Paraplegia **31** (1993) 653–659

Persistent hypercoagulation associated with heterotopic ossification in patients with spinal cord injury long after injury has occurred

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Three patients are presented with traumatic spinal cord injury (SCI) complicated by acute heterotopic ossification (HO), and concurrent deep vein thrombosis 15 months, 18 months and 22 years after SCI, accompanied by persistent hypercoagulation. The diagnosis of HO preceded deep vein thrombosis in all three patients. All were treated with etidronate disodium and therapeutic heparin followed by oral anticoagulation. As these patients were not acutely injured, the questions arose as to what predisposed them to deep vein thrombosis and when was the appropriate time to discontinue anticoagulation.

Over a course of 3 years following deep vein thrombosis, these patients were monitored for evidence of hypercoagulation by D-dimer assay, plasma fibrinogen estimation, and rate of whole blood clotting by Sonoclot® coagulation analyzer. The activity of acute HO was assessed by three-phase bone scan. A steady state of hypercoagulation, reflected by an increase in all three parameters, ran parallel to the extent of acute HO for the entire observation period. Moreover, hypercoagulation was persistently greater during increased acute HO activity even when the warfarin-induced prothrombin time ratio was 1.2–1.5. In addition, as acute heterotopic ossification activity decreased, the test values returned to near normal during warfarin therapy. However, when warfarin was discontinued, the clotting rate and D-dimer levels were found to again increase. Oral anticoagulation was therefore resumed for these patients and will be continued as long as laboratory evidence of hypercoagulation is present.

The usual practice following an episode of thromboembolism is to discontinue anticoagulation after a fixed period of 3 months to 1 year. However in patients with SCI who have acute HO, the hypercoagulation may be long term. Laboratory monitoring can assist in identifying those patients who may require a prolonged regimen of anticoagulation. The possible role of acute heterotopic ossification in the development of clotting abnormalities is discussed.

Keywords: hypercoagulation; spinal cord injury; heterotopic ossification.

Introduction

Patients in the acute phase following traumatic spinal cord injury are known to be hypercoagulable and are at high risk for the development of thromboembolism.[1] During the acute phase of SCI, preventive measures include anticoagulation by either prophylactic subcutaneous heparin or by oral anticoagulation, use of intermittent pneumatic compression hose, and functional electric stimulation. The duration of prophylaxis is uncertain and varies from 42 to 180 days, but is generally up to 120 days.[2] If an episode of deep vein thrombosis (DVT) occurs, it is initially treated with heparin and is then followed by warfarin for 3–12 months. There are no clear-cut guidelines on the duration of post DVT prophylaxis. Recommendations for treating the first episode vary from 1 to 12 months and have been based mostly on data from patients who have not sustained SCI.[3,4] Generally, the anticoagulation is maintained at a prothrombin time (PT) ratio of 1.3–1.5 for 3

months. The prophylaxis is then discontinued on the assumption that by this time the patient has become normal. Prolonged or lifetime anticoagulation is considered when there is recurrence, or when ongoing risk factors are present.

Little information is available regarding thromboembolism and the risk factors involved in patients with SCI following the acute phase of SCI. This paper presents three cases of concurrent DVT and acute HO occurring beyond the acute phase. As these patients were not acutely injured, the questions arose as to what predisposed them to deep vein thrombosis and when the anticoagulation should be discontinued. An investigation was begun by monitoring the coagulation status of these patients over a period of 3 years by the following three parameters for the assessment of hypercoagulation: (1) D-dimer levels—these are fibrin-specific end products of blood coagulation and subsequent fibrinolysis which serve as a marker for intravascular clotting;[5,6] (2) the rate of clotting of whole blood by Sonoclot® coagulation analyzer: the increased clotting rate is an index of hypercoagulation;[7,8] and (3) plasma fibrinogen concentration: increased fibrinogen is a risk factor for the development of thromboembolism.[9,10]

A steady but variable state of secondary hypercoagulation was found to persist beyond the first year following SCI, running parallel to the activity of acute HO. The presence of acute HO appeared to have predisposed these patients to the hypercoagulable state. The laboratory monitoring provided a means to observe the progress of chronic intravascular clotting and thereby identify the possible risk for thromboembolism which could occur with the ongoing state of hypercoagulation.[11,12] Hence, it was thereby possible to determine the dose and duration of prophylactic anticoagulation for the patients.

