Thrombocytopenia and Intra-cerebral Complications Associated with Low-Molecular-Weight Heparin Treatment in Patients Undergoing Total Hip Replacement. A Report of Two Cases

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Thrombocytopenia and Intracerebral Complications Associated with Low-Molecular-Weight Heparin Treatment in Patients Undergoing Total Hip Replacement

A Report of Two Cases

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The low-molecular-weight heparins are a group of agents widely used in the prevention of deep-vein thrombosis and pulmonary embolism in orthopaedic patients, especially those undergoing total joint replacement of the lower extremity. They have been in clinical use for almost twenty years and have proved to be at least as effective as other means of thrombosis prevention[1]. The American College of Chest Physicians has recommended them for routine use in total hip replacement for the past ten years, as an alternative to warfarin and adjusted-dose unfractionated heparin[2,3]. Their main advantages are that they can be used without laboratory monitoring and they have a favorable therapeutic index (less risk of bleeding compared with unfractionated heparin for a given antithrombotic effect)[4]. Bleeding and thrombocytopenia are, however, documented complications of the use of low-molecular-weight heparin[5-9], but, to our knowledge, cerebral hemorrhages secondary to thrombocytopenia have not been reported in association with orthopaedic procedures. We report the cases of two patients who had thrombocytopenia and cerebral complications after routine treatment with low-molecular-weight heparin for thromboembolic prevention following total hip replacement. Our patients or their families were informed and consented that data concerning their cases would be submitted for publication.

Case Reports

Case 1. A forty-six-year-old woman who weighed 55 kg had osteoarthritis of the hip secondary to developmental dysplasia. She had no history of bleeding predisposition or other medical problems, and she had never received any form of heparin. An uncemented total hip replacement was performed through a posterior approach. Postoperatively, the patient received a transfusion of two units of packed red-blood cells. An antithrombotic regimen of 40 mg of enoxaparin once daily was started six hours after surgery and was to be continued for four weeks. There were no bleeding complications in the wound or any other site during hospitalization. The patient was discharged on the sixth postoperative day but returned to the hospital on the ninth day complaining of headache and motor disturbances in the left arm. Neurological examination revealed no pathological signs or reflexes, except for reduced strength in the left arm. The blood pressure was 180/90 mm Hg, and the platelet count was 126,000/mm^3; the platelet count had been 250,000 preoperatively and 180,000 postoperatively (normal values at our hospital are 150,000 to 300,000/mm^3). Computed tomography of the brain performed on that day showed no notable findings. She was admitted to the neurology department of our hospital. On the following day (postoperative day 10), the platelet count fell to 35,000 and paresis developed in the left arm. The low-molecular-weight heparin was discontinued, but tests for antibodies to heparin were not performed. A repeat computed tomography scan was performed on the eleventh postoperative day and revealed bilateral parasagittal hemorrhages (Fig. 1). She was admitted to the intensive care unit because of a rapid deterioration in her neurological status and died later the same day. An autopsy was performed and confirmed brain hemorrhage as the cause of death.

Case 2. A forty-seven-year-old woman who weighed 65 kg had osteoarthritis of the left hip secondary to developmental dysplasia, for which an osteotomy of the hip had been previously performed. She had no history of coagulopathy or other medical problems and had no known allergies; previous exposure to heparin was not reported. An uncemented total hip arthroplasty was performed through a lateral ap-

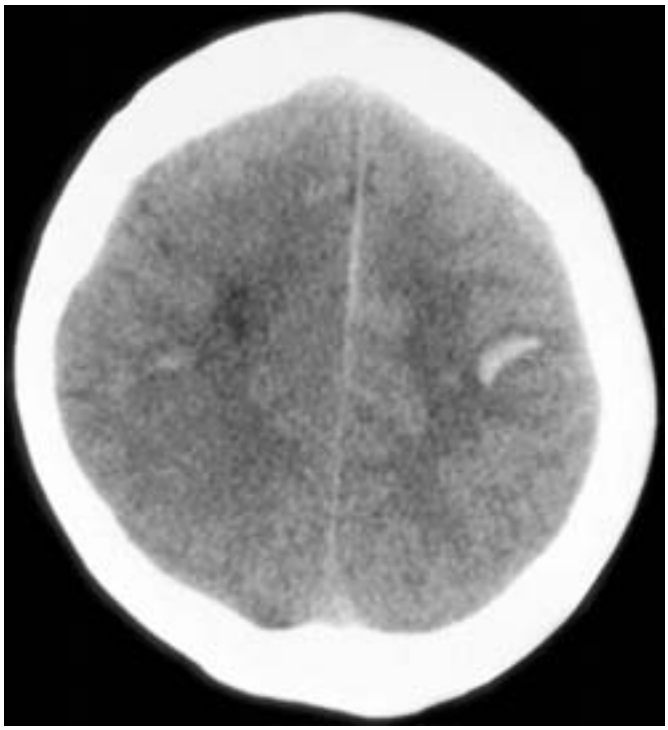

Fig. 1

Computed tomography scan of the brain of the first patient (Case 1) made on the eleventh postoperative day, showing parasagittal hemorrhages bilaterally, at the gray-white matter junction, in the high parietal region near the cortex.

