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Abstract

Background/Objective: Deep venous thrombosis and pulmonary thromboembolism are common within weeks of spinal cord injury (SCI) but clinically uncommon in the chronically paralyzed. Fibrinogen half-life (FHL) and fibrin uptake of the legs (FUT), as indicators of an active thrombotic process, have been used to test this clinical impression.

Methods: Data from the use of autologous preparations of radioiodinated fibrinogen to determine FHL and FUT in 17 men paralyzed at cervical (6), thoracic (10), and lumbar levels (1), at ASIA grades A (15) and C (2) in 1974 to 1976 were reviewed. Group A consisted of 12 subjects 29 ± 8 years of age and paralyzed 1 week to 5 months (median, 1 month). Group B consisted of 5 subjects 46 ± 17 years of age and paralyzed 24 to 96 months (median, 36 months). Group B subjects were older and paralyzed longer than Group A. Group C consisted of 4 able-bodied control subjects enrolled at the same time for FHL studies, and these subjects were 34 to 38 years of age.

Results: FHL was 61 ± 14 hours for all SCI subjects and 95 ± 23 hours for Group C ($P = 0.001$). Group A FHL was 59 ± 16 hours, and FUT was positive in 8 of 12 subjects. Group B FHL was 66 ± 7 hours, and FUT was positive in 3 of 4 subjects (1 FUT not done; $P = 0.30$ and 1.0 , respectively).

Conclusions: Fibrinogen metabolism was abnormal in patients with acute SCI at high risk for pulmonary thromboembolism (PE) but continued to be abnormal beyond the high risk period for PE, possibly because of the greater age of the patients in the long-term paralysis group.

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Key Words: Fibrinogen; Spinal cord injuries; Venous thrombosis; Fibrinogen metabolism

INTRODUCTION

Pulmonary thromboembolism (PE) is recognized as a life-threatening complication of acute spinal cord injury (SCI) (1–3). Nevertheless, fatal PE in the chronic paralytic state is rarely addressed in the literature, despite the countless days of immobility in bed caused by treatment of pressure ulcers, fractures, or septic episodes (4–7). Likewise, the prevalence of the typically silent deep venous thrombosis (DVT) has been reported in 47% of patients with acute SCI but in only 9% of those with chronic spinal cord injury (8,9). This raises the question whether the thrombotic risk of acute SCI that apparently subsides with chronic SCI can be shown and explained.

Fibrinogen is a bloodborne clotting protein that is converted by thrombin to fibrin and degraded by

plasmin to fibrin degradation products. Fibrinogen, fibrin polymers, and fibrin degradation products are found in a spectrum in the circulation and are eventually excreted in the urine (10,11). Fibrin, as the glue of any thrombus, is consumed by any thrombotic process. At the same time, fibrinolysis accompanies fibrin formation (12,13) and ultimately accounts for fibrinogen disappearance from the circulation, breaking the activated fibrinogen molecule into small fragments that eventually are cleared through the kidneys (11). Fibrin uptake (FUT) by the thrombus can be determined measuring radioactivity over the suspected site of thrombosis after administration of a radioactive fibrinogen tracer (14). The half-life of fibrinogen (FHL) is determined by measuring the disappearance of this tracer from the circulation. The FHL is shortened by thrombosis and other conditions (eg, infection, cancer, and cirrhosis) (11,15). It is suggested that data collected with these 2 techniques, FHL and FUT, might offer some insight into the recovery of the patient with acute SCI from an exceptionally high risk for deep venous thrombosis and pulmonary embolism.

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In previously studies of FUT in patients paralyzed for varying periods of time (16,17), the half-life of the tracer, 125-I fibrinogen, was sometimes measured, although not reported. These half-life data have been retrieved, matched with the FUT data, and examined for the effect of the duration of paralysis on FHL and FUT. It is hypothesized that early thrombotic activity as measured by FHL and FUT subsides with longer duration of paralysis.

METHODS

Subjects

Patients with FHL data collected from 1974 to 1976 at the time of FUT data collection (16,17) were described by age, level, grade of paralysis, and duration of paralysis at the time of the study. The patients with SCI were divided into Group A, paralyzed for 1 week to 5 months, and Group B, paralyzed for 24 to 96 months at the time of the study. At the same time, able-bodied volunteers were recruited for FHL studies. These were designated Group C. Institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Tracer

Autologous preparations of radioiodinated fibrinogen were used to avoid transmission of serum hepatitis (18). The preparation was carried out by separating fibrinogen from plasma by salting out with ammonium sulfate, radioiodinating the protein with Na 125-I by the chloramine T technique, purifying by a final salting out step, and sterilizing the final product by passage through a small pore size filter (19).

Fibrinogen Half-Life

Blood was collected daily for 4 days after tracer administration, and the radioactivity was measured in a deep well scintillation counter, corrections being made for radioisotopic decay. Survival curves were plotted semilogarithmically. From this plot, the tracer half-life was measured in hours. In 2 patients whose venipuncture was difficult, the precordial radioactivity collected from a marked site and measured serially was used to measure FHL.

Fibrin Uptake Test

After administration of the tracer, radioactivity of marked sites over the deep venous system of the lower

extremities was measured daily with a ratemeter (Jasins and Sales, Wellesley, MA) and expressed as a percent of precordial counts. A rise of 20 percentage points over baseline for 2 consecutive days constituted a positive FUT.

