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Disseminated Intravascular Coagulation Due to Intravenous Administration of Hetastarch

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ABSTRACT: Disseminated intravascular coagulation occurred in a patient after intravenous administration of hetastarch. The onset was acute within 3 hours after exposure to the agent and the course was fulminating. The patient died in 48 hours. Clinical, hematologic, and pathologic features are presented and possible pathophysiologic mechanism is discussed. In view of this experience and documented effects of hetastarch on coagulation, the use of hetastarch should be avoided if the patient has a history of coagulation disorder, and the patient receiving the agent should be closely monitored with appropriate coagulation tests. **KEY INDEXING TERMS:** Disseminated Intravascular Coagulation; Hetastarch; Hetastarch-induced Coagulopathy. [Am J Med Sci 1990; 300(5):301-303.]

Hetastarch, an artificial colloid derived from a waxy starch composed almost entirely of amylopectin that has been used as an intravascular volume expander, reportedly causes both in vitro and in vivo coagulation abnormalities.¹⁻⁷ The described abnormalities include prolonged prothrombin and activated partial thromboplastin times, shortened thrombin and reptilase times, acquired von Willebrand syndrome, accelerated fibrinolysis, decreased level of factor VIII, and functional platelet defects. Nonetheless, clinically significant coagulopathy has been unusual and no death has been attributed to hetastarch-induced coagulopathy. We report a patient who died of acute fulminating disseminated intravascular coagulation after intravenous administration of hetastarch.

Case Report

A 49-year-old man (HK) was admitted for repair of a thrombosed left femoro-aortic bypass graft with chief complaint of intermittent claudication of the left leg. Six years previously he had had acute thrombotic thrombocytopenic purpura, which had developed 5 days

after left femoro-popliteal bypass surgery for arteriosclerotic peripheral vascular disease. The following classical features of the diagnosis were present: microangiopathic hemolytic anemia, neurologic abnormalities of motor aphasia and right hemiparesis, and acute thrombocytopenia with the platelet count of 7,000/ μ L. After 26 exchange plasmaphereses, he achieved complete remission. One and a half years later the patient again underwent aorto-bifemoral bypass graft for occlusive peripheral vascular disease. Four days after the surgery, thrombotic thrombocytopenic purpura relapsed. The patient again required a total of 35 exchange plasmaphereses during 12 weeks, and complete remission was achieved. During both bypass surgeries the patient received heparin. Both times, when the diagnosis of thrombotic thrombocytopenic purpura was made, coagulation studies, including prothrombin time, activated partial thromboplastin time, and fibrinogen level, were all within normal limit. On this admission, the patient was alert and coherent and was not in acute distress. Vital signs showed blood pressure of 126/80, pulse rate 80 beat/min, and respiratory rate 22 breath/min. No conjunctival pallor was present. There was no cervical, axillary, or inguinal adenopathy. The liver and spleen were not palpable. Abdominal burit was not present. No edema was present in the left lower extremity, popliteal pulse was weak, and dorsal pedis pulse was absent. The above-knee amputation of the right lower extremity was noted.

Hemogram showed hemoglobin of 14.5 g/dL, hematocrit 42.7%, white blood cell count 8,800/ μ L, and platelet count 256,000/ μ L. Prothrombin time, activated partial thromboplastin time, fibrinogen level, and Ivy bleeding time were normal (Table 1). The patient underwent the resection of thrombosed left femoro-aortic bypass graft, and a new graft was inserted. During the surgery, the patient had a general anesthesia using isoflurane (Forane: Anaquest Division, DOC, Inc.) and received cefotaxime sodium (Claforan: Hoechst-Roussel Pharmaceuticals Inc.) 1 gm intravenously, and hetastarch (Hespan: Du Pont Critical Care, Inc.) 1000 ml intravenously. No heparin was used due to previous experience of post-surgery thrombotic thrombocytopenic purpura because the role of heparin couldn't be excluded.

Three hours after the surgery, the patient began to have uncontrollable bleeding at laparotomy and multiple intravenous puncture sites. Coagulation study showed markedly prolonged prothrombin time to 27 seconds and activated partial thromboplastin time 135 seconds with the platelet count of 59,000/ μ L. Reticulocyte count was 2.7% and blood smears showed no fragmented red blood cells. Fibrinogen level was less than 15 mg/dL with marked reduction of factors V and VIII (Table 1), and both fibrin degradation product and soluble fibrin monomer were present. The diagnosis of acute disseminated intravascular coagulation was established. Although the patient was treated with multiple blood transfusions, including fresh frozen plasmas, platelet concentrates, cryoprecipitates, and packed red cells, he became comatose and hypotensive. Haptoglobin level was normal at 59 mg/dL (normal range: 45-120 mg/dL), and serial blood slide examination showed no significant number of schistocytes. Acute renal failure followed. Thirty-six hours after the surgery, coagulation profile improved with prothrombin time of 16.5 seconds, activated partial thromboplastin time 39 seconds, and fibrinogen level was normalized (Table 1). However, clinical condition did not improve and the patient expired 48 hours after the surgery.

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Table 1. Coagulation Profile

	Prior to Heta starch	3 Hours Post Heta starch	36 Hours Post Heta starch
Platelet count (/μL) (150,000–450,000)	256,000	59,000	128,000
Prothrombin time (sec) (11–14)	12	27	16.5
Activated partial thromboplastin time (sec) (18–30)	27	135	39
Ivy bleeding time (min) (2.5–9.5)	5	—	—
Fibrinogen level (mg/dL) (200–450)	300	<15	225
Fibrin degradation product	—	present	—
Soluble fibrin monomer	—	present	—
Factor V (%) (65–120)	—	6	—
Factor VIII (%) (65–120)	—	15	—

The values within parentheses denote normal range.