proach, and she received two units of packed red-blood cells postoperatively. A regimen of 40 mg of enoxaparin once daily was started twenty-four hours after surgery and was to be continued for four weeks. The patient was discharged on the ninth day with no bleeding complications, but she returned to the hospital on the thirteenth postoperative day with a headache and sensory disorders of the left arm. The platelet count was 70,000. The low-molecular-weight heparin was discontinued, and the presence of antibodies to heparin was investigated. Magnetic resonance imaging showed a small focus of high intensity in the brain (Fig. 2). This was considered to be a thrombotic focus, and treatment with unfractionated heparin was started for thrombolysis. On the following days, the platelet count and hemoglobin decreased gradually (reaching a lowest point of 40,000 for the platelet count) and thrombolysis treatment was discontinued. The presence of antiheparin antibodies was confirmed two weeks after readmission. Paresis of the arms and legs developed progressively (Fig. 3), as a result of large cerebral hemorrhages. Decompression of the cerebral hematomas was performed twice. After forty-five days in the intensive care unit, the patient was discharged but was quadriparetic. She was readmitted one year later for a resection arthroplasty of the hip because of recurrent dislocations, discomfort, and consequent difficulties in nursing care. There had been no improvement in her neurological status at that time.

Discussion

Bleeding in association with the administration of a low-molecular-weight heparin in total joint replacement has been reported to occur in various anatomical sites, including the operative site and the epidural, intrahepatic, and retroperitoneal sites as well as in the gastrointestinal tract[6,7,10-12]. Low-molecular-weight heparin has also been implicated in abdominal wall hematomas in general surgery[8] and in intracranial hemorrhage in surgery for brain tumors[13]. This complication of the use of a low-molecular-weight heparin, however, has not been previously reported in orthopaedic patients, to our knowledge.

Low-molecular-weight heparin is associated with two forms of thrombocytopenia: type-I and type-II heparin-induced (or heparin-associated) thrombocytopenia. Type-I heparin-induced thrombocytopenia is associated with mild thrombocytopenia (100,000 to 130,000 platelets per microliter). It typically occurs one to four days after the initiation of heparin therapy, and screening tests for heparin-induced thrombocytopenia antibody activity are negative[9,14]. We are

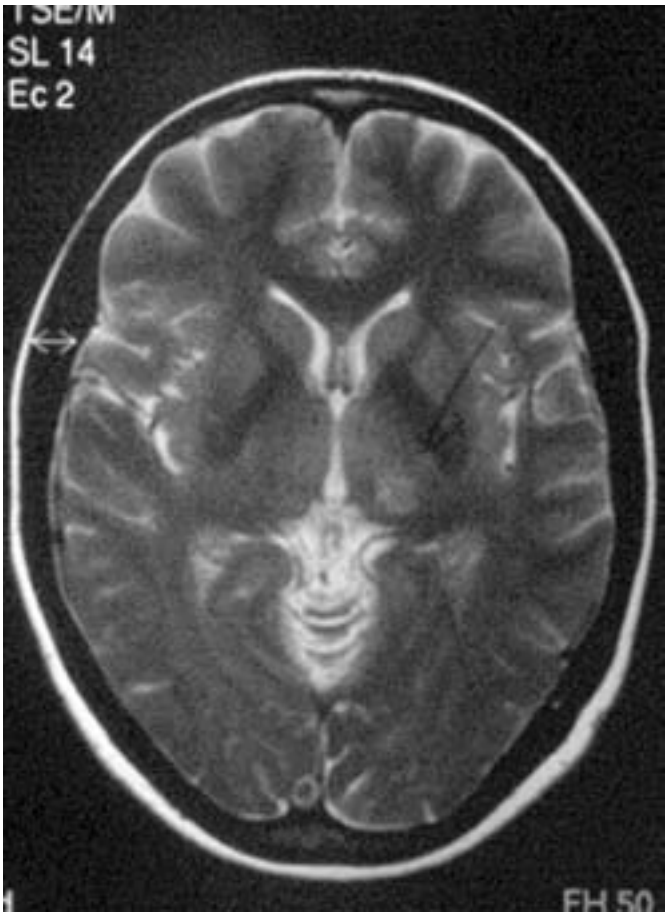

Fig. 2

T2-weighted magnetic resonance image of the brain of the second patient (Case 2) made on admission (thirteenth postoperative day), showing a small area of high signal intensity involving the left thalamus. This was interpreted as a thrombosis.

