Complications of Hydroxyethyl Starch in Acute Ischemic Stroke and Other Brain Injuries

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Key Words

Hydroxyethyl starch · Acute ischemic stroke · Brain injuries · Complications, hydroxyethyl starch · Safety, hydroxyethyl starch · Hemorrhages · Blood coagulation disorders · Mortality, brain injuries

Abstract

Serious complications of hydroxyethyl starch (HES) administration have been repeatedly demonstrated in clinical trials of acute ischemic stroke and other brain injuries. Such complications have prompted the premature termination of several randomized trials. Coagulopathy and bleeding have been the most frequently documented complications in the brain injury setting and have occurred after exposure to HES solutions of widely varying molecular weight and substitutions. Severe, protracted, refractory pruritus is another HES complication. Claims of safety for HES solutions have often been made on the basis of small trials with inadequate statistical power. Additionally, the safety has been typically assessed in highly selected low-risk patient populations receiving relatively small HES doses, so that the results cannot be generalized to routine clinical practice. The

preponderance of available evidence suggests that HES solutions should be avoided in acute ischemic stroke and other brain injuries.

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Introduction

In their recent report of a randomized trial on the use of hydroxyethyl starch (HES) with a molecular weight of 130 kDa and substitution of 0.4 (HES 130/0.4) in 40 patients with acute ischemic stroke, Woessner et al. [1] concluded that 'HES 130/0.4, even when infused in large quantities, has a high degree of therapeutic safety'. As this conclusion is unjustified for several reasons, an in-depth discussion of the use of HES in patients with acute ischemic stroke is presented. Copious prior evidence indicates serious safety problems of HES [2], especially when used in acute ischemic stroke and other brain injuries [3–15], as summarized in table 1. The trial of Woessner et al. [1] was not powered to assess safety adequately, and key safety data from the trial were not reported. Furthermore, a highly selected, low-risk patient population was enrolled, so that the results of the trial cannot be generalized to routine clinical practice.

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Table 1. HES complications in patients with acute ischemic stroke and other brain injuries

Study (year of publication)	Design	Fluid regimen	Complications
Toole [3] (1987)	Pharmacovigilance study	HES 450/0.7	Bleeding in 8 neurosurgical patients treated with HES; manufacturer recommendation issued against HES for cerebral vasospasm after SAH or other conditions requiring repeated use over several days
Hemodilution in Stroke Study Group [4] (1989)	Multicenter randomized trial of 88 acute ischemic stroke patients	Hypervolemic hemodilution with HES 200/0.5 vs. standard therapy 24 h after onset	Trial stopped prematurely because of significantly increased mortality related to cerebral edema in recipients of HES
Mast and Marx [5] (1991)	Randomized trial of 70 acute ischemic stroke patients	Isovolemic hemodilution with 10% HES 200/0.5 vs. no hemodilution	Trial discontinued due to clinical deterioration in 8 HES recipients vs. none of the control group patients ($p < 0.01$)
Treib et al. [6] (1995)	Nonrandomized controlled trial of 20 patients with cerebral circulatory disturbances without evidence of cardiac or renal insufficiency	500 ml 10% HES 200/0.5 with a C2/C6 ratio of 13.4 vs. 5.7 followed by 1,000 ml later on 1st day, 1,000 ml/day on days 2–4, and 500 ml/day on days 5–10	aPTT prolonged and factor VIII:C and vWF:Ag decreased in both groups throughout the 10-day study period ($p < 0.05$); effects greater for 13.4 C2/C6 group ($p < 0.05$); vWF:RC reduced in 13.4 but not 5.7 C2/C6 group ($p < 0.01$)
Trumble et al. [7] (1995)	Nonrandomized controlled trial of 85 patients with cerebral vasospasm after SAH	6% HES 450/0.7 vs. 5% albumin (plasma protein fraction)	HES infusion prolonged partial thromboplastin time ($p < 0.001$); 4 HES recipients required transfusion, 1 patient underwent re-exploration for bleeding, and 1 patient developed a delayed post-operative epidural hematoma necessitating evacuation
Treib et al. [8] (1996)	Randomized trial of 20 patients with cerebrovascular diseases	1,500 ml 10% HES 200/0.5 vs. 6% HES 40/0.5 on day 1, 1,000 ml/day on days 2–4, and 500 ml/day on days 5–10	Platelet number and volume declined in both groups during the 1st day of HES therapy ($p < 0.05$); no significant differences in platelet aggregation
Treib et al. [9] (1996)	Nonrandomized controlled trial of 30 patients with cerebrovascular diseases	1,500 ml 6% HES 200/0.62 vs. 10% HES 200/0.5 vs. 6% HES 40/0.50–0.55 on day 1, 1,000 ml/day on days 2–4, and 500 ml/day on days 5–10	Platelet number and volume declined in all groups during the 1st day of HES therapy ($p < 0.05$); the platelet volume reduction persisted throughout the 10-day observation period in all groups ($p < 0.05$)
Stoll et al. [10] (1997)	Cohort of 10 patients with acute infarction in the middle cerebral artery region	3,000 ml 6% HES 70/0.5 on 1st day and 1,500 ml on days 2–4	aPTT prolonged ($p < 0.05$)
Treib et al. [11] (1997)	Cohort of 10 patients with stroke or transient ischemic attack	Loading dose of 500 ml 10% HES 200/0.62 followed by 500 ml maintenance dose per day for 10 days	aPTT prolonged by 43% ($p < 0.01$); factor VIII:C, vWF:RC, and vWF:Ag reduced to values $< 30\%$ ($p < 0.01$ for all comparisons)
Jonville-Béra et al. [12] (2001)	Pharmacovigilance study of adverse events spontaneously reported to 31 French regional drug-monitoring centers during 1990–1997	HES 200/0.5 as hemodilution therapy for vasospasm secondary to SAH	Nine cases reported of acquired type I von Willebrand's disease associated with HES, including 4 cases complicated by cerebral hemorrhage and 1 by extradural hematoma; 3 of 4 cerebral hemorrhage cases fatal
Kimme et al. [13] (2001)	Cohort of 50 SAH patients	Hemodilution with HES	Delayed pruritus manifested as pruritic crises in 54% of the patients; pruritus persisted for a mean duration of 15 weeks
Rudolf [14] (2002)	Randomized phase II safety study in 106 acute ischemic stroke patients	Hypervolemic hemodilution with 10% HES 130/0.4 vs. 0.9% saline	Serious cerebrovascular adverse events in 5.7% of the HES 130/0.4 vs. 2.8% of the saline recipients
Neff et al. [15] (2003)	Randomized trial of 31 cranio-cerebral trauma patients	$\leq 70 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ HES 130/0.4 vs. $\leq 33 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ HES 200/0.5 for up to 28 days	Trial prematurely halted due to a high incidence of intracranial bleeding complications in both HES 130/0.4 (31%) and HES 200/0.5 (33%) recipients

