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Clinical Article

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J Korean Neurosurg Soc 42 : 377-381, 2007 10.3340/jkns.2007.42.5.377

A Comparative Coagulopathic Study for Treatment of Vasospasm by Using Low- and High-molecular Weight Hydroxyethyl Starches

Objective : High-molecular-weight hydroxyethyl starch (HES) compromises blood coagulation more than does low-molecular-weight HES. We compared the effects of low- and high-molecular-weight HES for the treatment of vasospasm and investigated the dose relationship with each other.

Methods : Retrospectively, in a series of consecutive 102 patients with subarachnoid hemorrhage (SAH), 35 patients developed clinical symptoms of vasospasm of these fourteen patients were treated with low-molecular-weight HES for volume expansion while the other 21 received high-molecular-weight HES as continuous intravenous infusion. Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen level, and platelet count were all measured prior to initiation, during treatment and after termination of therapy for symptomatic vasospasm. The total dose of HES ranged from 5 L to 14 L and median infusion duration was 10 days.

Results : A more pronounced PTT prolongation was observed in high-molecular-weight HES group compared with low-molecular-weight HES group. No other coagulation parameters were altered. Dosage (=duration) shows a positive correlation with PTT. Clinically, significant bleeding episodes were noted in four patients who received high-molecular-weight HES.

Conclusion : Coagulopathy was developed in direct proportion to molecular weight of starch and dosages. We propose the extreme caution in the administration of HES solution for the vasospasm treatment.

KEY WORDS : Coagulopathy · Hydroxyethyl starch (HES) · Partial thromboplastin time (PTT) · Subarachnoid hemorrhage · Vasospasm.

INTRODUCTION

Cerebral vasospasm typically starts 3-5 days after the initial SAH, achieves maximal vessel narrowing at 5-14 days, and thereafter resolves gradually[10]. The exact mechanisms by which SAH induces arterial vasospasm continues to be a subject of considerable research and debate. This mechanism appears to be a multifactorial process that involves the generation of free radicals, lipid peroxidation and activation of protein kinase C as well as phospholipase C and A2 with resultant accumulation of diacylglycerol and the release of endothelin-1[2].

More than half of SAH patients develop cerebral vasospasm and approximately one-third develop symptomatic vasospasm which is associated with neurologic signs and symptoms of ischemia[20]. Volume expansion is one of the cornerstones in the prevention and treatment of postsubarachnoid hemorrhage vasospasm[18]. It has been shown to decrease the size of ischemic infarct and improve hemodynamic parameters[4,18]. Recently, synthetic colloids are commonly used as a volume expander. Among these solutions, hydroxyethyl starch (HES) solution has become widely used with limited side effects. Nevertheless, a coagulopathy can occur during HES administration, consisting of a prolongation of the partial thromboplastin time (PTT) and a decrease in factor VIII[1].

We compared low- with high-molecular-weight HES that were used in the treatment of vasospasm and investigated the relationship between HES dosage and PTT prolongation to help in preventing further occurrences of bleeding pathologies.

MATERIALS AND METHODS

Between January, 2005 and December, 2006, 102 patients admitted to our hospital with a recent (<4 days of symptoms) SAH that required surgical clipping of an intracranial aneurysm

• Received : June 1, 2007
• Accepted : September 19, 2007
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Table 1. Hemorheological parameters at the beginning and end of treatment in patients receiving HES