Material and methods

Three patients with spinal cord injury and acute HO who developed concurrent lower extremity DVT have been treated for the past 3 years at the Spinal Cord Injury Center, VA Medical Center, Palo Alto, California. The clinical data on these patients are shown in Table I. Patient 3 has been reported on in an earlier publication.[13]

The diagnosis and follow up of the HO activity was achieved by xray and three-phase radionuclide bone scan studies. The latter has the advantage of identifying the lesion in the early phase before the bone matures.[14] New lesions in the vicinity of old bone formation which may not be differentiated by xrays can also be visualized. All patients were treated with etidronate disodium for acute HO. To correlate acute HO activity with the laboratory findings the bone scan observations on acute HO were graded as follows:

Grade 0 = No acute HO.
Grade 1 = One large or two small foci of acute HO with radioactive uptake less than bone.
Grade 2 = One larger focus or one to two small foci of acute HO with radioactive uptake equal to bone.
Grade 3 = One large focus or two to three small foci of acute HO with radioactive uptake greater than bone.
Grade 4 = One vary large focus or three or more small foci of acute HO with radioactive uptake greater than bone.

Prophylaxis for DVT was given in two forms: (1) in the acute phase of SCI prior to DVT, an adjusted dose of subcutaneous heparin was prescribed to keep the activated partial thromboplastin time (APTT) at the upper level of the normal and (2) following DVT, all patients were maintained on prophylactic warfarin anticoagulation.

Deep vein thrombosis was diagnosed by contrast venography and/or radionuclide venography. Follow up study was done by radionuclide venography as a part of the three-phase bone scan. Acute DVT in patients 1 and 2 was treated with therapeutic intravenous heparin to raise the activated partial thromboplastin time (APTT) to 2–2.5 times the normal. In patients 3 venous access was difficult; therefore, therapeutic heparin was given subcutaneously in divided doses at 8-hourly intervals. Heparin and

warfarin administration was overlapped for 3–5 days until the PT ratio was in the desired range. The warfarin dose was then monitored to maintain the PT ratio in the range of 1.2–1.5 times the normal mean. The varied lifestyle of the patients was considered in planning each specific anticoagulation regimen.

Laboratory tests included complete blood count, erythrocyte sedimentation rate (ESR), APTT (Actin FS, American Dade, Miami Florida), PT, (Dade – Thromboplastin-C, normal range 11–12.5 s), and D-dimer levels immunoassay by latex particle agglutination (Diagnostica, Stago, France; normal < 250 μg/ml). Since rheumatoid factor can cause a false positive increase in the level of D-dimers all patients were screened for rheumatoid factor. The rate of clotting of whole blood was done by Sonoclot® coagulation analyzer (Sienco, Colorado, USA). The normal rate is expressed as 0%. Fibrinogen concentrations were estimated by the Klaus method using Fibrometer® and Data-Fi® Thrombin reagent (Dade; normal range 170–340 mg/dl). All blood samples were collected fasting before 10 am by the two-syringe technique. All patients were screened for antithrombin III, protein C and protein S, anticardiolipin antibodies and lupus anticoagulant. Alkaline phosphatase (normal range 30–115 units/l) was done as part of the chemistry profile by Technicon®. In a control group of 15 age matched male patients who had SCI for more than a year and had no complication which could cause an elevation, the D-dimer value and fibrinogen level were within normal range.

Initially all patients were monitored for hypercoagulation by D-dimer levels and fibrinogen estimation. During the first year following DVT, the D-dimer levels and fibrinogen were found to be persistently elevated. At this time the test for whole blood clotting rate became available and was added as a third parameter to monitor hypercoagulation.

Results

Clinical data on the three patients are provided in Table I. All patients were male. They were 44, 46, and 55 years old. In all cases, the spinal cord injury was the result of a motor vehicle accident (MVA). Patient 1 is paraplegic while the other two are quadriplegic. In all patients the diagnosis of acute HO preceded the occurrence of DVT. Patients 2 and 3 developed HO soon after SCI. Subsequently fresh HO lesions continued to occur and were still active when the DVT was diagnosed during the second year following SCI. In patient 1 DVT occurred 22 years after SCI. HO was first diagnosed 12 years after SCI but multiple fresh foci of HO had continued to occur during the next 10 years and were also present at the time of DVT.

Patient 1 had no residual venous obstruction. In patient 2 the DVT had caused a moderate postthrombosis syndrome. In patient 3, extensive DVT involving the femoral, popliteal and calf veins resulted in severe postthrombosis syndrome.

The values for antithrombin III, protein C, and protein S were normal in all patients. All were negative for lupus anticoagulant, anticardiolipin antibodies and rheumatoid factor. The effect of the graded extent of acute HO and the type and degree of anticoagulation on the levels of D-dimers, rate of whole blood clotting and plasma fibrinogen before, during and after the DVT are shown in Table II.

All patients initially presented with a swollen, painful and warm proximal left lower extremity and were diagnosed to have acute HO with an activity grading of 3–4. D-dimer levels were elevated without evidence of DVT. The patients were given prophylactic subcutaneous heparin, the dose being adjusted to maintain the APTT at the upper limit of normal range. The D-dimer levels remained high during heparin prophylaxis. Then an episode of DVT occurred and at the time of the diagnosis of DVT but before therapeutic intravenous heparin, the D-dimer and fibrinogen levels became markedly elevated and were the highest seen in this study. The bone scan at this time showed that all patients had acute HO of grade 4.