HES = Hydroxyethyl starch; SAH = subarachnoid hemorrhage; aPTT = activated partial thromboplastin time; vWF = von Willebrand factor; RC = ristocetin cofactor.

HES in Acute Ischemic Stroke

Dramatizing the risks of HES in patients with acute ischemic stroke and other brain injuries has been the discontinuation of three randomized trials due to excess mortality [4], clinical deterioration [5], or intracranial bleeding complications [15] among HES recipients. Coagulopathy and hemorrhage have been the most frequently described complications of HES in the brain injury setting (table 1). Such complications have been encountered with HES solutions across the entire spectrum of molecular weights and substitutions, including HES 40/0.5, HES 70/0.5, HES 130/0.4, HES 200/0.5, HES 200/0.62, and HES 450/0.7 (table 1).

Another common HES complication is severe, prolonged refractory pruritus of delayed onset [13]. In the trial of Woessner et al. [1], pruritus occurred in 3 of 20 patients in the HES 130/0.4 group and in 2 of 20 crystalloid recipients. Thus, the incidence of pruritus was 50% higher in the patients exposed to HES 130/0.4. Although this difference was not statistically significant, the observed statistical power of the trial to detect a significant difference of this magnitude by Fisher's exact test was only 2.9%. The sample size for the trial was intended to afford 80% power. Safety claims for HES based on small, underpowered trials have been criticized [16]. Another example was a trial in acute ischemic stroke patients [14], in which the incidence of serious cerebrovascular events was twice as high in the HES 130/0.4 group (5.7%) as in the patients receiving saline (2.8%). Again, the difference was not significant, but the observed power to demonstrate such a difference was only 1.7%.

In the trial of Woessner et al. [1], essential data were omitted. Though recognizing that bleeding complications are 'a much feared side effect' of HES, Woessner et al [1] provided no data on such complications or on any other

adverse events except pruritus. They assessed hemostatic function by measuring platelets, prothrombin time, activated partial thromboplastin time, fibronectin, factor VIII:C, von Willebrand factor antigen, and von Willebrand ristocetin cofactor; however, they did not report the results of these measurements.

Patients with mild stroke (mean Barthel index score >90) entered the trial performed by Woessner et al. [1]. Exclusion criteria were intracranial hemorrhage, aphasia, cardiac insufficiency, coagulation disorders, trauma, blood loss, renal insufficiency, and treatment with thrombolytic medication. Thus, the underlying risk of complications in the trial population was low. Furthermore, contrary to the characterization by the authors, the HES 130/0.4 dose administered (mean 1,625 ml/day for 4 days) was not high as compared, e.g., with that in another recent brain injury trial [15], in which the HES 130/0.4 dose averaged 2,300 ml/day for a mean of 6.6 days.

Conclusions

The trial performed by Woessner et al. [1] 'shows that the newly developed 6% HES 130/0.4 is a safe drug'. Such an endorsement of HES 130/0.4 safety cannot be accepted due to the limitations of the trial. A more cautious conclusion would appear to be particularly warranted in the light of the disclosure that the manufacturer of HES 130/0.4 funded the study, defrayed the costs for the study medication, data analysis, insurance, and the ethics committee, and contributed to the research fund of the clinic at which the trial was conducted. Indeed, if all the currently available evidence is considered, there appears to be greater support for the conclusion that HES solutions are *not* safe in acute ischemic stroke and other brain injuries.

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