Comparisons

The effect of paralysis on FHL was determined by comparisons between spinal cord injury Groups A and B combined and the able-bodied subjects (Group C). The effect of the duration of paralysis on FHL and FUT was determined by comparing Group A with Group B. Comparisons for patient age, duration of paralysis, and FHL were assessed by the Student *t* test and for the number positive for FUT by the Fisher exact test. A probability of less than 0.05 was taken as significant for these tests. The statistical software was *Primer of Biostatistics* (20).

RESULTS

The SCI Groups A and B combined, comparable with Group C for age, showed a much shorter FHL than the controls (Table 1). When, however, Group A, the patients with short-term SC, was compared with Group B, the long-term patients, the severity of paralysis of the groups were similar, but the average age of Group B was older. Nevertheless, the FHL and the prevalence of FUT were similar between the groups (Table 2). The shortest FHL, 29 hours, occurred in the only patient with acute and massive deep vein thrombosis. This patient was not anticoagulated because of a negative lung scan and previous bleeding with prophylaxis. The other patients had not received anticoagulants at the discretion of the managing physicians, who, at the time, had no randomized evidence of effective prophylaxis for DVT in patients with SCI.

DISCUSSION

The high-risk period for DVT and PE of acute spinal cord injury is the first few months after injury (1). However, when FHL and FUT were adopted as parameters of thrombosis, no difference was found between patients paralyzed 5 months or less and those paralyzed 24 to 96 months. Thus, confirmation of the clinical impression that the thrombotic tendency of acute paralysis resolves several months after SCI is not apparent by FHL and FUT.

This contradiction is reconcilable, however. Fibrinolysis, which accompanies fibrin formation (10), ultimately

Table 1. FHL in Subjects With SCI and Able-bodied Persons

Subjects	N	Age (yr)	FHL (h)
SCI	17	34 ± 13.5	61 ± 14
Able-bodied	4	36 ± 1.9	96 ± 23
<i>P</i>		0.78	<0.01

Table 2. Patient Descriptions and Results of Fibrinogen Studies

Age (y)	Paralysis			FHL (h)	FUT
	Level	Grade (ASIA)	Duration (mo)		
Group A					
23	T	A	0.25	36	Negative
29	C	A	0.33	46	Positive
25	T	A	0.39	66	Positive
25	T	A	0.75	78	Negative
22	T	A	1	48	Positive
38	C	A	1	59	Positive
19	C	C	1	72	Negative
3	L	A	4	62	Positive
30	T	A	4	79*	Positive
48	T	A	4	60	Positive
31	C	A	5	29	Positive
23	T	C	5	68	Negative
N = 12			12	12	12
29 (8) [mean (SD)]			2.2 (2.0)	59 (16)	
FUT positive					8
Group B					
25	T	A	24	66	Negative
66	T	A	33	57	Positive
56	T	A	36	64	Positive
31	C	A	60	69	Positive
51	C	A	96	76*	
N = 5			5	5	4
46 (17) [mean (SD)]			49.8 (29)	66.4 (6.9)	
FUT positive					3
P	0.01		<0.01	0.31	1.0

Three patients with FHL by both blood sampling and precordial scanning showed FHL in blood differing from FHL by scanning at 2, 11, and -8 hours.

*Determination of FHL by precordial scanning alone. With removal of these data, the *P* value for differences between groups for FHL was 0.37.

C, cervical; T, thoracic; L, lumbar. FHL, fibrinogen half life; FUT, fibrin uptake test.

accounts for reduced fibrinogen survival in the circulation, breaking the activated fibrinogen molecule into small fragments that eventually are cleared through the kidneys (11). This action also accounts for the reduction in thrombus accumulation with or without pulmonary emboli, even as fibrin uptake continues (21). The sources of fibrinolytic activity are variable (eg, bloodborne plasminogen, the venous endothelium, or leukocytes), and the sites of fibrinolytic activity are variable within the circulation or any thrombotic process (22–24). The concept is that of a shift from predominant fibrin formation, resulting in clinically detectable thrombus accumulation and pulmonary embolism in the acute paralytic state, to continuing fibrin formation and compensating fibrinolysis, resulting in the reduction of clinically detectable thrombosis or pulmonary embolism in the chronic paralytic state.

Another factor in the reduction of accumulated thrombotic material may be the narrow venous system

of the lower extremities in subjects with chronic paralysis (25). Pooling of blood in the paralyzed lower extremities is minimal because of constricted venous capacitance, perhaps sufficient to remove stasis as a factor in the genesis of venous thrombosis.

The interpretation of the results of this study is subject to some uncertainty. First, infections are known to affect fibrinogen metabolism (26), and infections are common in the SCI population (27). However, none of the subjects were febrile at the time of the study. Second, it cannot be inferred that FHL is shortened or that a positive FUT is persistent for the life of the patient with SCI, because the longest duration of paralysis studied was 8 years. Third, Group B patients with paralysis of longer duration were older than Group A patients and might have sustained a shortened FHL for that reason. Age is a risk factor for thrombosis (28). Fourth, FHL itself does not indicate the balance of plasma fibrin and fibrin degradation products, a balance that might change with duration

of paralysis. With longer duration of paralysis, however, the patient is subject to factors favoring thromboembolism—older age, obesity, infection, malignancy, fractures, and surgery (28).

CONCLUSION

Fibrinogen metabolism is increased by SCI as evidenced by the rapid disappearance of fibrinogen from the blood stream and its deposit in the deep venous system in paralyzed subjects. This abnormality of metabolism extends beyond the period of risk characterized by clinically detectable thromboembolic disease and represents subclinical events. The early major thrombotic activity is eventually reduced to subclinical thrombotic events by the recruitment of fibrinolysis and the narrowing of the deep venous system. Whether the subclinical thrombotic activity of SCI subsides with longer duration of paralysis is undetermined.

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