	Case No.	Dose(cc/kg/h)	PT(sec)		PTT (sec)		PLT ($\times 10^9$/L)		FIB (mg/d)	
			Start	End	Start	End	Start	End	Start	End
HES 70	1	0.66	13.4	12.6	31.1	36.3	299	506	415	599.3
	2	0.7	12.3	11.8	26.3	27.4	324	425	309.7	240.8
	3	0.75	12.3	14.9	38.5	44.1	315	312	310.4	641.5
	4	0.64	11.6	12.2	30.1	36.3	238	332	421.1	263.5
	5	0.67	13.2	13.9	32.8	36.2	329	334	396.8	341.4
	6	0.7	12	12.5	21.2	27.4	228	324	281	435
	7	0.65	12.2	11.4	29.5	30.8	186	171	*	256
	8	0.76	11.7	12	26	28.5	203	237	484	493
	9	0.64	12	11.2	30.9	32.2	312	404	380	390
	10	0.57	11.4	13.8	27.5	36.1	312	316	*	361.1
	11	0.67	13.1	12.3	31.9	33.9	185	277	321	144
	12	0.7	12.4	11.9	27.4	32.9	195	207	*	387.6
	13	0.55	13	14.1	37.5	49.1	234	202	*	*
	14	0.69	12.6	17.9	37.1	40.9	274	294	182.9	302.5
HES 670	15	0.57	13.9	15.7	35.2	43.4	182	170	427.4	291
	16†	0.67	13.5	15.1	38.7	51.6	143	153	195.2	201.4
	17	0.75	12.2	13.1	27.8	55.3	147	149	228.4	135.6
	18	0.66	13.6	12.7	40.5	30.1	84	121	127.2	495.4
	19†	0.7	12.7	16.6	27.6	60.5	207	209	232.6	155.2
	20	0.75	13.5	13.2	33.1	39.5	180	157	212.7	277.8
	21	0.64	12.5	14	34.8	50.6	214	171	247.8	253.1
	22	0.67	12.6	13	29.9	38.4	204	171	154.4	188.4
	23	0.7	12.8	13.8	36.8	41.6	165	168	271.6	299.4
	24	0.65	13.1	13.3	31.5	48.5	371	398	340.8	190
	25‡	0.76	13	15.3	29.1	53.6	390	137	279.4	130.3
	26§	0.64	12.1	13.6	29.7	41	250	83	248.7	133.8
	27	0.57	12.7	13.9	41.8	54.7	223	200	255.7	168.2
	28	0.67	13.1	15	33.1	36.9	202	224	260	340.6
	29	0.7	13.1	13.7	28.9	31.5	309	205	239	164.2
	30	0.55	13.2	14.8	34.5	58.1	203	244	196.1	239.6
	31	0.69	12.4	12.7	29.3	41.4	179	188	436.8	339.8
	32	0.69	12.9	12.9	33.5	50.6	157	184	189.9	382.9
	33	0.65	12.5	13.4	25.4	38.8	269	147	450.6	312.5
	34	0.72	13.3	13.6	40.8	40.4	217	253	408.8	444.6
	35	0.64	12.7	16.2	38	61.6	281	192	392.2	366.6

Abbreviations : PT : prothrombin time, PTT : partial thromboplastin time, PLT : platelet count, FIB : fibrinogen level. *Not tested, †Subgaleal hematoma developed patients, ‡Delayed epidural hematoma developed patient, §Delayed epidural hematoma with microalveolar hemorrhage developed patient

underwent postoperative care in the neurosurgical intensive care unit.

Treatment of vasospasm

All patients received nimodipine for 21 days or until discharge. Hemodilution and hypervolemia were employed preventively in all patients using a crystalloid solution. Hunt and Hess grades were also documented on admission. Hematocrit was maintained between 30 and 35%. Systolic blood pressure was maintained above 180 mmHg. Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen level, and platelet count were all measured prior to the initiation during and termination of therapy for symptomatic vasospasm. There were no other differences in the treatment protocol and all patients were managed under the supervision of the senior author. Most data, including demographic data, clinical condition, radiographic findings, surgical details, onset and duration of vasospasm, use of medications (including hetastarch), complications, and outcome were collected retrospectively.

Administeration of HES

Of these 102 patients, 35 developed clinically significant vasospasm documented by a progressive postoperative neurological deficit that could not be explained on the basis of hydrocephalus, rebleeding, or other pathologies. The perio-

Table 2. Mean value of Hemorheological parameters at the beginning and end of treatment in patients receiving HES

	PT (sec)		PTT (sec)		PLT ($\times 10^9$/L)		FIB (mg/dl)	
	Start	End	Start	End	Start	End	Start	End
HES 70	12.37	13.04	30.55	35.15	259.57	310.07	350.19	373.52
HES 670	12.92	14.08	33.33	46.1	217.95	186.86	275.97	262.4