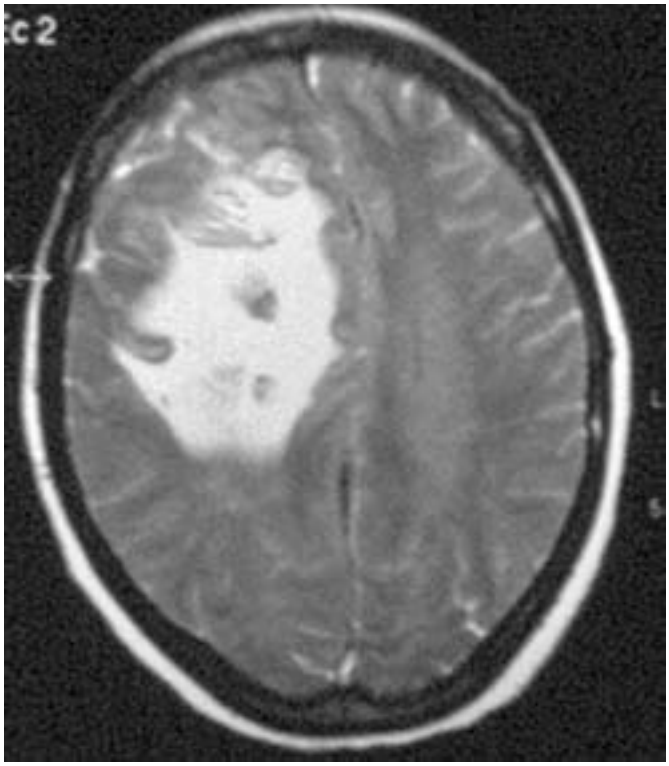

Fig. 3

T2-weighted magnetic resonance image of the brain of the second patient (Case 2), acquired twenty-two days postoperatively, showing a large hematoma in the right frontoparietal region. Large hematomas developed bilaterally.

aware of no data suggesting that patients with type-I heparin-induced thrombocytopenia have an increased risk of thrombosis[15] and, in fact, platelet counts may increase during subsequent heparin therapy[9]. Type-I heparin-induced thrombocytopenia is attributed to a direct, reversible, proaggregatory effect of platelets[16]. Patients do not require specific treatment[17].

Type-II heparin-induced thrombocytopenia appears typically five or more days after the start of heparin therapy[18,19]. It may, however, develop rapidly (mean, 10.5 hours) in patients who have received heparin within the previous 100 days[20], as previous exposure to heparin is a risk factor for type-II heparin-induced thrombocytopenia[18,20]. Conversely, a delayed-onset heparin-induced thrombocytopenia and thrombosis, developing after heparin discontinuation, has also been described[19]. The syndrome has an onset that is independent of heparin type, dosage, or route of administration[21], and its diagnosis requires both thrombocytopenia and the presence of antibodies to heparin[14]. A modified definition of type-II heparin-induced thrombocytopenia, in reference particularly to postoperative orthopaedic patients, requires a decrease of 50% in the platelet count from the postoperative peak[22]. After discontinuation of heparin, the platelet count increases to normal levels usually within five to seven days[17]. A prolonged recovery of the platelet count to normal levels should thus prompt investigation of other causes of thrombocytopenia[14].

Clinical scoring systems have been proposed to evaluate the probability of the syndrome. They are based on the severity of the thrombocytopenia, recovery following heparin withdrawal, the onset of thrombotic complications, and the exclusion of other causes of thrombocytopenia[23,24]. It is estimated that type-II heparin-induced thrombocytopenia develops in 1% to 5% of patients who receive heparin[25], with the occurrence varying depending on the clinical status of the patient (with the greatest risk, in descending order, after surgery, medical treatment, and pregnancy), the type of heparin preparation (bovine unfractionated heparin is associated with a greater risk than porcine unfractionated heparin, which carries a greater risk than low-molecular-weight heparin), the route of administration (intravenous administration is associated with a greater risk than subcutaneous injection), and the definition of thrombocytopenia used[17,26]. However, the proportion of patients who have antibodies to heparin but do not have thrombocytopenia develop is larger.

