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Use of Low Molecular Weight Heparin in Patients with Heparin-induced Thrombocytopenia Undergoing Carotid Endarterectomy

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CAROTID endarterectomy (CEA) is a common vascular surgical procedure for patients with severe carotid stenosis.[1] Heparin therapy, widely used during CEA, is not without risks and sometimes may be associated with a decrease in platelet count or thrombosis, a condition called heparin-induced thrombocytopenia (HIT).[2] This condition is believed to be immunologically mediated and involves the formation of heparin-dependent platelet antibodies (HDPA)[3] that recognize a complex of heparin and platelet factor 4. The estimated prevalence of HDPA in patients receiving heparin is 7.8%.[4]

In patients with HIT who are candidates for CEA, a substitute for unfractionated heparin (UFH) should be used. Low molecular weight heparins (LMWHs) have a favorably high anti-factor Xa-to-anti-factor IIa activity ratio, which implies an improved antithrombotic potential with fewer bleeding side effects. The antithrombotic intravenous dose of LMWH (enoxapirin)[5] during CEA has not been established. We report the intraoperative use (dose and monitoring) of enoxaparin (Lovenox, Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA) in three patients with documented HIT and HDPA who underwent four CEAs.

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Key words: Complications: heparin-dependent platelet antibody; heparin-induced thrombocytopenia. Drugs: low-molecular-weight heparin (enoxaparin); unfractionated heparin. Drug effect: anticoagulation. Surgery: carotid endarterectomy.

Case Reports

Three patients who were 73, 76, and 78 yr old and had 80 to 99% stenosis of the internal carotid artery underwent elective CEA under general anesthesia. All had a history of severe coronary artery and peripheral vascular diseases and underwent multiple vascular reconstructions with repeated exposure to UFH, complicated by either thrombosis or thrombocytopenia. All patients had positive HDPA to UFH as documented by the platelet aggregation method.[6,7] Results of the patients' preoperative coagulation profiles were within normal limits (table 1), and they had no history of bleeding tendencies immediately before these operations. Tests for HDPA to both UFH and LMWH were repeated before each CEA. In all cases, the test results were negative for LMWH. In two patients, repeated tests for HDPA to UFH became negative 4 (patient 1) and 12 months (patient 3) after the initial testing.

Enoxaparin, which was used as an anticoagulant in all cases, was given intravenously 5 min before carotid artery clamping. In one patient with symptomatic carotid disease (patient 3), a continuous intravenous infusion of 2 $mg \cdot kg^{-1} \cdot day^{-1}$ enoxaparin was administered before operation. This treatment was continued until carotid artery cross-clamping, when an additional intravenous bolus of 45 mg enoxaparin was given.

The antithrombotic effect of enoxaparin was monitored with anti-factor-Xa activity assays (Dupont ACA, Wilmington, DE) before surgery, 5 min after injection of enoxaparin, after protamine sulfate administration (when used), and on the first postoperative day. At these times, we also obtained prothrombin time, activated partial thromboplastin time, a platelet count, fibrinogen concentration, and activated clotting time. Table 1 lists all antithrombotic therapy and coagulation parameters. The operative and postoperative courses were uneventful and the patients had no thrombocytopenia, thrombosis, or bleeding. No hematoma formation was observed, and the average amount of neck drainage in the four operations was 25 ml, which is comparable to other CEAs.