Autopsy examination showed generalized massive hemorrhage in bilateral pleural spaces and abdominal cavity. Acute ischemic gangrene was present in the entire left lower extremity. Microscopic examination showed numerous arteriolar fibrin thrombi in the spleen (Figure 1). The only significant finding in the kidneys was the renal tubular necrosis; no arteriolar fibrin thrombi or ischemic infarcts were present. In view of his past history of thrombotic thrombocytopenic purpura, multiple areas of each organ were examined for any histologic findings, such as subintimal deposition of fibrin-platelet complex, proliferation of endothelial cells or aneurysmal dilatation at the arterio-capillary junctions as some have described in cases of thrombotic thrombocytopenic purpura. However, none of these were observed. Morphologically, the findings of arteriolar fibrin and platelet thrombi in the thrombotic thrombocytopenic purpura are expected to be similar to that of disseminated intravascular coagulation. But more typical autopsy findings of cerebral arteriolar fibrin and platelet thrombi seen in thrombotic thrombocytopenic purpura were not present in this patient.

Discussion

Disseminated intravascular coagulation is a common clinical syndrome which occurs with a variety of medical conditions, including extensive tissue damage due to either external or internal forces or due to certain pathologies, alteration of intravascular environment, and introduction of infectious organisms. This syndrome has been also reported to occur after use of certain pharmaceutical products, such as heparin, chemotherapeutic drugs, charcoal hemoperfusion, glacial acetic acid ingestion, and contrast medium administration.^{8–12} In our patient, careful evaluation of all used drugs and circumstances, and known effects of heta starch on coagulation, strongly support heta starch-induced coagulopathy.

Unlike previously reported cases of mild to modest heta starch-induced coagulopathy,^{4,6} our patient devel-

oped acute fulminating disseminated intravascular coagulation. Decreased level of factor VIII and marked reduction of fibrinogen concentration with presence of soluble fibrin monomers, and fibrin degradation products are diagnostic of the syndrome. Although the patient also received other drugs during the surgery, these drugs are not known to cause any significant coagulation abnormalities and their dosages were too small to implicate in the coagulopathy. Although the pathologic finding was not clearly distinguishable from that of thrombotic thrombocytopenic purpura, clinical course of acute onset, following heta starch administration, and laboratory features of decreased levels of fibrinogen and factor VIII with lack of evidence of microangiopathic hemolytic anemia and normal haptoglobin level support the diagnosis of disseminated intravascular coagulation. However, the possibility of etiologic relationship between the incidents of thrombotic thrombocytopenic purpura and the development of disseminated intravascular coagulation due to heta starch cannot be excluded. It is conceivable that if the patient were prone to develop thrombotic thrombocytopenic purpura after the surgery due to extensive vascular abnormalities, he also had propensity for heta starch-induced disseminated intravascular coagulation.

The pathogenic mechanism for heta starch causing disseminated intravascular coagulation is not certain. Available data of heta starch effects on coagulation indicate that clinically significant coagulopathy has occurred after administration of more than 1 liter of heta starch. Nonetheless, not all heta starch-induced coagulation abnormalities, such as prolonged prothrombin time, prolonged activated partial thromboplastin time, decreased factor VIII (coagulant, von Willebrand antigen, von Willebrand activity), decreased level of fibrinogen, and shortening of thrombin

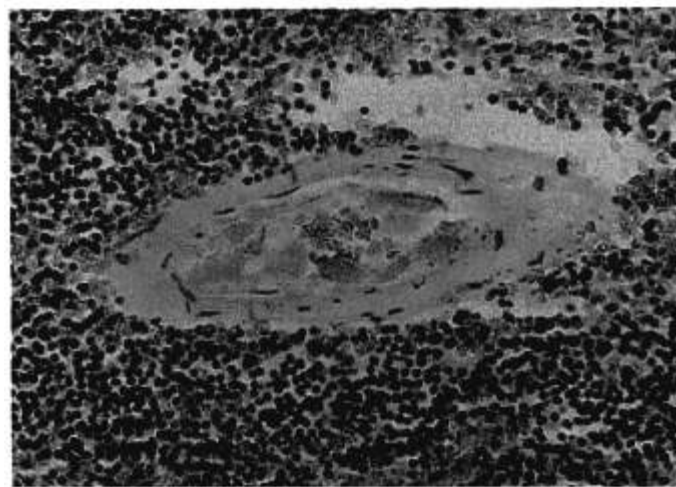


Figure 1. Microscopic pathology of the spleen section (X400). Note a typical fibrin thrombi formation in a blood vessel, a characteristic finding in disseminated intravascular coagulation.

time, could be explained by hemodilution alone.^{7,13} In view of our experience, direct effect of hetastarch on in vivo clotting process or on coagulation factors is postulated. It is possible that since the patient had defective endothelial function due to extensive vascular disease, defective clearing of procoagulant after surgery and activation of in vivo coagulation process by the introduction of a large volume of hetastarch could have triggered severe disseminated intravascular coagulation. However, it should be noted that unlike our patient, coagulation abnormalities that have been described with hetastarch have been more of a hemorrhagic nature, rather than suggesting a thrombotic tendency.

Based on our experience and known effects of hetastarch on coagulation, we recommended the use of hetastarch, if possible, to be avoided in patients with advanced vascular disease and history of previous coagulopathy. Further laboratory evaluation of hetastarch on coagulation is also warranted.

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