates during analysis. Nevertheless, data from our study will serve useful in designing a prospective RCT. Second, as in all database based studies errors in data collection and processing may exist.

We tried to overcome these errors by using a quality controlled database and by performing additional data verifications after the initial data collection. Thirdly, pathophysiology explaining the results is unclear. Although there is supportive data for the hypothesis we offer as explanations, the exact biological mechanism can be a subject of further research. Lastly, we did not report serial monitoring of coagulation profiles during the hospital stay, although we did report blood product usage between the study groups. This is because our data was obtained from routine medical records and laboratory investigations.

In conclusion, our results suggest that caution should be exercised while utilizing 6% HES 130/0.4 in patients with SAH and a future adequately powered, prospective randomized clinical trial into the safety of 6% HES 130/0.4 in this patient population is warranted.

Appendix 1: Definitions of outcomes

Delayed Cerebral Ischemia: Defined as the occurrence of focal neurological impairment or a decrease of at least 2 points on the Glasgow coma scale (either in total score or one of its individual components). This should have lasted at least 1 hour, was not apparent immediately after aneurysm occlusion, and could not be attributed to other causes (like bleeding or HCP) by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies.

Rebleeding: Defined as an acute deterioration in neurological status in conjunction with new hemorrhage apparent on CT while in the hospital.

HCP requiring CSF shunt: Recorded using appropriate Current Procedure Terminology (CPT) codes.

30 day mortality: Defined as a death occurring within 30 days of hospital admission. Outcome data was obtained from the DSR. The DSR contains updated death information for all patients which visited the Duke University Health System.

Peak Creatinine Rise (ΔCr): was calculated by the following formula:

$$\Delta Cr = (\text{Peak Serum Creatinine} - \text{Serum Creatinine at Admission}) / \text{Serum Creatinine at Admission}$$

Competing interests

Dr. T. J. Gan received research grant support from AcclRx, Fresenius, Merck, Pacira. The author received honoraria from Baxter, Hospira and Pacira (Unrelated to present project).

Dr. M. L. James has received grant support from Baxter and Hospira (Unrelated to present project).

Dr. McDonagh has received consulting fees from Cephalogics Corp. LLC (unrelated to this project).

Authors' contribution

SAK contributed to study design, conduct of the study, data collection, data analysis, and manuscript preparation. OA helped with data collection and manuscript preparation. TJG helped with study design, conduct of the study,

and manuscript preparation. UTN helped with data collection and manuscript preparation. TV helped with data collection and manuscript preparation. SG helped with data collection and manuscript preparation. WDW helped with data analysis, and manuscript preparation. GWB helped with manuscript preparation. ARZ helped with manuscript preparation. MLJ helped with manuscript preparation. DLM helped with study design, conduct of the study, and manuscript preparation. All authors read and approved the final manuscript.

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References

- Anonymous (2013) HIGHLIGHTS OF PRESCRIBING INFORMATION: Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection). <http://www.fda.gov/downloads/.../UCM083138.pdf>. Accessed 3/11
- Anonymous (2012) HES 130/0.4/9:1 effect on intracranial pressure, cerebral blood flow, oxygenation and cerebral vasospasm. *Anesteziol Reanimatol* 4:63–68
- Broderick JP, Brott TG, Duldner JE, Tomsick T, Leach A (1994) Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. *Stroke* 25(7):1342–1347
- Chen S, Zhu X, Wang Q, Li W, Cheng D, Lei C, Xiong L (2009) The early effect of Voluven, a novel hydroxyethyl starch (130/0.4), on cerebral oxygen supply and consumption in resuscitation of rabbit with acute hemorrhagic shock. *J Trauma* 66(3):676–682. doi:10.1097/TA.0b013e318173e7da
- Claus RA, Sossdorf M, Hartog C (2010) The effects of hydroxyethyl starch on cultured renal epithelial cells. *Anesth Analg* 110(2):300–301. doi:10.1213/ANE.0b013e3181ca03a4
- Corwin HL, Krantz SB (2000) Anemia of the critically ill: "acute" anemia of chronic disease. *Crit Care Med* 28(8):3098–3099
- Dagtekin O, Klisa MA, Gerbershagen HJ, Marcus H, Krep H, Teschendorf P, Fischer JH (2010) Effects of hydroxyethyl starch, gelatin and dextran on endothelium-derived relaxation in porcine coronary arteries. *Pharmacology* 86(5–6):267–272. doi:10.1159/000320955
- Dagtekin O, Krep H, Fischer JH (2008) Hydroxyethyl starch inhibits endothelium-derived relaxation in porcine coronary arteries. *Pharmacology* 81(3):241–245. doi:10.1159/000114448
- de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ (2007) Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry* 78(12):1365–1372. doi:10.1136/jnnp.2007.117655
- Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 41(2):580–637. doi:10.1097/CCM.0b013e31827e83af
- Dieterich HJ, Reutershan J, Felbinger TW, Eltzschig HK (2003) Penetration of intravenous hydroxyethyl starch into the cerebrospinal fluid in patients with impaired blood–brain barrier function. *Anesth Analg* 96(4):1150–1154, table of contents
- Estrada CA, Murugan R (2013) Hydroxyethyl starch in severe sepsis: end of starch era? *Crit Care* 17(2):310. doi:10.1186/cc12531
- Feng X, Zhang F, Dong R, Wang H, Liu J, Liu X, Li W, Yao J, Xu J, Yu B (2010) Effects of hydroxyethyl starch (130 kD) on brain inflammatory response and outcome during normotensive sepsis. *Int Immunopharmacol* 10(8):859–864. doi:10.1016/j.intimp.2010.04.020
- Fink MP (2004) Pathophysiology of intensive care unit-acquired anemia. *Crit Care* 8(Suppl 2):S9–S10. doi:10.1186/cc2410
- Giller CA, Wills MJ, Giller AM, Samson D (1998) Distribution of hematocrit values after aneurysmal subarachnoid hemorrhage. *J Neuroimaging* 8(3):169–170
- Godier A, Durand M, Smadja D, Jeandel T, Emmerich J, Samama CM (2010) Maize- or potato-derived hydroxyethyl starches: is there any