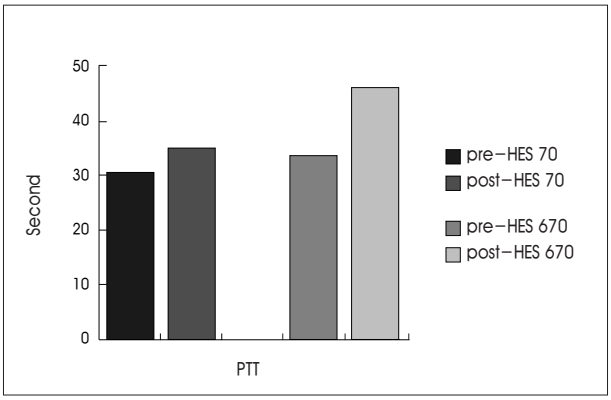

Fig. 1. Bar graph illustrating mean changes of partial thromboplastin time (PTT) in patients receiving either hydroxyethyl starch (HES) 70 or HES 670. The difference in PTT changes between HES groups is statistically significant ($p < 0.005$).

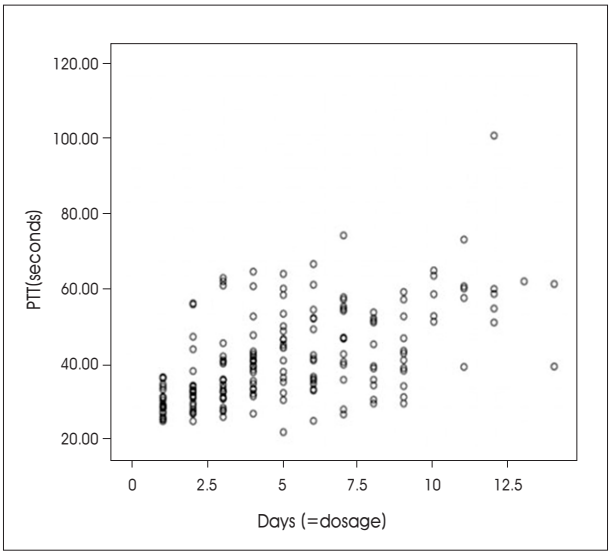

Fig. 2. Graph displaying the distributions of partial thromboplastin time and dosage (=duration) in patients receiving hydroxyethyl starch (Pearson correlation=0.564, $p < 0.005$).

perative transcranial doppler examinations were obtained in all patients by experienced examiners using the standard technique. In those patients who developed clinical signs of vasospasm, hypervolemic therapy with a colloid solution and hypertensive therapy with phenylephrine were instituted. Either HES 70 (6% hetastarch, with an average molecular weight of 70 kd) or HES 670 (6% hetastarch, with an average molecular weight of 670 kd) were used as a colloid solution. Fourteen patients received HES 70 and 21 patients received HES 670. Both colloids were administered intravenously at a median rate of 40 cc/hour. The total dose of hetastarch ranged from 5 L to 14 L and median infusion duration was 10 days (ranged from 6 to 14 days). High molecular weight HES (HES 670) was the preferred volume expanding agent because volume expanding effect was excellent and penylephrine use reduced.

RESULTS

At the beginning of therapy, PT and PTT were in the normal range. The mean infusion rate for hetastarch was 0.67 cc/kg per hour. Table 1 demonstrates the hemorheologic parameters at the beginning and end of the HES treatment. Mean value of post-treatment PT was slightly elevated above pre-treatment levels in both groups, whereas platelet and fibrinogen levels revealed no significant change. PTT was found to be significantly prolongated. In HES 70 group, it ranged from 30.55 to 35.15 sec and in HES 670 group, from 33.33 to 46.1 sec (Table 2). The difference in PTT changes between two groups was significant ($p < 0.005$ by Mann-Whitney test, Fig. 1). Dosage (=duration) shows a positive correlation with PTT (Fig. 2).

The elevation of PTT was evidenced clinically in high-molecular-weight hetastarch group but not in low-molecular-weight hetastarch group. Two patients (Case 16, 19), while receiving hetastarch, required re-exploration 4-5 days after surgery for subgaleal arterial bleeding from the operative site. Other two patients (case 25, 26), receiving hetastarch, developed delayed postoperative epidural hematoma that required evacuation. In case 26, additional microalveolar hemorrhage developed during hetastarch infusion. In all of these patients, outcome was believed to be negatively influenced by the aforementioned complications.