Discussion

Thrombotic complications after heparin therapy may involve different systems and are associated with significant morbidity and death.[8-10] Unexplained recurrent thrombocytopenia, thrombotic events, or both, in patients receiving UFH should raise the suspicion for HIT, and testing for HDPA is strongly indicated in these

Table 1. Coagulation Parameters and Enoxaparin Therapy in Three Patients with Heparin-induced thrombocytopenia during four Carotid Endarterectomies

Operation #		Pt #1 Op. #1				Pt #1 Op. #2				Pt #2 Op. #3			Pt #3 Op. # 4		
			Intraoperative				Intraoperative								
Coagulation Test	Normal Range	Pre-op	ENO 1.4 $mg \cdot kg^{-1}$	PS 50 mg	POD-1	Pre-op	Eno 1.4 $mg \cdot kg^{-1}$	PS 50 mg	POD-1	Pre-op (Eno-Inf. 2 $mg \cdot kg^{-1} \cdot day^{-1}$)	Intra-op (Eno-0.6 $mg \cdot kg^{-1}$)	POD-1 (Eno Inf. 2 $mg \cdot kg^{-1} \cdot day^{-1}$)	Pre-op	Intra-op (Eno 0.8 $mg^{-1} \cdot kg^{-1}$)	POD-1
Anti-Xa $IU \cdot ml^{-1}$	—	0.14	2.4	0.91	—	—	1.95	0.45	0.04	0.85	1.35	1.22	0.02	1.11	1.02
PT sec	8.8–13.3	12.3	—	12.4	11.5	11.1	12.2	11.7	10.7	10.4	12.7	11.7	11.3	11	11.4
INR	0.81–1.21	1.12	—	1.13	1.04	1	1.11	1.15	—	1.49	1.15	1.06	1.02	1	1.04
PTT sec	21.5–32.5	28.2	—	33.3	26.9	20.5	24.1	33.2	25.6	—	43	—	28.4	23.9	38.6
PLT $10^3 \cdot mm^{-3}$	150–400	225	—	178	231	231	196	171	171	84	85	137	203	202	200
FIB $mg \cdot dl^{-1}$	200–400	426	—	380	439	281	275	281	275	—	327	—	348	340	348
ACT sec	80–170	170	226	134	—	165	129	159	—	—	136	—	142	204	—

ACT = activated clotting time, performed using a Hemochron coagulation analyzers; Anti-Xa = anti factor Xa activity performed by a chromogenic assay (Dupont ACA); Eno = enoxaparin; FIB = fibrinogen, performed by the Clauss technique on the MLA Electra 1600; INF = infusion; INR = international normalized ratio; PLT = platelets count; POD = postoperative-day; PS = protamine sulfate; Pt = patient; PT = prothrombin time; PTT = partial thromboplastin time.

PT, INR, and PTT were all performed using Innovin and Actin FSL on an MLA Electra 1600.

patients. All of our patients had histories suggestive of HIT and all had documented HDPA by the platelet aggregation method.[6,7]

Heparin-dependent platelet antibodies can be detected by several methods. A routinely used platelet aggregation method appears to be highly specific but has low sensitivity.[6,7] The ^{14}C-labeled serotonin-release assay, presumably the standard for HDPA testing, has high specificity and sensitivity[4] but involves the use of radioactive material and therefore is unavailable in many clinical laboratories. A recently developed platelet factor 4/heparin enzyme-linked immunosorbent assay produces results that correlate closely with those of the serotonin-release assay.[11] Two of our patients (patients 1 and 3) had negative antibody test before CEA after previously being diagnosed with positive HDPA. It was suggested that after a period of 3 to 6 months HDPA may either disappear[12] or become undetectable using ^{14}C-serotonin release. At the same time, platelet aggregation tests are less sensitive for detecting HDPA during even acute events[6,7] and may fail to detect low antibody titer present several months after the initial diagnosis. In this case, this "test insensitivity" may create a risk for causing HIT after reexposure to UFH. Until all these issues are resolved, we believe that patients with clear histories of HIT and documentation of HDPA in the past should be considered positive for heparin antibodies.