- thromboelastometric difference? *Acta Anaesthesiol Scand* 54(10):1241–1247. doi:10.1111/j.1399-6576.2010.02306.x
- Gruber A, Rossler K, Graninger W, Donner A, Illievich MU, Czech T (2000) Ventricular cerebrospinal fluid and serum concentrations of sTNF- α , IL-1 α , and IL-6 after aneurysmal subarachnoid hemorrhage. *J Neurosurg Anesthesiol* 12(4):297–306
- Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, Forceville X, Feissel M, Hasselmann M, Heinger A, Van Aken H (2012) Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. *Crit Care* 16(3):R94. doi:10.1186/cc11358
- Horvath MM, Winfield S, Evans S, Slopek S, Shang H, Ferranti J (2011) The DEDUCE guided query tool: providing simplified access to clinical data for research and quality improvement. *J Biomed Inform* 44(2):266–276. doi:10.1016/j.jbi.2010.11.008
- Hwang SH, Won YS, Yu JS, Yang JY, Choi CS (2007) A comparative coagulopathic study for treatment of vasospasm by using low- and high-molecular weight hydroxyethyl starches. *J Korean Neurosurg Soc* 42(5):377–381. doi:10.3340/jkns.2007.42.5.377
- Kramer AH, Gurka MJ, Nathan B, Dumont AS, Kassell NF, Bleck TP (2008) Complications associated with anemia and blood transfusion in patients with aneurysmal subarachnoid hemorrhage. *Crit Care Med* 36(7):2070–2075. doi:10.1097/CCM.0b013e31817c1095
- Kramer AH, Zygun DA, Bleck TP, Dumont AS, Kassell NF, Nathan B (2009) Relationship between hemoglobin concentrations and outcomes across subgroups of patients with aneurysmal subarachnoid hemorrhage. *Neurocrit Care* 10(2):157–165. doi:10.1007/s12028-008-9171-y
- Lehmann L, Bendel S, Uehlinger DE, Takala J, Schafer M, Reinert M, Jakob SM (2013) Randomized, double-blind trial of the effect of fluid composition on electrolyte, Acid-base, and fluid homeostasis in patients early after subarachnoid hemorrhage. *Neurocrit Care* 18(1):5–12. doi:10.1007/s12028-012-9764-3
- Lovelock CE, Rinkel GJ, Rothwell PM (2010) Time trends in outcome of subarachnoid hemorrhage: population-based study and systematic review. *Neurology* 74(19):1494–1501. doi:10.1212/WNL.0b013e3181dd42b3
- Moretti R, Pizzi B (2010) Inferior vena cava distensibility as a predictor of fluid responsiveness in patients with subarachnoid hemorrhage. *Neurocrit Care* 13(1):3–9. doi:10.1007/s12028-010-9356-z
- Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA (2012) Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 367(20):1901–1911. doi:10.1056/NEJMoa1209759
- Naidech AM, Drescher J, Ault ML, Shaibani A, Batjer HH, Alberts MJ (2006) Higher hemoglobin is associated with less cerebral infarction, poor outcome, and death after subarachnoid hemorrhage. *Neurosurgery* 59(4):775–779. doi:10.1227/01.NEU.0000232662.86771.A9, discussion 779–780
- Naidech AM, Janjua N, Kreiter KT, Ostapkovich ND, Fitzsimmons BF, Parra A, Commichau C, Connolly ES, Mayer SA (2005) Predictors and impact of aneurysm rebleeding after subarachnoid hemorrhage. *Arch Neurol* 62(3):410–416. doi:10.1001/archneur.62.3.410
- Naidech AM, Jovanovic B, Wartenberg KE, Parra A, Ostapkovich N, Connolly ES, Mayer SA, Commichau C (2007) Higher hemoglobin is associated with improved outcome after subarachnoid hemorrhage. *Crit Care Med* 35(10):2383–2389. doi:10.1097/01.CCM.0000284516.17580.2C
- Naredi S, Lambert G, Friberg P, Zall S, Eden E, Rydenhag B, Tylman M, Bengtsson A (2006) Sympathetic activation and inflammatory response in patients with subarachnoid haemorrhage. *Intensive Care Med* 32(12):1955–1961. doi:10.1007/s00134-006-0408-y