Arterial and venous thromboses are the major clinical complications, as they cause ischemia to the limbs, with the potential for limb loss, and to the vital organs, with the potential for organ failure or death. They occur in up to 30% of patients with type-II heparin-induced thrombocytopenia[15], which is then commonly referred to as the "white clot syndrome." Common locations for arterial thromboses are the lower limb, the brain (thrombotic stroke), and the heart (myocardial infarction), while the most common complications for the venous system are deep venous thrombosis and pulmonary embolism. Thromboses may be noted in unusual locations (the mesenteric or renal artery, vascular graft occlusion of an artery, adrenal hemorrhagic infarction, or cerebral vein thrombosis), and disseminated intravascular coagulation can occur[14,27]. Other complications, such as skin lesions at injection sites, may also occur[27]. Rates of thrombotic events of 5% to 10% in the first one to two days have been observed, suggesting that many of these patients had subclinical thromboses at the time of diagnosis[28]. The rate of mortality has been reported to be 15% (eight) in a series of fifty-three patients with laboratory-confirmed type-II heparin-induced thrombocytopenia[21] (or 19% if only the patients with heparin-induced thrombocytopenia complicated with thrombosis were counted), two deaths in a series of twelve patients with delayed-onset heparin-induced thrombocytopenia and thrombosis, and almost 30% (twenty-five) in an earlier series of eighty-five patients with heparin-induced thrombocytopenia complicated with thrombosis[17].

The mechanism for thrombocytopenia in type-II heparin-induced thrombocytopenia is antibody-induced platelet activation, leading to platelet aggregation and a decrease in the platelet count. The principal antigen is a complex of heparin and platelet factor 4, and the antibodies can be detected by serological assays[29,30]. They form more frequently with the use of unfractionated heparin than with low-molecular-weight heparin. In a randomized study of 209 hospitalized patients receiving treatment with heparin, the prevalence of antibodies to heparin was 17% in those treated with unfractionated heparin and 8% in those treated with low-molecular-weight heparin[31]. In another

randomized, double-blind study of 665 patients who received heparin as prophylaxis after hip surgery, antibodies to heparin developed in 7.8% of the patients treated with unfractionated heparin compared with 2.2% of the patients treated with low-molecular-weight heparin[9].

In the first patient (Case 1) in this report, thrombocytopenia developed on the ninth postoperative day and led to brain hemorrhage. The presence of antibodies to heparin was not investigated, as heparin-induced thrombocytopenia was not included in our differential diagnosis; however, the clinical course of the syndrome was highly suggestive of type-II heparin-induced thrombocytopenia as there were no other obvious reasons for thrombocytopenia[9,22,26]. In the second patient (Case 2), type-II heparin-induced thrombocytopenia was established as the cause of the initial thrombotic incident. The administration of unfractionated heparin led to severe brain hemorrhages as there is cross-reactivity between the two heparinoids[5,9].

The current recommendations of the American College of Chest Physicians for prevention therapy with low-molecular-weight heparin in patients undergoing total hip replacement are to initiate therapy twelve hours before surgery or twelve to twenty-four hours after surgery at the usual high-risk dose, or four to six hours after surgery at half the usual high-risk dose and then increase to the usual high-risk dose the following day[3]. The recommendations for the prevention of type-II heparin-induced thrombocytopenia in postoperative patients receiving a prophylactic dose of low-molecular-weight heparin suggest monitoring of the platelet count every two or three days from day 4 to day 14 (or until heparin is stopped, whichever occurs first), when practical[26]. Screening for antibodies is not recommended. For patients with strongly suspected or confirmed heparin-induced thrombocytopenia, whether complicated by thrombosis or not, the immediate cessation of the heparinoid is mandated and the introduction of an alternative anticoagulation therapy, such as a direct thrombin inhibitor or danaparoid, is recommended[26]. Routine ultrasonography of the lower-limb veins is also recommended to identify deep-vein thrombosis in these patients, even if there is no clinical evidence to suggest thrombosis.

We believe that type-II heparin-induced thrombocytopenia is a syndrome that occurs in orthopaedic patients more frequently than is currently believed. We think that it remains underdiagnosed, reflecting a lack of awareness about the condition among orthopaedic surgeons. Its diagnosis requires clinical alertness, laboratory confirmation, and prompt treatment in order to prevent disastrous complications such as those seen in the two patients in the present report. ■

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