Patients with documented HIT and HDPA who undergo revascularization procedures require a substitute for regular heparin. Low molecular weight heparins have a higher antithrombotic-to-anticoagulation therapeutic ratio,[3,5] a lower rate of bleeding complications,[13,14] and probably a lower risk for HIT.[4] Recently several authors reported the use of LMWH in patients with HIT undergoing cardiopulmonary bypass[15] and in those having lower extremity arterial reconstruction.[16]

Although LMWHs cause only an attenuated inhibition of factor IIa (thrombin) by anti-thrombin III, their ability to inhibit factor Xa is maintained.[13] The standard coagulation tests, such as activated partial thromboplastin time and activated clotting time, are relatively insensitive and therefore inadequate for monitoring the therapeutic effect of enoxaparin. To monitor the effect of LMWHs, some authors suggest measuring anti-factor Xa activity in plasma.[17]

The antithrombotic intravenous dose of enoxaparin has not been established and is mainly a matter of individual experience. Anti-Xa activities during use of 4.5 mg/kg enoxaparin for cardiopulmonary bypass

have ranged from 1 to 3 IU/ml.[15] The intensity of anticoagulation needed for CEA is not well known, but the standard practice is to administer 7,500 to 10,000 units of UFH intravenously. Because this is approximately one third of the heparin dose used in cardiac surgery, we initially chose to use 1.4 mg/kg in our first two CEAs. Nevertheless, we believe now that even a smaller dose can be used safely during CEA. We found adequate anti-Xa activity and clinical safety when only 0.8 mg/kg of intravenous enoxaparin were used. A similar dose was used by Samama and associates[16] in patients undergoing arterial reconstructive surgery. An even smaller dose (0.6 mg/kg) of intravenous enoxaparin was given to one patient who was receiving a continuous infusion of 2 $mg \cdot kg^{-1} \cdot day^{-1}$ enoxaparin before CEA.

Reversing the heparin effect in CEA is controversial and was performed in the first two operations only. Furthermore, reversal of enoxaparin by protamine sulfate is unpredictable.[18] The anti-Xa activity in these two patients who received 50 mg protamine sulfate decreased from 2.4 to 0.91 IU/ml and from 1.95 to 0.45 IU/ml, respectively.

Potential drawbacks of LMWHs are their cost, the inability to measure anti-Xa activity in many hospitals, and the relatively high incidence of cross-reactivity with HDPA to UFH in patients with HIT. Therefore, use of LMWHs as anticoagulants in patients with HIT should be considered only if HDPAs are negative for LMWH. Cross-reactivity between LMWH and UFH *in vitro* is well documented, but its incidence *in vivo* and its clinical implications are controversial. Cross-reactivity as great as 25.5 to 94% was reported.[19–21] The wide variability in reported cross-reactivity in the literature is not clear; at the Cleveland Clinic, the cross-reactivity rate is 27% (unpublished data). Several factors might account for the low incidence reported at our institution. First, our physicians' threshold for requesting the test is low, which is reflected in the more than 2,000 HDPA tests performed each year in our laboratory. Second, when the quoted rate of cross-reactivity in our institution is calculated, we include all positive HDPA studies for UFH from patients who were also tested for LMWH regardless of the clinical diagnosis of HIT, whereas most studies in the literature have included sera from patients with definite clinical criteria for HIT. Third, Vun and colleagues[22] recently reported that the concentration of LMWH used in the platelet aggregation assay may influence the rate of cross-reactivity to UFH. In the case of enoxaparin, when a concentration of 0.1 U/ml was used, the percentage of positive test results was only 26%, which increased to 83% when 0.5 U/ml was added to the system. Although we were using concentrations of enoxapirin in the range that should give a maximal response according to these authors,[22] we have not performed detailed dose-response studies in our institution to address that question.

We described the uncomplicated use of enoxaparin in three patients with HIT and HDPA during four CEAs. Patients in whom thrombocytopenia or thrombosis develop while receiving UFH should be tested for possible HDPAs. Patients with documented HIT and HDPA in whom the use of LMWH is contemplated must also be tested for HDPA to LMWH. Enoxaparin given in an intravenous dose of 0.8 to 1.4 mg/kg provided sufficient anticoagulation during CEA. Further studies are indicated to establish the safety and therapeutic range of enoxaparin during CEA.

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