- National Heart L, Blood Institute (NHLBI) and Food and Drug Administration (FDA) Public Workshop National Heart, Lung, and Blood Institute (NHLBI) and Food and Drug Administration (FDA) Public Workshop (2013) Risks and Benefits of Hydroxyethyl Starch Solutions. <http://www.nhlbi.nih.gov/meetings/workshops/Hydroxyethyl.htm>. Accessed 03-24-2013
- Navickis RJ, Haynes GR, Wilkes MM (2012) Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: a meta-analysis of randomized trials. *J Thorac Cardiovasc Surg* 144(1):223–230. doi:10.1016/j.jtcvs.2012.04.009
- Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ (2009) Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. *Lancet Neurol* 8(7):635–642. doi:10.1016/S1474-4422(09)70126-7
- Nohe B, Burchard M, Zanke C, Eichner M, Krump-Konvalinkova V, Kirkpatrick CJ, Dieterich HJ (2002) Endothelial accumulation of hydroxyethyl starch and functional consequences on leukocyte-endothelial interactions. *Eur Surg Res* 34(5):364–372
- Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, Madsen KR, Moller MH, Elkjaer JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Soe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjaeldgaard AL, Fabritius ML, Mondrup F, Pott FC, Moller TP, Winkel P, Wetterslev J (2012) Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 367(2):124–134. doi:10.1056/NEJMoa1204242
- Perner A, Haase N, Wetterslev J, Aneman A, Tenhunen J, Guttormsen AB, Klemenzson G, Pott F, Bodker KD, Badstolokken PM, Bendtsen A, Soe-Jensen P, Tousi H, Bestle M, Pawlowicz M, Winding R, Bulow HH, Kancir C, Steensen M, Nielsen J, Fogh B, Madsen KR, Larsen NH, Carlsson M, Wiis J, Petersen JA, Iversen S, Schoidt O, Leivdal S, Berezowicz P, Pettila V, Ruokonen E, Klepstad P, Karlsson S, Kaukonen M, Rutanen J, Karason S, Kjaeldgaard AL, Holst LB, Wernerman J (2011) Comparing the effect of hydroxyethyl starch 130/0.4 with balanced crystalloid solution on mortality and kidney failure in patients with severe sepsis (6S—Scandinavian Starch for Severe Sepsis/Septic Shock trial): study protocol, design and rationale for a double-blinded, randomised clinical trial. *Trials* 12(1):24. doi:10.1186/1745-6215-12-24
- Rodriguez RM, Corwin HL, Gettinger A, Corwin MJ, Gubler D, Pearl RG (2001) Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness. *J Crit Care* 16(1):36–41
- Solenski NJ, Haley EC Jr, Kassell NF, Kongable G, Germanson T, Truskowski L, Torner JC (1995) Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. *Crit Care Med* 23(6):1007–1017
- Storow AB, Wrenn K (2006) Aneurysmal subarachnoid hemorrhage. *N Engl J Med* 354(16):1755–1757. doi:10.1056/NEJMc060439, author reply 1755–1757
- van Gijn J, Hijdra A, Wijdicks EF, Vermeulen M, van Crevel H (1985) Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. *J Neurosurg* 63(3):355–362. doi:10.3171/jns.1985.63.3.0355
- Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, Mendelow AD, Juvela S, Yonas H, Terbrugge KG, Macdonald RL, Diringer MN, Broderick JP, Dreier JP, Roos YB (2010) Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke* 41(10):2391–2395. doi:10.1161/STROKEAHA.110.589275
- Westphal M, James MF, Kozek-Langenecker S, Stocker R, Guidet B, Van Aken H (2009) Hydroxyethyl starches: different products—different effects. *Anesthesiology* 111(1):187–202. doi:10.1097/ALN.0b013e3181a7ec82
- Zacharia BE, Ducruet AF, Hickman ZL, Grobelny BT, Fernandez L, Schmidt JM, Narula R, Ko LN, Cohen ME, Mayer SA, Connolly ES Jr (2009) Renal dysfunction as an independent predictor of outcome after aneurysmal subarachnoid hemorrhage: a single-center cohort study. *Stroke* 40(7):2375–2381. doi:10.1161/STROKEAHA.108.545210

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