Over a period of 1–6 months following DVT, the acute HO activity remained from 3 to 4, and the D-dimer as well as fibrinogen values remained moderately elevated to

Table I Clinical data in three patients with spinal cord injury complicated by acute heterotopic ossification and concurrent deep vein thrombosis, more than 6 months after spinal cord injury

Clinical data	Patient 1	Patient 2	Patient 3
Age and sex	44 years, male	46 years, male	55 years, male
Life style	Athletic, nonsmoker	Sedentary, smoker	Sedentary, nonsmoker
Date and cause of injury	1967, motor vehicle accident	1988, motor vehicle accident	1988, motor vehicle accident
Level of injury	T4, uncomplicated	C6, multiple injuries	C5, uncomplicated
First HO	12 years postinjury	2 months postinjury	3 months postinjury
First DVT, concurrent with acute HO	22 years postinjury	15 months postinjury	18 months postinjury
Distribution of acute HO	Left hip, thigh, knee, shoulder Right hip, thigh, shoulder	Left hip, thigh, knee Right hip, knee	Left hip, thigh, knee, elbow, wrist Right lumbar spine, hip, wrist
Location of DVT	Left lower extremity, proximal	Left lower extremity, proximal	Left lower extremity, proximal and distal
Postthrombosis syndrome	No	Moderate	Severe

Table II Changes in the D-dimer levels, rate of clotting of whole blood, and plasma fibrinogen concentration in relation to the grade of activity of acute heterotopic ossification and degree and duration of anticoagulation. The values represent the range observed in the three patients

Clinical status		Acute HO activity Grade 0–4	D-dimers μg/ml ($n < 250$)	Rate of WB clotting % change from normal Patient 1, 2 & 3	Fibrinogen mg/dl (n 170–340)
1	Pre DVT, adjusted subcutaneous heparin	3–4	500–2000	—	—
2	At diagnosis of DVT, no anticoagulation	4	1000–4000	—	500–900
3	Immediate post DVT phase, therapeutic heparin, then on warfarin, PT ratio 1.3–1.5	4	500–4000	—	400–700
4	Approximately 6 months post DVT, on warfarin, PT ratio 1.3–1.5	3–4	< 250–500	—	370–650
5a	Approximately 1–2 years post DVT, on warfarin, PT ratio 1.3–1.5	2–3	< 250–500	+100, +100, +200	350–500
5b	Attempt to discontinue or lower the dose in patients 1 & 2	2–3	250–1000	+100, +100	350–600
6	Approximately 2.5 years post DVT on warfarin PT ratio 1.2–1.5	1–2	< 250	+50, +20, −25	350–450

1000–2000 μg/ml and 400–700 mg/dl respectively. These levels persisted despite warfarin anticoagulation with a PT ratio of 1.3–1.5.

Approximately 1–2 years following DVT, the acute HO activity had decreased to grade 2–3 and a parallel decrease was seen in fibrinogen values (370–650 mg/dl) and D-dimer levels ($<$ 250–500 μg/ml). Since the blood levels of D-dimer and fibrinogen had remained high for such a prolonged period, the hypercoagulable state appeared to persist. To further confirm this observation, the test for estimating the rate of clotting of whole blood was added as a third parameter of hypercoagulation. Despite warfarin anticoagulation, all patients showed an increase in the rate of whole blood clotting, the increase being 100% above normal in patients 1 and 2 and 200% above normal in patient 3. During this period, an attempt was made in patients 1 and 2 to either discontinue or lower the dose of warfarin to a minimal level. This reduction or discontinuation of anticoagulation resulted in an increase of D-dimers to 250–1000 μg/ml and the clotting rate remained elevated by 100%; therefore, anticoagulation was resumed in these two patients. Discontinuation of warfarin was not attempted in patient 3 because of his severe postthrombosis syndrome and a sedentary life style.

Approximately $2\frac{1}{2}$ years following DVT, while still on warfarin anticoagulation, the acute HO activity had decreased to grade 1 and D-dimer levels were normalized ($<$ 250 μg/ml) in all three patients. Fibrinogen levels had decreased to the upper limit of the normal range in patients 1 and 2 and slightly above normal in patient 3. The whole blood clotting rate was only mildly elevated to 50% and 20% above normal in patients 1 and 2 respectively, while in patient 3, it decreased to 20% below normal.

The erythrocyte sedimentation rate was invariably increased during increased acute HO activity. The level of alkaline phosphatase ranged between 90–124, 90–164 and 170–726 units/l in patients 1, 2, and 3 respectively and was a poor indicator of the acute HO activity.

No subsequent episode of DVT and no hemorrhagic complications have occurred during the observation period.