DISCUSSION

Hydroxylethyl starch (HES) is often used for plasma-expanding agent. Since bleeding complications have been reported repeatedly, a strict dose limitation of maximum of 1500 ml 6% solution per day is recommended[1,18].

The use of plasma-expanding agents for the treatment of vasospasm requires a different treatment regimen than fluid resuscitation. The literature supports the use of various plasma substitutes for optimum hemodynamic and hemorheological effects in the cerebral circulation[9]. Previous studies have reported a reduction in cerebral infarct size with the use of these agents[8,12] and improvement in cerebral blood flow in ischemic as well as normal brain[6,19]. Although the etiology

of this improvement was unclear, they suggested theories including hemodilution, decreased plasma viscosity, increased cardiac output, or mild elevation of clotting time[7,12,20]. The mild elevation of clotting time was ascribed to precipitation by hetastarch of factor VIII[5,7,10,15]. Studies in humans used doses lower than those necessary for the treatment of vasospasm in normal volunteers[8,15]. We thought that 500 cc/day of hetastarch was inadequate to maintain pulmonary capillary wedge pressure and hemodilution. More than 1 L/day was usually necessary, and this dose was maintained as long as there was clinical concern about symptomatic vasospasm. Even these higher doses were less than the previously recommended maximum dose of 20 ml of hetastarch per kilogram of body weight for 24 hours.

In a recent series of 85 patients with cerebral vasospasm, Trumble et al.[18] demonstrated that the infusion of hetastarch solution, instead of plasma protein fraction, increased the incidence of clinical bleeding and significantly prolonged PTT from 23.9 to 33.1 sec ($p<0.001$). Sanfellippo and Suberviola[13] reported a patient with cerebral vasospasm who developed gingival bleeding after 10 days of hetastarch infusion at a rate of 1000 ml/day. The present study demonstrated that PTT was found to be significantly elevated in both groups. High-molecular-weight hetastarch significantly affected PTT prolongation than low-molecular-weight Hetastarch and also dosage (=duration) showed in direct proportion to PTT prolongation. The prolonged PTT may be associated with a disorder of the intrinsic clotting system caused mainly through a change in factor VIII/von Willebrand factor. von Willebrand factor supports the adhesion of the platelets to the injured blood vessel. A decrease in factor VIII/von Willebrand factor rarely leads to spontaneous bleeding but may considerably prolong after-bleeding from even small injuries[17]. In our study cases, we thought subgaleal bleeding and epidural hematoma developed from operation site at hemovac removing time (mainly postoperative 2-3 days) were from these cases.

The high molecular weight hetastarch used in this study has a high molecular weight (670 kd) and high degree of substitution (0.75) compared with low molecular weight hetastarch [molecular weight (70 kd), degree of substitution (0.5-0.55)] that would be difficult to be degraded and may induce an unexpected side effect[3,11]. Hetastarch is a very heterogeneous product, raising concern that its half-life may be extended further by its higher molecular weight and high degree of substitution. Most hetastarch is cleared by the kidney after enzymatic degradation by amylase[17]. Of particular importance is the fact that high molecular weight hetastarch is difficult to be degraded and cause accumulation in vivo. This affects factor VIII/von Willebrand factor which can lead to an acquired von Willebrand syndrome[3,14,16,17]. On the basis of this hetastarch-associated coagulopathy and recent experimental data shows that pentastarch causes lesser hemostatic abnormality than hetastarch[16] and plasma protein fraction (5% PPF, which is albumin) may well be the most effective agent to increase cerebral blood flow and prevent infarction[15]. We discontinued the use of hetastarch in the neurosurgical intensive care unit and now use PPF exclusively.

CONCLUSION

The advantages of hetastarch use have been weighed against the disadvantages. The present study serves to point out one potentially serious disadvantage of this agent, especially, the coagulopathy. Such coagulopathy developed in direct proportion to molecular weight of starch and dosages.

This study suggests that daily coagulation screening shoud be monitored in all patients given hetastarch infusions, especially high-molecular-weight hetastarch. Additionally, an evaluation for potential intracranial hemorrhage must be followed in patients who receive hetastarch infusions especially there is a decline in mental status.

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