Discussion

The results indicate that in these patients a secondary hypercoagulable state was present running parallel to the extent of acute HO activity. During the 3 year study, higher acute HO activity correlated with increased D-dimer levels, increased rate of whole blood clotting, and elevated plasma fibrinogen while the patients were receiving warfarin anticoagulation. As the acute HO activity decreased, the three coagulation parameters returned to near normal values while the degree of anticoagulation remained the same. During attempts to discontinue the anticoagulation, the D-dimer levels and the whole blood clotting rate increased again. Acute HO seems to have predisposed these patients to developing DVT since other factors such as acute phase of SCI, prior episodes of DVT, medical history, family history and laboratory tests for other known causes of predeliction for DVT were not found.

Since these patients were already at risk for DVT because of paralysis following SCI, past episode of DVT, and (in two patients) presence of postthrombosis syndrome, they were felt to be at an additional high risk due to the unpredictable and asymptomatic onset with which acute HO and subsequent hypercoagulability can occur. In consideration of all these factors warfarin anticoagulation was given to these patients for a period longer than the recommended 3–12 months and will be continued for as long as the clinical risk factors and/or laboratory evidence of hypercoagulation is considered significant.

The prophylactic anticoagulation regimen for DVT was adjusted according to the degree and duration of the hypercoagulation and clinical considerations such as lifestyle of the patient, compliance in taking medication, modifications during surgical procedures and drug interactions. Patient 1 is paraplegic, and is a motivated individual

and nonsmoker, actively involved in competitive swimming and wheelchair rugby. He was maintained at a lower degree of anticoagulation as long as D-dimer levels were less than 500 μg/ml. This allowed him greater freedom in pursuing an active life style, while minimizing the risk of bleeding. Patient 2 is a smoker, less physically active and has a moderate postthrombosis syndrome. The D-dimer values in this patient have frequently been greater than 500 μg/ml. Patient 3 is a physically frail person with sedentary habits and has a severe postthrombosis syndrome. In this patient the increase in the clotting rate was the highest seen in this study and the fibrinogen concentration has yet to return to normal. Patients 2 and 3 have been maintained at a slightly higher degree of anticoagulation and the overall risk in patient 3 was considered to be too high to discontinue the prophylaxis for evaluation. During perioperative periods warfarin was discontinued and the thromboembolic risk was managed by subcutaneous heparin and intermittent pneumatic compression hose in all patients. The placement of a venacaval filter as an alternative prophylaxis for thromboembolism was not considered suitable in these patients because if the DVT recurred the venacaval filter would prevent pulmonary embolism but would not prevent a possible deterioration of the preexisting postthrombosis syndrome.

The mechanism of hypercoagulation induced by acute HO is not clear. One possibility is that it is mediated through the acute inflammation and associated tissue injury that occur at the site of acute HO. As long as the inflammation persists, there is constant activation of coagulation *in vivo* with consequent formation of intravascular thrombin.[15] This activation is thought to increase the rate of clotting of whole blood as observed *in vitro*. The intravascular thrombin leads to the conversion of fibrinogen into fibrin which is then lysed by the fibrinolytic enzymes to release the D-dimers, raising the D-dimer levels in the blood. Generally speaking, the higher the D-dimer levels rise, the greater the degree of hypercoagulation, with and without obstructive thrombosis.[11,12] The interpretation of D-dimer levels for the diagnosis of hypercoagulation needs to be done in the context of the patient's overall clinical status. The D-dimer levels in a control group of SCI patients were within normal range but any infection, wound, surgery, or inflammation can cause elevation of D-dimer levels.[12] Test values selected in this paper represent time periods when no other pathology could have accounted for the elevated D-dimer levels except acute HO. Serial determinations give a better evaluation of the process. The normalization of serially estimated D-dimer levels in these patients may have been either due to the resolution of the inflammatory stage of HO or the effect of the anticoagulant therapy or both. The increase in fibrinogen and ESR is a component of the acute phase response invoked by inflammation.[16] The elevated fibrinogen increases the viscosity of the blood and thus slows down blood flow.[17,18] In SCI patients, where the blood flow in the paralyzed limb is already compromised, increased fibrinogen can further aggravate the stasis.

In conclusion, the presence of acute HO lesions in SCI patients was associated with a persistent secondary hypercoagulable state which may have predisposed them to the development of concurrent DVT although the acute phase of SCI was over. Laboratory monitoring for hypercoagulation was helpful in identifying the patient at risk for recurrence[11,12] and in guiding the dose and duration of the post DVT anticoagulation. There are several reports of concurrent HO and DVT in the literature;[19,20] however, all patients with acute HO do not develop DVT. Investigations are in progress for determining the prevalence of hypercoagulation, and the factors which may precipitate an episode of thromboembolism in patients with SCI and acute HO.

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